Day 2

Sunday, 29 August 2004

TRENDS AND RISK FACTORS IN CARDIOVASCULAR DISEASE

117 Desire and acceptance for genetic testing in patients with suspected premature coronary artery disease

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Background: The aim of this study was to evaluate the general acceptance of genetic testing in patients with suspected premature coronary artery disease (CAD).
Methods: Patients referred for diagnostic left heart catheterization were prospectively recruited. Presence of stenotic coronary atherosclerosis [CAD] (stenosis of more than 50%) and presence of myocardial infarction [MI] (documented NSTEMI/STEMI or regional wall motion abnormality on cineventriculography) were assessed. In a standardized questionnaire a subgroup of 167 patients (81 males before the age of 55, 86 females before the age of 65) were asked if the would support the testing for potential genetic risk factors for premature CAD, if these test could be used for a prevention program. Furthermore there were asked if these tests should be performed at early childhood (0-6 years), adolescence (7-18 years), early adulthood (18-30 years), or later (>30 years), and if the test results should be given solely to the patients, or the health insurance or other insurances.
Results: 45% had neither MI nor CAD, 49% had stenotic CAD and 39% had MI. Of all patients 96% would support the testing of genetic risk factors. These patients 43% stated the test should be offered at early childhood, 21% voted for adolescence, 25% recommended young adulthood, and 11% wanted the test later in life. 92% of all patients would asked for these tests for themselves and their families. However 75% stated that these results should never be given to any insurances, 19% would agree to share the results with their health insurances, and 7% would agree to share the results with other insurances. The answer were not influenced by gender or the presence of MI or CAD.
Conclusion: There is a very high acceptance rate and desire for genetic tests in individuals with suspected premature CAD. The majority think these tests should be offered early in life. However, most of the patients want the results to be kept confident. The contrast between the strong desire of patients and the absolute lack of evidence of the prognostic value of genetic tests is of special ethical importance. Furthermore the wish for confidence of genetic tests is of special importance.

118 Trends in fatal and non-fatal coronary heart disease events in Finland during 1991–2001

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Purpose To analyse the trends in fatal and non-fatal coronary heart disease (CHD) events in Finland during an 11-year period 1991-2001 among persons 25 to 74 years of age.
Methods: Data on hospitalisations due to CHD in the Finnish Hospital Discharge Register (CHD part) were linked to the National Causes of Death Register using personal identification codes in order to produce a Cardiovascular Disease Register including data on 888 313 events in 640 003 individuals. Case selection for CHD in the Hospital Discharge Register included the main diagnosis and the additional diagnoses. From the Death Register, the data covered deaths with CHD as the underlying (Ic) or immediate (Ia) cause of death, or with myocardial infarction (MI) as a contributing cause of death. In Finland, the International Classification of Diseases (ICD) edition was changed from the ninth to the tenth in January 1, 1996. The trends in mortality, incidence and case-fatality of CHD events were determined with the use of Poisson regression analysis.
Results: The annual average decline in the age-standardized CHD mortality rate in 1991-2001 was 5.2% (95% CI, -5.6, -4.8%) among men and 6.1% (-6.6, -5.6%) among women. The incidence of first MI declined annually on average by 5.5% (-5.9, -5.1%) from 1991 to 1995 and by 2.4% (-3.0, -1.7%) from 1996 to 2001 among men. The respective changes among women were -5.9% (-6.5, -5.2%) and -1.7% (-2.7, -0.6%). The case-fatality due to first MI for days 0-27 declined annually on average 1.2% (-1.6, -0.91%) among men and 1.4% (-2.0, -0.9%) among women. The number of hospitalisations due to unstable angina pectoris increased between 1991-1996 (p=0.0002) and remained stable for the rest of the study period. The number of hospitalisations due to stable angina increased until 1996 and decreased since that.
Conclusions: The CHD mortality and case-fatality rates declined significantly in Finland in 1991-2001 among both men and women aged 25 to 74. Similarly, a decline was observed in the incidence of first MI. Despite the increase in the number of unstable angina-related hospitalisations, the rate of acute coronary events remained declining. The transient increase in the number of hospitalisations due to stable angina probably reflects the increase in the number of coronary angiographies and interventions in the end of 1990s.

119 Physical exercise is associated with decreased myocardial damage in patients with acute coronary syndromes: a case of ischaemic preconditioning?

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Objective: Regular physical exercise in patients with coronary heart disease has been associated with decreased extent of myocardial damage and, hence, improved short-term prognosis. We evaluated the hypothesis whether life-time physical activity is related with Troponin I (TnI) levels, in patients who admitted for acute coronary syndromes.
Methods: From October to December 2003, 546 patients from 7 major hospitals in Greece and with a discharge diagnosis of acute coronary syndromes were enrolled into the study. Of them, 75% were men (65 ± 11 years old) and 25% were women (71 ± 13 years old). Among several bio-markers, TrI levels were measured at entry as well as during hospitalization in all patients. Cox proportional hazard models were applied to evaluate the effect of physical activity status (as assessed by a special index that evaluated duration, intension and time devoted to occupational or leisure time activities) on the 30-day outcome of cardiovascular events (death or hospitalization due to CVD), after adjusting for several potential confounders.
Results: During the 30-day follow up 8% of the patients had an event. Moreover, 43% of the patients reported any type of physical activity (26% of them were engaged to vigorous exercise at least 3 times per week). Increased physical activity levels were associated with less severe acute coronary syndromes (i.e. unstable angina) as compared to sedentary lifestyle, in both genders ($p < 0.05$). Furthermore, an inverse association between the level of physical activity and TnI measurements was observed ($p < 0.001$). In particular, patients who were devoted to vigorous physical activities (> 4 times/w and > 7 kcal/min expended) were 45% less likely to be classified in the upper quartile of TnI levels, as compared to those who reported sedentary life (odds ratio = 0.55, $p < 0.001$), after controlling for age, sex, body mass index, type of syndrome, and history of cardiovascular risk factors. Finally, patients who reported even moderate exercise (>4 kcal/min expended and > 2 times/w) had 12% lower risk of a 30-day event as compared to sedentary (hazard ratio = 0.88, $p < 0.001$), after controlling for several confounders.
Conclusion: Our findings may suggest the time devoted to physical exercise might have a cardioprotective – necrosis-limiting effect during an acute coronary syndrome, through the process of ischaemic preconditioning.

120 Cardiovascular disease risk profiles among healthy siblings of patients with premature cardiovascular disease. Application of the new SCORE system

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Purpose Cardiovascular disease (CVD) occurs more frequently in individuals with a family history of premature CVD. Within families the demographics of CVD are poorly described. New European guidelines on cardiovascular disease prevention suggest treating asymptomatic individuals who are at high risk of developing atherosclerotic CVD (≥15% risk of a fatal CVD event over 10 years or when projected to age 60). We examined the risk estimation based on the SCORE (Systematic Coronary Risk Evaluation) system for older unaffected siblings of patients with premature CVD (previous myocardial infarction, unstable angina, or stable angina with angiographic evidence of coronary artery disease, onset [≤] 55years for males and [≤] 60 years for females). Present Joint British recommendations suggest treating healthy individuals with an absolute risk [≥30%] over 10 years reducing to those with a coronary heart disease (CHD) death risk [≥15%] when higher risk patients have first been treated.
Methods: Between 1999 and 2003 demographic and laboratory details were collected on probands with premature CVD and their older unaffected siblings (greater than three years older than the index case at first presentation). Siblings (sibs) were screened for clinically overt CVD by a standard questionnaire and 12 lead electrocardiogram (ECG).
Results: We identified 935 sibs; 77 were already on lipid lowering therapy and were excluded (68 statins, 4 fibrates, 5 statins and fibrates). Complete data for analysis were available for 675 sibs. Mean age was 55.0 years (SD 8.3), 305(45%) male, 202(30%) were smokers, 27(4%) had diabetes mellitus and 334(49%) had hypertension (on anti hypertensive therapy or systolic BP[≥]140mmHg). Mean plasma cholesterol was 5.83 mmol/l (SD 1.01), HDL 1.45 mmol/l (SD 0.43) and cholesterol/HDL ratio 4.33 (SD 1.34). Using the SCORE system 152 sibs (23%) had a present 10 year risk of death [≥]5% increasing to 297 (44%) when projected to age 60 (224 of 305 males (73%) and 73 of 370 females (19%). Using existing Joint British guidelines (based on the Framingham function): 11(2%) have a 10 year CHD death risk [≥]30% and 161(24%) [≥]15%.
Conclusions: Large numbers of these high risk individuals meet existing BCS guidelines for primary prevention of CVD. This number has increased dramatically with the new European guidelines. These individuals should be considered for multiple risk factor intervention. The financial burden of this is great. However given the low mean age the benefit in terms of years gained is high.

121 Fifteen-year trends in lipid profiles of adolescents in changing Russia (1989–2003)

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Hyperlipidemia is a known risk factor for CVD. The reduction of elevated serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels in childhood may reduce cardiovascular risk in adulthood. During the 1990s the Russian population has been exposed to major political, economic and social changes accompanying by remarkable variation in health status.

Aim: Aim of the study was to assess trends in lipid profile of adolescent population in Novosibirsk during and after the reforms (1989-2003).

Methods: Four cross-sectional surveys of school children aged 14-17 in 1989 (656), in 1994 (620), in 1999 (626) and in 2003 (667) were carried out. Total sample was 2569 (1214 males and 1355 females). Blood total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), were measured by enzymatic methods. LDL-C was calculated with Friedwald's formula. Associations of blood lipids with age, sex, year of study, body mass index (kg/m^2), blood pressure and main nutrients of diet were measured by GLM method. Prevalence of dyslipidemia was evaluated with NCEP-peds criteria. Diet was estimated using 24-hour dietary recall.

Results: During the period of reforms (1989-1999) mean TC decreased from 175 to 158 mg/dl in males and from 191 to 175 mg/dl in females ($P < 0,001$). Average levels of LDL-C also have fallen significantly during the period, but no changes in HDL-C levels were found. During the post-reform period (1999-2003) average levels of TC and LDL-C slightly increased in boys and girls. Females had significantly higher mean TC and LDL-C than did males at all surveys ($P < 0,001$). According to NCEP-peds criteria, prevalence of high TC (200 mg/dl and more) during the period (1989-2003) significantly decreased from 22% to 8% ($P<0,01$) in males and from 32% to 17% ($P<0,05$) in females. Significant regression coefficients for TC, controlled by age, sex and year of study were revealed with body mass index, diastolic blood pressure and triceps skinfolds. Trends in diet during the period of reforms (1989-1999) showed significant decreasing of total energy intakes.In 2003 year average consumption of energy and basic nutrients in adolescent population slightly increased.

Conclusion: During the period of socioeconomic reforms in Russia the lipid profile of adolescents significantly changed following by changes of body mass indices and diet. No significant changes of the investigated parameters were revealed in 2003.

122 Determinants of serum high-sensitive C-reactive protein in young adults. The cardiovascular risk in young finns study

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Background: Inflammation has become a central concept in the pathogenesis of atherosclerosis. In recent years, high-sensitive C-reactive protein (hs-CRP) has shown to be an independent risk factor for atherothrombosis and a predictor of future cardiovascular events. Only few studies have addressed the associations between cardiovascular risk factors and hs-CRP in young adults. Also, the data on normal values of hs-CRP in young adults are limited.

Methods: Age- and gender-specific reference ranges were calculated for hs-CRP and the interaction between hs-CRP levels and established cardiovascular risk factors were evaluated in a cohort of 2,319 subjects aged 24 to 39 years participating in the longitudinal study of Cardiovascular Risk in Young Finns.

Results: Women had higher median hs-CRP concentrations compared to men (0.86 vs 0.59 mg/l, $p<0.0001$). In multivariate model in women, hs-CRP was directly associated to BMI ($p<0.0001$), waist circumference ($p=0.0146$), serum triglyceride concentration ($p<0.0001$) and oral contraceptive use ($p<0.0001$) and inversely associated to age ($p<0.0004$). In men, the multivariate correlates of hs-CRP included waist circumference ($p<0001$) and smoking ($p=0.0032$).

Conclusions: In healthy young adults, hs-CRP levels are higher in women, and increase with obesity in both sexes. The behavioral determinants that are associated with elevated levels of hs-CRP include oral contraceptive use in women and cigarette smoking in men.

RISK FACTORS MANAGEMENT IN PREVENTION

123 Predicting mortality in survivors of acute coronary syndrome using the 4 drug (4 D) score: risk stratification by discharge medication

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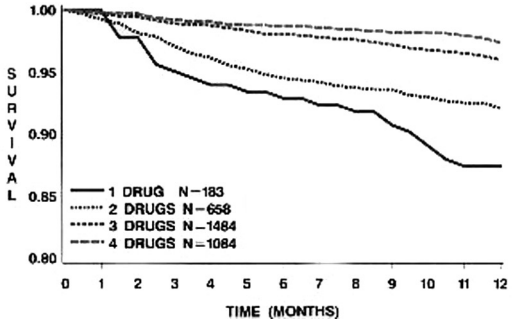
Background: Risk assessment following an acute coronary syndrome (ACS) has traditionally focused on the extent of the inflicted myocardial damage and its functional consequences. However, attempts to predict future events by the present cardiac condition may become increasingly problematic as powerful therapeutic interventions emerge that are bound to alter the natural course of cardiovascular disease. We hypothesized that the simple number of secondary prevention drugs at discharge (from 1 to 4) will independently predict mortality of ACS survivors.

Methods: 3407 patients of the Israeli ACS surveys 2000 and 2002 were included in the analysis. A score from 1 to 4 was assigned to each patient according to the number of secondary prevention drugs at discharge - platelet inhibitor, beta blocker, statin, and angiotensin converting enzyme inhibitor (or receptor blocker) – irrespective of combination or dosage.

Results: The crude 1-year mortality for a score from 1 to 4 was 12.6%, 7.9%, 4.0% and 2.6%, respectively ($p < 0.0001$). There was a 60% risk reduction associated with the use of 3 or 4 versus 1 or 2 drugs (odds ratio 0.4; 95% confidence interval: 0.28 - 0.56), which was independent of age, sex, past ACS, diabetes, heart failure during hospitalization, ejection fraction, or the presence of ST elevation.



1-year mortality

Conclusion: Use of a higher number of secondary prevention drugs at discharge is associated with incremental survival benefits. The 4D score is a powerful predictor of 1-year mortality in ACS survivors.

124 Efficacy of two strategies using cardiac rehabilitation nurses to promote long- term adherence to lifestyle changes and to medical treatment in patients with coronary artery disease

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Background: long-term adherence to lifestyle changes and medical treatment is low after phase II cardiac rehabilitation (CR).

Aim: to determine the efficacy of 2 low-cost long–term strategies (12 months) using a CR nurse to achieve (1) a better control of risk factors (RF), (2) a better compliance to medical treatment (MTh) and (3) to physical activity (PAP) as prescribed at the end of CR.

Methods: after 8 weeks of CR 611 pts (57±9 y),were randomized into 3 groups: usual-care (G1, 214 pts); phone-follow-up group (G2, 193 pts), intensive long-term intervention CR (G3, 204 pts). The G2 were called every month by a nurse to reinforce adherence to MTh and to check progress regarding lifestyle changes; the G3 underwent, every 3 months, 2 hours of CR, managed by nurses, which consisted of individual aerobic physical training and counseling sessions in our CR center. After 1 year all pts were evaluated for RF, MTh, PAP.

Results: 579 (95%) pts completed the follow-up(FU): the LDL-cholesterol was 125±19 mg% in G1, 106±16 mg% in G2 ($p<0.01$ vs G1), and 101±22 mg% in G3($p<0.01$ vs G1 and G2); among the 364 pts smoking before CR, the % of smokers at FU was 38% in G1, 40% in G2 and 10% in G3 ($p<0.01$ vs G1 and G2). The complete adherence to MTh was 47% in G1, 66% in G2, and 91% in G3 ($p<0.01$ vs G1 and G2),while the complete adherence to PAP was 15% in G1, 49% in G2 and 83% in G3 ($p<0.01$ vs G1 and G2).

Conclusion: both long-term strategies using CR nursing were effective in increasing adherence to lifestyle changes and compliance to MTh and PAP. In addition, a more direct and intensive strategy had better efficacy.

125 Substantial improvement of adherence to national guidelines – preliminary results of the Swedish quality improvement in cardiac care project

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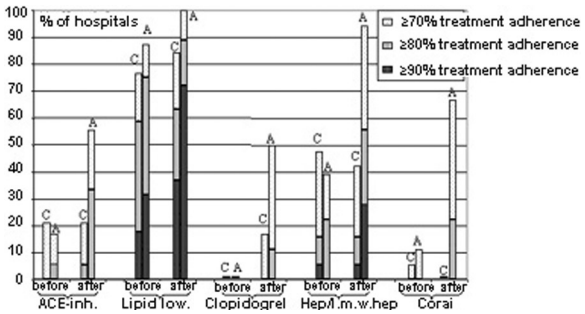
Data from the National register(RIKS-HIA) have repeatedly shown a considerable gap between optimal treatment of acute myocardial infarction (AMI) according to current guidelines and what is actually given. Therefore, we have started a national project in order to improve the treatment of AMI engaging one fourth of the Swedish hospitals.

Methods: Multidisciplinary teams from 19 hospitals (A) participating in RIKS-HIA, ranging from small to large hospitals, were trained in quality improvement methodology, 19 matched hospitals also participating in RIKS-HIA served as controls (C). The work was focused on finding and applying tools and methods suited to the local situation in order to increase adherence to the national guidelines for 5 different treatments in AMI. The base line level of treatment was determined during the year prior to start of the project. The initial 6 months were a training and implementation phase. After this phase the effects were measured - so far for 8 months - and compared with the "spontaneous" changes in the control hospitals.

Results: In the control and the active hospitals the mean absolute increase of patients receiving ACE-inhibitors was 2 & 10% (p=0.02); lipid lowering agents 1 & 7% (p=0.19); clopidogrel 24 & 38% (p=0.02); heparin or l.m.w heparin 1 & 16% (p=0.001) and coronary angiography 2 & 17% (p=0.01), respectively. The number of hospitals reaching ≥70%, ≥80% and ≥90% adherence to the guidelines before and after start of the project, respectively, are shown in the figure.



Conclusions: By applying a continuous quality improvement methodology in conjunction with the use of the national register it is possible to improve the adherence to guidelines considerably and thereby improve the acute cardiac care.

126 Evaluation of the efficacy of an easy and inexpensive intervention to optimise secondary prevention measures in patients who undergo cardiac surgery

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Aim: To assess whether a hospital intervention can improve the use of secondary prevention (SP) measures in patients who undergo cardiac surgery.

Methods: The indications of SP pharmacological therapies were reviewed in a number of clinical guidelines and the conclusions abstracted, presented and accepted by all the members of the Cardiac Surgery Department. A document that included a) the indications of SP interventions, b) their use, c) cause of non use, and d) alternative therapy employed was developed. It was accepted by consensus to fill the document for each patient before hospital discharge during year 2003 (n=298, 11 mo.). With the same document, the use of SP measures on patients discharged during year 2002 (n=372) was retrospectively recorded and results pre- and postintervention were compared.

Results: Baseline characteristics, prevalences of CAD, PAD, LV systolic dysfunction, and atrial fibrillation were similar in both groups, with the exception of smoking (41% in 2002, 30% in 2003; p=0.005) and cerebrovascular disease (10.6% in 2002, 4.3% in 2003; p=0.003). Table shows the rate of use of SP pharmacological interventions in optimal candidates (those with indication and without absolute or relative contraindications) before and after the intervention.

Secondary prevention pre- & post-intervention

Treatment	2002	2003	p value
Aspirin (%)	81.8	95.2	0.15
Statins (%)	56.0	94.3	<0.001
ACEIs (%)	75.5	97.3	<0.001
Beta-blockers (%)	73.6	95.1	<0.001

Conclusions: We have demonstrated that secondary prevention can be substantially improved in patients who undergo cardiac surgery with an easy and inexpensive hospital intervention.

127 Attitudes of physicians towards the treatment of risk factors in patients with CHD: how do physicians comply with clinical guidelines? Results from the COSIMA study

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The EUROASPIRE I and II surveys have shown a persistent gap between evidence based guidelines on secondary prevention of CHD and their implementation in clinical practice. The aim of the COSIMA (Coronary secondary prevention in the Münster area) study is to identify factors explaining the observed gap in the EUROASPIRE region of Münster. To achieve its aim COSIMA applies a physician and patient survey. We report here on the results from the physician survey. In 2002, a postal questionnaire with questions on knowledge and attitudes towards guidelines on secondary prevention of CHD was sent to all general practitioners (GP) and internists working in private practice in the region of Münster (N=1,023). The impact of socio-demographic factors, specialty, duration of medical practice and characteristics of private practice were assessed using multivariate logistic regression. In total, 681 physicians participated in the survey. 58% of physicians claimed good or very good knowledge of the guidelines of the German Society of Cardiology, whereas the respective ESC guidelines were much less known (15%). Generally, physicians rated the treatment of risk factors such as smoking (94%), hypertension (90%), diabetes (84%), hypercholesterolemia (71%) and overweight (69%) as very important. With regard to smoking cessation, however, the importance of behavioural therapy and nicotine replacement therapy (NRT) was acknowledged as very important by only 17 and 5% of physicians, respectively. 36% of physicians reported to start antihypertensive drug treatment at a systolic blood pressure of ≥150 mmHg and 38% of physicians stated to start drug treatment only at total cholesterol values of ≥250 mg/dl or LDL-cholesterol values of ≥150 mg/dl. Internists were more likely to start drug treatment of hypercholesterolemia at a LDL-C level ≥100 mg/dl (OR 1.39 95% CI 0.95-2.05) and drug treatment of hypertension at systolic blood pressure ≥140 mmHg (OR 1.42; 1.0-2.02) as compared to general practitioners. In general, physicians expressed positive attitudes towards the usefulness of guidelines. However, the need for vigorous treatment of risk factors, such as smoking, hypertension, and hypercholesterolemia in patients with CHD was grossly underrated. Our findings provide physician-related explanations for the persisting gap between guidelines and treatment of risk factors in the Münster region. Stronger emphasis has to be put on information dissemination and the continuous medical education of physicians to ensure higher standards of knowledge on recent developments in evidence based medicine.

128 Association between cardiovascular risk factors and erectile dysfunction

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Purpose Recent epidemiological studies have shown the association between cardiovascular diseases and erectile dysfunction (ED). One of the study objectives was to evaluate the impact of cardiovascular diseases on the prevalence of erectile dysfunction, adjusting for other risk factors. In addition, a risk score was calculated that estimates a patient's individual probability of erectile dysfunction based on various risk factors, including cardiovascular diseases.

Methods: A subset of case records (n = 4,396) from the Cologne Male Survey, which is a cross-sectional study investigating male sexuality by means of a validated questionnaire, was used to build a multivariable logistic regression model for the prevalence of ED. Besides cardiovascular diseases, other risk factors like age, specific comorbidities, and the life-style habit smoking were investigated for significant association with ED. The regression equation was both internally and externally validated.

Results: Arterial circulatory disorder, hypertension and heart disease were significant predictors of erectile dysfunction. The final regression equation including age (OR 1.1), pelvic surgery (OR 5.9), diabetes mellitus (OR 3.8), arterial circulatory disorder (OR 2.0), heart disease (OR 1.9), smoking (OR 1.5) and hypertension (OR 1.4) reached an area under the ROC curve (discriminatory index) of 0.839 (95% confidence interval 0.825-0.854). The external validation results (AUC: 0.750; 95% CI: 0.728-0.772) are similar to those of other popular risk scores, such as the Framingham coronary heart disease prediction score. A simple scoring scheme was developed in order to enable the physician to estimate a patient's risk of ED on the basis of the values of the above mentioned risk factors.

Conclusion: The validated ED risk score model may provide an alternative approach to identification of ED high-risk patients not requiring the administration of a questionnaire asking sensitive questions. Physicians may be able to identify patients who may be at a high risk of ED, based on simple risk factors. This study shows evidence that arterial circulatory disease, hypertension and heart disease, along with other risk factors may be significantly associated with erectile dysfunction. The risk score may facilitate interaction between the physician and his/her patients for individual diagnosis of ED.

PREDICTIVE FACTORS IN DILATED CARDIOMYOPATHY

129 Arg16Arg genotype of the beta2-adrenergic receptor predicts lower risk for major arrhythmic events in patients with idiopathic dilated cardiomyopathy

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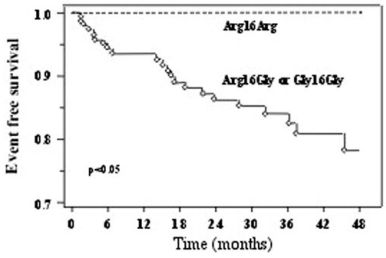
Arrhythmia risk stratification in patients (pts) with dilated cardiomyopathy (DCM) is a relevant issue in clinical practice. Neverthless, parameters predicting major arrhythmic events occurrence are not yet well defined. Since DCM is a multifactorial disease with a strong genetic component and for the crucial role played by adrenergic pathway in the arrhythmogenesis, we sought to investigate a possible involvement of beta2-adrenergic receptor (AR) polymorphisms in susceptibility to ventricular arrhythmias.

We prospectively evaluated 184 consecutive unrelated pts (mean age 50±14 years, 139 men, NYHA class 1.9±0.7, left ventricular ejection fraction LVEF, 35±10%) with idiopathic dilated cardiomyopathy while receiving optimal medical therapy including betablockers. All patients were characterised for the 5' leader cistron-Arg19Cys, Arg16Gly and Gln27Glu polymorphisms of the beta2-AR on the basis of PCR amplified DNA using RFLP analysis.



During a median follow-up of 33 months, 8 pts died suddenly, 12 had sustained ventricular tachycardia and 2 resuscitated ventricular fibrillation. Kaplan-Meier survival curves showed that patients carrying Arg16Arg genotype were at significantly lower risk of developing lifethreatening ventricular arrhythmias compared with those carrying at least one copy of Gly16 allele (Figure). The sensitivity of the predictive role for Gly16 variant was 100%, its specificity 17%, and its positive and negative predictive power were respectively 14% and 100%. No differences were found in terms of age, gender, NYHA class, LVEF and use of medication according to genotypes.

In patients with DCM, the Arg16Arg genotype of the beta2-AR seems to represent a protective factor of major arrhythmic events.

130 The prognostic meaning of coronary flow reserve assessed by Doppler echocardiography in non-ischaemic dilated cardiomyopathy

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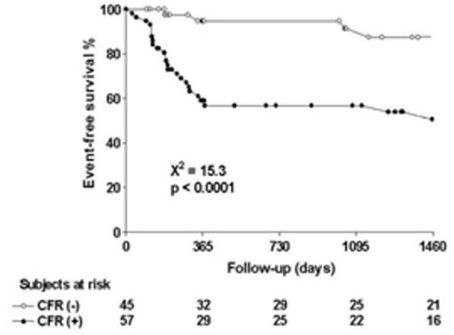
Background: Coronary flow reserve (CFR) can be impaired in idiopathic dilated cardiomyopathy (DC), unmasking a coronary microcirculatory dysfunction of potential prognostic impact.

Aim: To evaluate the prognostic value of CFR in patients with DC.

Methods: We evaluated 102 DC patients (68 male; age 63±11 years) by transthoracic or transesophageal dipyridamole (0.84 mg/kg in 10') stress echocardiography. All patients had an ejection fraction <45% (mean 33±7) and angiographically normal coronary arteries. CFR was assessed on LAD by pulsed Doppler as the ratio of maximal vasodilation (dipyridamole) to rest peak diastolic flow velocity.

Results: Mean CFR value was 2.0±0.6. At individual patient analysis, 45 patients had normal CFR >2 and 57 had abnormal CFR <2. Patients with normal CFR had lower left ventricular end-systolic volume (118±50 vs 158±56 ml; p<0.0001), and higher left ventricular ejection fraction (37±7 vs 30±6%; p<0.0001) than those with abnormal CFR. During follow-up (30±24 months), 10 patients died for cardiac reasons, and 23 showed worsening of NYHA class at periodic oupatient visit. Four-year event-free survival was 51% in subjects with abnormal and 87% in those with normal CFR (p<0.0001) (Figure). Of 10 clinical and echo variables analyzed, abnormal CFR (HR=3.66; 95% CI=1.34-10.11; p=0.01)was the strongest prognostic predictor.



Conclusion: In DC patients, assessment of CFR is feasible by either transthoracic or transesophageal echocardiography. CFR is often impaired. A reduced CFR is associated with worse prognosis.

131 Stimulating autoantibodies targeting the cardiac beta1-adrenergic receptor predict increased mortality in dilated but not in ischaemic cardiomyopathy

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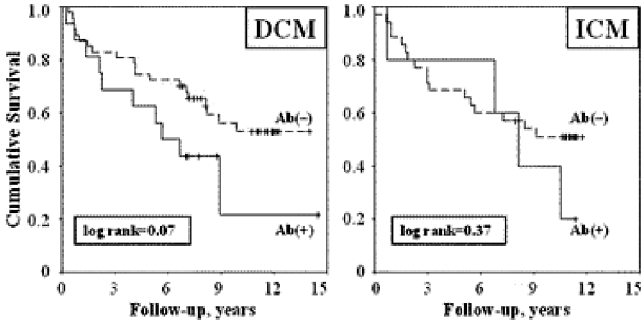
Background: Stimulating autoantibodies directed against the cardiac beta1-adrenergic receptor (beta1-AR) play an important role in the initiation and progression of human cardiomyopathy.

Methods: To estimate the independent and incremental prognostic value of presence of stimulating beta1-AR autoantibodies, long-term follow-up data of patients with dilated (DCM, n=65) and ischemic cardiomyopathy (ICM, n=39) was analyzed (Cox).

Findings: Anti-beta1-AR autoantibodies were found in 26% of patients with DCM and 10% with ICM. During a mean follow-up of 10.7±2.5 y, mortality in antibody-positive patients was 63% with DCM and 80% with ICM, and in antibody-negative patients 43% and 49%, respectively. In univariate analysis (P<0.15), presence of anti-beta1-AR autoantibodies was associated with increased mortality in DCM (RR=1.99 [0.92-4.31]; P=0.066), but not in ICM (RR= 1.53 [0.54-4.86]; P=0.379). Multivariate regression analysis identified autoantibodies, cardiac index, relaxation (-dP/dt), and PCWP as independent predictors of mortality in DCM (all P<0.05). Information on antibody status improved the prognostic capacity even in models containing already extensive information on clinical profile, Holter readings, and invasive hemodynamic measurements (area under the ROC curve, 0.91 [0.85-0.97] vs. 0.85 [0.78-0.92]; P<0.05).



Antibody (Ab) status and survival.

Interpretation: Our data indicate that presence of anti-beta1-AR autoantibodies independently predicts a markedly increased mortality risk in DCM and confers incremental prognostic value in addition to clinical, Holter, and hemodynamic information. The clinical benefit of cardioselective beta1-blockers in heart failure might be partly attributable to the pharmacological neutralization of stimulating anti-beta1-AR autoantibodies.

132 Independent prognostic role of arterial baroreflex control of heart rate in predicting heart failure progression in idiopathic dilated cardiomyopathy

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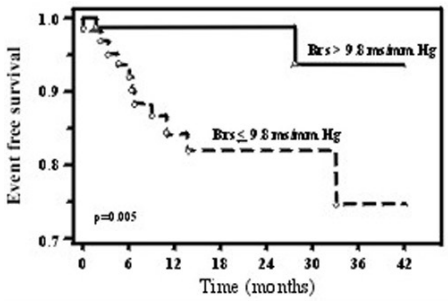
The role of baroreflex sensitivity in predicting outcome of patients with dilated cardiomyopathy is controversial. Therefore, we prospectively evaluated whether arterial baroreflex sensitivity (BRS) predicts heart failure (HF) progression in 144 patients (48±14 years, 108 male, NYHA class 1.8±0.6) with idiopathic dilated cardiomyopathy. All of the patients were taking optimal medical therapy (betablockers 83%, ACE inhibitors and/or AT1R antagonists 93%) and underwent an echo-Doppler assessment of left ventricular end-diastolic diameter (LVEDD, mean 61±7 mm) and left ventricular ejection fraction (LVEF, mean 36±11%). Peak of O2 consumption during exercise test (VO2 peak, mean 19±6 ml/kg/min) was also evaluated. BRS was non-invasively evaluated by using sequence method (mean 12±11 ms/mm Hg). HF progression was defined as worsening of symptoms leading to re-hospitalization or heart transplantation or death.

During follow-up (mean 23±15 months, median 24 months), 7 patients were hos-



pitalised, 3 underwent heart transplantation and 3 died after HF worsening. At univariate analysis, NYHA class, LVEF, LVEDD and BRS were significantly related to heart failure progression. At multivariate analysis, BRS remained significantly associated to events (HR: 0.87; p < 0.05). Figure shows Kaplan-Meyer curves of patients with BRS above and below median value (9.80 ms/mm Hg).
In patients with idiopathic dilated cardiomyopathy, the assessment of sympathovagal balance by non invasive evaluation of BRS predicts HF progression independently from other clinical variables.

133 Causes and prognosis of syncope in patients with idiopathic dilated cardiomyopathy

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Syncope associated with heart disease is a factor of bad prognosis; however, syncope could have various mechanisms and therefore different prognostic significance. The purpose of this prospective study was to determine the causes of syncope and their prognostic significance in patients with idiopathic dilated cardiomyopathy (DCM).
Methods: Non invasive studies, including 24 hour Holter monitoring and head-up tilt test and invasive studies, including coronary angiography and electrophysiological study (EPS) were performed in 66 patients with DCM admitted for syncope. EPS consisted of atrial and ventricular programmed stimulation in control state and if necessary after isoproterenol. Patients were followed from 1 to 6 years (mean 4±1).
Results: Left ventricular ejection fraction (LVEF) varied from 10 to 40% (mean 27±10); non sustained ventricular tachycardias (VT) were present on Holter monitoring in 26 patients (39%); tilt test was positive in 6 patients (9%). Coronary angiography was normal; the following abnormalities were noted at EPS: sustained monomorphic VT (<270 b/min) was induced in 14 patients (21%); ventricular flutter (>270 b/min) or fibrillation (VF) was induced in 9 patients (14%); atrial tachyarrhythmia was induced in 17 patients (26%); conduction disturbances were noted in 7 patients (11%). Syncope remained unexplained in 15 patients (23%). Cardiac mortality was 22% in patients with inducible VT/VF and 12% in those without VT/VF (NS). However, the induction of ventricular flutter was a significant predictor of sudden death ($p < 0.01$); the only predictors of total cardiac deaths were a significantly lower LVEF (24±11%) in those who died than in alive patients (29±7%) ($p < 0.05$) and the female sex (50% vs 14%). Multivariate analysis indicated that cardiac mortality was only related to LVEF. The presence of nonssustained VT on Holter monitoring was not a significant predictor of death (70 vs 39%).
In conclusion, causes for syncope were identified in 77% of patients with DCM; they are various and therefore need a complete evaluation to indicate a specific treatment; ventricular tachyarrhythmias represent 35% of the causes; only induced ventricular flutter was associated with a higher risk of sudden death. Atrial tachycardia, vagal hypertonia and bradycardia represent the other causes. The general prognosis only depended on the left ventricular ejection fraction.

134 The left ventricular diastolic filling pattern as prognostic predictor in patients with idiopathic dilated cardiomyopathy

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Background: Previous studies have demonstrated that the presence of restrictive left ventricular (LV) diastolic filling pattern in patients with dilated cardiomyopathy have an unfavorable prognostic.
Aim: 1. Establish the value of LV diastolic filling pattern as prognostic predictor in patients with idiopathic dilated cardiomyopathy. 2. Assessment of the betablocker treatment on these patients.
Material and method: Prospective study on 143 patients (63%male, mean age 52±15) with dilated cardiomyopathy who were divided in 2 groups regarding LV diastolic filling pattern. 1.Group A – 87pts with restrictive LV diastolic filling pattern, 2. Group B – 56pts with nonrestrictive LV diastolic filling pattern. 49pts (56%) from group A and 31pts (55%) from group B underwent betablocker treatment (carvedilol). Patients were evaluated every 3 months during a 2 year follow-up. Statistical analysis used SYSTAT and SPSS programs for the simple and multiple liniar regression analysis, correlation coeficient and relative risk calculations.
Results: 1. Mortality rate after 2 year follow-up was significantly higher in group A (68.96%) compared to group B (51.78%). The restrictive LV diastolic filling pattern (E wave deceleration time tDE<130msec, E/A>2) has increased twice the risk of death (RR=2.6, p=0.007). 2. Clinical amelioration after 2 years was more frequent in patients with nonrestrictive diastolic filling pattern(tDE>130msec, E/A<2). 3. Survival rate in patient undergoing betablocker treatment was similar in both groups (46.93% vs 51.61%) but significantly higher in these pts versus pts without betablocker treatment (46.93%vs 10.53% in group A, p=0.002, respectively 51.61%vs 44%in group B, p=001). 4. The LV diastolic pattern has remained restrictive at 2 year follow-up in 84.21%pts without betablocker treatment and only in 30.6%pts with betablocker treatment.
Conclusions: 1. The persistence of the restrictive LV diastolic filling pattern at 2 years is associated with an increasing in the risk of death in patients with cardiac failure due to nonischemic dilated cardiomyopathy. 2. The association of restrictive LV diastolic filling pattern leads to a more unfavourable prognostic, with increasing the risk of death and worsening the clinical status of these patients in a 2 year follow-up. 3. The restrictive LV diastolic filling pattern is reversible on betablocker treatment.

NEW APPLICATIONS OF STRAIN AND STRAIN RATE IMAGING

135 Two-dimensional myocardial strain estimation by ultrasound: an in-vivo comparison with sonomicrometry

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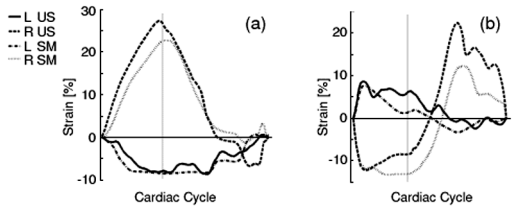
One-dimensional strain (S) and strain rate (SR) imaging have been shown to be angle dependent. Fully resolved two-dimensional (2D) strain would solve this problem. Therefore, a new methodology for estimation of 2D strain based on 2D radio frequency (RF) processing has been developed in our lab. It has earlier been shown to give accurate angle independent strain values in an in-vitro setup.
Aim: To validate this new methodology in the in-vivo setting.
Methods: In 5 open chest sheep, US RF data were acquired in a parasternal long axis view using a Toshiba PowerVision 6000 equipped with an RF interface for research purposes. Myocardial radial (R) and longitudinal (L) strains were simultaneously estimated in the inferolateral wall using the new methodology from single RF data sets. Four segment-length sonomicrometry crystals (SM) were placed in a tetrahedral configuration just lateral to the imaging plane giving a continuous reference for the L and R strains. After baseline (BL) acquisitions, the deformation was modulated by 1) esmolol infusion (ES), 2) dobutamine infusion (DOB) and 3) inducing ischemia by occlusion of a distal branch of the circumflex coronary artery. Peak systolic strains (Smax) were compared by means of linear regression and the correlation coefficient.
Results: For both the R and L Smax strong correlations were found between the US and the SM measurements ($r = 0.95$ and $r = 0.98$ respectively, $p<0.001$). Example strain curves are given in Fig. 1 (a) and (b) for BL and ISC respectively.



Conclusion: Simultaneous estimation of 2D myocardial L and R strain using US RF tracking showed to be a robust method in an in-vivo setting. Myocardial strain could thus be assessed independent of insonation angle.

136 Alterations of left ventricular myocardial characteristics associated with obesity

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Obese patients are prone to the development of heart failure. We sought whether the new, sensitive echocardiography techniques could identify subclinical myocardial dysfunction, independent of co-morbidities. Standard echo, tissue Doppler imaging, strain rate imaging and tissue characterization with integrated backscatter were performed in 97 overweight (BMI 25-29.9) or obese (BMI>30) subjects and 20 controls with no co-morbidities. There was significant linear relationship between LV mass index, LV posterior and LV septal wall thickness with BMI. ($p<0.001$) LV end- diastole diameter also increased with BMI. Obese subjects with BMI>35(IV) had reduced LV systolic function and increased

reflectivity compared with controls, evidenced by lower resting long axis peak strain ($p<0.001$), lower cyclic variation integrated backscatter cvib ($p<0.001$) and lower calibrated integrated backscatter. cIB ($p<0.001$) while LV Ejection Fraction remained normal. Similar but lesser degrees of reduced systolic function and increased reflectivity were present in mildly (BMI 25-29.9)(II) and moderately obese (BMI 30-35)(III) groups evidenced by reduced basal septal strain and cIB. ($p<0.05$) Subgroup comparison also demonstrated differences LV peak strain between the severe obese vs. the mild obese and moderate obese groups. (<0.05) Severely obese pts had reduced myocardial early diastolic peak velocity (LVe') compared to the controls ($p<0.01$).

	BMI<25 (gpI)	BMI25-29.9 (gpII)	BMI30-35 (gpII)	BMI>35 (gpIV)	
LV sw (cm)	0.87±0.12	0.99±0.15	1.03±0.16	1.07±0.14	<0.001
septal strain (%)	-27.1±5.9	-19.8±8.1	-21.2±9.1	-16.7±6.6	<0.001
average peak strain(%)	-25.5±5.0	-23.1±3.9	-24.0±4.8	-20.1±4.3	<0.001
septal cIB (dB)	-24.4±5.9	-16.3±7.6	-15.9±7.0	-14.0±7.6	<0.001
LV em (cm/s)	9.5±2.9	8.5±2.7	8.6±2.1	6.9±2.9	0.007

Overweight subjects without overt heart disease have subclinical left ventricular dysfunction and structural changes, independent to blood pressures, age, gender and increased left ventricular mass. Subgroup analysis in the obese pts did not demonstrate association of these changes with duration of obesity and insulin sensitivity.

137 Atrial myocardial deformation properties predict maintenance of sinus rhythm after DC cardioversion of recent onset lone atrial fibrillation: a colour Doppler myocardial imaging, TTE and TEE study

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Background: Accurate echocardiographic parameters for predicting the maintenance of sinus rhythm in atrial fibrillation (AF) patients after electric cardioversion are poorly defined.
Objectives: This study was conducted 1- to assess the atrial myocardial properties during AF, using myocardial velocity, strain rate (SR) and strain (S); 2- to compare their prognostic value for maintenance of sinus rhythm in patients with lone AF to that of standard transthoracic (TTE) and transesophageal echocardiography (TEE).
Methods: Sixty-eight consecutive patients with lone AF of < 3 months duration underwent TTE, TEE and myocardial velocity, S and SR imaging examinations before successful external cardioversion. Maintenance of sinus rhythm was assessed during 9-month follow-up. Atrial myocardial velocity, S and SR values of AF patients were compared to those of 40 age and sex comparable controls. Moreover, clinical and echocardiographic parameters of patients with maintenance of sinus rhythm over the 9-month follow up period (26 patients) were compared to those of patients in which there was AF recurrence (42 patients).
Results: Atrial myocardial properties assessed by myocardial velocity, SR and S were significantly reduced in patients compared to controls ($p<0.001$). At univariate analysis the predictors of sinus rhythm maintenance were atrial appendage velocity assessed by TEE ($p=0.04$) and atrial S and SR peak systolic values ($p<0.0001$). By multivariate analysis only atrial S and SR parameters were confirmed as independent predictors of sinus rhythm maintenance. A cut-off value of 22% for atrial S and 1.8sec-1 for atrial SR showed a positive predictive value for manteinance of sinus rhythm of 77%.
Conclusions: Atrial myocardial deformation properties are severely compromise during recent onset lone AF. Patients with more severe reduction of atrial myocardial deformation properties seem to be at higher risk to develop a recurrence of AF.

138 Direct assessment of the left atrial reservoir function using tissue strain imaging

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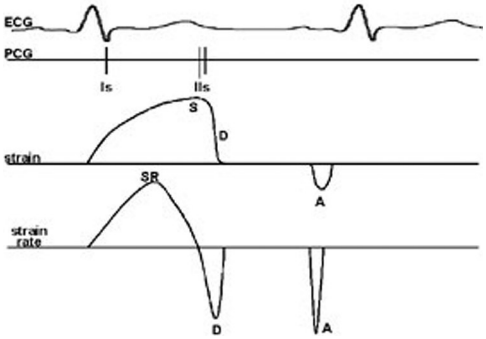
Background: The left atrial (LA) reservoir function has been evaluated analyzing pulmonary venous flow (PVF) velocities. The newly developed tissue strain imaging (TSI) enabled us to evaluate regional myocardial function by measuring strain and strain rate. We hypothesized that the TSI could evaluate LA reservoir function precisely.
Purpose: To directly assess LA reservoir function in the normal heart using TSI.
Methods: Transesophageal echocardiography was performed for 8 normal volunteers (32 ± 5years). From the recording of pulsed Doppler PVF profiles, we measured systolic (PVSvti) and diastolic (PVDvti) velocity time integrals and their systolic fraction PVSvti/(PVDvti + PVSvti). The color tissue Doppler image was acquired from transverse view including LA lateral wall. The peak systolic strain (S) and strain rate (SR) at LA lateral wall were calculated off-line using a customized program (Apli-Q, Toshiba, Japan). The LA preload was increased using the lower body positive presser device (LBPP).
Results: 1) At rest, the LA strain and strain rate profiles were obtained as shown in the figure. 2) During LBPP, the maximum LA area at end-systole measured from apical four chamber view significantly increased. The PVSvti (10.2 vs 15.7cm, $p < 0.01$), PVDvti (6.8 vs 8.0cm, $p < 0.01$) and their systolic fraction (0.53 vs 0.66, $p < 0.05$) significantly increased reflecting preload increase. 3) The peak systolic S (0.80 vs 1.01, $p < 0.01$) and SR (3.5 vs 5.6s-1, $p < 0.01$) significantly increased.



Strain and strain rate profiles.

Conclusions: In the normal subjects, the peak systolic S and SR increased corresponding to the increase in LA preload as evidenced by changes in the PVF velocities. The parameters obtained from TSI can be potentially applied for direct assessment of the LA reservoir function.

139 The interventricular septum: a functionally bilayered structure? A radial strain study

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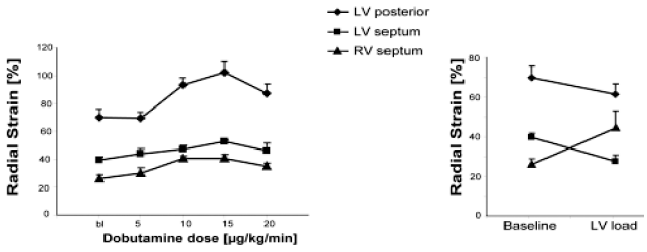
Purpose: The function of the interventricular septum is poorly understood. In echocardiography a bright line can be consistently detected which separates the left (L) from the right (R) side. Morphologic studies suggest that the line is an acoustic interface due to differences in fiber direction. We performed a study to investigate if the right and left septal layers act as two distinct functional units with different stimuli. To evaluate radial function, local deformation parameters (strain imaging) were analysed under changes in global contractility and left ventricular (LV) loading.
Methods: In 10 crossbred pigs, transthoracic LV short axis radiofrequency ultrasound data (high framerate, 4.5-MHz transducer) were taken. Radial strain values were obtained from the LV posterior wall and from both sides of the septum. Contractility was modulated by incremental dobutamine infusion (5-20 μg/kg/min) and afterload was increased (>20%) by balloon placement in the descending aorta. LV cavity pressure was measured with a micromanometer-tipped catheter (Millar).
Results: Maximal radial systolic strain at baseline was found to be highest in the LV posterior wall and lowest in the R septum (graph). During dobutamine infusion, the LV posterior wall and both septal sides showed a similar response. However, with LV afterload, L-sided septal strain decreased whereas R-sided strain increased, which may be due to a R-sided radial compensation of impaired septal longitudinal function.



Radial strain.

Conclusion: Both sides of the septum show a different response in radial strain to increased LV afterload. The difference cannot be seen in global alteration of contractility. The findings suggest the presence of two functionally different layers in the interventricular septum.

140 Strain and strain rate are more accurate for assessment of myocardial viability after myocardial infarction than myocardial velocity during low-dose dobutamine stress echocardiography

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Objectives: Tissue Doppler imaging is a promising method for the assessment of myocardial viability after myocardial infarction. This study sought to evaluate the comparative accuracy of myocardial velocity, strain and strain rate for the assessment of myocardial viability after myocardial infarction during low-dose dobutamine stress echocardiography.
Methods: The study population consisted of 20 patients with myocardial infarction who underwent coronary angioplasty. Tissue Doppler imaging during low-dose dobutamine stress echocardiography (10 μg/kg/min) was performed in 20 patients (mean age 64$\pm$5 years, male 16 and female 4) with myocardial infarction before coronary angioplasty. The myocardial systolic velocity, strain and the strain rate were measured for each left ventricular segment along the longitudinal axis of the left ventricle at baseline and low dose dobutamine stress. The myocardial segment with movement recovery after successful coronary angioplasty was considered as viable myocardium.
Results: In the viable myocardium, significant increases from the baseline to low dose dobutamine stress were found for the myocardial systolic velocity (2.0$\pm$1.5 cm/s to 3.2$\pm$2.4 cm/s, $p<0.05$), strain (-0.3$\pm$0.1 to -1.0$\pm$0.5, $p<0.01$) and strain rate (-0.2$\pm$0.2/s to -1.0$\pm$0.6/s, $p<0.01$). In the nonviable myocardium, although the systolic velocity increased from 1.9$\pm$1.4 cm/s at baseline to 2.7$\pm$1.8 cm/s during low dose dobutamine stress ($p<0.01$), the strain (-0.3$\pm$0.2 to -0.4$\pm$0.5, $p>0.05$) and strain rate (-0.1$\pm$0.2/s to -0.3$\pm$0.3/s, $p>0.05$) did not change. Conclusions: Strain and strain rate are more accurate for assessment of myocardial viability after myocardial infarction during low-dose dobutamine stress echocardiography than myocardial velocity, which seems to be significantly altered by plane motion of the heart and/or tethering from the adjacent segments.

FROM MICE TO MEN: LESSONS IN MYOCARDIAL PROTECTION AND HYPERTROPHY

149 Transgenic mice with cardiac-specific inhibition of GRK3 display phenotype with cardiac hypertrophy and alpha1-adrenergic receptor hyperresponsiveness

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Background: G protein-coupled receptor kinase 2 and 3 (GRK2 and GRK3) are expressed in cardiac myocytes and mediate desensitization of G protein-coupled receptors through specificity controlled by their carboxyl-terminal (CT) domain. The cardiac function of GRK2 has been extensively investigated. However, the role of cardiac GRK3 remains unknown.
Methods and Results: We designed a minigene encoding a CT fragment of GRK3 (GRK3CT: amino acids 495-687) containing the pleckstrin homolgy domain and generated transgenic (TG) mice using the cardiac myocyte-specific alpha-MHC promoter. Three founder lines were established and transgene expression was verified. The TG mice were normal in appearance and behaviour. However, analysis of blood pressure (BP) in conscious mice using the tail-cuff method revealed elevated systolic BP in the TG mice versus non-TG littermates (130.0 ± 3.0 vs 119.8 ± 3.1, $p<0.005$). Furthermore, heart weight to body weight ratios were significantly increased in the TG compared to non-TG mice. To investigate the effects of the transgene to hypertrophic stimuli, subpressor doses of phenylephrine (PE) and endothelin-1 (ET-1) were administered s.c. for 14 days using micro-osmotic pumps. PE did not alter BP, but induced significant cardiac hypertrophy in both TG and non-TG groups. However, changes from baseline were substantially greater in TG mice compared to non-TG mice, as evidenced by significantly increased heart to body weight ratios, increased septal and posterior wall thickness, and reduced left ventricular cavity dimensions. ET-1 did not cause cardiac hypertrophy despite slightly increased BP in both TG and non-TG mice. Isolated working mode analysis of hearts paced at 8 Hz revealed that TG hearts displayed increased contractility and work capacity at normal filling pressures resulting in increased cardiac output.
Conclusion: TG mice with cardiac-specific inhibition of GRK3 display phenotype with cardiac hypertrophy and increased cardiac output with elevated systolic blood pressure. Hyper-responsiveness to alpha1-adrenergic receptor stimulation may be an important contributor to the phenotype of GRK3CT mice.

150 Molecular regulation of endothelin-1-induced cardiomyocyte hypertrophy: the role of nitric oxide

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Cardiac hypertrophy is a compensatory mechanism in response to a variety of cardiovascular diseases. Recently, reactive oxygen species (ROS) and nitric oxide (NO) have been demonstrated to be involved in the pathogenesis of atherosclerosis, however, the role of these free radicals in the development of cardiac hypertrophy remains unclear. In this study, we investigate NO modulation of cellular signaling in endothelin-1 (ET-1)-induced cardiomyocyte hypertrophy in culture. Northern blot and reverse transcription-polymerase chain reaction (RT-PCR) analysis revealed ET-receptor subtype ETA predominated on cardiomyocytes. ET-1 treatment of cardiomyocytes increased constitutive NO synthase activity and induced NO production via the stimulation of ET-receptor subtype ETB, the minority subtype on cardiomyocytes. We previously reported that ET-1 induces ROS generation via ETA receptor and ROS modulate c-fos expression [Cardiovas Res, 41 (1999): 654-662]. In this study, using Northern blot analysis and chloramphenicol acetyltransferase (CAT) assay, we found that NO suppressed ET-1-induced c-fos mRNA level and promoter activity. Contrarily, ET-1 stimulation of c-fos expression was augmented by depletion of endogenous NO generation with the addition of NO scavenger PTIO into cardiomyocytes. Cells cotransfected with the dominant negative and positive mutants of signaling molecules revealed that the Ras/Raf/extracellular-signal regulated kinase (ERK) signaling pathway is involved in ET-induced c-fos gene expression. We further demonstrated that NO directly inhibited ET-1-induced ERK1/2 phosphorylation and activation in a cGMP-dependent manner, indicating that NO modulates ET-1-induced c-fos expression via its inhibitory effect on ERK signaling pathway. Using electrophoretic mobility shift assay, the ET-1-stimulated activator protein-1 (AP-1) DNA binding activity was attenuated by NO. Furthermore, we showed that NO significantly inhibited ET-1-stimulated promoter activity of hypertrophic marker gene beta-myosin heavy chain via suppression of the AP-1 transcriptional activity. Finally, using [^{3}H]-leucine incorporation and immunocytochemistry, we established that NO attenuates the enhanced protein synthesis and sarcomere assembly, the characteristic morphological change induced in cardiomyocytes by hypertrophic agonist ET-1. Taken together, our findings provide the molecular basis of NO as a negative regulator in ET-1-induced cardiac hypertrophy.

151 The Wnt/Frizzled/Dishevelled pathway is involved in development of cardiac hypertrophy in mice

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Background: Cardiac hypertrophy is a cellular response to a number of stimuli that create an overload of the heart. Prolongation of this process can lead to heart failure. The goal of this study was to evaluate the role of the Wnt/Frizzled/dishevelled (Wnt/Fz/Dvl) pathway in cardiac hypertrophy development. Normally, without Wnt stimulation, cytoplasmatic β-catenin associates with APC and axin, is phosphorylated by GSK-3β, and thereby marked for degradation. Wnt stimulation acts to stabilize β-catenin levels by binding to the Fz receptor. This activates the Dvl protein, which antagonizes the action of GSK-3β, a potent suppressor of the hypertrophic response. Stabilized β-catenin translocates to the nucleus, where it activates both Tcf/Lef signaling and transcription of β-catenin target genes, including the proto-oncogenes c-fos and c-myc.
Methods and results: Mice lacking the Dvl-1 gene (Dvl-/-) and wild-type littermates (WT) were subjected to left ventricular pressure overload by transverse aortic constriction (TAC). At day 7 after TAC, there was an upregulation of Fz2 mRNA in both Dvl -/- and WT mice. Compared to WT mice, Dvl-/- mice developed reduced ventricular hypertrophy, as measured by left ventricular weight/tibia length index and by echocardiography of the left ventricular posterior wall thickness in systole and in diastole. This was accompanied by lower expression of ANF, a marker of cardiac hypertrophy, in Dvl-/- vs. WT (a 3 vs. 7 fold increase compared to SHAM, $P<0.05$). Western blot analysis showed higer protein levels of axin. Q-PCR analysis showed a reduction in the expression of the proto-oncogenes c-fos and c-myc in Dvl -/- mice compared to WT. The expression of c-fos was found to be upregulated 1.3 fold in Dvl-/- vs. 3.3 fold in WT after TAC. For c-myc, a 1.8 fold upregulation was observed after TAC in WT, whereas in Dvl-/- no significant upregulation was observed.
Conclusions: In summary, disruption of the Dvl-1 gene attenuates the development of cardiac hypertrophy induced by pressure overload and thus demonstrates a role for the Wnt/Fz/Dvl pathway in hypertrophy development. A higher axin protein expression and reduced induction of c-fos and c-myc suggests that these proteins play a role in this attenuated response.

152 Nuclear expression of H11 kinase represents a novel mechanism of cardioprotection

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H11 kinase is a protein of unknown function preferentially found in heart, where its expression increases during ischemia and pressure overload, together with cytoprotective genes. We tested the hypothesis that H11 kinase modulates cardiac cell survival and growth, using a transgenic mouse model and cardiac myocytes in culture. Cardiac overexpression of H11 kinase in a transgenic mouse induced significant ($P<0.05$) hypertrophy (30% increase in cell size and volume) without hyperplasia. After an episode of 45 min LAD occlusion, infarct size measured by TTC staining was decreased by 80% in transgenic mice compared to wild-type ($P<0.001$). Such protection was quantitatively similar to the cardioprotection conferred by a protocol of ischemic preconditioning (6 episodes of 4 min occlusion/4 min reperfusion before 45 min occlusion), the most powerful cytoprotective mechanism described to date. Overexpression of H11 kinase was associated with the coordinated activation of complementary growth and survival mechanisms, including a significant ($P<0.05$) increase in HSP70, HSP40 and HSP27 proteins, as well as a 2-fold activation of the Akt/mTOR signaling. H11 kinase expression was found in both the cytosol and the nucleus of heart from wild type mice, but in the transgenic mouse, the cytoprotective effect correlated with a nuclear accumulation of the protein. Reciprocally, a cytosolic overexpression of H11 kinase in isolated cardiac myocytes inhibits Akt and p70S6K, and promotes cell death. In larger mammals and in human heart, H11 kinase is only expressed in the nucleus of the cardiac myocytes, and its expression increases during ischemia or chronic hypertrophy. Therefore, H11 kinase represents a novel and powerful mechanism of cell survival by the activation of complementary pathways of cytoprotection. In addition, H11 kinase illustrates the novel case of a protein with reciprocal effects on cell survival and death depending on its subcellular localization, acting as a survival promoter in the nucleus and as a tumor suppressor in the cytosol. Regulation of this protein in human heart shows a novel mechanism of cell growth and survival in patients with ischemic heart disease.

153 Reduction of myocardial infarct size by chronic treatment of oleuroperin, a natural olive product, in normal and hypercholesterolemic rabbits

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Oleuropein (Oleu) is a phenolic antioxidant which is present in olives and olive oil. Oxygen-derived free radicals produced upon reperfusion of ischemic myocardium is the predominant cause of lethal reperfusion injury.

Purpose: To evaluate the efficacy of long term oral treatment with oleu in two dosages (10 and 20 mg/kgBW/day) in reducing the myocardial infarct size after ischemia (isc)-reperfusion (rep) in normal and hypercholesterolemic rabbits and to evaluate its efficacy against the oxidative damage.

Methods: Fifty six rabbits were subjected in 30 min regional isc followed by 180 min of rep. Rabbits were randomly assigned into 8 groups as follows: Control (CTL, n=7): placebo; OLEU-6/10, n=8): 6 weeks of 10 mg/kg BW/day oleu; OLEU-6/20 (n=7) 6 weeks of 20 mg/kg/BW/day oleu; OLEU-3/20 (n=7): 3 weeks of 20 mg/kg/BW/day oleu. CHOL-6 (n=8): the rabbits fed for 6 weeks with 2 g/day of cholesterol (chol) product; CHOL-6-OLEU-6/10 (n=5): 6 weeks chol and oleu 10 mg/kg/day; CHOL-6-OLEU-6/20 (n=7): 6 weeks chol and oleu 20 mg/kg/day; CHOL-6-OLEU 3/20 (n=7): 6 weeks chol and 3 weeks oleu 20 mg/kg/day. Infarct size was determined and blood samples were drawn at different time points for determination of malondialdehyde (MDA) as an index of lipid peroxidation, for total superoxide dismutase (SOD) activity as an index of the antioxidant status and for 1H-NMR spectra for the evaluation of the changes in the metabolic profile.

Results: Treatment for 3 and/or 6 weeks with oleu reduces the infarct size in both dosages tested in normal rabbits (16.1±2.9% in group OLEU-6/10, 20.7±4.1% in group OLEU-6/20 and 21.7±2.2% in group OLEU-3/20 vs 47.4±2.6% in CTL group $p<0.05$), whereas the reduction in infarct size was significant in the group treated with the 20 mg/BW/day dosage in hypercholesterolemic rabbits (34.7±4.3% in CHOL-6-OLEU-6/20 vs 46±3.5% in CHOL group, $p<0.05$). Lipid peroxidation product levels were elevated in the control groups, whereas oleu decreased them in both doses in all the groups. The SOD activity was reduced in the control groups; oleu kept SOD activity unchanged during isc-rep. No significant changes were observed in the low molecular weight metabolites according to NMR spectra.

Conclusions: Long-term oral treatment for 3 or 6 weeks with 2 doses of oleu decreases the infarct size in normal rabbits, and protects the reperfused myocardium from the oxidative damage in vivo. Furthermore, higher dose of oleu reduces the infarct size in hypercholesterolemic rabbits.

154 S100A1: a novel cardioprotective factor

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The EF-hand Ca-binding protein is specifically expressed in cardiomyocytes and released in the extracellular space during cardiac injury. To test the impact of extracellular S100A1 protein on ventricular cardiomyocytes, cultured neonatal cardiomyocytes (NVCM) were incubated with rhodamin-coupled S100A1 protein (rh-S100A1; 1μM). Confocal analysis revealed that extracellularly added rh-S100A1 protein was internalized into NVCM's via a Ca-dependent clathrin-based endocytotic process after 5 min and routed to the endosomal compartment. S100A1 endocytosis specifically enhanced p44/42 activity in NVCM's in a dose- (0.001-1μM rh-S100A1) and time-dependent (0-30 min) manner. However, internalized S100A1 protein neither affected p38, p54/46 nor Akt signaling. S100A1-mediated activation of p44/42 was blunted by phospholipase C (PLC; U-73122), protein kinase C (PLC; calphostin-c) and MEK1 (PD98095) inhibition. Internalized S100A1 protein protected NVCM's from 2-deoxyglucose- and H202-inducd apoptosis as assessed by diminished uptake of trypan blue, decreased release of cytochrom-c, lower activity of caspase-3 and preserved activity of mitochondrial dehydrogenase in S100A1-treated cells compared with vehicle-treated control cells. MEK1 inhibition abrogated the cytoprotective effect of extracellular S100A1 in vitro confirming the p44/42-based antiapoptotic effect of endocytosed S100A1 protein. Attenuated infarct size and reduced mortality after left coronary artery ligation (MI) in transgenic mice with cardiac-restricted S100A1 overexpression (TG-S100A1) confirmed the cardioprotective effect of S100A1 protein in vivo compared with non-transgenic littermate control (NLC). After MI, TG-S100A1 mice, in turn, exhibited a smaller decline in contractile function compared with NLC. Beneficial effects of S100A1 in vivo were partially blunted by intravenous application of anti-S100A1 antibodies prior to MI. The present study shows for the first time the cardioprotective effect of S100A1 protein on injured myocardium in vivo and in vitro. The latter effect was based on S100A1-mediated activation of p44/42 signaling and might underlie the beneficial effects of S100A1 protein on infarcted myocardium in vivo. Thus, attenuated cell death by S100A1 protein might provide a novel therapeutic approach for the protection of injured myocardium in vivo and might prove beneficial in the therapy of MI.

IMPACT OF NON SURGICAL TREATMENT AND PHYSIOLOGICAL STRESS ON THE GUCH-HEART

155 Sildenafil in the treatment of Atrial Septal Defect with moderate to severe pulmonary arterial hypertension

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Background and Aim: The role of sildenafil as a pulmonary vasodilator is being extensively evaluated in the treatment of primary pulmonary hypertension. Severe pulmonary hypertension (PH) of other etiologies should theoretically respond equally well. This was a prospective study to assess the benefit of adding sildenafil in patients with high pulmonary artery pressures secondary to atrial septal defect (ASD), already receiving the conventional therapy.

Methods: Thirty consecutive patients with ASD and moderate to severe PH were included in this study. All the patients were diagnosed previously and were receiving the conventional therapy with digoxin, diuretic and a calcium channel blocker. Sildenafil was added in the dose of 50 mg twice a day without changing the previous regimens. Changes in the New York Heart Association (NYHA) symptom class, distance covered during the six minute walk test and modified Borg dyspnea score were evaluated monthly. Acceptance of the new drug was assessed every week in the first month and then at the monthly follow up. Echocardiography and Doppler study was undertaken at baseline and every month for a period of six months. The parameters studied were the pulmonary artery systolic pressure (PASP) by tricuspid regurgitation (TR) jet and pulmonary artery diastolic pressure (PADP) by pulmonary regurgitation (PR) jet.

Results: Mean age of the subjects was 52.6±12.3 years. Seventeen (56.7%) were males and 13 (43.3%) were females. Sildenafil was well tolerated and there was no dropout because of undesireable effects of the drug. Changes in the heart rate and systemic blood pressure were not significant enough to warrant withdrawl of the drug. One patient died during the follow-up period.

Twenty three (76.7%) patients were in NYHA Class III or IV prior to initiation of sildenafil therapy. At six months, only 7 (24.1%) of them remained in this class ($P<0.05$). The distance covered in a six minute walk test improved from 188.7±120.4 meters to 308.7±160.4 meters ($P<0.05$). The modified Borg dyspnea score reduced from 5.3±1.3 to 3.4±1.0 ($P<0.05$). PASP by TR jet reduced from 81.3±14.7 mmHg to 54.4±11.6 mmHg ($P<0.05$). PADP by PR jet reduced from 54.2±11.5 mmHg to 35.6±9.2 mmHg ($P<0.05$).

Conclusion: Sildenafil is well tolerated, improves symptoms, and reduces the systolic and diastolic pulmonary artery pressures in patients with atrial septal defect and moderate to severe pulmonary arterial hypertension.

156 Prospective evaluation of pregnancy and aortic complications in the Marfan syndrome

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Objective: There is still debate regarding the aortic root diameter above which pregnancy should be discouraged in female Marfan patients. Recent guidelines suggest that an aortic root diameter up to 44 mm should carry an acceptable risk for the mother. Aim of this study was to evaluate these recent guidelines and to assess whether pregnancy has a negative impact on long term aortic growth.
Methods: Between 1993 and 2003, 125 women (mean age 31(16-68) years) were observed prospectively in 2 university hospitals. Of these women 64 (mean age 26(16-68) years) were childless, and 61 women (mean age 35 (18-59) years) had been pregnant before 2003. In 22 women 31 pregnancies were followed prospectively for aortic diameters. One woman had a previous Bentall procedure for type A dissection (limited to the ascending aorta). In the other 21 women no aortic complications had occurred before pregnancy. Out of the 64 childless women a comparison group of 21 women was selected, individually matched for age, initial aortic root diameter, family history and duration of follow up.
Results: Mean initial aortic root diameter at pregnancy was 37 (6) mm. In 10 women the initial aortic root diameter was $\geq$ 40 mm (range 40-46 mm). No or little change in aortic root diameter occurred throughout these pregnancies (0.5 (0.8) mm/year). During a mean follow-up of 9 (3) years, aortic root growth in these patients and in the matched childless group was similar (0.4 (0.4) mm/year vs 0.3 (0.4) mm/year, p=ns). Only the woman with a previous type A dissection developed a type B dissection during her second pregnancy. None of the other 21 women developed aortic complications. During 9 years of follow up in the entire population of 125 women, aortic complications were more common and at younger age in the childless group (38%, 31 (14-61) years old) compared to the group of 61 women with children (26%, 44 (34-62) years old).
Conclusion: Pregnancy in female Marfan patients seems to be relatively safe up to an aortic root diameter of 44 mm, unless aortic complications have occurred before child bearing age.

157 Safety and tolerability of bosentan in adults with Eisenmenger physiology

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Introduction: Patients with congenital heart disease and Eisenmenger physiology (EP) have pulmonary arterial hypertension with associated cardiovascular morbidity and reduced survival. Bosentan has an established role in the management of primary pulmonary hypertension. Concerns have been raised regarding potential side-effects and desaturation from the use of Bosentan in patients with EP.
Methods: We examined safety and tolerability of oral Bosentan therapy in adult patients with EP in an intention to treat, non-controlled, dose escalation study. Patients were recruited from our adult congenital heart clinic following informed consent. Baseline assessment included NYHA class, oxygen saturation, 6-minute walk test, transthoracic echocardiography and respiratory mass spectrometry and was repeated after 3 months of therapy with oral Bosentan. Patient clinical status and liver enzymes were closely monitored throughout the study.
Results: Ten patients (8 female) with EP aged 42±4 years participated in our pilot study. Patients tolerated Bosentan well; no major adverse events were observed, nor a significant rise in liver enzymes. All but one patients felt better; none felt worse. Four patients had transient leg oedema. There was no drop in oxygen saturations (83±5 vs 80±5% vs P=0.011) or systolic and diastolic blood pressure by the end of the study from baseline. There was a change on the 6-minute walk test (348±112 vs 249±117m, P=0.004) and on certain echocardiographic parameters (Vmax Ao vs l.3±0.1 vs 1.1±0.2ms and PA ACT 66±10 vs 58±12m/s, P=0.013 and 0.02 respectively) and cardiac output (2.58±1.0 vs 3.45±1.2 L/min, P=0.008) suggesting improved haemodynamics.
Conclusions: Bosentan appears to be safe and well tolerated in adults with Eisenmenger physiology both at initiation and after 3 months of oral therapy. Clinical status of the patients and haemodynamics appear to improve, but this clearly needs to be investigated further.

158 Impaired endothelial function in the coronary artery after Kawasaki disease and the effects of intravenous administration of vitamin C

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Objectives: We attempted to analyze coronary endothelial function after Kawasaki disease by observing the change in diameter of the left main coronary artery induced by cold pressor test using echocardiography and to investigate whether the acute administration of vitamin C could restore such endothelial dysfunction. Methods. We compared 39 patients (7.1±2.7 years) 1.0 to 9.6 years after acute Kawasaki disease with 17 matched healthy subjects (7.0±3.1 years) as controls. Measurements of the cold pressor test-induced and nitroglycerin-induced changes in the left main coronary artery diameter by echocardiography were performed. Results. The percent change in diameter of the left main coronary artery induced by cold pressor test in the patients with history of Kawasaki disease (4.7±1.0%) was significantly lowed than that in the control group (11.1±3.8%, p< 0.0001). No significant difference could be found in percent change in diameter induced by sublingual administration of nitroglycerin between the control (17.1±5.2%) and the patients with history of Kawasaki disease (16.5±3.9%, p = 0.28). There was no significant difference in percent change in diameter of the left main coronary artery induced by cold pressor test between the patients who received gamma globulin (4.8±1.2) and those who did not receive gamma globulin (4.5±1.1, p = 0.42). Intravenous infusion of 100 ml of 0.9% saline containing 3 g vitamin C during 10 min significantly increased the percent change in diameter of left main coronary artery induced by cold pressor test in 19 patients with history of Kawasaki disease (4.6±1.3% to 10.4±4.5%, p < 0.001), whereas, no significant increase was seen in the percent change in diameter of left main coronary artery induced by cold pressor test in 20 patients with history of Kawasaki disease after placebo administration (4.5±1.1% to 4.3±1.4%, p = 0.25). Conclusions. Our study showed decreased percent change in diameter of the left main coronary artery induced by cold pressor test in patients with history of Kawasaki disease compared with the healthy children, indicating that endothelial dysfunction in coronary artery exits after Kawasaki disease. Although such endothelial dysfunction after Kawasaki disease is not influenced by early treatment with high dose gamma globulin in the acute stage of Kawasaki disease, it can be restored by the acute intravenous administration of vitamin C.

159 Myocardial ischaemia and scars are not common in the systemic right ventricle at long-term follow-up

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Background: The systemic right ventricle (RV) in patients after atrial switch operation or patients with congenitally corrected transposition of the great arteries (ccTGA) often fails. Because some studies have found a high incidence of myocardial ischemia and scars, it has been proposed that myocardial ischemia and scars are a reason for failure of the systemic RV. However, this is not in accordance with our clinical observations. The aim of this study was therefore to test the hypothesis that myocardial ischemia and scars are common in patients with systemic RV. For this study, we used newer imaging modalities (positron emission tomography, PET and late enhancement magnetic resonance imaging, LE-MRI) in 40 consecutive patients with systemic RV.
Methods and Results: 40 patients with systemic RV were studied by PET and LE-MRI (25 patients 21.8 ± 4.4 yrs after atrial switch operation, age at operation: 1.3 ± 1.5 yrs and 15 patients with ccTGA, age: 31.1 ± 16.6 yrs, no previous operation). Two investigators analyzed PET and LE-MRI studies and were blinded to the findings of the other method. None of the patients after atrial switch operations had myocardial ischemia or scars. Only one patient with ccTGA had an anterolateral ischemia of the systemic RV and only one patient with ccTGA had a subendocardial scar of the systemic RV.
Conclusions: This study shows that the hypothesis that myocardial ischemia and scars are common in patients with systemic RV is not correct. Therefore myocardial ischemia and scars are not a reason for failure of the systemic RV.

160 Detrimental effects of long-term apical right ventricular pacing, on left ventricular dyssynchrony, morphology and function, in patients with congenital heart block

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Although, dual-chamber pacing improves cardiac function in patients with congenital heart block (CHB) by restoring physiological heart rate and atrioventricular synchronization, the long-term detrimental effect of asynchronous electromechanical activation induced by apical right ventricular pacing (RVP) has not been well clarified. We assessed in such patients consequences of long-term permanent RVP on exercise performance and left ventricular (LV) function, morphology and dyssynchrony.
Methods: Twenty-one CHB adults (23±5 years, 62% male), with a DDD transvenous pacemaker, underwent 1] before implant, a conventional echocardiography 2] after at least 5 years of RVP, an exercise testing and an echocardiography coupled with Doppler tissue imaging (DTI) and tissue tracking. They were compared with 30 age sex and weight-matched healthy controls.
Results: After 8±3 years of RVP, CHB adults had significantly higher values vs controls in terms of intra-LV asynchrony (respectively 59±18 vs 19±11ms;p<0.001), extent of LV myocardium displaying delayed longitudinal contraction (39±15 vs 10±7%;p<0.01) and septal-to-posterior-wall-motion-delay (87±23 vs 18±9ms;p<0.01). The ratio of early-activated septal to late-activated posterior wall thickness was lower before vs after implant (1.1±0.2 vs 1,3±0.2; p=0.05) and vs controls (1±0.1;p<0.05). The percentage of patients with increased LV end-diastolic diameter was higher after long-term RVP than be-

fore implant and controls (62 vs 15%; $p<0.05$; vs 0% $p<0.01$). CHB patients with long-term RVP had a lower cardiac output vs controls (3.8±0.6 vs 4.9±0.8 l/mn;$p<0.05$) and exercise performance (123±24 vs 185±39 watts; $p<0.001$).
Conclusion: In CHB patients with long-term endovenous RVP, asynchronous LV activation induced asymmetrical hypertrophy associated with an increased LV dilatation, an LV function impairement and exercise performance lowering. Alternative sites of ventricular pacing should be investigated to preserve ventricular synchrony and LV function in patients requiring long-term permanent pacing.

VASCULAR GROWTH AND COLLATERAL VESSELS: OPPORTUNITIES AND DRAWBACKS

161 Human tissue kallikrein gene transfer stimulates reparative neovascularization and prevents left ventricular remodelling in a murine model of myocardial infarct

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Purpose: Gene deletion/insertion studies support a role for the Kallikrein-Kinin System (KKS) in the control of myocardial vascularization and function. Furthermore, human gene polymorphisms of KKS result in disproportionate hypertrophic response to physical stress. We hypothesized that biological revascularization of ischemic myocardium by gene transfer with human tissue kallikrein (hKLK) could improve contractile function and prevent left ventricle (LV) remodelling.
Methods: Following basal measurements of SBP and HR, male CD-1 mice were anaesthetised and submitted to left descending coronary artery permanent occlusion. Subsequently, an adenoviral vector carrying the hKLK gene (Ad.hKLK, 107p.f.u.) was injected into the MI borderline zone. Control groups received saline or Ad.nul. Four days later, myocardial expression of endothelial nitric oxide synthase (eNOS) and VEGF-A was determined by real-time RT-PCR (n=6). Phospho-Akt (p-Akt) and total Akt protein levels (tot.-Akt) were quantified by Western-Blot (n=6). Expression of hKLK was evaluated by ELISA/Immunohistochemistry. At 14 days from MI, SBP and HR were measured non-invasively. Afterwards, hearts were stopped in diastole, excised and morphology was analysed using Image-ProPlus-software. Capillary density was evaluated on silver stained sections. Apoptosis was determined by TUNEL staining.
Results: Expression of hKLK was documented in the LV, but also at the right ventricle (RV). Ad.hKLK did not change VEGF-A expression (p=N.S.), while inducing a 3.5-fold increase in eNOS expression ($p<0.005$) and a 1.3-fold increase in p-Akt/tot-Akt ratio ($p<0.05$). At 14 days from MI, SBP was normal in the Ad.hKLK group (p=N.S. vs. basal), while it was reduced by 11mmHg in the control groups ($p<0.05$ vs. basal and vs. hKLK). HR did not change in any group. MI size did not differ between groups (p=N.S.). However, Ad.hKLK reduced the thickness of LV and Septum (both 13.5% less) and of RV (28% less). The intra-LV cavity diameter and calculated LV chamber volume were similar in the 3 groups. Ad.hKLK increased capillary density (6210±167 vs. 5432±144 capillaries/mm^2 in controls, $p<0.05$) and reduced the number of apoptotic cardiomyocytes in the border zone 1.4-fold ($p<0.05$).
Conclusions: Intramyocardial Ad.hKLK induces angiogenesis seemingly through an Akt-eNOS-dependent, but VEGF-independent mechanism. Improvement of collateralisation in the area at risk and reduction of cardiomyocyte apoptosis by hKLK support efficacy of early biological revascularization of the ischemic heart for prevention of post-MI remodelling.

162 Endothelial cells expanded from CD34$^+$ cells improve left ventricular function in experimental myocardial infarction by vessel generation

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Purpose: Mobilization and recruitment of endothelial progenitor (EPC) cells contributes to vasculogenesis in vivo. So far the number of available cells limits the applications for cell therapy. Expansion of EPC may, therefore, facilitate therapeutic use of EPC in ischemic disease. Aim of the study was to expand CD34+ cells, characterize them and investigate their potential to generate new vessels in vivo.
Methods and Results: CD34+ cells from cord blood were isolated using immunomagnetic beads (Miltenyi Biotech) and cultured in endothelial cell medium. Cells were expanded up to 10'15 cells. Immunhistochemistry and FACS analyses confirmed that the cultured cells expressed endothelial markers (vWF, CD31, CD102, CD105 and CD146) and lacked leukocyte markers (CD45, CD14). DNA microarray analysis showed a high degree of similarity between the cultured and human umbilical vein-derived (HUVEC) cells. The capacity of the cells to generate new vessels was confirmed by matrigel assays in vitro and by injection into ischemic myocardium in vivo. Athymic, nude rats were thoracotomized and ligation of the left anterior descending coronary artery was performed. Then cells were injected in the border of the infarct zone and two weeks thereafter animals were sacrificed. Human EPC were detected by staining of the myocardium with anti-human CD31 antibodies and revealed that transplanted cells formed vessel-like structures. Serial echocardiographic examinations showed a decrease in left ventricular ejection fraction from 56+0.7% to 44+1% after experimental myocardial infarction, whereas cell transplantation improved left ventricular function as shown by a decrease in left ventricular ejection fraction from to 50+2% (P=0.01).
Conclusions: Endothelial-like cells derived from CD34+ cells proliferate and resemble HUVECs in the expression profile of surface markers and endothelial specific genes. The capacity of these cells to generate new vessels was demonstrated in vitro and in vivo. Furthermore, cell transplantation in experimental myocardial infarction improves left ventricular function. Autologous transplantation of endothelial-like cells derived from CD34+ cells may be beneficial in the treatment of ischemic disease.

163 A common variant of endothelial nitric oxide synthase is associated with collateral development in patients with chronic coronary occlusions

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In case of total occlusion of a coronary artery, the collateral circulation may be an alternative source of blood supply to the myocardium at risk. However, collateral development remains difficult to anticipate and there is considerable inter-individual variability in this process. Since experimental studies support an important role for eNOS in the regulation of angiogenesis, we hypothesized that a functional polymorphism in the eNOS gene may be associated with collateral development in patients with chronic coronary occlusions.
We studied 291 consecutive patients who underwent coronary angiography and who had at least one chronic (> 15 days) coronary occlusion. Collateral development was graded by two independent observers using two previously validated methods: the collateral flow grade and the recipient filling grade (Gibson et al. Am Heart J 1999;137:169-79). Genomic DNA was extracted from white blood cells and the Glu298Asp eNOS polymorphism was determined. Previous studies have suggested a decreased NOS activity in patients with the Asp298 variant.
Baseline characteristics did not differ between patients with the Asp298 variant and Glu-Glu homozygotes. Angiographic evidence of collateral development was lower in patients carrying the Asp298 variant than in Glu-Glu homozygotes (collateral flow grade: 2.64±1.08 and 2.89±0.86, respectively, p=0.04; recipient filling grade: 3.00±1.04 and 3.24±0.78, respectively, p=0.04). Multivariate predictors of collateral development are shown in the table below.

Predictors of collateral development

	Collateral Flow Grade		Recipient Filling Grade	
	Beta	p	Beta	p
Female gender	- 0.49	0.009	- 0.22	0.23
Smoking	- 0.34	0.05	- 0.12	0.47
Diabetes mellitus	- 0.23	0.06	- 0.20	0.09
Asp298 variant	- 0.26	0.03	- 0.24	0.03

Conclusion: This is the first study to show a relationship between the Glu298Asp eNOS polymorphism and coronary collaterals in humans. It demonstrates that collateral development is lower in patients with the Asp298 variant. Further studies will have to determine whether increasing eNOS activity in humans is associated with coronary collateral development.

164 Plasma tissue factor levels predict collateral development in humans: a study based on 364 consecutive patients with occluded coronary arteries

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Purpose: Regulation mechanisms of collateral circulation are not well described, and collateral circulation remains variable between patients. Because previous in vitro and in vivo animal studies have demonstrated that Tissue Factor (TF) has a pro-angiogenic effect, we hypothesized that TF pathway could modulate collateral circulation in humans. Our purpose was to investigate the relation between biological parameters of TF pathway and collateral coronary circulation evaluated by angiography.
Methods: 364 consecutive patients with at least one coronary artery occlusion of a major branch detected by angiography were analyzed. Blood sampling for TF (plasma TF antigen) and other biological analyses was performed at the time of angiography. Collateral coronary circulation was analyzed in a semi-quantitative way by angiographic score (collateral flow grade). Clinical parameters were recorded.
Results: In univariate biological analysis of collateral coronary circulation variation, mean collateral flow grade were 2,36 ± 1,10 for low TF plasmatic value

(< 173 pg/ml) and 2,76 ± 1,04 for high TF plasmatic value (> 173 pg/ml) (p=0,0004). In multivariate analysis of collateral coronary circulation variation, we found 6 factors with a negative significant effect: recent coronary occlusion (<15 days) (p<0,0001), diabetes mellitus (p=0,005), female sex (p=0,006), smoking (p=0,008), number of coronary arteries occlusion (p=0,01) and a low TF plasmatic value (p=0,0067). We found no relation with all other biological markers, including activated Factor VII, free Tissue Factor Pathway Inhibitor and CRPus.
Conclusion: A high plasmatic TF level independently predicts a better coronary collateral development in patients with occluded vessels. Our findings suggest that TF pathway plays a critical role in collateral development in humans and support the use of FT modulation to increase collateral coronary arteries for non-revascularisable patients with coronary occlusion.

165 Results of the START-trial; STimulation of ARTeriogenesis using subcutaneous application of granulocyte macrophage colony stimulating factor as a new treatment for peripheral vascular disease

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Introduction: GM-CSF was recently shown to increase collateral flow index in patients with coronary artery disease. Experimental models showed beneficial effects of GM-CSF on collateral artery growth in the peripheral circulation. Thus, in the present study we evaluated the effects of GM-CSF in patients with PAD.
Methods: A double-blinded, randomized, placebo-controlled study was performed in 40 patients with moderate to severe intermittent claudication. Patients were treated with placebo or s.c. GM-CSF (10 μg/kg) for a period of 14 days (total of 7 injections). Primary endpoint was the change in walking distance from day 0 to day 14 (exercise treadmill test). Secondary endpoints were ankle-brachial index (ABI) at rest and after exercise, pain-free walking distance and cutaneous microcirculatory alterations as assessed by laser Doppler fluxmetry (LDF). All measurements were repeated at day 90.
Results: GM-CSF treatment led to an increase in monocyte fraction as well as CD34+ cells, peaking between day 6 and 8. Values then gradually decreased over the consecutive treatment period, leading to a significantly decreased monocyte fraction at day 14. Both the placebo group as well as the treatment group showed a significant increase in walking distance (placebo: 126 ± 66 meters vs. 189 ± 66 meters, P<0.05, GM-CSF: 121 ± 68 meters vs. 187 ± 91 meters, P<0.05). No statistical significant difference was found between groups. ABI did not change in either group from day 0 to day 14. Also at day 90 no differences were found between the treatment and the control group for any of the endpoints, except for the LDF measurements which showed a significant decrease in microcirculatory flux reserve in the control group (p<0.05) and no change in the GM-CSF group.
Conclusion: in the present study no beneficial effect of GM-CSF on walking distance was found in patients with moderate to severe intermittent claudication. The microcirculatory flow reserve remained unchanged in patients treated with GM-CSF whereas a gradual decrease was found in the placebo group. The decrease in CD34+ cells as well as monocyte fraction after day 8 of treatment indicates a sub-optimal dosing scheme in the present study that warrants further evaluation in future studies.

166 Mobilization of bone marrow pluripotent cells with granulocyte macrophage colony stimulating factor did not affect infarct size or left ventricular remodelling in the setting of experimental acute myocardial infarction

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Background: Stem-cell therapy appears a promising treatment for cardiac repair in experimental and small-scale clinical studies in the setting of acute myocardial infarction (AMI). However, bone-marrow aspiration and in-vitro expansion of the desired cell lines are time-consuming techniques, impractical for implementation during an acute event.
Purpose: To evaluate the effect of bone-marrow pluripotent stem-cell mobilization with GM-CSF on infarct size and left ventricular function in AMI, with a protocol easily applicable in everyday clinical practice.
Methods: Ten pigs weighing 30 ± 5 kg were subjected to left thoracotomy and occlusion of the left anterior descending coronary artery for 1 hour, followed by reperfusion. At 50 minutes of ischemia, the animals were randomized to placebo (Group A, n=5) or GM-CSF (Group B, n=5). Subsequently, the thoracotomy was closed and the animals recovered. In Group B, 20 μg/kg GM-CSF (molgrastim) was administered subcutaneously, daily, for 15 days. All animals underwent echocardiographic evaluation at 5 and 28 days after AMI. At 30 days, they underwent a new thoracotomy and determination of the infarct size as a percentage of the whole left ventricular area (with the use of tetrazolium chloride).
Results: No difference was observed between the two Groups in infarct size (7.8 ± 6.1% vs 7.5 ± 7.7%, p= 0.951, for Groups A and B, respectively). There was also no difference in shortening fraction (short axis view at the mid-papillary level, 34 ± 0.6% vs 35 ± 0.5%, p= 0.907), left ventricular end diastolic diameter (32 ± 0.2 mm vs 34 ± 0.3 mm, p= 0.361), left ventricular end systolic diameter (21 ± 0.2% vs 22 ± 0.4 mm, p= 0.584) and systolic thickness of the infarcted left ventricular wall (0.97 ± 0.2 mm vs 0.98 ± 0.2 mm, p= 0.972), in Groups A and B, respectively at 28 days of follow-up. Group B animals showed a trend for reduction of the systolic thickening from day 5 to day 28, in comparison to Group A (-32% vs +23%, p=0.066). Histologic analysis revealed a greater mononuclear infiltration of the infarcted area in Group B.
Conclusions: Subcutaneous administration of GM-CSF in the acute phase of acute MI and early post-infarction period does not result in either a decrease in infarct size or an improvement in LV function. Other protocols for adequate stem-cell mobilization and concentration in the injured area should be determined in order to combine efficacy and clinical applicability.

DRUG ELUTING STENT IN COMPLEX LESION SUBSETS

176 Restenosis after rapamycin-eluting stents for the treatment of bifurcated coronary lesions

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Background: Rapamycin-eluting stents have been shown to reduce restenosis in many types of coronary lesions. However, bifurcation lesions remain at a high risk for restenosis.
Objectives: To identify the sites of restenosis within the stented bifurcation after rapamycin- eluting stents and the technical factors influencing this complication.
Methods: Between June 2002 and April 2003, 91 consecutive patients with true coronary bifurcation lesions were treated with Rapamycin-eluting stents. Eighty two of them were angiographically revaluated at 6-month follow-up and were included in our study series. The mean age was 59±12 years. All patients received a Rapamycin-eluting stents at the main vessel, covering the side branch (SB); 40 patients received a second stent at the SB origin and 42 were treated with balloon dilation of the involved SB. Final kissing balloon was used in 62 patients (75%) and Abciximab in 54 (65%). Proximal or distal geographic miss (balloon inflation outside the stent) occurred in 22 patients (27%).
Results: Eleven patients (13%) developed restenosis (>50% stenosis at parent vessel or SB at 6- month re-evaluation). Restenosis of the main vessel was observed in 3 patients, restenois of the SB in 6 and restenosis of both vessels in 2. The site of restenosis was located as follows: proximal border of the parent vessel stent: 1 (8%); body of the parent vessel stent unrelated with the bifurcation: 1 (8%); parent vessel stent immediately under SB origin: 3 (23%); and at SB origin 8 (61%). Restenosis rate was not significantly influenced by any technical or procedural factor: stenting vs balloon dilation of SB (17% vs 10%), final kissing balloon (14% vs 13%) or the occurrence of geographic miss (14% vs 13%).
Conclusions: Restenosis rates after treatment of bifurcation lesions with rapamycin-eluting stents are low and unpredictable. The weakest part of the stented bifurcation is the side branch origin whether fully stented or not. Restenosis is not reduced by side branch stenting or final kissing balloon.

177 Six-month follow-up intravascular ultrasound study after rapamycin-eluting stent for the treatment of bifurcated coronary lesions

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In vitro studies have demonstrated stent deformation when struts have been opened to dilate a side branch (SB). Based on these studies, final kissing-balloon has been proposed to avoid this phenomenon. However, there is no in vivo information as yet available.
Aim: To investigate the six-month ultrasonic appearance of the parent vessel stent in patients (pts) with bifurcation lesions treated with rapamyicin- eluting stents (RES).
Methods: From a total number of 91 pts included in the randomized CORPAL study for bifurcation lesions, 37 who had a six-month angiographic and ultrasound follow-up study were analyzed. All pts received a RES at the main vessel; 21 pts (group A) were treated with balloon dilation of the involved SB and 16(group B) received a second stent at the SB origin. Intra-stent ultrasound-measurements were obtained in the main vessel at the edges, at the minimal lumen diameter, immediately under the SB origin and at the maximal stent diameter.
Results: Measurements were similar in both groups, except at the level of the minimal lumen area (table). The luminal and stent areas immediately under the SB origin were significantly smaller than at maximal stent area in both groups (loss of stent area), but only one pt developed restenosis at this point. This stent underexpansion was not influenced by the use of final kissing-balloon (loss of

stent area 2.2±1.9 versus 1.6±1.3 mm^2; ns) or by the SB type of treatment (loss of stent area 1.7±1.5 in group A and 2.1±1.8 mm^2 in group B; ns).

Lumen area (mm^2)	Group A	Group B	p <
Proximal reference	11 ± 6	10 ± 5	ns
Proximal edge	8.8 ± 4.5	8 ± 4	ns
Maximal lumen	6.8 ± 1.9	6.5 ± 1.7	ns
Minimal lumen	4.9 ± 1.5	4 ± 0.9	0.05
Under SB origin	5.2 ± 1.2	4.8 ± 0.9	ns
Distal edge	7 ± 3	5.4 ± 1.8	ns
Distal reference	7 ± 3	6 ± 2	ns

Conclusions: Some degree of stent underexpansion under the SB origin is a frequent finding after RES treatment of bifurcation lesions. This stent deformity is not prevented by kissing balloon inflation or by the type of SB treatment and does not influence restenosis rates.

178 Early and mid-term results of cypher stents in unprotected left main

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The safety and efficacy of percutaneous coronary intervention in unprotected left main (ULM) coronary arteries confronts with the problems associated with restenosis.

Methods: From April 2002 to January 2004 43 consecutive patients (pts) were electively treated in our Instutions with the implantation of sirolimus-eluting stent (Cypher, Cordis, Johnson and Johnson Company, Warren, NJ) in unprotected left main.

Results: 7 patients (16.3%) were diabetics, 11 (26.2%) had unstable angina, mean age was 61.2±11.9 years, and EF was 50.7±8.3%. The site of the lesion in LM was ostial in 2 (4.6%) patient, mid-portion of the artery in 4 patients (9.3%) and distal in 37 (86%) patients (bifurcation in 31pts and trifurcation in 7). In 30 (81%) patients with distal LM disease both branches were stented with SES, kissing balloon inflation was performed in 25 (67%). Angiographic as well as procedural success was achieved in all patients. Elective intra-aortic balloon pump was used in 7 patients and GP IIb/IIIa antagonists were used in 19 (44%) patients. During hospitalization, no patient died, nor had myocardial infarction (MI) or CABG, one patient had repeated PTCA due to residual dissection distal to the Cypher stent. At 6 month clinical follow-up 2 patients died (one died after discontinuing antiaggregant theraphy because of acute pancreatisis and the other because of pulmonary edema due to severe aortic regurgitation), 8 (18%) patients had TLR (6 re-PCI and 2 CABG) and 1 had MI. Angiographic follow-up was achieved in 31 pts (81%). Restenosis occurred in 9 patients (in 8 patients 3 mm Cypher stents were used); all restenostic lesions were located in the distal LM.

Conclusions: In this early experience with Cypher stents in ULM we can state that the problem of in-stent restenosis is still present mainly at the level of the bifurcation. We can speculate that the usage of 3 mm stents (6 cells) in vessels usually larger than 3.5mm could have contributed to inhomogeneous drug delivery to the vessel wall.

179 Sirolimus-eluting stent implantation for the treatment of aorto-ostial lesions

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Purpose: The safety and effectiveness of sirolimus eluting stents (SES) for the treatment of aortoostial lesions have not been demonstrated.

Methods: We identified 40 consecutive patients who underwent percutaneous coronary interventions using SES (49 stents) in 45 aorto-ostial (7 saphenous vein graft, 16 left main, and 22 right coronary) lesions. B2 or C type, and chronic total occlusions were found at baseline in 64%, and 15% of the lesions respectively; 24% of the patient population had diabetes mellitus, and 38% unstable angina.

Results: All stents were implanted successfully and 57% of the patients were treated with glycoprotein IIb/IIIa inhibitors. There were no major in-hospital complications. Non-Q-wave MI occurred in 5 (12%) patients. Six-month clinical follow up was available in all patients. At long-term follow-up (mean: 16.2 ± 7.8 months) 7 (17.5%) patients underwent target lesion (TLR) and 11 (27.5%) target vessel revascularization due to new lesions. There were no other major adverse cardiac events at follow-up. Angiographic follow-up was available in 31 (78%) patients and binary restenosis occurred in 7 patients (22.5%). Pre-, post-intervention and follow-up quantitative coronary angiographic analysis is shown in Table 1.

Table 1. Quantitative coronary angiography in aorto-ostial lesions treated with SES

Preintervention	RVD (mm)	3.38 ± 1.00
	MLD (mm)	1.07 ± 0.68
	Lesion Length (mm)	12.47 ± 10.80
Postintervention	RVD (mm)	3.68 ± 0.81
	MLD (mm)	3.32 ± 0.80
Follow up	RVD (mm)	3.56 ± 0.50
	MLD (mm)	2.55 ± 0.92
	Late loss (mm)	0.77 ± 0.54
	Binary restenosis (%)	7 (22.5)

Conclusions: SES implantation in aorto-ostial lesions appears safe with no increase in major in-hospital complications but with higher than expected rate of angiographic restenosis and TLR at long-term clinical follow-up.

180 Paclitaxel-eluting stents for treatment of complex lesion subsets: promising results of a TAXUS CTO registry

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Background and Method: The concept of local drug delivery from stent surfaces to avoid in-stent restenosis following stent implantation is a novel, promising strategy. Recent study results with Sirolimus, Paclitaxel and Everolimus show the advantage of stents delivering anti-proliferative agents in comparison to conventional non-eluting stent designs in treatment of focal native de-novo lesions. However, up to date, there is no data on the treatment effect of these new stent concepts with more complex lesion subsets. Therefore, we have conducted a complex lesion registry including 31 consecutive chronic total coronary occlusions (CTO), successfully treated with implantation of the Paclitaxel eluting TAXUS stent. All patients have been followed for 6 months with elective follow-up angiography. Primary endpoint was MACE at 30 days and 6 months as well as binary restenosis rate and angiographic late lumen loss. A total of 30 patients with 31 CTOs have been included (mean CTO age 5,8 months). In 5 patients, the CTO was documented for more than 1 year. Target lesions were located in LAD (n=8, 25,8%), RCX (n=5, 16,1%) and RCA (n=18, 58,1%). The stent/lesion ratio was 1,8. (1-5 stents/lesion). A total of 55 TAXUS-stents in length of 8-12mm (n=6), 16-24mm (n=28) und 28-32mm (n=21) have been implanted. Only patients with successful lesion revascularisation in the index procedure have been included.

Results: Up to date, angiographic 6 month follow-up is available in 23 patients. Six out of 23 patients developed a target lesion restenosis (26.1%), an in-stent restenosis was observed in 4 cases (17.4%). An acute stent thrombosis was observed in one patient one day post stent implantation, resulting in a 30 day MACE rate of 3.3%. There was no evidence of further subacute stent thromboses. At time of presentation, we will present the complete 6 month follow-up results including clinical as well as QCA data of this high complex patient cohort.

Conclusions: Implantation of the Paclitaxel eluting Taxus stent in treatment of chronic total coronary occlusions is safe and feasible. The preliminary 6 month follow-up results suggest a promising efficacy of the TAXUS stent design in this high risk lesion subgroup. However, the target lesion morphology remains to be a predictor of the target vessel failure, indicated by the elevated binary restenosis rate of 17.4% as compared to the results observed in focal de-novo lesion subsets.

181 Treatment of chronic total occlusion with the sirolimus-eluting stent – initial results from the e-CYPHER registry

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Background and Aim: Despite the use of bare metal stents for Chronic Total Occlusion (CTO), the combined rate of restenosis and re-occlusion remains high (ca. 30-50%). The introduction of drug-eluting stents has markedly reduced restenosis rates for de novo, non-occlusive lesions. However, there are no data concerning the use of drug-eluting stents in this challenging lesion subset. The aim of this analysis is to assess the real life use and clinical outcome of the CYPHER stent in CTOs.

Method and Design: The present data were collected from a multi-center, international registry (the e-CYPHER Registry) since April 02. Patient inclusion is still ongoing, and clinical follow-up is being obtained at 1, 6 and 12 months.

Results: 471 centers enrolled a total of 12,186 patients. Among them, 367 patients (3.0%) had a chronic total occlusion of the target lesion (defined as an occlusion > 3 months old). In this subset, mean patient age was 59.5 ± 11.5 years, 79.8% were males and 31.3% were diabetic. 51% had a previous MI (34.3% Q wave) and 32.7% had previous PCI. Indication for PCI included stable angina 57.2%, unstable angina 20.7% and silent ischemia 13.4%. Occlusive in-stent restenosis was noted in 13.2% of target lesions. Mean estimated occlusion length was 25.1 ± 11.7 mm with a reference vessel diameter of 2.8 ± 0.3 mm. A single stent was used in 77.4% (mean length 24.8 ± 7.6 mm), while 22.6% required multiple stenting (mean length of 48 mm ± 15.1mm).

Follow-up is ongoing, and at time of submission is available for 172 patients at 6 months (54% of those eligible). The overall rate of site-reported major adverse cardiac events (MACE) was 5.2%. This included 0 deaths, 4 MIs (2.3%), 5 TVRs (2.9%) of which 1 patient underwent CABG. Comprehensive 6-month follow-up data, including clinical status and adjudicated events, will be presented.

Conclusions: These highly encouraging preliminary results suggest that the use of the CYPHER stent is safe and appears effective in the treatment of CTO lesions.

GENE VARIANTS IN HYPERTENSION, CORONARY ARTERY DISEASE AND DILATED CARDIOMYOPATHY

182 Angiotensinogen gene and hypertension: evidence of intragenetic recombination by haplotype-tagging SNP analysis

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Background: Haplotype analysis has now become an popular tool to localize the susceptibility gene(s) for complex trait diseases. Finding of haplotype-tagging single nucleotide polymorphisms (htSNPs), instead of typing the whole SNPs, has been developed to define the major haplotypes, to capture most of the haplotype diversity, and to decrease the genotyping effort. However, most of these htSNP studies were focusing on marker SNPs in normal individuals, and little information has been available about the status of htSNPs within a specific functional gene, and its applicability to association study. The present study was designed to explore the differences of htSNP status within the angiotensinogen gene between patients with hypertension and normal individuals.
Methods and Results: A total of 408 patients with hypertension (hypertensives) and 286 controls had been recruited for this study. G-217A, G-152A, A-20C, G-6A, T174M and M235T polymorphisms of the angiotensinogen gene were genotyped. HtSNPs were searched by the BEST 1.0 program, and haplotype blocks were defined by the HaploBlockFinder-0.6b program. In the first stage analysis, A-20C was significantly associated with hypertension ($P<0.006$) and the angiotensinogen gene haplotype profiles were also significantly different between hypertensives and controls (P=0.001). For htSNP analysis, all the 6 polymorphisms were htSNPs and necessary to capture most of the haplotype diversity in hypertensives; however, only G-217A, G-152A, G-6A and T174M were htSNPs in controls, indicating more haplotype diversity in hypertensives than in controls. A-20C and M235T were not htSNPs and were possible the susceptibility loci, although M235T was not significant in the first stage analysis. There were more haplotype blocks in hypertensives, some of which were broken down from those in controls, indicating more historical recombination within the angiotensinogen gene in hypertensives.
Conclusion: Other than differences of allele, genotype or haplotype frequencies to show evidence of association in conventional genetic case-control study, differences of htSNP status and haplotype diversity, and evidence of intragenetic recombination could also help define the susceptibility gene for a complex trait disease.

183 The clinical significance of a common, functional, X-linked angiotensin II type 2-receptor gene polymorphism (–1332 G/A) in 509 families with premature coronary artery disease

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Background: A common intronic polymorphism, (-1332 G/A) of the angiotensin type 2 (AT2) receptor gene, located on the X-chromosome, was reported to be biochemically functional.
Methods: We investigated 509 families from the GRACE cohort, a national registry, with a matching genomic DNA library, of families with history of premature coronary artery disease (CAD), in the form of sibling trios, one affected with premature CAD and two unaffected siblings. Genotyping of subjects was performed using a restriction enzyme digestion of an initial 310 bp fragment that included the AT2 (-1332 G/A) locus.
Results: The mean age for the cohort was 57.0±9.0 yrs with 857 (55.1%) male and 611 (39.3%) affected by premature CAD. Conditional logistic regression analysis confirmed a significant predictive value of premature CAD for the covariates of hypertension, diabetes, dyslipidaemia, history of smoking, as well as male gender ($p < 0.005$). The genetic data were analysed using the XS-TDT statistics program. In men we observed evidence for linkage, between the AT2 (-1332 G/A) locus and a causative locus for premature CAD; p-exact value = 0.024. The data were further analysed to investigate linkage between this locus and a causative locus for hypertension. In men we observed a trend towards linkage; p-exact value = 0.08.
Conclusion: We have found evidence of statistically significant linkage between the AT2 (-1332 G/A) locus, located on the X-chromosome, and a causative locus for premature CAD in men.

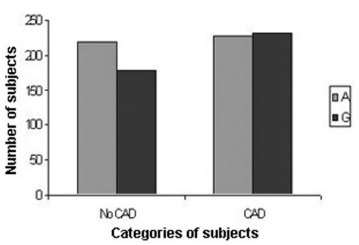

Fig. 1. Higher frequency of G allele in CAD.

184 Endothelial nitric oxide synthase gene variant modulates the relationship between serum cholesterol levels and blood pressure in the general population: new evidence for a direct effect of lipids in blood pressure

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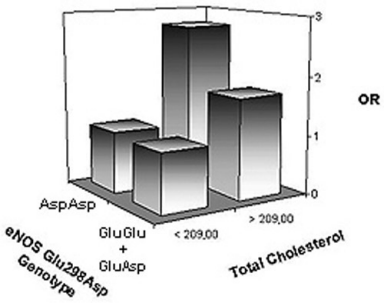
Background: A causal relationship between plasma cholesterol and blood pressure remains poorly understood. It has been postulated that the decrease in NO availability is a potential mechanism by which hypercholesterolemia may stimulate blood pressure elevation. However, evidence supporting the role of the L-arginine-NO pathway on the interaction between hypertension and hypercholesterolemia is still lacking.
Methods and Results: We tested for an interaction between the eNOS Asp298Glu gene variant and plasma levels of lipids and lipoproteins in the determination of systolic blood pressure levels in a large sample of 1,500 individuals randomly selected from the general population. Significant interactions could be disclosed either between total-cholesterol and the Glu298Asp gene variant (p = 0.02), log-transformed triglycerides (p = 0.004), and non-HDL-cholesterol (p = 0.003) in the determination of systolic blood pressure. In addition, although the presence of the AspAsp genotype did not significantly increase the risk of hypertension in individuals in the 50% lowest percentile of total cholesterol, presence of this genotype significantly increased the risk of hypertension in individuals in the 50% highest percentile (Figure). Finally, in a multiple logistic regression model allowing for age, sex, diabetes, smoking status and BMI, the AspAsp genotype significantly increased the risk of hypertension only in individuals with total cholesterol above 209 mg/dL (p = 0.04, OR = 1.9).



Conclusion: Taken together, these results provide evidence supporting the role of the eNOS Asp298Glu gene variant in modulating blood pressure through an interaction with lipid levels.

185 Mitochondrial DNA mutations in patients with inflammatory heart muscle disease

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Structural changes in the mitochondrial DNA (mtDNA) have been implicated in the pathogenesis of a number of diseases. This is not unlikely since mitochondria occupy a pivotal position in energy metabolism. MtDNA mutations are described to be involved in the pathogenesis of DCM. In this study we screen the whole mtDNA for mutations by dideoxy fingerprinting (ddF).
Methods: Total DNA from leucocytes of 55 patients with inflammatory heart disease, of 45 patients with DCM, and of 62 normal controls has been obtained. Amplifications of mtDNA fragments are performed using the method of PCR. After purification, ddF analysis is performed by electrophoresis of a dideoxy termination reaction through a non-denaturing polyacrylamide gel. Subsequently, a cycle-sequence analysis is carried out with samples of detected mutations.
Results: In both groups of patients an increased number of missense mutations in the mtDNA could be detected. Furthermore a number of mtDNA missense mutations that have not been described until now could be detected. The number of point mutations in each individual is variable and up to 8 mutations could be detected in one patient.

Table. Detected mtDNA mutations in patients with inflammatory heart disease and DCM

	Controls (n= 62)	Inflammatory heart disease (n=28)	DCM (n=27)
Detected mutations/different mutations[#]	64/33	39/30*	50*/26*
Mutations per sample	1.03/0.53	1.44/1.07	1.85/0.96
Novel mutations	23/18	16/15	14/11
Novel mutations per sample	0.37/0.29	1.39/0.54	0.96/0.41

[#]Mutations in tRNA-, 12s and 16s rRNA - genes and missense mutations in protein coding genes (*$p<0.05$ vs controls).

Conclusions: The enlarged appearance of mtDNA mutations in patients heart diseases seem to be rather a consequence than a reason of the disease. This may have an effect of the energy of the cells. These effects have to be investigated.

186 A missence mutation in desmin tail domain linked to human dilated cardiomyopathy abolish its z-disk localization in cardiomyocytes

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A missence mutation in the tail domain of desmin (Ile451Met) has been identified in a human family with restricted cardiac phenotype and suggested to be the genetic cause of the observed idiopathic dilated cardiomyopathy in these patients. In order to confirm and establish this link and further study the role of the desmin tail domain in this cardiomyopathy and the mechanism of disease development we have generated transgenic mice expressing the mutated desmin (Ile451Met) in the cardiac tissue. Immunofluorescence analyses of transgenic hearts revealed that mutated desmin is localized only in the intercalated discs of cardiomyocytes and not in the z-discs as is the case of the wild-type animals. This finding is of particular significance suggesting for the first time a critical role of this tail domain in localization and function of desmin.

187 Prevalence of cardiac troponin T gene mutation in a large dilated cardiomyopathy population

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Introduction: Dilated cardiomyopathy (DCM) is a heritable disorder in 20-35% of the cases, mainly with autosomal dominant transmission. To date, 10 genes have been found mutated in DCM, each of them with a low frequency. Accordingly, only two independent mutations have been found in the gene encoding cardiac Troponin T (TNNT2) in DCM patients. The aim of the study was to estimate the frequency of TNNT2 mutation in DCM.
Materials and Methods: We screened a large population consisting on 96 independent familial (54) and sporadic (42) cases presenting with isolated DCM phenotype. Whole blood extracted genomic DNA was used for TNNT2 coding exons and exon-intron boundaries PCR amplification. PCR products were analysed by direct sequencing on an ABI 3100 sequencing apparatus.
Results: We identified 2 different heterozygous missense mutations in 3 independent index-cases: 1 in a family and 2 in sporadic cases. None of these mutations was found by PCR-RFLP genotyping of more than 200 control DNAs. One is a new mutation substituting a conserved Histidine residue with a Leucine at position 91 of cardiac Troponin T (H91L) in a male subject diagnosed for DCM at 28 years of age. The two other subjects (1 sporadic and one familial case from different ethnical origin) carried the same and previously reported mutation, an Arg to Trp substitution at position 141 (R141W). The R141W was associated with complete penetrance in the family (all 4 carriers affected), an early onset disease in two patients diagnosed before 3 months of age (mean age at diagnosis 21±23 years) and arose de novo in the sporadic case as none of his parents carried the mutation.
Conclusion: We identified a mutation in TNNT2 gene in 3 independent patients with DCM, setting the gene mutation frequency around 3% in our population. The mutation R141W was observed twice and as a de novo mutation in a sporadic case, suggesting a mutation hot spot rather than a founder effect at this position. Specific screening of R141W in DCM subjects could therefore be useful for the molecular diagnosis of this disease.

MARKERS OF SEVERITY IN HYPERTROPHIC CARDIOMYOPATHY

188 Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy: a Doppler echocardiography study

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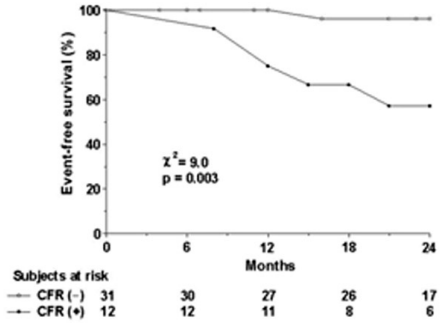
Background: Microvascular dysfunction, reflected by an inadequate increase in myocardial blood flow in response to dipyridamole infusion, is a recognized feature of hypertrophic cardiomyopathy (HCM) and may have prognostic impact. Coronary flow reserve (CFR) can be assessed on left anterior descending coronary artery (LAD) noninvasively with Doppler 2D-echocardiography.
Aim: To prospectively evaluate a cohort of patients with HCM after they had undergone quantitative assessment of CFR on LAD with ultrasound.
Methods: 43 patients (New York Heart Association class I or II) with HCM were followed for a mean (±SD) of 29±15 months after dipyridamole (0.84 mg/kg over 10')-Doppler echocardiography.
Results: CFR on LAD was normal (>2.0) in 31 and abnormal (<2.0) in 12 patients. Fourteen events occurred during follow-up: 8 left atrium dilations, 2 atrial fibrillations, 2 hospitalizations for unstable angina, 1 cardioverter-defibrillator implantation, and 1 pacemaker implantation. The 24-month event-free survival was 96% in patients with normal and 56% in patients with abnormal CFR (p=0.003) (Figure). With a Cox analysis, abnormal CFR on LAD (HR=4.92; 95% CI=1.26-19.2; p=0.02), interventricular septal thickness at end-diastole (HR=1.36; 95% CI=1.05-1.85; p=0.02), and diabetes (HR=3.00; 95% CI=1.09-8.28; p=0.03) were independent prognostic indicators.



Conclusions: In patients with HCM, the ultrasound-based assessment of the degree of microvascular dysfunction is a strong, independent predictor of clinical deterioration. Severe microvascular dysfunction is often present in patients with mild or no symptoms and may precede clinical deterioration by years.

189 Relationship of atrial fibrillation to sudden cardiac death in patients with non-obstructive hypertrophic cardiomyopathy: a long-term follow-up study

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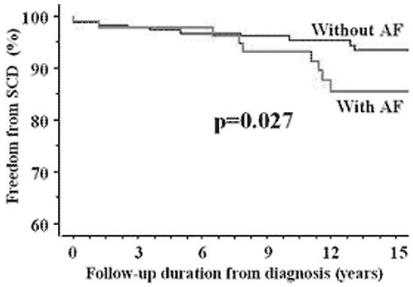
It is suggested that atrial fibrillation (AF) in obstructive hypertrophic cardiomyopathy (HCM) significantly increased the risk of cardiovascular mortality compared with AF in non-obstructive HCM (N-HCM) and no association was evident between AF and sudden death in HCM. Few data are available regarding relationship between AF and HCM-related mortality or sudden cardiac death (SCD) in patients (pts) with N-HCM. In this study, we evaluated the clinical significance of AF for long-term prognosis in pts with N-HCM.
Methods: A retrospective study of 350 pts with N-HCM, who were diagnosed and followed-up in our hospital, was performed (the mean age at diagnosis was 49 years). HCM-related morbidity(stroke, syncope, and heart failure), HCM-related mortality (sudden death, heart failure-related death, and stroke-related death) and a probability of SCD were analyzed. Mean follow-up duration was 13 years.
Results: Of 350 pts with N-HCM, AF was documented in 104 (30%) pts (paroxysmal AF in 87 pts and chronic AF in 17 pts, Age at diagnosis=51 years). The remaining 246 pts (Age at diagnosis=48 years) did not develop AF in a 13-years follow-up. HCM-related morbidity and mortality among pts with AF were significantly higher than that among pts without AF (60.6% vs.19.9%; p<0.001, 13.5% vs.6.9%; p=0.025, respectively). Moreover, the probability of SCD among pts with AF was significantly higher than that among pts without AF (p=0.027, figure).



Conclusions: In patients with N-HCM, AF was associated with HCM-related morbidity and mortality during 13-year follow-up. Furthermore, there was a significant relationship between AF and the probability of SCD. Therefore, it is suggested that AF is an important prognostic indicator of long-term cardiovascular mortality including SCD in patients with N-HCM.

190 Maximal oxygen consumption predicts outcome in hypertrophic cardiomyopathy

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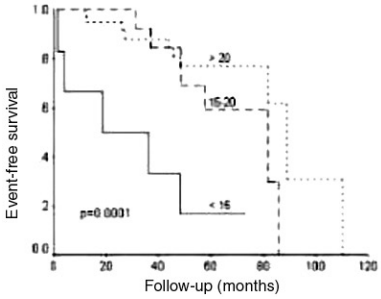
Background: Exercise intolerance is common in patients with hypertrophic cardiomyopathy (HCM). This study aims at evaluating if abnormal exercise capacity, assessed by maximal oxygen consumption (Max VO2), predicts the development of heart failure in patients with HCM.
Methods: 68 patients with HCM were included (47 men; mean age 41±15 years). No patient was in the dilative stage or in atrial fibrillation. All patients were off drugs at the time of protocol, and underwent symptom-limited exercise soon after echocardiography. Expired gases were analyzed and Max VO2 was measured. Patients were clinically and echocardiographically followed up for 45±28 months. Composite end point included: death, myotomy-myectomy, heart transplant, new onset atrial fibrillation, and progression to NYHA class 3 or 4.
Results: Event-free survival was significantly lower in patients with a Max VO2 < 15 ml/min/kg as compared to those with Max VO2 between 15 and 20 ml/min/kg, and those with Max VO2 > 20 ml/min/kg (figure).



Conclusions: Patients with HCM and severely impaired exercise tolerance carry a high risk of heart failure-related events; in contrast, a moderately depressed exercise tolerance does not imply additive risk over patients with normal exercise capacity.

191 Plasmatic N-terminal-pro brain natriuretic peptide is a sensitive marker of left ventricular dysfunction severity in hypertrophic cardiomyopathy

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Objectives: this study sought to determine the diagnostic utility of measurement of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with hypertrophic cardiomyopathy (HCM), and the capacity of the method to assess the severity of left ventricular (LV) dysfunction.
Background: plasma BNP is useful in heart failure and HCM. Plasma NT-proBNP has been increasingly used in cardiac diseases but there is no report of NT-proBNP measurement in HCM.
Methods: we studied 70 ambulatory patients (mean age 32.6 ± 11.4 years) with HCM (septal thickness >15mm, a non-dilated LV with normal ejection fraction). 15 (21,4%) patients had a resting outflow gradient>30mmHg (obstructive) and 55 did not have (non-obstructive). A control group of 20 normal volunteers age and sex matched were enrolled. The pts were examined by Doppler echocardiography and a blood sample was drawn for NT-proBNP measurement (electrochemiluminescence immunoassay Roche). Comparisons were made between HCM and normals, and between subgroups of HCM. Correlations were verified between levels of NT-proBNP and echocardiographic variables.
Results: in the HCM group, the mean plasma NT-proBNP was 1312 ± 1364 pg/ml, versus 41.2 ± 28.3 pg/ml in the control group ($p<0.0001$). The levels of the peptide were correlated with LA diameter (r=0.39; p=0.001), septal thickness (r=0.24; p=0.04). There was no linear correlation with obstruction but there were differences in the concentrations of NT-proBNP between obstructive (2116 ± 1812 pg/ml) and non-obstructive (1103 ± 1176 pg/ml) HCM groups (p=0.02). Patients with Doppler derived validated signs of LV filling pressure elevation presented statistically significant higher levels of NT-proBNP than the others.
Conclusions: measurement of plasma NT-proBNP in HCM pts is a sensitive method for diagnostic and functional evaluations. Further studies are necessary to verify the prognostic value of the test in HCM.

192 Cardiopulmonary responses to exercise in young patients with hypertrophic cardiomyopathy

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Cardiopulmonary parameters of peak exercise response during incremental upright testing have been shown significantly reduced in patients (pts) with hypertrophic cardiomyopathy (HC). We examined peak exercise cardiopulmonary parameters in a subgroup of young HC pts ≤ 20 years.
Methods: Between 1999-2004, 321 pts (223 male, mean age 44±16 years) with HC underwent cardiopulmonary incremental upright exercise testing at their routine initial evaluation in our cardiomyopathy clinic. Thirty three (10%) were ≤ 20 years old: mean age 17±2 years (range 13-20), 25 male, maximum LV wall thickness 21±6 mm (range 13-35), 4 had resting left ventricular outflow obstruction and 24 (72%) were asymptomatic. We examined peak VO2 values in this subgroup of very young pts as well as in the whole pt population.
Results: In the group of young pts mean peak VO2 value was (80±15)% of the predicted (pred) values (33.5±8 ml/min/kg). Half of them (17 pts, 51%) had peak VO2 values within normal (>80% pred) and a sizeable number (9 pts, 27%) had peak VO2 values >90% pred, while 2 pts exceeded 100% pred. Eight pts were engaged in sports at the time of diagnosis and all had peak VO2 >90% pred. In contrast, the whole patient cohort presented a mean peak VO2 of (70±17)% pred (22.4±8 ml/min/kg) and 27% of them were within normal range.

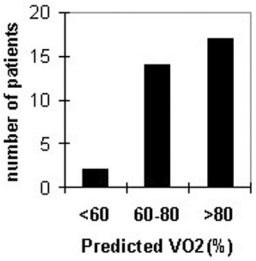

Fig. 1. Peak VO2 distribution in <20y old pts

Conclusions: A considerable number of very young patients with HC reach peak VO2 values within normal range during cardiopulmonary incremental upright exercise testing. Such young patients often present with minimal or mild hypertrophy as the disease phenotype has not been fully expressed yet. Exercise testing parameters should therefore be interpreted with caution in the investigation of very young patients being evaluated for hypertrophic cardiomyopathy.

193 Plasma levels of brain-type natriuretic peptide reflect compensatory hypertrophy, left ventricular dysfunction and collagen formation in hypertrophic cardiomyopathy

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Aim: Hypertrophic cardiomyopathy (HCM) is characterized by sarcomere dysfunction causing compensatory myocyte hypertrophy and interstitial fibrosis. Myocyte stretch is the predominant stimulus controlling the release of B-type natriuretic peptide (BNP) from the heart. We tested the hypothesis that N-terminal proBNP (NT-proBNP) is an early marker of cell stress in HCM patients.
Methods: 24 HCM patients with the TMP1-Asp175Asn mutation of the α-tropomyosin gene were studied. Radioimmunoassay was used to measure plasma NT-proBNP. Cardiac collagen formation was monitored by measuring serum aminoterminal propeptide of type III procollagen (PIIINP). Left ventricular mass index (LVMI) and ejection fraction (EF) were measured three-dimensionally using cine magnetic resonance imaging (MRI). The extent of regional myocardial dysfunction was measured as the proportion of hypokinetic segments (segmental fractional thickening < 30%) using cine MRI. On the basis of NT-proBNP the HCM patients were divided into three groups.
Results: HCM patients in the highest tertile of NT-proBNP had higher PIIINP levels (median 4.2 μg/L, range 2.5-8.7 vs 3.3 μg/L, 2.2-3.6, $p<0.05$), LVMI (86 g/m^2, 70-146 vs 69 g/m^2, 50-91, $p<0.05$) and proportion of hypokinetic segments (50%, 30-75 vs 27%, 8-42, $p<0.05$) than patients in the lowest tertile of NT-proBNP. NT-proBNP correlated with PIIINP (r=0.52, $p<0.01$), LVMI (r=0.47, $p<0.05$) and proportion of hypokinetic segments (r=0.47, $p<0.05$). There was no difference in EF between the tertiles and NT-proBNP did not correlate with EF either.
Conclusions: The current study demonstrates that NT-proBNP is associated with regional myocardial dysfunction as well as the extent of collagen formation in patients with HCM. Our results indicate that plasma NT-proBNP level is elevated before apparent global left ventricular dysfunction. Therefore, measurement of NT-proBNP could be useful in the clinical assessment of HCM patients.

HOW TO PERFECT CORONARY ARTERY BYPASS GRAFTING?

199 Optimising extracorporeal circulation: reduced need for blood transfusions and reduced hemodilution in coronary artery bypass

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Purpose: Aim of the study was to evaluate the effect of PRECiSe (Priming reduced extracorporeal circulation setup), a new low priming system with all features of cardiopulmonary bypass (CPB), on perioperative hemodilution, need of transfusions and resulting priming volume.
Methods: PRECiSe incorporates the Deltastream diagonal pump, which pumps blood from the right atrium to the aorta via a membrane oxygenator and a filter; the system is placed beneath the patient's head resulting in extremely short tubings. A reservoir allows the use of suckers and vents. Autologeous blood priming furthers reduces hemodilution. 80 patients undergoing elective coronary artery bypass grafting (CABG) were included in this prospective matched trial.
Results: Both groups were comparable regarding age, weight, height, sex and left ventricular function. No adverse events were noted intraoperatively. There were no myocardial infarctions or need for inotropic support. Mean effective priming volume was 289 and 1524 ml in the PRECiSe and control group, respectively. Course of perioperative hematocrit showed significant reduction of hemodilution in the PRECiSe group. Freedom from transfusion during hospital stay was 90% in the PRECiSe group and 65% in the control group, respectively.

Perioperative hematocrit

	Preoperative	Anesthesia	Begin CPB	End CPB	6 hrs postop.	POD #1
PRECiSe (n=40)	40.5 (4.5)	36.4 (4.7)	30.3 (2.7)	31.6 (4.1)	31.0 (3.3)	32.0 (3.4)
Control (n=40)	40.3 (3.6)	36.7 (4.1)	25.6 (6.0)	27.3 (2.7)	29.8 (3.3)	30.8 (3.0)
p	ns	ns	<0.05	<0.05	<0.05	<0.05

Hematocrit: mean (standard deviation); CPB: cardiopulmonary bypass, POD: postoperative day

Conclusion: The use of PRECiSe for extracorporeal circulation in CABG is safe and effective and leads to significant reduction of priming volume, perioperative hemodilution and transfusion requirements.

200 Cardiac revascularisation in nonagenarians

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Objective: The number of old patients referred to coronary revascularization is growing because of the ageing of population and progress in surgical and anestetic technics and postoperative care. The aim of present study is to review our experience with cardiac revascularization in nonagenarians.
Methods: The study group consisted of 35 (28 male and 7 female) patients,mean age 84,5years (range 80-89 years), underwent surgical revascularisation between 1st January 2001 and 30th June2003. Main risk factors in this group were: hypercholesterolemia(71,43%),arterial hypertension (54,28%),obesity (45,71%),diabetes (31,43%). 3 of them were after cerebral insult,13 have one and 18 two myocardial infarction and 11 patients have severe peripheral atherosclerosis. In angiography the dominant was triple vessel disease (77,15%). Surgery was performed on 4 (11,43%) as an emergency and 22 (62,86%) on an urgent basis. Pre operatively 27 (77,15%) were NYHA functional class 3 or 4. Average Euroscore was 9,3 (range 5-16 points). In 22 (62,86%) cases LITA were used for LAD grafting, the average number of grafts were 3,2 (range 2-5) anastomosis for patients. Operation were performed with extracorporeal circulation and blood cardioplegic cardiac arrest in 29 patients (82,86%), and in OPCAB technique in 6 (17,14%) patients.
Results: Perioperatively, 2 (5,72%) patients died due to low cardiac output syndrome and in consequence MOF, for another 4 we successfully used IABP and for 19 (54,28%) inotropic support. 5 (14,28%) patients needed longer than average 8 hours postoperatively mechanical ventilation. Exercise test m. Bruce was performed 6 month postoperatively and in 24 cases was negative, only one patient showed with exertion angina. 24 (68,56%) patients were in NYHA functional class 2. Actuarial survival was 91,43% and 85,72% at 1 and 2 years, respectively.
Conclusions: Surgical revascularization could be performed in selected nonagenarians with an acceptable mortality and morbidity.
- Post operatively old patients attain an excellent quality of life and survival.
- The main risk factor is urgent operation for unstable angina with low ejection fraction

201 The obesity paradox three years later: body mass index and long-term outcomes in the ARTS trial

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Background: Obesity is considered one of the major modifiable risk factors for coronary heart disease. However, the impact of body mass index (BMI) on the outcomes after coronary artery revascularization remains controversial. The purpose of the study was to assess the impact of BMI on the three-year outcomes after either stenting or CABG in patients with multivessel disease.
Methods: We studied 1,203 patients with multivessel coronary artery disease who underwent either stenting (n=599) or CABG (n=604) in the Arterial Revascularization Therapies Study (ARTS). Patients were divided into three groups according to BMI: normal BMI between 18.5 and 24.9, overweight with a BMI between 25 and 30 and obese with a BMI greater than 30. The primary clinical endpoint was freedom from major adverse cardiac and cerebrovascular events (MACCE).
Results: At three-years follow-up, the incidence of death, cerebrovascular events or myocardial infarction was similar for each one of the three BMI categories, regardless the revascularization technique employed. Repeat revascularization procedures were significantly higher among patients randomized to stenting, but similar among the different BMI groups. For patients randomized to CABG, there was a trend towards lower repeat revascularization procedures in obese patients (p=0.07). Among patients who underwent stenting, BMI had no impact on the three-year MACCE rates. Among patients who underwent CABG, MACCE rates were significantly lower for obese or overweight patients compared to normal BMI patients (p=0.012), as shown in the Table.
Conclusions: In a large cohort of patients with multivessel coronary artery disease who underwent either surgical or percutaneous revascularization: 1) BMI had no impact on the three-year outcome of patients who underwent stenting. 2) Among patients who underwent CABG, overweight and obese patients had a significantly better outcome than normal BMI patients regarding MACCE-free survival, mainly due to a lower rate of repeat revascularization procedures. Therefore, obesity should not be a factor favoring stenting in multivessel disease.

202 Defining the appropriate threshold of troponin-I elevation for the diagnosis of acute myocardial infarction in coronary artery bypass grafting surgery

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Objective: To assess the threshold levels of troponin I (TnI) for the diagnosis of perioperative myocardial infarction (MI) in patients undergoing coronary artery bypass grafting surgery (CABG).
Background: Despite modern intraoperative myocardial protection, 5 to 15 percent of patients undergoing (CABG) experience a perioperative myocardial infarction (MI). The diagnosis of MI after cardiac surgery is difficult because of the nonspecific ST-T wave abnormalities on ECG and elevation of creatine kinase (CK) levels postoperatively. Also, experience with TnI, a more sensitive serum marker of cardiac injury, is limited in this clinical set.
Methods: TnI was analyzed in blood samples obtained preoperatively and 6, 12 and 24 hours postoperatively, in 147 consecutive patients undergoing to CABG, using standardized operative procedures and myocardial protection. The serum concentration of TnI was determined with standard technique (upper normal level ^{3} 0.5 ng/mL). Patients were eligible for enrollment if they had one of the following criteria's: new Q-wave our left bundle-branch block and more them three times elevation of creatine kinase MB (CK-MB); non electrocardiography changes and more them eight times elevation of CK-MB.
Results: Eighteen (12%) patients had perioperative MI. The mean ($\pm$SD) TnI levels at 6, 12 and 24 hours were, respectively, 13 ($\pm$14) ng/mL, 57 ($\pm$32) ng/mL, 45 ($\pm$33) ng/mL in MI group and 8 ($\pm$11) ng/mL, 12 ($\pm$19) ng/mL, 8 ($\pm$20) ng/mL in non MI group. TnI values were statistically different at 12 and 24 hours. Also, TnI levels were significantly elevated above their threshold level within 12 hours after CABG (ROC curve: 0.89). Sensitivity and specificity of TnI in diagnosing perioperative MI, at fixed cut-off level of $>$ 9.15 ng/mL (Odds Ratio: 36, confidence interval: 5-283; $p<0.001$), were 94% and 68%, respectively.
Conclusions: TnI levels greater than 9.15ng/mL, within 12 hours after CABG, seems to be an appropriate threshold for diagnosis of myocardial damage in this group of patients.

203 Determinants of peri-operative myocardial injury after off-pump and on-pump coronary artery bypass surgery. Association with one-year cardiac outcome

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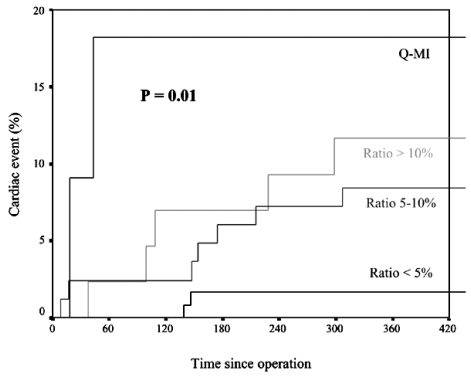
Background: Peri-operative myocardial injury (PMI) defined by the elevation of cardiac markers has prognostic value after conventional coronary bypass surgery (on-pump CABG). However, the determinants and clinical significance of PMI after off-pump bypass surgery (off-pump CABG) are unknown.
Methods and Results: The population comprised the patients who underwent off-pump and on-pump CABG in the Octopus Study. PMI was defined by a creatine kinase MB to total creatine kinase ratio $>$ 5% during the first 48 hours post-operatively and categorized in 1)ratio 5% to 10%, $>$ 10% without new Q-waves and $>$ 10% with new Q-waves (Q-MI). Finally, 260 of 284 patients randomized to off-pump and 117 of 139 patients randomized to on-pump CABG were analyzed. PMI was present in 52.5% and 91.6% of the patients after off-pump and on-pump CABG, respectively. Using univariate regression analysis, age, hypertension, previous arterial disease, nitrate use, diuretic use, full sternotomy, and coronary occlusion time were positively associated and male sex, history of hypertension, and presence of collaterals inversely associated with PMI after off-pump CABG. The presence of PMI after off-pump CABG showed an unadjusted odds ratio of 6.89 (95% CI: 1.53 – 30.95) for an adverse cardiac event at one year. After adjustment for the baseline characteristics age, sex, multivessel disease, and impaired left ventricle function, which were considered confounders of the examined association, the odds ratio was 6.81 (95% CI: 1.43 – 30.37).



Kaplan Meier survival.

Conclusions: Off-pump compared with on-pump bypass surgery reduced the incidence of post-operative myocardial injury. However, patients who sustained a peri-operative myocardial injury after off-pump surgery were still at risk of adverse cardiac outcome.

204 Off-pump coronary artery bypass surgery. A meta-analysis of randomised trials

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Purpose Our objective is to summarise the evidence on the effects of OPCAB on the post-operative risk for death, stroke and myocardial infarction (MI). We pool the results of randomised trials comparing the effects of off-pump coronary artery bypass graft surgery (i.e. without cardiopulmonary bypass: OPCAB), with the conventional procedure (CABG).
Methods: Full trial reports, published before January 01, 2004, were harvested from PubMed, EMBASE, CINAHL, Web of Science and CENTRAL. After methods appraisal and data extraction results of individual trials were expressed as odds-ratio (OR) with a 95% confidence interval (95%CI). Using a random effects model (Meta procedure, STATA 7.0.) trial results were pooled according to DerSimonian and Laird. Pooled results are expressed as OR and 95%CI.
Results: In total of 52 reports were retrieved, concerning 42 randomised trials. For 12 trials no full report was available, and for 3 trials effect estimates for none of our endpoints were reported. So, 27 trials including 2061 patients (1031 OPCAB and 1030 CABG) remained for further analysis. Methods appraisal showed $<$10% missing data and conversion rates $<$5% for nearly all trials. But, very few trials concealed random treatment allocation, standardised post-surgical care, and blinded outcome assessment of stroke and MI. On average most trials included young and male patients, while OPCAB patients received a bit fewer grafts. With the exception of MI up to 2 weeks post-surgery, effects for all our endpoints consistently favour the effect of OPCAB. For the composite endpoint (death, stroke and MI) the risk reduction in favour of OPCAB is 24%, 25%, 45%, and 35% at respectively 2-week, 1-month, 3-month and 1-year follow-up. However, none of the OR reach statistical significance at the conventional level.
Conclusions: The pooled results show important reductions in risk of death, stoke and MI that clearly favour OPCAB. But these reductions still fail to reach statistical significance.
Between January 1 and February 14, 2004, 7 randomised trials are reported as full paper, at least 12 other await publication as full report and longer follow-up of trials included here also await publication.
At the conference we will present results of our meta-analysis for death, stroke, MI and their composite endpoint, that are updated accordingly.

INTRAVASCULAR ULTRASOUND AND PLAQUE CHARACTERISATION

209 C-reactive protein levels and vulnerable plaque detection with three-dimensional intravascular palpography

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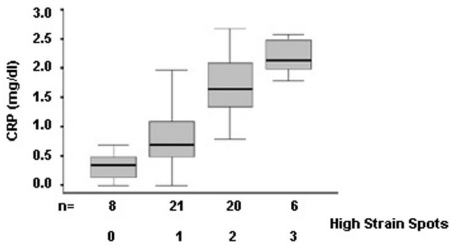
Rupture of thin-cap fibroatheromatous (TCFA) plaques is a major cause of acute myocardial infarction. Such plaques can be identified in vitro by three-dimensional intravascular palpography with high sensitivity and specificity. By using this technique in patients undergoing percutaneous intervention we found out that patients with myocardial infarction and unstable angina have more mechanically deformable plaques than patients with stable angina pectoris. Atherosclerosis and plaque rupture are highly associated with inflammation, but the relation between the inflammation marker C-reactive protein (hsCRP) and the number of TCFA is unknown.
Methods and Results: We studied 55 patients (29 male, 26 female). Patients were divided into three groups based on clinical presentation (stable or unstable angina, acute myocardial infarction). In patients with myocardial infarction the non-culprit vessel was studied. Palpography was performed in 55 vessels (28 LAD, 27 RCA). We identified 97 typical high strain patterns. In 8 vessels no high strain spot was detected, in 21 vessels one spot, in 29 vessels two spots, and in six vessels 3 spots.
The number of high strain spots per artery was positively correlated with the hsCRP level (R2=0.65, p$<$0.0001). For zero high strain spots the hsCRP level was 0.3 $\pm$ 0.2 μg/mL, for one 0.8 $\pm$ 0.5 μg/mL, for two 1.7 $\pm$ 0.5 μg/mL, and for three 2.2 $\pm$ 0.3 μg/mL (see figure).



Conclusion: Levels of C-reactive protein were positively correlated with the number of mechanically deformable plaques.

210 Two-year follow-up after intravascular beta-irradiation in Yucatan micropigs. In-vivo assessment with optical coherence tomography

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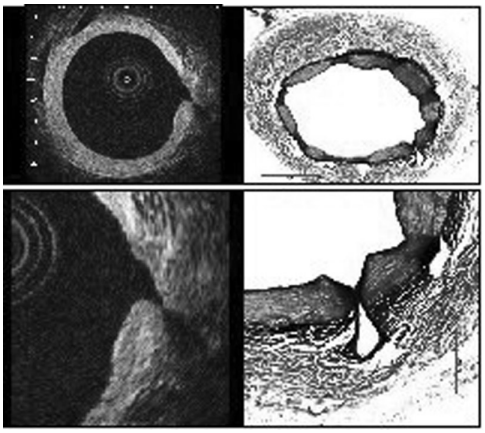
Brachytherapy has become an established therapy. Mechanisms of action include antiangiogenic effects, decrease or inactivation of smooth muscle cells and myofibroblasts or complete elimination of their proliferative capacity. Long-term effects, however, are complex, dose dependent and poorly understood. "Catch-up" neointima proliferation as well as positive remodeling have been described.
Aim: To investigate long-term effects of beta-brachytherapy.
Methods: Juvenile Yucatan micropigs underwent balloon injury followed by beta-radiation (20Gy) of the illiac arteries. At 2 year follow-up, repeat angiography and intravascular OCT (0.016 inch imaging catheter, motorized pullback at 1mm/s, 1300nm light source) was performed. After imaging animals were sacrificed and the arteries prepared for histology staining.
Results: OCT showed significant lumen narrowing and negative vessel remodeling. These changes were accompanied by increased signal density and thickness for both, media and adventitia, indicative for fibrous tissue. Both qualitative and

quantitative changes were corroborated by histology. Neointimal thickening, as observed in the injured segments was indistinguishable by OCT from fibrosed media due to invisibility of the lamina elastica interna and/or externa.



Example of in-vivo OCT (left) and post mortem histology of the internal illiac artery. The irradiated segment shows media thickening (max. thickness 0,26mm by OCT vs. 0,270 mm by histomorphometry) and severe adventitial fibrosis. Adventitial fibrosis.

Conclusion: In-vivo OCT two years after intravascular beta-radiation demonstrates lumen narrowing, negative remodeling as well as marked fibrosis and thickening of both, the media and adventitia.

211 Intravascular ultrasound radiofrequency analysis identifies plaque composition: virtual histology

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Ex-vivo, intravascular ultrasound (IVUS) radiofrequency (RF) data analysis has been demonstrated to predict coronary plaque composition. Fibrous, fibrolipidic, calcified, and lipid-rich areas can be identified within coronary plaques ("virtual histology"). We examined the first clinically available virtual histology system (Volcano Therapeutics Inc., Orange County, CA) in 25 patients (60 $\pm$ 11 years, 17 males,8 females) undergoing coronary angiography. Using 30-MHz 3.2F mechanically rotating IVUS catheters (Boston Scientific Corp.). Automated pullback was performed (LAD in 13 patients, LCX in 6, RCA in 8). Average cross-sectional plaque area (without media) was 5.2 $\pm$ 3.8 mm^2, fibrous plaque area was 3.1 $\pm$ 2.3 mm^2, fibrolipidic 1.1 $\pm$ 1.5 mm^2, calcified 0.1 $\pm$ 0.1 mm^2, and lipid core 1.0 $\pm$ 0.8 mm^2. Average plaque volume was 216 $\pm$ 137 mm^3, fibrous 126 $\pm$ 89 mm^3, fibrolipidic 51 $\pm$ 81mm^3, calcified 2.4 $\pm$ 1.7 mm^3 and lipid core 35.9 $\pm$ 28.7 mm^3. HDL-cholesterol (HDL, p=0.016) is independently associated with overall plaque area. There was a significant inverse association between HDL-cholesterol and lipid core area (Fig. 1, p=0.004) and lipid core volume% (p=0.006) as well as fibrous plaque area (p=0.037), whereas no association was observed with calcified and fibrolipid plaque components.

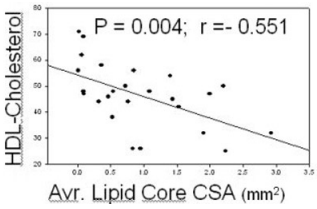

Fig. 1. HDL-cholesterol vs. lipid core area.

Virtual histology IVUS RF analysis allows characterization of plaque composition in-vivo and detects differences depending on risk factor profile. This may have implications for prognosis and assessment of treatment effects in patients undergoing invasive diagnostics.

212 Impact of patient age on plaque characterization by intravascular ultrasound virtual histology analysis

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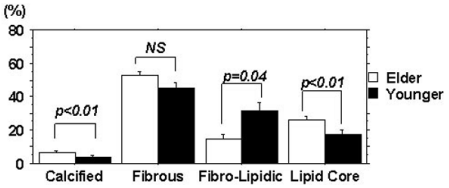
In previous studies the impact of age on plaque characterization has not been well assessed.

Purpose: The aim of this study was to evaluate coronary plaque characterization of elder patients using intravascular ultrasound radiofrequency data analysis. The algorithms have been derived and validated in vitro.
Methods: Sixty-four de novo native coronary lesions were imaged in vivo with the use of 30-MHz IVUS catheters. The ECG-gated image acquisition and digitization was performed by a workstation designed for 3D reconstruction. In our system, the averaged spectrum from regions of interest (ROI) was normalized and parameters were identified from the normalized spectrum within the bandwidth of 17 to 42 MHz. Database of parameters was then used to compute classification tree for plaque characterization. The values of radiofrequency signal from each ROI were classified into four plaque characterizations: calcified, fibrous, fibro-lipidic, and lipid core. We divided lesions into 2 groups according to patients' age: 1) elder ($\geq$65 years old, 30 lesions) and 2) younger ($<$65years old, 34 lesions).
Results: Baseline clinical characteristics were similar between both groups. IVUS data indicated no significant differences in lumen area, external elastic membrane area and plaque area at minimum lumen site and both reference sites in both groups. In elder patients %calcified plaque volume (6$\pm$7% vs. 3$\pm$6%, p$<$0.001) and %lipid core plaque volume (26$\pm$11% vs. 17$\pm$15%, p$<$0.001) were greater and %fibro-lipidic plaque volume (15$\pm$16% vs. 32$\pm$28%, p=0.04) was smaller compared to younger patients (figure).



Virtual histology findings.

Conclusion: Calcified and lipid core plaque volumes are larger and fibro-lipidic plaque volumes are smaller in patients $\geq$65 years of age compared to younger patients.

213 Correlation of serum lipids and inflammatory markers with intravascular ultrasound characteristics of culprit plaques in acute coronary syndromes

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Background: Serum lipids and inflammatory markers have been associated with the pathogenesis of atherosclerosis and acute coronary syndromes (ACS). However, no association has been reported between the levels of these markers and the IVUS characteristics of culprit plaques (CPs) in ACS. Previously, we have demonstrated that CPs show distinct IVUS characteristics, namely thinner fibrous caps, larger plaque areas and burdens, higher indices for remodelling and eccentricity, and lower mean grayscale level (MGL) and grayscale variance, reflecting a predominance of echolucent tissues, when compared to non-culprit plaques. This study aims at examining the relation between the levels of serum lipids, interleukin-6 (IL-6) and C-reactive protein (hsCRP), and the IVUS characteristics of CPs in ACS.
Methods: IVUS examination was performed on 30 angiographically identified CPs (18 patients with post-MI angina and 12 with unstable angina) by motorized pullback of the transducer in the culprit vessel at 0.5 mm/s. The IVUS images were digitized during acquisition at 10 frames/s to preserve image quality and resolution and were analysed offline. The frame with the smallest lumen area was used to calculate plaque area, lesion plaque burden, reference plaque burden, minimum thickness of the fibrous cap, remodelling index and the eccentricity index. Computer-assisted measurements of grayscale parameters included the MGL, variance and contrast. Blood samples were taken immediately prior to the IVUS run for estimation of the serum levels of total cholesterol (Chol), LDL, HDL, triglycerides (TG), CRP, and IL-6.
Results: Chol and LDL showed a positive correlation only with the mean reference plaque burden (r=0.51, p=0.004 and r=0.57, p=0.001 respectively) and no other IVUS parameters. HDL and TG showed no significant correlations. IL-6 (mean$\pm$SD=12.3$\pm$11.8 pg/ml) showed a significant positive correlation with the remodelling index (1.07$\pm$0.2; r=0.5, p=0.01) and eccentricity index (0.63$\pm$0.22; r=0.43, p=0.04) as well as a negative correlation with MGL (14.4$\pm$3.0; r=-0.52, p=0.009), variance (22.7$\pm$6.8; r=-0.74, p$<$0.001) and contrast (62.8$\pm$18; r=-0.7, p$<$0.001). CRP was not correlated with any IVUS parameter.
Conclusion: Chol and LDL were correlated with the extent of atherosclerosis of the culprit vessel but not with the characters of the CP. IL-6 correlated with most IVUS characteristics of the CP possibly supporting current evidence of production of IL-6 in the CPs. The relatively late production of CRP in the inflammatory cascade might explain its lack of correlation with CP characteristics.

214 Plasma ACE level and neointimal proliferation after stent implantation: a 3D intravascular ultrasound study

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Background: The angiotensin-I converting enzyme (ACE) is involved in vessel thrombosis, vasoconstriction, and smooth muscle cell proliferation. The aim of this study was to examine, using three-dimensional intravascular ultrasound vessel reconstruction (3D-IVUS), the role of ACE plasma level in neointimal proliferation after coronary stenting.
Methods: Serial 3D-IVUS analyses (pre-, post-stenting and at 6-month follow-up) were performed in 41 de novo lesions (41 patients, mean age 58±10, female 15%). Standard stent deployment techniques were used. The total vessel volume, lumen volume, stent volume, neointimal (in-stent) proliferation volume (ISV) and plaque area (PA) were calculated after 3D IVUS reconstruction. The plasma ACE level was measured in all patients using a quantitative kinetic determination.
Results: From the multivariate analysis of the clinical (pre-procedural variables) the plasma level of ACE emerged as the only independent predictor of ISV (p=0.009). Volumetric IVUS measurements were normalized by stent length; and a multivariate model containing the IVUS variables identified the basal plaque area before stenting as the strongest predictor of ISV (p=0.0003, OR 0.35, 95%CI: 0.3-0.5). Linear regression analysis showed a significant correlation between basal ACE level and the amount of neointimal proliferation volume (ISV) at follow-up in the whole population (r=0,4; p=0.009) and in patients not treated with ACE-inhibitor therapy (r=0,5; p=0.01).
A subgroup analysis was performed according to a cut-off value of plasma ACE previously identified as a predictor of restenosis (>34U/L). Patients with ACE level >34U/L (no. 11) had a significantly higher f-up proliferation volume (166.27±109) compared to patients with lower plasma ACE level (69.39±43.8, p=0.015). Similar results were observed when only non-ACE inhibited patients were compared (163.9±115 vs. 64.2±32, p=0.02).
Conclusions: The plasma level of ACE is a simple clinical variable that correlates significantly with the amount of neointimal proliferation after coronary stent implantation as assessed by accurate 3D-IVUS.

EPIDEMIOLOGY AND TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

215 Systematic cardiac echoscreening is effective in detecting early stage pulmonary arterial hypertension in systemic sclerosis

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Pulmonary arterial hypertension (PAH) is a severe complication of systemic sclerosis (SSc). The WHO guidelines recommend yearly cardiac echoscreening in SSc patients for early diagnosis and treatment of PAH. This approach has never been tested in a nationwide multicenter prospective study with a standardized methodology.
A prospective screening program was conducted in 21 French university-hospitals specialized in the management of SSc. SSc patients without severe pulmonary function abnormalities (defined as FVC, TLC or FEV1 < 60%) were referred to a senior cardiologist in each center who screened for PAH with echocardiography according to a predefined algorithm: a tricuspid regurgitation velocity > 3 m/s or between 2.5 and 3 m/s associated with an unexplained dyspnea indicated high risk of PAH and warranted right heart catheterization. Diagnosis of PAH was confirmed if mean pulmonary artery pressure (mPAP) was > 25 mmHg at rest or > 30 mmHg on exercise, in the absence of left heart disease.
From September 2002 to July 2003, 650 patients were enrolled, including 29 with a known PAH (duration of PAH since diagnosis was 18.8 ± 20.0 months [1.3-96.2]) and 18 who were diagnosed for PAH during the study.
These 2 groups of PAH patients were compared (Table 1).

Table 1. Known PAH vs PAH diagnosed

Clinical	PAH known	PAH diagnosed during
characteristics	at entry (n = 29)	study (n = 18)
Gender (% males)	11%	38% (p < 0.05)
Age (years)	65 ± 12	59 ± 13
SSc type (% diffuse)	52%	44%
Duration of SSc (years)*	12 ± 13	8 ± 6
mPAP (mmHg)**	49 ± 17	30 ± 9 (p = 0.0008)
Cardiac index (l/min/m^2)**	2.76 ± 0.73	3.18 ± 1.74 (p = 0.08)
TPR (dyn.sec/cm^5)**	1007 ± 614	523 ± 381 (p = 0.006)

* time from 1st symptom other than Raynaud syndrome; ** on last evaluation.Data given as mean ± SD.TPR: total pulmonary resistances

Conclusion: Patients diagnosed during the study had significantly less severe PAH than patients with a known history of PAH, suggesting that systematic cardiac echoscreening allows detection of PAH patients at an earlier stage. The clinical relevance of an early therapeutic intervention in this subset of patients should be evaluated.

216 Incidence, prevalence and prognostic impact of pulmonary arterial hypertension: a population-based study

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Background: In recent years there has been increasing interest in the detection and effective management of pulmonary arterial hypertension (PAH). However, apart from reports from specialist centres, there are few data describing the incidence, prevalence and prognostic impact of PAH within whole populations.
Methods: Using the Scottish Morbidity Record Scheme, we identified all patients discharged from hospital in Scotland (population 5.1 million) with incident PAH for the period 1985-2001. Using WHO criteria we identified all cases of idiopathic PAH +/- associated right ventricular failure (+RVF) and that relating to congenital abnormalities ("congenital PAH") and connective tissue disorders ("connective PAH").
Results: During the 16-year study period we identified 4,882 new cases of PAH. Of these, 319 were idiopathic, 379 idiopathic +RVF, 202 congenital and 211 connective PAH. In all three sub-sets, there were more female than male cases (idiopathic PAH – ratio 2:1 and connective PAH – ratio 4:1). The number of incident cases for each form of PAH and the age of detected adult cases steadily increased. In 2001 the incidence of idiopathic, idiopathic +RVF, congenital and connective PAH in women was 8, 13, 7 and 4 cases/million, respectively. In men the equivalent cases were 3, 7, 3 and 3 cases/million. The point prevalence of idiopathic, idiopathic +RVF, congenital and connective PAH in Scottish women aged > 16 years at that time was 3.2, 10.9, 4.0 and 2.8/100,000, respectively. In men the equivalent figures were 2.4, 5.6, 1.2 and 1.2/100,000. Overall, case-fatality rates were high. In women, one-year case fatality rates in those with idiopathic, idiopathic +RVF, congenital and connective PAH was 38%, 42%, 35% and 32%, respectively. In men, the equivalent rates were 38%, 44%, 22% and 38%. Age and sex adjusted analysis showed that 16-year survival rates were as low as 15% (idiopathic PAH +RVF) and high as 35% (congenital PAH). Multivariate modelling showed that 2-16 year case-fatality rates steadily improved over time (30% risk reduction reaching significance in 1998 relative to 1986).
Conclusions: These data provide a unique picture of the epidemiology of PAH within a whole population. Whilst confirming some data (e.g. a rare condition with more women affected), they indicate that the number of "detected" cases of PAH is higher than data from specialist PAH centres would suggest. It does appear likely, however, that new therapeutic modalities are making a positive impact on PAH-related survival rates.

217 L-arginine supplementation in pulmonary arterial hypertension

A. Manes, E. Bautista, H. Olchewski, A. Torbicki, N. Galie' on behalf of the PHAST study group. *University of Bologna, Institute of Cardiology, Bologna, Italy*

Purpose: Nitric oxide, a potent pulmonary vasodilator is synthesized from the amino acid L-arginine by Nitric Oxide-synthase. Intravenous administration and oral supplementation of L-arginine have been shown to improve hemodynamics and exercise capacity of patients with pulmonary arterial hypertension (PAH) in preliminary experiences. We designed an international, multicenter, double-blind, controlled study with a planned sample size of 120 NYHA functional class II and III PAH patients to assess the effects of 3 g of L-arginine daily oral supplementation or matching placebo on exercise capacity and clinical status.
Methods: The study was interrupted prematurely due to a slow enrollment rate caused in part by competing trials. The data of 75 patients with PAH (36 randomized to L-arginine and 39 to placebo) were analyzed on an intent-to-treat basis. Clinical evaluation (as assessed by NYHA functional class, signs and symptom score, fatigue-dyspnea score and serious adverse events) and 6-minute walk tests (6mwt) were performed at baseline and after 2, 6 and 12 weeks of treatment.
Results: Baseline clinical and functional characteristics were similar in the placebo and L-arginine groups. Eighty six percent of the patients had idiopathic PAH and 14% PAH associated with scleroderma, mean age was 45±14 years, 61% were females. The majority of the patients at baseline were in NYHA functional class II (65%). At the end of 12 weeks 6mwt distance slightly increased as compared to baseline in both groups (from 400.1±93.9 m to 411.1±126.1 m in the L-arginine group and from 411.7±68.8 m to 431.6±112.9 m in the placebo group) and no statistically significant difference was observed. Also Borg dyspnea score was unchanged. No difference among groups were also observed in the changes of NYHA functional class, signs and symptom score, fatigue-dyspnea score and serious adverse events. No patients died or required additional rescue treatments during the study period.
Conclusions: L-arginine oral supplementation seems not to provide clinical and exercise capacity improvements in this group of predominantly NYHA functional class II PAH patients.

218 Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension

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Background: Treprostinil has been approved for therapy of PAH (US and Canada) as continuous subcutaneous infusion. However, local pain at the infusion site is a major drawback. Inhaled therapy with another stable prostacyclin analogue (iloprost) has been approved for PPH (EMEA). In this study we investigated the acute hemodynamic response to inhaled treprostinil.
Methods: Open-label, single blind placebo-controlled clinical study. After placement of a Swan-Ganz catheter and a femoral artery line, patients inhaled solvent solution (placebo) (n=8) or treprostinil for 6 min (OptiNeb ultrasound nebulizer, Nebu-tec, Germany) in concentrations of 16, 32, 48, and 64 μg/ml (n=6, 6, 6, and 3 patients). Measurement was performed before and after 0, 15, 30, 60, 90, 120, 150 and 180 min. The mean area between the placebo and the treprostinil curves (ABC186) was calculated (baseline=100%).
Results: We investigated idiopathic PAH (n=10), collagen vascular disease (n=5), chronic thromboembolic disease (n=9), and pulmonary fibrosis (n=5), f/m = 19/10, age 56 ± 3 years, PAP, PAWP, and CVP 51.3 ± 2.2, 9.2 ± 0.8, and 6.6 ± 0.6 mmHg, CO 4.4 ± 0.3 l/min, SvO2 62.3 ± 1.2%, PVR 885 ± 72 dyn s cm^{-5}. At 16μg/ml there were no significant adverse events. Headache, cough or bronchoconstriction were observed in 2, 1, and 2 patients at 32, 48, and 64 μg/ml. These were mild and transient in all patients but one (64 μg/ml) who complained of major headache for 1 hour. Placebo inhalation was followed by slowly increasing PVR. Compared to this, the maximum treprostinil effect was reached after about 50 min and half-maximal effects at about 110 min. The ABC186 for PVR was –24.7 ± 4.4, -28.7 ± 4.9, and –29.0 ± 4.7%; PAP –14.4 ± 3.3, -13.5 ± 5.2, -13.1 ± 2.6%; SAP –5.1 ± 3.0, -6.0 ± 3.1, -3.8 ± 2.1% at 16, 32 and 48 μg/ml.
Conclusion: Treprostinil inhalation results in a significant long-lasting pulmonary vasodilatation. With the applied technology, at a concentration of 16μg/ml, near maximal pulmonary vasodilatation is achieved without adverse effects. At higher doses, local and systemic side effects may occur, whereas pulmonary selectivity is preserved.
This study was supported by Lung Rx.

219 The endothelin-receptor antagonist bosentan for the treatment of pulmonary arterial hypertension associated with congenital heart defects

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Background: Treatment with the oral dual endothelin-receptor antagonist bosentan has been shown to be an effective alternative option to intravenous epoprostenol in functional class (FC) III idiopathic pulmonary arterial hypertension (PAH) patients. In patients with PAH associated with congenital heart defects (CHD), an improvement of exercise capacity and hemodynamics has been demonstrated with epoprostenol in one uncontrolled study (Rosenzweig et al. Circulation 1999; 99: 1858-65).
The aim of this retrospective study was to evaluate the efficacy and safety of bosentan in FC III-IV CHD-PAH patients.
Study population consisted in 24 patients (22 females, mean age 35 ± 15 years [8-68]) with CHD-PAH: atrial septal defect (ASD: 13), ventricular septal defect (VSD: 4), partial abnormal pulmonary venous return (3, associated with ASD in 2 and repaired common atrium in 1), patent ductus arteriosus (PDA: 2), VSD associated with PDA (1), aortopulmonary window (1). Four patients had undergone previous cardiac surgery.
Patients had deteriorated despite conventional therapy (including oral anticoagulants, oxygen, diuretics) and were treated with chronic oral bosentan.
Results: Before starting bosentan, 22 patients were in FC III and 2 in FC IV, with a resting O2 saturation (SaO2) of 89 ± 9%. Mean 6-min walk distance (6MWD) was 288 ± 94 m and mean Borg index 3.0 ± 1.9. At last evaluation performed after 10 ± 9 months of bosentan treatment, 1 patient was in FC I, 8 were is FC II, 13 remained in FC III and 2 in FC IV. The mean 6MWD improved by 49 m (349 ± 85 m, p = 0.008) with no change in Borg index (3.0 ± 1.8) and resting SaO2 (89 ± 6%). There were no differences between pre and post-tricuspid shunt subgroups in terms of baseline characteristics and response to bosentan therapy. After 13 ± 9 months of follow-up, all patients are alive on bosentan, but 3 (1 ASD, 1 VSD, 1 aortopulmonary window) required combination therapy with intravenous epoprostenol after 5, 7 and 9 months on bosentan.
Conclusion: Chronic oral bosentan treatment improves exercise capacity in patients with PAH associated with CHD who deteriorated despite conventional therapy. Bosentan had no adverse effect on arterial oxygen saturation. As previously demonstrated in patients with idiopathic PAH, long term bosentan may be an important therapeutic option for patients with PAH associated with CHD.

220 Sildenafil in the treatment of primary pulmonary hypertension

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Backgroud: The role of sildenafil as a pulmonary vasodilator is being extensively evaluated in the treatment of pulmonary hypertension.
Aim: This was a prospective study to assess the benefit of adding sildenafil in patients with high pulmonary artery pressures secondary to atrial septal defect (ASD), already receiving the conventional therapy.
Methods: Thirty consecutive patients with moderate to severe primary pulmonary hypertension were included in this study. All the patients were diagnosed previously and were receiving the conventional therapy with digoxin, diuretic and a calcium channel blocker. Sildenafil was added in the dose of 50 mg twice a day without changing the previous regimens. Changes in the New York Heart Association (NYHA) symptom class, distance covered during the six minute walk test and modified Borg dyspnea score were evaluated monthly. Acceptance of the new drug was assessed every week in the first month and then at the monthly follow up. Echocardiography and Doppler study was undertaken at baseline and every month for a period of six months. The parameters studied were the pulmonary artery systolic pressure (PASP) by tricuspid regurgitation (TR) jet and pulmonary artery diastolic pressure (PADP) by pulmonary regurgitation (PR) jet.
Results: Mean age of the subjects was 42.6±9.3 years. Twenty seven (90%) were females and 3 (10%) were males. Sildenafil was well tolerated and there was no dropout because of undesireable effects of the drug. Changes in the heart rate and systemic blood pressure were not significant enough to warrant withdrawl of the drug. Two patients died during the follow-up period. At the beginning of the therapy, 22 (73.3%) patients were in NYHA Class III or IV while at the end of six months, only 8 patients remained in either of these classes ($p<0.05$). By the 6 min walk test, functional capacity improved from 181.5±122.4 meters to 302.7±150.3 meters p(<0.05). Modified Borg dyspnea score improved from 5.6±1.2 to 3.3±1.1 ($p<0.05$). PASP by TR jet (mmHg) was down from 81.3±14.7 to 51.4±11.7 ($p<0.05$). PADP by PR jet (mmHg) reduced from 56.2±11.7 to 33.4±9.1 ($p<0.05$).
Conclusion: Sildenafil is well tolerated, improves symptoms, and reduces the systolic and diastolic pulmonary artery pressures in patients with moderate to severe primary pulmonary arterial hypertension.

REVISITING THE ELECTROCARDIOGRAM AND ELECTROPHYSIOLOGIC MARKERS OF ARRHYTHMIC EVENTS

221 Prevalence of brugada-type ecg in an apparently healthy european population

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Background: The Brugada Syndrome ECG is characterized by ST-segment elevation in right precordial leads and elevated risk of lethal arrhythmias in absence of identifiable structural heart disease. Few data are available on the Brugada type ECG, especially in Europeans. No epidemiological study has applied the diagnostic criteria recently proposed by the Study Group of the Molecular Basis of Arrhythmias of the ESC.
Methods: We analysed the ECG and clinical data of apparently healthy European adults undergoing routine medical examinations for occupational reasons. At each examination subjects underwent a medical interview, physical examination, blood pressure measurement and 12-lead ECG. Enrolment was confined to persons without a history of heart disease at the time of first attendance in whom at least one 12-lead ECG of good quality was recorded. The ECG records of all 7483 subjects (89.6% male, age 29,5±10,8 years at first attendance) were reviewed by three cardiologists. We reviewed 1,97±2,1 ECGs for each subject. We considered a patient having a Brugada ECG pattern if 2 or more of the cardiologists judged that at least one of that persons ECGs fulfilled the criteria of the ESC Study Group.
Results: The Brugada pattern was present in 26 patients (0.35%), all male (table). In 17 cases (65.4%), information was available about the progress of the subject subsequent to the ECG on which the Brugada pattern was first recorded. No sudden death or cardiac arrhythmia was recorded among these patients in a follow-up of 5.2±4.6 years (total follow-up 87.8 patient-years).

	Total	Pattern 1	Pattern 2	Pattern 3	Tot. Brugada
Pts (n)	7383	2	21	3	26
Male	6618	2	21	3	26
Female	765	0	0	0	0
Male prevalence (*10000)	–	3,02	31,73	4,53	39,29
Total Prevalence (*10000)	–	2,71	28,44	4,06	35,22

Conclusions: The Brugada ECG pattern, as currently defined, is uncommon but not rare in a young healthy European population. In the absence of other markers of risk, the ECG pattern does not confer an excessively high risk of sudden death.

222 Short pr interval, high circadian index and bradycardia – pattern with high risk of syncope and sudden death in children with catecholaminergic ventricular tachycardia

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Idiopathic catecholaminergic (polymorphic bidirectional) ventricular tachycardia (CT) not so often observed in young. Despite on high incidence of the syncope and sudden death (S/SD) in this pts, individual prognosis in children with CT uncertain. The purpose of this study was to reveal specific features of heart rhythm for children with CT that predispose to the highest risk of S/SD. Methods and Results: CT was diagnosed in 16 children 6 - 14 years (10,1 $\pm$ 2,5 years, 10 boys, 6 girls) by rest 12 channels ECG in 6 pts (37,5%), treadmill test - in 2 (12,5%) and by 24 hr Holter monitoring (HM) - in 8 pts (50%). In all children have been excluded heart diseases and prolongation of the QT interval (QTc $<$ 440 ms). 11 of the 16 children had on rest ECG a short PR interval (SPRI) $<$ 0,11 sec (mean 0,1 $\pm$ 0,01 sec, range 0,08-0,11 sec) whithout other criterias of the Wolf-Parkinson-White syndrome. Among this pts was 80% boys (8) vs 40% (2) in pts whithout SPRI. All children with SPRI had in history S or aborted SD with rate 9,1 $\pm$ 9,2 in year vs 0,6 $\pm$ 0,89 S in year in 2 pts whithout SPRI. A family history of SD was present in 4 cases only in pts with SPRI (4/11- 36,4%). Heart rate in rest ECG was 55,5 $\pm$ 9,1 bpm in children with SPRI (mean age 9,6 $\pm$ 2,7 years) vs 78,1 $\pm$ 2,8 bpm in children whithout SPRI (mean age 11 $\pm$ 1,7 years). Circadian index (CI) was calculated by results of HM as ratio mean heat rate (bpm) during awake period to mean heat rate during sleep. Normal values of the CI - 1,32 $\pm$ 0,06 (Makarov L. 2000). In pts with SPRI CI was 1,45 $\pm$ 0,17 vs 1,4 $\pm$ 0,06 in pts without SPRI. Absence of the SPRI in pts with this arrhythmia in series reports before (A. Leenhardt 1995, H. Swan 1999, S. Viskin 1998) possibly reflected ethnic specific of the russian population and need in further electrophysiological and genetic studies.

Conclusion: Combination of the catecholaminergic ventricular tachycardia, short PR interval, increasing of the circadian index ($>$ 1,45) and bradycardia is a specific ECG pattern or syndrome with high risk of syncope and sudden death in children.

223 Past and present prognostic value of heart rate variability in postinfarction patients

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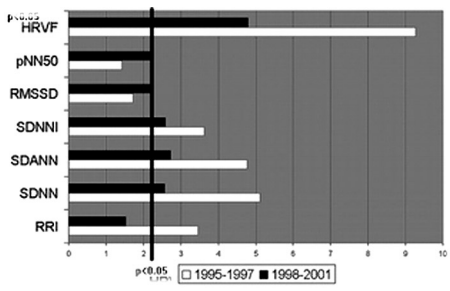
We aimed to evaluate the prognostic value of HRV analysis in two cohorts of post-MI patients referred to our ECG Lab in two periods: between 1995-1997 (early, treated with trombolysis) and 1998-2001 (recent, treated interventionally). 198 patients (42f, 156m) aged 57$\pm$9 years and 185 patients (39f, 146m) aged 59$\pm$8 years were included, resp. Mean LVEF and NYHA were 43$\pm$13 vs 41$\pm$13 (NS) and 1.4$\pm$0.6 vs 1.7$\pm$0.8 ($p<0.01$), resp.

In each patient a 24-hour ambulatory ECG was recorded and analyzed. Standard HRV analysis included time domain measures. Additionally, the HRV Fraction, based on a numerical processing of Lorenz plot, was analyzed. Patients were followed for at least 24 months. The association of HRV with total and cardiac mortality was compared.

Results: The mean follow-up did not differ between two groups (34$\pm$21 vs 32$\pm$17 months). There were 28 deaths in the early group (14%) and 28 in the recent group (15%). Cardiac deaths were confirmed in 21 and 23 cases, respectively. All HRV parameters (except pNN50, RMSSD) were significantly higher in the survivors in both groups. However, the strength of the association was significantly lower in the recent group. Adjusted (for age, sex, LVEF, diabetes and beta-blocker use) values of relative risk for cardiac mortality is presented below.



Prognostic value of HRV measures.

Conclusions: In the modern treatment era the prognostic value of HRV seems to be less significant, but HRV measures are still independent predictors of cardiac death. HRV Fraction – the index based on scatterplot analysis, which combines all features of HRV, appears to be most useful.

224 Does electrophysiologic study predict the outcome of patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia?

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The first objective of management strategy in patients with arrhythmigenic right ventricular cardiomyopathy (ARVC/D) is to prevent arrhythmic sudden death (SD). However, risk stratification is still not well established and there are no precise guidelines to determine which patients need to be treated. Whether electrophysiologic study with programmed ventricular stimulation (PVS) is able to predict life-threatening ventricular arrhythmias in patients with ARVC remains to be established. We analysed the predictive value of PVS in 132 patients (93 males, 39 females, aged 40$\pm$15 years) with ARVC/D who received an implantable cardioverter- defibrillator (ICD) because of a high risk of sudden death. Implant indications were a history of cardiac arrest in 13 (10%) patients; sustained ventricular tachycardia in 82 (62%); syncope in 21 (16%); and other in 16 (12%). Electrophysiologic study prior to ICD implantation was carried out in 111 of 132 patients (84%). All antiarrhythmic drugs were discontinued ^{3}5 half-lives (^{3}6 weeks for amiodarone) before the study. PVS included a minimum of 2 drive cycles length and up to 3 ventricular extrastimuli while pacing from two right ventricular sites. Ninety-eight patients (88%) were inducible to either sustained ventricular tachycardia (67 patients; 68%), with a mean cycle length of 284$\pm$66msec (range 210 to 415 msec), or ventricular fibrillation (31 patients; 32%). Of 98 patients who were inducible at PVS, 50 (51%) did not experience ICD therapy during the follow-up (39$\pm$27 months), whereas 7 of 13 (54%) not inducible patients had ICD interventions. Overall, the positive predictive value of PVS was 49%, the negative predictive value 54%, and the test accuracy 49%. The incidence of ICD discharges on ventricular fibrillation/flutter, which in all likelihood would have been fatal in the absence of ICD therapy, did not differ between patients who were and were not inducible at PVS (22 of 98, 22%; vs 3 of 13, 23%; p=NS), regardless of clinical presentation. The type of ventricular tachyarrhythmia inducible at the time of electrophysiologic study did not predict the occurrence of ventricular fibrillation/flutter during the follow-up. In conclusion, electrophysiologic study was of limited value in identifying patients with ARVC/D at risk of sudden death. The low predictive value of PVS makes its application in risk stratification questionable.

225 Does programmed ventricular stimulation still have a role in stratifying arrhythmic risk in patients with post-MI dilated cardiomyopathy?

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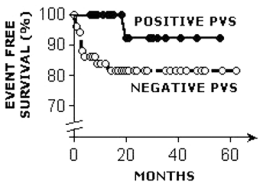
Purpose: the role of the implantable cardiac defibrillator (ICD) in reducing total and sudden death in patients with post-MI dilated cardiomyopathy (IDCM) is established. It is crucial to identify patients at risk who might benefit the most from ICD implantation. A MADIT II sub-study has recently called into question the role of programmed ventricular stimulation (PVS) in predicting the arrhythmic risk in patients with IDCM.

The present study evaluated the role of PVS in predicting arrhythmic risk in patients with IDCM.

Methods: Eighty-two pts with IDCM (age 61$\pm$7 yrs, LVEF 27$\pm$8%; NYHA class 2.3$\pm$0.6) underwent PVS from RV apex and outflow tract with 2 cycles length (500 and 400 ms) and up to 3 extrastimuli. A sustained ventricular arrhythmias (VA) was induced in 52 pts (63%): in 1 pt (2%) VF, in 8 (15%) ventricular flutter and in 43 (83%) sustained VT. An ICD was implanted in 59 (72%) pts.

Results: During a mean follow-up of 22 months, 13 pts died (2 suddenly and 11 for heart failure), 3 underwent urgent heart transplantation and 9 had a VF treated by the ICD. The combined end point of sudden death and VF was more frequent in pts with VA inducible at PVS (19% vs 3%, p=0.04, see figure). PVS showed a negative predictive value of 97%.



Event-free survival according to PVS.

There were no difference in age, NYHA class, LVEF, QRS duration, antiarrhythmic therapy between inducible and non-inducible pts.

The combined end-point tended to occur more frequently among positive PVS pts also in the subgroup of pts with EF$\leq$30% (23% vs 5%, p=0.07, negative predictive value 95%).

Conclusions: PVS may still help in assessing the arrhythmic risk of patients with post MI dilated cardiomyopathy. A negative PVS identifies a subgroup at low risk even among pts with LVEF$\leq$30%.

226 Is isoproterenol infusion required during electrophysiologic study in patients with history of myocardial infarction and unexplaiend syncope?

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Syncope in patients with myocardial infarction (MI) is sometimes associated with a high risk of sudden death SD). To determine the precise cause of syncope is important. The purpose of the study was to evaluate the results of electrophysiologic study (EPS) after infusion of isoproterenol in patients with myocardial infarction, studied for syncope and in whom EPS remained negative in the control state, to determine if this drug added prognostic informations.

Methods: population included 51 patients, aged 59±19 years, who had unexplained syncope, a history of MI, no documented arrhythmia and a negative EPS in the control state; 5 of them had exercise or stress-related syncope. EPS consisted of study of AV conduction, programmed atrial stimulation up to 2 extrastimuli and programmed ventricular stimulation up to 3 extrastimuli; the study was performed in control state and repeated after infusion of 2 to 4 μg/kg of isoproterenol. Arterial blood pressure was continuously monitored.

Results: after isoproterenol, EPS remained negative in 28 patients; in 23 patients, an arrhythmia was identified as the symptom associated with syncope: ventricular tachyarrhythmia (VT) was induced in 15 patients; one of them had also inducible supraventricular tachyarrhythmia (SVT). SVT was only induced in 3 patients; infrahisian 2nd or third degree AV block (AVB) occurred in 2 patients and vasovagal reaction developed in 3 patients. Patients were followed during 1 to 6 years (mean 3±1). Patients with isoproterenol-induced VT and those without VT differed significantly ($p < 0.05$) by a lower left ventricular ejection fraction (34±8% vs 48±15), a higher incidence of exercise-related syncope (4 vs 1) and a higher risk of sudden death (6/15 vs 0/36).

In conclusion, electrophysiologic study should be repeated after isoproterenol infusion, in patients with myocardial infarction, with a negative study in control state and with syncope related or not to exercise. An arrhythmia might be identified as the cause of syncope in 45% of them. Patients with inducible VT are at high risk of SD. At the opposite, a negative study or another arrhythmia as SVT, vagal hypervagotonia or AVB, identified a group at favourable prognosis.

NURSING ASPECTS OF ACUTE CARDIAC CARE

229 Early use of kinetic therapy integrated in a standardized care program reduces complications and shortens respirator dependency in patients with cardiogenic shock: a nursing study

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Background: Prolonged immobilization and respirator therapy increase the risk of complications such as respirator-dependent pneumonia and decubital ulcer. Moreover, they prolong hospitalisation in patients with cardiogenic shock requiring ventilatory support. Use of kinetic therapy (KT) has been postulated to shorten hospital stay; however, data are inconclusive. Goal of this study was to test if standardized KT improves outcome in patients with cardiogenic shock.

Methods: Consecutive patients (pts) with cardiogenic shock administered to the ICU of 1 center were included in the study between August, 2002 and January, 2004. Inclusion criteria was an oxygenation index (see below) < 300 mmHg after 48 hours of respirator therapy. After informed consent of the next relative, pts were randomly assigned to standard care (control group, CO) or to the protocol group (PRO) with the following goals: 1. Treatment with continuous KT using oscillating beds (TriaDyne, KCI, San Antonio, USA)

2. Regular use of percussion therapy (10 min of percussion every 4 hours realized by the automated percussion mode of the rotational beds).

Oxygenation indices (defined as arterial oxygen partial pressure divided by inspiratory oxygen concentration using the Horowitz formula), APACHE II score, SOFA score, decubital ulcer, rates of pneumonia, length of respirator therapy, and length of ICU and of hospital stay were determined in all patients.

Results: 120 patients were included in the study. 61 pts were randomly assigned to CO and 59 to PRO. Baseline APACHE II and SOFA scores, age, and gender were comparable in both groups. Baseline oxygenation indices were 165 mmHg in PRO and 198 in CO (p=0.003). Length of respirator therapy was 15,0 days in PRO and 18,2 days in CO (p=0.03). Pneumonia occurred in 11 pts in PRO and 33 pts in CO; decubital ulcer were reduced from 38 in CO to 20 in PRO. Length of ICU stay (24,47 days in CO and 18,86 days in PRO) and length of hospital stay (27,23 days in CO and 21,49 days in PRO) were significantly reduced in the patients subjected to kinetic therapy. The significant improve of outcome may even be underestimated since the basal parameters were worse in PRO. By calculating the cost of ICU care, KT lead to a net reduction of about 4.000 euro per patient.

Conclusion: Early use of KT shortens hospital stay and reduces rates of pneumonia and decubital ulcer as compared to standard care. In addition, kinetic therapy proved to be highly cost effective. Thus, this study supports the early use of KT in pts with cardiogenic shock requiring prolonged respirator therapy.

230 Nursing workload by invasive coronary procedures: a comparison between transradial and transfemoral approach

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Transradial approach (TRA) is known to prevent access-site complications, to favour patient's self care and to reduce in-hospital stay after invasive (both diagnostic and interventional) coronary procedures (ICP).

Aim: to prospectively compare cath-lab (CL) and bedside (BS) nursing workload (NWL) during and after ICP in case of TRA or transfemoral approach (TFA).

Methods: Over a three-months period we evaluated baseline characteristics, procedure-related times (including sheath removal), access-site complications, length of in-hospital stay, number of bedside nursing procedures, in consecutive patients undergoing ICP, performed by skilled operators (>100 ICP with TRA/year). We excluded patients undergoing: chronic-occlusion recanalisations, urgent ICP for cardiogenic shock, right and left catheterisation, other investigative protocols. The choice between TRA and TFA was left to the operator. CL-NWL for each patient was calculated as the time spent, multiplied by the number of nurses involved, in each phase of the procedure. BS-NWL for each patient was calculated as time spent/day, multiplied by the number of nurses involved, for each bedside nursing procedure, and by the days of in-hospital stay.

Results: 260 pts (52 planned TFA/208 TRA, mean age 65±10 yrs) met the inclusion criteria. TFA included more urgent patients than TRA group (50 vs 26%, p=0.001). Despite a cross-over of 19%, TRA were shorter than TFA ICP (36±18 vs 50±25 min, p=0.001). CL-NWL was 180±61 and 102±57 min, respectively in the TFA and TRA group (-43%, $p<0.001$). Among all variables, TFA and interventional ICP were the only independent predictors of higher CL-NWL. Among the study population, 176 pts (56 performed TFA/120 TRA, mean age 65±11) were admitted at our hospital after ICP. Despite no significant difference in urgent cases, TFA were more likely to stay in ICU than TRA pts (71 vs 43%, $p<0.001$), had longer in-hospital stays (6±3 vs. 4.5±2 days, $p<0.001$), and more access-site complications (11 vs. 0%, $p<0.001$). BS-NWL was 844±555 and 479±318 min, respectively in the TFA and TRA group (-44%, $p<0.001$). Among all variables, TFA, interventional ICP, and admittance to ICU were the only indipendent predictors of higher BS-NWL.

Conclusions: In case of ICP performed by TRA, shorter CL room occupancy, fewer access-site complications, shorter in-hospital stays translate in both reduced CL and BS-NWL, particularly for interventional ICP admitted to ICU, in comparison to TFA.

231 Controlled comparison of early versus late ambulation after femoral sheath removal in coronary angioplasty

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Purpose: Early ambulation after femoral sheath removal might increase patients' comfort and may facilitate earlier discharge after PCI. Whether this approach is safe and does not increase bleeding complications, is unknown. This study investigates ambulation 4 hours after sheath removal is not inferior to ambulation 10 hours or more with regard to puncture site complications.

Methods: PCI was done by femoral approach in 561 heparinised patients. (100 IU/kg). Two hours after heparin ACT's were measured, and if < 275sec, the sheath was removed by registered nurses of the ward. Hemostasis was achieved by manual compression. After bed rest with a compression bandage for 4 hours the patients who had PCI before noon were ambulated (early ambulation group: walking at least 200m). The patients with a PCI performed in the afternoon stayed in bed till the next morning (control group). Nurses took care of the inguinal inspections, except the final inspection at discharge by the physician. Study endpoint was the composite of puncture site complications: haematoma (>5x5cm), bleeding at ambulation (requiring compression and prolonged bed rest), false aneurysm and arteriovenous fistula (both by ultrasonography). The power calculation required 445 patients (assumed complication rate 3%) to obtain 80% power to show equivalence in a 1-sided non-inferiority test with alfa= 0.05.

Results: Patient characteristics were comparable (age 60.2±9.9 vs. 61.3±10.4):

Number of puncture site complications (%)

Endpoint (%)	Haematoma	Bleeding	False aneurysm	Arteriovenous fistula	Any complication
Early ambulation group (n=352)	5 (1.4)	2 (0.6)	2 (0.6)	0 (0.0)	9 (2.6)
Control group (n=209)	2 (1.0)	1 (0.5)	1 (0.5)	2 (1.0)	6 (2.9)

The null hypothesis that the complication rate in the early ambulation group is more than 4% higher than in the control group was rejected (p = 0.002) and hence non-inferiority accepted.

Conclusions: Early ambulation 4 hours after femoral sheath removal by registered nurses is feasible and safe. The incidence of puncture site complications is not increased in comparison to prolonged bed rest (>10 hrs). Patient comfort is probably increased and patients may be discharged earlier after PCI, allowing PCI in an ambulant setting.

232 Telephone appointments as an alternative to clinic visits post percutaneous coronary intervention: do they work and what do patients think?

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Background: At Harefield Hospital follow up care for patients post Percutaneous Coronary Intervention (PCI) is a nurse led service.
Patients are reviewed in clinic at 1 and 6 months post procedure. If they remain well the 1-year appointment is carried out via the telephone. This innovative method of follow up was introduced in 2001 and had not been used previously at Harefield. It was established to facilitate patient monitoring whilst reducing the need for clinic visits.
Methods: In the first 18 months of the nurse led service, 252 patients have reached the 1-year review period. A questionnaire was sent to patients to ascertain how they felt about telephone follow up. The questionnaire examined how convenient they found the telephone appointment, if they had any concerns or problems, were these addressed appropriately and also if they would be happy to have this method of follow up in the future?
Results: 211 questionnaires were returned (84%). 94% (n=202) of patients found the telephone follow-up convenient. 93% (n=200) of patients felt their concerns and problems were addressed appropriately. 85% (n=183) said they would be happy to be followed up via the telephone in the future as long as they remained well.
Discussion Telephone use is common amongst health care providers; however there has been very little evidence of its use in routine follow up in place of a clinic appointment. This method of follow up has enabled continued monitoring of patients together with reinforcement of risk factor modification. It has saved patients time, money and the need to travel to the hospital for their review. This is particularly significant as patients treated at Harefield Hospital come from a large geographical area.
Conclusion: Telephone follow up is an effective way of monitoring progress post PCI and is also well accepted by patients. Due to its success patients annual follow up now alternates between clinic visits and telephone appointments. In addition this change in practice has had a minimal impact on nursing time and has enabled clinic appointments to be utilised for patients with on going symptoms or new problems.

233 Nurse-led assessment of quality of life in patients undergoing coronary angiography and interventions

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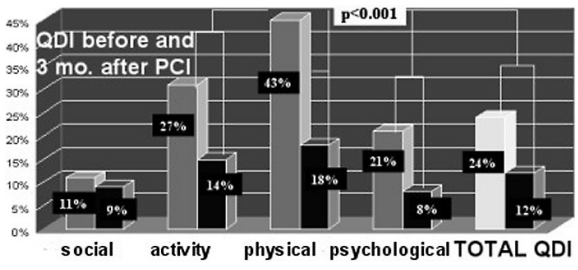
Percutaneous coronary interventions (PCI) are a routine modern treatment of coronary disease. The quality of life (QoL) of patients (pts) undergoing PCI, however, need not reflect the objective benefit of the procedure. We have introduced a questionnaire-based assessment of quality of life by nurses before and 3 months after PCI to detect possible changes in the self-assessment of health status.
Methods: We studied 96 pts undergoing planned coronary angiography (34%women, 63% post-infarction, age 59±9), of whom 79% proceeded to PCI and 3 to bypass grafting. QoL was measured using visual analog scale (VAS), Spitzer test and own multifactorial questionnaire (MQ) assessing physical and psychological well-being and total and social activity, with outcome summarized as QDI - quality decrease index (100% scoring worst and 0%-best).
Results: The acceptance of invasive procedures was high-93%. Self-assessmentof health after invasive procedures improved in 86% of pts without significant disease, 89% of pts with 1-2 vessel disease but only in 70% of those with 3-vessel disease($p<0,05$). QoL measured on VAS improved from 43% to 55% after angiography ($p<0.01$) and from 46% to 64% after PCI ($p<0.001$). Spitzer test detected the improvement in categories: health and depression, but not in: support, activity, daily life. QDI fell from 24% to 12% after PCI due to improved activity, physical and psychological but not social component (see figure).



Components of Quality Decrease Index.

Conclusions: Patients undergoing planned PCI have high level of acceptance of the procedure and benefit significantly according to QoL measured with 3 independent tools. 3-vessel disease patients derive the least improvement whereas angiography with no need for further PCI is as "healing" as PCI in patients with 1 or 2-vessel disease.

234 Transthoracic versus transoesophageal cardioversion of persistent atrial fibrillation: nursery assistance

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Background: Transthoracic electrical cardioversion (EC) with biphasic waveform shock which shows a higher success rate than monophasic and requires lower energy to deliver, has been recently used in patients (pts) with persistent atrial fibrillation (AF) and flutter (AFl). Recently a new transesophageal approach (TE), which uses a dipole between thoracic surface and oesophagus, has been introduced, with even lower energies and high success rate.
Aim: Aim of the study was to compare TE versus transthoracic EC in pts with persistent AF. Were considered: 1) sinus rhythm restoration, 2) delivered energy, 3) tolerability of the procedure, 4) time required of nursery assistance, 5) incidence of complications.
Method: Fourty-four pts (mean age 66 ± 8 ys) with AF (34 pts) and AFl (10 pts) were randomized to TE EC (20 pts, GR.A) and transthoracic EC (24 pts, GR.B). A biphasic waveform shock (Medtronic Physio-Control Lifepak) was delivered in both groups. Mean arrhythmia duration was 2.4 ± 1.2 months. Pts, after proper anticoagulation and without contraindications to the procedure, were submitted to mild sedation with i.v. midazolam without anaesthesiologic assistance in GR.A, and deeper sedation with the assistance of an anaesthesiologist in GR.B.
Results: Sinus rhythm restoration was achieved in 19/20 (95%) pts in GR.A and in 20/24 (83%) in GR.B ($p<0.05$). Delivered energy was 40 ± 10 J in GR.A and 70 ± 20 J in GR.B. When applying a scale 1 to 4 (from absent to untolerable chest discomfort), mean patient tolerability was 1 in GR.A and 3 in GR.B. Mean times required for nursery assistance are reported in table 1. No complication occurred in both groups.

Table 1

	Procedure set up	Procedure carrying out	Patient preparation	Patient stabilization	Total time
Gr A	15 ± 5 m'	5 ± 3 m'	12 ± 3 m'	5 ± 3 m'	37 m'
Gr B	20 ± 10 m'	10 ± 4 m'	15 ± 4 m'	20 ± 10 m'	105 m'
p	ns	<0.01	ns	<0.01	<0.001

Conclusions: TE EC may be considered as an effective technique for AF and AFL interruption, does not show any complication, is well tolerated, does not require the presence of the anaesthesiologist and requires a nursery assistance time significantly shorter than transthoracic EC.

FOLLOW-UP IN THE PACEMAKER AND IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR ERA: OLD AND NEW ISSUES

244 Congenital atrioventricular block: long-term prognosis

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Purpose: Congenital complete atrioventricular block (CABc) has variable prognosis, determined by Stoke-Adams (SA) attacks, existing, however, some controversy concerning the indications of pacemaker implantation. We investigated its long-term evolution, studied its predictive factors of mortality or SA attacks and confirmed the reasons for pacemaker implantation.
Methods: We studied patients (pts) with CABc according to the definition proposed by Yater, without associated structural cardiopathy. We analysed clinical, laboratorial and echocardiographic variables along 12±6 years.
Results: Of 41 cases identified, 5 were diagnosed in utero (mean: 29 weeks), 3 as neonates (mean: 15.3 days), 14 as children (mean: 6.6 ± 4.6 years) and 19 as adults (mean: 29.2±8.5 years). Age at last follow-up was 32.4±19.1 years. Twenty-six (63.4%) pts implanted a pacemaker at a relatively late average age of 27.9±18.2 years, significantly lower for CABc diagnosed before the age of 1 year (7.4±15.6 vs 34.0±14.2 years; $p<0,05$). Reasons for pacemaker insertion were: syncope (7 cases), low heart rate (HR) for age (4 cases), heart failure (4 cases), pauses > 3 seconds (2 cases), ventricular arrhythmias (2 cases), heart failure plus syncope (1 case), heart failure plus ventricular arrhythmia (1 case), HR<40 bpm plus syncope (1 case) and no apparent cause (3 cases). Three pts had a re-intervention and one patient had a superior vena cava obstruction.
Syncope of SA type occurred in 8 pts (19.5%) and 11 (36.6%) pts were in NYHA class II-III. Only in 4 pts, those symptoms occurred before the 15 years of age. Ten pts had a change of CABc into a lower degree of block, in rest ECG or in exercise tests. One of these pts had neurocardiogenic syncope and 3 implanted a pacemaker. Twenty-four percent of pts had a decrease in HR with age. Mortality was 0%. The predictors of SA attacks were a lower HR at diagnosis (50.1±11.9 vs 43.5±3.1 bpm; p=0.01) and a lower % peak/predicted HR (for age) in stress test (62.1±16.1 vs 46.8±12.5%, p=0.03).
Conclusions: CABc, in our population, caused a non despicable frequency of functional disability and potentially fatal syncopal episodes, related to basal HR and with its response to exercise. Pacemaker insertion was relatively high, related to symptoms and to HR. Prognosis was equally good in the group without a pacemaker as in the pacemaker group.

245 Pacemaker longevity: are we getting our moneys worth?

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Background: Pacemaker manufacturers provide projections on pulse generator(PG) longevity. The purpose of this review was to compare the calculated longevity(CL)to the actual longevity(AL).
Methods: Patients(pts) who had a PG explanted between 1998-2003 at the Grey Nuns Hospital were included. The cell capacity (in ampere-hours) and the static (inhibited) current drain (SCD) for each PG model was obtained from the manufacturer. The programmed parameters were collected for each pt at each clinic visit. The total current drain (TCD) between two clinic visits was determined by summing the SCD with the active current drain calculated from the voltage, pulse duration, lead impedance, operating cell voltage, mean pacing rate and percent pacing. The mean current drain during the entire implanted life of each PG was calculated by using the TCD and the time between two clinic visits. This value together with the total cell capacity of each PG was used to determine the CL for each PG and then compared to the AL(the time in yrs. between implant and explant). PG replacements done for reasons other than battery depletion were excluded.
Results: 124 pts - M = 73 (58.9%); F = 51 (41.1%); Age Mean 75.5 $\pm$ 1.1 (SEM) yrs - were included. The distribution of the pacing modes were: AAIR = 6 (4.8%); VVI = 10 (8.1%); VVIR=22 (17.7%); DDD=25 (20.2%); DDDR = 36 (29.0%); VDD = 10 (8.1%). The manufacturers included were: Guidant/Intermedics = 70 devices (56.4%); Medtronic = 24 (19.30%); St. Jude Medical = 23 (18.5%); Vitatron = 7 (5.6%). The mean CL was 8.64 $\pm$ 0.28 yrs with the AL being 7.29 $\pm$ 0.26 yrs. The PGs lasted a mean of 1.34 $\pm$ 0.25yrs less than expected. The shortfall in expected longevity appeared to be greater for dual-chamber devices (1.44 $\pm$ 0.31yrs) compared to single chamber devices (0.98 $\pm$ 0.50yrs) although the difference did not reach statistical significance.
Conclusion: There appears to be a significant discrepancy between the CL (based on the available cell capacity together with the actual output parameters of PGs) and the AL. These findings confirm that battery depletion occurs earlier than expected and suggests that the current drain expended for other ancillary functions may be considerable. Another factor involved in this discrepancy may be the pre-implantation SCD between the times of manufacture and implant. Vigilance with programming of outputs, modes, sensors, heart rates and ancillary functions (where necessary) based on clinical indications could potentially extend PG longevity and postpone or obviate the need for costly repeat surgery with it's attended (small but definite) risk of complications.

246 Mammography in women with the implanted pacemaker

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Purpose: Routine cardiologic check-ups revealed that patients with implanted pacemakers rarely undergo mammography. The purpose was to evaluate selected aspects of mammography in women with pacemakers compared to controls.
Methods: The study evaluated the questionnaires and mammograms of 42 women with the implanted pacemaker-group 1 (average age-60, mean 65.6 months after implantation- examinations were conducted in cooperation with the cardiologic center) and of 150 women (average age-55) constituting the group 2 (control) diagnosed in the oncological center. In 61.9% patients, pacemaker was typically implanted under the pectoral muscle, in 26.6%- under its fascia; 9.5% underwent cosmetic surgery. The questionnaires contained questions about previous breast examinations, fears related to mammography. In group 1 ECG was performed before and after mammography.
Results: In group 1, only 16.7% women were earlier subjected to mammography. In control group, 80.6% underwent earlier mammography. On mammography, 42.9% group 1 patients complained of: compression discomfort-19.0%,pain -23.8%. The location of complaints were: 4.8%-one mammary gland, 21.4% - both, 16.6%- the pacemaker's bed. General symptoms in group 1: chest pain, dizziness, arrhythmia-one case each. Various fears before planned mammography were reported by 47.6% in group 1 and 98.0% in group 2. The most frequent anxiety was uncertainty about the diagnosis, (40.4% vs 94.6%), pain on breast compression (28.6% vs 68.7%), exposure to radiation (16.6% vs 80.0%); additionally the group 1 patients feared the pacemaker's damage (31.0%).
In group 1, 97.6% patients have claimed that the cardiologist's supervision during mammography made them feel safer; 90.5% plan to undergo diagnostic mammography regularly.
The women with pacemakers had to have exposure parameters on the pacemaker's side set manually. On interpretation, the pacemaker was visible in one mammographic projection in 23 cases (54.8%); only in 6 cases it impeded the evaluation of upper outer quadrant of the breast.Postmammography ECG showed no disorders of heart rhythm or pacemaker's functions.
Conclusions: 1.Pacemakers may be the factor limiting prophylactic mammography; the main cause of rarer mammography is the fear of pacemaker's damage. 2.Patients with pacemakers examined with the cardiologist show lesser anxieties before planned examinations compared to those examined in the oncological center.
3.Mammography in patients with pacemakers is safe and only in rare cases the pacemaker significantly reduces the diagnostic value of the examination.

247 Elderly recipients of implantable cardiovertor defibrillators: does survival justify implantable carioverter-defibrillator implantation?

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Indications for implantation of ICDs are increasing and the elderly constitute the most rapidly expanding segment of the general population. Further, the most common substrate for malignant cardiac arrhythmias, coronary artery disease and heart failure, are more common in the elderly, and these patients are therefore being increasingly referred for ICD implantation. The purpose of this study was to determine whether elderly patients are less likely to survive after ICD implantation when compared to the young. A survival analysis is presented of 534 consecutive patients who underwent ICD implantation in our hospital (first system) between May 1990 and September 2003. Patients 75 years of age and above are compared with those under 75.
Results: The overall follow up was 33.5$\pm$32.8(Mean$\pm$SD) months. A total of 92 patients (17.2% of the entire group) were identified as 75 years or older at the time of implantation. Their mean age was 77.8$\pm$2.6 years (85.5% male) compared with 60.2$\pm$1 years (83.2% male) in the young group. Elderly and young matched closely for left ventricular ejection fraction (33.4$\pm$13.1% vs 36.6$\pm$15.9%) and an ischaemic aetiology (82.6% vs 80.0%). During the study period, there were 14 deaths (15.2%) in the elderly group and 65 deaths (14.7%) in the young group. Survival curves determined that there was no difference between the groups in the probability of being alive at 12, 24 and 36 months: 88.9%, 79.1% and 79.1% for the elderly and 88.4%, 77.9% and 69.4% for the young. Predictors of a better survival in the elderly group were: male sex, left ventricular ejection fraction, VT rather than VF as presenting arrhythmia, non-ischaemic aetiology, no therapy from ICD on follow up, and not on amiodarone at presentation.
Conclusion: Medium term survival in the elderly receiving an ICD is identical to a younger population and justifies their use in this group.

248 Long-term follow-up after implantation of an additional transvenous pace sense lead in patients with an implantable carioverter-defibrillator

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Purpose: No information is available about the clinical outcome after implantation of an additional transvenous pace-sense lead (add. P/S) in patients (pts) with an ICD. The follow up (FU) of pts receiving an add. P/S lead at our institution due to various complications was investigated.
Methods: 151 P (male 125, age 55$\pm$14 y, LVEF 48$\pm$18%, CAD in 86 [57%], DCM in 24 [16%], ARVCM in 11 [7%]) were implanted with an ICD in combination with a transvenous pace/sense and defibrillation lead (HV-P/S) between 1989 and 2002 and received an add. P/S during FU. Reasons for implantation of the add. P/S were: oversensing 83 [55%], inacceptable sensing/pacing threshold/impedance 51 [34%], visible insulation defect 7 [5%], parameters at implantation of HV-P/S inacceptable 6 [5%], others 4. First defects of the HV-P/S were documented 41$\pm$32 months after implantation. The FU of these pts was studied retrospectively and was ended in July 2003. Statistical analysis was done using Kaplan-Meier survival curves.
Results: The average FU after implantation of the add P/S was 43$\pm$27 months. 117 pts [78%] remain implanted (92$\pm$32 months after first ICD implantation). 22 pts died cardiac related. Two pts had a heart transplantation. After a FU duration of 23$\pm$23 months 43 pts [29%] experienced lead-related problems after implantation of the add P/S: oversensing 23 [54%], insulation defect only 3 [7%], fracture 1 [2%], system infection 4 [9%], defect of HV-P/S 6 [14%], others 6. The event free cumulative survival after add. P/S implantation after 1, 2 and 5 years was 87%, 81% and 62%, respectively. The only significant difference between pts who experienced a lead problem and those who did not was the add. P/S model [p 0,018]. 14 [33%] pts received a new add. P/S, 13 [30%] a new HV-P/S, insulation was repaired in 7 [16%], re-positioning of the add. P/S in 3 [7%], a new epicardial P/S in 1 and others in 6.
Conclusions: Implantation of an add. P/S in case of failure of an integrated defibrillation lead is safe. However, it is associated with a substantial rate of complications during FU. The estimated event free cumulative survival is only 62% after 5 years. If the implantation of an additional HV-P/S or a new HV-P/S after explantation of the old one is the better way of treatment has to be investigated.

249 Impedance measurements from implanted devices provide automated prediction of CHF hospitalization

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Introduction: 65% of ICD patients (pts) and all CRT pts suffer from heart failure (HF), and many of them have repeated hospitalizations due to pulmonary volume overload. There is a significant clinical need for these implantable devices to also offer ambulatory diagnostic information to help guide HF medical therapies and reduce hospitalization. The MIDHeFT study investigated the ability of intra-thoracic impedance (Z) measured from the implanted device to predict CHF admission.
Methods: Thirty-three HF pts in NYHA functional class III-IV were implanted with a special pacemaker in the left pectoral region and an ICD lead in the right ventricle (RV). Z was measured between the RV coil electrode and the pacemaker case. Averaging was used to remove short-term impact, such as from cardiac and respiratory activities, on Z. The emergency room (ER) records were reviewed for self-reported time when pts first noticed worsening symptoms prior to ER visit. Retrospectively, an automated algorithm to detect impending admission from changes in Z was developed and performance was evaluated.
Results: During a mean follow-up of 18±8 months, 10 pts had a total of 26 hospitalizations for worsening HF, including 25 due to fluid overload and one due to dehydration. In all congestive episodes, Z gradually decreased before admission, over a mean duration of 14±7.7 days ($p<0.0001$) and a total reduction of 11.3±6.0% ($p<0.0001$). For the 18 admissions with available symptom onset data, the decline in Z also preceded the onset of symptoms by a mean lead-time of 10.3±8 days ($p<0.0001$). Using a single threshold for all patients, the algorithm detected 76% of the eligible congestive admissions with a median of 17 days of early warning. One false warning occurred for every 322 days of pt monitoring. For the dehydration episode, Z increased 8% over the 3 days before admission.
Conclusions: Intra-thoracic impedance from the implanted device predicts hospitalization for worsening heart failure with a high sensitivity and low false alarm rate. When combined with ways to notify patients and/or clinicians, an advanced-warning system may be feasible and enable clinicians to initiate early medical therapy and potentially reduce/prevent HF hospitalizations. Further studies are needed to confirm these findings and demonstrate clinical outcome in a larger population of HF patients with implantable devices.

THREATENING COMPLICATIONS WITH SOPHISTICATED DEVICES

250 The Prospective Evaluation Of Pacemaker Lead Endocarditis (PEOPLE study): 12 months incidence and risks factors of pacemaker-related infections

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The PEOPLE Study is a multicenter prospective study designed to assess the incidence and the risks factors of infectious complications occurring after Pacemaker (PM) and ICD implantations. In 47 centres, 6319 consecutive patients (mean age = 73±13, 3771 males), implanted from 01-01-2000 to 31-12-2001 have been included and followed during 12 months.
All infectious complications were collected and their occurrence related to several factors as: operator experience, implantation conditions and duration, type of system implanted, patients characteristics, venous access route, presence of temporary pacing wire, occurrence of other early complications such as haematoma and lead displacement as well as prophylactic use of antibiotics. Implanted devices were the following: 5866 PM (1960 single lead, 3789 dual lead and 117 multisite pacing systems) and 453 ICD (275 single lead and 178 dual lead systems). The procedure was: a first implantation (n=4461), a pulse generator or lead replacement (n=1858). Re-intervention before discharge occurred in 91 patients (84 PM, 7 ICD). At 12 months follow-up definite PM related infections were reported in 42 patients (0.68%, [0.47-0.89]). PM exteriorization and impending exteriorization occurred in 7 and 24 additional patients respectively. Definite or possible infection occurred in 73 patients (1.19%, [0.92-1.46]). Definite infection was significantly correlated with fever [RR=5.8 (2.0-16.9)] and temporary pacing wire before implantation [RR=2.5(1.1-5.1)], first implantation [RR=0.5 (0.2-0.8)], early re-intervention [RR=11.2 (5.5-22.8)] and antibiotic prophylaxis [RR=0.4 (0.2-0.8)]. ICD, dual chamber PM, vein access and used of drain were not associated with infection.
Conclusion: In our population which is representative of the PM and ICD implantations in France, the incidence of definite infection was 0.68% at 12 months. Risks factors of PM related infection were: fever, temporary pacing wire, re-intervention (early or elective PM replacement) and the absence of antibiotic prophylaxis.

251 Pacing and defibrillating leads transvenous removal: results and complications in a single-centre experience

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During last 20 years, the transvenous techniques for the removal of chronically implanted Pacing (PL) and Defibrillating Leads (DL) have achieved an high success rate. However the procedures are often complex and are associated with a small but significant risk. The experience of the operators and the availability of different approaches for difficult cases seems to affect both results and complications.
Purpose: this paper presents the results of more than ten years experience in the field of transvenous extraction procedures performed in a single Italian center.
Materials and methods: Since December 1989, we managed 797 patients (581 men, mean age 66.4 years, range 6-93) with 1291 leads (mean pacing period 64 months, range 1-336). 1189 were PL (741 ventricular, 437 atrial and 11 coronary sinus leads), 102 were DL (86 ventricular, 5 atrial and 11 SVC leads). The indications to removal were: 33.9% class I, 66.1% class II. We performed mechanical dilation using the Cook Vascular extraction kit and other intravascular tools, if necessary (Catchers and Lassos, Osypka). In case of free-floating leads or when the removal through the implant vein was not possible (difficult exposed leads), since 1996 we developed a new approach, using the internal jugular vein (Jugular Approach-JA).
Results: Removal was attempted in 1277 leads; among these 1109/1142 PL (97.1%) and 100% DL were removed. In 14 PL (1.1%) the transvenous mechanical removal technique was not applicable. After the introduction of JA, 1056 leads were submitted to removal and 1046/1056 (99%) leads were removed in this period. The JA was performed in 36 free-floating and 127 difficult exposed leads allowing the removal of 151/153 (98.7%) leads. Before the introduction of JA (1996) the success rate had been 84% (199/237 leads). Major complications in the overall experience were: 3 cardiac tamponade (with 1 death) and 2 chronic PL dislodgement, without complications directly related to JA.
Conclusions: The success rate and the incidence of complications are highly affects by the staff experience. The use of the JA, in presence of free-floating or difficult exposed leads, increased safety and success rate.

252 Axillary vein puncture with and without contrast venography for implanting pacemaker and defibrillator leads: a prospective study

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Background: pacemaker (PM) and implantable defibrillator (ICD) leads are usually implanted via subclavian puncture or cephalic venous cutdown. The former may result in subclavian crush, and the latter may be time-consuming. Axillary vein puncture is an alternative that avoids these drawbacks.
Aim: to prospectively evaluate implantation success and risk associated with axillary vein puncture, with and without contrast venography.
Methods: patients addressed for PM or ICD implantation in a single tertiary care centre, in whom axillary vein puncture was chosen as the primary technique. Puncture was guided by injecting diluted contrast dye via an ipsilateral peripheral vein (group A), or without venography using a novel radiological landmark (the lateral intersection between the borders of the second and third rib), followed by contrast injection in case of failure (group B).
Results: 172 patients (110 males, age 75±11 years) were included, with implantation of 1-3 leads per patient. In group A, implantation was successful in 99/106 (93%) patients. In group B, puncture using the radiological landmark (without a venogram) was successful in 43/66 (65%) of patients ($P < 0.001$ compared to group A). Subsequent contrast injection led to successful implantation in 21/23 of these patients, with an overall success rate for the study population of 163/172 (95%). Venous access was achieved after a mean of 10.4±3.2 min of skin incision in group A as compared to 9.4±3.0 min in group B (p=NS). When venography was used, there were a mean of 1.1±0.4 contrast injections (7.6±3.8cc) per patient. Pneumothorax resulted in 2 patients (1% overall), in whom non-contrast guided axillary puncture was attempted.
Conclusion: axillary vein puncture using venography with minimal contrast injection allows safe and rapid introduction of multiple PM and ICD leads, with a high success rate. Non-contrast guided puncture using a novel radiological landmark is successful in a majority of patients, and may be useful in the absence of ipsilateral peripheral vein access, or in case of contrast allergy.

253 Is asynchronous pacing dangerous? Results of a worldwide survey

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The safety of asynchronous pacemaker stimulation, occurring with magnet application or noise reversion mode, is a point of controversial discussion, based only on anecdotal reports. Therefore, a survey was performed to assess the frequency of asynchronous pacing induced ventricular tachyarrhythmias during pacemaker follow up.
Methods: An e-mail questionnaire was sent worldwide to 145 physicians being

active in cardiac pacing. First, active years in pacing and number of follow-ups were asked. Second, they were asked to report all cases in which asynchronous stimulation induced ventricular tachycardias (VT) or ventricular fibrillation (VF) and to comment on this.
Results: 102/145 physicians answered (70%). Pacing experience ranged from 3 to 40 years, mean 20 $\pm$ 8 years (median 20 years). The cumulative experience was 1,974 years. Pacemaker follow-ups performed per year ranged from 50 to 12,000, mean 2,326 $\pm$ 2,082 (median 1,550). Overall 230,305 follow-ups are performed annually.
Induction of ventricular arrhythmias were reported by 34/102 physicians (33%) with a total of 48 cases. 25 of these were due to secondary causes, or clinically not relevant: 14 cases had PVCs or short runs, mostly asymptomatic. 5 were due to anodal stimulation, occurring 20-25 years ago. 5 happend during an acute myocardial infarction, or with ischemia or electrolyte imbalance immediately after cardiac surgery. One patient had spontaneous VTs without stimulation as well.
The remaining 23 cases were classified as major complications. In 13 pts VT/VF was induced. In 4 of these ejection fraction was $<$ 30%, thus being ICD candidates using current criteria. 1 pt. did not survive. To avoid underestimation of serious events, 10 additional cases were included in whom no detailed information was reported. 4 of these occurred 15 to 20 years ago. No cases occurred in the last 7 years.
Conclusion: Asynchronous pacing is safe. However, inducement of a ventricular tachyarrhythmias during asynchronous pacing is possible, but this is extremely rare, and therefore clinically irrelevant. Based upon the experience of the surveys participants, one relevant case of asynchronous pacing induced arrhythmia happens every 85.8 years.

254 Implantable cardioverter defibrillator failure associated with death in the U.S. food and drug administration database

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Purpose: The implantable cardioverter defibrillator (ICD) may be a lifesaving device for patients at risk for sudden cardiac death. ICD failure may result in catastrophic events, including death. The medical community and industry should understand the causes of ICD failure so that they may be prevented. For this reason, we analyzed ICD pulse generator (PG) and lead failures associated with death in the U.S. Food and Drug Administration's (FDA) Manufacturer and User Facility Device Experience(MAUDE) database.
Methods: The ICD database(www.fda.gov/cdrh/maude.html)was searched for death events reported by manufacturers and users worldwide to the FDA between September 1996 and December 2003. Of 230 death events reported, 152 contained information from manufacturers analyses of returned devices(113), data obtained from ICD PG interrogation (110), or both (71). The remaining 77 events were excluded from the study because no device information was available (55),death was related to a procedure(10), or the device was damaged postmortem (12).
Results: Based on the manufacturer's analysis and/or device interrogation, 109 of 152 death events (72%) were associated with defective or malfunctioning ICD PGs(57), leads (40), or both (12). Pulse generator electrical overstress damage, often associated with lead insulation failure (29), component defects(13), and high voltage lead failure (15) were common findings. Manufacturers safety alerts affected 78 devices; 9 were found "out of specification" or exhibited the suspect behavior, including rapid pacing (3), charge time-out with no therapy delivered (2), and lead failure associated with a long terminal pin (5). While a direct causal relationship could not be determined, clinical and device data implicated ICD failure in 55 deaths involving 42(76%)defective leads and 13(24%)malfunctioning PGs. Ten deaths occurred in patients whose PGs were found in the monitor only mode; all involved models that may be disabled by a magnet.
Conclusions: These findings underscore the need for more reliable ICD technology, especially leads. ICD follow-up systems should include new methods that can identify ICD PG or lead defects before they cause adverse clinical events. PG therapy deactivation by a magnet is a feature that should be discontinued; patients with such models should be cautioned. Prospective studies should be developed that assess ICD performance and guide patient management when device problems arise.

255 Implantable cardioverter-defibrillator therapy of short QT syndrome is associated with an inherent risk of inappropiate implantable cardioverter-defibrillator discharges

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Introduction: A congenital short QT-interval constitutes a new primary familial electrical abnormality, which is associated with syncope and/or sudden cardiac death. We report on the performance of ICD therapy in patients with inherited short QT-interval with respect to sensing abnormalities and detection issues.
Methods and Results: In five consecutive patients of two unrelated European families with structurally normal hearts, strong positive family history of sudden cardiac death and excessively shortened QT-intervals ICD devices were implanted for primary and secondary prevention (Atlas VR V-199, n=1, Photon Micro VR-194, n=3, St. Jude Medial Inc, Marquis VR 7230, n=1, Medtroinc Inc.). Mean QT-intervals were 252 $\pm$ 13 ms (QTc 287 $\pm$ 13 ms). Four of five patients experienced 54 $\pm$ 52 days after implantation inappropriate shock therapies for T-wave oversensing despite normal sensing behaviour during intra- and postoperative device testing. In two cases decrease of the R-wave amplitude or an increase of the T-wave amplitude were responsible for the detection of the short coupled T-wave by the automatic sensing algorithm. In one patient revision of the ventricular electrode had to be performed after inadequate shock therapies due to T-wave oversensing after a decrease of the maximal R-wave amplitude $<$ 3 mV. Programming of lower sensitivities and decay delays in 3 of 4 patients prevented further inappropriate discharges.
Conclusions: In patients with a short QT-syndrome and implanted ICD an increased risk for inappropriate therapy is inherent due to detection of short coupled and prominent T-waves. Careful testing of ICD-function and adaptation of sensing levels and decay delays without sacrifycing correct arrhythmia detection is essential.

NEW RISK MARKERS OF SUDDEN DEATH AFTER ACUTE MYOCARDIAL INFARCTION

256 Simple cardiovascular reflex tests in prediction of sudden death after myocardial infarction: which method to prefer?

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Some evidence exists that heart rate (HR) response to simple provocative maneuvers is related to sudden cardiac death (SD) after myocardial infarction (MI). However optimal test has not been determined yet. Aim of this study was to compare prognostic value of different noninvasive reflex tests after MI.
Methods: Four reflex tests were performed in 188 patients on days 4-11 of MI (68% men, age 34-75 years, 93.6% on beta-blockers, without heart failure NYHA IV on the day of tests). Time- and frequency domain HR variability measures were obtained during 5 min at active standing and at bed rest with controlled breathing 6 and 15 per minute. Difference between average maximal and minimal heart rate at first minute of breathing 6 per minute (HRD) and Valsalva ratio (VR) were also calculated. ROC analysis was used to determine cut-off values of studied measures and these values were used in logistic regression analysis.
Results: During follow up for 2.1$\pm$0.8 years there were 9 SDs. Univariate predictors of SD are listed in the table.
HF power $<$65 ms2 during active standing (OR 28.8, 95% CI 4.1-104.2; p=0.0001) and VR $<$1.13 (OR 6.0, 95% CI 1.02-34.3; p=0.04) were independent predictors of SD. Combination of these parameters increased OR to 34.9 (95% CI 6.7-181.6; p$<$0.001), positive predictive value to 50%.

Univariate predictors of sudden death

Test	Parameter	Odds ratio (95% CI)	Positive predictive value
Standing	PNN50 $<$2.5	9.6 (1.2-79.7)	8.5
	Total power $<$1021 ms2	4.2 (1.01-17.8)	10.6
	LF power $<$229 ms2	8.1 (1.6-41.6)	11.1
	HF power $<$65 ms2	23.1 (4.9-108.3)	29.4
Breathing 15/min	PNN50 $<$2.3	10.6 (2.5-44.8)	17.6
	LF power $<$129 ms2	9.6 (1.9-47.9)	13.2
	HF power $<$111 ms2	7.9 (2.0-31.6)	17.2
Breathing 6/min	HRD $<$3.36	4.7 (1.2-18.4)	11.6
Valsalva maneuver	VR $<$1.13	7.8 (1.6-39.0)	11.5

Conclusion: Among simple noninvasive reflex tests in survivors of acute MI mostly on beta-blockers and without severe heart failure active standing with calculation of HF power seems to be preferable method for prediction of SD after MI. Its predictive value may be enhanced by combination with Valsalva ratio.

257 Heart rate variability and mode of death in chronic heart failure

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Purpose: Progressive pump failure is the leading cause of death in patients with chronic heart failure (CHF), while sudden death is responsible for 30 to 50% of overall mortality. Variables capable to identify patients at different risk of sudden or non-sudden death could be useful for making clinical decisions.
Methods: We analyzed 24-hour heart rate variability (HRV) in 330 consecutive CHF patients in sinus rhythm admitted between 1991 and 2001 and prospectively evaluated under optimized therapy at the Heart Failure Unit of the Scientific In-

stitute of Montescano. Indexes derived from time domain, spectral domain and fractal analyses of 24-hour automatic HRV were evaluated. Data from clinical assessment, 2-D echocardiography, right heart catheterization, exercise test, blood biochemical examination and arrhythmia pattern were analyzed. Patients were followed-up for 3 years (median 34; range 1-36 months).
Results: Two simple multivariate models (Cox proportional hazard regression), both including 24-hour spectral indexes, were able to identify respectively patients at higher risk of progressive heart failure + urgent transplantation and sudden death. Depressed power of night-time HRV (< 509 ms2) below 0.04 Hz (VLF), high pulmonary wedge pressure (PWP > 18 mmHg) and low left ventricular ejection fraction (LVEF < 24%) were independently related to death for progressive pump failure, while the reduction of power between 0.04 and 0.15 Hz at night (LF < 20 ms2) and increased left ventricular end systolic diameter (LVESD > 61mm) were linked to sudden mortality.
Conclusions: Automatic spectral analysis of 24-hour HRV provides independent risk indexes related to mode of death in sinus rhythm CHF patients. The results of the present study well integrate with the current debate created by the practical implications of the results of the MADIT-II trial. The emerging variables should be considered in the design of future cost-effectiveness studies about identification of patients likely to benefit from ICD implantation.

258 Beat-to-beat variability of repolarisation is increased before sudden arrhythmogenic death in dogs with remodelled hearts

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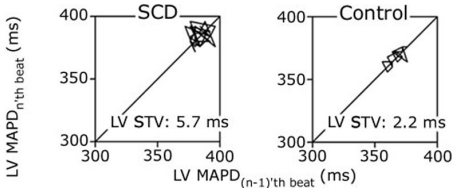
Introduction: The increased proarrhythmia in dogs with chronic, complete AV block (CAVB) has been explained by ventricular remodelling causing a decrease in repolarisation reserve. Beat-to-beat variability of repolarisation (BVR) has been suggested to quantify repolarisation reserve, in which a high BVR represents a diminished reserve and a larger propensity for repolarisation-dependent ventricular tachycardias. A small subset of CAVB dogs (11%) suffer sudden arrhythmogenic death. When repolarisation defects are the basis for SCD, we expected that SCD dogs will show an increased BVR as compared to matched control CAVB dogs.
Methods: Retrospectively, from a population of >200 CAVB dogs, 2 groups were chosen: 8 dogs that died suddenly (SCD; 7±2 weeks AVB) and 8 control dogs (non-SCD; 12±3 weeks AVB). All these dogs had undergone an extensive electrophysiological test under anaesthesia where ECG and biventricular endocardial monophasic action potentials (MAP) were recorded. Beat-to-beat variability of repolarisation from 30 consecutive beats was quantified using Poincaré plots where short-term variability (STV) was calculated as the width of the plot. RR and QT intervals and durations of left (LV) and right ventricular MAP were measured every 5 minutes and averaged over a half-hour period.
Results: Short-term variability of the LV MAP (LV STV, Figure) was significantly higher in dogs that later died suddenly (5.1±2.7 vs 2.5±0.4, P<0.05). STV of the QT interval (6.3±3.2 vs 4.6±1.7) as well as temporally averaged electrophysiological parameters were unable to differentiate the two groups.



Poincaré plots.

Conclusions: CAVB dogs prone to SCD display a larger beat-to-beat variability of repolarisation, indicative for a reduced repolarisation reserve.

259 Phase-rectified signal analysis is superior to left ventricular ejection fraction in prediction of mortality after acute myocardial infarction

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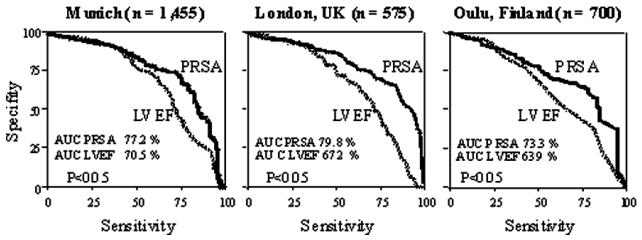
Introduction: Phase-rectified signal analysis (PRSA) is a novel signal processing algorithm which is able to detect periodicities in noisy non-stationary time series, e.g. longtime records of the human heart beat. Aim of this study was to blindly test the hypothesis that (1) PRSA is superior to LVEF and (2) to standard heart rate variability (HRV) in prediction of mortality after acute MI. Superiority was defined as a significantly larger area under the receiver-operator curve (AUC).
Methods: PRSA was developed in an open training sample including 1,455 post-MI patients. Subsequently, PRSA was blindly applied to the populations of two large and independent post-infarction trials, the St George's Hospital post-infarction database (SGHPID, London, UK) and the Multiple Risk Factor Analysis Trial (MRFAT, Oulu, Finland) including 575 and 700 consecutive post-MI patients, respectively. Statistical analyses were performed in two independent study centres in London and Oulu, respectively. Primary endpoint was total mortality.
Results: In the training sample as well as in both validation samples PRSA was highly significantly associated with the primary endpoint. In all three collectives, PRSA yielded significantly larger AUC than LVEF and standard HRV (figure, p<0.05 for all differences).



Areas under the curves for PRSA and LVEF.

Conclusion: PRSA is superior to LVEF and standard HRV in prediction of total mortality after acute MI. Our findings might have great clinical implication for post-MI risk stratification and prophylactic ICD implantation.

260 Sudden death in non-ischaemic cardiomyopathy – risk stratification with the HFSS score

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Introduction: Sudden death (SD) is a major problem in patients with non-ischemic cardiomyopathy. Prophylactic measures (ICD) are not routinely used because there are no established markers of risk stratification in this patient population.
Methods: We analyzed retrospectively data of 747 patients, which were submitted for elective heart transplantation to our center in the years 1989-2003. The Heart-Failure-Survival Score (HFSS) was calculated according to Aaronson et al. and patients were divided according to the presence of coronary artery disease (CAD-/+) in 3 risk groups: high risk (score <7,2), n= 39-/161+, medium risk (score 7,2-8,09), n= 114-/114+ and low risk (score >8,1), n= 242-/77+. Survival was calculated with Kaplan meier curves (table).

risk group	SD 1 year CAD-	SD 5 year CAD-	SD 1 year CAD+	SD 5 year CAD+
high	32% *	60%*	15%	32%
medium	8%	21%	12%	25%
low	4%	16%	4%	25%
p	*<0.01 vs other	ns*<0.01 vs other	ns	ns

Results: The risk of SD increased continuously over time. HFSS <7,2 definied a subgroup of patients with non-ischemic cardiomyopathy and an especially high sudden death risk. In contrast HFSS in CAD patients did not differentiate between different SD risk groups.
Conclusion: HFSS could be used for risk stratification of SD in patients with non ischemic cardiomyopathy, but is not useful in ischemic patients. ICD studies in patients with non ischemic cardiomyopathy should consider especially the HFSS high-risk group.

261 Determinants of recurrent ventricular arrhythmias or death in 300 consecutive patients with ischaemic heart disease who experienced aborted sudden cardiac death

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Introduction: Out of hospital sudden cardiac death is the first sign of coronary heart disease in 70% of patients. Survivors of life-threatening ventricular arrhythmias (VA) are at increased risk of death and recurrences. We evaluated the relation between clinical characteristics and the incidence of recurrent VA or death during long-term follow-up in a cohort of 300 consecutive patients (pts) with ischemic heart disease (IHD) who had survived an episode of aborted sudden death.
Methods: From 1994 until 2002,300 consecutive survivors of life-threatening VA with IHD (249 male, age 64±13 yrs) were included in a standardized screening and evaluation protocol (echocardiography, coronary angiography, electrophysiological (EP)study) in order to optimize patient-tailored therapy (revascularization, ICD implantation, catheter ablation, anti-arrhythmic drugs). Follow-up was performed via outpatient clinic visits and chart review. Multivariable (MV) Cox' regression analysis with backward deletion (cut-off at p<0.25) of the clinical variables was performed to determine the relation between these clinical variables at baseline and the incidence of recurrent VA and/or all cause mortality.
Results: The presenting arrhythmia was VT in 156 (52%) pts and VF in 144 (48%)

pts. VA was inducible in 226 (75%) pts during EP study. Revascularization was performed in 78 (26%) pts and an ICD was implanted in 216 (72%) pts. During follow-up (median 27 months) 37 (12%) pts died and 88 (29%) pts experienced a recurrence. After MV regression analysis the following clinical variables proved to be independent predictors for the composite of recurrences and all-cause mortality: advanced age (adjusted Hazard's Ratio (HR) 2.0;1.2-3.3), history of heart failure (HR 1.8;1.2-2.6) and amiodarone use (HR 3.1;2.1-4.6). VT as presenting arrhythmia was an independent predictor for all cause mortality only (HR 2.4;1.2-4.8). Moreover a decreased risk of recurrences was determined by beta-blocker use (HR 0.5;0.4-0.8) and coronary revascularization (HR 0.3;0.2-0.6).
Conclusion: In a cohort of 300 consecutive survivors of aborted sudden cardiac death the incidence of recurrent VA and death is dependant on pts age, history of heart failure, use of amiodarone and VT as presenting arrhythmia, whereas coronary revascularization and use of beta-blockers improve the outcome.

INOTROPIC INTERVENTION: NEW MECHANISMS

275 The Ca^{2+}-sensitizer levosimendan vesrsus dobutamine on oxidative stress, brain natriuretic peptide and pro-inflammatory cytokine levels in patients with advanced decompensated heart failure

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Purpose: Brain natriuretic peptide (BNP) levels are both a diagnostic and a prognostic tool for heart failure and a guide to effective pharmacologic therapy. In addition, elevated circulating levels of lipid peroxidation and pro-inflammatory cytokines predict adverse mortality outcomes in patients with heart failure. The purpose of this study was to investigate the effect of levosimendan, a new inotropic and vasodilator drug versus dobutamine on the levels of BNP, interleukin-1β (IL-1β), interleukin-6 (EL-6), TNF-α, and malondialdehyde (MDA), a marker of lipid peroxidation and oxidative stress in patients with severe decompensated heart failure.
Methods: 29 consecutive patients (22 males and 7 females), mean age 70.5 ± 9.85 years, with decompensated heart failure on standard medical therapy with diuretics, ACE-inhibitors, digitalis, beta-blockers, aldosterone inhibitors, were randomized to receive either a 24h infusion of levosimendan (n =15) (Group A) or dobutamine (n=14) (Group B). Blood samples were drawn for BNP, IL-6, IL-1b, TNF-α and MDA at baseline, 48h and 5 days post infusion.
Results: Levosimendan therapy produced a significant reduction in BNP levels at 48h and 5 days compared to dobutamine, (Group A, 1136.3±93.7, 744.1±100, 446±119.3, Group B, 1581.4±371.2, 1437.4±370, 1801±550.1 at baseline, 48h and 5 days respectively, p=0.025, 48h p=0.037, 5days) (Mann-Whitney test). IL-6 values were similar at the baseline (8.6±1.5 and 7.9±1.12 in Group A and B, respectively) whereas decreased after 5 days to 4.8±1.3 in Group A versus 13.08±2.7 in Group B (P=0.003) (Mann-Whitney test). MDA levels were significantly lower after 5 days treatment with levosimendan compared to dobutamine treatment (Group A, 3.05±0.27, 2.3±0.22, Group B, 3.2±0.36, 3.7±0.5 at baseline and 5 days respectively, p=0.012) (Mann-Whitney test). TNF-a and interleukin 1b levels did not differ between groups both at baseline, 48h and 5 days (p=ns). Furthermore, BNP and MDA levels in patients of group A were significantly reduced overtime from 48 to 5 days compared to baseline values (Repeated Measures Analysis of Variance).
Conclusion: Treatment with levosimendan in advanced decompensated heart failure exerts a beneficial hemodynamic, anti-inflammatory and antioxidant effect. These findings may give an insight into the favorable impact on mortality that levosimendan appears to have in published multicenter trials.

276 Acute haemodynamic effects of levosimendan after primary percutaneous coronary intervention in patients with severe left ventricular dysfunction

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Background: Positive inotropic agents may be associated with increasing myocardial ischemia or malignant arrhythmias. Levosimendan, a new calcium sensitizer, with its little effect on myocardial oxygen demand is better tolerated by patients with ischemic cardiomyopathy.
We sought to evaluate the acute haemodynamic effects of levosimendan on left ventricular (LV) function in patients with a severe LV dysfunction undergoing primary percutaneous coronary interventions (PCI) for an acute myocardial infarction (AMI).
Methods: 34 consecutive AMI patients (mean age 58±4 years; 21 males, 13 females) with severe LV dysfunction (EF£30%) were randomised to a 24h infusion of levosimendan (10 minutes bolus with 12 mcg/kg/min followed by 0.1 mcg/kg/min) or with placebo immediately after a primary PCI. Evaluation of haemodynamics with right heart catheterisation were performed at baseline and after bolus.
Results: Procedural success (TIMI 3 flow) was achieved in all patients (26 anterior, 3 lateral and 5 inferior AMI). At baseline, mean values of heart rate (73±12/min), PCP (22±6 mmHg), CI (1,7±0.4/min m^2), SVR (1467±356 dyn sec/cm^5) and PVR (276±151 dyn sec/cm^5) were comparable between groups. After bolus, patients with levosimendan (n=18) showed a significant decrease of PCP (from 24±5 to 20±5; p=0.008) and a significant increase of CI (from 1.8±0.4 to 2.2±0.6; p=0.004) resulting in a significant decrease of SVR (from 1364±331 to 1076±269; p=0.01). On the other hand, no statistically significant changes have been observed in the placebo group (n=16).
Conclusions: Levosimendan, given intravenously after a PCI procedure in AMI patients, is safe and efficacious and significantly improves LV function compared to placebo.

277 Vitamin C enhances inotropic response to beta-adrenergic stimulation in patients with increased oxidative stress after anterior myocardial infarction

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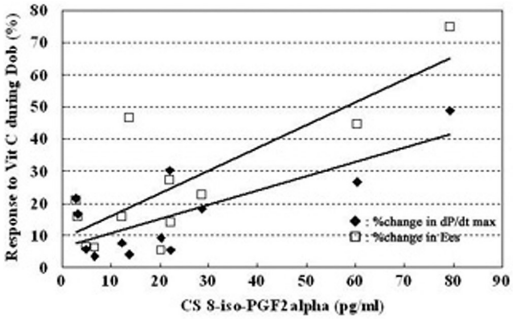
Background: Increased oxidative stress may contribute to the myocardial and subsequently left ventricular (LV) dysfunction and remodeling in patients after anterior myocardial infarction (MI). We evaluated the effects of an antioxidant, vitamin C on β-adrenergic responsiveness in this population, simultaneously assessing their oxidative stress.
Methods: 12 patients with first time anterior MI (LV ejection fraction; 42±1%) were instrumented with manometer-tipped LV conductance catheter four weeks after the onset of MI. Oxidative stress were assessed by plasma 8-iso-prostaglandin F2alpha levels of coronary sinus (CS 8-iso-PGF2alpha). Indices of LV contractility (dP/dt max, the maximum first derivative of LV pressure, Ees; the slope of end-systolic pressure-volume relation) were measured in response to the intravenous infusion of dobutamine (4 μg/kg/min) before (Dob) and during the intravenous infusion of ascorbic acid (Vit C; 2.0 g bolus injection and subsequent 50 mg/min infusion for 10 minutes).
Results: Dob increased dP/dt max (1725±102 to 2884±183 mmHg/s, $p<0.001$) and Ees (2.18±0.42 to 3.34±0.43 mmHg/ml/m^2, $p<0.01$). Addition of Vit C with Dob derived 15±5% increase in dP/dt max (to 3322±243 mmHg/s, $p<0.05$) and 21±6% increase in Ees (to 4.01±0.53 mmHg/ml/m^2, $p<0.05$) over Dob alone. CS 8-iso-PGF2alpha ranged from 2.9 to 79.4 pg/ml independent of LV ejection fraction. The responses of dP/dt max and Ees to Vit C during Dob infusion were significantly correlated with CS 8-iso-PGF2alpha (r=0.77; $p<0.01$, r=0.81; $p<0.01$, respectively) (figure).



Conclusion: The administration of an antioxidant vitamin C enhances the inotropic response to beta-adrenergic simulation in patients with increased oxidative stress after first time anterior myocardial infarction.

278 Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigation Group (DIG) trial: a retrospective analysis

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Introduction: Controversy continues concerning the clinical utility of digoxin in women with heart failure. Detailed characterization of the relationship between serum concentration and outcomes in women is needed to better determine the risk benefit ratio of this drug for heart failure in women.
Methods: We performed a retrospective analysis of data from the Digitalis Investigation Group trial to further investigate the relationship between clinical outcomes and serum digoxin concentration in women and men. The principal study analysis reviewed a total of 5209 patients with heart failure due to left ventricular systolic dysfunction who survived for at least four weeks (all 3366 patients randomized

to placebo and 1843 of 3372 patients randomized to digoxin who had a serum concentration measured at 4 weeks). Multivariable modeling was performed to determine the association between serum digoxin concentration and mortality and morbidity and to evaluate the possibility of gender differences in response to digoxin therapy.
Results: A significant linear relationship between serum digoxin concentration and the risk of death relative to placebo was found in both men ($p<0.001$) and women ($p<0.001$) with better outcomes at low serum concentrations in both genders. For women with a serum concentration from 0.5 to 0.7 ng/ml, the hazard ratio for mortality was 0.80 (95% confidence interval 0.58 to 1.10, p=0.166) and for serum concentrations from 0.5 to 0.9 ng/ml, the hazard ratio was 0.84 (95% confidence interval 0.62 to 1.13, p=0.246). The test for an interaction between gender and the relationship of serum digoxin concentration to mortality was nonsignificant (p=0.783). For women with a serum concentration from 0.5 to 0.9 ng/ml, the hazard ratio for the risk of death or hospitalization for heart failure was 0.74 (95% confidence interval 0.58 to 0.93, p=0.011).
Conclusion: Retrospective analysis of patients from the Digoxin Investigators Group trial indicates that digoxin is an effective treatment for heart failure in women when this drug is used at low serum concentrations. A beneficial effect on morbidity and no excess mortality was observed at serum concentrations < 1.0 ng/ml.

279 Effect of GIK infusion on left ventricular functions in thrombolysed patients of acute myocardial infarction

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Purpose To assess whether high dose GIK with thrombolysis leads to better myocardial salvage and better left ventricular (LV) functions or not.
Methods: Between December 2002 to November 2003, we enrolled 150 consecutive patients of suspected first ST elevation myocardial [MI] presenting within 12 hours of chest pain and having none of the exclusion criteria [contraindications to thrombolysis, S.creatinine >2 mg%, S.K+ >5.5 mmol/L, insulin dependent diabetes, > Killip's class II heart failure, prior MI]. All eligible patients were randomized in a ratio of 1:1 to GIK or control. Patients in GIK arm received GIK solution [500 ml 25% dextrose + 25 U regular insulin + 40 mmol/L KCl] at a rate of 1.5 ml/hour for 24 hours started within 15 minutes of thrombolysis. GIK was stopped if patient developed >Killip's III heart failure, S. glucose >350 mg%, S. K+ >6.0 mmol/L. Extra insulin was given for S. glucose >250 mg%. For S. K+ >5.5 GIK infusion rate was halved. LV functions were seen by echocardiography at predischarge and at follow up.
Results: Of the 150 patients enrolled, 75 patients were given GIK and 75 were controls. Both the groups were fairly matched for baseline clinical characteristics [age, risk factors, number of patients with small size infarct (ST elevation in2-3 leads), modest size infarct (ST elevation in 4-6 leads) and large size infarct (ST elevation in > 7 leads)] and for the treatment recieved. By 30 days there were 6 [8%] deaths in GIK Vs. 10[13.3%] in control [OR 0.57, CI 0.17-1.82, p=0.29], 2 patients in control group did not turned up for follow-up echocardiography. At 30 days LV functions were better in GIK group (EDV 95.17+24.73 ml vs 107.29+33.00ml, p<0.05; ESV 43.67+17.15ml vs 57.54+29.51ml, p<0.01; EF 55.43+9.53 vs 48.41+9.52, p<0.001). When GIK and control group were compared according to the size of infarct, the differences remained statistically significant for smaller infarcts only (Table 1).

Table 1

	All patients	Small infarct	Modest infarct	Large infarct
EDV	-10.4%,p<0.05	-6.1%,p0.05	-13.1%,p0.15	-5.4%,p0.50
ESV	-24.1%,p<0.01	-27.2%,p<0.02	-13.3%,p0.07	-10.1%,p0.35
EF	+14.5%,p<0.001	+20.3%,p<0.001	+11.6%p0.07	+2.7%,p0.55

Relative effect of GIK on 30 days LV functions as compared to controls

Conclusion: GIK as an adjunct to thrombolysis results in better LV function, more so in smaller infarcts.

280 Cardioselective or non-selective beta-blockers during dobutamine stress echocardiography: does it really matter?

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Background: Dobutamine has a positive chronotropic effect on the heart by direct stimulation of B1-adrenergic receptors in the myocardium and indirectly because of a vagal tone withdrawal due to peripheral vasodilatation through B2-adrenergic stimulation.
Aim: to determine whether patients on cardioselective (CS) beta-blockers (BBL), acting on B1-adrenergic receptors (bisoprolol, atenolol, and metoprolol), compared to non-selective BBL acting on both B1- and B2-adrenergic receptors (carvedilol) have different hemodynamic effects and long-term prognostic value of dobutamine stress echocardiography (DSE).
Methods: 1161 and 307 patients using respectively CS and non-cardioselective BBL were evaluated for hemodynamic response, stress induced myocardial ischemia, and long-term cardiac events (cardiac death and myocardial infarction). Patients were followed for 6±4 years.
Results: During low-dose dobutamine infusion hemodynamics were comparable in both groups (Table), however, during high-dose dobutamine heart rate increased significantly more in patients on CS BBL, while blood pressure was significantly lower. After the addition of atropine the differences in heart rate response was abolished. Stress-induced ischemia during DSE occurred in respectively 445 and 131 patients on CS and non-cardioselective BBL. The 6-year cardiac event rate in patients with stress induced ischemia was similar(28%).

Hemodynamic response

stage	HR CS vs. non-CS	p-value	RR CS vs. non-CS	p-value
rest	70 - 70	NS	133/75 - 131/75	NS
10	76 - 74	NS	135/72 - 134/74	NS
20	88 - 84	<0.01	135/70 - 137/75	NS
30	99 - 92	<0.001	133/69 - 139/74	<0.01
40	106 - 100	<0.01	131/69 - 140/75	<0.001
atropine	133 - 131	NS	131/71 - 144/79	<0.001

(non)CS = (non) cardioselective beta-blocker; HR = heart rate; RR = bloodpressure; NS = not significant

Conclusion: The hemodynamic response to low-dose dobutamine during DSE is similar in patients with CS and non-selective BBL. However, during high-dose dobutamine heart rate increment was reduced in patients on non-selective BBL compared to selective BBL, which is only abolished after the addition of atropine. The prognostic value of the test was comparable in both groups.

MUSCLE WASTING AND CACHEXIA IN HEART FAILURE: READY FOR INTERVENTION

281 Relationships among body mass index and serum levels of soluble TNF receptors and brain-type natriuretic peptide in patients with heart failure

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Recently, several investigators reported improved event-free survival of overweight and obese patients with heart failure (HF) compared to normal and underweight patients. The reasons for these findings are unknown. Adipose tissue is a source of the proinflammatory cytokine TNF-alpha (TNFa) and levels are increased in individuals who are overweight or obese. Chronic exposure to increased TNFa in overweight/obese individuals prior to developing HF may result in down-regulation of the subsequent inflammation that occurs in response to HF. We hypothesized that overweight and obese patients with HF would have lower serum levels of proinflammatory cytokines. We also hypothesized that B-type natriuretic peptide (BNP), a clinical marker of HF severity, would be lower in overweight and obese patients. The purpose of this study was to compare serum levels of BNP, TNFa, soluble TNF receptor 1 and 2 (sTNF-R1 and sTNF-R2) among patients with HF who were normal-weight, overweight, and obese.
Results: 40 patients (20 males and females) recruited from HF clinics in the Midwestern U.S. with a mean age of 60 (±14) years and a left ventricular ejection fraction <40% participated in the study. Table 1 lists the comparisons among HF patients divided into tertiles based on body mass index (BMI). The patients in the normal-weight group (BMI < 25.8) had the highest serum levels of all cytokines and BNP. sTNF-R2 levels in the normal-weight group were significantly higher than the obese group (BMI > 33) [t(21) = 1.8; p < .05]. Overweight and obese patients had significantly lower BNP levels than normal-weight patients [F(2,37) = 4.2; p <.05].

Table 1. Comparison by BMI

	< 25.8	25.8 to 32.9	>33
TNFa (pg/ml)	7.1 (0.9)	7.5 (1.3)	5.7 (1.3)
sTNF-R1 (pg/ml)	3298 (516)	2556 (410	2570 (290)
sTNF-R2 (pg/ml)	5128 (700)	3635 (524)	3691 (519)
BNP (fmol/ml)	1195 (296)	644 (168)	516 (128)

Conclusion: These results are consistent with the hypothesis that overweight and obese HF patients may experience less systemic inflammation, which may be one reason for better event-free survival.

282 Increased expression of MafBx ubiquitin ligase mRNA in skeletal muscle after induction of heart failure: role of inflammatory cytokines

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Background: Muscle wasting is a common complication of many hypercatabolic states such as sepsis, cancer and chronic heart failure. The overexpression of MafBx ubiquitin ligase, also known as atrogin –1, in skeletal muscle myocytes resulted in the induction of atrophy. So far nothing is known about MafBx expres-

sion in the skeletal muscle after induction of heart failure, and its regulation by inflammatory cytokines.
Methods: Male Wistar Kyoto rats were subjected to LAD ligation. After 12 weeks the development of CHF was confirmed by invasive monitoring and echocardiography. The expression of MafBx in the skeletal muscle of 10 CHF-rats (CHF) and 8 sham operated (S) animals was assessed by real-time RT-PCR. To investigate the potency of inflammatory cytokines to regulate MafBx expression, the level of MafBx mRNA was analyzed in L6 rat skeletal myoblasts after incubation with either IL-1β (50 ng/ml), gamma-IFN (100 U/ml), TNF-alpha (20 ng/ml) or with combinations of the cytokines.
Results: Twelve weeks after LAD ligation the animals showed a significant LV contractile dysfunction (dp/dtmax: 4.47±0.24 versus 6.03±0.42 mm Hg/ms; p=0.003). Analyzing MafBx mRNA-expression in the skeletal muscle revealed a 2-fold increase in the CHF animals as compared to the sham group (CHF: 5.54±1.12 versus S: 2.21±0.62 arb. Units; p=0.02). Incubation of L6 cells with either IL-1β, TNF-alpha or gamma-IFN alone failed to stimulated MafBx mRNA expression, whereas the combination of TNF-alpha/IL1β (1.8-fold increase vs. control) or of all 3 cytokines (2.4-fold increase versus control) lead to a significant increase of MafBx expression.
Conclusion: The results of this study demonstrate, that an elevation of inflammatory cytokines in the situation of heart failure may lead to an increased expression of MafBx. The increased expression of this ubiquitin ligase may be one step in initiating muscle wasting.

283 Deficiency in anabolic hormones is related to clinical severity and increased mortality in men with chronic heart failure

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Background: Male aging is accompanied by a deficiency in anabolic hormones (total testosterone [TT], dehydroepiandrosterone sulphate [DHEAS], insulin-like growth factor 1 [IGF1]), which is related to increased morbidity and mortality in a general population.Clinical and prognostic significance of anabolic hormone deficiency in male patients (pts) with chronic heart failure (CHF) has not been comprehensively studied.
Methods: We assessed serum TT, DHEAS, IGF1 levels using immunoassays in 86 consecutive male CHF pts (age: 60±1y, LVEF: 32±1%, NYHA I/II/III/IV: 9/45/26/6, peak VO2: 14.4±0.5 mL/min/kg). Reference group consisted of 592 healthy men aged 30-80, recruted from the same local population.
Results: Men with CHF demonstrated a significant deficit in DHEAS and IGF1 as compared to age-matched controls (mean: 53% and 69% of normal values), but there was no TT deficiency in the whole group of CHF pts (mean: 98% of normal values). However, when men were divided according to CHF severity, substantial differences were revealed in all hormones (NYHA I/II/III/IV: TT - 109/108/87/52%; DHEAS - 98/51/48/26%; IGF1 - 66/70/70/66%, all % of reference values). Gonadal andropenia (TT<3ng/mL), adrenal andropenia (DHEAS<600ng/mL), IGF1 deficiency (IGF1<200ng/mL) were observed in 19%, 50%, 44% of CHF pts, respectively vs 7%, 2%,1.5% of controls (all p<0.0001). TT and DHEAS levels (but not IGF1) were inversely related to CHF severity expressed as NYHA class (NYHA I/II/III/IV: TT - 5.0±0.8/4.8±0.3/3.9±0.4/2.3±0.5ng/mL, r=-0.33, p=0.002; DHEAS - 1660±274/755±78/619±86/388±77ng/mL, r=-0.43, p<0.0001). IGF1 level (but not TT, DHEAS) correlated borderline with peak VO2 (r=0.37, p=0.06). During the follow-up (mean: 477±146 days) 10 (12%) CHF pts died. In a univariate Cox analysis, reduced levels of IGF1 (p=0.01), DHEAS (p=0.04) and TT (p=0.03) (but not LVEF, NYHA class, CHF etiology - p>0.1) predicted poor survival. In a trivariate model,independently reduced levels of IGF1 (p=0.03) and borderline DHEAS (p=0.06) (but not TT) were predictors of poor survival. In CHF pts with IGF1 deficiency, adrenal or gonadal andropenia, a 1-year survival rate was 76% (95%CI: 62-90%), 81% (95%CI: 70-93%) and 69% (95%CI: 46-91%) (respectively) as compared to 98% (95%CI: 94-100%) (p=0.002), 95% (95%CI: 89-100%) (p=0.03) and 93% (95%CI: 86-99%) (p=0.003) in those with normal IGF1, DHEAS and TT levels, respectively.
Conclusions: IGF1 deficiency,gonadal and adrenal andropenia are common in men with CHF, and are related to CHF severity and predict poor outcome. Whether a pharmacological correction of anabolic deficiency might constitute another therapeutic target in men with CHF, remains further clinical studies.

284 Impaired differentiation and proliferation of endogenous stem cells in the skeletal muscle of patients with chronic heart failure

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Background: Patients (Pt) with chronic heart failure (CHF) are characterized by an impairment of skeletal muscle function. The discovery of small primitive cell - that express stem cell antigens - within the skeletal muscle (SM) suggests that this organ normally comprises a subpopulation of cells with a remarkable capacity of tissue regeneration. However, it is currently unknown, whether the number and differentiation of those primitive cells into different lineages in impaired in the SM of Pt with CHF as compared to healthy individuals.
Methods: Forty patients that had developed CHF (n=40, NYHA II/III/IV: 5/30/5, LVEF 21±2%) on the basis of a dilative cardiomyopathy or an ischemic heart disease as well as fourteen age-matched healthy subjects were included into the study. The number of endogenous, c-kit expressing stem cells was determined by immunohistochemistry in skeletal muscle biopsies in patients with CHF and healthy subjects. Myocyte-lineage commitment of c-kit positive cells was recognized by the co-expression of the myocyte specific transcription factor "myocyte enhancer factor 2", cycling c-kit positive cells were identified by the co-expression of the cell proliferation marker Ki67 applying immunohistochemistry.
Results: The number of primitive c-kit-expressing cells in the SM of Pt with CHF (20±5 cells/cm^2 SM area) was significantly reduced as compared to healthy individuals (90±20 cells/cm^2, p<0.05 vs. CHF). In Pt with CHF a lower number of c-kit positive cells showed a "myocyte lineage commitment" as determined by the co-expression of the myocyte specific transcription factor "myocyte enhancer factor 2" (5±2 cells/cm^2) in comparison with healthy subjects (40±10 cells/cm^2, p<0.05 vs. CHF). Moreover, the subpopulation of c-kit positive cells that expressed the cell cycle marker Ki67 was significantly smaller in Pt with CHF (CHF: 3±1 cells/cm^2, healthy subjects: 20±8 cells/cm^2, p<0.05). However, the c-kit positive cells were negative for CD4, CD11b and CD68, respectively, which excludes an inflammatory response in the SM with the invasion of lymphocytes, monocytes and macrophages in Pt with CHF as well as in healthy subjects.
Conclusion: The reduced number, the attenuated differentiation and proliferation of small primitive c-kit expressing stem cells in the SM of Pt with CHF might be partially responsible for the impairment of skeletal muscle regeneration and contribute to SM dysfunction in those patients.

285 Ghrelin improves biventricular function and attenuates autocrine/paracrine activation in monocrotaline-induced pulmonary hypertension

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We recently showed that ghrelin (ghr), an endogenous peptide with several cardiovascular actions, attenuates pulmonary hypertension (PH), right ventricular and pulmonary vascular remodelling in monocrotaline (MCT) rats. We also showed, in this model of selective right ventricular (RV) overload, failure of the non-overloaded left ventricle (LV), which correlated with autocrine/paracrine activation. In the present study we evaluated the effects of ghr on biventricular function and autocrine/paracrine activation in MCT-induced PH.
Adult Wistar rats were injected with MCT (60 mg/kg, sc) or just the vehicle (day 0). One week later, animals treated with MCT were randomly divided and treated with ghr (100 μg/kg, BID, sc) or with a similar volume of vehicle. The study resulted in 3 groups: (i) control (Ctrl, n=7), (ii) MCT (n=9), (iii) MCT+ghr (n=9). At days 21-25 the animals were instrumented to record RV and LV peak systolic (Psys) pressures, dP/dtmax and time constant Tau. RV and LV transmural free-wall samples were collected to quantify, by real time RT-PCR, IGF-1, ppET-1 and ACE mRNA levels, which were normalized for GAPDH and expressed in arbitrary units (AU). Results, presented as mean±SEM, are summarized in the table (P<0.05: a vs. Ctrl; b vs. MCT).

	RV-Ctrl	RV-MCT	RV-MCT+Ghr	LV-Ctrl	LV-MCT	LV-MCT+Ghr
Psys (mmHg)	25.1±1.7	48.2±1.6 a	35.9±1.9 a,b	98.4±4.3	67.4±3.5 a	85.0±4.2 b
dP/dtmax (ms)	1228±67	1602±91 a	1692±113 a	5513±545	3442±325 a	5510±604 b
Tau (ms)	6.6±0.9	27.8±2.5 a	17.1±1.9 a,b	18±1.2	21.9±0.9	15.9±1.7 b
IGF-1(AU)	1.0±0.2	2.2±0.4	1.8±0.6	1.0±0.1	1.5±0.4	1.3±0.2
ppET-1 (AU)	1.0±0.1	4.6±0.8 a	1.9±0.8 b	1.0±0.4	30.1±7.5 a	8.0±1.8 b
ACE (AU)	1.0±0.2	19.8±7.0 a	12.6±9.5 b	1.0±0.2	7.3±2.4 a	4.1±1.3 b

MCT rats presented LV systolic dysfunction, biventricular diastolic dysfunction and increased expression of ppET-1 and ACE. All these effects were attenuated by ghr. Therefore, ghr exerts beneficial effects on cardiac remodelling independently of local IGF-1 expression and cardiac overload, but potentially related with blunting of local activation of ET-1 and renin-angiotensin systems.

286 Ghrelin improves cardiac function, exercise capacity and cardiac cachexia in patients with heart failure

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Background: Ghrelin is a novel growth hormone (GH)-releasing peptide. This peptide also induces vasodilation, inhibits sympathetic nerve activity, and stimulates feeding through GH-independent mechanisms. We investigated the effects of ghrelin on left ventricular (LV) function, exercise capacity, and muscle wasting in patients with chronic heart failure (CHF).
Methods and Results: Human ghrelin (2 μg/kg twice a day) was intravenously administered to 10 patients with CHF for three weeks. Echocardiography, cardiopulmonary exercise testing, dual X-ray absorptiometry, and blood sampling were performed before and after ghrelin therapy. A single administration of ghre-

lin elicited a marked increase in serum GH (25-folds). Three-week administration of ghrelin resulted in a significant decrease in plasma norepinephrine (1132 ± 188 to 655 ± 134 pg/ml, P < 0.001). Ghrelin increased LV ejection fraction (27 ± 2% to 31 ± 2%, P < 0.05) in association with an increase in LV mass and a decrease in LV end-systolic volume. Treatment with ghrelin increased peak workload and peak oxygen consumption during exercise. Food intake was significantly increased during ghrelin therapy. Ghrelin improved muscle wasting, as indicated by increases in muscle strength and lean body mass. These parameters remained unchanged in 8 patients with CHF who did not receive ghrelin therapy.
Conclusions: Repeated administration of ghrelin improves LV function, exercise capacity, and muscle wasting in patients with CHF.

PERCUTANEOUS CORONARY INTERVENTION AND BEYOND FOR ST-ELEVATION ACUTE MYOCARDIAL INFARCTION

304 Primary versus facilitated percutaneous coronary intervention (tenecteplase plus stenting) in patients with ST-elevated myocardial infarction: the final results of the GRACIA-2 randomized trial

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Background: Combined reperfusion therapies widely applicable could benefit the still high proportion of pts with STEMI for whom primary PCI is not available.
Methods: In this randomized, controlled trial, 212 pts with STEMI were recruited to compare the safety and efficacy of two strategies: 1) primary PCI (stenting under abcximab within 3 h from onset); 2) facilitated combined strategy consisting of immediate thrombolysis with tenecteplase followed by angiography and stenting if indicated within 12 h of randomization. Primary endpoints were the infarct size (area under the curve of CK-MB mass and cTnT release), 6-week left ventricle angiographic evolution (volumes, ejection fraction and wall motion index) and myocardial reperfusion (complete normalization of ST segment at 3 and 6 h of randomization). The incidence of major bleeding and 6-month cardiac events rate were also compared.
Results: Both groups of pts had similar delay between onset and randomization (3.2 hours). Time from randomization to angioplasty was 1.1±0.5 hours in pts allocated to primary angioplasty. Facilitated pts got intervention 7.5±14.6 hours after randomization. There were no differences between primary and facilitated strategies in terms of infarct size (area under the curve of CK-MB mass: 4732±3691 vs 4709±3452 ug/L x h, p= 0.15; area under the curve of cTnT release: 271±211 vs 245±157 ug/L x h, p=0.24), 6-week LVEF (53±14 vs 53±10%, p= 0.31); wall motion index at six weeks (-1.48±0.45 vs –1.47±0.40, p= 0.97) and myocardial perfusion (complete normalization of ST segment at 3 hours: 47 vs 43%, p= 0.64; and at 6 hours 45% vs 59%, p= 0.10). Both groups had similar incidence of major bleeding (primary: 3%, facilitated; 2%, p=0.97) and cardiac events at 6 months (13% vs 11%, p=0.59).
Conclusions: In pts with STEMI, PCI after facilitation with TNK is as safe as primary PCI. In spite of the longer delay of intervention in the facilitated group, both strategies seem to be equivalent in restoring myocardial perfusion, reducing infarct size, preserving LV evolution, and beneficing clinical outcome.

305 Abciximab-supported infarct artery stent implantation for acute myocardial infarction and long-term survival. A randomized trial comparing infarct artery stenting plus abciximab

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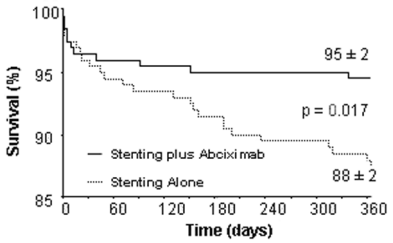
Background: The impact on survival of routine use of abciximab as adjunctive treatment to routine infarct artery stenting for acute myocardial infarction is not defined. We sought to determine the effect of abciximab on 1-year survival and other major adverse cardiac events of patients with acute myocardial infarction undergoing routine infarct artery stenting.
Methods and Results: The Abciximab and Carbostent Evaluation (ACE) Trial was an unblinded, randomized, controlled trial that compared abciximab with placebo in 400 patients undergoing routine infarct artery stent implantation for acute myocardial infarction. The 1-year mortality rate was 5.5% in the abciximab group and 12.5% in the stenting alone group (p=0.014). The reinfarction rate was 1% in the abciximab group and 6.0% in the stenting alone group (p=0.0006), while there were no differences between groups in target vessel revascularization rate (16.5% in the abciximab group, and 17.5% in the stenting alone group, p=0.790).
Conclusions: Abciximab as adjunctive treatment to routine infarct artery stenting for acute myocardial infarction resulted in improved 1-year survival and lower reinfarction rate.



Survival curves.

306 Primary coronary angioplasty reduces free wall rupture and improves mortality and morbidity of acute myocardial infarction

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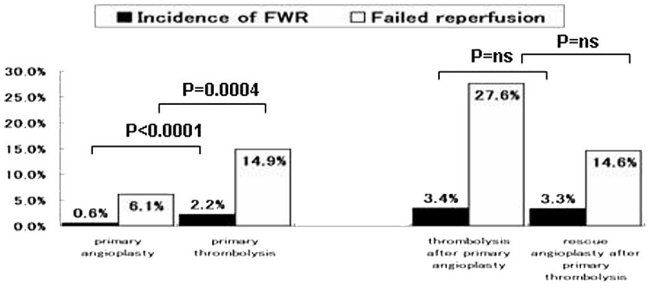
Background: Free Wall Rupture (FWR) is one of the major causes of mortality of AMI. To what extent primary coronary angioplasty (PA) for acute myocardial infarction (AMI) would modify the predictors of free wall rupture (FWR) is not clear.
Methods: In our prospective database of consecutive 3138 AMI patients seen between May 1985 to May 2002, 3096 patients who underwent emergent CAG was analyzed retrospectively.
Results: PA was the mode of therapy in 2308 patients (73.6%), primary thrombolysis in 579 patients (18.5%) and emergent CABG in 62 patients (2.0%). Thronbolytic agent was added in 87 (2.8%) patients after PA and rescue angioplasty was performed in 213 (6.9%) patients after primary thrombolysis. FWR occurred in 40 (1.3%) patients after emergent CAG. PA yielded lower incidence of failed reperfusion (6.1% v.s. 14.9%, P<0.0001) and FWR (0.6% v.s. 2.2%, P=0.0004) than primary thrombolysis. Higher rate of FWR was associated with: i) without PA (3.2% v.s. 0.6%, p<0.0001), ii) thrombolytic agents usage (2.4% v.s. 1.0%, p=0.004), iii) female gender (2.5% v.s. 1.1%, p=0.0004), iv) failed reperfusion (5.4% v.s. 0.9%, p<0.0001) and v) LMT- related infarct (4.7% v.s. 1.2%, p=0.02) (univariate analysis). In multivariate logistic regression analysis five conditions were identified as significant protective or predictive factors of FWR: not having PA (odds ratio [OR]: 3.57, 95% confidence interval [95%CI] 1.42-8.99, p=0.007), failed reperfusion (OR: 5.16, 95%CI: 2.45-10.87, p<0.0001), LMT-related infarct (OR: 5.37, 95%CI: 1.16-25.00, p=0.03), female gender (OR: 2.30, 95%CI: 1.11-4.78, p=0.03) and age (OR: 1.03, 95%CI: 1.00-1.07, p=0.05).



Incidence of FWR and failed reperfusion.

Conclusion: Prompt successful reperfusion by PA reduced FWR complicating AMI.

307 In-hospital time to treatment ("door-to-needle" time) in patients with acute ST-elevation myocardial infarction treated with primary angioplasty: determinants and outcome

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Background: An increase in the time from hospital admission until the start of primary angioplasty (PA) ("door-to-needle" time = DTN-T) may be associated with an increase in mortality. However, there a no up-to-date data on current DTN-times as well as their clinical impact in Germany.
Methods: We analysed the data of the prospective registry of percutaneous coronary interventions in acute myocardial infarction (AMI) of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK).

Results: Between 1994 and 2000 4815 patients (pts) at 80 hospitals presenting with a ST-elevation AMI and a pre-hospital delay < 12 hours treated with PA were analysed. DTN-T was <31 minutes in 31% of pts, 31-60 minutes in 37%, 61-90 minutes in 15% and > 90 minutes in 17% of pts. Hospital mortality was 9.3%, mortality in the 3 tertiles of the DTN-T was 9.2% (0-30minutes), 8.3% (31-90 minutes) and 10.5% (>90 minutes), p=0.552.
The table shows the results of the logistic regression analysis on hospital mortality.

	mortality	adjusted OR (95%CI)	p-value
shock/no shock	41.6%/4%	16.6 (12.9-21.2)	<0.0001
TIMI flow <3/3	29.2%/6.5%	4.9 (3.7-6.4)	<0.0001
age≥70y/<70y	16.5%/6.6%	2.6 (2.0-3.3)	<0.0001
3 vessel disease/<3VD	16.5%/6.8%	2.0 (1.5-2.2)	<0.0001
anterior AMI/others	12.0%/7.4%	1.8 (1.4-2.3)	<0.0001
volume of PA: ≥20PA/y/<20PA/y	8.3%/11%	0.8 (0.6-0.9)	<0.0001
tertiles of the DTN-T: ≤30m/31-60m/>60m	9.2%/8.3%/10.5%	1.1 (0.8-1.5%)	0.397

Conclusions: In current clinical practice of PA for AMI in Germany DTN-T is less than 90 minutes in the majority of pts (83%). Within these short DTN-T hospital mortality is not time dependent.

308 Randomized comparison of prehospital combination fibrinolysis versus prehospital initiated facilitated percutaneous coronary intervention in acute myocardial infarction. Final results

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Background: Prevention of myocardial necrosis expansion is the main goal of all reperfusion strategies in acute myocardial infarction. As a consequence of a shorter time to reperfusion prehospital fibrinolysis has equal efficacy as primary angioplasty, generally considered the preferred reperfusion strategy. The optimal reperfusion strategy might be a prehospital initiated pharmacological reperfusion with subsequent angioplasty if not accompanied by an excess in bleeding complications.
Methods: Patients with a ST-elevation myocardial infarction were randomized to either prehospital fibrinolysis (half dose Reteplase + abciximab) (n=76) or a prehospital initiated facilitated stenting (n=77). Primary endpoint was infarct size assessed by delayed enhancement magnetic resonance. Secondary endpoints were ST-segment resolution at 90 min., and a composite of mortality, re-myocardial infarction, major bleeding and stroke at six months.
Results: Infarct size was lower after facilitated stenting with 7±6 percent of the total left ventricular mass, as opposed to 12±11 percent after prehospital fibrinolysis (P=0.004). There was an improved tissue perfusion as assessed by ST-segment resolution; the percentage of complete resolution was 81.3 percent after facilitated stenting versus 54.8 percent (P<0.001). In the facilitated stenting group there was a trend towards a lower event rate in the combined clinical endpoint (16 vs. 27 percent, P=0.11, relative risk 0.69, 95 percent confidence interval, 0.38 – 1.09).
Conclusions: In patients with acute myocardial infarction additional facilitated stenting after prehospital fibrinolysis results in a an improved tissue perfusion which leads to a smaller infarct size as opposed by prehospital fibrinolysis alone. There is a trend towards a better clinical outcome.

309 Percutaneous coronary intervention versus fibrinolysis in acute myocardial infarction: the importance of timing

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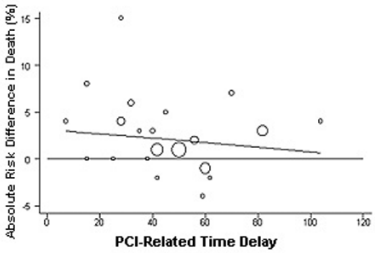
Background: Restoration of coronary blood flow at the earliest possible time in the treatment of ST-segment elevation myocardial infarction is critical. Although percutaneous coronary interventions (PCI) have been shown to be superior to fibrinolysis (lysis), this approach is not universally available and substantial time delays might restrict their benefits.
Objective: To assess the relationship between angioplasty-related time delay and the effectiveness of the intervention in reducing death compared with lysis in patients with acute MI.
Methods: We included in this analysis data from 21 randomised trials comparing primary PCI with lysis in patients with AMI. Linear regression analysis was used to assess the relationship between PCI- related delay and mortality.
Results: Our analysis included a total of 7350 patients. Of these, 3678 were treated with PCI, while the remaining 3672 received lysis. Mean delay from randomisation to balloon inflation was 95 minutes and time to needle was 51 minutes, accounting for a PCI-related time delay of 44 minutes. The mean absolute mortality difference between PCI and lysis was 2.7. The absolute survival benefit of angioplasty compared with fibrinolytic treatment decreased by 0.24% for every additional 10-minutes delay (figure). The regression showed that when PCI- related time delay reached 130 minutes the mortality rates for angioplasty and lysis were equivalent.



Conclusions: Although an expeditious approach remains necessary, the superiority of mechanical reperfusion over lysis might still be demonstrated when time to balloon remains shorter than 130 minutes.

IIB OR NOT TO BE IN ACUTE MYOCARDIAL INFARCTION?

310 Underuse of GP IIb/IIIa receptor blockers in diabetics undergoing percutaneous coronary intervention for acute coronary syndromes in Europe: results of the Shakespeare registry

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Background: A meta-analysis of randomised trials using GP IIb/IIIa receptor blocker (GP IIb/IIIa) in acute coronary syndromes (ACS) indicated a significant reduction of mortality at 30 days in diabetic patients (pts) with ACS undergoing PCI.
Methods: Since February 2002 the international Shakespeare Registry has been enrolling consecutive patients undergoing PCI in 7 different countries in Europe (D, F, I, IL, P, PL, UK)to document interventional and medical treatment as well as outcome. We examined the use of GP Ib/IIIa in diabetics versus non-diabetics with ACS in clinical practice in Europe.
Results: Out of 11195 consecutive PCI pts 6611 (59%) underwent PCI for ACS, 1564/6611 (24%) were diabetics. Independent determinants for the use of GP IIb/IIIa during PCI for ACS were male gender (OR 1.30, 1.16-1.45) and cardiogenic shock (OR 1.69, 1.24-2.30). Determinants against GP IIb/IIIa were age >70 years (OR 0.64, 0.58-0.71), prior MI (OR 0.68, 0.68-0.77) and prior CABG (OR 0.69, 0.58-0.82). Known diabetes did not influence the decision for the use of GP IIb/IIIa (OR 0.96, 0.86-1.07).

ACS in diabetics vs non-diabetics

	Diabetics	Non-Diabetics	p-value
Age (years)	64	69	<0.001
Male Gender	65.4%	77.7%	<0.001
Prior MI	26.5%	21.2%	<0.001
Prior Stroke	5.9 %	3.2%	<0.001
Cardiogenic Shock	3.8%	2.2%	<0.001
3-Vessel-Disease	28.3%	20.8%	<0.001
GP IIb/IIIa	45.9%	47.0%	ns
Reason for GP IIb/IIIa			
ACS	61.2%	65.6%	<0.001
Pt considered high risk	16.5%	11.2%	<0.001
30-Day-Mortality	3.7%	2.3%	<0.001

Conclusion: Less than half of diabetic pts undergoing PCI for ACS in Europe received GP IIb/IIIa during PCI. Despite the evidence of an improved outcome, the frequency of GP IIb/IIIa use during PCI for ACS was not different from that in non-diabetics in clinical practice. In a multivariate analysis diabetes mellitus was no determinant for the use of GP IIb/IIIa for ACS in Europe.

311 Platelet aggregation inhibition – ERAMI substudy

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Introduction: ERAMI Study is a double blind randomized study comparing ab-

ciximab early administration in the Emergency room (ER) in patients (Pts) with an acute myocardial infarction (AMI) being submitted to an urgent angiogram. Platelet aggregation inhibition rate (PlqAgIn) is associated to the cardiovascular events (CVE) in elective PCI.
Objective: Determine PlqAgIn rate induced by abciximab early administration, and its relation to the 1st month CVE.
Population and methods: Abciximab bolus (0.25 mg/kg) was administrated in the ER (Gr1, n= 40) or in the cath lab (Gr2; n= 40). A 0.125 mg/kg abciximab infusion maintained during 12 hours. Placebo bolus was given to Gr1 Pts, in the cath lab. PlqAgIn determined with Ultegra at admission and 10 minutes after the bolus in the cath lab, and the PlqAgIn rate determined. Sixty two pts completed all protocol determinations. Pts were grouped accordingly to the therapeutics (Gr1 and Gr2) and to the PlqAgIn rate 80% cut off. CVE composite of death, reinfarction and urgent revascularization determined at the 1st month. Eight pts had a CVE. Statistics: Qui square and Fisher test's with odds ratio (OR) determination and student's group t-Test.
Results: (1) There was no significant difference between Gr1 and Gr2 for PlqAgIn rate (94.0 ±17.0 vs. 91.8 ±17.0; p NS), and for the proportion of pts with PlqAgIn rate below 80% (11% vs. 8.6%, p NS) within the two therapeutics groups. (2) No significant difference between Gr1 and Gr2 for the CVE (10% vs. 12.5%, p NS). (3) Pts with PlqAgIn <80% had higher CVE rate (50% vs. 7.1%; p=0.016). The table expresses the OR for the CVE in relation to the PlqAgIn rate cut off 80%.

Odds Ratio (OR) for CVE

PlqAgIn	<80%	>80%	
N	6	56	
OR	7.86 (1.95-31.60)	0.60 (0.31-1.10)	p=0.016

Mean, 95% confidence interval

Conclusion: Early abciximab administration in the ER didn't decrease the CVE at 1st month. PlqAgIn rate below 80% associates to a higher risk of CVE at 1st month.

312 Early versus late administration of GP IIb/IIIa inhibitors in ST-segment elevation myocardial infarction undergoing primary PCI: a meta-analysis

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Background: Primary percutaneous coronary intervention (PCI) in ST elevation myocardial infarction (STEMI) is the treatment of choice for coronary reperfusion in the present era. GP IIb/IIIa inhibitors improve myocardial reperfusion and clinical outcomes, but optimal timing of administration remains debated. We performed a meta-analysis of available studies which tested the effect of an early (during transfer) versus a late (just before PCI) administration of intravenous GP IIb/IIIa inhibitors. Initial TIMI grade flow and 30-day outcome were evaluated.
Methods: We identified 6 randomised trials, enrolling 931 STEMI patients treated with abciximab (3 trials) or tirofiban (3 trials) in combination with primary PCI. Early use of GP IIb/IIIa inhibitors was defined as an administration in the emergency room (ER) or in the ambulance, whereas late administration was defined as an administration in the cathlab just before PCI. End-points were TIMI grade flow 3, TIMI grade flow 2 or 3 on the initial coronary angiogram; mortality and the composite end-point of death/re-infarction/repeat revascularisation at 30 days, as defined in each trial. Relative risk (RR) evaluated the treatment effect.
Results: There were no differences between the 2 groups for all baseline characteristics. TIMI grade flow 3 and TIMI grade flow 2/3 were significantly more frequent in the early group than in the late group (RR 1.50, 95% CI 1.13 to 2.16, p<0.01 and RR 1.34, 95% CI 1.13 to 1.60, p<0.001 respectively). The incidence of the combined end-point appeared lower with the early use of GP IIb/IIIa inhibitors (RR 0.80, 95% CI 0.5 to 1.24, p=0.32). A strong trend in the reduction of mortality was found with the early administration of GP IIb/IIIa inhibitors (RR 0.53, 95% CI 0.24 to 1.15, p=0.11).
Conclusion: The early administration of GP IIb/IIIa inhibitors in ST elevation myocardial infarction significantly improves coronary patency at the time of initial angiography preceding PCI and tends to improve clinical outcome. Further evaluations in larger trials are necessary to confirm the clinical benefit of this strategy.

313 Angioplasty with early administration of abciximab in high-risk acute myocardial infarction patients improves clinical outcome

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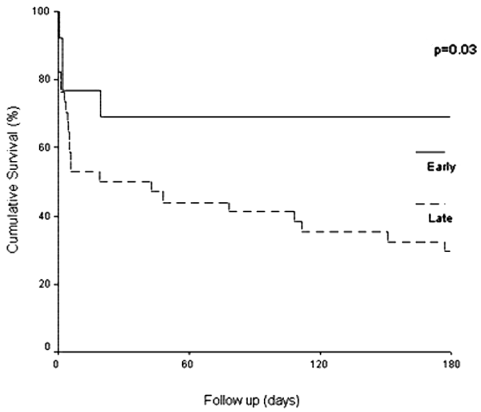
Purpose: Acute myocardial infarction (AMI) complicated by cardiogenic shock or out of hospital cardiac arrest is associated with a poor prognosis. We studied if early abciximab (ABX) administration could improve clinical outcome in these pts.
Methods: From May 1999 to March 2002, 57 consecutive patients with AMI complicated by out of hospital cardiac arrest and/or a sustained systolic blood pressure <80 mmHg, referred for urgent percutaneous coronary intervention (PCI), were included. ABX was started before transport (Early group) or just before the intervention (Late group).
Results: In comparison to pts in the Late group (n=43; 67% male; age 58±14 yr), pts in the Early group (n=14; 64% male; age 60±13 yr) received ABX 45±15 min earlier. Baseline data were comparable in both groups. Mortality was 31% (n=4) in the Early group vs 42% (n=16) in the Late group (NS). Major adverse cardiac events <6 months were less frequent in the early group (n=4; 31% vs. n=24; 71%; p=0.013). Log rank testing revealed a significant MACE-free survival between both groups (p=0.03; see figure)



Cumulative Survival % in 180 days.

Conclusion: 6-month clinical outcome of pts with AMI complicated by cardiogenic shock or out of hospital cardiac arrest is better if ABX is initiated before transport for primary PCI.

314 In clinical practice GP IIb/IIIa antagonism in non-ST-elevation myocardial infarction is less effective in women compared to men – results of the ACOS registry

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Patients (P) with acute coronary syndromes (ACS) showed a highly significant gender difference with a risk increase in women after treatment with glycoprotein IIb/IIIa inhibitors (GPI) in a meta-analysis of large randomised GPI trials (PRISM, PRISM-PLUS, PURSUIT, PARAGON-B, GUSTO IV). This difference disappeared if troponin status was added to the multivariable regression equation.
Aim: To examine gender differences after therapy with GPI in P with non ST elevation myocardial infarction (NSTEMI) in clinical practice.
Methods: From 6/00 to 12/02 a total of 6835 consecutive P (34% female) with NSTEMI were registered in the ACOS (Acute COronary Syndrome)registry, 2320 of them (34%) received GPI. We examined differences in clinical characteristics, acute therapy and hospital outcome between women and men.
Results: See table. After adjustment for age there is still a reduction in hospital mortality in men with NSTEMI receiving GPI versus men receiving no GPI (OR 0.64,95%CI 0.46-0.89). In women with NSTEMI there is no difference in age-adjusted hospital mortality in the group receiving GPI versus the rest receiving no GPI (OR 1.05,95%CI 0.71-1.54).

Gender differences in NSTEMI

	Women receiving GPI (n=649)	Women receiving no GPI (n=1702)	Odds ratio (95% CI)
Age (median), yrs	71.5	76.1	0.96 (0.95-0.97)
Prior PCI/CABG (%)	18.6	11.9	1.66 (1.29-2.13)
History of diabetes mellitus (%)	36.2	39.9	0.94 (0.77-1.13)
Smoker (%)	23.1	15.1	1.14 (0.89-1.46)
Acute reperfusion** (%)	45.8	16.4	3.79 (3.09-4.65)
Hospital mortality (%)	5.8	7.8	0.74 (0.51-1.07)
Hospital mace***	4.2	5.9	0.71 (0.52-0.96)
	Men receiving GPI (n=1670)	**Men receiving no GPI (n=2813)**	**Odds ratio) (95% CI)**
Age (median), yrs	64.2	67.8	0.98 (0.97-0.98)
Prior PCI/CABG (%)	22.5	20.0	1.25 (1.08-1.45)*
History of diabetes mellitus (%)	23.5	29.5	0.79 (0.69-0.91)*
Smoker (%)	51.5	46.5	1.04 (0.91-1.18)*
Acute reperfusion** (%)	57.7	26.7	3.52 (3.08-4.01)*
Hospital mortality (%)	3.1	5.9	0.51 (0.37-0.70)
Hospital mace***	2.8	5.3	0.52 (0.41-0.66)

*age adjusted, **PCI or thrombolysis, ***death or myocardial infarction

Conclusion: In clinical practice there is a gender difference in outcome after therapy with GPI in NSTEMI. Whereas in men with NSTEMI therapy with GPI is associated with a lower hospital mortality, this difference can not be seen in

women with NSTEMI. After adjustment for age there is no difference in mortality between women with NSTEMI which receive GPI and women which receive no GPI.

315 Abciximab treatment during the organization phase of primary angioplasty in STEMI results in early recanalization of the infarct-related artery

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Purpose: The aim of the ReoPro-BRIDGING Austrian multicenter randomized study was to compare the effect of early (in the organization phase) versus late (immediately before primary percutaneous coronary angioplasty, pPCI) administration of the GP IIb/IIIa antagonist Abciximab (ReoPro) on early reperfusion in ST-segment elevation myocardial infarction (STEMI).
Methods: Fifty-five patients with STEMI were randomized either to start Abciximab (0.25 mg/kg bolus followed by 10 ug/min infusion) already during the organization phase for pPCI (Group 1, n=28) or after diagnostic coronary angiography immediately before angioplasty (Group 2, n=27). Serial measurements of serum creatine kinase (CK), CKMB and myoglobin and ECGs were performed at clinical presentation and at every 2 hours on the first day and qualifying angiograms were analysed. Selvester QRS score (index of size of myocardial infarction) was calculated at 7 days after onset of STEMI.
Results: ST-segment resolution $\geq$50% (as a sign of tissue reperfusion) before pPCI occurred in 61% (Group 1) vs 22% (Group 2) (p=0.004). Angiography revealed early signs of recanalization of the infarct-related artery in patients in Group 1 as compared to Group 2: TIMI flow grade 2+3: 61% vs 34% (p=0.042); corrected TIMI frame count: 58.4$\pm$32.7 vs 78.9$\pm$28.4 frame (p=0.018), respectively. Quantitative coronary angiography revealed significantly larger pre-pPCI minimal lumen diameter (0.69$\pm$0.69 vs 0.26$\pm$0.38 mm, p=0.014) and less severe diameter stenosis (74$\pm$23 vs 89$\pm$16%, p=0.016) in patients in Group 1 vs Group 2.
Furthermore, rapid release of cardiac enzymes was observed in Group 1 as compared to Group 2: rate of rise of CK 210$\pm$209 vs 97$\pm$95 U/l/h (p=0.015). The peak levels of cardiac enzymes were similar in the groups, achieving the peak values earlier in Group 1; the serum levels of CK (764$\pm$734 vs 336$\pm$355 U/l, p=0.016), CKMB (80$\pm$58 vs 43$\pm$44 U/l, p=0.034) and myoglobin (1296$\pm$929 vs 628$\pm$670 ng/ml, p=0.041) were significantly higher in Group 1 vs Group 2 patients 2 hours after clinical presentation, indicating a washout phenomen in patients of Group 1. Selvester QRS score indicated smaller infarct size in Group 1 as compared to Group 2 (4.8$\pm$3.8 vs 7.6$\pm$3.5, p=0.011).
Conclusions: Administration of Abciximab as early as possible in STEMI patients planned to undergo pPCI results in early epicardial and myocardial reperfusion, better TIMI flow grade and limitation of infarct size. Therefore, "bridging" the organization phase for pPCI in STEMI with preprocedural Abciximab might become an important therapeutic tool for myocardial salvage.

MODERATED E-POSTERS I

CARDIAC DYSFUNCTION: NEW INSIGHTS

P356 Myocardial stiffness is an important determinant for plasma brain natriuretic peptide concentration in patients with chronic heart failure

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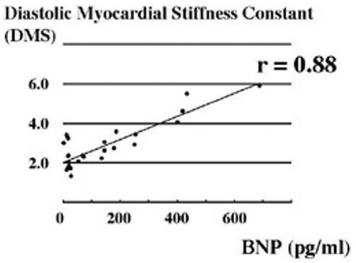
Plasma brain natriuretic peptide (BNP) levels increase according to the degree of left ventricular (LV) systolic and diastolic dysfunction in response to volume expansion and pressure overload. Despite the widespread clinical use, BNP levels ranged widely independent of LV size and wall motion indices. We speculate that LV compliance may be a major determinant of BNP levels. To assess this hypothesis, objective analysis of myocardial passive stiffness was performed in patients proved to be chronic heart failure (CHF).
Methods: We recruited 30 patients (23 male, 63 $\pm$ 11 years) of stable CHF patients with no evidence of acute congestive heart failure, prior myocardial infarction and renal dysfunction. After measurement of plasma BNP levels, a simplified echocardiographic-hemodynamic method was performed. We measured the changes of LV dimensions and wall thickness by two-dimensional echocardiography with simultaneous measurement of LV pressure by high-fidelity micromanometer catheter, during repeated intravenous injection of phenylephrine or nitroglycerine to alter loading condition. Diastolic myocardial stiffness constant (DMS) was calculated with stress-strain analysis and other echocardiography and hemodynamic parameters were obtained, and these were compared with BNP levels.
Results: (see figure): BNP levels ranged from 11.5 to 688 pg/ml (mean 136 $\pm$ 169 pg/ml). LV end diastolic pressure, PCWP and LV ejection fraction had weak correlations with BNP levels. On the other hand, significant strong correlation was observed between DMS and BNP levels (r=0.88, p$<$0.05). Mean DMS were 2.82 $\pm$ 1.11 (1.33 - 5.90).



Conclusions: These data suggest that myocardial passive stiffness (LV compliance) may be an important determinant of plasma BNP concentration in patients with CHF.

P357 Differential effects on amyloid-induced myocardial dysfunction and N-terminal-pro brain natriuretic peptide release of different amyloidogenic proteins

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Amyloid myocardial involvement results in severe dysfunction and is the leading cause of death in systemic amyloidoses, due to either refractory heart failure or arrhythmic sudden death.
Several lines of evidence indicate that the degree of myocardial dysfunction does not only depend on the extent of amyloid deposits but also on the biochemical characteristics of the amyloidogenic proteins which dictate the aggregation process. In order to test this hypothesis, serum N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration was measured at presentation in patients with transthyretin (ATTR; n=17) or light-chain (AL; n=17) amyloidosis, who were matched for left ventricular wall thickness (median: 15 mm in both groups, range: 11-22 mm in AL and 11-23 mm in ATTR), gender (13 males in both groups) and age (median: 52 years, range: 31-70, in ATTR; median: 58 years, range: 46-69, in AL, p=0.28). Left ventricular wall thickness was assumed as an estimation of the amount of the cardiac amyloid deposits. Since NT-proBNP serum concentrations may be altered in the presence of renal dysfunction, patients with serum creatinine $>$1.2 mg/dL were excluded.
Results: NT-proBNP was significantly higher in AL (median: 686.2 pmol/L, range: 295.7-2954.7) than in ATTR (median: 84.5 pmol/L, range: 18.8-1088.3) patients (p=0.0004). None of the patients with AL and 2 (12%) of the patients with ATTR had a normal NT-proBNP (upper reference limit: 39 pmol/L in females and 28 pmol/L in males aged $>$50 years). Survival of patients with ATTR was significantly better than that of patients with AL (p=0.02).
Conclusions: These data show that amyloidogenic light-chains with cardiac tropism generate more severe myocardial dysfunction than transthyretin amyloidogenic variants, despite virtually indistinguishable echocardiographic features. Thus, the degree of cardiac dysfunction depends not only on the amount of amyloid deposited, but mainly on the biochemical characteristics of the amyloidogenic protein.

P358 Negative inotropic effect of selective AT2 receptor stimulation and its modulation by endocardial endothelium, nitric oxide, prostaglandins and endothelium-derived hyperpolarising factor

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Angiotensin II (AT-II) is an endogenous peptide whose effects are mediated by two types of receptors, AT1 and AT2. AT1 receptors are responsible for the vasoconstrictor, positive inotropic and growth promoting properties of AT-II, while AT2 receptors have been linked to vasodilator and anti-mitogenic properties. In this study we investigated the effects of selective AT2 receptor stimulation on myocardial contractility, which are not yet known.
Effects of selective AT2 receptor activation were evaluated in rabbit right papillary muscles (n=35) by adding, to the superfusing solution (Krebs-Ringer; 1.8mM CaCl2; 35°C), increasing doses of AT-II (10^{-8}, 10^{-7}, 10^{-6}, 10^{-5} M) in the presence of a selective AT1 receptor antagonist (ZD7155, 10^{-6} M). Selective AT2 receptor activation was performed in the absence (n=12) and in the presence of NG-

nitro-L-Arginine (L-NA; 3×10^{-5} M; n=9), Indomethacin (INDO; 10^{-5} M; n=7) or Proadifen (PRO; 10^{-6} M; n=9), as well as, after removal of endocardial endothelium (EE; n=7). Calculated parameters: active tension (AT), peak rates of tension rise and decline (dT/dtmax and dT/dtmin, respectively), peak shortening (PS) and peak rate of shortening (dL/dtmax). Results are presented as mean±SEM in % of baseline ($p<0.05$).
Selective AT2 stimulation induced a dose-dependent negative inotropic effect, decreasing, at 10^{-5} M of AT-II, 29.3±7.7% AT, 26.1±7.0% dT/dtmax, 27.9±7.5% dT/dtmin, 30.7±9.3% PS and 22.0±5.7% dL/dtmax. This effect was not influenced by L-NA (-32.5±10.2% AT, -25.7±7.8% dT/dtmax, -26.7±8.6 dT/dtmin, -16.90±7.1 dL/dtmax), INDO (-34.4±7.1% AT, -27.9±6.1 dT/dtmax, -33.2±7.9 dT/dtmin, 20.2±5.0 dL/dtmax, 36.6±10.2 dL/dtmin, 25.3±7,1 PS) or PRO (26.0±8.3% AT, 25.5±6.6% dT/dtmax, 26.4±7.6% dT/dtmin, 23.7±8.0% PS, 22.9±7.0% dL/dtmax, 30.4±9.7% dL/dtmin), but was completely abolished after selective removal of the EE.
Selective AT2 stimulation induces a negative inotropic effect, which is modulated by the EE, but mediated neither by NO, prostaglandins nor EDHF. Such findings might help to better understand the therapeutic effects of selective AT1 antagonists, which are increasingly used in for treating cardiovascular diseases.

P359 Increased contractility of Ang II in the aorta of cardiomyopathic hamsters is mediated by an increased Ang II-binding capacity and release of ET-1

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Heart failure (HF) is a multifactorial and progressive disease that has been associated with multiple systemic and vascular alterations. Previous reports from our laboratory showed that in 2-month-old Bio-To2 Syrian cardiomyopathic hamsters (SCH) that have not yet developed the clinical manifestations of HF, the vascular contractility induced by 0.1 mM angiotensin II (Ang. II) was approximately 44% greater than in control animals (1.3 ± 0.1g vs. 0.9 ± 0.1 g respectively, n=9, $P < 0.05$). This finding was observed concomitantly with an increased aortic ACE activity. To further evaluate the mechanisms underlying Ang II-enhanced vascular contraction, concentration-response curves for Ang II (0.01 nM - 10 mM) were constructed in the presence and absence of prazosin (a-1 blocker), NS-398 (selective COX-2 blocker) and BQ-123 (ETA-receptor antagonist) in aortic rings from 2-month-old SCH. Age-matched golden hamsters were used as controls (CTL). The binding capacity and affinity of the AT1 receptor were also evaluated in aortic homogenates using 125I-Ang II. Our results indicate that incubation with neither 10 mM prazosin or 10 mM NS-398 modify EC50 or Emax values for Ang II indicating that norepinephrine and prostaglandins are not involved in the contractile action of Ang II. However, 10 mM BQ-123 reduced by 40% the contraction induced by 1.0 mM Ang II (from 1.05±0.04 to 0.6475 ±0.06 g/mg tissue, n=5, $P<0.05$), suggesting that the action of Ang II is mediated in part, by ET-1 release. The ET-1 dependent contraction decreases to 29% at 0.1m M Ang II concentration. Although dissociation constants for labeled Ang II were found to be similar in the aorta of SCH and CTL animals (Kd: CTL=2 nM and SCH=8 nM), 125I-Ang II binding capacity was about 10-fold greater in SCH than in CTL (Bmax: CTL= 140 and SCH = 1270 fmol/mg protein). Altogether these results suggest that in 2-month-old SCH the action of Ang II is mediated both, by an increased binding capacity for the hormone and ET-1 release.

P360 Functional evidence for the existence of two subtypes of ETB receptors in the heart

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ET-1 acts on two types of receptors, ETA and ETB. The later can be further subdivided in ETB1 (endothelial), which promote vasodilation and ETB2 (muscular), which mediate vasoconstriction. This study investigated the distribution and the effects of ETB stimulation in the heart.
The study was performed in papillary muscles from New Zealand white rabbits (n=73; Krebs-Ringer: 1.8mM CaCl2, 35°C). ET-1 (10^{-9}M) was given in absence (n=9) or presence of BQ-123 (selective ETA antagonist, n=9). Effects of IRL-1620 (ETB1 agonist; 10^{-10}M to 10^{-6}M) and Sarafotoxin-S6c (SRTXc 10^{-10}M to 10^{-6}M; ETB agonist) were evaluated in muscles with intact (IRL1620 n=7; SRTXc n=6) or damaged endocardial endothelium (EE; IRL1620 n=8; SRTXc n=7). SRTXc effects were also studied in presence of: (i) NG-Nitro-L-Arginine (L-NA; nitric oxide synthase inhibitor, n=8), (ii) Indomethacin (INDO; cyclooxigenase inhibitor, n=7), (iii) BQ-788 (ETB2 antagonist) with intact (n=6) and damaged EE (n=6).
ET-1 alone increased 64±18% active tension (AT), but decreased it by 4±2% in presence of BQ-123. In muscles with intact EE, SRTXc alone did not significantly alter myocardial performance. SRTXc (10^{-6}M) increased, however, AT by 120±27%, when EE was damaged, and by 39±8% or 23±6%, in presence of L-NA or INDO, respectively. In presence of BQ-788, SRTXc decreased AT (21±3% at 10^{-6}M), in muscles with intact EE, an effect that was abolished when EE was damaged. IRL-1620 also decreased AT (22±3% at 10^{-6}M) in muscles with intact EE and this effect was also abolished when EE was damaged.
The present study showed that ETB mediated negative inotropic effect is presumably due to ETB1 stimulation, requires an intact EE and is mediated by NO and prostaglandins; while, ETB mediated positive inotropic effect, observed when EE was damaged, or NO and prostaglandins synthesis inhibited is presumably due to ETB2 stimulation.

P361 Evidence of adherence of radiolabeled selected bone marrow stem cells to the previously infarcted non-viable anterior myocardial segment after intracoronary administration

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Background: Recent reports using intramyocardial (surgical or percutaneous) or intracoronary administration have focused on using bone marrow (BM) derived stem cells (BMSC) for myocardial regeneration. The latter method of delivery employs an angioplasty balloon catheter, through which BMSC can be slowly infused into the appropriate vascular territory. The percentage of BMSC thus adhering to the vascular bed is presumably low, but such documentation in patients (pts) with ischemic cardiomyopathy is lacking. We sought to evaluate the adherence of BMSC in the arterial vasculature following intracoronary administration.
Methods: Four male pts (age 50±12) with an old non-viable myocardial infarction (dating 32±19 months) were included in the study. The left ventricular ejection fraction was 35.1±4.6%. After BM harvesting (3 pts) or peripheral blood stem cell collection after mobilization with GCSF (1 pt), AC133+ hematopoetic stem/progenitor cells were isolated using the immunomagnetic method MACS (Magnetic Activated Cell Sorting). The selected BMSC were then incubated for 10 min and labeled with Tc-99m in conjuction with HMPAO, a white blood cell binding substrate (exametazime). Subsequently they were slowly infused into the proximal left anterior descending artery (LAD) (BMSC number 14.1±9.8 X106). The procedure was uncomplicated in all pts. A myocardial SPECT imaging was performed one hour after the procedure and in one pt again after 12 hours.
Results: In all pts we observed adherence of the radiolabeled BMSC in the LAD territory. High quality images with significant uptake were clearly documented corresponding to the anatomical vascular bed of infusion. Minimal uptake was seen in the liver and spleen.
Conclusions: In this first documentation in humans, radiolabeled BMSC were clearly seen adhered to the infarcted anteroapical wall. The intracoronary route of administration allows for homogeneous delivery of BMSC, that remained in situ at least for 12 hours after delivery.

ATHEROSCLEROSIS I – BASIC SCIENCE

P362 One-year efficacy and safety of pravastatin in children and adolescents with heterozygous familial hypercholesterolemia

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Heterozygous familial hypercholesterolemia (HeFH) is a common genetic disease due to mutations of low-density lipoprotein (LDL) receptor. HeFH is associated with significantly elevated cholesterol levels, early-onset atherosclerosis and, if untreated, shortened lifespan. In children with HeFH, dietary interventions are often insufficient, and cholesterol lowering treatment with drugs is considered appropriate. We have recently reported the pharmacokinetics of pravastatin in children. However, the long-term safety of pravastatin in children is poorly known.
Aim: To assess the efficacy and safety of pravastatin in children and adolescents with HeFH.
Methods: The criteria were the following: diagnosis of FH verified by LDL receptor mutation analysis or lymphocyte test (assaying functional LDL receptors on lymphocytes); patient age > 4 years; serum total cholesterol > 6 mmol/L regardless of dietary intervention. Thirty-five patients (22 girls, 13 boys; age range 4.1 - 18.5 y) were enrolled. Pravastatin was started at 10 mg/d with a forced titration by 10 mg at 2, 4 and 6 months, until the target cholesterol level (< 5 mmol/L) was reached. The primary efficacy outcome measures were total and LDL cholesterol levels, carotid artery intima-media thickness, and the prevalence of Achilles tendon xanthomas, carotid artery plaques, and corneal arcus. Primary safety measures were growth and development.
Results: By 2, 4, 6 and 12 months, the total cholesterol levels had decreased by 19%, 20%, 23% and 27%, and the LDL cholesterol levels by 25%, 26%, 29% and 33%, respectively. A slight increase in the carotid artery intima-media thickness was seen. Before treatment, 2 patients had xanthomas, 2 carotid artery plaques, and 2 corneal arcus. At 1 y, the xanthomas in 1 patient had disappeared, and 1 additional patient had developed xanthomas, 1 carotid artery plaque, and 2 corneal arcus. Growth and pubertal development remained normal. The side effects were mild, and no clinically significant elevations in alanine aminotransferase, creatine kinase, or creatinine were seen.

Conclusions: Pravastatin was safe and well tolerated; no concerns regarding growth or pubertal development were raised. The efficacy of pravastatin in children with slight or moderate hypercholesterolemia was satisfactory, but the sufficiency in prevention of atherosclerosis in children with severe hypercholesterolemia remains to be determined.

P363 Statin restores sympathovagal dysfunction associated with monogenic heterozygous familial hypercholesterolemia

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Background: Hypercholesterolemia may alter autonomic function. No previous study investigated the effects of monogenic heterozygous familial hypercholesterolemia (MHFH) on the autonomic cardiovascular regulation.
Purpose - 1- to investigate if MHFH is associated with cardiovascular autonomic dysregulation and 2- to evaluate the role of statin treatment in modulating the cardiovascular autonomic control in these subjects.
Methods: Spectral analysis of RR interval and systolic arterial pressure (SAP) variability were obtained in 7 carefully selected normotensive and non-obese patients with MHFH [LDL-C=265 $\pm$ 26 mg/dL] (MHFH) and compared to 6 normal control subjects [LDL-C=124 $\pm$ 20 mg/dL] (CO) during supine rest position. After simvastatim treatment (40-80 mg; 3 months) hypercholesterolemic patients [LDL-C=157 $\pm$ 26 mg/dL] (SVT) repeated the same protocol.
Results: We observed that in MHFH group, total variance of RR interval was lower (807 $\pm$ 20 ms) compared to CO group (1502 $\pm$ 129 ms) [$p < 0.001$] and it was normalized after treatment (1671 $\pm$ 109 ms). The LFNU (index of sympathetic and vagal modulation) was increased in MHFH group (60 $\pm$ 2) versus CO group (46 $\pm$ 4) [$p< 0.001$] but normalized after simvastatim treatment (43 $\pm$ 3). Moreover, HFNU (index of vagal modulation) with was significantly decreased in MHFH group (40 $\pm$ 2) versus CO group (54 $\pm$ 4) [$p < 0.001$] restored after treatment (57 $\pm$ 3). LF/HF ratio (index of sympathovagal balance) was increased in MHFH group (1.5 $\pm$ 0.1) compared to CO group (0.9 $\pm$ 0.1) [$p < 0.001$], and normal in SVT group (0.8 $\pm$ 0.1). In addition, we observed that SAP variance was higher in MHFH group (17 $\pm$ 3 mmHg) versus CO group (9 $\pm$ 2 mmHg) [$p < 0.001$] and comparable in SVT group (7 $\pm$ 0.4 mmHg). The LF component of SAP (index of sympathetic modulation) in MHFH group (22 $\pm$ 3 $mmHg^2$) was greater than in both CO and SVT groups (11 $\pm$ 0.1 $mmHg^2$; 7 $\pm$ 3 $mmHg^2$ [$p < 0.001$], respectively). Furthermore, the LF component of alpha index (spontaneous baroreflex sensitivity) was significantly reduced in MHFH group (4.6 $\pm$ 0.1 ms/mmHg) compared to CO group (6.2 $\pm$ 0.3 ms/mmHg) [$p < 0.05$] and normalized after treatment (6.8 $\pm$ 0.6 ms/mmHg), indicating improvement in baroreflex function.
Conclusions: Our data are the first to show that MHFH is characterized by an increase in cardiac and vasomotor sympathetic drive, decrease in cardiac vagal modulation, and baroreflex impairment (autonomic markers of cardiovascular risk). In addition, statin promotes restoration of the physiological cardiovascular autonomic control.

P364 Effects of periadventitial vascular endothelial growth factor gene transfer

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Purpose: We compared the effects of low-efficiency (liposome-mediated) and high-efficiency (adenoviral) VEGF gene transfer on the formation of macrophage-rich lesions in hypercholesterolaemic rabbits.
Method: Macropahge-rich lesion formation was induced by collar placement around the left carotid artery of male NZW rabbits, fed on a 1.5% cholesterol diet. The endothelium remained intact throughout the experiment. At day 5, either liposome-mediated VEGF-A (n=10) and LacZ (n=10) plasmids (25μg), or adenoviruses encoding either VEGF-A (n=8) or LacZ (n=8) genes (5 x109 pfu) were transferred to the periadventitial space within the collar. Carotid arteries were analysed 9 days after gene transfer. Endothelial cells and macrophages were identified by CD31 and Ram11 immunostaining.
Results: VEGF-A transgene expression was confirmed by both RT-PCR and immunostaining. Ad-LacZ gene transfer resulted in markedly enhanced transduction efficiency compared to liposome-LacZ, as determined by b-gal staining. Compared to liposome-LacZ, liposome-VEGF transfer caused a 67% reduction in intimal thickening ($p<0.001$) and markedly reduced neointimal macrophage recruitment (224$\pm$66 vs 453$\pm$88/mm^2 neointima, $p<0.02$) without significant adventitial neovascularization. Inhibition of neointimal macrophage accumulation was associated with decreased endothelial VCAM-1 expression ($p<0.001$), but not ICAM-1. In contrast, Ad-VEGF exerted no significant effect on either intimal thickening or macrophage recruitment, compared to Ad-LacZ transfer, but stimulated a significant increase in adventitial neovascularization ($p<0.01$).
Conclusion: These results show that low- and high-efficiency VEGF gene transfer (liposome-mediated and adenoviral transduction, respectively) have differential effects on arterial intimal thickening and macrophage accumulation. Low-efficiency VEGF expression is arterioprotective, whereas high-efficiency expression induces adventitial neovascularization and is not arterioprotective. This indicates that local VEGF concentration in the arterial wall is a key determinant of the biological effects of this cytokine, with implications for its therapeutic use in cardiovascular disease.

P365 The inhibitory effect of 17β-estradiol on VEGF-induced endothelial NAD(P)H-oxidase activation is mediated by SHP-1

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Purpose: NAD(P)H-Oxidase dependent endothelial superoxide formation is inhibited by 17β-Estradiol (E2) The underlying mechanism is largely unknown, but seems to involve rac1. We investigated in cultured endothelial cells, whether the tyrosine phosphatase SHP-1 (SH2-domain-containing tyrosine phosphatase-1) inhibits VEGF-induced superoxide formation, whether this is due to decreased NAD(P)H-Oxidase activity, and whether SHP-1 also participates in E2-mediated inhibition in endothelial NAD(P)H-Oxidase activity.
Methods and Results: VEGF (10 ng/ml) enhanced endothelial superoxide formation by 46% (n=28, $P<0.01$), which was caused by a duplication of NAD(P)H-Oxidase activity (n=12) and prevented by the specific NAD(P)H-Oxidase inhibiting peptide gp91ds-tat, but not by a scrambled peptide (n=9, $P<0.01$). E2 (100 nM) reduced VEGF-induced superoxide levels to basal values (n=18, $P<0.01$). Inhibiting endothelial SHP-1 with a specific inhibitor of SHP-1, sodium stibogluconate (SS, 10 μg/ml, n=20) or antisense oligodesoxynucleotides against SHP-1 (n=20) significantly increased basal endothelial superoxide formation. VEGF-dependent superoxide formation was also significantly increased by pretreatment of cells with antisense oligodesoxynucleotides against endothelial SHP-1 (n=9, $P<0.01$). The inhibitory effect of E2 on VEGF induced superoxide formation, however, was lost following preincubation of endothelial cells with SS (10 μg/ml, n=6) or by pretreatment of cells with antisense against SHP-1 (n=6). Both, VEGF and E2 significantly enhanced SHP-1 activity (by 47% and 32%, respectively). Inhibition of SHP-1 by SS also prevented VEGF-dependent endothelial nitric oxide production, probably due to increased superoxide formation (Griess-Reaction).
Conclusions: SHP-1 mediates E2-dependent inhibition of endothelial NAD(P)H-Oxidase. As VEGF enhances NAD(P)H-Oxidase activity and SHP-1 activity at the same time, SHP-1 seems to function as an important auto-inhibitory regulator of NAD(P)H-Oxidase and superoxide release from the endothelium, which also mediates the effects of Estradiol.

P366 Previous statin therapy associated with lower acute inflammatory response and lower in-hospital mortality in the setting of ST-elevation myocardial infarction

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Background: The beneficial effect of treatment with statin on the long term prognosis in pts with coronary artery disease is unequivocal. Additionally, it has been shown that statins decrease plasma C-reactive protein (CRP) levels in these pts. However, the influence of previous statin therapy on the acute inflammatory response and the prognosis in the case of acute coronary event has not been previously evaluated. The aim of the present study was to investigate the impact of previous statin therapy on both the plasma CRP levels upon admission and in-hospital mortality in the setting of ST elevation myocardial infarction (STEMI).
Methods: A total of 2654 consecutive pts who admitted in our department during the last 5 years were studied. The patients were divided into 3 groups: Non-hypercholesterolemics (I); hypercholesterolemics without previous statin therapy (II); and hypercholesterolemics with previous statin therapy for at least 1 month before the current STEMI (III). Hypercholesterolemics were consider those pts with previously known treated or utreated hypercholesterolemia, or total cholesterol levels upon admission >200mg/dl.
Results: There were 993(37.4); 1284(48.4%); and 377(14.2) pts in the I; II; and III group respectively. The whole incidence of in-hospital mortality was 12.8%. There was no any difference in either plasma CRP levels (1.21mg/dl vs 1.23mg/dl; p=0.9 for groups I and II) or in-hospital mortality (13.4% vs 13.6; p=0.7 for groups I and II) between group I and II. However, group III pts had lower plasma CRP levels (0.79mg/dl vs 1.21mg/dl; p=0.02 for groups III and I, 0.79mg/dl vs 1.23mg/dl; p=0.01 for groups III and II) and lower in-hospital mortality (9.1% vs 13.4; p=0.004 for groups III and I, 9.1% vs 13.6; p=0.001 for groups III and II) than the other 2 groups. After adjustment for baseline differences between the study groups previous therapy with statin was an independent predictor of more favourable in-hospital prognosis.
Conclusions: The results of the present study suggest that previous statin therapy restrain acute inflammatory response and in-hospital mortality in the setting of STEMI.

P367 Atorvastatin improves endothelial function by decreasing vascular superoxide and expression of gp91phox NAD(P)H oxidase sub-unit in dyslipidemic rabbits

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Purpose: Vascular superoxide anion (O2.-), mainly produced by NAD(P)H oxidases (NOX), is one of the major reactive oxygen species responsible for atherogenesis. The aim of our study was to assess: 1) the effects of atorvastatin (ATOR) on vascular O2.- levels, 2) the expression of endothelial NOX sub-unit p67phox and gp91phox, 3) endothelial function, 4) cardiac functional parameters following an ischemia-reperfusion sequence.
Methods: 20 NZW rabbits were randomised in CONTROL group (CTRL, n=9) or ATOR group (n=11, 10 mg.kg-1.d-1, p.o) and fed for 30 days with 0.5% cholesterol chow. At 30 days, infra-renal aortas were tested to assess vascular O2.- with Dihydroethidium (DHE, 5 μM) as an O2.- fluorescent probe. Aortas were immunostained for p67phox and gp91phox. Endothelium-dependent and independent vasodilatation of iliac arteries was studied by constructing cumulative concentration-response curves to acetylcholine (ACh) and Sodium Nitroprusside (SNP) respectively. Finally, the hearts were perfused (Langendorff method) to study functional recovery after local ischemia.
Results: Aortic O2.- levels evaluated with DHE were lower in the ATOR group in comparison with CTRL (21.4 $\pm$ 1.2 vs 13.8 $\pm$ 1.4% fluorescence, $p<0.001$). Immunostaining for p67phox was not significantly modified by ATOR treatment in comparison with CTRL (0.45 $\pm$ 0.11 vs 0.78 $\pm$ 0.21, ns). In contrast, there was a marked decrease for gp91phox staining in the ATOR group compared to CTRL (0.46 $\pm$ 0.11 vs 1.54 $\pm$ 0.18, $p<0.001$). ATOR improved endothelium-dependent vasodilatation induced by ACh compared to CTRL (Emax = 32 $\pm$ 4.6% vs 13 $\pm$ 3.7%, $p<0.05$) when endothelium-independent vasodilatation induced by SNP was not modified (Emax = 76.45 $\pm$ 3.8% vs 70.0 $\pm$ 4.3%, ns). Concerning cardiac functional parameters (such as rate pressure product) following ischemia, ATOR treatment did not have a significant effect compared to CTRL.
Conclusion: Modulated global vascular levels of O2.- induced by ATOR were associated with improved endothelial function and lower expression of endothelial NOX gp91phox sub-unit with no modification of cardiac functional parameters. These data show that, in our model, the main effects of ATOR concern arteries, especially the aorta rather than the heart. Further studies are required to determine whether long-term ATOR therapy could improve heart recovery following ischemia-reperfusion sequences.

P368 Effect of simvastatin on coronary atherosclerosis and endothelial function

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Background: Hypercholesterolemia and coronary atherosclerosis are often accompanied by endothelial dysfunction. Angiography of coronary arteries only reflects changes in luminal dimensions. With intravascular ultrasound (IVUS) cross-sectional and longitudinal images of both lumen and the vessel wall can be obtained. From this the volumes of plaque, lumen and vessel can be calculated using ECG-triggered three-dimensional IVUS. The aim of the study was to investigate the effect of lipid-lowering by simvastatin on coronary atherosclerotic plaques as changes in plaque volume and on endothelium dependent vasodilation (EDD) in the brachial artery.
Methods: In 40 male patients with hypercholesterolemia and a non significant coronary artery lesion IVUS during ECG-triggered pullback was performed and brachial artery responses to reactive hyperemia and to nitroglycerin (NTG response) were measured with a 7.5 MHz linear-array ultrasound transducer. Measurements were assessed at baseline, after 3 months on a lipid lowering diet and further 12 months on simvastatin 40 mg/day.
Results: Mean age was 57.7 $\pm$ 8.7 year. No patients were diabetics and 42.5% were smokers. During 12 months on simvastatin a significant reduction in total cholesterol of 31.0% (6.1 $\pm$ 0.8 vs. 4.2 $\pm$ 0.7, $p<0.001$) and LDL cholesterol of 42.6% (4.0 $\pm$ 0.8 vs. 2.2 $\pm$ 0.6, $p<0.001$) was obtained. At the end of the 12 months simvastatin therapy period a significant reduction in coronary plaque volume of 6.3% ($p<0.001$) was seen and endothelial function in the brachial artery was improved with a significant increase in EDD of 36.7% (p=0.008). Neither coronary plaque volume, EDD nor lipids were influenced by 3 months diet. By univariate multiple linear regression analysis no independent predictors for relative changes in plaque volume after simvastatin therapy were found.
Conclusion: Lipid-lowering therapy with simvastatin for 12 months produced significant regression of coronary atherosclerosis as measured by IVUS accompanied by an improvement in brachial artery EDD.

P369 Effects of maximal doses of Atorvastatin on indices of inflammation, thrombogenesis and matrix remodelling in "high-risk" patients with ischaemic heart disease

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Recent evidence suggests that higher doses of statins could improve clinical outcomes compared to conventional doses, but whether this benefit is due to 'additional' pleiotropic effects is uncertain. We hypothesised that high risk patients show abnormal indices of inflammation (C-reative protein, CRP), thrombogenesis (prothrombin fragment 1+2, F1+2), and matrix remodelling (matrix metalloproteinase-1, MMP-1, and its tissue inhibitor, TIMP-1) in spite of being treated with a 'standard' dose of atorvastatin (40 mg/day), and that using the highest doses of atorvastatin (80 mg/day) would beneficially improve these research indices.
Methods: We studied 27 'high-risk' patients (inclusion criteria: severe triple vessel but rejected for by-pass for extensive coronary disease, severe effort angina after coronary artery by-pass and premature coronary disease with 3 or more risk factors) with an abnormal lipid profile despite 40 mg atorvastatin/day, at baseline and at 3 months after increasing the dose to 80 mg/day. Baseline results in patients were compared to 24 healthy controls.
Results: At baseline, patients still showed a pro-inflammatory and prothrombotic state, with decreased levels of MMP-1 (the most important enzyme in the extracellular degradation of collagen) and raised levels of its inhibitor, TIMP-1. When atorvastatin was increased to 80 mg/day, significant reductions in LDL-cholesterol, CRP and F1+2 levels were observed, whereas MMP-1 and TIMP-1 levels increased. No adverse effects were observed in any patients.

Research indices

	Controls	Patients (at baseline, on atorvastatin 40mg)	Patients (after 3 months on atorvastatin 80mg)
LDL-Chol (mg/mL)	127±27	163±49*	122 ±47**
CRP (mg/dL)	0.10 (0.03-0.35)	0.30 (0.15-0.60)*	0.14 (0.09-0.31)**
F1+2 (nmol/dL)	0.32 (0.27-0.42)	0.50 (0.42-0.63)*	0.42 (0.30-0.45)**
MMP-1 (ng/mL)	4.28 (3.91-5.28)	3.92 (3.07-4.75)*	4.20 (3.51-5.74)**
TIMP-1 (ng/mL)	551 (437-670)	649 (530-808)*	686 (597-832)**

$p<0.05$ *patients vs controls and **40mg vs 80mg

Conclusions: In spite of atorvastatin 40mg daily, 'high risk' patients still demonstrated a proinflammatory and prothrombotic state, with abnormal extracellular remodelling. Doubling the dose of atorvastatin resulted in significant improvements in these pathophysiological processes.

P370 Detection of increased temperature of the culprit lesion after recent myocardial infarction: the favorable effect of statins

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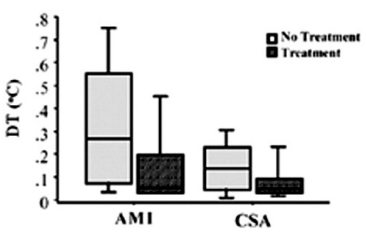
Background: Increased thermal heterogeneity has been demonstrated in atherosclerotic plaques, with the higher temperature recorded in acute myocardial infarction (MI). Dietary or treatment interventions reduce heat production. Purpose of the study is to investigate whether increased plaque temperature is maintained for a prolonged period after MI and the role of statin administration.
Methods: We enrolled 55 patients, 29 with recent MI (2-4 months) and 26 with chronic stable angina (CSA). All patients underwent coronary plaque temperature measurements. Temperature difference (DT) was designated as the temperature of the culprit atherosclerotic plaque minus the temperature of the proximal healthy vessel wall.
Results: Under treatment with statins were 19 patients with recent MI and 14 with CSA. In patients with recent MI DT was 0.19±0.18°C, while in patients with CSA was 0.10±0.08°C (p=0.03). Patients treated with statins had lower DT compared to untreated patients (0.10±0.11 versus 0.20±0.18°C, p=0.01). Treated patients with recent MI had similar DT compared to CSA patients treated with statins (0.13±0.13 versus 0.07±0.06°C, p=0.14), while untreated patients with recent MI had substantially increased DT compared to untreated patients with CSA (0.28±0.22 versus 0.14±0.10°C, p=0.04) (figure).



Conclusion: Increased plaque temperature is observed for an extended period after myocardial infarction, indicating that the inflammatory process is sustained

after plaque rupture. Statins have a beneficial effect after MI on plaque temperature.

P371 The effect of fenofibrate on inflammatory markers and serum paraoxonase activity in patients with combined hyperlipidaemia

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Inflammation and oxidation of LDL cholesterol constitute the initial stages in atherogenesis. It has been suggested that paraoxonase, an enzyme present on HDL, protects lipoproteins from oxidative modifications and has an antiatherogenetic effect. Recent meta-analyses indicate that elevated triglycerides are also an independent risk factor for coronary artery disease. Fibrates are used for the treatment of patients with combined hyperlipidemia. However less is known about pleotropic effect of fibrates. In this study we investigated the effects of fenofibrate on serum paraoxonase activity and inflammatory markers in addition to their lipid lowering functions in patients with combined hyperlipidemia.

Methods: Fifty patients (mean age 50±8.7 years) with a history of combined hyperlipidemia were enrolled into the study. Laboratory parameters, including serum lipids, inflammatory markers (high sensitivity C-reactive protein (hs-CRP) and fibrinogen) and paraoxonase activity were determined before and after 8 weeks of 250 mg per day fenofibrate treatment.

Results: After eight weeks of treatment, there had been a decrease of 28% in total cholesterol, 32% in LDL cholesterol, 55% in triglycerides and an increase of 18% in HDL cholesterol level when compared with baseline. All the changes in lipid levels were statistically significant. There had been a decrease of 41% (from 3.9±0.9 mg/dl to 2.3±0.48 mg/dl, $p<0.0001$) in the plasma fibrinogen levels and 71% (median value: from 1.28 mg/dl to 0.36 mg/dl; $p<0.0001$) in hs-CRP levels when compared with baseline levels. It was found that serum paraoxonase level was significantly increased after fenofibrate treatment (from 200±77U/L to 232±82U/L; $p<0.001$). We found significant correlation between changes in HDL cholesterol and paraoxonase activity after eight weeks treatment ($r=0.46$, $p=0.018$).

Conclusion: In conclusion eight weeks treatment with fenofibrate reduced the markers of inflammation and improved be antioxidant status in addition to lipid modifing effects.

P372 The AUDIT Study: a worldwide survey of physician attitudes about diabetic dyslipidaemia

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In controlled clinical trials, patients with diabetes benefit from lipid-lowering therapy, but in practice treatment rates remain low and only small numbers achieve lipid goals. The objective of the AUDIT study is to investigate and compare current worldwide clinical practice patterns in the evaluation and treatment of dyslipidaemia in type 2 diabetes. The survey assesses the prevalence of cardiovascular disease (CVD) and lipid abnormalities, lipid goals that physicians aim to achieve, factors that influence lipid goals, lipid-lowering drugs used, guidelines followed, and reasons for poor lipid control. Diabetes specialists in 50 countries across five continents were invited to complete a confidential, Internet-based survey. Preliminary analyses of the first 1128 questionnaires show that ≥90% of physicians assess at least one of the following: total cholesterol, LDL-C, HDL-C or triglycerides. Relatively few physicians utilize total cholesterol:HDL-C ratio (36%) and non-HDL-C (15%). A higher percentage of physicians aim to achieve a lower LDL-C treatment goal in patients with CVD versus those without CVD (table). Only one in five physicians believe that ≥80% of patients reach their LDL-C goal. Most physicians (36%) follow national society guidelines for lipid management; 28% globally follow ADA guidelines. Blood pressure control (30%), lipid management (27%), glycaemic control (23%) and smoking cessation (20%) are considered to have the greatest impact on reducing CVD risk.

LDL-C goal, mmol/L (mg/dL)	<2.5 (<100)	2.5-3.5 (100-130)	3.6-4.2 (131-160)
Patients with CVD	74%	24%	2%
Patients without CVD	19%	76%	5%

Percentages of physicians using different LDL-C treatment goals

Conclusion: The AUDIT study has shown a disparity in the management of dyslipidaemia in patients with type 2 diabetes with CVD versus those without CVD. These results demonstrate the need for further educational efforts to ensure that all patients with diabetes receive appropriate lipid-lowering therapy to reduce the global burden of CVD.

P373 Effect of physical fitness on C-reactive protein in subjects with the metabolic syndrome

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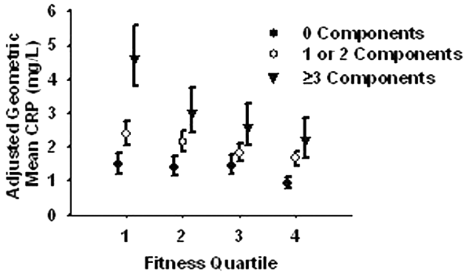
Background: Recent studies have shown an association between the metabolic syndrome (MetS) and subclinical inflammation, as determined by elevated C-reactive protein (CRP). Physical fitness is associated with multiple salutary effects including lower risk for diabetes and improved insulin resistance. We studied the effect of fitness on CRP levels in relation to the MetS.

Methods: Physical fitness was assessed in a cross sectional study (n = 1640; age, 50 ± 10 years) using the Bruce treadmill protocol. CRP was measured using a high-sensitivity assay.

Results: Geometric mean CRP levels were calculated across quartiles of physical fitness in subjects without metabolic abnormalities, subjects with 1-2 components of the MetS (e.g. hypertension and low HDL), and subjects with the MetS (≥ 3 metabolic abnormalities) after adjustment for age, gender, smoking habit, presence of coronary disease and use of medications. A strong inverse trend for decreasing CRP levels with increasing fitness quartiles was present in subjects without metabolic abnormalities ($P = 0.001$), subjects with 1 or 2 components of the MetS ($P < 0.0001$) and subjects with the MetS ($P < 0.0001$). The effect of fitness was particularly robust among subjects with the MetS (Figure). When used as a continuous variable in a linear regression model, the geometric mean of CRP decreased by 0.058 mg/L (95% CI 0.038 to 0.078 mg/L) for each 1 unit increase in metabolic equivalents (METs).



CRP According to Fitness Quartile.

Conclusion: Physical fitness is an important determinant of CRP levels in subjects with the MetS. The effect of physical fitness on individuals with the MetS appears to be more pronounced as compared to subjects without metabolic abnormalities, emphasizing the potential beneficial effects of exercise in these subjects.

P374 Adipocytes release a heat- and trypsin-resistant growth factor for vascular smooth muscle cells: effects of obesity and aging

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Purpose: Adipocytes release hormonal substances regulating vascular smooth muscle cell (SMC) proliferation. The present study investigated the effects of adipocytes and perivascular adipose tissue on SMC proliferation in obesity and aging.

Methods and Results: Conditioned medium was prepared from cultured premature and differentiated 3T3-L1 adipocytes, from peri-aortic adipose tissue of male young (3 months) and old (24 months) WKY rats, and from lean and obese Zucker fa/fa rats (3 months) which genetically develop the key components of metabolic syndromes i.e. obesity, dyslipidemia, insulin resistance and diabetes mellitus. The conditioned medium from differentiated (but not premature) adipocytes stimulated human SMC proliferation, which was resistant to heat or trypsin, although over 70% inhibition of p42/44mapk activation by the conditioned medium was observed by both treatments. While charcoal fully eliminated the growth promoting effect of the conditioned medium, phospholipase B which hydrolyses lysophosphatidic acid inhibited SMC proliferation only by 33±3%. Treatment of adipocytes with the cyclooxygenase inhibitor indomethacin did not affect the growth promoting effect. Moreover, conditioned medium prepared from 400 mg of peri-aortic adipose tissue (4 hours conditioning) also stimulated SMC proliferation. This effect was significantly enhanced in aged rats, but not in obese Zucker fa/fa rats. However, it is of particular importance to notice that obese rats, compared to the lean littermates, have significantly increased body weight (451±19 vs 330±5 g), more peri-aortic fat (0.79±0.01 vs 0.44±0.05 g) and higher peri-aortic fat/body weight ratio [$(1.8\pm0.1$ vs $1.3\pm0.1)\times10^{-3}$] ($p<0.05$).

Conclusions: Adipocytes release a so far undescribed heat- and trypsin-resistant SMC growth factor(s) with lipophilic characteristic. Perivascular adipose tissue stimulates SMC proliferation, which is enhanced in aged WKY rats and also in obese Zucker fa/fa rats, if the absolute amount of perivascular fat mass was taken into account in the obese animals. These results implicate a potential

role of the novel adipocyte-derived SMC growth factor in vascular disease under pathological conditions.

P375 Vascular superoxide production in human coronary artery disease. Relationships between Nox expression and oxidase activity

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Oxidative stress plays important roles in the pathogenesis of atherosclerosis. Expression of NAD(P)H oxidase (nox) has been recently shown to correlate with the extent of human coronary atherosclerosis. However, the differences in oxidase activities, in relation to nox protein expression between patients with and without coronary artery disease (CAD) are still unclear.

Methods: Accordingly, we studied vascular superoxide production (O2-.) and NADPH oxidase activity (by lucigenin (5uM)enhanced chemiluminescence; ferricytochrome c and dihydroethidium), as well as NAD(P)H oxidase protein and mRNA subunit expression (by immunoblotting and real-time PCR) in human coronary artery (hCA) segments from explanted failing hearts from 16 patients with CAD and generalized atherosclerosis (TIA, PAD) and from 16 patients without CAD.

Results: Superoxide anion production was greater in hCAs from CAD patients(19.5±1.8 vs 14.5±1.4 RLU/s/mg; $p<0.01$). DHE confirmed that O2-. was increased in CAD, also in vessels without atherosclerotic plaque. In coronary arteries without atherosclerotic plaque (nonCAD), O2-. production was doubled within branch points (of D1), when compared to continuous LAD. Superoxide production was inhibited by an NAD(P)H oxidase inhibitor apocynin (65% inhibition; $p<0.001$) and by oxypurinol (xanthine oxidase inhibitor; 30% inhibition, $p<0.01$). Substrate stimulation studies showed similar results confirming that in human coronary arteries NAD(P)H oxidases (65%) and xanthine oxidase (30%) are primary sources of O2-. NAD(P)H oxidase activity was higher in hCAs from CAD pts (1.6±0.2 vs 0.9±0.3; $p<0.01$) and this difference was abolished by preincubation with PKC inhibitor chelerethrine (3uM) (80% inhibition; $p<0.001$). Protein and mRNA levels for p22phox and nox2 were increased in hCAs from CAD patients. Multiple stepwise regression indicated that nox4 mRNA levels were independently associated with oxidase activity (Beta=+0.46; $p<0.001$). p22phox and nox2 were associated with oxidase activity only after taking into account the levels of MfCSFR mRNA (inflammatory cell marker).

Conclusions: NAD(P)H oxidases are predominant sources of superoxide production in human coronary arteries. Their activity and expression is increased in CAD. Nox4 mRNA levels appear to be the strongest determinants of total NAD(P)H oxidase activity in human coronary arteries. NAD(P)H oxidase inhibitors could in future be useful in the prevention of coronary atherosclerosis.

P376 Erythropoietin delays endothelial cell senescence by preserving telomere length

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Purpose: Replicative senescence and telomere shortening of endothelial cells has been suggested to play a critical role in atherogenesis. In line with this proposal, recent findings have shown that the rate of telomere attrition is increased in patients with coronary artery disease (CAD). Accumulating evidence suggests that the kidney erythroid cytokine erythropoietin (EPO) has cardiovascular protective effects. Here we examined the effects of EPO on endothelial cell senescence.

Methods: Human umbilical vein endothelial cells (HUVECs) were kept in culture by continued passaging up to passage 18. RhEPO (100ng/ml) was added to the cultures from passage 7 every 48 hours. Senescence was determined by staining HUVECs with senescence associated (SA)-beta-galactosidase (pH 6.0). Telomere length was measured by a novel PCR-based method in which a relative quantification (rq) ratio of telomere sequence to single copy gene (36b4) is determined for each sample. Telomerase activity was determined using the Telomeric Repeat Amplification Protocol (TRAP) assay.

Results: RhEPO significantly reduced the number of SA-beta-galactosidase positive cells starting at passage 9 (34 ± 7% reduction) with a maximal effect at passage 14 (51 ± 9% reduction, $p<0.05$). Inhibition of endothelial cell senescence was associated with a delay in the telomere attrition rate in EPO treated cells evident at passage 8 (rq ratio of 1.11 vs. 1.00 in controls, $p<0.05$), maximal at passage 11 (rq ratio of 1.16 vs 0.96, $p<0.01$) and still present at passage 16 (rq ratio of 0.87 vs. 0.72). Moreover, telomerase activity was significantly augmented following EPO stimulation (2 fold increase at passage 10 and 3 fold increase at passage 14).

Conclusions: EPO delays endothelial cell senescence via activation of telomerase and maintenance of telomere length. EPO or EPO-mimicking drugs may have a protective action against plaque formation and CAD.

P377 Different apoptosis rates of vascular smooth muscle cells from human coronary artery bypass vessels

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Long-term patency of coronary artery bypass grafts is determined by vascular smooth muscle cell (VSMC) proliferation leading to neointima formation and atherosclerosis. Radial artery (RA) patency rates seem to be in between those from internal mammary artery (MA) and saphenous vein (SV). We therefore examined whether and, if so, why growth of VSMC from these vessels differs accordingly. After 6 days of serum stimulation, RA VSMC number and 3H-thymidine incorporation was lower than SV, but higher than MA. In contrast, RA VSMC exhibited only minimal growth to PDGF-BB, which was comparable to MA and differed from SV. Propidium iodide incorporation after PDGF stimulation showed identical cell cycle distribution in VSMC from all three vessels. Similarly, Western blotting for cell cycle proteins revealed an identical expression pattern of the cyclin-dependent kinase inhibitors (CKI) p21, p27, p57, cyclin-dependent kinase 2 (cdk2), and cyclin E. Cdk2 kinase assay confirmed that G1 progression was identical in VSMC from all three vessels. In contrast, cell death as determined by LDH release, Hoechst staining, and FACS-measurement of fragmented DNA was higher in VSMC from MA than those from RA and even more so from SV, indicating that different cell death rates determine cell growth. Addition of the caspase inhibitors Z-VAD-fmk and Boc-D-fmk during PDGF stimulation abrogated the differences in growth, suggesting that the different cell death rates are related to apoptosis. Levels of activated and total Akt were determined by Western blotting analysis, which revealed lower expression in VSMC from MA than those from RA and even more so from SV. As Akt can inhibit apoptosis, different activation levels of Akt likely determine the different apoptosis rates in these VSMC. Because the aorta is prone to develop atherosclerosis, we also compared VSMC from MA with those from aorta. Growth rates of aortic VSMC in response to PDGF-BB were higher than those from MA. Analogous to the observations in coronary artery bypass vessels, the difference in growth was abolished by the two caspase inhibitors, suggesting that different VSMC apoptosis is not only relevant for bypass graft disease, but also for the heterogenic distribution of atherosclerotic lesions. Thus, our observations indicate that different VSMC apoptosis due to different Akt activation rather than different proliferation rates determine the heterogenous manifestations of atherosclerotic changes in coronary artery bypass grafts and the aorta.

NUCLEAR CARDIOLOGY/MAGNETIC RESONANCE IMAGING AND CARDIAC RADIOLOGY

P378 A combined single-session analysis of adenosine perfusion and of high-dose dobutamine stress cardiovascular magnetic resonance improves diagnosis of ischaemia

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Purpose: With CMR, both the analysis of myocardial perfusion during adenosine stress (Perfusion-CMR) and of wall motion during dobutamine stress (Stress-CMR) were shown highly accurate for the diagnosis of myocardial ischemia. A combined single session dual stress protocol has not been reported so far. We compared the diagnostic accuracy of perfusion-CMR and stress-CMR in an unselected patient population, and determined whether a combined single-session assessment of myocardial perfusion and wall motion improves diagnosis of ischemia, with invasive quantitative coronary angiography (QCA) serving as reference standard.

Methods: 100 consecutive patients (62±9 years; prior myocardial infarction: 30%; prior PTCA: 48% and CABG: 27%) were examined (1.5 T Philips) prior to clinically indicated invasive coronary angiography. Myocardial perfusion was visually assessed during the first pass of a contrast agent bolus during adenosine infusion (140 μg.kg-1.min-1) and at rest (3 short axis images per heartbeat; TFE-EPI hybrid sequence; pp-delay 200 ms; TR/TE/flip 3.6/12/30). Stress-CMR images were acquired at rest and during a standardized high-dose dobutamine-atropine protocol in 3 short-axis (same 3 short-axis views as for perfusion-CMR), a 4-, a 3- and a 2-chamber view (single slice steady state free precession technique; TR/TE/flip 3.0/1.5/55). Regional wall motion was assessed using a multiple screen format, a 16 segment model, and a 4-point scoring system. A new or worsening wall motion abnormality in ≥1 segment was considered positive for ischemia. In the absence of ischemia, failure to attain 85% of age-predicted maximal heart rate was defined as a non-diagnostic result.

Results: Significant coronary artery disease (≥50% diameter stenoses by QCA) was found in 69% of patients. No significant adverse effects occurred during stress testing. Sensitivity, specificity and diagnostic accuracy of stress-CMR were 87%, 84% and 86%, respectively, with one non-diagnostic test (1%; target heart rate not reached). For perfusion-CMR, sensitivity, specificity and diagnostic accuracy were 88%, 77% and 85%, respectively, with 3 non-diagnostic tests (3%;

poor image quality). For a combined approach, these values were 97%, 71% and 89%, respectively, with 100% diagnostic tests.
Conclusions: A combined single session assessment of perfusion-CMR and stress-CMR is safe and feasible. Visual assessment of perfusion-CMR has similar diagnostic accuracy than stress-CMR. A combined analysis only marginally improves diagnostic accuracy and marginally increases the number of diagnostic examinations.

P379 Can quantitative assessment of coronary artery stenosis severity improve the diagnostic accuracy of multidetector row computer tomography and magnetic resonance?

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Background: Both multislice CT and 3D navigator gated MRI are promising new techniques for the non-invasive detection of coronary artery disease. We assessed whether quantitative measurements of stenosis severity by CT (QCT) and MR (QMR) would improve diagnostic accuracy to detect coronary artery stenosis.
Methods: Fifty-one patients (42 M, 65±10 years) underwent coronary CT and MRI prior to conventional diagnostic coronary angiography. MSCT was performed using a gated 16 slice CT (IDT, Philips) while MRI was performed on a 1.5 T (Intera CV, Philips) system using a T2 prepped 3D balanced field echo sequence with respiratory navigators. Reference vessel (RVD) and minimal luminal diameter (MLD) as well as stenosis severity were computed quantitatively by two blinded observers in all vessels >1.5 mm diameter on all three modalities of coronary imaging (QCT, QMR and quantitative coronary angiography - QCA). Diagnostic accuracy of QCT and QMR was compared to visual assessment of coronary artery stenosis severity using QCA as gold-standard.
Results: A total of 469 segments >1.5 mm were assessed. Measurements of MLD, RVD and stenosis severity by QCT were highly correlated with those obtained by QCA (r=0.67, r=0.74 and r=0.72 respectively, all p<.001), however QCT significantly overestimated RVD (3.61±0.9 vs. 2.85±0.81mm, p<.001) MLD (2.51±0.98 vs. 2.21±0.93 mm, p<.001) and stenosis severity (33±24% vs. 27±25%, p<.001) as compared to QCA. QMR by opposition underestimated RVD (2.76±0.44 mm vs. 2.85±0.81 mm, p<.001) and MLD (1.53±0.63 mm vs. 2.21±0.93 mm, p<.001), while it also overestimated stenosis severity (49±22% vs. 27±25%, p<.001) vs. QCA. The correlations between measurements of RVD, MLD and stenosis severity by QMR and QCT were lower (r=0.42, r=0.43, r=0.32 respectively). ROC analysis demonstrated that QCT had significantly higher diagnostic accuracy than QMR to predict >50% stenosis by QCA. Quantification of coronary artery stenosis severity by QCT significantly improved diagnostic accuracy vs visual readings to detect >50% stenosis by QCA (83% vs 80% accuracy, p<.01). This was not the case for QMR (64% for quantitative vs 63% for visual assessment of stenosis severity)
Conclusions: Although it systematically overestimates RVD, MLD and stenosis severity as compared to QCA, QCT is superior to QMR for quantitative measurements of coronary artery stenosis severity. Quantitative measurements of stenosis severity enhance diagnostic accuracy of CT but not of MR as compared to visual readings.

P380 Cardiac perfusion magnetic resonance imaging for the quantitative assessment of symptomatic coronary artery disease. A comparison with pressure derived fractional flow reserve, coronary angiography and SPECT

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Cardiac magnetic resonance imaging (MRI) is a rapid envolving and promising method for the noninvasive assessment of symptomatic coronary artery disease (CAD). However, the used parameters are various and experience is limited. Despite several methodological problems coronary angiography (CA) and Single Photon Emission Computer Tomography (SPECT) are commonly used for morphological and functional evaluation of coronary stenoses. The pressure derived fractional flow reserve (FFR) is the well established new gold standard to invasively evaluate the functional severity of coronary lesions.
The aim of our study was to compare certain MRI derived parameters with invasive and noninvasive functional and morphological tests for the assessment of CAD.
Methods: 25 Patients with suspected CAD received a SPECT(99mTC-sestamibi, one day protocol) and MRI (Siemens Sonata, Erlangen, GE) within one week of the scheduled CA. Signal intensity curves of the first pass of a Gadolineum –DTPA bolus at rest and during hyperemia (Adenosine 140μg/kg/min) were investigated and input function corrected time to peak myocardial densitiy (TPD) and steepness of the signal intensitiy curve's upslope (US) were determined for each myocardial perfusion area. A coronary artery with lesions < 50% diameter reduction as assessed by standardized CA was stated as normal. A coronary lesion > 50% and FFR (PressureWire, Radi, SE) > 0.75 was called intermediate. If diameter reduction >50% and FFR < 0.75 was present, the lesion was defined as severe.
Results: 75 perfusion areas were evaluated. SPECT was positive in 4 of 38 (10%) normal coronary arteries, 8 of 17 (47%) intermediate and 16 of 19 (84%) severe coronary lesions. TDP was not significantly different between the three groups (11 ± 3.4; 15 ± 5.7; 13 ± 5.1; p=ns). US at rest was comparable (0,08 ± 0,17; 0.10 ± 0,035; 0.07 ± 0.01; p=ns). During stress US increased and was significantly different beween normal coronary arteries and severe coronary stenoses (0.28 ± 0.12 vs. 0.08 ± 0.01; p<0.05). The ratio US at stress and rest was 3.4 ± 1.5 (2.0-6.3) for normal coronary arteries and 1.4 ± 0.3 (1.2-1.7) and 1.1 ± 0.1 (1.0-1.3) for intermediate and severe coronary lesions, respectively (p<0.05).
Conclusion: TDP as single parameter was not able to discriminate between normal and severly stenosed coronary arteries. US and US ratio between stress and rest was significantly different between normal and functionally significant dieseased coronary arteries. The use of these MRI parameters may therefor improve the sensitivity and specificity of noninvasive identification of relevant CAD.

P381 Coronary artery disease diagnosis by magnetic resonance imaging: comparison of semi-quantitative assessment of myocardial perfusion after dipiridamol stress with single photon emission tomography

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Magnetic resonance (MR) can be used as a second level evaluation of coronary artery disease (CAD). Its accuracy is higher than that of stress-Echo or single photon emission tomography (SPECT) if a quantitative assessment of myocardial perfusion is made both at rest and after stress. In a clinical scenario a simplified cardiac MR evaluation, with a semi-quantitative assessment of a single perfusion study after pharmacologic stress, was compared with SPECT.
Methods: pts with known or suspected CAD underwent to myocardial perfusion assessment by SPECT and MR. For both tests we used a pharmacological stress (dipiridimale 0.56 mg/kg i.v. in 4 minutes). Two operators, blinded with respect to the other test result, assessed the size and the degree of perfusion defects, using a 16-segments model of left ventricle. IR turboFLASH sequences on 8 contiguous short axis planes after Gd (Magnevist Schering; Multihance Bracco) 0.15-0.20 mmol/kg i.v. bolus injection were performed. Coronary angiography, scheduled at attending physician judgment, was considered to be positive if almost one significant coronary stenosis was present.
Results: we studied 98 pts(28 female and 70 male; mean age 64±11 years), 52 with angina symptoms, 35 with a healed myocardial infarction and 11 with ischemic dilated cardiomiopathy. Agreement between MR and SPECT was found in 72 cases (74%); in 16 pts(16%) MR showed perfusion defects but SPECT was negative and in 10 pts(10%) perfusion defects were found at SPECT but not at MR. Coronary angiography was performed in 57 pts (58%). Sensitivity and specificity of MR and SPECT were similar considering significant coronary stenosis >75% (see table). With a lower cut-off (stenosis >50%) MR sensitivity and specificity values were better than those of SPECT. MR performance was optimal after an adequate learning period of the method.

MR and SPECT sensitivity/specificity

	Stenosis>75%			Stenosis>50%		
	SPECT	MR	MR*	SPECT	MR	MR*
Sensitivity	77	77	86	78	86	90
Spesificity	60	70	75	75	75	100

MR* excluded exams made in the first 9 months

Conclusion: in a clinical scenario, a semiquantitative assessment of myocardial perfusion by MR, with a single evaluation after Dipiridamole stress, shows an accuracy in CAD diagnosis at least comparable to SPECT.

P382 Incomplete resolution of ST-segment elevation is associated with severe microvasculatory dysfunction evaluated by magnetic resonance imaging

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Background: Rapid ST-resolution (STR) after reperfused acute myocardial infarction (AMI) is associated with improved long-term survival and preserved left ventricular function. In addition STR is a global index of microcirculatory function, and contrast enhanced MRI can characterize microvascular obstruction and myoardial necrosis. The aim of the present study is to clarify the relationship between STR and microcirculatory function in patients with acute myocardial infarction.
Methods: Seventy seven patients who presented with their first AMI and who were successfully revascularized during the acute phase (TIMI III) underwent cine and ceMRI of their heart between day 5 and 7. First-pass images (FPI) and De-

layed Contrast-Enhanced (CE) images were analyzed using a 17-segment model, and the extent of transmural damage was scored visually from 0 to 4. Relative Wall thickening (RWT) was measured in all segments related to to culprit artery. Serial 12-lead ECG were performed at baseline and 90 minutes after intiation of therapy. ST resolution was defined as incomplete (STR < 50%) and complete (STR > 50%).

Results: 372 segments related to the culprit artery were analysed: 293 segments related to STR > 50% and 79 segments STR < 50%. Despite successful reperfusion (TIMI 3 Flow) at the acute phase, patients with incomplete STR present residual microcirculatory dysfunction at 5 days evaluated by FPI. However, the extent of transmural infarction evlauated by CE and the segmental function revealed no difference between the two groups (Table 1).

Table 1

	STR≤50%	STR>50%	p
RWT (%)	39.1 ± 4.0	44.9 ± 2.1	ns
FPI	1.62 ± 0.19	0.84 ± 0.07	<0.002
CE	2.03 ± 0.21	1.92 ± 0.90	ns

Conclusion: These results confirm that microcirculatory dysfunction is a major factor during the post MI period. Further studies are required to evaluate the segmental relationship perfusion and function, especially with regard to developping therapeutic strategies.

P383 Detection of intraventricular thrombi by contrast enhanced magnetic resonance imaging of the heart

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Background: The presence of an intracardiac thrombus denotes an increased risk of both embolism and death. Echocardiography is known to be the gold standard for detecting intracardiac thrombi, but especially if located in the left or right ventricular apex, they might be overseen. We investigated the potential of contrast enhanced magnetic resonance imaging (ceMRI) for detecting intraventricular thrombi.

Methods: 72 consecutive patients (pts) (60±11y) with dilative cardiomyopathy or myocarditis with left ventricular ejection fraction below 35% or history of myocardial infarction, underwent transthoracic echocardiography (TTE) and ceMRI (Siemens Sonata, 1.5 T). For ceMRI, bolus tracking was done with 3 mL of contrast agent Gd-DTPA (Magnevist, Schering) in order to assess the time to peak signal intensity in the left ventricular cavity. 1 mmol/kgBW Gd-DTPA was administered followed by 20 mL of saline flush. Image acquisition was done by 3D-FLASH inversion recovery sequence, covering the left ventricle in 2-chamber view orientation and both ventricles in 4-chamber view orientation during intracavity first-pass. Image acquisition was repeated after 1 minute for delineation of intracardiac thrombi from myocardium. Same sequences were used for viability imaging by detecting areas with delayed hyperenhancement 8-15 minutes after injection of contrast agent.

Results: By TTE, 7 out of 72 pts (9.7%) had an intracardiac mass identified as thrombus located in the apex of the left ventricle. By ceMRI, 12 pts (16.7%) could be found having 13 intracavity thrombi (R=0.73) with a mean volume of 7.9±2.9 qcm. All patients with positive TTE had positive ceMRI. Additional thrombi were found by ceMRI in the right ventricular apex (n=1), left ventricular apex (n=3) and as a thin layer along aneurysmatic anterior wall myocardial scar (n=4). 9 pts had transmural myocardial scar after infarction. 1 patient had myocarditis and thrombi within both ventricles. 2 pts had severely impaired LV function without regional scar tissue. The used protocol allowed complete delineation of all thrombi against blood pool and myocardium or scar tissue, respectively. Poor image quality or limited echocardiographic window were the primary reasons for missing thrombi by TTE.

Conclusions: Contrast enhanced MRI is an accurate tool for detecting intraventricular thrombi, being even superior to transthoracic echocardiography in this patient population. Furthermore, myocardial viability imaging can be done without additional contrast agent application, providing important data regarding the etiology of thrombus formation.

P384 Quantitative myocardial perfusion assessment with magnetic resonance imaging in patients with coronary artery disease: clinical application

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Purpose: to demonstrate the feasibility of the absolute myocardial blood flow (MBF), total coronary resistance (TCR) and myocardial blood flow reserve (MBFR) quantification using MRI in patients with CAD.

Methods: A total of 19 patients with angiographically documented CAD and 9 healthy subjects were studied by MR using double-slice saturation-recovery Turbo-FLASH sequence for monitoring the myocardial first pass kinetics of Gd-DTPA-BMA at rest and during hyperemia (dipyridamole 0.56 mg/kg). The signal intensity (SI) curves were acquired within ROI for perfusion beds of the three main coronary arteries (LAD, LCX and RCA) and left ventricle cavity. Eighty five myocardial segments were included in final analysis (group 1 - supplied by "normal" coronary arteries (n=26), group 2 - supplied by arteries with non-significant diameter stenoses <50% (n=27), group 3 - supplied by arteries with significant stenoses ≥50% (n=32). Sixteen segments were revascularized subsequently (PCI or CABG). One-compartment model and slope-method were used for flow calculation. Myocardial and blood signal intensities were converted to concentration of Gd-DTPA-BMA according to the "in vitro" calibration curve.

Results: MBF was similar in groups at base line (group 1 - 0.98±0.54, group 2 - 1.24±0.53 and group 3 - 1.28±0.48 ml/g/min) but significantly lower in group 3 during hyperemia (2.57±1.23, 2.99±1.14 vs. 1.79±0.94 ml/g/min, $p<0.05$). MBFR (the ratio of flow during hyperemia to flow at base line) was significantly lower in group 3 than in groups 2 and 1 (1.4±0.7 vs. 2.7±1.3 vs. 2.9±1.2, respectively, $p<0.01$). Receiver-operator characteristic analysis of MBFR (value ≤1.6) revealed a sensitivity and specificity of 81% and 85%, respectively, for the detection of CAD as defined by quantitative coronary angiography (diameter stenosis ≥50%). TCR (mean arterial pressure divided by the flow) significantly decreased (78.8±42.2 vs. 41.3±17.3 mmHg x min x g/ml, $p<0.01$), MBF accordingly increased (1.61±0.77 vs. 2.58±0.91, $p<0.01$) during hyperemia and MBFR "normalized" (1.3±0.6 vs. 3.0±1.3, $p<0.001$) in myocardial segments after revascularization.

Conclusions: absolute myocardial blood flow and MBFR calculation by first-pass contrast perfusion MRI are feasible in patients with CAD before and after revascularization. These measurements were in agreement with modern notion of coronary circulation in patients with CAD.

COMPUTERS IN CARDIOLOGY

P385 A novel Tele-electrocardiogram system for event recording and emergencies in cardiovascular patients

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Background: Cardiovascular patients suffering from ischemic heart disease and/or arrhythmias are limited in their quality of life by the fear being faced to an unexpected heart attack. Consequently, mobility of cardiovascular patients is reduced. In the case of arrhythmias, immediate documentation is required to improve diagnostics and to enable therapy. We describe the 1-year experience with a novel Tele-ECG system in combination with a Medical Service Center.

Methods: Patients with ischemic heart, arrhythmias or on high risk for cardiovascular diseases (hypertension, diabetes mellitus, and coronary artery disease) used the Cardiophone on their own cause. The Cardiophone is a regular GSM mobile phone (Dual Band 900/1800 MHz) with 3 additional properties: Electrodes of the backside of the shell to record an ECG, integrated GPS module for tracking via satellite navigation system, and an emergency alert button with direct link to a Medical Service Center (MCS) with permanent presence of nurses and physicians on 24h duty.

Results: Within 12 months of operation 288 patients performed 12,871 voice calls to contact the MCS. Incoming calls are automatically recognised and the corresponding patient data file opens immediately. Associated to the voice calls 12,941 ECGs were transmitted and analysed on the screen. ECG analysis could be achieved in 90.6% of ECGs with the following distribution among the day: 10 p.m. – 5 a.m.: 95.5%, 5 a.m. – 3 p.m.: 88.5%, 3 p.m. – 10 p.m.: 89.4%. Contact to the MCS did not show a circadian rhythm. Call volume was 1072 per month. In average, a patient performed 3.7 calls per month. With the aid of the global positioning system, the caller's position could be determined. In the Geographic Information system (GIS) the address of the next ambulance closest to the patient's present position is shown. Dispatching of the ambulance was necessary in 7 of 1,000 cases (0,7%). Patients contacted the MSC in average 44 minutes after onset of symptoms. Admission to hopital was realised within 90 minutes.

Conclusions: The novel telemedical service concept with the Cardiophone shows rapid contact to the MSC by the patients affected. Early decision by the MSC physician fastened admittance to hospital. Overall, 91% of transmitted ECG could be analysed. The GPS-technology enhances mobility of cardiovascular patients in out-door areas.

P386 Telecardiology reduces avoidable delay in patients with ST-segment elevation myocardial infarction

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The delay between onset of symptoms and coronary care unit admission is decisive in the outcome of patients with acute myocardial infarction.

Purpose: To evaluate the impact of telecardiology for reducing the avoidable delay (AD) in acute myocardial infarction treatment.

Methods: In this retrospective study we compared the AD of patients with ST-segment elevation myocardial infarction admitted to our coronary care unit in usual care environment (group A) with those hospitalized by General Practitioners using telecardiology (group B), in the coronary care units of the same urban area. Patients with AD > 6 hours were considered as admitted during the seventh hour.
Results: In a 18-months period data about 77 group A patients (mean age 65.3±11.6 years) and 144 group B patients (mean age 70.1±14.3 years) were collected. Twenty-one patients (27.3%) of group A and all patients of group B were hospitalized using the emergency medical service system. Eleven patients (14.3%) of group A and 76 patients (52.8%) of group B were directly admitted in the coronary care unit, avoiding emergency department admission. Percentage of patients admitted within 1 hour from onset of the symptoms was 9.1% for group A and 16.7% for group B. Median time was 5 hours for group A and 3.7 hours for group B; AD was significantly reduced in group B patients ($p < 0.01$).
Conclusions: Telecardiology reduces AD in patients with ST-segment elevation myocardial infarction and increases number of patients who benefit from the so-called "golden hour".

ECHOCARDIOGRAPHY/DOPPLER

P387 Asymptomatic systolic left ventricular dysfunction: preliminary results of the DAVES study (Disfunzione Asintomatica del VEntricolo Sinistro)

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Aim: Aim of the study. This observational multicenter study was designed to assess the prevalence of asymptomatic systolic left ventricular dysfunction (LVD) in a large cohort of subjects referred for echocardiographic evaluation.
Methods: We screened 11363 patients who underwent an echocardiogram for different reasons. Patients with shortness of breath, heart failure, significant valvular heart disease, or previous heart surgery were excluded. Finally, 4136 patients (mean age 57±15 years, M/F 2113/2023) were selected and represent the final study population. Diagnosis of systolic LVD was based on either: 1. indexed left ventricular diastolic volume (biplane Simpson's method) >102 ml/m^2, or 2. left ventricular ejection fraction (biplane Simpson's method) <50%. All the measures were calculated averaging the values of 3 cardiac cycles.
Results: The prevalence of asymptomatic systolic LVD in the overall group was 8.2% (male 12.1%, female 4.1%, OR 3,1, CI 95% 2,4-4,1). According to age, the prevalence of systolic LVD was as reported in Table I. Variables associated with systolic LVD were: previous myocardial infarction (OR 5,7, CI 95% 4,3-7,4), diabetes mellitus (OR 1,8, CI 95% 1,3-2,4), coronary artery disease (OR 1,8, CI 95% 1,1-2,9), hypertension (OR 1,4, CI 95% 1,1-1,7). In a stepwise regression logistic model, predictors of systolic LVD were age (OR 1,009, CI 95% 1,001-1,018), male gender (OR 2,5, CI 95% 1,9-3,3), previous myocardial infarction (OR 1,9, CI 95% 1,2–3,2), coronary artery disease (OR 4,38, CI 95% 3,2-5,8).

Table I

Age	20-44	45-49	50-54	55-59	60-64	65-69	≥70	Overall
Nr	38	33	42	50	43	36	98	340
%	4,5	9,6	8,9	9,9	8,1	6,5	11,1	8,2
Nr of pts	849	343	471	507	528	552	886	4136

Conclusions: In this multicenter, large scale study the prevalence of asymptomatic systolic LVD was 8.2%, higher than that reported in previous observational community studies, which can be due to the different selection of patients and echocardiographic criteria. Age, male gender, and ischemic heart disease emerged as independent predictors of asymptomatic systolic LVD. Thus, echocardiographic laboratory can be a crucial gateway for screening patients at clinical risk, possibly preventing the development of symptoms of heart failure.

P388 Effect of moderate-intensity exercise training on systolic and diastolic indexes of left-ventricular function in young male individuals

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Background: Doppler tissue imaging has been frequently used to assess left ventricular function in various cardiovascular conditions. To assess the influence of exercise training on the systolic and diastolic properties of normal hearts, we studied 23 male sedentary healthy individuals, mean age of 30.8 years at baseline and after 6 months' exercise training.
Methods: all individuals underwent moderate-intensity aerobic training (1 hour/day, 3 times a week) for 6 months. Two-dimensional guided M-mode measurements of left ventricular (LV) diameters, end-diastolic thickness, ejection fraction (EF) and mass, as well as mitral, pulmonary venous inflow and LV outflow tract (LVOT) Doppler tracings were obtained at baseline and after training. Tissue Doppler velocities were obtained from mitral annulus at the septal and lateral wall.
Results: heart rate did not decrease after training (60.0±7.1 vs. 57.2 ±8.7 bpm). Septal and posterior wall thickness increased from 8.7 ±1.1 to 9.4±1.3 cm and from 8.1±1.1 to 8.9±1.2 cm, respectively ($p<0.05$), with resultant increase in LV mass and mass index ($p <0.001$). LV diameters, LVOT velocity time integral and EF were unchanged. Mitral inflow showed a decrease in late (A) wave velocity ($p<0.0001$) and an increase in Early (E)/A ratio (1.6±0.3 vs. 1.9±0.5, $p<0.05$), and a prolongation of E deceleration time (DT), $p< 0.005$. Pulmonary venous Doppler measurements (systolic and diastolic velocities and A wave velocity and duration) were unchanged. Tissue Doppler showed an increase in peak annular septal (Sa sep) and lateral (Sa lat) systolic velocities ($p<0.05$) and peak early (Ea) lateral annular velocities ($p<0.01$),shown on table 1. E/Ea ratio decreased slightly after training (6.2±4.4 vs. 5.3 ±1.1, $p<0.01$).

Table 1

	LV Mass	Mass index (g/m^2)	Peak A	DT	Sa sep	Sa lat	Ea
Baseline	151 ± 29	79±13	47±9	164±28	8.6±1.4	10.2±2.3	12.3±2.4
6 months	171±38	91 ± 18	38±7	194±16	9.5±1.3	11.3±2	13.8±2.7

Echocardiographic variables at baseline and after 6 months exercise training; for all variables, $p< 0.05$

Conclusion: The physiological increase in LV mass in response to regular exercise in healthy young men occurs in parallel with a decrease in atrial contribution to flow. LV longitudinal systolic function estimated by tissue Doppler velocities is improved despite the lack of changes in other echocardiographic systolic indexes.

P389 Load-independent asymptomatic left ventricular diastolic dysfunction in severe obesity: a Doppler tissue imaging study

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Aim: Aim of present study was to analyze early functional effects on the heart induced by isolated severe obesity, through Pulsed Wave Doppler Tissue Imaging at mitral annular level, which explores global contraction and relaxation myocardial fibers velocities and is relatively independent by load conditions. Obese subjects (O) were carefully selected in Endocrinologic Department; 19 obese (O) (13 female) (mean age: 38.5±5.3 and mean weight: 119±18 kg) and 19 healthy, non obese subjects (C) of comparable age and sex were studied. Severe Obesity was defined by BMI >35 kg/m^2 (44 ± 4 kg/m^2). All study subjects are normotensives, no diabetic and have a negative maximal exercise stress test. All subjects performed conventional 2D-Color Doppler echocardiography. PW DTI was performed in apical 4-chamber view, with sample volume placed at mitral annular level in correspondence both with basal posterior septum and lateral wall. Left ventricular mass indexed by height2.7 was significantly higher in group O: 60.1±15 vs (C) 41.6±6 g/m^2; $p<0.001$) due to a slight but significant increase in end diastolic volume ($p<0.05$) and in myocardial thickness (septum: $p<0.0001$). So, both higher heart rate ($p<0.001$) and cardiac output ($p<0.01$) induced in O an increase in preload (left atrium dilatation: $p<0.001$). Of consequence left ventricular systolic function revealed an hyper dynamic status: Ejection Fraction (EF): 78 ±5% in O vs. 63±7% in C; <0.0001). Conventional analysed left ventricular diastolic function showed a slightly but significant impairment in O group (E/A ratio of mitral flow pattern: 1.2±0.3 vs. C: 1.6 ±0.3, $p<0.05$). The ratio between Em/Am sampled at septum and lateral wall level was significantly lower in O compared with C ($p<0.001$).An impairment of active relaxation phase realised (significantly lower Em velocity in O group), while the passive relaxation phase overlapped in both groups. If we considered E/Em ratio, a load independent parameter (related with capillary wedge pulmonary pressure), it was significantly higher in O than in C ($p<0.0001$). DTI parameters better defined the real existance of diastolic dysfunction in severe obesity, a complex physiopathological model of volume overload associated with increase in pre- and after load, neuroendocrine activation, renal-sodium retention and heightened systemic oxidative stress. Experimental demonstration of cardiac steatosis and lipoapoptosis and of atrial and ventricular specific genes activation in response to overfeedings, at the light of previous data, presses us to further exploration in humans.

P390 Myocardial performance index as an independent predictor of heart failure in the acute phase of myocardial infarction

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Myocardial Performance Index (MPI) is a new doppler index that combines data of systolic and diastolic function. Our aim was to assess the usefulness of MPI as independent predictor of heart failure (HF) in the acute phase of myocardial infarction (AMI).
Methods: 100 consecutive patients with AMI comprised the study group. All of them underwent a complete echocardiography study within the 2 first days of admission. Systolic function was measured using ejection fraction (EF) (modified Simpsom rule) and the wall motion score index (WMSI). Diastolic function was asessed by transmitral inflow doppler pattern. MPI was calculed as (a-b)/b where "a" is the time interval between cessation and onset of transmitral flow and "b" is

the ejection time measured below the aortic valve. Every patient was classified according to the presence of HF signs, using the Killip classification.
Results: 65 patients were classified as Killip I, and 35 patients developed HF (Killip >I). MPI was different between both groups (0,38±0,19 vs. 0,55±0,21, p<0,0005) and simple logistic regression analysis also showed MPI as a significant predictor of HF (p<0,0005). The Receiver Operator Curve (ROC), showed an area under the curve of 0,77 (p<0,0005) and 0,46 as the cutoff point to identify patients with HF. After adjustment with backwards steps, multiple logistic regression analysis, the only significant independent predictors for developing heart failure after AMI were MPI>0,46 (OR 7'381, p=0,003), EF<0,42 (OR 16,526, p=0,001), age>68 (OR 11'595, p=0,001) and diabetes(OR 6,234, p=0,025).

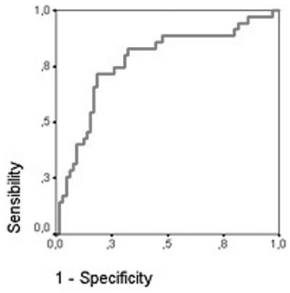

Fig. 1. ROC curve of MPI.

In conclusion MPI is a powerful predictor of heart failure after AMI, with independence of the values of conventional parameters of systolic and diastolic function.

P391 Combined right ventricular systolic and diastolic dysfunction represents a strong determinant of poor prognosis in patients with heart failure

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The presence of right ventricular (RV) systolic dysfunction is known to significantly worsen prognosis of patients with heart failure. However, the prognostic impact of RV diastolic dysfunction and of its combination with RV systolic dysfunction has not yet been systematically studied. The aim of this study was to assess the prognostic impact of RV systolic and diastolic dysfunctions and of their combination in patients with symptomatic heart failure due to ischemic or idiopathic dilated cardiomyopathy.
Methods: The study included 177 consecutive patients with symptomatic heart failure (mean left ventricular ejection fraction of 23%). All patients underwent clinical examination, standard echocardiography completed by Doppler tissue imaging of the tricuspid annular motion, and right-sided heart catheterization. They were followed up for a mean period of 16 months.
Results: During the follow-up, there were 28 cardiac-related deaths and 35 non-fatal cardiac events (31 hospitalizations for heart failure decompensation and 4 hospitalizations for malignant arrhythmias requiring the implantation of a cardioverter-defibrillator). The multivariate stepwise Cox regression modeling revealed the RV systolic (represented by the peak systolic tricuspid annular velocity - Sa) and diastolic (represented by the peak early diastolic tricuspid annular velocity - Ea) functions to be the independent predictors of event-free survival or survival ($p < 0.01$). However, the strongest predictive information was obtained by the combination of Sa and Ea. The Sa/Ea I category of patients (Sa $\geq$ 10.8 cm.s-1 and Ea $\geq$ 8.9 cm.s-1) had excellent prognosis. On the other hand, the Sa/Ea IV category (Sa $<$ 10.8 cm.s-1 and Ea $<$ 8.9 cm.s-1) was found to be at a very high risk of cardiac events ($p < 0.001$ vs Sa/Ea I). Imbalanced categories of patients (Sa/Ea II and III) with only one component (Sa or Ea) pathologically decreased were at medium risk when assessing event-free survival. However, a significantly better survival ($p < 0.05$) was found in patients with Ea $\geq$ 8.9 cm.s-1 (Sa/Ea I and III categories) as compared with those having Ea $<$ 8.9 cm.s-1 (Sa/Ea II and IV categories).
Conclusion: The assessment of RV systolic and diastolic function provides complementary information with a very high power to stratify prognosis of patients with heart failure. The combination of RV systolic and diastolic dysfunction identifies those with a very poor prognosis.

P392 The association of increased left ventricular sphericity and elevated wall stress affects the outcome of patients with dilated cardiomyopathy

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Background: Data in literature are controversial as regards the value of increased left ventricular (LV) sphericity in predicting prognosis of patients with dilated cardiomyopathy. Since a low ratio of LV wall thickness to cavity radius (h/R) may reflect increased wall stress, it may be worthwhile to investigate whether the association of a more spherical-shaped ventricle with a reduced h/R ratio may have an influence on the outcome of these patients.
Objectives: We sought to evaluate the impact on prognosis of the association of an increased LV sphericity index (SI) and a reduced h/R in patients with either ischemic or non ischemic dilated cardiomyopathy.
Methods: Three-hundred and ninety-five patients with LV systolic dysfunction (EF <50%) and LV end-diastolic volume index >75 ml/m^2 in NYHA class I-IV were consecutively submitted to a M-mode and two-dimensional echocardiographic study. LV SI was calculated by the ratio of short to long-axis end-diastolic dimensions. Patients were categorized into subgroups according to tertiles of SI (<0.64, 0.64 to 0.70, and >0.70) and of h/R ratio (<0.34, 0.34 to 0.39, and >0.39). The Cox regression and Kaplan-Meier techniques were applied in survival analyses. All patients were followed-up for a mean period of 19±15 months.
Results: Overall, LV EF was 33±8%, LV end-diastolic volume index was 116±32 ml/m^2, LV mass index was 161±35 g/m^2, and 38% of patients were in NYHA class III and IV. Sixty-three percent had a diagnosis of coronary artery disease. During follow-up, 50 patients died from cardiac causes. For patients in the upper SI tertile and lower tertile of h/R ratio, the mortality rate was 24% as opposed to a global 11.7% in the other groups. On multivariate Cox regression model, EF (hazard ratio [HR]: 2.64, p=0.0013), left atrial size (HR: 2.42, p=0.014), the combination of SI >0.70 and h/R ratio <0.34 (HR: 2.32, p=0.042) and age (HR: 1.47, p=0.02) were independent predictors of fatal outcome. Patients with SI >0.70 and h/R ratio <0.34 exhibited a 55% survival at 36 months with respect to a combined 77% in the other groups (p=0.027 by Log-rank).
Conclusions: The association of a more spherical-shaped left ventricle with elevated wall stress, as reflected by an increased LV SI associated with a reduced h/R ratio, appears to be a factor that negatively affects prognosis in patients with ischemic and non-ischemic dilated cardiomyopathy.

P393 Right ventricular global and regional function in patients with dilated cardiomyopathy

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Objectives: Since right ventricular function has an independent prognostic value in patients with heart failure, its detailed assessment has become an important clinical practice. The aim of this study was to determine the correlations of right ventricular global and regional function to other echocardiographic and hemodynamic parameters in patients with dilated cardiomyopathy (DCMP) and to compare the findings with a healthy control group.
Methods: The study group consisted of 32 patients with DCMP (10 female, 22 male, mean age 60±12 years) and 20 age and sex matched controls. Global ejection fraction and diastolic filling were determined for both right and left ventricles. Pulsed-wave tissue Doppler recordings were made at lateral site of the tricuspid annulus and basal, mid and apical right ventricular free wall and regional Sm, Em, Am and deceleration time of Em were determined. For left ventricle, the recordings were made at 4 sites (septal, anterior, lateral and inferior) of the mitral annulus.
Results: In DCMP patients, right ventricular ejection fraction, tricuspid annular and right ventricular basal Sm velocities were significantly lower than the controls (p<0.001, p=0.05 and p=0.04 respectively), whereas right ventricular mid and apical Sm velocities showed no differences between the study groups. In patients group, right ventricular ejection fraction determined by Simpson's method was negatively correlated with NYHA functional capacity (r=-0.37, p=0.04), right ventricular diameter (r=-0.45, p=0.009), left ventricular end-systolic diameter (r=-0.47, p=0.009), pulmonary artery systolic pressure (r=-0.34, p=0.02), severity of tricuspid regurgitation (r=-0.64, p<0.001), and positively correlated with left ventricular ejection fraction (r=0.47, p=0.01), regional Em deceleration times measured at all sides of right and left ventricle. Tricuspid annular, right ventricular basal, mid and apical Sm velocities were also significantly negatively correlated with NYHA functional capacity, but other correlations observed for right ventricular ejection fraction were not detected for these parameters.

NYHA	RV diameter	LVESD	PAP	Tricuspid regurgitation	LVEF
r=-0.37, p=0.04	r=-0.45, p=0.009	r=-0.47, p=0.009	r=-0.34, p=0.02	r=-0.64, p<0.001	r=0.47, p=0.01

Conclusion: In patients with DCMP right ventricular ejection fraction determined by the Simpson's method was significantly associated to both right and left ventricular hemodynamic parameters. Assessment of global right ventricular systolic function seems to be more valuable than measurements of the regional pulsed-wave Doppler velocities.

P394 Left ventricle volumes and ejection fraction with 3D-echo: overcoming geometrical assumptions or optimal alignment of structures?

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Background/objectives: Estimation of left ventricle (LV) volumes and ejection

fraction (EF) with 2D echo is based on geometrical assumptions that many patients (PP) frequently do not meet. 3D-echo allows a direct calculation of these parameters, yielding more accuracy in such patients. We try to answer the question of what is the factor which plays the most important role in this advantage of 3D-echo: overcome of geometrical assumptions or the possibility to align optimally the planes of the LV?
Methods: 20 consecutive PP with cardiomyopathy of any sort were enrolled into the study, informed consent previously obtained. LV end-diastolic (EDV) and end-systolic (ESV) volumes were measured with 2D and RT3D echo, using biplane Simpson's method and direct quantification of the image obtained with FV, respectively. Measurements in the FV were done considering 2,4 and 8 longitudinal planes (LP). MRI was performed, EDV and ESV measured with Simpson's method. Intraclass correlation coefficient (ICC) was calculated for each echocardiographic method respect to MRI.
Results: As we display on table below, 3D correlates better than 2D with MRI. This correlation improves, and the confidence interval (CI) of the difference decreases, if we increase the number of LP employed in the FV calculation. That is, the fewer geometrical assumptions required, the more precision. Nevertheless, the greater improvement in agreement is observed between 2D biplane Simpson and 3D with 2 planes. These methods require exactly the same geometric assumptions, and the only factor that can explain this improvement is the optimal alignment of LV planes.

Table

	EDV			ESV			EF		
	ICC	95% CI difference	P	ICC	95% CI difference	P	ICC	95% CI difference	P
2D-MR	0,76	0,51-0,89	<0,001	0,83	0,64-0,92	<0,001	0,91	0,80-0,96	<0,001
3D 2planes-MR	0,86	0,13-0,96	<0,001	0,93	0,66-0,97	<0,001	0,98	0,95-0,99	<0,001
3D 4planes-MR	0,97	0,94-0,99	<0,001	0,99	0,98-0,99	<0,001	0,98	0,98-0,99	<0,001
3D 8planes-MR	0,98	0,95-0,99	<0,001	0,99	0,99-0,99	<0,001	0,99	0,98-0,99	<0,001

Conclusion: The possibility of an optimal alignment of LV planes with 3D-echo seems to play a more important role than the direct non-geometric measurement, in order to increase the accuracy in calculation of LV volumes and EF.

P395 Application of a novel non-tissue Doppler-based method for real-time quantitation of myocardial function in normal subjects during exercise echocardiography

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Purpose: Feasiability of a novel software for real-time quantitative assessment of myocardial function during exercise echocardiography.
Methods: 12 patients underwent standard exercise echocardiography. Apical views at baseline and peak exercise were stored in a cineloop format for off-line analysis. The novel software is based on the estimation that a discrete set of tissue velocities per each of many small elements on ultrasound image show only mild shift on subsequent frames. Tracking can be controlled in real-time by the operator. Tissue velocities, strain and strain rate at baseline and at peak exercise were obtained and displayed in real time by the software. We also introduced a new parameter: Strain acceleration index - the ratio of systolic strain and time to peak systolic strain corrected for heart rate. Average (over the left ventricle) strain rate, strain and strain acceleration index at rest and after the exercise are demonstrated below (Table).
Results: 216 myocardial segments were assessed. Adequate tracking of the myocardium by the new software was possible in 93% of the segments at rest and in 80% at peak exercise.
Longitudinal velocities were maximal in basal segments. Strain was homogenous over the myocardium. Velocities, strain and strain rate were significantly higher at peak exercise. Corrected time to the peak systolic strain was shorter at peak exercise than at rest; strain acceleration index was higher at peak exercise than at rest.

Stress echo quantitation

	Rest	Stress	p value
Strain rate, sec-1	1.02±0.39	1.43±0.6	<0.00001
Strain, %	16.71±5.06	18.09±6.23	<0.03
SAI	1.42±0.63	1.88±0.97	<0.00001

SAI - strain acceleration index = Strain/time to peak strain, %/CU (CU-corrected units)

Conclusion: This novel non-Doppler based software may provide real-time quantitative assessment of global and regional myocardial function at rest and during exercise echocardiography.

P396 Critical heart rate of force–frequency relationship during dobutamine stress echo predicts outcome in medically treated heart failure patients

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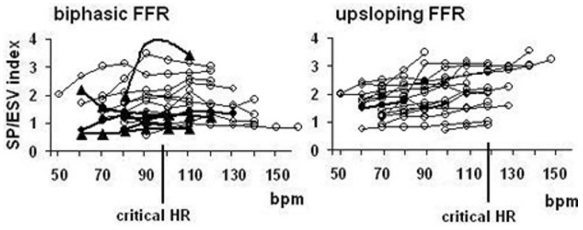
Background: Force-Frequency relationship (FFR) can be assessed noninvasively during dobutamine stress echo and provides a conceptually robust index of left ventricular contractile reserve of potential prognostic value in patients with severe left ventricular dysfunction, in whom outcome is poor but heterogeneous.
Aim: To assess the prognostic value of FFR in medically treated heart failure patients.
Methods: We enrolled 39 consecutive heart failure patients (32 males, age 67±11 years, ejection fraction= 29±6%, end-diastolic volume =203±44 ml, NYHA class 2-3) referred for dobutamine stress echo (up to 40 mcg/kg/min). The underlying etiology of heart failure was coronary artery disease (n=20), chronic severe valvular heart disease (n=3) or dilated cardiomyopathy (n=16).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). All patients were followed-up on medical therapy for 5.3±3.2 months. Pre-defined events were cardiac death or increase > 1 grade of NYHA class.
Results: Twenty patients had an abnormal biphasic, and 19 a normal upsloping FFR (figure). Events (black symbols in figure, triangles = death) occurred in 6/20 with biphasic and 1/19 patients with upsloping FFR (30%vs 5%, p<0.05). Patients with and without events showed similar resting EF at study entry (28±7% vs 30±6%, p=ns), but different critical heart rate (i.e., is the cardiac frequency at which FFR starts its descending limb): 90±17 vs 110±19 bpm, p<0.05.



Conclusions: In patients with similar baseline values of ejection fraction, a biphasic FFR pattern during dobutamine stress echo identifies a higher risk subset.

P397 Assessment of systolic and diastolic left-ventricular function by tissue Doppler imaging in patients with type 2 diabetes mellitus: predictive value of B natriuretic peptide

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Objectives: We sought to evaluate left ventricular (LV) systolic and diastolic function in asymptomatic patients with type 2 diabetes mellitus (DM) using tissue Doppler (TD) analysis of mitral annulus dynamics and to investigate the potential value of brain natriuretic peptide (BNP) as an early marker of systolic and/or diastolic failure in this group of patients.Background:Epidemiological data document a greater risk of congestive heart failure (CHF), in patients with DM. Since BNP is a marker of early heart failure, it may serve to identify diabetic patients with preclinical abnormalities before progression to CHF.
Methods: We studied 39 patients with type 2 DM aged 37 to 70 years; without evidence of diabetic complications, hypertension, coronary artery disease or CHFand 15 age and sex matched healthy subjects. Peak velocity and time-velocity integral were measured from TD tracings at the septal and lateral borders of the mitral annulus. BNP was measured in plasma by enzyme-linked immunosorbent assay.
Results: The lateral TD systolic(Sann)wave velocity was significantly lower in DM group compared to controls (10.1 ± 1.9 vs. 11.5 ± 2.0 cm/sec. respectively; p<0.005). The septal and lateral TD early diastolic velocities Eann were significantly lower in DM group compared to controls (8.3 ± 2.2 vs. 12.1 ± 3 cm/sec and 12.1 ± 3.8 vs. 17.5 ± 3.8 cm/sec respectively; both p<0.0001).The septal and lateral TD early to late diastolic velocity ratio Eann/Aann were significantly lower in DM group compared to controls (0.8 ± 0.3 vs. 1.4 ± 0.5 cm and 1.1 ± 0.5 vs. 1.9 ± 0.6 cm respectively; both p<0.0001). Septal TD showed significantly prolonged regional isovolumic relaxation time in DM group compared to controls (78.6 ± 13.5 vs. 64.3 ± 13.4 sec respectively; p<0.0001). Plasma BNP level was significantly higher in DM group compared to controls (311.2 ± 112.6 vs. 38.2 ± 4.8 pg/ml respectively; p<0.0001). A significant negative correlation was detected between plasma BNP level and septal TD Sann velocity (r = -0.6; p<0.001). A

significant negative correlation was also detected between plasma BNP level and lateral and septal TD Eann/Aann velocity ratio (both r = - 0.5; p<0.001).
Conclusion: Mitral annular contraction and relaxation velocities detected by TD imaging, are reduced in patients with type 2 DM compared to controls. The significantly higher plasma BNP level identified in diabetics correlated well with the degree of systolic and diastolic dysfunction detected by TD analysis of mitral annulus dynamics and so may be a useful marker for early heart failure in this group of patients.

P398 Association of brain-type natriuretic peptide levels with left ventricular diastolic function and longitudinal function: a comparison with Doppler echocardiography

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Background: Left ventricular (LV) diastolic dysfunction (DD) is recognized as a major cause of morbidity and mortality, advanced DD reflecting a poor prognosis. Longitudinal (subendocardial) LV function assessment is a sensitive marker of early changes in systolic function caused by subclinical disease. B-type natriuretic peptide (BNP) is a powerful marker of heart failure and correlates well with LV filling pressures.
Purpose: To assess the relationship of BNP to LVDD and to LV longitudinal function.
Methods: 75 consecutively admitted pts (53 men, 73±10 years), referred for LV function assessment were studied. A comprehensive Doppler echocardiography study was performed, including measurements of transmitral flow: E, A, E/A ratio, Edt at baseline and during a standardized Valsalva maneuver; flow propagation velocity Vp; PW pulmonary venous flow: S, D, S/D ratio, Ar; M-mode derived mitral annular plane systolic excursion (MAPSE) at four sites of the mitral annulus; LV ejection fraction (EF). E/Vp ratio; Ar-A duration; A velocity change (Achange) during Valsalva; and mean MAPSE values were then calculated. Global LV systolic function was assessed by LVEF; longitudinal (subendocardial) LV function by mean MAPSE values; and global LV diastolic function was staged as normal, stage 1 DD (E/A≤0.75, Ar-A<0, Achange<0, E/Vp<1.5), stage 2 DD (E/A between 0.75 and 1.5, Edt>140, Ar-A>30, Achange>0, E/Vp≥1.5), and stage 3 DD (E/A>1.5, Edt<140, Ar-A>30, Achange>0, E/Vp≥1.5). At least 2 criteria consistent with stage 2 or 3 DD were required to be so classified. Blood taken immediately before echocardiography was assayed for BNP levels (ADVIA centaur, Bayer). Log-transformed BNP values were used for analysis because BNP distribution was positively skewed.
Results: BNP levels increased progressively with increasing LVDD stage (p<0.001). In univariate regression analyses, BNP also correlated with LVEF (r=-0.60, p<0.001), and with mean MAPSE (r=-0.65, p<0.001). By stepwise multiple regression analysis BNP was independently predicted by DD stage, in association with mean MAPSE (r=0.73, r^2=0.53, p<0.001). A BNP value of 234 pg/ml had a 85% sensitivity and a 84% specificity for detecting stage 2 and 3 LVDD (area under the ROC curve of 0.85).
Conclusions: Plasma BNP levels had the best correlations with parameters of LVDD and LV longitudinal function, while global LVEF was not an independent predictor of BNP. Properties of LV diastolic function and longitudinal function are important determinants of BNP levels. Measuring BNP levels may be useful in detecting advanced stages of DD.

P399 Pro-brain natriuretic peptide reflects diastolic function after aortic valve replacement, detected by tissue Doppler imaging in patients with aortic stenosis

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Objective: 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 ± 21) and we sought to investigate whether rest pro-BNP plasma levels are correlated with diastolic function of both ventricles in patients with severe degenerative aortic stenosis after AVR.
Methods: We enrolled 43 consecutive patients (27 men, 65 ± 12 years old and 16 women, 69 ± 7 years old) who were scheduled for AVR. TDE images obtained from the apex, visualizing triscupter and mitral free wall annulus. RV and LV systolic and diastolic velocities were compared 24 hours before, 15 days, 3 and 6 months after AVR, based on the Analysis of co-variance for repeated measurements. LV stiffness (K), the ratio E velocity/flow propagation (E/FP), mitral and triscupted diastolic velocities (E, A) were also measured and E/A ratio was calculated. Pro-BNP levels was measured in all patients after rest in supine position in each examination.
Results: Pro-BNP levels were inversely associated with Em (b3m = - 1.15, p < 0.01, b6m = - 1.3, p < 0.01) and Etv (b3m = - 1.15, p < 0.01, b6m = - 1.25, p < 0.01) velocities in 3 and 6 months post-operation. Furthermore, pro-BNP levels were inversely associated with Sm and Stv (b3m = - 1.17, p = 0.04, b6m = - 1.15, p < 0.01 and b3m = - 1.32, p < 0.01, b6m = - 1.35, p = 0.05, respectively)In addition Em/Am, Etv/Atv ratios showed inverse parabolic associations with pro-BNP levels (b for 2nd order term = 1.2, p = 0.001, and b = 1.1, p = 0.01, respectively), after controlling for age, sex, heart rate. Particularly, values of both ratios within 1.5 – 2.5 range were associated with higher values of BNP, were lower or higher values of the ratios were related with lower values of BNP. The ratio E/Emv was positively correlated with the levels of pro-BNP (r = 0.12, p = 0.03), while transmitral E and A velocities as well as the ratio E/Etv did not show any correlation with pro-BNP levels (r = 0.09, p = 0.22, r = 0.1, p = 0.05 and r = 0.01, p =0.28, respectively).
Conclusion: We revealed that pro-BNP, reflecting the level of left ventricle end-diastolic pressure, may constitute a reliable index for the evaluation of diastolic performance and relaxation capacity of the left ventricle in patients after AVR. LV chamber stiffness increases in the first month post AVR, and restores six months later, coming in accordance with an early increase in pro-BNP levels and late restoration in normal limits.

P400 TIMP-1 as a marker of diastolic dysfunction in type 2 diabetes and hypertension

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Background: Tissue inhibitor of metalloproteinase-1 (TIMP-1) is associated with increased fibrosis of the extracellular matrix (ECM). Myocardial stiffness is a feature of diastolic dysfunction. We compare circulating TIMP-1 as a marker of diastolic dysfunction in patients with type 2 diabetes(DM) and hypertension.
Methods: We recruited 54 patients (68±5yrs,43M) with treated type 2 DM, 35(69±8yrs,30M) treated hypertensives, and 31 healthy controls (66±5yrs,18M) (Table) that were age and gender matched. Circulating TIMP-1 was measured by ELISA. Early (E) diastolic mitral inflow velocity was measured with pulse wave Doppler and early mitral annular velocity (e'), a recognised index of diastolic relaxation, measured with tissue Doppler on transthoracic echocardiogram.
Results: There were significant differences in diastolic parameters between the three groups (table). Circulating TIMP-1 was significantly different between patients and controls, however there was no difference between the DM and hypertension group (table). In both groups only e' correlated negatively with TIMP-1, the relationship was stronger amongst the hypertensive group (Spearman r = -0.544, p=0.001) compared to the diabetic group (r = -0.341, p=0.011).

Table 1 (Data as Mean (SD) or Median (IQR))

	Diabetics (n= 54)	Hypertensives (n =35)	Control (n=31)	p
SBP (mmHg)	139(16)	145(14)	130(13)	<0.0001
DBP (mmHg)	76(9)	81(100	78(8)	0.040
HbA1c (%)	7.3(6.7- 8.2)	5.4(5.3-5.7)	5.5(5.3-5.5)	<0.0001
Cholesterol (mM)	4.8(1.0)	4.9(1.2)	5.7(1.2)	0.011
E/A	0.9(0.2)	0.9(0.2)	0.9(0.2)	0.391
e'	0.07(0.01)	0.08(0.01)	0.10(0.02)	<0.0001
E/e'	10.9(1.3)	10.6(2.0)	8.1(2.0)	<0.0001
LVMI	102(81-142)	127(105-182)	72(50-90)	<0.0001
TIMP-1 (ng/ml)	380(300-450)	350(300-400)	270(215-380)	0.006

SBP, systolic blood pressure; DBP, diastolic blood pressure; TIMP, tissue inhibitor of metalloproteinase

Conclusion: Lower E' and higher E/E' suggest impaired diastolic relaxation and elevated left ventricular filling pressure respectively. The relationship between TIMP-1 and E' may reflect increased myocardial fibrosis and consequent diastolic dysfunction which may be more prominent in hypertension.

P401 Myocardial dysfunction in hypertensive patients with isolated diastolic heart failure is reversible. A randomized trial of aldosterone antagonism

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Background: Diastolic dysfunction is a common cause of heart failure (HF) for which specific disease-modifying treatments are lacking. Experimental studies implicate aldosterone in the genesis of myocardial fibrosis and diastolic dysfunction. We assessed effects of aldosterone antagonism on myocardial function in hypertensive pts with suspected diastolic HF using sensitive quantitative echo techniques.
Methods: Thirty medically-treated hypertensive pts (19 women, 62±6y) with exertional dyspnoea, ejection fraction >50%, diastolic dysfunction (E/A<1, E deceleration time >250msec), and negative exercise echo for ischaemia were randomised to spironolactone 25mg/day or placebo for 6 months. Cardiac dimensions were assessed with conventional echocardiography. Cyclic variation of integrated backscatter (CVIB), strain rate (SR) and peak systolic strain were averaged from 6 walls in 3 standard apical views to quantitate myocardial function.
Results: Pts were overweight (BMI 30.5±4.6kg/m^2) with reduced treadmill exercise capacity (Bruce protocol: 5.2±2.4min). Mean 24hr ambulatory blood pressure at baseline (133±17/80±7mmHg) did not change in either group. The spironolactone group exhibited a reduction in posterior wall thickness (p=0.042)

and a trend to reduced left atrial area (p=0.09). SR, peak systolic strain, and CVIB improved in the spironolactone group and remained unchanged with placebo (table).

	Baseline		p	End		p
	Placebo	Spironolactone		Placebo	Spironolactone	
SR, 1/s	-1.63±0.61	-1.57±0.46	0.71	-1.57±0.46	-1.91±0.36*	0.048
Strain, %	-21.4±3.7	-20.3±5.0	0.48	-20.3±5.0	-26.9±4.3**	0.022
CVIB, dB	6.91±1.28	7.37±1.71	0.41	7.16±1.34	8.58±1.71***	0.019

*p<0.01, **p<0.001, ***p=0.079 compared with spironolactone at baseline.

Conclusions: Aldosterone antagonism improves myocardial function in hypertensive heart disease and may provide a specific treatment for diastolic HF.

ATHEROSCLEROSIS I – BASIC SCIENCE

P402 Familial hypercholesterolemia patients present defects in the removal from plasma of both free and esterified forms of cholesterol that are improved by Simvastatin: study with artificial emulsions

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Background: Cholesterol is present in LDL as either the esterified and the free, unesterified form. The two forms of cholesterol have distinct chemical-physical properties that may lead to different metabolical fates and pathophysiological implications. Recently, we showed that in normocholesterolemic patients with coronary artery disease (CAD), the removal of the free cholesterol contained in a LDL resembling artificial microemulsion that binds to the LDL receptor (LDL-R) by apolipoprotein E (LDE)was faster than in non-CAD control subjects whereas the removal of the cholesterol ester was not different. Patients with heterozygous familial hypercholesterolemia (HFH) bear defects in the LDL-R that lead to diminished LDL plasma clearance, as evaluated by the plasma kinetics of LDL labeled in the apo B moiety.
Objective: To study the kinetics of both cholesterol forms contained in LDE in HFH as compared to a control normolipidemic group of subjects and under the effects of high dose simvastatin treatment.
Methods: 21 FH patients (44.2 ± 13.1 years, 12 females, LDL-C 276.0 ± 66.0 mg/dL)and 23 normolipidemics (44.1 ± 15.0 years,10 females,LDL-C 124.0 ± 24.0 mg/dL) were intravenously injected 14C-cholesterol oleate and 3H cholesterol labeled LDE. FH patients were also evaluated after 2 months of simvastatin treatment with 80 mg/day. Plasma samples were collected during 24 hours for determination of the residence time (RT, in hours)of LDE both labels by compartmental analysis and are expressed as median (lower and upper 95% confidence intervals).
Results: The RT (hours)of both 14C-cholesterol oleate and 3H-cholesterol were increased in FH when compared to NL respectively: 35.7 (26.5-59.7) vs. 19.15 (14.8-27.2), p=0.0091 and 50.8 (36.4-84.1) vs. 15.1 (11.46-22.0), p<0.0001. The mean reduction of LDL-C by statin treatment was 36% (p<0.0001) and the median reduction of the RT of 14C-cholesterol oleate and 3H-cholesterol were respectively 49% (p=0.0029 vs. baseline) and 44% (p=0.019 vs. baseline), these reductions were similar between both labels (p=0.84). After treatment the values of the RT of 14C-cholesterol oleate became similar to NL (p=0.58).
Conclusion: HFH patients present defects on the removal from plasma of both free and esterified forms of cholesterol that are improved by statin treatment. Improvement in LDL plasma removal by statins, as mimicked by LDE might have anti-atherogenic implications.

P403 HDL particle size and lipid transfer proteins in familial hypercholesterolemia

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Familial hypercholesterolemia (FH) is associated with premature atherosclerosis. It is due to mutations in the LDL receptor gene resulting in elevated LDL cholesterol levels. Furthermore, there are alterations in the HDL metabolism in FH patients that were not yet fully explored. Herein, we measured HDL particle size using a laser light scattering-based approach and in vitro plasma activities of cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) in 20 age-matched subjects (8 FH and 12 normolipidemics-NL). Besides higher LDL-C, FH patients had similar HDL-C levels when compared to NL, 221 ± 94 vs 95 ± 28 mg/dL, (p < 0.001) and 44 ± 11 vs. 50 ± 10 mg/dL (p=0.19), respectively. However, HDL size (nm) was smaller in FH patients when compared to NL (8.9 ± 0.5 vs. 8.04 ± 0.3, p <0.001). The activities of both CETP and PLTP (in % lipids transferred/mL plasma/h/mg/dL HDL-c) were greater in FH than in NL: 1.15 ± 0.3 vs. 0.87 ± 0.17 (p=0.019) and 2.83 ± 0.6 vs. 2.26 ± 0.4 (p=0.03) respectively. These results suggest important differences in HDL metabolism in FH, including HDL size and transfer protein activities. These alterations might be the result of a compensatory mechanism to increase cholesterol efflux that would lead to lower HDL size.

P404 Local VEGF165 gene transfer reduces lumen area loss through positive remodeling after experimental coronary angioplasty

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Arterial remodeling plays a major role in the pathophysiology of restenosis after coronary intervention. Recent studies have even shown that preinterventional arterial remodeling predicts neointimal hyperplasia after implantation of coated stents, but the underlying mechanisms are still incompletely understood. In a previous study we have shown that adventitial microvessel regression after balloon injury is associated with constrictive remodeling. The purpose of this study was to inhibit adventitial microvessel regression through a local gene therapy with vascular endothelial growth factor (VEGF), and to examine the effect of VEGF on adventitial microvessels, arterial remodeling and the resulting lumen area.
Methods: 15 pigs underwent balloon angioplasty in two major coronary arteries followed by (peri)adventitial injections of plasmids containing either the VEGF165 gene or the control gene LacZ using a needle injection catheter. Arterial cross sections were examined 7, 14, and 28 days after angioplasty/gene transfer.
Results: In the VEGF group we observed a significant external elastic lamina (EEL) area gain (positive remodeling) at days 14 and 28 after intervention associated with a significant reduction of lumen area loss. In the LacZ group there was a distinct lumen area loss, mainly due to negative remodeling. Positive remodeling in the VEGF group was associated with an increased adventitial microvessel and endothelial cell density at days 14 and 28 after intervention.

	Day 7		Day 14		Day 28	
	LacZ	VEGF	LacZ	VEGF	LacZ	VEGF
Lumen area loss, %	17.3±6.2	-9.5±12.3	40.1±2.9	5.1±7.5*	49.0±1.6	-5.34±18.3*
EEL area gain, %	-8.4±5.9	10.0±8.9	-13.7±6.6	7.9±2.9*	-25.3±2.3	38.2±11.8*
Microvessel density, %	7.5±2.6	11.2±4.0	2.5±0.8	8.5±0.8*	1.7±0.5	7.2±1.6*
Endothelial cells/mm^2	52.5±20.2	102.5±24.7	47.9±10.0	75.8±5.3*	37.0±8.9	79.1±6.9*

VEGF versus LacZ: *p<0.05.

Conclusion: Local (peri)adventitial VEGF gene transfer after coronary balloon injury reduces lumen area loss through induction of positive remodeling associated with improved adventitial vascularization. Adventitial microvessels possibly inhibit tissue contraction by reducing local tissue hypoxia, and it is conceivable that endothelial cells contribute to positive remodeling through their supply of vasodilatory nitric oxide (NO).

P405 The impact of lipoproteins on endothelial function and thrombotic mechanims in young individuals

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Risk factors for atherosclerosis are associated with endothelial dysfunction and increased thrombogeneicity. Enhanced lipoprotein levels may increase cardiovascular risk, but their effect on endothelial function and thrombotic process in young subjects is unknown.
Aim: We investigated the ineractions between lipoproteins, thrombotic mechanisms and vascular endothelium in a low-risk group of healthy volunteers.
Methods: This study included 57 healthy individuals with no risk factor for atherosclerosis (37±4 yrs old, 29 males 28 females). Forearm blood flow was measured using venous occlusion strain-gauge plethysmography. Endothelium dependent dilation (EDD) and endothelium independent dilation (EID) were expressed as the % change of flow from rest to the maximum flow during reactive hyperemia or after sublingual nitroglycerin administration, respectively. Levels of cholesterol, triglycerides, HDL, lipoprotein-a (Lp-a), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB) and apolipoprotein E (ApoE) were determined with standard methodology, and von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA) were determined with ELISA.
Results: All subjects had normal cholesterol levels (178±12 mg/dl) triglycerides (113±8mg/dl), HDL (46±1.9 mg/dl), Lp-a (14.5±3.1 mg/dl), ApoA1 (129±5.1 mg/dl), ApoB (95.2±4.2 mg/dl), PAI-1 (14.2 ±2.2 ng/ml), vWF (78.2±4.4%) and tPA (4.2±0.4 ng/ml). EDD was correlated with triglycerides levels (r=-0.347, p=0.009), HDL (r=0.597, p=0.0001) and apoA1 (r=0.269, p=0.043). PAI-1 levels were correlated with cholesterol (r=0.284, p=0.033), triglycerides (r=, 0.390, p=0.003) and ApoA1 (r=-0.304, p=0.021). tPA was correlated with triglycerides (r=0.529, p=0.0001), HDL (r=-0.347, p=0.018), ApoA1 (r=-0.413, p=0.0003), ApoB (r=0.343, p=0.015) and PAI-1 (r=0.465, p=0.001). Furthermore, the PAI-1/tPA ratio was correlated with Lp-a levels (r=0.307, p=0.01). EID was not associated with the examined parameters.
Conclusions: These findings suggest that abnormal lipoprotein levels are associated with endothelial dysfunction and increased thrombogeneicity in young adults. Therefore, lipids may affect endothelial function, stimulate the thrombotic mechanisms and enhance the process of premature atherogenesis.

P406 Withdrawal of statin therapy is associated with an adverse cardiovascular outcome after non-ST-elevation acute coronary syndromes

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Landmark clinical trials have shown that statins reduce the incidence of stroke and myocardial infarction when chronically given over prolonged periods. Besides, recent prospective trials support the idea that these drugs may have favourable effects even on short-term outcome when given immediately after an acute coronary syndrome (ACS). On the other hand, there is increasing clinical evidence that withdrawal of statin medications acutely impairs vascular function and may negatively affect outcome. Aim of the present study was to assess the effects of the withdrawal of statin therapy after ACS. The study population included 874 consecutive patients (mean age 69 years, 34% females) discharged from our institution on statin therapy after a non-ST-elevation ACS over a 24 month period.
In the whole study population 6-month cardiovascular mortality was 6,9%, while non-fatal acute myocardial infarction (AMI) occurred in 8,5% and stroke in 3,2% of all patients. Within 3 months from discharge 209 (24%) had discontinued statins. The 6-month unadjusted composite event rate (cardiovascular death, non fatal AMI and stroke) was 16,8% in patients on statins and 24,8% in patients who discontinued statin therapy (OR 1,63, 95% CI 1,10-2,41, p=0,013).
After adjustment for the propensity to discontinue statin therapy, as well as for all other potential confounders and interactions, statin withdrawal remained associated with a higher risk of adverse cardiovascular events at 6 months (HR 1,16, 95% CI 1,02-1,33, p=0,032).
We therefore conclude that withdrawal of statin therapy after a non-ST-elevation ACS is independently associated with a higher risk of major adverse cardiovascular events.

P407 HMG-CoA reductase inhibitors suppress certain functions of human dendritic cells: implications for atherosclerosis

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Background: The beneficial effects of HMG-CoA reductase inhibitors (statins) on atherosclerosis have been partly attributed to their immunomodulating properties on endothelial cells and macrophages. Dendritic cells (DC) - professional antigen-presenting cells - were recently detected in atherosclerotic plaques. It is assumed that DC play a critical role in the immunological processes related to atherosclerosis. Thus, we investigated the effect of statins on certain functions of human monocyte-derived DC.
Methods: DC were differentiated from mononuclear cells of healthy donors using GM-CSF and IL-4. DC-maturation was stimulated by a cytokine cocktail consisting of TNF-Alpha (1.25 ng/mL), IL-1Beta (1 ng/mL), and prostaglandin E2 (0.5 μg/mL), by LPS (1 μg/mL), or by CD154 (1 μg/mL). Previous to stimulation, DC were incubated with simvastatin or atorvastatin (1-10 μM) for various periods of time (1-48h).
Results: In contrast to statin-untreated DC, statin preincubation of stimulated DC led to a significantly lower expression of the maturation-associated markers CD83, CD40, CD86, HLA-DR, and CCR-7 (FACS). This inhibitory statin effect was dose- and time-dependent and independent of the kind of the used maturation stimulus. The addition of mevalonate or geranylgeranylpyrophosphate completely reversed the statin-induced suppression of maturation marker expression on DC, suggesting that the statin effect is mediated through the inhibition of Rho-isoprenylation. The functional relevance of the inhibitory statin effect on certain DC functions was investigated: 1. The ability of stimulated DC to induce T cell proliferation was significantly suppressed by statin preincubation (mixed leukocyte reaction). 2. The release of the pro-inflammatory and Th1-promoting cytokine IL-12 from stimulated DC was significantly suppressed by statin-preincubation, while the secretion of the anti-inflammatory and Th2-promoting IL-10 was not affected (cytokine bead array). 3. In addition, statins suppressed the uptake of FITC-dextran or FITC-ovalbumin of stimulated DC (endocytosis assay). Comparing simvastatin and atorvastatin, a similar extent of their inhibitory effects on different DC-functions was observed.
Conclusions: In our study, we showed that statins are able to suppress certain pro-inflammatory and Th1-promoting functions of human matured DC, contributing to their beneficial effects in atherosclerosis. Therefore, the use of statins as immunomodulators might be a new therapeutic approach to other immunological diseases beyond atherosclerosis.

P408 The influence of simvastatin on the levels of proinflammatory cytokines IL-18, MCP-1 and activity of elastolytic cathepsin G in acute myocardial infarction in 6 month follow-up. FLAME study

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Purpose: The elevated levels of monocyte chemoattractant protein-1 (MCP-1) and IL-18 may have prognostic value incremental to hsCRP i patients with stable and unstable CAD in prediction of MACE. The enzymatic degradation of elastin by leukocytes may be an additional factor facilitating the plaque destabilization in acute coronary syndromes. The use of statins was shown to supress the inflammatory response both in ACS and stable CAD. The aim of the study was: 1) to evaluate the influence of simvastatin administered within 12 hours after AMI on plasma levels of IL-18, MCP-1, hsCRP and activity of cathepsin G in 6-month follow-up; 2) to compare the efficacy of two doses of simvastatin (20 and 40mg/d); 3) to assess the influence of hsCRP and LDL-C reduction on the effect of simvastatin on IL-18, MCP-1 and cathepsin G.
Patients and methods: 62 patients with AMI (< 12 hours) not treated previously with statins, 15 pts with stable angina (SA) and 15 healthy controls were enrolled. AMI patients were randomized to receive either 20mg (n=30) or 40mg (n=32) of simvastatin daily. The measurements were done on admission, after 30 days and 6 months.
Results: Table 1 shows the changes of IL-18, MCP-1 levels and activity of cathepsin G. Simvastatin significantly reduced CRP levels by -63% after 30 days and -78% after 6 months ($p<0.0001$).

Table 1

	Dose	IL-18 [pg/ml]	MCP-1 [pg/ml]	Cathepsin G [IU/ml]
Control	(-)	47.8 [24-81]	131 [90-196]	9.3 [2.3-14.6]
SA	(-)	53.4 [21-90]	198 [103-254]	8.25 [3.5-17.4]
AMI baseline	(-)	93.5 [74-146]	444.3 [370-510]	31.4 [9.3-48.9]
AMI 30 days	20mg/d	- 43.1%	- 17.4%	- 36.7%
	40mg/d	- 50.8% ($p<0.05$)	- 19.5% (p=ns)	- 47.4% ($p<0.05$)
AMI 6 months	20mg/d	- 52.5%	- 21.2%	- 70.3%
	40mg/d	- 55.4% (p=ns)	-20.7% (p=ns)	- 73.1% (p=ns)

Data are expressed as median and range; p values denote the difference between 20 and 40mg/d

Conclusion: Simvastatin treatment initiated within 24 hours after AMI significantly reduces elevated plasma levels of IL-18, MCP-1 and activity of elastolytic cathepsin G in 6-month follow-up. After 30 days higher dose of simvastatin is associated with a more pronounced decrease of tested parameters than lower dose independently on reduction of hsCRP and LDL-C.

P409 Short treatment with atorvastatin lowers platelet CD40 ligand expression and soluble CD40 ligand in hypercholesterolemic patients

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Background: CD40 ligand (CD40L), a surface-bound protein, 95% of which is produced by human platelets, is essential in the development of atherosclerosis because of its inflammatory and pro-thrombotic effects. In addition to their lipid lowering effects, many studies have suggested antiinflammatory pathways of statins (HMG-CoA reductase inhibitors), such as a decrease of PCR. In the present study we investigated in vitro the hypothesis that statins may interfere with the CD40 ligand expression by platelets.
To explore this issue we undertook an in vitro and in vivo study to assess if atorvastatin directly affects CD40 ligand expression by platelets in hypercholesterolemic patients.
Methods: Cytofluorimetric analysis of CD40 ligand expression was performed on washed human platelets stimulated at 37C° for 10 min with collagen in presence or absence of scalar(0.1-10 mM) concentrantions of atorvastatin. Clinical trial consisted in randomly assigning 30 patients, affected by polygenic hypercholesterolemia, to diet (n=15, males 8 females 7) or atorvastatin 10mg/day (n=15, males 7 females 8).At baseline and after 3 days of treatment serum lipids, collagen-induced platelet CD40L expression, plasma levels of sCD40L and prothrombin fragment F1+2,a marker of thrombin generation,were analysed.
Results: In vitro study demonstrated that atorvastatin dose-dependently inhibited platelet CD40L expression and thrombin generated by CD40L-activated human monocytes.
Compared to controls,patients with hypercholesterolemia had higher values of platelet CD40L expression,sCD40L and F1+2. Platelet CD40L significantly correlated with sCD40L(r=0,87);the latter significantly correlated with F1+2(r= 0,83). In patients assigned to diet alone, no changes of serum lipids, platelet CD40 ligand expression, sCD40L and F1+2 were observed. In atorvastatin-assigned patients no changes of serum lipids but a significant decrease of platelet CD40 ligand expression (- 30%, $p<0,0005$), plasma levels of sCD40L (-32%,$p<0,0005$) and F1+2(-33%, $p<0.005$) were detected.

Discussion: This study shows that in hypercholesterolemia platelet overexpression of CD40L may account for enhanced plasma levels of sCD40L and F1+2. Our findings (in vitro and in vivo) provide evidence that atorvastatin exerts a direct antiinflammatory and antithrombotic effect via inhibition of platelet CD40L and CD40L-mediated thrombin generation, independently of its cholesterol lowering effect.

P410 Inhibition of 3-hydroxy-3-methylgluralyl coenzyme A reductase attenuates expression of inducible nitric oxide synthase in cardiac myocytes-A link with myocardial protection during ischaemia-reperfusion

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Cytokine-induced nitric oxide (NO) is implicated in myocardial apoptosis. Since statins reduce myocardial apoptosis, we examined the effects of simvastatin (S) on inducible NO synthase (iNOS) expression in cardiac myocytes. H9c2 cardiac myocytes were treated with S ± mevalonate (M), geranyl-geranyl-pyrophosphate (G), farnesyl-pyrophosphate (F) or the Rho kinase inhibitor Y-27632 (Y) for 30 min, then stimulated for 0-24 h with interleukin (IL)-1apha or tumor necrosis factor (TNF)-alpha. S concentration-dependently inhibited IL/TNF induced expression of iNOS protein and mRNA (by rt-PCR), as well as nitrite production. All such effects were reverted by M and G, but not by F. Y alone enhanced IL-induced nitrite production and iNOS expression, while S+Y did not revert these effects suggesting that the inhibitory effects of S are not related to the Rho/Rho kinase pathway. Gel mobility shift assay revealed significant decrease in nuclear translocation of the p65/RelA subunit of NF-kB in IL-stimulated H9c2 cells after 24 h pretreatment with S. Immunoblotting of the same nuclear extracts showed decreased accumulation of p65 protein after S pretreatment while total proteins showed unchanged levels of p65 protein, indicating no effects of S on protein synthesis. Interestingly, immunoblotting of total proteins demonstrated a significant accumulation of the phosphorylated inhibitor IkBalpha after S pretreatment.

iNOS protein expression

untreated cells	34±5	untreated cells	45±4
IL	160±5*	TNF	120±9*
IL+S 10 nmol/L	71±5**	TNF+S 10 nmol/L	65±18**
IL+S 10 nmol/L+M	56±8	TNF+S 10nmol/L+M	77±10
IL+S 600 nmol/L	42±10**	TNF+S 600 nmol/L	48±13**
IL+S 600 nmol/L+M	106±10#	TNF+S 600nmol/L+M	105±8#
IL+S 1 micromol/L	20±4**	TNF+S 1 micromol/L	33±3**
IL+S 1 micromol/L+M	131±14#	TNF+S1micromol/L+M	75±8#

In the Table: n=3 experiments; *p<0.05 vs basal; ** p<0.05 vs cytokine without S; #p<0.05 vs S+TNF or S+IL.

In conclusion, at clinically achievable concentrations, S inhibits iNOS expression by inhibiting a geranyl-geranylated signaling pathway, which targets a NF-kB element in the iNOS gene promoter. Such effect may contribute to cardioprotection against excess NO production observed in in vivo models.

P411 Elevation of high density lipoprotein cholesterol and not anti-inflammatory effect accounts for the reduction in clinical events with combination gemfibrozil, niacin and cholestyramine therapy

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Purpose: The non-lipid-modifying effects, particularly the anti-inflammatory effect, of statins has been recently emphasized. There is little evidence, however, to support the clinical importance of these effects by agents other than statins. The Armed Forces Regression Study was a randomized double-blind, placebo-controlled trial in non-diabetic patients assessing the effect of gemfibrozil, niacin, and cholestyramine on a baseline of aggressive dietary and lifestyle interventions. In the study a 36% increase in high density lipoprotein cholesterol (HDL-c), a 20% reduction in low density lipoprotein cholesterol (LDL-c) and a 50% reduction in triglycerides with drug therapy resulted in a significant, 52% reduction in combined cardiovascular events and net angiographic regression. This sub-study was designed to examine the impact of inflammation and and it modulation by combination lipid therapy on cardiovascular events.
Methods: We analyzed fibrinogen levels in addition to lipid panels and demographic characteristics in all patients before and after 12 months of therapy. A stepwise multiple logistic regression analysis was preformed in the combined cohort using backward and forward selection to assess predictors of freedom from cardiovascular events. Factors examined included the assigned treatment and baseline values of and percent changes in total cholesterol, HDL-c, LDL-c, triglycerides and fibrinogen.
Results: Baseline fibrinogen levels were similar in patients with or without clinical events (299 ± 80 vs. 287 ± 65 mg/dL). Fibrinogen levels increased during treatment by 15% in the group with events and 14% in patients without events, p=NS. Regression analysis revealed that change in HDL-c was the lone significant predictor of improved outcome, with a 2.2% decrease in the odds of a cardiovascular event for each 1% increase in HDL-c during treatment (p=0.02).
Conclusion: Fibrinogen levels at baseline or with therapy do not predict the risk of cardiovascular events in patients receiving gemfibrozil, niacin and cholestyramine combination therapy. The response of HDL cholesterol to therapy best predicts freedom from cardiovascular events with a 2% reduction in clinical events for every 1% increase in the HDL.

P412 Raised levels of vascular endothelial growth factor and angiopoietin-2 are related to atherosclerosis and endothelial damage/dysfunction in diabetes: effect of treatment

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Background: Abnormal angiogenesis is linked to endothelial damage/dysfunction and atherosclerosis. We hypothesised that the relationship between plasma vascular endothelial growth factor (VEGF), angiopoietin-2 (Ang-2), atherosclerosis (by carotid intima-media thickness, CIMT) and endothelial damage/dysfunction (by plasma von Willebrand factor, vWf and urine albumin:creatinine ratio, UACr) in diabetes (DM) is altered by clinically overt cardiovascular disease (OCVD), with different response to intensive cardiovascular risk intervention in DM.
Methods: We measured UACr and plasma vWf, VEGF and Ang-2 in 97 patients with DM (41 with, and 56 without OCVD) and 34 age/sex-comparable controls. Of the 97 patients, 33 with and 31 without OCVD underwent a year of intensified therapy.
Results: CIMT, vWf, VEGF and Ang-2 were higher in patients compared to controls [Table]. VEGF and Ang-2 correlated with HbA1c (Spearman r=0.362 and r=0.380, both p<0.01) only in patients without OCVD. VEGF also correlated with CIMT (Spearman r=0.322, p=0.019), Ang-2 with vWf (Spearman r=0.405, p=0.002) and UACr (Spearman r=0.278, p=0.042) in patients without but not in patients with OCVD. LDL cholesterol and HbA1c fell by over 15% and 9% in both groups (both p<0.001), which was associated with reduction in plasma VEGF, Ang-2 and vWf (all p=0.001) in patients without OCVD but only VEGF and vWf (both p<0.01) in patients with OCVD.

Table: data as mean (SD) or median (IQR)

	Controls (n=34)	DM without OCVD (n=56)	DM with OCVD (n=41)	p value
Age (years)	66 (7)	69 (6)	68 (6)	0.106
HbA1c (%)	5.4 (0.3)	7.5 (1.5)	7.8 (1.2)	<0.001*
UACr (mg/umol)	0.52 (0.42-0.64)	1.4 (0.5-3.1)	1.4 (0.6-6.5)	0.012*
vWf (IU/dl)	109 (37)	148 (73)	165 (71)	0.002*
VEGF (pg/ml)	90 (10-230)	180 (125-480)	200 (123-775)	0.001*
Ang-2 (ng/ml)	4.0 (2.5-5.0)	6.0 (4.0-9.2)	5.5 (3.4-7.4)	0.001*
CIMT (mm)	0.81 (0.11)	1.09 (0.17)	1.13 (0.13)	<0.001*

*difference between patients and controls but not between patient groups (ANOVA and Tukey's post hoc test)

Conclusions: The relationship between plasma indices of angiogenesis, endothelial damage/dysfunction and atherosclerosis is altered by the development of OCVD, which is associated with more limited response to treatment in patients with clinically OCVD.

P413 Endothelial cells cultured in high glucose paradoxically escape premature senescence and display delayed telomere erosion: role of glutathione peroxidase up-regulation

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Background: Increased levels of reactive oxygen species (ROS) play a central role in the pathogenesis of diabetic vascular disease. Chronic mild oxidative stress induces premature replicative senescence in human endothelial cells, due both to accelerated telomere erosion and the generation of pathologically long telomeres. Endothelial cell senescence has been implicated in endothelial dysfunction and the development of atherosclerosis. Here we investigated the effect of long-term culture under high glucose conditions on telomere dynamics and the onset of senescence in human umbilical vein endothelial cells (HUVEC).
Methods and Results: HUVEC were cultured under normal (5.5 mM glucose) and high glucose (30 mM glucose; HG) conditions. HG led to a measurable increase in intracellular oxidative capacity, and during the first 4 days induced both a decline in DNA synthesis (as measured by ^{3}H-thymidine incorporation) and increased cell death (lactate dehydrogenase release). However, during serial passage HG cultures rapidly overcame this replicative delay and 90-day growth curves were not significantly different between conditions. Furthermore, there was

no premature induction of a senescent phenotype under HG, as assessed by morphology and senescence-associated beta-galactosidase activity. Under control conditions, HUVEC mean telomere length decreased at a linear rate of about 80 base pairs/population doubling (bp/PD) throughout the replicative life span. In contrast, mean telomere shortening of cultures grown under HG conditions displayed a biphasic pattern, which initially paralleled control conditions, but then paradoxically slowed to a level of about 20 bp/PD. This behaviour was accompanied by the up-regulation of glutathione peroxidase expression (2-fold increase) and activity (1.8-fold increase) under HG conditions.
Conclusions: HUVEC undergoing continued proliferation under high glucose conditions adapt to increased levels of ROS by up-regulating glutathione peroxidase. This was associated with escape from the premature senescence otherwise associated with oxidative stress. Indeed, telomere erosion was reduced under high glucose compared to control culture conditions. These findings suggest an additional mechanism which may contribute to the derangement of vascular homeostasis associated with diabetes.

P414 Insulin resistance is an independent predictor of vascular events in diabetic patients with coronary artery disease

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Purpose: Patients with both diabetes and established coronary artery disease (CAD) are at a high risk of cardiovascular events. Insulin resistance (IR) is a central feature of diabetes mellitus type 2 (DM2). Therefore, the impact of IR on the incidence of vascular events in diabetic patients with established CAD is of particular interest.
Methods: We estimated insulin resistance by the HOMA index in 495 patients with angiographically proven CAD and recorded the incidence of vascular events over a mean follow-up time of 2.3 $\pm$ 0.4 years.
Results: The HOMA index was higher in coronary patients with DM2 (n = 127) than in nondiabetic coronary patients (6.5 $\pm$ 5.9 vs. 3.0 $\pm$ 4.2; p $<$0.001). Thirty-one (23.8%) patients with DM 2 and 60 nondiabetic patients (14.5%) experienced at least 1 vascular event. In Cox regression analysis adjusting for age, gender, and baseline extent of coronary artery disease (number of angiographic stenoses 50% or more) diabetes was an independent predictor for the incidence of vascular events (OR = 1.725 [1.116 - 2.667], p = 0.014). Equally, the HOMA index proved independently predictive for the incidence of vascular events in the total study cohort: the standardized OR adjusted for age, gender, and baseline extent of CAD was 1.178 [1.026 - 1.351], p = 0.010. In subgroup analyses with respect to diabetes status, the HOMA index was significantly predictive for vascular events in patients with diabetes (OR = 1.354 [1.083 - 1.694; p = 0.008]), but not among nondiabetic patients (OR = 1.022 [0.729 - 1.432]; p = 0.901) Conclusions: In the setting of secondary prevention, IR is a strong and independent predictor of vascular events among patients with DM2. Thus, the degree of IR significantly contributes to the adverse effects of diabetes on the prognosis in coronary patients.

P415 DNA damage as a predictor of oxidative stress and its association with severity of coronary artery disease

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Objective: Oxidative stress has an important role in the whole steps of atherosclerotic process. In our study, the association of DNA damage that is an indirect finding of oxidative stress with severity of coronary artery disease (CAD) is determined.
Material and Method: 30 patients (26 male) with CAD and 40 healthy people (28 male) were included. Basic features and mean ages were similar both groups (range of age: 36-78 years). The malondialdehyde (MDA) and protein carbonyle (PC) levels were determined as indicators of oxidative stress. DNA damage was detected with Comet Assay. DNAs isolated from lymphocytes were incubated with formamidopyrimidine-DNA-glycosilase (Fpg) and endonuclease III (endo III) and under fluorescence microscopy DNA damage levels were quantified between 0 and 4. The severity of CAD is quantified with Duke score.
Results: The findings are shown in the table. Furthermore, there was a significant association between the endogen and Fpg incubated DNA damage levels and severity of CAD which was assessed by Duke score (respectively r=0.364, p$<$0.05 and r=0.480, p$<$0.001).

	CAD	Control	p
MDA (nmol/mL)	6.5$\pm$1.7	3.2$\pm$1.4	$<$0.001
PC (nmol/mL)	1.08$\pm$0.4	0.91$\pm$0.2	$<$0.01
Endogen DNA damage (Comet unit)	202.8$\pm$36.4	173.4$\pm$38.4	$<$0.001
Endo III incubated DNA damage (comet unit)	288.4$\pm$54.2	255.6$\pm$43.2	$<$0.01
Fpg incubated DNA damage (Comet unit)	342.7$\pm$53.9	283.1$\pm$53.9	$<$0.001

Conclusion: The MDA, PC and DNA damage levels were found high in CAD group indicating the relation between oxidative stress and CAD. As a positive relation was found between oxidative stress induced DNA damage levels and severity of CAD, detection of DNA damage may be used in determination of severity of CAD.

P416 Systematic evaluation of anti-apoptotic signaling by the Platelet-derived growth factor b receptor in vascular smooth muscle cells

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Platelet-derived growth factor (PDGF) plays an important role in the pathogenesis of vascular diseases. βPDGFR dependent signaling was shown to mediate cell survival in several cell types, and its signals are mediated through binding and activation of receptor-associated signaling molecules such as Src, RasGAP, PI3 kinase (PI3K), SHP-2 and PLCg. Here we investigated the signal relay mechanisms of the antiapoptotic effect in vascular smooth muscle cells (VSMC).
To explore the importance of each of these signaling molecules we expressed mutated βPDGFRs in VSMC in which the tyrosine residues required for binding of the above signaling molecules were mutated to phenylalanin. To bypass endogenous PDGFRs in VSMC we used chimeric βPDGFRs (ChiRs) with altered ligand binding specificity. ChiRs contain the extracellular ligand binding domain of the M-CSF receptor, which is not expressed in VSMC, and the cytoplasmic signaling domain of the mutated βPDGFRs.
Apoptosis of ChiRs expressing VSMC was induced by UV irradiation or H2O2 treatment. Irradiation caused a 2.4 $\pm$ 0.4 fold increase of apoptotis after 8 h compared to non-stimulated cells. H2O2 treatment led to a 2.51$\pm$0.3 fold increase of apoptotic cell death after 12 h. Selective activation of the ChiR-WT with M-CSF reduced the apoptosisrate (UV: 41$\pm$1%, H2O2: 51$\pm$1%). Deletion of the binding site for PI3K but not Src, RasGAP, SHP-2 and PLCg completely abolished the antiapoptotic effect. Consistently, a ChiR mutant which only binds PI3K was fully able to mediate cell survival as efficently as the ChiR-WT receptor. Further studies showed that PDGF-BB protects non-transfected VSMC from UV- or H2O2-induced apoptosis to the same extend as M-CSF in ChiR-WT expressing VSMC (UV: reduction by 47$\pm$14%, H2O2: 42$\pm$21%). Furthermore the PDGF-BB dependent antiapoptotic effect was completely abolished by the PI3K inhibitor wortmannin, whereas inhibitors against Src, PLCg, Erk or p38 MAP kinase had no effect. Exploration of downstream signaling events revealed that PDGF-BB activates the antiapoptotic Akt signaling pathway in a PI3K dependent manner. Moreover Akt phosphorylates and thus inactivates the proapoptotic proteins BAD and Forkhead transcription factors (FKHR, FKHRL1).
We conclude that PDGF-BB dependent cell survival via the βPDGFR is mediated only by activation of the PI3K/Akt pathway, whereas all other signaling molecules do not play a significant role.

P417 Different migration rates of vascular smooth muscle cells from human coronary artery bypass vessels

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Migration of vascular smooth muscle cells (VSMC) is involved in the pathogenesis of atherosclerosis and bypass graft disease. Long term patency rates of coronary artery bypass grafts differ according to graft origin; indeed, 10 year patency rates of the internal mammary artery (MA) are above 95%, while those of the saphenous vein (SV) are below 50%, and the radial artery (RA) seems to be in between. We therefore examined whether migration of VSMC from these vessels differs accordingly. To be able to compare migration, we first analyzed attachment of VSMC, which is a prerequisite for migration. No difference between VSMC from MA, RA, and SV could be determined (MA: 24'405$\pm$2'338 attached cells/dish, n=6; RA: 25'587$\pm$1'195 cells/dish, n=5; SV: 23'506$\pm$2'124 cells/dish, n=6). VSMC migration was analysed using a modified Boyden's chamber. VSMC were stimulated with PDGF-BB (1 ng/ml, 3 ng/ml, 10 ng/ml) or Tissue factor/FactorVIIa-complex (0.1 nM, 0.3 nM, 1 nM) for 5 hours. After stimulation with PDGF-BB, a concentration-dependent increase in the number of migrated cells occurred. Migration was lower in MA and to a lesser extent in RA as compared to SV (cell number as % of maximal response to PDGF-BB: MA: 1 ng/ml: 7$\pm$2.4, 3 ng/ml: 20.1$\pm$4.3, 10 ng/ml: 32$\pm$8.5; RA: 1 ng/ml: 18.7$\pm$7.8, 3 ng/ml: 38.7$\pm$7.1, 10 ng/ml: 55.7$\pm$9.7; SV: 1 ng/ml: 44.7$\pm$8.4, 3 ng/ml: 85.3$\pm$6.9, 10 ng/ml: 100$\pm$20.9). There was a significant difference between MA and SV at all three concentrations examined (10 ng/ml: p=0.0001, 3 ng/ml: p$<$0.0001, 1 ng/ml: p=0.01; n=5). Between RA and SV, there was a significant difference at 10 ng/ml (p$<$0.005; n=5) and 3 ng/ml (p$<$0.001; n=5), but not at 1 ng/ml (p= n. s.). A similar pattern was observed with Tissue factor/FactorVIIa-complex (cell number: MA: 0.1 nM; 13.4$\pm$7.3, 0.3 nM: 12.6$\pm$3.3, 1 nM: 22.2$\pm$7.3; RA: 0.1 nM: 10$\pm$1.6, 0.3 nM: 24.2$\pm$5.7, 1 nM: 35.6$\pm$14.4; SV: 0.1 nM: 16$\pm$3.4, 0.3 nM: 35.6$\pm$8.1, 1 nM: 42.2$\pm$15.4). Thus, migration of VSMC from MA, RA, and SV in response to both platelet-derived and coagulation-derived mediators correlates to patency rates of the respective bypass graft. The lower migration rates of VSMC from MA and RA as compared to SV may be important determinants of neointima formation and bypass graft disease.

NUCLEAR CARDIOLOGY/MAGNETIC RESONANCE IMAGING AND CARDIAC RADIOLOGY.

P418 Cut-off values for magnetic resonance flow parameters to detect significant stenoses in coronary artery bypass grafts

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Purpose: Cardiovascular magnetic resonance (CMR) is a potential noninvasive method to measure flow in vein grafts. The purpose was to evaluate vein graft disease using CMR, and to formulate cut-off values that maximally separate normal from diseased grafts.
Methods: A total of 68 patients underwent coronary angiography and CMR with flow mapping at rest and during adenosine stress. Volume flow, systolic and diastolic peak flow (SPF; DPF) were derived from flow maps. Coronary flow reserve (CFR) and diastolic-to-systolic flow ratio (DSFR) were calculated. Quantitative coronary angiography was performed to evaluate stenoses objectively.
Results: In multivariate analysis using all flow parameters, for single vein grafts (n=81) sensitivity and specificity of 79% and 87% were found to detect stenoses $\geq$50% ($p<0.001$). For sequential vein grafts (n=44) sensitivity and specificity were 62% and 94% (p=0.001). Optimal cut-off values for the separate flow parameters are shown in table 1.

Table 1

	Single vein grafts	Sequential vein grafts
Flow parameter	Cut-off	Cut-off
Volume flow baseline (ml/min)	24.2 †	40.9 *
Volume flow stress (ml/min)	48.7 †	93.6 *
SPF baseline (ml/s)	0.83 †	1.17 *
SPF stress (ml/s)	1.49 †	2.28 *
DPF baseline (ml/s)	1.18 †	1.48
DPF stress (ml/s)	2.03 †	3.60 *
CFR	1.56 †	1.87
DSFR baseline	0.93 †	0.99
DSFR stress	1.08 †	1.41

Optimal cut-offs for MR flow parameters. † $p<0.005$; * $p<0.05$.

Conclusion: CMR with flow mapping has a good performance in the detection of stenoses $\geq$50% in single and sequential vein grafts. Cut-off values can be used for accurate interpretation of flow maps of bypass grafts.

P419 Heterogeneity of cardiac systolic strain: stability over time and during load variations

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Background: In the normal left ventricle (LV), variables describing blood flow and metabolism are highly heterogeneously distributed. However, until now, heterogeneity of myocardial fiber-shortening is not known. The present study investigated the spatial distribution of systolic midwall circumferential strain (CSsys; estimate of midwall fiber-shortening) and the persistence of its distribution under various conditions.
Methods: In intact anesthetized dogs, CSsys was determined using MR-tagging (5 short axis slices x 32 sectors, i.e. sample size of 0.4% LV weight). Heterogeneity Index (HI) was determined as SD of CSsys. Serial scans were performed to investigate persistence of CSsys distribution a) after one week (n=5); b) during increased preload (plasma expander infusion, increasing end-diastolic LV volume by 25%, n=6); and c) after induction of left bundle branch block (LBBB, by RF-ablation, n=6).
Results: CSsys averaged -0.127$\pm$0.020 and HI was 0.050$\pm$0.008. Distribution of CSsys was not related to anatomical structures (i.e. papillary muscles and RV attachments). Increase of preload elevated CSsys by 16$\pm$7% ($P<0.05$), but did not change CSsys HI (0.056$\pm$0.021, representing a coefficient of variation of $\sim$40%). Significant correlations were found between local CSsys values obtained during 2 scans at one-week time-interval (r=0.68$\pm$0.05) and between normal and increased preload (r=0.74$\pm$0.08). LBBB significantly decreased CSsys in the septum (-0.041$\pm$0.019) and increased CSsys in the LV free wall (-0.178$\pm$0.039). After subtraction of a second order harmonic fit, describing the gross redistribution of CSsys, a significant correlation was observed between local CSsys before and during LBBB (r=0.58$\pm$0.11) indicating unchanged CSsys differences between adjacent regions.
Conclusions: Local CSsys is heterogeneously distributed and this distribution is stable under various conditions. This data suggest considerable local differences in intrinsic contractility in the normal heart, the cellular and molecular basis of which deserves further study.

P420 Magnetic resonance imaging assessment of the efficacy of septal alcohol ablation for hypertrophic cardiomyopathy

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Of 49 patients with hypertrophic obstructive cardiomyopathy (HOCM) treated by transcoronary ablation of septal hypertrophy (TASH) in our institution from March 2000 to January 2004, 11 pts had systematic pre and post-TASH cine and perfusion MRI. The main exclusion criterion was a previous pacemaker implantation. All procedures were performed under contrast echocardiography guidance. Septal ablation was performed successfully with 2.3$\pm$1.3cc alcohol injected into 1 or 2 septal arteries per patient without acute complications. Intraventricular gradient measured by transthoracic echocardiography was 125.2 $\pm$ 49.2 mmHg pre-procedure and 18.6$\pm$21.7mmHg post procedure($p<0.000$). Percent area of early hypoenhancement (Ehypo) on first pass MR images and percent area of late hyperenhancement (Lhyper) relative to total area of interventricular septum were assessed by planimetry.
In all cases, post procedure delayed contrast-enhanced MR imaging showed a typical and consistent pattern, corresponding to a central "black hole" surrounded by circumferential hyperenhancement.

MRI results

	Septal thickness (mm)	Systolic septal wall thickening (%)	Ehypo (%)	Lhyper (%)
Pre	26.1$\pm$6.0	17.4$\pm$8.6	0$\pm$0	2.6$\pm$3.2
Post	24.7$\pm$6.0	12.5$\pm$7.5	16.8$\pm$7.4	24.6$\pm$10.2
p value	0.093	0.001	0.000	0.000

Conclusion: MRI is an accurate technique for assessing the efficacy of septal alcohol ablation in patients with hypertrophic obstuctive cardiomyopathy. It provides a precise measurement of the size of the septal infarction and could predict late clinical outcome and thinning of the septum.

P421 Visualization of the whole coronary arterial tree in a Single 3D-Volume for advanced coronary magnetic resonance angiography

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Background: In order to integrate magnetic resonance coronary angiography (MRCA) into clinical routine, it is crucial to reliably depict the whole coronary arterial tree in an acceptable total examination duration. Thus, the objective of the present study was to develop a MRCA approach for complete coverage of the coronary arterial tree within a single measurement.
Methods: 20 patients with suspected coronary artery disease underwent free-breathing, navigator-gated MRCA using a 3D-volume with a transversal slice orientation and nearly isotropic spatial resolution (1.2x1.2x1.4mm) with coverage of the whole heart in a single scan (SSFP, TR/TE/flip: 5.3/2.6/90°; Philips Intera CV 1.5T). The acquisition duration per heart beat was individually adapted to the cardiac rest period. Correction of respiratory motion was done using an affine prospective navigator algorithm (2 navigators: cranio-caudal position on the dome of the right hemidiaphragm and anterior-posterior position on the right chest wall; gating window 10mm).
Results: Effective scan duration was 17$\pm$7min (navigator efficiency: 68$\pm$16%). In all examinations the LAD, LCX and RCA were visualized down to their distal segments and a reliable visualization of the major side branches was achieved (LAD: 1.9$\pm$0.9, LCX: 1.7$\pm$0.7, RCA: 2.3$\pm$0.9). Based on a 16-segment model 81% of all coronary arterial segments were evaluable.

Conclusions: For the first time, combining a MRCA-sequence with an intrinsically high contrast (SSFP) together with an optimized navigator algorithm allowed for the visualization of the whole coronary arterial tree including distal segments and main side branches. This new, single 3D-volume MRCA-approach had an acceptable examination duration providing a high and nearly isotropic spatial resolution.

P422 In-hospital magnetic resonance imaging-derived bi-ventricular volumes and ejection fraction predic late occurrence of congestive heart failure after successful primary stenting for uncomplicated acute myocardial infarction

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We assessed the correlation between in-hospital MRI-derived bi-ventricular volumes and ejection fraction, and the late occurrence of congestive heart failure (CHF) after uncomplicated acute myocardial infarction (AMI).
We assessed right (RV) and left ventricular (LV) volumes by cine magnetic resonance imaging 7±2 days after successful primary stenting for a first ST-elevation AMI in 76 consecutive patients with no in-hospital complication, including CHF. All patients were followed-up for 44±4 months.
During the follow-up, death, non-fatal AMI and revascularization occurred in 4 (5.3%), 5 (6.6%) and 17 (22.4%) patients respectively. Congestive heart failure occurred in 14 (18.4%) patients. The comparison of RV and LV volumes and ejection fractions between patients with and those without CHF is reported in the table.

MRI-derived biventricular parameters

	CHF (n=14)	No CHF (n=62	p
RVEDV (ml/m^2)	64±20	9±16	NS
RVESV (ml/m^2)	40±15	31+/10	0.003
RVEF (%)	38±9	46±12	0.01
LVEDV (ml/m^2)	81±30	59±21	0.001
LVESV (ml/m^2)	53±24	30±17	0.0001
LVEF (%)	37±13	51±14	.0009

CHF: congestive heart failure, RV & LV: right and left ventricular, EDV & ESV: end-diastolic & end-systolic volumes, EF: ejection fraction

Conclusion: The late occurrence of CHF in patients with uncomplicated, successfully reperfused AMI, is correlated to higher MRI-assessed in-hospital bi-ventricular volumes and ejection fractions. MRI-derived parameters could be used to identify a high-risk subgroup of patients in this generally low-risk population.

P423 Cardiac resonance imaging after emergency coronary artery stenting is associated with a similar rate of stent thrombosis compared to controls

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Background: Whether cardiac magnetic resonance imaging (CMRI) very early after emergency coronary artery stenting is associated with an increased risk for subsequent stent thrombosis is not known.
Methods and results: From January 1999 until November 2003, 300 consecutive patients underwent emergency coronary artery stenting with angiographic follow-up. 51 patients had clinically indicated CMRI within a median of 4 days (range 0 - 11) after stenting. CMRI was performed in 25 (49%) patients within 3 days and in 42 (82%) patients within 6 days after stenting. All CMRI-patients underwent evaluation of myocardial structure and function, using state of the art sequences on a clinical 1.5 T CMRI system, optimized for cardiovascular applications. CMRI-patients were significantly younger; other demographic and procedural characteristics were similar (table). CMRI was not associated with procedural complications. At angiographic follow-up, stent thrombosis was documented in 1/51 (1,97%) CMRI-patient, compared to 7/249 (2,81%) patients of the non-CMRI-group (P = 1.000, Fisher's exact test). CMRI was not found to be a predictor of stent thrombosis in multivariate regression analysis which remained consistent after adaptation for age.

Patient characteristics

	CMRI	non-CMRI
Age (yrs)	58 ± 11.9 *	62 ± 11.3
Male (%)	78	76
Cigarette smoker (%)	43	38
Diabetes (%)	24	32
Hypertension (%)	63	66
Hyperlipidemia (%)	47	50
Ejection fraction (U)	58 ± 12.8	60 ± 14.8
Implanted stent-length (mm)	21 ± 11.9	21 ± 10.8

*P<0.05

Conclusion: CMRI after emergency coronary artery stenting is not associated with an increased rate of stent thrombosis. CMRI can be performed safely and early after emergency coronary stenting without the fear of increased risk for subsequent stent thrombosis.

P424 Head-to-head comparison of visual and quantitative assessment of transmural extent of infarction on contrast-enhanced magnetic resonance imaging

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Purpose: Contrast-enhanced MRI (ce-MRI) allows precise delineation of infarct transmurality. An issue of debate is whether data analysis should be performed visually or quantitatively. Accordingly, a head-to-head comparison was performed between visual and quantitative analysis of infarct transmurality on ce-MRI. In addition, infarct transmurality was related to the severity of resting wall motion abnormalities.
Methods: In 27 patients with chronic ischemic left ventricular dysfunction (LVEF 33 ± 8%) and previous infarction, cine MRI (to assess regional wall motion) and ce-MRI were performed. Using a 17-segment model, each segment was assigned a wall motion score (from normokinesia to dyskinesia) and segmental infarct transmurality was visually assessed on a 5-point scale (0=no infarction, 1=transmurality 1-25% of LV wall thickness, 2=transmurality 26-50%, 3=transmurality 51-75%, and 4=transmurality 76-100%). Quantification of transmurality was performed using threshold analysis; myocardium showing signal intensity above the threshold was considered scar tissue and the percentage of transmurality was calculated automatically.
Results: Wall motion was abnormal in 56% of the 459 segments and 55% of segments revealed hyperenhancement (indicating scar tissue). The agreement between visual and quantitative analysis was excellent: 90% (kappa 0.86) of segments were categorized similarly by visual and quantitative analysis. Infarct transmurality paralleled the severity of contractile dysfunction; 96% of normal or mildly hypokinetic segments had infarct transmurality <25%, whereas 93% of a- and dyskinetic segments had transmurality >50% on visual analysis.
Conclusion: Visual analysis of ce-MRI studies may be sufficient for assessment of transmurality of infarction.

COMPUTERS IN CARDIOLOGY

P425 Heart failure case disease management program: a pilot study of home telemonitoring versus usual care

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Background: Previous studies have shown that about 50% of readmissions for chronic heart failure can be prevented by a multidisciplinary approach. Telemonitoring care can be integrated into health care provision as a substitute for routine clinical follow-up. The performance of a telemonitoring service integrated into the process of chronic heart failure care has not so far been evaluated.
Objectives: In this study we describe our comprehensive heart failure home telemonitoring management program and evaluate the outcomes of this approach in comparison to the usual program of care after discharge from a Heart Failure Unit.
Methods: One hundred and thirty-three patients discharged from a Heart Failure Unit, underwent risk cluster classification for cardiac events and were prospectively randomized to two management strategies: 66 patients to usual community care and 67 to a management program delivered by the telemonitoring service (TMS). Telemanagement compliance outcomes were evaluated and combined clinical outcome including re-hospitalization, cardiac death, and emergency room access, was compared between two strategies.
Results: Patients were allocated in the following cluster risk groups for cardiac events: 51 patients at low risk, 43 at moderate risk and 39 at high risk. The compliance to telemonitoring strategy was 82%. A total of 294 accesses were recorded: 246 were related to transmission of vital signs and symptoms and while 48 vocal messages were left on the 24-hour answering machine. The compliance to system follow-up was (81%). The mean individual access rate to the TMS was 4.6±3.3 calls. Active interventions were made following 54% of the accesses. After 10±6 months of follow-up, 135 events had occurred in all patients: 103 in the usual care group and 32 in telemonitoring group (p<.001). The TMS patients were readmitted to hospital less frequently than the usual care ones (22 vs 77 p<.009). Cluster risk classification intercepted patients' increased health care demands (low risk: .34±0.62; moderate risk 1±1.2; high risk 1.9±1.5 events)
Conclusion: A management program delivered by a telemonitoring service can reduce health care demands by CHF patients.

ECHOCARDIOGRAPHY/DOPPLER

P426 Tele-monitoring facilitates a sustained 12-month response to exercise training in patients with chronic heart failure

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Background: Exercise training (ExT) improves exercise capacity in heart failure (CHF), but results with ongoing home-based training have been variable. De-training occurs rapidly in pts who comply poorly. We sought whether tele-monitoring could lead to sustained improvement of functional capacity in pts undergoing 8 months of home ExT, following 4 months of hospital-based ExT.
Methods: Sixteen pts (14 men, age 64±8) with symptomatic CHF due to coronary disease (n=6) or unknown causes (n=9) and LVEF <35% (29±9%) were provided with heart rate monitors (HRM) and exercise diaries during 8-months home ExT. Weekly telephone contact was established and heart rate data was downloaded bi-monthly from HRM to a PC. We monitored change in peak VO2, Quality of Life (QOL) and exercise adherence, calculated from percentage of target exercise sessions undertaken.
Results: After 4 months of hospital ExT, peak VO2 increased by 26% (12.4±4.6 vs 15±4.9, p<0.001). At 12 months peak VO2 had fallen to 13.1±3.8, a change of 14% from 16 weeks, but a 12% (p=0.05) improvement from baseline. Exercise adherence (46±40%) correlated with change in peak VO2 (r=-.50, p=0.05) from weeks 16-52. QOL improvements were sustained; Minnesota Living with Heart Failure (base 46.9, 16 weeks 32.2 [p=0.01], 12 months 31.9[p=0.006]) and Hare-Davis depression questionnaire (base 97.8, 16 weeks 81.6 [p=0.002], 12 months 78.7[p=0.03]).
Conclusions: Functional capacity and QOL changes following hospital-based ExT are sustainable when home ExT is combined with a tele-monitored system requiring regular reporting and verification from patients.

P427 Early filling by pulsed wave and tissue Doppler velocities ratio correlates well with conventional indices of cardiac dysfunction

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The relationship between left atrial pressure (LAP), and the ratio of early transmitral filling divided by early myocardial diastolic velocity (E/Em)has been shown to be significant, since E/Em > 15, is associated with LAP > 20 mmHg.
Aim: to determine the utility of E/Em ratio in detection of impaired cardiac systolic (EF) and diastolic function (DF) including elevated LAP, in the indiginous population.
Methods: Patients referred to the Echo-Lab had standard echocardiographic and doppler studies including transmitral interrogation for early filling (E)wave; atrial (A) wave; E/A ratio,isovolumic relaxation time (IVRT) and deceleration time (DT). Left atrial pressure (LAP) was calculated non-invasively, if mitral regurgitation was present. Early myocardial diastolic velocity (Em) was obtained by interrogating the basal ventricular septum, in its axial plane at the mitral annulus in apical 4-chamber views, and E/Em ratio determined. A variable frequency transducer (2.5 to 4.0 MHz) was used. Spectral pulsed wave doppler signal was adjusted to obtain a Nyquist limit of 15 or 20 cm/s, with the lowest wall filter settings and the minimum optimal gain. Pearson correlation coefficient (Pr)was obtained between EF; E/Em and LAP; for all subjects including normal controls (A)and diseased subjects (B) where cut-points (EF<50%; LAP>20 mmHg and/or E/Em > 10.0) were applied. Spearman rank correlation (Sr)was determined for E/Em and DF grade, where DF I/IV =normal filling; DF II/IV= delayed relaxation; DF III/IV = pseudonormal, and DF IV/IV = restrictive filling.
Results: 108 patients were included. Group A (normal controls)= 35/108 subjects(32.4%)included 16 females. Their mean age= 46.9, and mean EF= 65.5%. Group B (diseased subjects) = 73/108 subjects(67.6%),also included 16 females. Their mean age = 59.9, and mean EF= 46.3%. Mean LAP was 29.9 mmHg in twenty subjects in the latter group (B). Pr was obtained between the following: 1) EF and E/Em, r = -0.59 2) E/Em and LAP, r = 0.82 and 3) EF and LAP, r = -0.79. Furthermore, mean E/Em for DF I/IV (Group A, n=35) was= 7.6 (±1.2); E/Em= 8.84 (±2.0) for DF II/IV (n=27); E/Em = 10.16 (±3.5) for DF III/IV (n=29), and E/Em =11.71 (±3.5) for DF IV/IV (n=18). Sr between E/Em and DF grade was: r = 0.58 (95% CI= 0.38 - 0.73) with p = 0.0001 (two tailed).
Conclusions: An E/Em ratio cut-point of >10, had a significant corrrelation between E/Em and LAP, and between E/Em and DF grade, in our study population. E/Em as an index of DF, showed not only unimodal distribution, but even a linear relationship to DF grades.

P428 The peak ejection intraventricular pressure difference measured by Doppler echocardiography is a strong index of global left ventricular contractility

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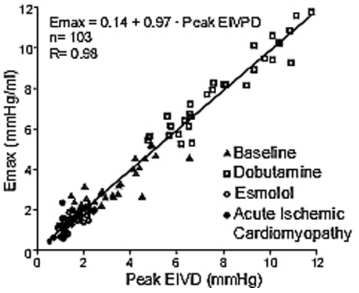
We have recently developed a method for measuring regional pressure gradients by processing color-Doppler M-mode recordings (CDMM). Using high-fidelity micromanometers, we have validated this method for measuring ejection intraventricular pressure differences (EIVPD) inside the LV. The purpose of this study was to assess the correlation between Doppler-derived EIVPD and reference indices of contractility obtained using the conductance method.
Methods: Simultaneous CDMMs of the LV outflow (apical view) and pressure-volume data (pressure-conductance catheters) were obtained in 9 anesthetized mini-pigs undergoing pharmacological interventions (esmolol and dobutamine). In 4 animals, acute ischemic LV cardiomyopathy was induced by injection of polystyrene microspheres in the left main coronary artery. CDMM images were processed using a custom-built algorithm that decodes flow velocity and solves inertial and convective acceleration, providing instantaneous EIVPD curves between the apex and the outflow tract. Three consecutive beats were averaged. Peak systolic elastance (Emax) and preload recruitable stroke work (PRSW) were calculated from the instantaneous pressure-volume loops obtained during caval occlusion.
Results: A wide range of inotropic states was achieved (n=103 datasets; Emax=2.7±4.0; range= 0.5-12 mmHg/ml). Acute ischemic cardiomyopathy induced a significant depression of Emax, parallel to simultaneous LV dilatation. A very strong linear correlation was obtained between peak EIVPD and invasive indices of contractility (Emax R=.98; PRSW R=.81; and preload corrected dP/dtmax R=.81; p<.0001 for all).



Conclusions: Peak EIVPD is a strong index of global myocardial contractility that closely correlates with currently established gold standards.

P429 Tissue Doppler imaging for assessment of filling pressures- impact of left ventricular performance and stroke volume

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Background: Mitral annular velocities (S', E', A') assessed by tissue Doppler imaging (TDI) complement traditional Doppler variables in evaluating left ventricular (LV) performance. The mitral E/E'-ratio has been suggested as an estimate of LV filling pressures in selected subsets of patients (pts). We attempted to define the impact of LV performance and stroke volume (SV) in this setting.
Methods & Results: After excluding pts with pacemakers, atrial fibrillation or bundle branch block, LV end-diastolic pressures (EDP) were obtained during left heart catheterization in 38 patients (pts) with preserved LV function (defined by an ejection fraction (EF) > 50%, age 56±14 y., PF group) and in 46 pts. with reduced LV function (EF <50%, age 60±11y., RF group). Echocardiographic measurements comprised LV dimensions, volumes and mass, SV index (SVI, biplane Simpson's method), EF and mitral inflow (E, A, deceleration time (DT)). TDI derived mitral annular velocities (S', E', A') were obtained at the septal and lateral annulus and averaged.
Results:

Group	SVI (ml/m²)	EF (%)	DT (ms)	S' (cm/s)	E' (cm/s)	E/E'	LVEDP (mmHg)
PF (n=38)	40±21	66±11	206±54	8.9±2.6	10.6±3.6	7.5±3.2	13±6
RF (n=46)	26±12**	26±11**	162±79*	4.7±1.2**	5.6±1.3**	15.7±4.6**	21±7**

* p<0.01, ** p<0.001 PF vs. RF group.

E/E' was significantly related to LVEDP in the RF group (r=0.54, p<0.001), but not in the PF group (r=0.17, p=ns). In the RF group, an E/E' > 14 identified pts. with LVEDP > 15 mmHg with a sensitivity of 71% and a specificity of 100% (area under the curve: 0.91±0.04). SVI was significantly related to E' in the PF group (r=0.67,

p<0.001), but not in the RF group (r=0.15, p=ns). Stepwise multiple regression analysis identified SVI as the strongest independent predictor of E' in the PF group, and DT in the RF group.
Conclusion: In subjects with reduced LV performance, E/E' is a reliable estimate of filling pressures. In subjects with preserved LV performance, filling pressures can not accurately be predicted by E/E', which may be attributable to the impact of stroke volume (or loading conditions) on E' in this patient population.

P430 Comparative value of tissue Doppler Imaging and mitral flow propagation velocity for the evaluation of left ventricular filling pressure

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Background: recently, two new indexes based on the ratio of transmitral early diastolic velocity (E) to tissue doppler imaging (TDI) early diastolic velocity of mitral annulus (E') and E to propagation velocity (Vp) have been proposed to predict LV filling pressures. However, little is known about the comparative value of these two indexes.
Methods: we studied 71 consecutive patients reffered for coronary angiography (age 65±11yrs, 21pts with LV ejection fraction <50%). Complete Doppler echocardiographic examination including TDI and Vp measurements using a Sequoia 256 (Siemens) and direct measurement of LV end diastolic pressure were performed simultaneously in the cathlab. Left ventricle filling pressures were considered elevated when LVEDP > 15mmHg.
Results: the correlation coefficients between E/E' and E/Vp and LVEDP were respectively 0.68 (p=0.01) and 0.54 (p=0.01) in the overall population; the correlations were better in patients with low LV EF (< 50%), respectively 0.8 (p=0.01) and 0.77(p=0.01), and poor in patients with normal LV EF,respectively 0.57 (p=0.05) and 0.41 (ns). Moreover Vp measurements had higher interobserver variability compared to E' (14% vs 7%). The cut off values for both E/E' and E/Vp giving the best sensitivity and specificity in identifying LVEDP >15 mm Hg were given 9 and 2 (Table 1)

Sensitivity, Specificity for E/E', E/Vp

	EF<50%		EF>50%	
	Sensitivity	Specificity	Sensitivity	Specificity
E/E' = 9	86%	83%	60%	84%
E/Vp = 2	85%	83%	48%	76%

Conclusion: Both E/E' and E/Vp can be used for the evaluation of LV filling pressures. However E/E' has a lower variability than Vp and appears to be preferabre tool in estimation of filling pressures especially in patients with EF>50%.

P431 Crosstalk between infarcted and non-ischaemic myocardium – a mechanism of apparent post-systolic shortening in myocardium with normal function

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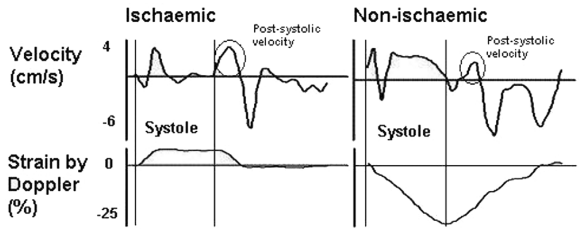
Introduction: Post-systolic shortening measured by tissue Doppler imaging (TDI) has been introduced as a sensitive marker of myocardial dysfunction due to regional ischaemia. We investigate the hypothesis that abnormal post-systolic velocities may also occur in normal myocardium due to mechanical interactions with the ischaemic region.
Methods: In 8 patients with acutely occluded LAD, we measured myocardial velocities by TDI and regional shortening by strain Doppler echocardiography (SDE). Myocardial segments proximal to the occluded vessel and segments supplied by the CX were used as non-ischaemic control regions (no stenosis on angiography).
Results: In the infarcted area of the apical septum peak systolic strain was 4.1 ± 0.9* %, indicating systolic lengthening. (*=p<0.002 vs non-ischaemic myocardium). In the mid-septal, mid-lateral, basal septum and basal lateral regions strains were -15 ± 1.6%, -15 ± 1.7%, -18 ± 2.2% and -17 ± 1.7%, respectively, consistent with essentially normal systolic shortening. In these regions, however, TDI showed markedly positive IVR velocities with peak values of 1.4 ± 0.5 and 1.4 ± 0.6 cm/s in the mid-septal and mid-lateral regions, respectively and 1.6 ± 0.4 and 0.4 ± 0.6 cm/s in basal septum and basal lateral regions. In apparent contrast to this finding, none of these segments demonstrated significant post-systolic shortening by SDE. The Figure shows representative patient.
Conclusions: Using TDI, this study shows that abnormal post-systolic velocities are found in regions outside the infarcted area. However, no true post-systolic shortening was found by SDE. Most likely the apparent post-systolic shortening in non-ischaemic regions represents motion caused by the same force that leads to passive recoil of the infarct.



P-S velocity in non-ischaemic myocardium.

P432 Hypertensive left ventricle: different remodeling – different longitudinal function

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Background: Left ventricle (LV) longitudinal function in systemic hypertension may be reduced, while radial function remains normal, or even may show compensatory increase. LV remodeling is important factor in the progression to congestive heart failure. Based on LV mass indexed for body size and relative wall thickness (RWT), LV remodeling in hypertension can be characterized by geometric subtypes with different prognosis.
Aim: Aim of the study was to determine the longitudinal LV function in the different types of hypertensive LV remodeling.
Methods: Pulsed tissue Doppler imaging was performed in 132 patients (72 male, 57.2±11.3 years) with essential hypertension. Mitral annular velocities were measured lateral and septal from apical 4-chamber view, anterior and inferior from 2-chamber view. Systolic (Vs), early (Ve) and late (Va) diastolic annular velocities were averaged from the four sites.
45 patients were with eccentric hypertrophy (normal RWT and LV hypertrophy), 32 patients with concentric hypertrophy (increased RWT and LV hypertrophy), 22 patients with concentric remodeling (increased RWT and normal LV mass) and 33 patients - with normal LV mass and RWT.
Results: Table I

Table I

	Vs (cm/s)	Ve (cm/s)	Va (cm/s)
Eccentric hypertrophy	8,1±2,9*#	9,1±2,3*#	10,9±3,3
Concentric hypertrophy	6,9±2,2*	7,8±1,7*	11,1±4,2
Concentric remodeling	8,9±3,1#	9,0±1,9*#	12,5±2,0
Normal LV geometry	9,8±2,4	11,2±2,5	12,9±2,9

* p<0,05 vs normal geometry; # p<0,05 vs concentric hypertrophy

Conclusion: Longitudinal LV function differs in the types of LV remodeling in essential hypertension.

P433 Longitudinal left ventricular myocardial contraction abnormality in hypertrophied heart evaluated by tissue strain imaging

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Background: The left ventricular (LV) myocardial contractile characteristics in hypertrophied heart have not been precisely evaluated. Tissue strain imaging (TSI) has enabled us to quantitatively assess regional myocardial contractility.
Purpose: To precisely assess longitudinal LV myocardial contractility in hypertensive heart disease (HHD) and asymmetric septal hypertrophic cardiomyopathy (ASH) using TSI.
Methods: Subjects consisted of 22 normal control, 21 patients with HHD and 19 with ASH. Color tissue Doppler image was recorded from apical four chamber view and the TSI at the ventricular septum (VS) and postero-lateral (PL) wall was analyzed. A custom software (ApliQ, Toshiba Corp.) was applied for an off-line analysis. Peak systolic displacement (Dp), time from IIA to Dp, corrected time from ECG-Q wave to Dp, and peak systolic strain (SR) were measured.
Results: 1) There was no significant difference in Dp between the normal and HHD, whereas that in ASH both in VS and PL was significantly smaller compared to the normal and HHD. 2) The SR in HHD and ASH was significantly smaller than that in the normal both in VS and PL, with significant difference between HHD and

	Normal	HHD	ASH
Dp (VS) (mm)	10.2±1.4	9.1±0.8	6.5±2.1**#
(PL) mm	8.8±1.4	8.1±0.8	6.9±1.7*#
SR (VS)	0.49±0.13	0.35±0.12*	0.28±0.13**#
(PL)	0.41±0.12	0.36±0.10*	0.26±0.13**#
C-time from Q to Dp (VS) (ms)	285±25	300±57	359±59*#
(PL) (ms)	287±33	301±53	312±39*#
Time from II_A to Dp (VS) (ms)	−51±15	−38±29*	28±17**#
(PL) (ms)	−49±11	−39±27*	−24±17*#

*p < 0.01, **p < 0.001 vs Normal, #p < 0.01 vs HHD.

ASH. 3) Time from Q wave to Dp in ASH was significantly longer compared to that in HHD, and was significantly greater ($p < 0.01$) in VS than in PL. 4) The timing of Dp in VS in ASH was especially delayed even after aortic valve closure.
Conclusions: This study demonstrates impaired longitudinal LV myocardial contractility in hypertrophied heart especially in ASH even in the non-hypertrophic postero-lateral wall. There was a contractile asynchrony as evidenced by the difference in tissue displacement and strain between ventricular septum and postero-lateral wall.HHD

P434 Coupling of tricuspid annular plane systolic excursion and tricuspid regurgitant jet-derived pulmonary artery systolic pressure for prognostic stratification of patients with chronic heart failure

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Background: Studies have shown the negative prognostic impact of the association of pulmonary hypertension and reduced right ventricular (RV) systolic function in patients with chronic heart failure (HF).
With the introduction of the measurement of the tricuspid annular plane systolic excursion (TAPSE) it is now possible to accurately assess RV systolic function noninvasively.
Aim: To evaluate whether the coupling between TAPSE and tricuspid regurgitant jet-derived pulmonary artery systolic pressure (PASP) may add to prognostic stratification in patients with chronic HF.
Methods: A series of 143 patients consecutively examined at our laboratory and diagnosed with chronic HF secondary to left ventricular dysfunction (ejection fraction [EF] <50%) was evaluated at the index Doppler echocardiogram. RV systolic function was assessed by means of the TAPSE. PASP was obtained by adding the estimated right atrial pressure to the peak pressure gradient of tricuspid regurgitation. In case of weak or poor Doppler signals, PASP was measured after intravenous administration of physiological saline. Patients were divided according to coupling between TAPSE and PASP: group 1: TAPSE $\leq$ 14 mm and PASP $\geq$ 40 mmHg (n= 18), group 2: TAPSE >14 mm and PASP $\geq$ 40 mmHg (n= 63), group 3: TAPSE $\leq$ 14 mm and PASP <40 mmHg (n=10), group 4: TAPSE > 14 and PASP < 40 mmHg (n=52). Plasma for N-terminal pro-brain natriuretic peptide (NT-proBNP) was sampled and patients were followed-up for a mean period of 6 $\pm$ 3 months.
Results: In the entire study population, EF was 33 $\pm$ 9%, TAPSE was 18 $\pm$ 5 mm and PASP was 35 $\pm$ 10 mmHg. During the follow-up, 8 patients died for cardiac causes and 18 were hospitalized for worsening HF. At 9 months, event-free survival was 47% in those with the worst TAPSE and highest PASP (group 1), while it was 80% in group 2, 68% in group 3 and 89% in group 4 ($p<0.0001$ by Log-rank). NT-proBNP was 3824 $\pm$ 2258 pg/ml in group 1, 2501 $\pm$ 1199 pg/ml in group 2, 733 $\pm$ 378 pg/ml in group 3 and 686 $\pm$ 297 pg/ml in group 4 ($p<0.001$ group 1 vs group 3 e 4, $p<0.004$ group 1 vs group 2).
Conclusion: Noninvasive estimates of RV systolic function and PASP by Doppler ultrasound may contribute to prognostic stratification of patients with chronic HF. Patients with more compromised RV function and pulmonary hypertension had both the highest levels of NT-proBNP a the worst prognosis.

P435 Discrepancies in the prevalence of ventricular asynchrony in patients with systolic dysfunction by using different parameters of intraventricular asynchrony. Results from the RAVE registry

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Some recent studies showed that the EKG is not sensitive enough for reliable identification of patients with correctable mechanical asynchrony. Echo-Doppler provides non-invasive insights into regional asynchrony and may help to improve asynchrony detection. Nevertheless, a large number of methods have been described. Our aim was to assess the prevalence of echocardiographically detected ventricular asynchrony by using different methods.
Methods: we have designed a prevalence registry (RAVE registry) in order to evaluate this issue. 316 consecutive patients referred for an echo study in 13 hospitals comprised the study group. All of them had a left ventricular ejection fraction <40%. We also enrolled 29 control patients without systolic dysfunction. Intraventricular asynchrony was evaluated using four different methods: a) septal-to-posterior wall motion delay (SPWMD) obtained by M-mode (cut-off point=130 ms); b) difference between time from Q wave to left ventricular ejection end as assessed by pulsed Doppler and time from Q wave to the end of the systolic wave of the most delayed basal segment as assessed by pulsed DTI (ejection-DTI time; cut-off point: 50 ms); c) Standard deviation of the time from the Q wave to the end of the systolic wave of all 4 segments (Systolic SD; cut-off point$\geq$ 2SD of the control group) and d) the maximum difference in the time from the Q wave to the end of the systolic wave of all 4 segments (Systolic Max; cut-off point > 100 ms).
Results: Mean age was 62.14$\pm$13.5 years (75.7% men). Clinical and echocardiographic baseline characteristics were similar in both groups of patients with systolic dysfunction. The prevalence of intraventricular asynchrony is shown in the table below.

	1. Controls	2. Narrow QRS	3. Wide QRS
PWMD > 130 ms	0	75 (40.3%)	56 (60.9%)
Ejection-DTI time > 50 ms	0	73 (38.4%)	41 (39.8%)
Systolic Max > 100 ms	0	40 (20.8%)	27 (26.2%)
>+2 systolic SD of controls	0	136 (72.8%)	82 (79.6%)

Conclusion: The prevalence of intraventricular asynchrony depends on the method and criteria that we use to evaluate it. Further studies are needed to establish the most accurate echocardiographic marker of asynchrony to predict which patient is going to respond to CRT.

P436 Location of the segment with the most delayed contraction in patients with left ventricular systolic dysfunction. Results from the RAVE registry

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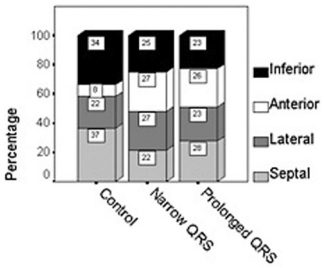
Echo-Doppler provides non-invasive insights into regional asynchrony and may help to improve asynchrony detection. Some studies have reported that the location of the segment with the most delayed contraction could be crucial before implanting a biventricular pacemaker. Our aim was to assess the echocardiographically detected location of the left ventricular segment with the most delayed contraction in patients with narrow and prolonged QRS complexes.
Methods: we have designed a prevalence registry (RAVE registry) in order to evaluate this issue. 316 consecutive patients referred for an echo study in 13 hospitals comprised the study group. All of them had a left ventricular ejection fraction <40%. We also enrolled 29 control patients without systolic dysfunction. Time from the Q wave to the end of the systolic wave in four basal segments was evaluated by using pulsed-DTI.
Results: Mean age was 47.4$\pm$16.7, 60.9$\pm$13.8 and 63.4$\pm$13.3 years in control, narrow QRS and prolonged QRS groups respectively ($p<0.001$) (62.1%, 78.3% and 71.3% men). Clinical and echocardiographic baseline characteristics were similar in both groups of patients with systolic dysfunction. Results are shown in figures below. There was no statistical significant difference between different groups.



Conclusion: The location of the segment with the most delayed contraction is similar in patients with narrow and with prolonged QRS complexes. Echo-Doppler methods are necessary to detect it in order to optimize the resynchronization therapy.

P437 Automatic visualization of the time of contraction in echocardiographic sequences: a new tool for analyzing segmental wall motion abnormalities

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Purpose: A parametric method: Parametric Analysis of Main Motion (PAMM) is proposed to describe in one synthetic image the regional wall motion of the left ventricle, from a set of echocardiographic images.
Methods: A fast processing of the image sequence has been developed to measure the mean time between the increase and the decrease of the pixel intensity during the cycle. This mean time has been used to build parametric images encoding automatically the wall motion: red for positive values close to the corrected QT interval, blue for negative values close to the corrected QT interval, yellow and green for more delayed motions. The parametric images were read as follows: wide red=normal, narrow red=hypokinetic, narrow green or yellow=akinetic, blue=dyskinetic. The evaluation was carried out on 168 segments (15 apical four-chamber views and 9 apical two-chamber views). A consensus reading of dynamic gray-scale images by two experienced reviewers was used as the gold standard (segment grading of regional wall motion: normal=54; hypokinetic=69; akinetic=22; dyskinetic=19; not classified=4). The experts also classified all seg-

ments according to their homogeneity and visualization. An expert independently read the parametric images.
Results: On the entire population sensitivity and specificity were fair although 49 segments (30%) could not be classified especially due to poor image quality and apical localization (70% of apical segments could not be classified). When considering high quality segments regarding homogeneity and visualization (58 segments) sensitivity and specificity were higher.

Table 1

	Overall				High quality segments			
	Sensitivity [IC 95]		Specificity [IC 95]		Sensitivity [IC 95]		Specificity [IC 95]	
Normokinetic	70%	[61%-78%]	90%	[84%-95%]	83%	[73%-93%]	93%	[86%-99%]
Hypokinetic	70%	[64%-80%]	72%	[64%-80%]	85%	[76%-94%]	84%	[75%-94%]
Akinetic	38%	[29%-47%]	94%	[89%-98%]	67%	[55%-79%]	98%	[94%-99%]
Dyskinetic	70%	[61%-78%]	96%	[92%-99%]	100%	[98%-100%]	98%	[95%-99%]

Conclusions: PAMM may be of valuable diagnostic help to the clinician in the detection and follow up of contraction abnormalities. Reading rules could be more clarified especially for segments scored akinetic. Further studies are needed to evaluate its usefulness for the analysis of asynchronism and resynchronization.

P438 A new symple method to assess global left ventricular systolic function based on the sum of regional myocardial velocities

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Background: Left ventricular ejection fraction (LVEF) is the first determinant of prognosis in heart disease patients (pts). Although echocardiography is used to assess LVEF, its main limitation is variability. Tissue Doppler imaging (TDI) sampling a localized point of the myocardium may also suffer from significant inter-subject variability. We hypothesized that the placement of a sample volume greater enough to include the entire LV for assessment of global LV velocities would suffer from lower variability; and that this global value may correlates with LVEF.
Methods: We performed 72 two-dimensional and TDI studies (59 at rest and 13 under stress with dobutamine) in 59 consecutive pts (mean age 64±12 years; 35 males). LVEF was measured by the biplane Simpson's rule. Mean LVEF was 0.59±0.15 (range 0.26-0.87), and wall motion score index 1.2±0.4 (range 1.0-2.3). Colour TDI was performed in the apical 4- and 2-chambers views including the entire LV cavity in each view with a mean frame rate of 116±19 per second (range 77 to 134). The sample was digitized when the LV cavity achieved its maximal dimension and it was performed around the external myocardial border to include all the myocardial signals. From the colour TDI we obtained the global peak systolic TDI (s-TDI), strain rate (SR) and strain (S) values by the mean of the obtained values in the 2 views.
Results: The mean time to measure s-TDI, SR and S was 172±32 secs, whereas it was 93±15 secs for the assessment of LVEF ($p<0.01$). Smooth and easily assessable SR, S and TDI curves were obtained for all patients with this method. Intra-observer variability for assessment of LVEF, s-TDI, SR and S was not different (8±7%, 7±9%, 6±13% and 18±45%, respectively); whereas inter-observer variability for LVEF (23±8%) was higher than inter-observer variability for s-TDI, SR and S (8±17%, 4±3% and 4±3%, respectively, $p<0.001$ between LVEF and Doppler variables). Significant correlations were found between LVEF and s-TDI ($r=0.52$, $p<0.001$, SEE=0.13), SR ($r=0.61$, $p<0.001$, SEE=0.12) and S ($r=0.42$, $p<0.001$, SEE=0.14). The best cut-off values to detect abnormal (<50%) LVEF was provided by s-TDI <1.8 cm/s (sensitivity 78%, specificity 80%, AUC=0.81), SR > -0.5/sec (sensitivity 74%, specificity 78%, AUC=0.85), and S > -7.5% (sensitivity 72%, specificity 72%, AUC=0.77).
Conclusion: Global assessment of s-TDI, SR and S correlates with LVEF and may constitute an alternative method to measure LV global systolic function.

P439 The prognostic power of six-month remodeling in patients with left ventricular systolic dysfuntion after coronary bypass graft surgery

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Purpose: Progressive left ventricular (LV) dilation is associated with adverse cardiovascular events. However the prognostic value of remodeling after coronary artery by-pass graft surgery (CABG) has still to be defined. We sought to investigate whether mid term (six month) LV dilation after CABG gives prognostic information in patients with moderate to severe LV dysfunction.
Methods: We prospectively enrolled 223 consecutive CABG patients (192 Males - 86%, 65 ± 8 yrs), with LV ejection fraction (EF) ≤ 35%, referred for residential cardiac rehabilitation (CR). Complete echocardiographic study was performed early (11 ± 9 days) after CABG and at 6 months. Follow-up data were also collected at 1 year after CABG for all survivors. LV remodeling was defined by ≥ 15% increase in EDVi.
Results: At six months, end-diastolic volume index (EDVi, from 86 ± 25 to 88 ± 25 ml/m^2, NS) and EF (from 28% ± 6% to 32% ± 9% NS) slightly increased, whereas wall motion score index (WMSi) decreased (from 2.18 ± 0.3 to 2.06 ± 0.3, NS). A subset of 75 patients (33%) showed severe LV dilation (from 72 ± 21 to 93 ± 24 ml/m^2, p 0.0001). During 1-year follow up, 4 (2%) pts died and 42 (19%) had cardiovascular events requiring hospitalization (myocardial infarction 3 pts, congestive heart failure 30 pts, new cardiovascular surgery 5 pts, unstable angina 4 pts): 1-year event-free survival was 80%. Clinical history pre-CABG (heart failure, previous cardiovascular surgery, three-vessel disease, left main coronary artery disease), early complications after surgery, clinical, biological and functional status during CR (NYHA, major cardiovascular complications, hospitalization length, hypertension, lipid profile, high white cells count, low hemoglobin and ability to perform a six-minute walking test), and six-month LV remodeling were all significantly ($p < 0.01$) related to cumulative (death and hospitalizations) events. Multivariate analysis selected six-month LV remodeling (Chi^2 11.1, RR 3, 95% CI 1.5 - 6, p 0.0008) and NYHA class at admission to CR (Chi^2 5.9, RR 2.4, 95%CI 1.1 - 5.2, p 0.01) as the only independent predictors of cumulative 1-year events.
Conclusions: Patients with left ventricular systolic dysfunction after CABG have a significant rate of short-term cumulative events. LV remodeling is a powerful predictor of prognosis in patients with LV dysfunction after CABG; its evaluation is strongly recommended for risk stratification and management of appropriate secondary prevention strategies.

P440 Relationship between right ventricular function and pulmonary artery pressure: a combined flow and myocardial Doppler echocardiographic study

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Background: Right ventricular function is affected by increase in pulmonary artery pressure (PAP). Myocardial Doppler echocardiography may provide useful information on right ventricular (dys)function, giving new insights in the non invasive estimation of PAP.
Aim of the study: We sought to evaluate the potential role of myocardial Doppler echocardiography for estimating the impact of PAP on right ventricular function.
Methods: We studied 57 patients (mean age 69 ± 11 years, M/F 23/34) with detectable tricuspid regurgitation and measurable tricuspid velocity gradient (TVG) by continuous wave flow Doppler. All patients were in sinus rhythm, with normal left ventricular function (LVEF >50% by Simpson's biplane), and no bundle branch block. From apical 4-chamber view, tricuspid annulus was sampled by pulsed wave Doppler and the corresponding velocity profiles were digitised and stored on a DICOM server. From the myocardial velocity profiles, the following parameters of right ventricular function were measured: systolic velocity (Stric), early diastolic velocity (Etric), late diastolic velocity (Atric), isovolumic relaxation time (IVRT, measured from the end of Stric to the onset of Etric). The relationships between TVG and myocardial Doppler parameters were assessed using regression analysis.
Results: In the study group, TVG ranged from 9 to 55 mmHg. There was no correlation between TVG and Stric, Etric, Atric ($r= 0.105$, $r=-0.055$, $r=-0.101$, respectively). However, TVG was strongly related to right ventricular IVRT ($r=0.688$, $p<0.0001$). When TVG >25 mmHg was considered abnormal and suggestive for elevated PAP, a right ventricular IVRT >15 msec showed a positive predictive value of 88% and a negative predictive value of 100% for the presence or absence of pulmonary hypertension.
Conclusions: An elevation of pulmonary artery pressure leads to a prolongation of right ventricular IVRT and does not significantly affect right ventricular myocardial velocities. Thus, right ventricular IVRT measured by myocardial Doppler echocardiography at tricuspid annulus may provide an alternative method for estimating pulmonary artery pressure, especially in patients with tricuspid regurgitation not detectable or spectral Doppler not properly interpretable.

P441 Hypoxemia at high altitude is related to size of right-sided cardiac cavities at low altitude

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Background: There is a substantial interindividual variation of oxygen saturation (SaO2) at high altitude. In particular, subjects susceptible to high altitude pulmonary edema (HAPE) have lower SaO2 when exposed to high altitude, causing pulmonary hypertension. It is unknown if this chronically affects right-sided cardiac cavities. Therefore, we investigated the correlation between low SaO2 at high altitude and dimensions of right-sided cardiac cavities at low altitude and whether this correlation is influenced by prophylactic HAPE therapy.
Methods: 15 healthy subjects with adequate echocardiographic recordings who received no active treatment during the course of the study were analysed. Among them, 8 had a history of HAPE (placebo). In addition, separate analysis was performed in 18 HAPE susceptible subjects treated with prophylactic therapy (10 subjects on dexamethasone 8mg bid, 8 on tadalafil 10mg bid). SaO2 and partial O2 pressure (pO2) values measured after a 48h stay at an altitude of 4559m were correlated with echocardiographic recordings at low altitude.

Results: As expected, SaO2 was significantly lower at high altitude. HAPE susceptible subjects on placebo had a SaO2 of 74±5%, which was significantly lower than in the controls (83±2%, p<0.001). In treated HAPE susceptibles, SaO2 was higher than in the untreated (dexamethasone 86±5%, p<0.001; tadalafil 80±4%, p=0.007). There were moderately significant correlations between echocardiographically estimated pulmonary artery pressure and both SaO2 (r=-0.49, p=0.004) and pO2 (r=-0.54, p=0.001). These correlations were not influenced by therapy, showing the direct influence of SaO2 on pulmonary artery pressure. In subjects without prophylactic therapy, highly significant negative correlations between right atrial area indexed for body surface area and both SaO2 (r=-0.76, p<0.001) and pO2 (r=-0.79, p<0.001) at high altitude were detected. In subjects with prophylactic therapy, these correlations were no longer statistically significant (SaO2 r=-0.37, pO2 r=-0.43), indicating the influence of therapy on individual response to hypoxia. Also, diameter of right ventricle was negatively correlated with SaO2 in subjects without (r=-0.55, p<0.05), but not in those with prophylactic therapy (r=0.08).
Conclusion: Subjects with reduced O2-content in the arterial blood at high altitude show dilation of right-sided cardiac cavities at low altitude.

MODERATED POSTER SESSION I
ARTERIAL HYPERTENSION

P442 Vasorelaxation by inhibition of Rho-kinase is NO-independent

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Vasoactive factors, like catecholamines, angiotensin, urotensin II, activate Rho-kinase (ROK) and inhibition of the ROK-pathway represents a novel therapy for different cardiovascular diseases with hypertensive syndrom. The disbalance of relaxing endothelial NO-producing system and vasoconstrictive pathways, including ROK, can be especially important during diseases where hypertension is accompanied by endothelial dysfunction. We tested the hypothesis that the inhibition of the ROK-pathway is beneficial for the treatment of vascular hypercontractility in models with compromised vasorelaxation.
Vascular function in two animal models of hypertension and endothelial dysfunction, particularly eNOS (-/-) mice and SHR rats was analyzed by means of standard organ chamber techniques. Furthermore, effect of ROK-inhibition on blood pressure was measured. Y27632, a selective Rho-kinase inhibitor, induced relaxation in a dose-dependent manner in arteries of eNOS (+/+) and eNOS (-/-) mice, and in LNAME-treated arteries after phenylephrine-induced contraction.
Arteries of SHR rats showed an enhanced sensitivity to ROK-inhibition than arteries from control animals. This may indicate that hypercontractility depends on hyperactivation of ROK, which is not counterbalanced by the endogenous NO-producing system. Blood pressure measurements revealed that ROK-inhibition effectively reduces blood pressure in SHR with an IC50 of 0.5 mg/kg Y27632. Our results suggest that in models of genetically reduced endothelial NO-production (arteries of eNOS (-/-) mice and SHR rats) or in models of pharmacologically reduced endogenous NO-production (LNAME treated arteries), Rho-kinase inhibition induced strong vasodilation indicating independence of Rho-kinase pathway from the NO-producing system. Therefore, inhibition of Rho-kinase represents a promising possibility to treat hypertension that is accompanied by endothelial dysfunction.

P443 In vivo induced changes in shear stress patterns affect the expression and the intracellular localization of endothelial nitric oxide synthase

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Introduction: Shear stress variations in the arterial tree appear to direct the distribution of atherosclerosis. However, atherosclerosis cannot be studied correctly in vitro. Here we present a new method to assess the effect of shear stress alterations in vivo on endothelial nitric oxide synthase (eNOS) expression in transgenic mice.
Methods: Tapered casts are placed around the carotid artery of transgenic mice expressing human eNOS in fusion with a Green Fluorescent Protein (GFP). The casts are designed to lower the shear stress upstream and to induce vortices downstream from the cast. In addition, a region with gradual increments in shear stress is created inside the cast. The eNOS-GFP expression along these regions is studied using confocal microscopy. Shear stress patterns are calculated by 3D reconstruction and by using computational fluid dynamics (CFD).
Results: We provide direct evidence that eNOS expression is shear stress responsive in an in vivo situation (Fig. 1.)There is a distinct pattern of eNOS-GFP redistribution on cellular level in response to shear stress (Fig. 2). The distribution of eNOS into the Golgi is reduced to 50% of control in the low, oscillatory and high shear stress regions. High shear stress increases the amount of eNOS bound to Golgi complex and cell membrane by 3-fold and 2-fold over control respectively, and increases Ser1177 phosphorylation of eNOS by 6-fold over control.

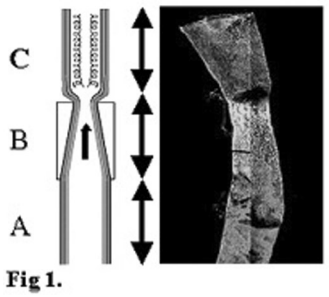

Fig 1.

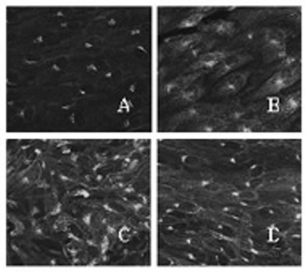

Fig 2.

A = upstream region, B = cast region, C = vortices region, D = control vessel.
Fig. 1. Effect of cast placement on eNOS-GFP expression in carotid artery of tg mouse.
Fig. 2. eNOS-GFP expression in endothelial cells of cast treated vessel.

Conclusion: We demonstrate using a novel in vivo model that eNOS responds strongly to alterations in shear stress. This method allows to study, for the first time, the modulating effect of atherosclerosis on the relationship between shear stress and gene expression.

P444 Human insulin and leptin receptor number in healthy normotensives with high normal blood pressure

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High normal blood pressure (HNBP) seems to be related to increased cardiovascular risk in healthy normotensives (N), while it is well known that essential hypertension is associated with hyperinsulinemia and hyperleptinemia, as well. Aim of our study was to determine human insulin (hINR) and leptin receptor (hLR) number in healthy N with HNBP and to compare the findings to those of healthy N with optimal and normal blood pressure (ONBP) matched for age, sex and BMI.
Methods: Thirty six (19M, 17F) N with HNBP mean age 42±8 yrs and BMI 23±1,5 kg/m^2 (Group A) and 40 (23M, 17F) N with ONBP mean age 43±7 yrs and BMI 23,2±1,4 kg/m^2 were studied. The hINR and hLR number (ELISA method) and immunoreactive insulin and leptin plasma levels (RIA method) were determined in the study population.Blood samples were collected between 8.00 and 9.00 after 12H of fasting.
Results: The results and the differences between the two groups are shown in the table:

	Group A (n=36)	Group B (n=40)	p
hINR (receptorX103/red cell)	6±1,5	8±1,3	<0.001
hLR IU/ml	18±7	27±9	<0.001
Insulin (μIU/ml)	21±10	15±6	<0.01
Leptin (ng/ml)	10±4,8	6±2,7	<0.001

Conclusions: Our findings suggest that normotensives with high normal blood pressure have significantly increased insulin and leptin plasma levels and significantly decreased hINR and hLR number. This group of individuals may need a closer follow-up and further examination.

P445 Prothrombotic/fibrinolytic balance is impaired even in white-coat hypertension

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Purpose: Essential hypertension (EH) is associated with impairment of normal prothrombotic/fibrinolytic balance. White-coat hypertension (WCH) is a common syndrome accompanied by increased cardiovascular risk. Fibrinogen and plasminogen activator inhibitor-1 (PAI-1) are mediators of the coagulation pathway, which increase in ES and predict progression of atherosclerosis. Aim of the present study was to comparatively evaluate these markers of thrombogenicity in patients (pts) with ES and WCH.
Methods: We studied 4100 consecutive non-diabetic pts with chronic uncomplicated EH (age 53±12 years, 2401 men) and 1414 non-diabetic WCH pts (age 52±13 years, 614 men). Diagnoses were established according to office and 24-hour ambulatory BP measurements, after a two-week wash-out period in case of antihypertensive drug treatment. WCH was defined as office BP>140/90 mmHg in 3 repeated readings on different days,and mean daytime ambulatory

BP<135/95 mmHg. Then plasma fibrinogen (nephelometry method, BN II, Dade Behring) and serum PAI-1 (chromo-method, BCT, Dade Behring) were measured. Pts in both cohorts were allocated in 5 groups according to their age (<40, 40-49, 50-59, 60-69 and >70 years).
Results: In the whole study cohort, pts with ES differentiated from WCH pts in office systolic BP (165 vs 156 mmHg, p<0.001), but not in office diastolic BP (103 vs 101 mmHg, p=NS). In the EH population we found a significant stepwise increase across the 5 age groups for both fibrinogen (279, 290, 301, 315 and 336 mg/dl for <40, 40-49, 50-59, 60-69 and >70 years respectively, p<0.00001) and PAI-1 (2.23, 2.47, 2.57, 2.6 and 2.85 IU/ml, p<0.00001). The same change was certified in WCH pts for fibrinogen (266, 285, 295, 306 and 316 mg/dl, p<0.00001) and PAI-1 (1.99, 2.39, 2.46, 2.44 and 2.56 IU/ml, p<0.00001). When we compared fibrinogen and PAI-1 levels within each age group, pts with ES aged 40-49 or 50-59 years did not differentiate from WCH pts of the same age, while if aged 60-69 years they were marginally more burdened from the corresponding WCH pts. Concerning fibrinogen, p values for comparison between ES and WCH pts within the same age group were 0.003, NS, NS, 0.05 and 0.002 for <40, 40-49, 50-59, 60-69 and >70 years respectively. For PAI-1 the respective p values were 0.02, NS, NS, 0.04 and 0.01.
Conclusions: White-coat hypertension is not an innocent phenomenon. On the contrary, it confers a prothrombotic and hypercoaggulable state which is indistinguishable from that ascribed to essential hypertension, except for pts <40 or >70 years old.

P446 Left ventricular structural and functional characteristics in patients with acromegaly

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Objective: In patients with acromegaly a specific cardiomyopathy, characterized by interstitial fibrosis and myocyte cell death, has been described. Left ventricular (LV) systolic function at endocardium has been reported increased in early phase of acromegaly, while prolonged untreated acromegaly is characterized by LV dysfunction. The aim of this study is to evaluate LV anatomy and function, and LV wall structure, by ultrasonic tissue characterization.
Design and methods: Seventeen consecutive untreated patients with acromegaly (6 M, 10 hypertensives, mean age 51±12 yrs, disease duration range 1 month-10 years) and 17 age, sex and blood pressure matched controls, underwent an echocardiographic study for LV anatomy and function assessment. LV mass index (LVMI), endocardial (end FS) and midwall FS (mid FS) were calculated to assess chamber and midwall systolic performance; Doppler transmitral E and A flow velocities, E deceleration time and isovolumic relaxation time (IVRT) were measured for diastolic filling evaluation. Integrated backscatter signal (IBS) was analyzed with an acoustic densitometry method; the signal was sampled in the mid portion of the interventricular septum (IVS) and of the posterior wall (PW). Amplitude of systo-diastolic variation (CV) of IBS was considered.
Results: LV hypertrophy and concentric geometry prevalence were significantly greater in acromegalic patients. Systolic performance at the midwall was significantly reduced in acromegalic patients (18±3 vs 21±2, p < 0.02). Diastolic dysfunction (according to ESC criteria) was present in 3 acromegalic patients and in none of controls. CV at IVS was lower in acromegalic patients in respect to controls (6.6±2.4 vs 8.2±2.3, p < 0.06), possibly suggesting an increase in collagen content. No significant correlations were observed between GH or IGF-1 circulating levels and LV mass, systolic or diastolic performance parameters.
Conclusions: the results of this study indicate that patients with acromegaly have lower systolic performance at the midwall, as compared to age and sex matched controls. Abnormalities in ultrasound tissue characterization, possibly related to collagen content, are observed in acromegalic patients, possibly contributing to cardiac dysfunction in these patients.

P447 Abnormal nocturnal blood pressure fall affects target organ damage even in white coat hypertension

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Purpose: White coat hypertension (WCH) is a common clinical entity, but its impact on target organ damage and the overall cardiovascular morbidity and prognosis has not been fully elucidated. The prognostic significance of abnormal nocturnal blood pressure (BP) fall in essential hypertensive patients (pts) is increasingly recognized. Aim of the present study was to investigate the effect of nocturnal BP fall patterns on target organ damage, in non-diabetic pts with WCH.
Methods: We studied 1000 consecutive never treated non-diabetic pts (440 men, 560 women, age 51.3±12.9 years old) with WCH (office BP >140/90 mmHg, mean daytime ambulatory BP <135/85mmHg). According to their nocturnal systolic BP fall, they were classified in extreme dippers (47 pts with >20% nocturnal systolic BP fall), dippers (503 pts with >10% but <20% fall), nondippers (347 pts with >0% but <10% fall) and reverse dippers (103 pts with nocturnal increase of systolic BP). In echocardiographic examination, left ventricular mass index (LVMI) was calculated and LV geometry pattern determined. At the same time, microalbumin, α1-microglobulin and creatinine values were measured in a 24-h urine collection and the albumin/creatinine ratio (ACR) was calculated.
Results: Extreme dippers did not differ (p=NS) from dippers in regard to LVMI, microalbumin and a1-microglobulin excretion and ACR, but they exhibited a significantly higher incidence of LV concentric hypertrophy when compared to dippers (14.9 vs 4.0%, p=0.0009). In contrast, reverse dippers had significantly (p<0.0001) higher values compared with nondippers and dippers, for LVMI (136.2 vs 130.6 vs 120.0 g/m^2), microalbumin (38.3 vs 26.0 vs 14.1 mg/l), α1-microglobulin (9.18 vs 7.14 vs 5.34 mg/l) and ACR (51.3 vs 42.6 vs 19.3). Compared with nondippers, reverse dippers also had higher percentage (p=0.008) of LV eccentric and concentric hypertrophy.
Conclusions: Non-diabetic WCH individuals with reverse BP dipping pattern present with increased renal and cardiac damage compared with both nondippers and dippers. Dippers and extreme dippers generally behave in the same way as regards renal function and overall LVMI, although extreme dipping confers a more unfavorable outcome regarding LV geometry than normal dipping status.

P448 Characteristics of hypertensive patients associated with obstructive sleep apnea

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In patients with daytime hypertension (HT), Obstructive sleep apnea (OSA) is very often associated. The relationship between OSA and daytime HT could be due to many confounding factors such as age, gender, obesity, and race. However, exact mechanism by which OSA can lead to daytime HT is still unclear.
Methods and Results: In a cross-sectional study, we examined independent factors associated with daytime HT using multiple logistic regression analysis among a group of consecutive 752 patients with OSA in our sleep laboratory. The diagnosis of OSA was established by polysomnography prior to introduction of nasal continuous positive airway pressure therapy.
The patients population was aged mean 52±12yrs, and 75 females, with an apnea hypopnea index (AHI) of 41±23/hr. Patients were classified into 2 groups; 474(63%) patients with daytime HT (mean 148/92 mmHg) and 278 without it (mean 122/72 mmHg). In each group, we analyzed risk factors for OSA such as severity of AHI (cutoff of 20, 40 and 60), Arousal index, desaturation, total sleep time, gender, body mass index (BMI), excessive daytime sleepiness, smoking, alcohol and polynocturia. Univariate results indicated that hypertension was significantly associated with age (per one year; OR 1.27, P<0.001), BMI (per one; OR 1.62, P<0.001) and polynocturia (existence; OR 2.39, P<0.001). Multivariate adjustment results indicated that hypertension was significantly associated with age (per one year; OR 1.07, p<0.001), BMI (per one; OR 1.13, P<0.001), polynocturia (existence; OR 1.62, P=0.029).
Conclusions: Age, BMI and polynocturia but not the severity of sleep apnea show independent factors associated with daytime HT. This is the first study that demonstrated positive relationship between polynocturia and daytime HT in patients with OSA. Futher investigation is needed to elucidate the mechanism underlying between polynocturia and daytime HT with sleep apnea.

P449 Increase in ambulatory PP during a 10-year period was significantly higher in white coat hypertensives compared to normotensives and established hypertensives

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Purpose: Pulse pressure (PP) is an established predictor of cardiovascular morbidity and mortality.
The purpose of the present study was to evaluate the development in ambulatory PP during a 10-year period in white coat hypertensives (WCH) compared to normotensives (NT) and established hypertensives (EH).
Methods: Of a study population originally consisting of 76 WCH's, 92 NT's and 344 EH's, 61 WCH's (87.1% of those still alive), 72 NT's (92.3%) and 241 (79.5%) had a second ambulatory blood pressure monitoring (ABPM) 10 years after inclusion in the study. WCH at inclusion was defined as an office blood pressure < 140/90 mm Hg combined with a daytime ambulatory blood pressure (ABP) < 135/90 mm Hg.
Results: At follow-up 9.1% in the NT group, 50.8% in the WCH group and 76.8% in the EH group was in treatment with antihypertensive medication. Daytime PP at baseline was 44.2 ± 9.4 mm Hg in the NT group, 39.9 ± 6.7 mmHg in the WCH group and 51,2 ± 14,5 mm Hg in the EH group, at the follow-up examination the corresponding values were 54.1 ± 11.5, 56.4 ± 11.6 and 59.7 ± 13.3 mm Hg. Increase in PP during the 10-year period was 9.9 ± 12.8mm Hg in the NT group, 16.5 ± 12.2 mm Hg in the WCH group and 8.5 ± 15.3 mm Hg in the EH group. The difference between the NT and the WCH group was significant with a p-value < 0.001 and between the WCH group and the EH group with a p-value of 0.002,

there was no significant difference in increase in PP between the NT and the EH group. It is important to notice that most of the EH's were treated hypertensives.
Conclusions: The increase in ambulatory PP during a 10-year period was significantly higher in a group with WCH compared to a group with NT and a group with treated hypertension. When the increase in PP is taken as a measure of stiffening of the arteries and as a consequence an increase in cardiovascular risk, this result indicates that white coat hypertensives are at increased risk of cardiovascular morbidity and mortality.

ATRIAL FIBRILLATION

P450 N-terminal-pro brain natriuretic peptide is an independent predictor of the precence of atrial fibrillation in outpatients with systolic heart failure

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Background and aim: Brain natriuretic peptides are elevated in patients with heart failure (HF) due to left ventricular systolic dysfunction (LVEF) and in patients with atrial fibrillation (AF) with normal left ventricular function. However, it is unknown whether AF influences the concentration of natriuretic peptides in patients with systolic HF.
Methods: We studied a population of 246 patients (72% males, mean age 70 years) with systolic HF referred to a specialized HF clinic. Plasma levels of N-terminal pro brain natriuretic peptide (Nt-proBNP) were measured at the time of referral (baseline). Data were registered prospectively in a database. Follow-up with registration of sinus rhythm (SR) versus AF ranges from 0-45 months.
Results: At baseline 26% had AF. Ischemic heart disease was the predominant underlying aetiology (58%). Patients with AF were older, 73 $\pm$ 9 years (mean $\pm$ SD) than patients with SR 69 $\pm$ 10 years (P=0.008). Patients with AF and SR, had similar mean left ventricular ejection fraction (LVEF) and NYHA class distribution (NYHA class I 10%, II 66% and III 24%). At baseline 81% received ACE inhibitor and/or AT2 antagonist with no significant difference between patients with AF and SR. Among patients with SR and AF 40% and 24% received a betablocker, respectively (P=0,02).
Patients with AF had higher median Nt-proBNP levels than patients with SR (2528 pg/ml vs.902 pg/ml, $p<0.0001$). In a logistic regression analysis including age, sex, NYHA, LVEF and log Nt-BNP, Nt-BNP was the only significant predictor of baseline AF ($P< 0.001$). Adding ACE inhibitor and beta-blocker treatment to this model, did not alter the results significantly. At follow-up 33% of the surviving patients had AF and their baseline Nt-proBNP levels were significantly higher than patients in SR ($p<0,001$) with Nt-proBNP as the only significant predictor of AF ($p<0.001$).
Conclusion: Nt-proBNP levels are higher in HF patients with AF than patients with SR. Nt-BNP is a potent independent predictor of AF in HF patients with left ventricular systolic dysfunction.

P451 Reduction of brain-type natriuretic peptide after recovery of sinus rhythm in patients with persistent atrial fibrillation

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Measurements of B-type natriuretic peptide (BNP) have a role in screening for left ventricular systolic dysfunction and predicting outcome in patients with heart failure. The increase in atrial and BNP plasma concentration observed in these patients is largely due to cardiac wall stretch and volume expansion. The abnormal stretch of atrial myocites and the altered ventricular filling pattern associated with atrial fibrillation (AF) may represent an adequate stimulus for atrial and BNP elevation. Aim of the study was to evaluate whether the recovery of sinus rhythm could be associated with a reduction BNP values.
Methods: We measured with an electrochemiluminescent assay NT-proBNP in 9 patients (aged 67$\pm$3.3 years; mean$\pm$SD) with preserved left ventricular ejection fraction, who underwent electrical cardioversion for persistent AF. NT-proBNP plasma concentrations were determined before (BNP1) and 3 weeks after cardioversion (BNP2).
Results: Cardioversion was successful in all 9 subjects. One patient had an early AF recurrence. Persistence of sinus rhythm was associated with a reduction in NT-proBNP values (from 703$\pm$258 to 318$\pm$202 pg/ml; p=0.002). No significant reduction was observed in the subject who had an early recurrence (broken line in the figure).
Conclusions: These preliminary data indicate that in patients with persistent AF, recovery of sinus rhythm is associated with a marked reduction of NT-proBNP values likely to be due to the restoration of a more physiological hemodynamic function in the atria. This finding has to be taken into account when considering the application of BNP testing in heart failure patients. The presence of AF may determine an increase in BNP values independent of the extent of left ventricular dysfunction.

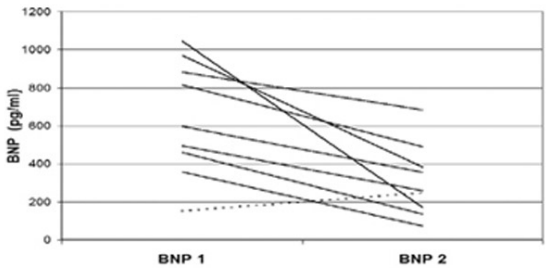

Fig. 1. BNP values.

P452 Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrence or conversion of atrial fibrillation

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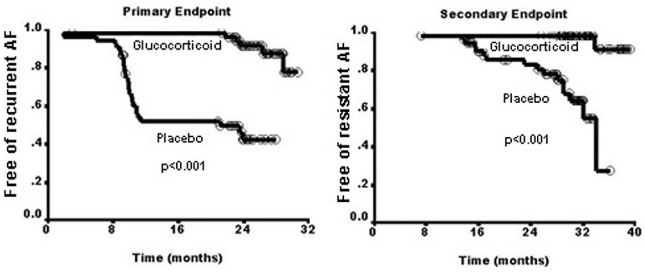
Background: Little direct information is available on the effect of C-Reactive Protein (CRP) lowering on the conversion of atrial fibrillation (AF) and on the reduction of recurrent (AF).
Methods: We compared low-dose glucocorticoid therapy and placebo in 104 patients who had episodes of AF $<$ 48 hours duration and had been cardioverted in normal sinus rhythm (NSR) and thereafter they were followed-up for hospitalization of recurrent AF (group A). Furthermore, we compared low-dose glucocorticoid therapy and placebo in 134 patients who had episodes of AF $>$ 48 hours duration and received amiodarone for cardioversion of AF (group B).
Results: In group A, methylprednisolone reduced hospitalization for recurrent AF (primary end point) from 50% in the placebo group to 9.6% in the glucocorticoid group and resistant AF (secondary end point) from 29% in the placebo group to 2% in the glucocorticoid group. In group B, conversion to NSR was achieved in 47 (70%) patients who received pretreatment with methylprednisolone and in 31 (46%) who received placebo ($P<0.001$). Survival distributions for methylprednisolone were significantly different (for both primary and secondary end point in group A, $P<0.001$, as well as in group B, $P<0.005$). In group A, RR= 0.101 ($P<0.001$) for the primary end point and for the secondary end point, RR= 0.031 ($P<0.001$); while in group B for the conversion to NSR, RR= 1.976 ($P<0.005$). Furthermore, CRP was the only independently significant factor affecting time to primary and secondary end-point in group A as well as time to conversion in group B ($P<0.001$ for all).



Conclusions: Glucocorticoid therapy appears to be effective in prevention of hospitalization of recurrent AF and resistant AF as well as in termination of episodes $>$ 48 hours duration of AF.

P453 C-reactive protein and soluble thrombomodulin: biochemical markers of maintenance of sinus rhythm at 1-year follow-up in patients with non-valvular atrial fibrillation

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Background: We have previously reported that C-reactive protein (CRP) is increased in patients with atrial fibrillation (AF), and that these elevated levels could predict lack of sinus rhythm maintenance at long-term follow-up. Yet, no data have been reported relating endothelial/dysfunction and/or hemostatic/platelet markers and sinus rhythm maintenance in AF patients.
Purpose: We sought to determine whether levels of soluble thrombomodulin (sTM), as an endothelial/dysfunction marker, soluble P-selectin (sP-sel), as a marker of platelet activation, and thrombin-antithrombin (TAT) levels, as a marker of activation of the coagulation, along with CRP, inflammatory marker, could contribute to predict cardiac rhythm at 1-year follow-up in patients with non-valvular AF.
Methods: We prospectively studied 130 patients (70 males, mean age 67 $\pm$ 13 years) with newly diagnosed AF, none of whom received antithrombotic or an-

tiplatelet therapy before admission. Baseline CRP, sP-sel, sTM and TAT levels were compared to those levels in 20 matched healthy control subjects in sinus rhythm. Transesophageal echo was performed in all the subjects within the first 24 hours of admission.
Results: AF patients had significantly higher CRP (10.5 ± 2.2 versus 3.25 ± 0.3 mg/L, p = 0.001), sP-sel (219 ± 141 versus 126 ng/ml, p = 0.01), and TAT (54 ± 237 versus 2.7 ± 3.3 ng/L, p = 0.001) plasma levels than the control group. Soluble TM levels, although higher than controls, did not reach statistical significance (52 ± 111 versus 44 ± 10 ng/mL, respectively). No significant correlations were found among the different markers. Multivariate regression analyses showed that elevated CRP (OR = 4.8, p = 0.02) and sTM (OR = 1.05, p = 0.04) were the only 2 predictors of lack of sinus rhythm at 1 year follow-up, independently of age, echocardiographic parameters of atrial and left ventricular function, sP-sel and TAT levels.
Conclusions: This study confirms the existence of an altered inflammatory, hemostatic, endothelial and platelet enviroment in newly diagnosed AF patients. However, only inflammatory (CRP) and endothelial/dysfunction (sTM) markers contributed to predict the status of cardiac rhythm at 1-year follow-up in these patients.

P454 Antihypertensive, antiinflammatory and antisympathetic effects of ACE-inhibitors and beta blockers therapy: possible contributors in prophylaxis of new-onset atrial fibrillation after cardiac surgery

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Atrial fibrillation (AF) is a common complication after coronary surgery (CABG) occurring in up to 30% of patients (pts). It was proved, that higher risk of AF occurrence is influenced by advanced age, low ejection fraction or atrial fibrosis. We analysed the possible reasons of ACE-inhibitors (ACE-I) and beta-blockers effectiveness in prophylaxis of new-onset AF.
Methods: retrospective analysis of medical records of 217 pts(156men/61women) with no history of AF between Jan.2000 and Jun.2003, hospitalized in cardiological department from 4th till 14th day after cardiac surgery. Mean age: 62.3 yrs; BMI: 27.1, mean history of coronary disease: 4.9 years.
Results: AF occurred in 28% (61/217) of pts with no previous history of AF. Age of pts with AF was higher: 65.2±7.7 (SEM 1.1) vs 61.2±9.4 (SEM 0.8), p=0.0033. They had longer history of coronary disease: 6.3 ±5.7 (0.8) vs 4.6 ±4.9 (0.4), p=0.0417. More of pts with AF had 3-vessel disease: 50% vs 32% (p<0,02) and more of pts with AF had > 3 grafts: 14 vs 2%. Low ejection fraction (<40%) was significant risk factor of arrhythmia: 51% with AF vs 23% (p=0.0004). Pts with AF had significantly higher mean heart rate (HR) before AF episode: 101±36 vs 77±15 (p<0.00001). Pts with AF had higher level of leukocytes after surgery (+3700±4300, p<0.0001).
After CABG 99% event free pts were on beta-blockers vs 66% with AF (p<0.0001). Pts treated had lower incidence of AF: before CABG - 29% vs 77% not treated (p=0.005) and after: 25% vs 95% not treated (p<0.0001). Pts with AF not treated with beta-blockers had mean HR: 116±35 per minute.
Before the CABG 64% of pts without AF were treated with ACE-I in comparison with 15% with AF (p<0.0001). After CABG 75% event free pts were on ACE-I vs 24% with AF (p<0.0001). Pts treated with ACE-I before and after CABG had lower incidence of AF as well: before CABG: 11% vs 53% not treated (p<0.0001) and after CABG: 14% vs 61%, p<0.0001). For the pts treated with ACE-I hypertension was not risk factor of AF (ns). For the pts not treated with ACE-I hypertension caused greater risk of AF occurrence, relative risk 4,6 (1.4-15.0, p<0.01).
Conclusions: besides demographic and coronary disease related factors (age, duration of CAD, number of grafts, ejection fraction), high heart rate, inflammatory state and hypertension are possible predictors of post-discharge AF following cardiac surgery. The proven efficacy of beta-blockers and ACE-inhibitors may be due to their antihypertensive, antiinflammatory (ACE-inhibitors) and antisympathetic (beta-blocker, ACE-I) mechanisms of action.

P455 Oral vitamin C administration reduces early recurrence rates after electrical cardioversion of persistent atrial fibrillation

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Purpose: Atrial fibrillation (AF) induces electrophysiological alterations in the atria, termed atrial remodelling, favouring early recurrences after cardioversion (CV). Inflammation and oxidative stress have been recently implicated in the pathophysiology of this process. The aim of this prospective study was to examine the effects of vitamin C, on the early recurrence rates and inflammation indices after successful CV of persistent AF.
Methods: We prospectively studied consecutive patients with persistent AF admitted for elective external electrical CV. Patients with valvular disease, thyroid dysfunction, malignancies, inflammatory diseases, recent infection, heart failure, or recent coronary event, were excluded from the study, as were patients in whom CV was unsuccessful. Patients were randomised in one to one fashion to no treatment or to vitamin C orally started 12 hours before cardioversion (2gr) and continued for the following 7 days (500mg bid). A 12-lead ECG, complete blood count, and serum C-reactive protein (CRP) were obtained at baseline, on the first, third, and seventh day post-CV. Differences in relapse rates between groups were compared using Yates corrected chi square and differences in continuous variables were compared using ANOVA, followed by Tukey's test.
Results: The final study population consisted of 41 patients (25 males, 16 females, mean age: 68±8 years). Clinical and demographic characteristics were comparable between the two groups. On day 7, AF had relapsed in 1/21 patients in vitamin C group and in 8/20 patients in the control group (p=0.01).

	WBC baseline	WBC day 1	WBC day 3	WBC day 7
Vit. C	7288 ± 1224	6399 ± 1233*	6168 ± 1272*	5863 ± 1174*
Control	6905 ± 1495	6889 ± 1582	6652 ± 1423	6400 ± 1492
	CRP baseline	**CRP day 1**	**CRP day 3**	**CRP day 7**
Vit. C	0.37 ± 0.18	0.35 ± 0.19	0.27 ± 0.15	0.19 ± 0.09*
Control	0.43 ± 0.52	0.47 ± 0.52	0.37 ± 0.29	0.28 ± 0.15

*<0.05 compared to baseline

Conclusions: Vitamin C significantly reduces early recurrence rates of AF after electrical CV. This action may be mediated by an anti-inflammatory action, as evidenced by a decrease in white blood cell (WBC) count and CRP levels (table).

P456 The microcapillary density and expression of VEGF, bFGF in the progression from paroxysmal to chronic atrial fibrillation in humans

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Purpose: Atrial fibrillation (AF) is a progressive disease associated with atrial ischemia in dogs. Angiogenic growth factors are often involved in the ischemic process. Therefore, we investigated the expression of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and the microcapillary density in the atrium in patients with lone paroxysmal AF (PAF), lone chronic AF (CAF), non-ischemic patients in sinus rhythm (NISR) and ischemic patients in SR (ISR).
Methods: During cardiac surgery, atrial tissue samples were obtained from patients with lone AF (n=26) or sinus rhythm (n=13). VEGF, bFGF protein levels were measured by quantitative Western Blotting techniques. Histological tissue samples were used for calculating microcapillary density.
Results: The bFGF protein expression was significantly and systematically increased in patients in ISR (2,20±0,13; n=9) and CAF (1,91±0,26; n=14; p<0,05) vs. PAF (1,11±0,09;n=12; both p<0,05). We found significantly enhanced expression of bFGF in ISR (p<0,001), PAF (p<0,05) and CAF (p<0,01) vs. NISR (0,75±0,07; n=4). The expression of VEGF exhibited similar results, however there was no significant difference between NISR and PAF. Interestingly, the microcapillary density was decreased in ISR (2,33±0,49; n=3; p<0,05) and CAF (3,34±0,47; n=9; p<0,05), both compared to NISR (6,3±0,24; n=4), while in PAF capillaries (4,37±0,75; n=11) were not significantly decreased.
Conclusion: The progression of AF from PAF to CAF is associated with an increased expression of angiogenetic growth factors accompanied with a declining microcapillary density. Therefore, we speculate that lone AF is associated with ischemic conditions in humans.

P457 High versus low heart rate in patients with atrial fibrillation and chronic heart failure: differences in clinical and neurohormonal characteristics

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Background: Recent data show that rate control may be an acceptable alternative to rhythm control in many patients with atrial fibrillation (AF), and this may also apply to those with left ventricular (LV) dysfunction and chronic heart failure (CHF). Hypothetically, heart rate may be associated with neurohormonal activation in patients with AF and CHF.
Methods: We studied 77 patients with AF and CHF (NYHA III/IV), mean age 70±7 yrs, mean LVEF 0.23±0.08, 61% ischemic/39% non-ischemic. Patients were divided according to their heart rate (≤ or > 80 bpm), and split into two groups. 39 Patients had a heart rate ≤ 80 (mean 71±7 bpm) and 38 patients had a heart rate 38 patients had a rate > 80 (mean 96±16 bpm, difference p<0.001). Patient characteristics and neurohormone profiles were analyzed.
Results: Patients with a high heart rate had a higher (=more impaired) NYHA functional class (p< 0.05), and tended to have lower blood pressure and lower LVEF and fractional shortening (all p=NS). Regarding neurohormones, patients with higher heart rate had higher levels of plasma renin (median 75 versus 203 μU/mL; p=0.01), while other neurohormones ([N-]ANP, [N-] BNP, endothelin, aldosterone, [nor-]epinephrine) were not significantly different. High heart rate was a predictor of higher levels of renin (absolute difference 110.5 μU/mL; p=0.03),

and this showed trends for norepinephrine and aldosterone (both $p < 0.1$). AF with high rate was no predictor of other neurohormones. No independent predictors of AF with high heart rate were found.
Conclusion: A high heart rate in CHF patients with AF is associated with more impaired functional class, and higher plasma renin levels, while other parameters related to severity of CHF show similar trends. High heart rate was an independent predictor of higher renin plasma levels, and therefore seems a important determinant of clinical prognosis. These data suggest that rigid rate control leads to less neurohumoral activation.

P458 Significance of T-type Ca channel blockade in preventing atrial electrical remodelling

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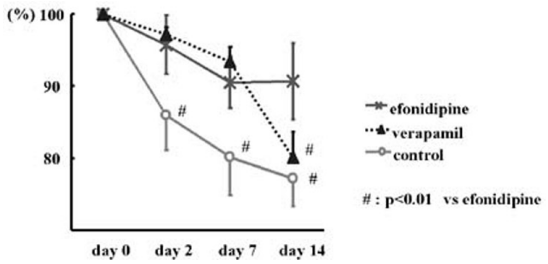
Background: Calcium overload plays an important role in the development of atrial electrical remodeling. The effect of an L-type Ca channel blocker in preventing this remodeling has been reported to be shortlasting, partly due to downregulation of this channel and persisting Ca entry through the T-type Ca channel.
Methods: To prove if efonidipine, a dual L- and T-type Ca channel blocker may exert a greater effect than an L-type Ca channel blocker verapamil, 21 dogs underwent rapid atrial pacing at 400 ppm for 14 days. Seven of these dogs received pretreatment with efonidipine(E; 5mg/kg/day), while another 7 dogs received pretreatment with verapamil(V; 8mg/kg/day). The remaining 7 dogs served as control (C). We measured the atrial effective refractory period (ERP) at 2 basic cycle lengths (BCLs) serially for 14 days of rapid pacing.
Results: In response to rapid pacing, ERP decreased progressively in C. In contrast, in E and V, ERP remained greater than ERP in C ($p<0.01$) on day 2 through day 7. However, on the 14th day, ERP in V decreased to the level of ERP in C, whereas ERP in E remained relatively unchanged and significantly longer than ERPs in C or V($p<0.01$).



ERP at BCL 300msec.

Conclusions: Efonidipine, a dual L- and T-type Ca channel blocker, showed a more sustained effect than an L-type Ca channel blocker verapamil in preventing shortening of atrial ERP. The blockade L type Ca channel alone is not sufficient in preventing atrial electrical remodeling, but the addition of T type Ca channel blockade appears to be important in preventing atrial electrical remodeling for a sustained period of time.

P459 Effects of acute atrial dilation on atrial effective refractory period in langendorff-perfused rabbit heart and intervention by verapamil

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Purpose: Atrial fibrillation (AF) is frequently occurred under conditions associated with atrial dilation (stretch). To study the effects of acute atrial dilation on myocardial electrophysiological parameters and the vulnerability to AF by a Langendorff-perfused rabbit heart model. Additionally,the effects of verapamil on electrophysiological changes induced by acute atrial dilation and the vulnerability to AF were also investigated.
Methods: Twenty isolated Langendorff-perfused rabbit hearts were randomly divided into two groups: the control group (n=10, normal Tyrode's solution) and verapamil group (n=10, Tyrode's solution with verapamil 0.5μmol/L). All the hearts underwent a protocol with stepwise increase of right atrial pressure from 0 to 12 cmH2O. At each pressue level, sinus cycle length (SCL), atrial effective refractory period (AERP), atrioventricular Wenckebach cycle length (AVWCL) and AV interval were measured.The methods of S1S2 stimulation and Burst were used to evaluate the vulnerability to AF. Meanwhile,the inducibility of AF was also recorded.
Results: (1) In control group,the increase of right atrial pressure from 0 to 12 cmH2O significantly shortened AERP from 98.60±11.89 to 61.78±21.32ms ($P<0.01$). And right atrial pressure had a high Spearman correction with AERP ($rs=-0.664$, $P<0.01$). (2) In control group, the elevation of right atrial pressure from 0 to 12 cmH2O significantly increased the inducibility of AF induced by S1S2 stimulative method from 0/10 to 9/10 ($P<0.01$). (3) In verapamil group, the myocardial electrophysiological parameters and inducibility of AF had no statistically significant differences between any two right pressure levels ($P>0.05$).
Conclusion: Acute atrial dilation shortens AERP and increases the vulnerability to AF significantly.Verapamil may attenuate these effects and prevent pressure-related AF.

P460 Chronic complete AV block in the goat induces atrial dilatation, local intra-atrial conduction delays and a substrate of atrial fibrillation

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Atrial dilatation is an independent risk factor for the development of atrial fibrillation (AF) in humans. However, little is known about the underlying electrophysiological mechanisms.
Methods: In 7 goats (sinus rhythm, 114±5bpm) the His bundle was ablated to create complete AV block and a slow idioventricular rhythm (53±3bpm). After 4 weeks the atria were dilated by 14±4% in diameter and the duration of induced AF episodes increased from 6s to 5min. The atrial refractory period (AERP) was measured at 9 epicardial sites (right and left atrium and Bachmann's bundle). Mapping of the right atrial free wall (240 electrodes, spacing 2.4mm) was performed during slow (400ms) and rapid (200ms) atrial pacing. The amount of atrial hypertrophy and collagen was quantified histologically (azan and Sirius red staining). Six goats without AV block served as control.
Results: After 4 weeks of AV block the mean AERP was 125±9ms vs. 104±6ms during control ($p= 0.09$). The spatial heterogeneity (longest minus shortest AERP) was 49±6ms after AV block vs. 78±5ms during control ($p<0.01$). Mapping during slow pacing did not reveal differences in conduction. However, during rapid pacing local slow conduction velocities (<30cm/s) were more frequent in the AV block group than in control (3.7±1.0% vs. 0.9±0.5%, $p<0.05$). The atrial myocytes were clearly enlarged (length 106±7μm vs. 84±2μm, width 16.4±1.1μm vs. 13.0±0.9μm, $p<0.05$). No signs of cell degeneration or fibrosis were found (collagen positive area 13.7±1.0% vs. 9.9±0.8% in control, $p<0.05$).
Conclusions: In a goat model of atrial dilatation the increased stability of atrial fibrillation was not associated with atrial fibrosis. Also changes in AERP did not play an important role. However, rate dependent local conduction disturbances were associated with the development of a substrate for AF.

P461 The role of angiotensin receptor blockers and/or angiotensin-converting enzyme inhibitors in the prevention of atrial fibrillation in patients with cardiovascular diseases

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Background: The inhibition of the renin-angiotensin system has demonstrated both experimental and clinical effects in preventing atrial fibrillation. However, there is still uncertainty about the role of these drugs in clinical practice.
Objectives: The objective of this review has been to assess the effects of angiotensin II type-1 receptor blockers (ARBs) and/or angiotensin-converting enzyme inhibitors (ACEIs) for preventing atrial fibrillation.
Search strategy: We searched the Cochrane controlled Trials Register (Cochrane Library Issue 4, 2002), MEDLINE (January 1980 to June 2003), EMBASE (January 1980 to June 2003) and reference list of articles. We also contacted manufacturers and researchers in the field.
Selection criteria: We conducted a meta-analysis of all randomized controlled clinical trials that compared ARBs and/or ACEIs with either placebo or conventional therapy in patients with either hypertension, heart failure, ischemic heart disease or diabetes mellitus. The pooled outcome was the development of new-onset atrial fibrillation.
Data collection & analysis: Two reviewers independently assessed trial quality and extracted data. In some cases, the study authors were contacted for additional information.
Main Results: Six trials involving a total of 19,849 patients were included (8822 randomized to active therapy and 11027 to control). There was a significant statistical difference in the pooled development of atrial fibrillation between the treatment and control group. (OR: 0.50; 95% CI: 0.30 to 0.82); test for overall effect z=-2,71 p=0.007).
Reviewer's conclusions: Treatment with ACEIs/ARBs markedly reduces the risk of development or recurrence of atrial fibrillation.

P462 Rate control versus rhythm control in patients with persistent atrial fibrillation: a meta-analysis

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Purpose: Restoration and maintainance of sinus rhythm vs plain heart-rate control in patients with persistent atrial fibrillation is still a matter of debate. The purpose of this analysis was to systematically assess, in patients with persistent atrial fibrillation and with risk factors for stroke, the risk/benefit ratio of a rhythm-control strategy vs a rate-control approach.

Methods: We performed a Medline and manual literature search up to February 2004. Individual and pooled fixed-effect odds ratios (OR [95%CI]) were calculated for the combined end-point (CEP) of all-cause death and thromboembolic stroke, major bleeds (intra and extracranial), and systemic embolism. Risk differences (95% CI), number needed to treat (NNT) or to harm (NNH), and heterogeneity tests were also assessed.
Results: Four studies, in 5034 patients with persistent atrial fibrillation, compared rate control versus rhythm control. The latter was achieved by pharmacological and/or electrical means. Average follow up ranged from 1 to 3.5 years. The rate-control strategy showed a significantly reduced risk of CEP (OR 0.85 [0.74, 0.99], p=0.03), with a trend towards a reduced risk of death (OR 0.88 [0.70, 1.03], p=0.10) and thromboembolic stroke (OR 0.85 [0.62, 1.11], p=0.20). Rate vs rhythm control yielded a risk difference for CEP of -0.02 (-0.04, 0.00), resulting in an NNT to save one CEP of 50. There was no significant difference, between rate vs rhythm control, in risk of systemic embolism (OR 0.93 [0.43, 2.02], p=0.90) and major bleeds (OR 1.10 [0.87, 1.40], p=0.40), despite a trend towards an increased rate of intra/extracranial bleeds (with an NNH of 100). No significant heterogeneity was found in any of the analyses ($p \geq 0.17$).
Conclusion: This up-to-date meta-analysis in more than 5000 patients with persistent atrial fibrillation shows a marginal superiority of the rate-control approach over the rhythm-control strategy (NNH/NNT ratio of 2). The significantly reduced risk of all-cause death and thromboembolic stroke (and the trend towards more frequent major bleeds) using rate compared to rhythm control may result from discontinuation of anticoagulant therapy in a number of patients treated by rhythm control. Whether rate control is superior to rhythm-control (associated with continued and rigorous anticoagulation) warrants further investigation.

P463 Propafenone added to ibutilide significantly increases conversion rates of persistent atrial fibrillation

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Ibutilide (I), a class III antiarrhythmic, is effective for pharmacologic conversion of persistent atrial fibrillation (AF). However, variable success rates have been reported with the use of this agent. Moreover, data on pharmacologic drug combinations with I are scarce. We hypothesized that propafenone (P), a sodium channel blocker without affecting repolarization time, may act synergistically with I, without significant proarrhythmic effects.
Methods: Consecutive patients with persistent AF(duration between 1 and 12 months) were studied. Patients with a recent (<3 months) acute coronary syndrome, uncontrolled hypertension, hypo- or hyperkalemia, valvular heart disease, hyper-or hypothyroidism, malignancies, inflammatory diseases, or congestive heart failure were excluded, as were patients on antiarrhythmic medications. Beta-blockers were discontinued 12 hours prior to study entry. All patients were fully anticoagulated for a minimum of 3 weeks prior to admission. An echocardiogram was obtained on admission, and a 12-lead ECG was obtained at baseline, hourly for the first 6 hours, and every 8 hours thereafter until hospital discharge. The patients were randomized in an 1:1 fashion to either I (1mg IV over 10 min, repeated after 10 min if unsuccessful) or P(600mg PO) followed by I(1mg IV over 10 min, repeated after 10 min if unsuccessful). All patients were continuously monitored for approximately 24 hours. Acute conversion rates were recorded 6 hours post-randomization. Yates corrected chi square and t-test for independent variables were used for statistical analysis. Statistical significance was defined at an alpha level of 0.05.
Results: 85 patients (69 male, mean age 65±9 years) entered the study. 45 patients received P+I and 40 patients received I. Patient demographics, arrhythmia duration, left atrial dimensions and left ventricular function were comparable between the two groups. No complications were noted and no significant differences in the QT interval were found.

	Success	Failure
Propafenone + ibutilide	33	12
Ibutilide	19	21

p=0.026.

Conclusion: Concurrent administration of P+I is safe and more effective compared to I alone, for pharmacologic conversion of persistent AF.

P464 P wave duration and P wave dispersion in hyperthyroidism and risk of paroxysmal atrial fibrillation: efficacy of antithyroid treatment

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Objective: Atrial fibrillation is frequently encountered in patients with hyperthyroidism and onset of this arrhythmia is associated with high risk of thromboembolic complications. Previously, it was shown that prolonged maximum P wave duration and increased P wave dispersion on 12-lead surface electrocardiograms (ECG) are closely related to the development of paroxysmal atrial fibrillation (PAF). In this study, these P wave parameters were measured from 12-lead surface ECG in hyperthyroid patients with or without PAF during sinus rhythm and compared to euthyroid controls. In addition, influence of pharmacologic antithyroid therapy on these P wave parameters was investigated.
Methods and results: Fifty-two hyperthyroid patients were included in the study. All patients underwent 24-hour Holter recordings and then, patients were divided into two groups according to the presence (PAF+; n=29) or absence (PAF-; n=23) of PAF. Maximum P wave duration (P max), minimum P wave duration (P min) were measured from the 12-lead surface ECG and P dispersion (PWD=P max-P min) values were then calculated. P max values were found to be significantly longer in both PAF+ (114.8±11.6 ms) and PAF- (105.6±11ms) patient groups as compared to controls (91±7.6 ms; $p<0.001$ for both comparisons). PWD values of both PAF+ and PAF- groups were also significantly higher than the controls (53.3±12 ms, 43.6±10 ms and 31.2±5 ms, respectively; $p<0.001$ for both comparisons). Besides, P max and PWD values were significantly higher in PAF+ group as compared to PAF- group (p=0.006 for P max, p=0.003 for PWD). There were no significant differences in P min among groups. After restoration of euthyroidism by antithyroid therapy, P max (106±10ms, $p<0.001$) and PWD (42.2±6.4 ms, $p<0.001$) were found to be significantly decreased in PAF+ group as compared to baseline. In PAF- patients, P max (97.7±14 ms, p=0.001) and PWD (34.5±6.4 ms, $p<0.001$) were also decreased. In both groups, no significant changes were detected in P min values between baseline and after treatment. However; after restoration of euthyroidism, P max as well as PWD values were still significantly higher in PAF+ group as compared to PAF- group(p=0.002 for P max; p=0.001for PWD).
Conclusion: It is concluded that prolongation of P max and PWD in hyperthyroid patients could reflect a propensity to develop atrial fibrillation. However, significant decline in both of these P wave parameters after management of hyperthyroidism is thought to be the result of decreased unfavorable effects of circulating thyroid hormones on atrial electrophysiology.

P465 Magnesium increases the safety of ibutilide when given for converting atrial fibrillation to sinus rhythm

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Background: The most serious complication of ibutilide is torsades de pointes (TdP) which is due to QT prolongation caused by ibutilide. Magnesium (Mg) has been successfully used for the treatment of TdP, but its use as a prophylactic agent for this arrhythmia is not yet established. The aim of this study was to investigate whether Mg increases the safety of ibutilide administration.
Methods: 122 patients with AF, candidates for convertion to SR with ibutilide were included. The pts were divided into 2 groups. Group A: consisted of 60 pts who received ibutilide (iv infusion of 1mg for 10 min and another 1mg iv for another 10 min, with a 10 min interval between the two infusions - the 2nd infusion was omitted if SR had been already achieved) in order to convert AF to SR. Group B: consisted of 62 pts who received iv infusion of 5mg magnesium sulfate for 1 hour prior to the administration of ibutilide. Ibutilide was given (after the completion of iv infusion of 5mg magnesium sulfate, as described before) using the same protocol as in group A. After the completion of the iv infusion of 5mg magnesium sulfate, another 5mg of the same agent was infused for two more hours, from another vein without interrupting ibutilide infusion protocol. Patients with QTc > 500ms after the 1st infusion of ibutilide, were not given the 2nd dose and if within 4 hours SR was not achieved, they were recorded as a failure of ibutilide. The maximum value of QTc, the increase in QTc value, and the ventricular arrhythmias that appeared (sustained, non-sustained ventricular tachycardia and TdP) were recorded.
Results: 41 pts of group A (68.3%), and 53 pts of group B (85.5%) (p=0.04) were converted to SR. Max QTc didn't differ between the two groups (445 ± 48 ms for group A vs 432 ± 28 ms for group B, p=0,069) but the increase of QTc was lower in the Mg group (50 ± 27 ms vs 39 ± 20 ms, p=0,012). Ventricular arrhythmias were more often (but not significantly) in group A (5% vs 1,6% of group B, p = 0,58). Only 1 patient of group A had TdP. The administration of Mg (despite the high doses used) was well tolerated, with no complications.
Conclusions: Magnesium not only enhances the conversion efficacy but also increases the safety of ibutilide.

P466 Flecainide versus ibutilide for immediate cardioversion of atrial fibrillation of recent onset

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Purpose: This study compared the efficacy and safety of flecainide (a class I-C drug) and ibutilide (a class III drug) for immediate cardioversion of atrial fibrillation (AF).

Methods: We conducted a prospective, randomized, multicenter trial, including 207 hemodynamically stable patients with AF of recent onset (≤ 48 hours). Patients with atrial flutter were not eligible. Flecainide was given by infusion over 20 minutes at a dose of 2 mg/kg body weight (maximum 200 mg), ibutilide was infused at a dose of 1 mg (or 0.01 mg/kg body weight if less than 60 kg) over 10 minutes, followed by a 10-minute observation period and an identical second dose if AF did not convert to sinus rhythm (SR). Treatment was considered successful if SR occurred within 90 min of starting medication.
Results: The conversion rate was 56.4% in patients given flecainide and 50.0% in patients given ibutilide (p = 0.34). Multivariable analysis revealed that lower age for women independently increased the probability of conversion. None of the other variables, including left atrial size, left ventricular systolic function, presence of left ventricular hypertrophy, plasma levels of potassium or magnesium at baseline, or concomitant use of digoxin, betablocker, diltiazem or verapamil were predictors of conversion. Adverse events were reported in 11.9% of patients assigned to flecainide and in 6.6% of patients assigned to ibutilide (p = 0.19).
Conclusion: There was no significant difference in the cardioversion efficacy or in the risk of adverse events between flecainide and ibutilide in patients with AF of recent onset. In this population with short-lasting AF, the marked differences in the electrophysiological actions of the drugs (class I-C versus class III) appeared to play only a minor role from a clinical viewpoint.

MECHANISMS OF ARRHYTHMIAS

P467 Structural remodelling in atrial fibrillation – role of p38, Bcl2 and estrogen

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Background: The cellular changes from electrical to structural remodeling in persistent atrial fibrillation (AF) are not all known.
Methods: Myocardial samples from both atria and ventricles were obtained from the hearts of 43 goats which had undergone cardiac pacemaker (660ppm) implantation to induce AF in 29 goats. Goats were grouped according to AF duration, ranging from 2 to 430 days. Cardiac samples from the other 14 goats remaining in sinus rhythm (SR) were used as controls. Apoptosis was evaluated histo- and biochemically.
Results: Persistent AF for 3 months was characterized morphologically by an up to 9-fold increase in atrial myocyte apoptosis (TUNEL staining, 0.27 ± 0.05% vs. 0.03% ± 0.01%, $p<0.001$) and biochemically by agarose gel electrophoresis and Western blots for Bax, Bcl2, Cytochrome C, activated Caspase-3(p20)and p38 peaking after 90d in AF; the percentage of ventricular myocytes labeled with Bcl2 was 5-times higher for goats in AF than in SR ($p<0.005$). The percentage of apoptotic atrial myocytes, but not fibrocytes, correlated with the duration of AF ($p<0.05$). After peaks of apoptotic myocytes, atrial volume corrected by heart weight increased and fibrosis and glycogen deposition progressed over time ($p<0.01$). Goats in AF for 430 days revealed apoptosis in atrial and Bcl2 expression in ventricular myocytes at baseline levels (ns.). Estrogen receptor status was determined by PCR in 5 samples. Estrogen receptor expression was higher in the controls (n=3) vs in goats in AF (n=4).
Conclusions: In this model, programmed death of myocytes increases within 90 to 120 days of AF, despite enhanced Bcl2 expression and prior to atrial stretch and fibrosis, and reaches baseline levels after 210 to 430 days of AF. This transient phenomenon may contribute to the progression of electrical and structural remodeling associated with AF. The role of estrogen will be discussed.

P468 Coronary arteries interfere with the wave propagation and cause the reentrant waves, in a thin ventricular myocardium

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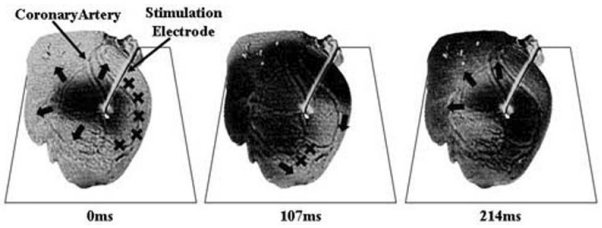
Purpose: To investigate whether the coronary vessels interfere with the wave propagation as a cause of reentrant arrhythmias, in a thin ventricular myocardium.
Methods: Five Langendorff-perfused rabbit ventricles were stained with voltage sensitive dye (di-4-ANNEPS 2 μmol/L). To make a 2mm thick myocardium, each ventricle was frozen from the endocardial side concentrically. Single point stimulation was applied to the left ventricular epicardium, and movies of the left ventricular epicardium were obtained using a high-speed digital video camera (spatial resolution 0.12mm, scan rate 700 frame/sec). The coronary vessels and wave propagation were simultaneously visualized clearly as 3-dimensional images using computer graphics.
Results: The wave propagation often delayed or ceased along the coronary artery. This occurred, especially when a wave propagation perpendicularly collided with the distal part of coronary arteries. Some of the waves formed unidirectional block along the distal part of the coronary arteries, inducing spiral wave reentry (figure: the black colors mean the high voltages). The induced spiral waves often terminated spontaneously by colliding with the coronary arteries.



Conclusions: In a thin ventricular myocardium, coronary arteries interfere with the wave propagation and possibly cause ventricular arrhythmias.

P469 Cardiac conduction and resistance to hypothermia cardiac arrest in siberian hibernator ground squirrel citellus undulatus

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Introduction: Most nonhibernating mammals experience cardiac arrest during hypothermia due to ventricular fibrillation or full conduction block which ensues at critical temperatures near 15-27°C. In contrast, hibernators maintain cardiac output even at hibernation heart temperatures from -2°C to +8°C. Our goal was to provide direct evidence that the heart of hibernator ground squirrel Citellus undulatus maintains safe cardiac conduction and to quantify excitation patterns during hypothermia.
Methods: We imaged electrical conduction in intact isolated hearts of summer active (SA, n=5) and winter hibernating (WH, n=5) ground squirrels from Siberia (Lena river valley, Yakutsk region). The hearts (n=10) were isolated and Langendorff-perfused with normal Tyrode solution at different temperatures varying from +37°C to +2°C. Electrical activity was optically mapped with CCD camera (Dalsa) at 500 frames/sec and voltage-sensitive dye di-4-ANEPPS. No excitation-contraction uncouplers were used. Imaging was conducted during normal sinus rhythm (n=6) and pacing at 100-2000 ms coupling interval (n=10).
Results: Hearts were able to maintain spontaneous sinus rhythm and normal pattern of epicardial excitation throughout the whole range of studied temperatures. Neither spontaneous tachyarrhythmia nor asystole were observed in all 10 experiments during both cooling from 37 to 2°C and rewarming the heart back to control 37°C. Reduction of temperature from 37 to 2-5°C resulted in decreasing of the spontaneous sinus rhythm from 160±13 to 6±1 beats/min ($p<0.01$), respectively. Moreover, we observed no evidence of AV block at any temperature. Ventricular conduction velocity significantly decreased from 71±4 to 14±1 cm/sec and from 88±12 to 9±1 cm/sec with decrease of temperature from 37°C to 5-9°C (SA) and to 2°C (WH), respectively. We observed slightly but significant difference in conduction velocity of SA and WH hearts at high temperatures. At low temperatures, conduction velocity was the same in both states of the myocardium: SA and WH.
Conclusion: We presented for the first time excitation patterns of intact hibernator's SA and WH hearts at different temperature. We observed that isolated heart of ground squirrel Citellus undulatus maintains sinus rhythm and normal pattern of excitation in the range of temperatures +37°C - +2°C. Future studies will target molecular mechanisms of hypothermia resistance, which are likely due to changes in function and expression of sodium, calcium and gap junctional channels.

P470 Modifications of ventricular fibrillation frequencies induced by local stretching

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Stretching modifies the electrophysiological properties of myocardial cells and accelerates ventricular fibrillation (VF). It is not known whether the changes in VF activation patterns produced by local stretching influence the activation of other distant zones not subjected to stretch.
Sixteen Langendorff-perfused rabbit hearts were used to record VF activity with two epicardial multiple electrodes (121 and 115 unipolar electrodes) before, dur-

ing and after local stretching induced with a left intraventricular device. Time-frequency analytical techniques were used to obtain the VF dominant frequency (FrD) and to investigate the VF spatiotemporal characteristics in the stretched (SZ) and a non-stretched (NSZ) zone of the left ventricular free wall.
In SZ the dominant frequency significantly increased during stretch (18.8±2.5 Hz vs 15.2±1.9 Hz, $p<0.0001$), but did not vary significantly in NSZ (15.3±2.5 Hz vs 15.2±2.1 Hz). Similar results were obtained on analyzing the V-V intervals during VF, with significant shortening in SZ (53±6 ms vs 63±8 ms, $p<0.001$) but not in NSZ (65±8 ms vs 66±8 ms). Both parameters supply complementary information, and the regression straight line between FrD and the inverse of the mean V-V proved significant and with a slope of close to unity (FrD=0.94*invV-V + 0.38; R=0.90; $p<0.0001$). The spatiotemporal characteristics of VF activation patterns were analyzed determining the grouping of contiguous electrodes with a common frequency (blobs). The number of coexisting blobs during periods of 50 msec. increased in SZ during stretch (12.6±6.3 vs 9.2±3.6; $p<0.02$) and failed to modify significantly in NSZ (12.5±5.7 vs 10.9±4.8) - though the life span of blobs was not modified by stretching in either of the zones (SZ=0.650±0.169 sec. vs 0.563±0.212 sec.; NSZ=0.677±0.287 sec. vs 0.666±0.283 sec.). In both zones the number and life span of the blobs identified for high frequencies (percentile 75 of FrD) did not vary significantly with respect to those identified for FrD, both at baseline and during stretching.
Conclusions: Local stretching accelerates and increases the complexity of VF in the stretch zone, without significantly modifying the VF activation patterns at a distance from the mentioned zone. Local FV acceleration is not accompanied by an increased persistence in time of zones with common frequency.

P471 Hormonal therapies of prostate cancer that induce androgen deficiency: the impact of testosterone on the QT interval of the electrocardiogram – a potential unrecognized cardioprotective effect

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Purpose: Drugs that prolong the QT interval of the ECG are associated with an increased risk of a life-threatening arrhythmia, Torsades de Pointes ventricular tachycardia (TdP). Females are at a higher risk of TdP with any cardiac or non-cardiac drug that prolongs repolarization (R); a two to four-fold increase risk of TdP compared to males. These consistent observations across varied drug classes resulted in a focus on estrogens and their role in modulating the expression of K-channels, especially HERG or Ikr. Less is understood regarding the role of testosterone (T). The purpose of these studies was to examine the role of T in cardiac R.
Methods: Four separate regimens that induce androgen deficiency for prostate cancer were evaluated. Serial plasma T measurements made at the same time of the 12-lead ECG. The first trial was a one-year comparison of abarelix to goserelin plus bicalutamide. The abarelix arms of trials 2 and 3 (24 weeks) are combined.
Results: Increases in QTc of 10-20 msec occurs with all treatments resulting in androgen deficiency (plasma T <50 ng/ml); all $p<0.01$ (see Table).

QTc Effect of Androgen Deficiency

	Study 1 Goserelin plus Bicalutamide	Study 1 Abarelix	Study 2 Leuprolide	Study 3 Leuprolide plus Bicalutamide	Study 2&3 Abarelix
Baseline QTcB*	411.4	413.5	421.6	418.7	417.9
On Rx QTcB	428.0	426.8	441.6	428.1	431.7
On Rx C QTcB	16.7	13.3	20.0	9.4	13.8
Baseline QTcF	404.0	407.6	414.5	414.3	410.6
On Rx QTcF	422.4	419.5	432.1	424.2	432.4
On Rx C QTcF	18.3	12.0	17.6	9.9	12.8
Baseline Plasma T**	347	316	342	358	361
On Rx Plasma T	26	35	9	13	14

B=Bazett; F=Fredericia; T=testosterone (ng/ml); Rx=treatment; C=change from baseline. *All QTc data is mean (msec); **Plasma T data is median (ng/ml).

Conclusion: Androgen deficiency results in significant prolongation of the QTc interval. The magnitude of the QTc increase seen is comparable to low-dose sotalol or dofetilide. This data is consistent with an important role of T in cardiac R, possibly having a cardioprotective effect.

P472 Significant alterations of electrophysiological properties in vivo and of potassium channel expression in mice with a knockout of muscle LIM protein

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Background: Mice with a knockout (KO) of muscle LIM protein (MLP) exhibit morphological and clinical features of cardiomyopathy. In humans MLP expression is downregulated both in ischemic and dilative cardiomyopathy. In this study we investigated the electrophysiological phenotype in vivo and the expression of potassium channels in mice with KO of MLP.
Methods: 36 mice (25 MLP-/-; 11MLP+/+) were subjected to long-term electrocardiogram recording (LT-ECG,12 hours) and in vivo transvenous electrophysiological study (EP). Western blot (WB) analysis was performed for the evaluation of Kv1.2, Kv1.5, Kv2.1, Kv4.2 and Kv4.3 expression.
Results: LT-ECG revealed a significant prolongation of RRmean (110±7 vs 99±5ms), P (17±3 vs 15±2ms), QRS (17±3 vs 13±1ms), QT (70±6 vs 50±7ms), QTc (67±5 vs 50±8ms), JT (53±7 vs 37±7ms) and JTc (51±6 vs 37±7ms)($p<0.05$) in MLP-/- vs MLP+/+ mice. The results of the EP study are summarized in the Table below.

EP Parameters (*: $p<0.05$):

	SCL (ms)	QRS (ms)	QTc (ms)	JTc (ms)	AVERPs3 (ms)	RVERPs2 (ms)	RVERPs3 (ms)	RVERPs4 (ms)
MLP-/- (n=25)	171±20*	19±3*	62±6*	48±6*	77±14*	40±16*	40±16*	46±16*
MLP+/+(n=11)	156±15	15±1	48±5	36±5	66±9	18±8	19±8	20±8

Non-sustained VT was inducible in 12/25 MLP-/- vs. 3/11 MLP+/+ mice ($p<0.05$). The expression of Kv1.5 and Kv2.1 was significantly ($p<0.05$) upregulated in MLP-/- mice.
Conclusion: Mice with a knockout of muscle LIM protein exhibit significant prolongation of atrial and ventricular conduction and increased ventricular vulnerability. These alterations of electrophysiological properties may in part be explained by significantly altered expression of delayed-rectifier potassium channels.

P473 A locus for autosomal dominant sinus node disease is mapped on chromosome 7q21-q31

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Introduction: Sinusnode disease (SND) is a frequent cardiac arrhythmia, often a secondary phenomenon to coronary artery disease or corrective heart surgery. In one-third, the disease is idiopathic and related to intrinsic SND abnormalities, either in impulse formation, automaticity, or impulse conduction. Not unexpectedly, SND is associated with a spectrum of phenotypes, like sinus bradycardia, sinuatrial block/arrest, atrial fibrillation and others. So far, the HCN4 (pacemaker channel) gene has been identified as a genetic cause for SND. Here, we report about a large family with autosomal dominant sinuatrial disease and results of a linkage analysis to identify the disease locus.
Methods: A three-generation family (n=25 members) with a variable clinical expression of sinuatrial disease was clinically characterized. In the 11 affected family members, there were no extrinsic cause for sinuatrial abnormalities. So far, two adult patients required pacemaker implantation. No sudden cardiac death is known. DNA was extracted from EDTA-blood and genome-wide linkage analysis was done using the mapping set LMS-MD-10 (Applied Biosystems). Lod score calculations were performed using FASTLINK version of the LINKAGE 5.1 program package and MLINK.
Results: After analysis of all chromosomes, two-point analysis showed significant evidence of linkage to multiple markers between D7S491 and D7S2502. Centromeric, flanking markers D7S657- D7S2482 showed low positive lod scores of ~0.5 due to uninformativeness of the marker. Multipoint linkage analysis in this region demonstrated seven markers to have a positive LOD score above 3.0, with a maximum multipoint LOD score of 4.6 (theta=0) obtained within marker D7S491 until D72460 and 3.9 within marker D7S821 and D7S491. Other gene loci including HCN4 and SCN5A have particularly been excluded, retrospectively.
Conclusions: These data support the second disease locus for sinuatarial disease being located on chromosome 7q21-q31. The causing gene lies in a 16.8cM region between markers D7S821 and D72460. Here, an interesting series of potential candidates can be found including a connexin, G-protein receptors, laminins, caveolines, a proteinkinase and proteinphosphatase1 and others. Positional cloning of that genes is currently ongoing and will hopefully give further light into sinus node dysfunction with idiopathic origin.

P474 Upregulation of KCNE1 gene causes QT prolongation in CHF patients

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[Backgrounds] Abnormalities in repolarization process in patients with chronic heart failure (CHF) is a major cause of sudden cardiac death due to ventricular arrhythmias. QT prolongation is a common finding for these CHF patients, whereas underlying ionic mechanisms remain poorly understood. The slow component (IKs) and the rapid component (IKr) of the delayed-rectifier potassium current (IK) are known to be major determinants of APD, but less information is available on the genomic modulation of IK in the remodeled human heart. We considered that relative abundance of KCNE1 compared with KCNQ1 subunits might alter repolarization properties in human heart failure. To test this hypothe-

sis, we examined the relationship between QT interval in 12-lead ECG recordings and mRNA levels of KCNQ1, KCNE1, and KCNH2 in patients with chronic heart failure (CHF).
[Methods] Total RNA samples were extracted from right ventricle endomyocardial biopsy samples. In Xenopus oocytes, cRNAs for KVLQT1 (5 ng) with variable KCNE1 (0,0.2,1,5 ng) were co-injected to study IKs. For the later use of simulation, currents were recorded at 35°C by standard two-microelectrode voltage-clamp techniques 2 to 4 days after cRNA injection.The current traces above were analyzed and parameters of activation kinetics were incorporporated in the phase-2 Luo-Rudy (L-R) model of ventricular action potentials.
[Results] In 21 patients (age, 53 $\pm$ 4 years, mean $\pm$ EM) with hypertrophic cardiomyopathy (n=3), dilated cardiomyopathy (n=8), restrictive cardiomyopathy (n=1), and ventricular tachycardia (n=9), no significant differences were found in the KCNQ1 and KCNH2 levels between patients with CHF (NYHA II or III, n=11) and controls (NYHA I, n=10). The KCNE1 level was 6.7-fold higher in the CHF patients than in controls. The KCNE1-to-KCNQ1 ratio was higher in CHF patients than that in controls (2.55 $\pm$ 0.82 vs 0.66 $\pm$ 0.07, $p < 0.05$) and the KCNE1/KCNQ1 ratio was positively correlated with QT interval ($r=0.54$, $P<0.05$). The activation kinetics of the KCNQ1/KCNE1 currents were significantly slower in proportion to the increase in KCNE1. A decrease in IKs and prolongation of APD were well predicted in a modified Luo-Rudy model by incorporating data obtained from expressed KCNE1/KCNQ1 currents.
[Conclusions] The relative abundance of the KCNE1 compared to KCNQ1 genes may modulate the ventricular repolarization process by changing the kinetics of expressed IKs and an elevation of KCNE1 may explain QT prolongation in CHF patients.

P475 The effect of GG 176 polymorphism on interleukin-6 gene on the development of fatal arrhythmias in patients with dilated cardiomyopathy

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Background: It is well known that inflammatory process plays a major role in the pathophysiology of heart failure and predisposes to the development of fatal ventricular arrhythmias in these patients. Increased levels of interleukin-6 (IL-6), a pro-inflammatory cytokine, have been associated with cardiac fibrosis and worsening prognosis in patients with dilated cardiomyopathy. However, the potential role of GG 176 polymorphism on IL-6 gene in the development of fatal ventricular arrhythmias has not been investigated until now.
Methods: This study enrolled 80 patients with dilated cardiomyopathy (aged 47.7$\pm$5.2 years, 62 males and 18 females). Twenty three of those patients had a history of fatal arrhythmias and were carrying an AICD, while the rest of them had no history of this kind of arrhythmias (control group). The GG 176 polymorphism on IL-6 gene was determined by polymerase chain reaction (PCR) using sequencing (SSCP) analysis, while IL-6 serum levels were determined by commercially available ELISA tests.
Results: Among AICD patients there were 10 GG (43.4%) homozygotes, 2 CC (8.8%) homozygotes and 11 GC heterozygotes (47.8%). However, among controls there were 41 GG homozygotes (72.0%), 1 CC homozygote (1.7%) and 15 GC heterozygotes (26.3%). In GG homozygotes, the odds ratio for AICD was 1.654 (95%CI:1.01-2.71, p=0.022) compared to other genotypes. However, no significant difference was observed in IL-6 serum levels, between GG (2.59$\pm$1.15 pg/ml), GC (2.44$\pm$1.83 pg/ml) and CC (2.23$\pm$1.23 pg/ml) in patients with AICD (p=ns for all).
Conclusions: Genetic polymorphism GG 176 on interleukin-6 gene was associated with increased risk for ventricular arrhythmias in patients with dilated cardiomyopathy, indicating that this polymorphism may affect the prognosis of the disease.

P476 Involvement of the Kir2 gene family in catecholaminergic polymorphic ventricular tachycardia; analysis for mutations and identification of numerous pseudogenes

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare arrhythmogenic disorder characterized by recurrent syncopal events and sudden cardiac death (SCD) at young age triggered by physical stress or emotion, in the absence of structural heart disease. We previously collected twenty-seven CPVT probands with a structurally normal heart presenting with documented polymorphic ventricular arrhythmias occurring during physical or emotional stress. In 12 of these probands we were unable to find an underlying mutation in either the RYR2 or the CASQ2 gene, implying further genetic heterogeneity for CPVT. Mutations in the KCNJ2 (Kir2.1) gene underlie Andersen syndrome (AS), a disease characterized by a wide range of phenotypic abnormalities, including periodic paralysis, dysmorphic features and polymorphic ventricular tachycardia. Therefore, we sought to find out whether mutations of the Kir2 gene family might underlie some of the genetically unclassified CPVT cases. Systematic screening of all the four members of the Kir2 gene family led to the identification of an autosomal dominant missense mutation in the KCNJ2 gene, R67W. This mutation occurred in one individual in whom it presented solely as CPVT without any features of the Andersen syndrome. We assessed the clinical and genetic characteristics and the response to therapy of this KCNJ2 CPVT mutation. In addition, we identified a large number of KCNJ12-like pseudogenes and associated polymorphisms, which has consequences for mutational screening. Finally, we report on the exclusion of the candidate genes KCNJ12, KCNJ4 and KCNJ14 in our CPVT population of 27 probands.

P477 Myocardial creatine depletion dramatically increases acute mortality in rats with postinfarction heart failure

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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) acute mortality 2) ventricular arrhythmias, and 3) myocardial catecholamine content in rats with acute postinfarction heart failure (HF).
Methods: Male Sprague Dawley rats (BW) $\sim$ 200 g were randomly assigned to two groups: the rats treated with creatine analogue beta-guanidinopropionic acid (GPA) (n = 14) and normal controls (n = 15). GPA (1 M) was administered by subcutaneously implanted osmotic minipumps during 4 weeks prior to induction of MI. Myocardial infarction (MI) was induced by ligation of the left coronary artery resulting in a large ($\sim$50%) anterolateral MI and acute HF. The rats were examined in vivo by 31P magnetic resonance spectroscopy (MRS) prior to induction of MI for evaluation of myocardial energy status. A computerized ECG tracing was obtained continuously before induction of MI and up to 60 min. postinfarction. Invasive hemodynamics including intraventricular and arterial pressure was registered for 60 min. post MI. At 60 min posinfatrction or at the time of death 1 ml blood was drawn from the left ventricle for analysis of catecholamines. Qualitative as well as quantitative variables of ventricular arrhythmias were analyzed according to the 10-point arrhythmia score. HPLC was used for measurements of catecholamines.
Results: The arrhythmia score in the BGP group (6.9 $\pm$ 0.6) was higher compared to the control group (5.3 $\pm$ 0.3, $p < 0.05$). All rats (100%) in the BGP group died within 60 min after induction of large MI compared to 53% in the control group ($p < 0.01$). 78% in the BGH group died in ventricular fibrillation (VF) while 22% died in worsening HF and lung oedema. All rats in the control group died in VF wile survivors (47%) were sacrificed 1 week later without any additional deaths. Myocardial noradrenaline content was lower in the BGH group (36.9 $\pm$ 3.8 v. 50.8 $\pm$ 6.2 ng/g, p = 0.06). There was no difference in plasma NA content. Phosphocreatine-to-ATP ratio was 39% lower in the BGP group (1.6 $\pm$ 0.04 v. 2.6 $\pm$ 0.07, $p < 0.01$).
Conclusions: Creatine depletion in the heart results in 100% mortality during early phase of acute postinfarction HF and increases severity of malignant ventricular arrhythmias. Disturbed myocardial creatine metabolism interferes with catecholamine content in the heart. Intact creatine metabolism is essential for survival in acute postinfarction HF.

P478 Variation of autonomic tone in the right atrium induces repetitive rapid focal activities from the left atrium but does not induce atrial fibrillation

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Introduction: Variation of autonomic nerve tone has an important role for inducing paroxysmal atrial fibrillation (AF) originating from the left atrium, especially pulmonary veins (PVs). However, this mechanism is still unclear.
Methods and Results: To examine the effect of autonomic tone variation on AF induction originating from the left atrium, high resolution optical mapping technique was used to measure action potentials from the posterior left atrium during electrical stimulation (10-30 Hz) of intracardiac vagal nerves (IVS) to innervate the right atrium (i.e. sinoatrial fat pad stimulation), during isoproterenol infusion (0.4-1 μM) into both coronary artery and during IVS stimulation in the presence of isoproterenol as a surrogate for autonomic tone variation in 6 isolated arterially perfused canine both atria including 4 PVs. Monophasic action potentials were also measured from 2 sites on the right atrium. IVS caused sinus arrest for more than 2 s but did not induce AF in any preparation. Isoproterenol infusion decreased sinus cycle length (CL) from 540 $\pm$ 14 ms to 337 $\pm$ 4 ms and induced a number of premature beats, which did not induce AF. In contract, during IVS in the presence of isoproterenol the repetitive rapid electrical activities (CL = 117.4 $\pm$ 21.9 ms) from right atrium following sinus arrest for 2.4 $\pm$ 0.2 sec induced AF spontaneously in all 6 preparations. Interestingly, during the IVS in the presence of isoproterenol the repetitive rapid focal activities (CL = 151.5 $\pm$ 25.1 ms) were

also induced from the posterior left atrium following sinus arrest for 2.0 ± 0.5 sec but these activities did not induce AF.
Conclusion: Variation of autonomic tone increases the vulnerability to AF induction by causing repetitive rapid activities following the inhibition of sinus node activity. The autonomic tone variation in the left atrium may be required for AF induction originating from the left atrium.

P479 The temporal distribution of arrhythmia onsets and termination therapy efficacy in patients with paroxsymal atrial fibrillation

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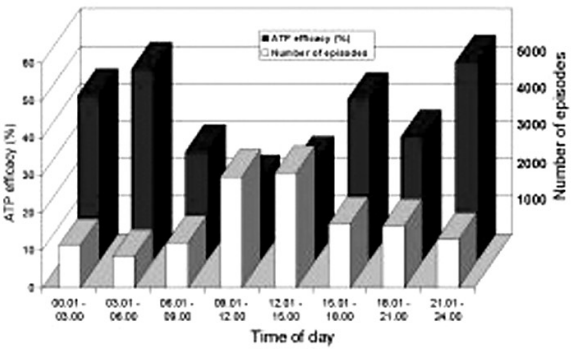
Purpose: The temporal distribution of arrhythmia onsets and termination therapy (ATP) efficacy in patients with paroxysmal atrial tachyarrhythmias (AT/AF) was assessed.
Methods: Forty patients, mean age 70±9 years, 55% male, were implanted with the Medtronic AT500 pacemakers for paroxysmal AT/AF. AT/AF onset times were determined from device holters.
Results: Over a follow period of 6 months, 13,579 episodes of AT/AF were recorded. The peak onset of AT/AF was diurnal with 42% of episodes initiating between 9AM and 3PM with the lowest proportion of episodes (15%) occurring nocturnally between midnight and 6AM ($p<0.0001$) (figure). ATP efficacy, however, peaked nocturnally between 9PM and 3AM, and was least effective between 9AM and 3AM, (49% versus 24%, p=0.0003). ATP significantly reduced the overall episode frequency (mean 710±263 ON versus 988±545 OFF, p=0.05) but did not alter the onset pattern ($p>0.13$).



Conclusions: There is a circadian distribution of onsets of paroxysmal atrial tachyarrhythmias with a diurnal predominance, suggesting adrenergic triggers. ATP efficacy was maximal at night. These findings may allow improved pacemaker and hybrid treatment of paroxysmal atrial fibrillation.

P480 Cardiac parasympathetic stimulation for ventricular rate control during atrial fibrillation: the chronaxie-rheobase relationship of cardiac neurostimulation

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Background: Ventricular rate control during atrial fibrillation (AF) is a challenge as the chaotic bombardment of the AV node by the fibrillating wavelets causes almost unpredictable sequences of ventricular activation leading to tachycardic as well as bradycardic episodes. In addition, apart from cardiac glycosides most of the drugs that exert negative dromotropic effects have also significant ventricular negative inotropic and vasodilating properties at dosages which effectively decrease the rapid ventricular rate during AF. This limits their benefit in patients with congestive heart failure or arterial hypotension. In acute human experiments we observed that selective catheter stimulation of parasympathetic nerves (PNS) which innervate the AV node decreases the ventricular rate during AF. The present study investigates which stimulation requirements are needed for chronic PNS using active fixation leads.
Methods: In 6 acute dog experiments permanent epicardial bipolar screw-in electrodes were fixed in the inferior inter-atrial ganglionated plexus which contains parasympathetic nerves which innervate the AV node. AF was induced and maintained via rapid atrial pacing. During AF neural stimulation was performed at various stimulation frequencies (1-100 Hz), impulse durations (0.05-2 ms) and stimulus intensities (0.02-12 V) to establish strength-duration curves for cardiac neurostimulation. At each set of parameters the ventricular rate during AF was recorded.
Results: For cardiac neurostimulation an inversely bell-shaped relationship between stimulation frequency and negative dromotropic effect was obtained. Maximal ventricular rate slowing during AF was observed for a frequency range between 30-50 Hz. The rheobase for an R-R interval prolongation of 50% during PS was 3.0 V and 4.7 V for AVB III°. A chronaxie time of 0.1 ms was calculated for both thresholds which is similar to the chronaxie time of current pacemaker leads during myocardial electrostimulation (0.2-0.4 ms).
Conclusions: A selective stimulation of cardiac parasympathetic nerves via active fixation leads allows a dynamic control of the ventricular rate during AF. Like myocardial stimulation and electrostimulation, cardiac neurostimulation follows a chronaxie/rheobase behavior. The stimulation parameters which are needed to achieve negative dromotropic effects up to AVB III° are within the limits of conventional pacemaker outputs used for myocardial stimulation which may allow implementation of neurostimulation capabilities in current pacemaker technology.

P481 Biochemical analysis of impaired cardiac autonomic function in patients with idiopathic right ventricular outflow tract tachycardia

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Idiopathic Right Ventricular Outflow Tract Tachycardia (RVO-VT)is generally considered a primary electrical disease. In the absence of cardiac morphological or functional abnormalities, the pathophysiological mechanisms of RVO-VT remain unexplained. However, ventricular tachyarrhythmias are frequently provocable by exercise, stress or catecholamine exposure, thus suggesting a potential role of the cardiac autonomic system in the arrhythmogenesis and, possibly, pathogenesis of RVO-VT. Accordingly, radionuclide studies confirmed this concept by showing regionally impaired presynaptic norepinephrine recycling.
Therefore we investigated sympathoadrenergic signal transduction in 20 pts. with RVO-VT. In RV endomyocardial biopsies, concentration of norepinephrine (NE), tyrosine hydroxylase (TH), norepinephrine uptake carrier protein (NET), inhibitory G protein (Gai1+2), cAMP and G protein coupled receptor kinase 2 (GRK2) were determined. Endomyocardial biopsies of 6 patients without arrhythmias or structural heart disease were used as controls.
Compared to controls tissue concentration of NE in pts. with RVO-VT was markedly reduced (942±531 vs. 1377±96 ng/g tissue, p=ns), indicating reduced vesicular stores of NE. This may be due to impaired uptake of NE, though, protein expression of total NET was not altered in RVO-VT pts. TH (6.6±11.6 x1000000 vs. 2.1±0.4x1000000 PI-Units, p=ns) and GRK2 protein expression tended to be higher in pts. with RVO-VT (5.9±0.2 x1000000 vs. 4.0±3.0 x1000000 PI-Units p=ns), both alterations can be interpreted as a compensatory mechanism. Formation of cAMP tended to be higher in RVO-VT pts.(827±690 vs. 755±96 pmol/l, p=ns). Gai1+2 protein expression was not altered as compared to controls.
Conclusion: Cardiac autonomic function is impaired in pts. with RVO-VT. Possible mechanisms include a reduced NET function despite normal protein expression and increased release of presynaptic NE, both resulting in elevated synaptic NE concentration, reduced presynaptic NE stores and compensatory upregulation of subsequent TH protein expression. Augmentation of adrenergic drive induces higher levels of cAMP and upregulation of GRK2 protein expression. These abnormalities alter intracellular calcium homeostasis and may induce dispersion of refractoriness and delayed afterdepolarization which may be arrhythmogenic. These new insights confirm and expand current concepts of the role of the myocardial autonomic modulation in RVO-VT and may have potential impact on risk stratification and the development of pathophysiologically based treatment options.

P482 Reflex versus tonic cardiac vagal activity in the subacute and chronic phase of myocardial infarction

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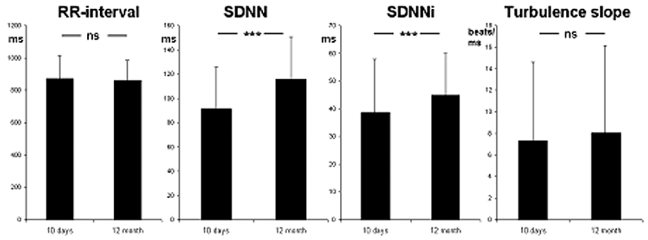
Depressed parasympathetic tone directed to the heart is associated with electrical instability and adverse outcome after myocardial infarction (MI). Both, heart rate turbulence (HRT), reflecting reflex vagal activity, and heart rate variability (HRV), reflecting tonic vagal activity have been shown to be significantly reduced in the subacute phase of MI. However, the course of each of these components of cardiac vagal control from the subacute to the chronic phase of MI has not yet been defined.
Methods and Results: We therefore investigated 100 consecutive patients (79 male, 21 female, 56.7±8 years of age with a first uncomplicated MI. HRT and HRV were determined from 24-hour-Holter-recordings ten days and twelve month after the index MI. There were no significant differences in mean RR-interval in the subacute and chronic phase of MI. Parameters of HRV (SDNN, SDNNi, SDANN, rMSSD, TI) significantly increased within the observation period, whereas there were no significant alterations of parameters of HRT (Turbulence Onset, Turbulence Slope).
Conclusion: In contrast to reflex vagal activity, there is a significant recovery of tonic vagal activity within 12 month after MI. These findings indicate different patterns of regeneration of reflex and tonic cardiac vagal control after MI, which



HRT and HRV after MI. ***p<0.001

has to be considered using these parameters for risk stratification in patients with ischemic heart disease.

P483 The effect of nitric oxide on electrical resitution and ventricular fibrillation in the isolated rabbit heart: mechanism underlying the antifibrillatory effects of vagus nerve activity?

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We have previously shown that vagus nerve stimulation decreases the susceptibility of the heart to ventricular fibrillation (VF), an effect which is reversed by nitric oxide (NO) synthase inhibitor. Steepness of the electrical restitution curve is suggested to correlate with VF initiation. This study examines the effect of NO on electrical restitution and VF induction in the isolated Langendorff perfused rabbit heart (n=7). Monophasic action potentials were recorded from the left ventricular epicardial surface and duration measured at 90% repolarisation (MAPD90). Standard restitution was studied using single right ventricular extrastimuli (S2) following a 20 beat drive train (S1, 300ms) down to effective refractory period (ERP). S2-MAPD were plotted against preceding diastolic intervals (DI) and fitted to an exponential curve with maximum slope measured. VF threshold (VFT) was determined as the minimum current required to induce VF with rapid pacing (30 x 30ms). Measurements were made in the absence (Baseline) and presence of the NO-donor, sodium nitroprusside (SNP, 25mM).
Results (table, mean±SEM): SNP significantly increased ERP, maximum MAPD (MAPDMax) and VFT whilst flattening the restitution curve and decreasing the maximum slope.

	Baseline	SNP	p value
ERP-ms	124.3±3.9	137.1±3.1	<0.02
MAPDMax-ms	115.4±4.6	129.6±4.8	<0.05
Slope	1.3±0.2	0.8±0.2	<0.03
VFT-mA	5.6±0.6	15.8±2.3	<0.005

Effect of SNP on ventricular electrophysiology

Conclusion: SNP flattens the electrical restitution curve and increases VFT, indicating direct effects of NO on ventricular electrophysiology. NO released during vagus nerve stimulation may play a central role in mediating the antifibrillatory effects by altering electrical restitution.

P484 The influence of autonomic tone in male endurance athletes with paroxysmal atrial fibrillation

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The influence of autonomic tone in male endurance athletes with paroxysmal atrial fibrillation.
Aims: To disclose the influence of autonomic tone and course of paroxysmal atrial fibrillation in endurance athletes.
Background: Atrial fibrillation is the main cause of symptoms in athletes and frequently disturbs the performance during the practising of sport. The course of the arrhythmia is seldom reported in this population.
Methods: In 1993 and 2002 symptoms and clinical presentation of atrial fibrillation was evaluated in 30 well-trained athletes with a specially designed questionnaire.
Results: In 1993 paroxysmal atrial fibrillation was present in 30 male athletes at the mean age of 48.1±7.8, 3 (10%) of them also had paroxysmal atrial flutter. Three (10%) of the athletes died before 2002. In 2002 paroxysmal atrial fibrillation continued in 15 (50%) athletes, permanent atrial fibrillation emerged in 5 (17%) of the athletes and 7 (23%) of them showed no atrial fibrillation anymore. In 1993 paroxysms of atrial fibrillation started at a relatively low level of training-intensity compared to the mean maximal training-intensity of 11±7 versus 8±4 h/week (p<0.05). Vagally induced AF was present in 1993 and 2002 in 10 (33%, n=30) and 10 (37% n=27) athletes, respectively. Adrenergically induced AF was shown in 7 (23%) athletes in 1993 and in 3 (11%) athletes in 2002 respectively. The first attack of adrenergically induced paroxysmal atrial fibrillation was more present in younger athletes (p<0.005) and vagally induced paroxysmal atrial fibrillation was more apparent in older athletes (p<0.05). In 10 (38%) of the athletes a familiar form of paroxysmal atrial fibrillation was present.
Conclusion: Vagally and adrenergically induced paroxysmal atrial fibrillation remained stable in 60% and 71% of the athletes respectively. In 20% of the athletes the vagally induced paroxysmal atrial fibrillation changed into permanent atrial fibrillation. A small proportion of the athletes (12%) was asymptomatic. Two athletes died in the group of autonomic induced paroxysmal atrial fibrillation.

P485 Association betweeen mean platelet volume and autonomic nervous system functions: increased MPV reflects sympathetic overactivity

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Platelets are thought to be involved in the pathogenesis of coronary artery disease, coronary occlusion and the development of atherosclerosis. Large platelets have been found immediately after myocardial infarction (MI) and shown to be an independent risk factor for MI and sudden death. Heart rate variability (HRV) analysis has been extensively used to evaluate autonomic modulation of sinus node and to identify patients at risk for an increased cardiac mortality. Some HRV parameters such as decreased SDNN and increased LF/HF ratio, are associated with an increased cardiac mortality in almost all clinical conditions characterized by an autonomic imbalance such as after MI. We aimed to study the relation between MPV and autonomic nervous system functions.
Fourty-seven patients admitted to our clinics, diagnosed to acute anterior myocardial infarction and underwent thrombolytic therapy were compared with age and genderly matched 32 patients with normal coronary arteries who underwent coronary angiography due to coronary heart disease suspicion. We applied 24-hr holter monitorization for HRV analysis to all patients on the sixth day post-MI and control group. Blood was taken for platelet count and volume measurements into the anticoagulant sodium citrate twice in the morning and night. Mean platelet volume was measured using a "SEQ500R Sysmex Rouche Counter" counting system.
There were no differences between two groups concerning age, gender, coronary risk factors and medical treatment such as beta blocking agents, ACE inhibitors. Mean heart rate (HR), LF, LF/HF ratio, MPV were higher, SDNN, RMSSD, PNN50, HF and thrombocyte counts were lower in the patients with anterior MI. LF, LF/HF, MPV were significantly higher and HF, platelet count measured during day time were significantly lower compared to those measured during night time. These differences in diurnal and nocturnal measurements were much more significant in the patients with MI. MPV was found to be positively correlated with ventricle score (r=0.7, p=0.001), degree of LAD stenosis (r=0.5, p=0.01), mean HR (r=0.4, p=0.007), LF (r=0.6, p=0.001), LF/HF (r=0.8, p=0.001) and negatively correlated with SDNN (r=-0.5, p=0.002), HF (r=-0.8, p=0.001) and platelet count (r=0.6, p=0.001).
As a result, MPV in both the patients with MI and control group is greatly affected by autonomic nervous system. We suggest that this increase in MPV and prognostic role of MPV in patients with MI are largely associated with increased sympathetic activity and decreased heart rate variability in these patients.

P486 Effect of autonomic nerves system on the transmural dispersion of ventricular repolarization in intact canine

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Aim: The effect of the autonomic nerves on the transmural dispersion of ventricular repolarization in intact canine was investigated.
Methods: By using the monophasic action potential (MAP) recording technique, monophasic action potentials (MAPs) of the epicardium (Epi), midmyocardium (Mid) and endocardium (Endo) were recorded simultaneously by specially designed plunge-needle electrodes at the left ventricular free wall in 12 open-chest dogs. MAPD90 and transmural dispersion of repolarization among three myocardial layers as well as the incidence of the EAD before autonomicnervous stimulation and during autonomic nervous stimulation were compared.
Results: The results showed that the MAPD90 of Epi, Mid and Endo before autonomic nervous stimulation were 278±11 ms, 316±16 ms and 270±12 ms respectively, the MAPD90 of Mid was significantly longer than that of Epi or Endo (P<0.01). MAPD90 of Epi, Mid and Endo were shortened by 19±4 ms, 45±6 ms, 18±3 ms respectively during sympathetic stimulation. Compared with that of the control, the transmural dispersion of repolarization during sympathetic stimulation was shortened from 44±4 ms to 15±3 ms (P<0.01), but early afterdepolarizations were elicited in the Mid of 5 dogs (41%) during sympathetic stimulation.Parasympathetic stimulation did not significantly affect the MAPD90 in the three layers.
Conclusion: It is concluded that there is the transmural dispersion of ventricular repolarization in intack canine. Sympathetic stimulation can reduce transmural dispersion of repolarization, but it can produce early afterdepolarizations in the Mid. Parasympathetic stimulation dose not significantly affect the transmural dispersion of ventricular repolarization.

P487 Baroreflex response to acute coronary reocclusion in late perfused myocardial infarction

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Background: Subnormal baroreflex sensitivity(BRS) is an important risk indicator for sudden death. The open artery hypothesis that late restoration of antegrade flow in the infarct-related artery(IRA) renders the border zone of the infarction more electrically stable, thereby diminishing the incidence of ventricular tachyarrhythmias and sudden death, does not have definite backgrounds to influence revascularization strategy in post-myocardial infarction(MI) patient.
Objectives: We studied the effect of acute coronary reocclusion on the change of arterial baroreflex function in MI patients with already depressed BRS.
Methods: Forty-three(31 men, 55±11years) consecutive MI patients, who presented late(>24hrs) after MI onset and fixed necrosis on MIBI myocardial perfusion scan, were included. ECG RR intervals and invasive beat to beat systolic blood pressure(SBP) were acquired before and during 3-min coronary occlusions. BRS was determined by conventional phenylephrine method. Heart rate variability(HRV) parameters, including LF, HF power, it's normalized power and LF/HF ratio were also calculated just before phenylephrine injection in each period before and during coronary occlusion.
Results: No significant changes of SBP and HRV parameters, except shortening of RR interval(768±27ms vs 796±27ms of baseline, p=0.043) were observed during the coronary occlusion. The BRS decreased from 5.02±1.00 to 2.67±0.75msxmmHg-1(p=0.010) by coronary occlusion in 32 patients with adequate pressure rise and correlation coefficient of the baroreflex slope after phenylephrine injection. Correlation coefficients of the baroreflex regressions decreased from 0.86±0.02 to 0.76±0.07(p=0.212) during coronary occlusion. Six of 11 patients who showed loss of baroreflex function had negative LV remodelling on follow-up echocardiographic examinations 6±3 months later.
Conclusions: Abrupt coronary reocclusion further deteriorate residual baroreflex function in postMI patients without significant hemodynamic changes. This result support the evidence that patency of IRA should be warranted even in case of late presented MI.

P488 The autonomic dysfunction as reason for recurrence of atrial fibrillation after successful car-dioversion: a twelve-month follow-up of 118 patients

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Background: An autonomic dysfunction characterised due to a neurovegetative imbalance between vagally and adrenergically tone could cause a shortening of the atrial refractory period which could evoke atrial arrhythmias. This stresses the influence of the autonomic nervous system to initiate paroxysmal atrial fibrillation. We want to test the hypothesis that the recurrence of atrial fibrillation can be predicted by an autonomic dysfunction.
Method: We measured the autonomic nervous system by the chemoreflexsensitivity among 118 patients (72m/46w) 24 hours after electrical cardioversion. The measurements were only managed in sinus rhythm. The ratio between the difference of RR intervals in ECG and venous pO2 before and after 10-minutes oxygen inhalation is measured (ms/mm Hg) in order to determine the chemoreflexsensitivity (CHRS). A pathologic CHRS (PCHRS) was defined as a CHRS below 3,0 ms/mm Hg. Each patient was followed up for twelve months at least. The mean follow up was of 16,3 months.
Results: A recurrence of atrial fibrillation was observed in 57 patients (48%) after a mean 25,7 ± 60,6 days (range 2-349 days). A significant difference was not detected in age, heart diseases, sex, ejection fraction, heart rate, use of drugs and energy of cardioversion. Subjects with recurrence of atrial fibrillation had a larger left atrial size (41,9 ± 4,0 vs. 39,3 ± 3,1 mm, $p < 0,0003$) and a significantly lower CHRS (2,66 ± 1,18 vs. 4,01 ± 1,66 ms/mm Hg, $p < 0,0001$). The diagnostic value of the PCHRS for identifying patients with recurrence of atrial fibrillation achieved a specificity of 67%, a sensitivity of 68%, a positive predictive value of 66%, a negative predictive value of 69% and an accuracy of 68%.
Conclusion: The results of our study suggest that a reason for recurrence of atrial fibrillation after electrical cardioversion could be a neurovegetative imbalance which could be detected by an analysis of CHRS. A PCHRS seems to be a risk factor for the recurrence of atrial fibrillation.

P489 Atrial fragmentation and decremental conduction in patients with echocardiographic evidences of increased left ventricular pressure and atrial dilatation but structurally normal heart

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The electroanatomical substrate of dilated atria is characterized by increased non-uniform anisotropy and macroscopic slowing of conduction, promoting reentrant circuits and has not been completely investigated in humans. Aim of the study: to analyze the relation between the modifications of electrophysiologic properties of atria and echocardiograhic markers of dilatation and increased filling pressure.
Method: 78 patients (pts) without structural heart disease, aged 53±22 years referred for electrophysiologic study were analyzed. To examine the atrial electrophysiologic characteristics we studied interatrial conduction time (iaCT), double potentials and fragmented atrial activity during premature stimulation of high right atrium; prior to EPS, all antiarrhythmic drugs were withdrawn for an appropriate period of time. Parameters: the duration of atrial activity, baseline iaCT (iaCTb) between high right atrium (HRA) and distal coronary sinus (CS), iaCT during HRA pacing S1S1 600ms (iaCTS1), maximum prolongation of iaCT during S2 and S3 delivery (iaCTS2, iaCTS3). We calculated the derived parameter: decremental index (DI)= iaCT S3- iaCTS1/iaCTS1%. The following echocardiographic parameters were assessed: left atrial dimensions, surface (LAs), volume using ellipse formula (LAv), right surface (RAs), total atrial surface (TAs=LAs+RAs), global myocardial index (GMI).
Results: pts were divided in two groups: gr 1: 37 pts with evidence of slow atrial conduction (atrial fragmentation/iaCTb>80ms/DI>50%/double atrial potentials) and gr 2: 42 pts without slow conduction properties. There were no significant difference concerning age, body mass index and left atrial parasternal dimension between gr1 and 2. 37 pts (32 pts gr 1) presented documented episodes of paroxistic atrial fribrillation; GMI, LAs, LAv and TAs was significantly higher in gr 1. We founded a statistically significant linear correlation between iaCTb and TAs ($r=0.52$ $p<0.0001$)/LAv ($r=0.50$ $p<0.0001$) There was a trend toward correlation between DI and TAs.
Conclusion: this study supports the role of stretch and dilated atria in electrophysiological changes which occur in structurally normal hearts; iaCT may be indirectly and noninvasive evaluated using echocardiograhic measurements.

P490 Staff exposure in interventional electrophysiology laboratory

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Aim of the study is to evaluate staff doses during different kinds of electrophysiologic procedures.
To this purpose fluoroscopy time and the Dose-Area-Product (DAP) were recorded during insertion of 36 pacemakers (PM) and 18 defibrillators (ICD), 46 radiofrequency (RF) ablation procedures for different arrhythmias performed by two cardiologists. The dose received by the physicians was also measured using thermoluminescent dosimeters (TLD) placed on their left shoulder and left ankle. Measured dose was then converted to effective dose using the algorithm proposed by Niklason. Results are reported in the table.

Procedure	n	SD (μSv)	AD (μSv)	ED (μSv)	DAP (Gy cm^2)	FT (min)
PM	36	9.6±11.1	15.0±11.5	0.3±0.3	3.7±3.0	4.3±3.6
ICD	18	29.0±31.7	62.3±64.2	0.9±1.0	13.4±11.5	10.2±7.9
AV nodal tach.	15	8.1±5.5	4.2±2.3	0.2±1.0	8.0±5.4	11.9±3.7
WPW	10	8.6±10.3	3.7±2.6	0.3±0.3	6.9±7.0	11.6±9.8
Atrial Flutter	21	14.0±13.0	7.4±15.5	0.4±0.4	12.5±7.4	12.3±4.9

n=number of procedures; SD=Mean Shoulder Dose; AD=Mean Ankle Dose; EF=Mean Effective Dose; FT=Mean Fluoroscopy Time

RF catheter ablation for atrial flutter and ICD implantation are associated with higher fluoroscopy times and DAP; beside ICD shows effective doses twofold higher compared with that of ablation for flutter. Moreover in this kind of procedure dose at ankle is very high compared with dose at shoulder. The main cause of this is that the cardiologist must work at the left of patient where no protective screen is available. This is quite true also for implantation of pacemaker, where the cardiologist works at the right of the patient but is only partially shielded by the protective lead screen.
In general, the mean values of times of fluoroscopy, DAP and effective doses are lower compared with the very few published data available. Assuming 800 procedures/year, radiation exposure to the medical staff is well below the upper recommended annual dose limit of 20 mSv.
The estimated low staff doses are explained by the low fluoroscopy time, the proper use of the angiographic equipment (low fluoroscopy mode, spectral filter and 15 pulse/s) and the use of suspended and curtain lead screens together with lead collar and apron.

P491 Comparison of two VF-induction methods during implantable cardioverter-defibrillator implantation: DC fibber vs. shock on T wave

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Aim of the Study: The aim of this study was to evaluate the effectiveness of two VF-induction methods, DC Fibber (9 Volt DC Pulse) and Shock on T wave, during ICD implantation.
Method: A multicenter, randomized and prospective study was conducted from

december 2001 to november 2003. VF induction at ICD implantation was randomly performed either by DC Fibber or Shock on T in a 1:1 ratio. Tests were stopped after two VF-induced episodes. After two failures in inducing VF with the randomized method, the alternative method was used. The primary endpoint (immediate success) was the number of patients with 2 successful VF induction using the randomized method. We also measured the total number of attempts until success of test (two VF episodes induced), time of each induction procedure and VF-induced intervals. 107 patients (88 M, 19 F, mean age 58,4 ± 16 years old, mean LVEF 0,40 ± 0,17), implanted with St Jude Medical ICDs, were included.

Results:

	DC Fibber (55 pts)	Shock on T (52 pts)	p
Immediate success	n = 49 (89%)	n = 29 (56%)	<0.001
Mean number of attemps	2.16 ± 0.6	2.79 ± 0.96	<0.005
Induction time (sec)	3.07 ± 0.57	5.46 ± 0.83	<0.005
VF-induced interval (ms)	197.54 ± 32.89	208.66 ± 33.72	NS

Conclusion: DC Fibber appears to be an efficient method in inducing VF, allowing to reduce the number of needed attempts and to shorten the induction time. This method should improve the patient tolerance during ICD implantation.

P492 Clinical depression and risk of out-of-hospital cardiac arrest? The pro arrhythmia study

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Background: The association of depression with coronary heart disease mortality has been widely recognized. Whether depression also contributes to sudden death risk is however unknown. We thus investigated the relationship between clinical depression and sudden death.

Methods: We conducted a population-based case-control study of risk factors for out-of-hospital cardiac arrest (CA) in a HMO in Western Washington State. Cases (n=2040) of incident out-of-hospital CA, 40-79 years old, were identified via paramedic records and death tapes between 1980-1994. Control subjects (n=3800) were randomly sampled within strata defined by index date, age, gender, and a marker of prevalent heart disease (treatment with digoxin and/or nitroglycerin). A review of the medical records and of the computerized pharmacy database of the enrollees identified physician's diagnosis of depression and/or antidepressants treatment within the year of the index date. The odds ratio (OR) of clinical depression for CA was estimated by conditional logistic regression taking non-clinically depressed as the reference category.

Results: Prevalence of clinical depression (<1y before the index date) was 11.3% in cases and 6.3% in controls (OR: 1.96 (1.62-2.39)). Similar results (OR: 1.55 (1.25-1.93)) were obtained after adjustment for confounders, in both genders and in middle-aged and elderly subjects (cut off 65 y). This greater risk existed in clinically depressed with (1.33 (1.03-1.72)) and without (2.05 (1.37-3.09)) prevalent heart disease (p for interaction=0.32). The risk of CA progressively increased from 1.39 (1.05-1.85) to 2.06 (1.44-2.93) respectively in clinically depressed without and with referral for depression in the past year (p for trend<0.001).

Conclusion: Clinical depression might be associated with an increased risk of CA independently of established coronary heart disease risk factors. These results emphasize the importance of routine depression assessment in clinical settings.

P493 16-slice multi-detector computed tomography for evaluation of stent patency in pulmonary veins of patients with acquired pulmonary vein stenosis following radiofrequency catheter ablation

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Background: Pulmonary vein (PV) stenosis following radiofrequency catheter ablation (RFCA) for curing atrial fibrillation is a serious complication (incidence up to 10%). Percutaneous transluminal balloon angioplasty (PTA) only leads very often to restenosis, so that more often stent implantation within the pulmonary vein is done. We investigated the 16-slice multi-detector CT as a diagnostic tool for follow-up in patients after stent implantation.

Methods: 10 patients with MR proven high grade PV stenosis (MLD 2.9±2.1) in 13 PV after RFCA underwent PTA with stent implantation (Cordis, mean diameter 9.3±0.9 mm, mean length 21.7±3.6 mm). A PV angiography was done using 16-slice CT (Siemens Sensation Cardiac) and intravenous bolus injection of 1 mL/kg BW Imeron 400 (Altana Pharma). Image acqusition was ECG-pulsed. Using multiplanar reconstruction, PV and implanted stent was measured. Additionally, pulmonary perfusion was analysed by dynamic magnetic resonance imaging (Siemens Sonata, 1.5 T; 20 mL Gd-DTPA i.v.; 3D-FLASH sequence).

Results: All examinations were free of complications. All stents were fully expanded. The lumen was evaluable in all stents. One day after implantation mean minimal lumen diameter was 7.9±0.74 mm, after one month 7.5±0.77 mm (p=n.s.). Two stents were exceeding the border of the PV ostium by 2-3 mm towards the left atrium and 5 stents were partially occluding a side branch confluence. There were no diameter reductions >10% detected at any time. By dynamic MR perfusion analysis of the lungs, one day after implantation a partial recovering and one month after implantation a nearly complete recovering of lung perfusion was observed.

Conclusion: 16-slice multi-detector computed tomography is an accurate imaging modality for morphological evaluation of PV and implanted stents after PTA. In follow-up exams there was no diameter reduction >10% detected.

Additional functional and clinically important information can be provided by dynamic MR analysis of lung perfusion which should be used in combination with CT in patients after PV stent implantation.

P494 Austrias nationwide public access defibrillation programme

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Introduction: Significant improvement of survival and neurological outcome has been reported in several public access defibrillation (PAD) projects. Well selected areas such as airports, casinos, cricket grounds and airplanes were studied. A nation wide non-governmental initiative implementing as many as possible public accessible automated external defibrillators (AED) has not been evaluated yet.

Methods: In November 01 the Austrian Red Cross launched a PAD programme called "Strom für's Leben". The Austrian public was informed by a media campaign covering TV, radio and newspapers. Since July 02 an all inclusive package is offered to companies, governmental institutions, public transport enterprises, medical doctors and private individuals. Each package includes an AED, basic life support (BLS) training and coaching for implementation in the particular setting according to existing evidence. Five year manufacturer guarantee, maintenance and annual retraining are provided for the purchasing companies. After AED operation single use items are refilled for free. The programme includes scientific evaluation of data recorded according to Utstein Style.

Results: The media campaign reached up to 78% of Austria's inhabitants. From Dec 2001 until Dec 2003 the Austrian Red Cross implemented 1352 defibrillators all over Austria and 37 incidences where reported. In 15 cases shock was necessary but advised by the AED in 14 arrests only. In presence of non shockable ECG-rhythms no shock was indicated correctly in 16 cases, six times no cardiac rhythm was recorded. Mean time from emergency call to first AED shock was 5.54 ± 2.77 minutes vs. 10.88 ± 2.85 (p=0,0039) minutes until EMS arrival, as first time point of possible AED shock by professional helpers. Nine patients (60%) with shockable rhythms left the hospital in good neurological condition, one (6,6%) survived with severe neurological deficit.

Conclusions: A media campaign seems suitable to inform the broad public about a PAD programme. The provided all inclusive package was well accepted. A significant reduction of "Call-to-shock-time" was observed resulting in improved survival and neurological outcome. Further research is necessary to clarify cost-effectiveness.

P495 Electrophysiologic characteristics of ventricular tachyarrhythmias arising from the muscle sleeves at the pulmonary artery and results of radiofrequency ablation above the pulmonic valve

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Background: Ventricular tachycardia and premature ventricular complex (VT/PVC) may originate above the pulmonic valve (PV), and can be eliminated by RF ablation in the root of pulmonary artery (PA). However, the electrophysiologic (EP) properties of the muscle sleeves of the PA have not been described.

Methods: To evaluate the EP properties and patterns of electrograms (EG) in the PA, 11 consecutive pts (37±10 y-o, 6 women) with left-bundle branch (LBB) morphology and inferior axis VT/PVC were evaluated. Two quadripolar catheters were inserted into the PA and RVOT. RV angiography (RAO view) was performed to identify the most distal location where EG were seen during sinus rhythm. Decremental, rapid, and programmed stimulation was performed into the PA to assess the effective refractory period and the characteristics of conduction from PA to RV. Pace mapping and the shortest endocardial activation time during VT/PVC were used to identify the optimum ablation target site and RF energy was set at 50°C, 60 sec to 50W. Echocardiogram was performed in the second day after ablation.

Results: EG was present in 8 (73%) pts (1.9±1.7 mm above the PA), and it was possible to capture the local muscle sleeve with conduction to RV in 7 (64%) of them (mean threshold – Sleeve: 5.0 mV vs. RV: 1.8 mV, p<0.05). Two patterns of EG were observed: sharp potential in 3 and fractioned potential in 4. In four pts the optimal ablation site was identified into the PA, where EG onset of -22 to -32 ms ahead of the QRS were observed. EG with coduction to RV were seen in 4 (100%) pts with PA foci vs. 3 (43%) with RVOT foci (p<0.05). Conduction time from PA to RV was variable during stimulation with the same cycle length, ranging from 27 to 77 mm. Decremental conduction was observed in 5 pts (3 with PA foci).

Effective refractory period of the PA was 352±78 ms and did not differ between pts with and without PA foci. No complications were observed during procedure and follow-up.
Conclusion: 1. Myocardial sleeves in the PA are seen in most pts with LBB morphology and inferior axis ventricular arrhythmias, a pattern that strongly suggests RVOT focus; 2. In some patients, these sleeves give rise to the arrhythmia and may be eliminated by RF energy.

P496 Cardiac resynchronisation therapy allows medical therapy optimization in patients with advanced congestive heart failure. Results of the InSync/InSyncICD Italian Registry

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Background: Neurohormonal modulating therapy is the most common medical therapy in congestive heart failure (CHF) pts, but those with advanced disease often do not tolerate these drugs at effective doses. Cardiac resynchronization therapy (CRT) by biventricular pacing has been proposed as an adjunct to medical therapy to improve cardiac function, hemodynamics and symptoms in pts with advanced CHF and inter-intraventricular conduction delay.
Objective: To verify whether medical therapy optimization is possible after CRT in advanced CHF pts already on maximal tolerated doses before the procedure.
Methods: Medical therapy before and after CRT was compared in 517 pts with at least six mos follow-up (FU) enrolled into InSync/InSyncIII/InSync ICD Italian registry (mean FU 12.9 ± 7.7 mos). Mean age was 66.7 ± 9.7 years, 97 were females (18.8%), etiology was idiopathic in 186 (36.0%), ischemic in 233 (45.1%), valvular in 35 (6.8%), ipertensive in 28 (5.4%), other in 45 (8.7%). Baseline NYHA class was 3.0 ± 0.6, QRS duration 167.5 ± 29.3 msec, echo LVEF 35.1 ± 18.6%, LVEDD 69.2 ± 9.1 mm. At baseline, pts were on full medical therapy: 383 (74.1%) were on ACE-inhibitors (average dose of enalapril: 18.7 ± 12.8 mg/die); 241 (46.6%) were on b-blockers (average dose of carvedilol 15.4 ± 11.8 mg/die); 475 (91.9%) were on diuretics (average dose of furosemide 107.9 ± 143.4 mg/die).
Results: After CRT, the percentage of pts on ACE-inhibitors did not change (74.1% vs 70.8%, p= 0.08), and the average doses of these drugs remained similar. On the contrary, pts on b-blockers significantly increased (46.6% vs 57.3%, $p<0.001$) compared to baseline and the average carvedilol daily dose increased significantly (15.4 ± 11.8 vs. 21.7 ± 16.3 mg, $p<0.00001$). Moreover, pts on diuretic therapy did not change (91.9% vs 91.5%, p=0.73), but the average of furosemide daily dose decreased significantly (107.9 ± 143.4 vs 87.2 ± 112.8 $p<0.05$).
Conclusions: In a population of patients with advanced CHF on maximal medical management, CRT contributes to further therapy optimization. The reduction of furosemide daily dosage was probably the result of improved HF. The increase of patients on beta-blockers and of carvedilol daily dosage taken by the patients, as well as the decrease of furosemide daily dosage, may have favourable prognostic implications.

P497 Increased resting heart rate with pollutants in a low polluted environment

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Background: Epidemiological studies have shown that air pollution is associated with increased cardiovascular mortality. The mechanisms involved in the increase of mortality are far from being understood. We investigated the relationships between air pollutant concentrations of SO2, O3 and NO2 and resting heart rate (RHR) in a cross-sectional population based-study.
Methods: A cross-sectional survey on cardiovascular risk factors was carried out in 1995-1997 by the Toulouse MONICA Centre. A sample of 863 middle-aged men and women (35 to 64 years), living in Toulouse (South-Western France) area, was randomly recruited. RHR was measured twice in a sitting position after a five-minute rest. Gas pollutant concentrations were measured hourly as part of the automated Midi-Pyrenees air quality network. Multivariate analyses with quintiles of RHR were performed using polytomous logistic regression, to test the association between each daily mean air pollutant concentration and RHR. A multiple adjustment for age, sex, season, meteorology and conventional risk factors was performed.
Results: After adjustment, the OR [95% CI] associated with an increase of 5 $\mu g/m^3$ in the concurrent daily mean concentration of NO2 was 1.12 [1.01-1.26] in quintile (Q) 5 of RHR (vs Q1), p for trend <0.05. Similarly, the relationship between the concentration of SO2 pollutant and the RHR was statistically significant (OR: 1.26 [1.02-1.49] in Q5 vs Q1, p for trend <0.01). No significant association was observed when we considered the daily mean concentration of NO2 or SO2 pollutants during the previous day as well as when we considered day lag 2 or 3 or cumulative concentrations.
Conclusions: We showed that RHR increases with air pollution concentration among an apparently healthy population in a metropolitan area characterised by a low level of air pollution. Alterations in pulse rate could reflect cardiac rhythm changes and may be part of the pathophysiological link between pollution and cardiovascular mortality.

P498 Comparison between two antitachycardia pacing therapies (Ramp vs Burst+) for the treatment of atrial tachyarrhythmias in patients paced for bradycardia. Preliminary results of PITAGORA study

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Background: In patients suffering from brady-tachy form of sinus node disease (BT-SND) very often atrial fibrillation and more regular atrial tachyarrhythmias (AT) coexist.
Aim: Aim of the PITAGORA prospective, randomized, multicentre study was to evaluate the impact of pharmacological agents and antitachycardia pacing therapies (ATP) in the treatment of AT episodes in BT-SND paced patients.
Methods: We enrolled 163 patients (65 M, mean age 71±9 years), implanted with a dual chamber DDDRP pacemaker (Medtronic AT500O). At implant, pharmacological therapy was randomized between IC class and III class agents. After an observational period of 5 months after implant, ATP therapies were enabled, selecting Ramp or Burst+ in a randomized way, maintained for 4 months and then crossed over.
Results: In a mean follow up of 13 months, 81 patients suffered 3816 AT episodes, with a median number of 35 episodes per patient. In 44 patients, 893 AT episodes were treated and 492 (55.1%) terminated. Burst+ terminated 187 out of 375 AT episodes (49.9%) in 32 patients. Ramp terminated 305 out of 518 AT episodes (58.9%) in 34 patients (p=0.008 vs Burst+). 22 patients suffered AT episodes in both cross over periods and allowed a paired comparison of ATP therapies efficacy: 124 episodes out of 236 (52.5%) were terminated by Burst+, while 230 episodes out of 359 (64.1%) were terminated by Ramp ($p<0.005$ vs Burst+). In 13 patients who had at least 6 episodes treated by both therapies, mean ATP efficacy per patient was 45.1 for Burst+ and 59.2% for Ramp (p=0.29).
Conclusions: These preliminary results show that, in BT-SND patients enrolled in PITAGORA trial, ATP therapies were able to terminate approximately half of treated episodes. In particular Ramp therapies were significantly more effective than Burst + therapies.

HEART FAILURE: CLINICAL ASPECTS

P499 Emergency diagnosis of congestive heart failure: impact of patient history and physical examination

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Background: The patient history and physical examination remain fundamental for the diagnosis of congestive heart failure (CHF). Unfortunately, little is known about the diagnostic impact of symptoms and signs in patients presenting with acute dyspnea.
Methods: Symptoms and signs of 452 consecutive patients presenting with acute dyspnea were recorded in the emergency department by the physician in charge. Using logistic regression analysis, significant predictors for the final discharge diagnosis of CHF were assessed.
Results: In 217/452 patients (48%), CHF was found to be the cause of acute dyspnea. Among symptoms, the odds ratios for CHF were highest for weight gain (3.6; 95% CI, 1.9-7.0), nycturia (2.4; 95% CI, 1.6-3.7), and paroxysmal nocturnal dyspnea (2.4; 95% CI, 1.6-3.5), and lowest for fever (0.36; 95% CI, 0.22-0.56). Among signs, the odds ratio was highest for elevated jugular venous pressure (4.3; 95% CI, 2.3-7.9), rales (3.1; 95% CI, 2.1-4.5), lower-extremity edema (2.8; 95% CI, 1.9-4.3), and hepatojugular reflux (2.7; 95% CI, 1.4-5.2), and lowest for wheezing (0.38; 95% CI, 0.24-0.61). Sensitivity was highest for rales (60%), specificity was highest for elevated jugular venous pressure (77%).
Conclusion: This study quantifies the diagnostic impact of common symptoms and signs for the diagnosis of CHF in patients with acute dyspnea. Emphasis on the symptoms and signs that differentiate the best between CHF and other causes of acute dyspnea may increase the yield of patient history and physical examination.

P500 Internal thoracic impedance monitoring: a new prospect in acute heart failure

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There is no sensitive and reliable method for diagnosing the preclinical stage of acute heart failure (AHF) in patients with AMI. Monitoring of lung bioimpedance may be useful but existing monitors are not sensitive. We used a novel monitor, more sensitive than previous devices since it specifically measures the internal thoracic impedance (ITI). As the fluid content of the lung increases measured ITI decreases.

317 patients (226 man and 91 women, mean age 62.9 years) with AMI and no signs of AHF on admission were studied. Of these, 42 patients (13%) developed AHF (Group 1) and the other remained without AHF throughout monitoring (Group 2). AHF was classified as mild (rales at lung bases), moderate (crepitations up to mid lungs) and severe (acute pulmonary edema). All Group 1 patients (n=42) developed mild AHF, 34 (81%) progressed to moderate stage and only 24 (57%) advanced to full acute pulmonary edema. Group2 patients did not manifest any signs of AHF and ITI decrease in this group was 4.8±2.8% (NS) from initial value (range from 0 to 11%). In contrast, all patients in group 1 demonstrated an ITI decrease ≥ 12% (range -12 to -53.3%). ITI in patients with mild AHF decreased from initial value of 61.2±9.9 Ohms to 47.9±7.8 Ohms ($p<0.05$), a decrease of 21.7±3.8% (-12.9 to -28.9%). In patients with moderate AHF, ITI further decreased to 44.8±7.7 Ohms, (-26.8±5.5%, $p<0.05$) (range, -19.5 to -37.9%). Patients that developed full pulmonary edema had ITI of 41±7.1Ohms, or a -34.6±7.5% decrease (-25.7 to -53.3%, $p<0.05$). All patients in whom ITI decreased ≥12% developed some degree of AHF. Therefore, an ITI decrease of 12% was taken as AHF threshold. The time interval from reaching threshold level to first signs AHF was 44.5±10.5 min (30 to 60 min).

Based on this experience we attempted for the first time to treat patients with AMI and ITI decrease ≥12% in the absence of AHF with IV furosemide. Therapy was initiated in 8 patients at ITI decrease of 12.9±0.83% (12-14%). Seven patients did not develop AHF or further ITI decrease within 12-24h monitoring. Only 1 patient developed mild AHF and additional ITI decrease of 2.2%. Clinical signs disappeared after 45' in parallel with ITI increase.

Conclusions: The extent of decrease in lung impedance correlated with AHF stage. This novel impedance monitor enables the diagnosis of AHF in its preclinical stage and at least 30 minutes before the appearance of first clinical signs. Our first preliminary experience with therapy initiation at the preclinical stage shows promise.

P501 A portable ultrasound for rapid evaluation of systolic ventricular function in critically Ill patients

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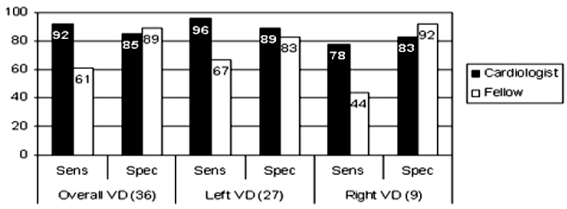
Purpose: Immediate, repetitive assessment of ventricular function in critically ill patients is frequently required. The feasibility of echocardiography (StdEcho) is limited by the cumbersome equipment and the need for expert personnel. The hand-carried cardiac ultrasound (HCU) is a portable, personal device that is precise for detection of ventricular systolic dysfunction (VD) in non-critical patients. However, its reliability is unknown in the enviroment of critical care units. We evaluated the accuracy of cardiology fellows and cardiologists in identifying VD in severely ill patients using a HCU device.

Methods: Forty-five mechanically ventilated patients (53% women), age 61 ± 23 yrs, had a HCU study (OptiGo®) performed by cardiology fellows and cardiologists with echocardiographic experience. VD was defined as an ejection fraction < 50%. Diagnostic accuracy was validated with StdEcho interpreted by echocardiographers unaware of the HCU results.

Results: StdEcho identified 27/45 (60%) patients with left VD, and 9/45 (20%) with right VD. Mean duration of HCU study was 5 ± 2 min for both cardiologists and fellows. Cardiologist HCU image quality was satisfactory in all the cases; however, fellows were unable to evaluate ventricular function in 7% of the cases due to poor HCU imaging. Cardiologists were superior to fellows in identifying left VD and right VD as shown in the figure.



Conclusions: In critically ill patients, HCU operated by experienced personnel can accurately identify left ventricular systolic dysfunction; however, the assessment of right ventricular function is sub optimal. In the difficult environment of critical care units, operator expertise has major impact on the HCU results.

P502 The degre of cardiac troponin T elevation is predictive of poor prognosis in decompensated heart failure

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Purpose: Previous studies have demonstrated that cardiac troponins are useful predictors in advanced heart failure (HF). We sought to investigate if the degree of cardiac troponin T (cTnT) elevation may provide aditional prognostic information in decompensated HF during one-year of follow-up.

Methods: The study cohort consisted of 70 hospitalized patients (pts) with decompensated chronic HF (age: 21 - 80 yrs., LVEF: 31.3±8,4%, male: 68.6%, ischemic: 25.7%, NYHA class IV: 84.3%). Exclusion criteria were: infection, acute arrhythmia, uncontrolled hypertension, recent history (<30 days) of cardiac or non-cardiac surgery, unstable angina or myocardial infarction. cTnT was measured within 4 days of hospital admission. The association of cardiac troponin T levels and one-year mortality was performed through Cox regression analysis and Kaplan-Meier survival method.

Results: The mortality rate at one-year after the episode of HF decompensation was 62.9% (n = 44). A level of cTnT >0.020 ng/ml, identified through the ROC curve, was associated with an increased mortality rate compared with those with cTnT ≤0.020 ng/ml (77.3% vs. 53.9%, p = 0.041). Based on the degree of cTnT elevation, HF patients were stratified in three subgroups: Low (cTnT ≤0.020 ng/ml, n = 22), Intermediate (cTnT >0.020 and <0.100 ng/ml, n = 36) and High-cTnT (cTnT ≥0.100 ng/ml, n =12). The survival probability in the Low, Intermediate and High-cTnT levels were 54.2%, 31.5% and 16.7% (p = 0.020), respectively. In the multivariate Cox regression analysis the only independent predictors of one-year mortality were High-cTnT [hazard ratio (HR) = 3.6, p = 0.004] and mean blood pressure at hospital admission ≤90 mmHg (HR = 2.6, p = 0.006).

Conclusion: The elevation of cTnT levels is associated with poor prognosis in decompensated HF and the degree of this elevation may be used for risk-stratification of these patients.

P503 Acute pulmonary edema with hypertension: systolic or diastolic dysfunction?

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Background: Patients (pts) hospitalized with heart failure may later be noted to have normal systolic function,as evidenced by a normal left ventricular ejection fraction (EF) at echocardiographic examination. In this situation,the heart failure has been presumed to be due to isolated diastolic dysfunction. Pts with acute pulmonary edema (APE) often have marked systolic hypertension but,after reduction of the blood pressure (BP),have a normal EF (>50%). However,the EF is usually evaluated after the patient's clinical status has resolved. Thus,it is possible that APE was not the result of diastolic dysfunction but,instead, was due to transient systolic dysfunction,acute mitral regurgitation (MR) or both.

Aim: To test the hypothesis that many pts with APE in association with hypertension have diastolic dysfunction.

Methods: We studied 48 pts (28 men; mean age 66±14 years)with APE(acute onset of dyspnea,respiratory distress and pulmonary rales due to pulmonary congestion,as confirmed by chest radiography)and a systolic BP >160 mmHg. Echocardiographic examination was performed in each patient as therapy was being initiated; a second echocardiogram was obtained after 24-48 hours after clinical stabilization had occurred,so that the patient was normotensive and pulmonary congestion resolved. We evaluated the EF (Simpson),the presence and the severity of any MR and the wall motion score index (WMSI; 16-segment model).

Results: The mean systolic BP was 197±28 mmHg during the initial echocardiographic examination and was reduced to 135±18 mmHg ($p< 0.05$) at the time of follow up examination. The EF was similar during the acute episode (52±16%) and after treatment (51±15%). The EF after treatment correlated directly with the EF during the acute episode ($r=0.85$; $p< 0.01$).The WMSI was also the same during the acute episode (1.5±0.4) and after treatment(1.5±0.5). The WMSI at follow up correlated directly with the index at presentation ($r=0.95$; $p< 0.01$). No patient had severe MR during the acute episode. 26 pts (54.1%)had a normal EF (>50%) after treatment.In 23(88.4%)of these 26 patients the EF was >50% during the acute episode.

Conclusions: In pts with hypertensive APE,the EF during the acute episode is similar to that measured after treatment, when the BP has been controlled and pulmonary congestion resolved. A normal EF after the treatment of a patient with hypertensive APE indicates a high probability than pulmonary congestion was due to isolated,transient diastolic dysfunction,since transient systolic dysfunction and/or severe MR are infrequent during acute episodes in these pts.

P504 Pharmacokinetics of Levosimendan and its metabolites: results for infusion of a 0.2 μg/kg/min dose over 6-hours and a 0.1 μg/kg/min dose over 24 hours

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Background: Levosimendan (LEVO) is a novel agent for the treatment of acute heart failure (HF). LEVO acts via calcium-dependent binding of the drug to cardiac troponin C resulting in a positive inotropic response and via activation of ATP-dependent potassium channels in vascular smooth muscles causing vasodilation. In acutely decompensated HF patients, LEVO infusions result in clinically significant reductions in filling pressures and increases in cardiac output. The active LEVO metabolite, OR-1896, has a prolonged pharmacological half-life (>70 hrs) providing potential for sustained hemodynamic effect of short-term LEVO infusions. The study objective was to define the pharmacokinetic profile of the parent drug LEVO and its metabolites (OR 1855 and OR 1896) over 10 ± 1 days, after a 6-hour infusion (0.2 mcg/kg/min) or 24-hour infusion (0.1 mcg/kg/min) in CHF subjects.
Methods: We conducted a double-blind, placebo controlled trial in 42 subjects (male = 88%, NYHA III/IV, LVEF <35%, mean age: 60 ± 12 yrs) randomized to receive IV infusion of either 1) 24 hrs placebo (n = 11) or 2) LEVO 0.2 mcg/kg/min for 6 hrs then placebo for 18 hrs (n = 17) or 3) LEVO 0.1 mcg/kg/min for 24 hrs (n = 14). Pharmacokinetic parameters of LEVO and its metabolites included maximum observed plasma concentration (Cmax), time of Cmax (peak time, Tmax), and the area under the plasma concentration-time curve (AUC). AUCt ratio between OR-1896 and OR-1855 was used to classify slow vs. rapid acetylators.
Results: Mean Cmax of the 0.2 mcg/kg/min infusion was ~2 times that of the 0.1 mcg/kg/min dose; AUCt of the 0.2 mcg/kg/min-6 hour infusion was approximately half that of the 0.1 mcg/kg/min-24 hour infusion. Tmax for OR-1855 averaged approximately 70-80 hours and OR-1896 reached Cmax about 8-9 hours later than OR-1855. The mean apparent elimination half-lives for OR-1855 and OR-1896 were very similar; (~70-90 hrs). For both metabolites, the 6-hour infusion yielded lower Cmax and AUCt than 24-hour infusion. Cmax, AUCt and AUCinf of OR-1896 were markedly higher in rapid acetylators than in slow acetylators in both active treatment arms. Cmax, AUCt and AUCinf of OR-1855 were practically similar between slow and rapid acetylators. Differences in the metabolite pharmacokinetics for slow and rapid acetylators were not correlated with pharmacodynamic results.
Conclusions: In CHF patients (NYHA Class III/IV), LEVO pharmacokinetics are characterized by rapid distribution and elimination, while the pharmacokinetics of its metabolites are characterized by long Tmax and long elimination half-lives.

P505 Efficacy of carperitide, a recombinant human atrial natriuretic peptide, alone therapy in patients with acutely decompensated congestive heart failure

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Recently, it has been reported that treatment of acutely decompensated congestive heart failure (AD-CHF) with nesiritide, a recombinant human brain natriuretic peptide, improves hemodynamic function and symptoms more effectively than nitroglycerin. Furthermore, it is suggested that nesiritide in patients with AD-CHF may be associated with improved long-term survival compared to dobutamine. However, there are few data to guide the choice of vasodilator versus inotropic therapy for patients with AD-CHF. Therefore, we evaluated the efficacy of carperitide, a recombinant human atrial natriuretic peptide, alone therapy in patients with AD-CHF due to an impaired left ventricular ejection fraction (LVEF<40%) and then compared hemodynamic parameters between good-responders and poor-responders to carperitide alone therapy.
Methods: Thirty consecutive patients (mean LVEF=27%) with AD-CHF (NYHA IV) were enrolled. Inclusion criteria included LVEF <40%, systolic blood pressure (S-BP) >100mmHg, and an initial pulmonary-capillary wedge pressure (PCW-P) >16 mmHg. Hemodynamic parameters (central venous pressure; CVP, PCW-P, cardiac index; CI, systemic vascular resistance; SVR, and pulmonary vascular resistance; PVR) by right-heart catheterization and plasma BNP were evaluated before and after the administration of carperitide alone (0.025 to 0.075 ug/kg/min).
Results: Of 30 patients, 21 patients (70%) showed effective for carperitide alone (Good-Responders) and the remaining 9 patients (30%) showed ineffective (Poor-Responders). There was no significant difference in LVEF, PCWP, SVR and PVR at baseline between Good-Responders and Poor-Responders. However, both S-BP and CI at baseline in Poor-Responders were significantly lower than those in Good-Responders (108 vs.143mmHg, $p<0.01$ and 1.8 vs.2.4L/min/m^2, $p<0.05$, respectively). Furthermore, both CVP and plasma BNP at baseline in Poor-Responders were significantly higher than those in Good-Responders (16 vs.10mmHg, $p<0.05$ and 547 vs.1314pg/ml, $p<0.05$, respectively). Of 21 patients with S-BP >120mmHg at baseline, carperitide alone therapy was effective in 19 patients (90%). Moreover, among 14 patients with both S-BP >120mmHg and CVP <12 mmHg at baseline, carperitide alone therapy was effective in all 14 patients (100%).
Conclusions: In patients with AD-CHF, carperitide alone therapy is effective for patients with S-BP>120 mmHg and CVP<12mmHg at baseline. Therefore, these data could illustrate a potential importance of both S-BP and CVP for the prediction of efficacy of carperitide alone in patients with AD-CHF.

P506 Positive inotropic therapy decreases vascular endothelial growth factor in patients with low output syndrome

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Background: Vascular endothelial growth factor (VEGF) is overexpressed in patients with congestive heart failure (CHF). The aim of our study was to investigate the short term effects of positive inotropic therapy on hemodynamics and VEGF plasma levels in patients with low output syndrome.
Methods: 19 Patients (EF = 22±3%) were treated with levosimendan (n=13), milrinone (n=5) or dobutamine (n=3) for 24h. Hemodynamics were obtained with a balloon-tipped pulmonary artery catheter before and 30min, 1h, 6h, 12h, 24h after starting therapy. Blood was collected at baseline and after 24h, VEGF plasma levels were measured using an enzyme linked immunosorbent assay.
Results: Effects of inotropic therapy on hemodynamics and VEGF are shown in the table. The decrease in VEGF was most pronounced in patients with high baseline levels (> median value of 220pg/ml; $p<0.01$) while no change was seen in patients with initialy low levels. Whereas baseline VEGF levels were not different between ischemic and non-ischemic CHF, a significant decrease was seen in ischemic CHF (from 330.5±78.5 to 242.4±62.6 pg/ml; $p<0.05$). The same phenomenon was true in patients with de novo CHF (from 378.5±148.6 to 246.1±103.3 pg/ml; $p<0.05$) compared to those who deteriorated from chronic CHF (p=NS). As to hemodynamics, the decrease in VEGF was only significant (from 373.4±113.3 to 298.7±88.4 pg/ml; $p<0.05$) in patients responding to therapy (CO increase > 20%) which was paralelled by an increase in SvO2 (from 58.9±1.4 to 67.4±1.4%; $p<0.001$).

Hemodynamics and VEGF

	baseline	24h	p-value
mPAP mmHg	34.0	28.8	<0.01
PCWP mmHg	24.1	18.5	<0.001
CO l/min	3.3	4.6	<0.001
SvO2%	57.7	65.7	<0.001
VEGF pg/ml	340.3	264.1	<0.01

mean pulmonary arterial pressure, mPAP pulmonary capillary wedge pressure, PCWPcardiac output, COmixed venous oxygen saturation, SvO2

Conclusion: VEGF plasma levels are reduced by positive inotropic therapy in patients with low output syndrome. The decrease was most pronounced in patients with high VEGF levels, ischemic cardiomyopathy, acute heart failure and in hemodynamic responders. Conceivably, improved tissue oxygenation may explain this effect.

P507 Randomized comparison of intraaortic balloon support versus a percutaneous left ventricular assist device in patients with acute myocardial infarction complicated by cardiogenic shock

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Background: Mortality in cardiogenic shock following acute myocardial infarction (AMI) remains at an unacceptable level despite interventional treatment of the underlying cause and use of intraaortic balloon counterpulsation. Frequently patients succumb to low output before the myocardium is able to recover from the ischemic event. A newly developed percutaneous left ventricular assist device (VAD) (Tandem Heart, Cardiac Assist Inc., Pittsburgh, Pennsylvania, USA) with active circulatory support might decrease mortality.
Methods and results: Patients in cardiogenic shock after an AMI, with intended revascularization of the infarct related artery, were randomized to either IABP (n=20) or percutaneous VAD support (n=21). Predicted mortality probability was similar in both groups (68% vs. 75%, p=n.s.). By VAD support hemodynamic and metabolic parameters could be reversed more effectively in comparison to IABP treatment. However, complications as bleeding requiring transfusion of blood components (n=19 vs. n=8, p=0.005), limb ischemia (n=7 vs. n=0, p=0.007), or elevated temperature >38.5° C (n=16 vs. n=10, p=0.04) were encountered more frequently after VAD support. 30-day-mortality was similar (IABP 45% vs. VAD 42%, log-rank, p=0.86).
Conclusions: By a newly developed VAD hemodynamic and metabolic parameters can be reversed more effectively as by standard treatment. However, so far there is no mortality benefit, which may be accounted to more complications encountered by the highly invasive procedure and the extracorporeal support.

P508 Percutaneous transthoracic left ventricular aortic bypass: animal experimental study

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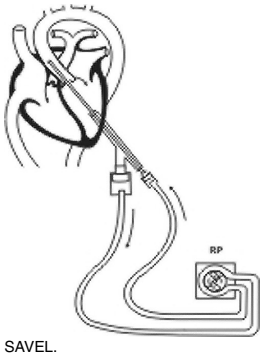
A new strategy was designed for a rapid installation of left ventricular-aortic (LV-AO) bypass.
Aim: To develop a simple and inexpensive system for emergency replacement of native LV pump function.
Methods: Percutaneous access via direct transthoracic LV puncture was used to create singled LV entry site in 10 pigs (40 kg) under general anesthesia. The Singled Aorto-Ventricular Line (SAVEL) consists of the 30Fr outer (LV) - and a 14Fr inner (AO) cannula. Both cannulas with dilators were introduced as a unit by Seldinger technique under fluoroscopy- or Echo-guidance. The proximal hub of the outer cannula is branched into a straight- and a sidearm. The inner (AO) cannula was passed through the straight arm while the sidearm was used for LV drainage. Proximal ends of cannulas were connected over the tubing loop via the roller pump (figure).
After partial heparinization, cardio circulatory arrest was induced by cardioplegia or fibrillation and the SAVEL pump system was applied.
Results: The time needed to institute the bypass varied between 1 and 5 min. Circulation with a flow rate of 2-3.5 liters/min could be maintained for 2-4 hours in 7 out of 10 attempts. Except for small pericardial effusion in 2 pigs, no bleeding was observed. While the large bore cannulas were in place no haemostatic measures appeared necessary to secure the LV entry site. The LV puncture site was closed with an Ivalon plug occluder in 2 pigs subsequently.
Conclusions: Singled Aorto Ventricular Line with a roller pump applied via percutaneous transthoracic route provides a rapid and effective circulatory support in terminal arrest.



SAVEL.

P509 Pre-admission and 4 week mortality in patients with acute decompensated heart failure: the EFICA study

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Background and objectives: Among patients admitted with the general diagnosis of heart failure (HF), those presenting to the emergency department with acute decompensated HF (ADHF) have life threatening symptoms and high mortality rate. Epidemiological studies so far enrolled patients admitted either to general or cardiology wards or to cardiac intensive care units (ICU) with almost exclusively ischemic ADHF. No study accounted for deaths occurring prior to admission. EFICA (Epidémiologie Francaise de l'Insuffisance Cardiaque Aiguë), is a prospective observational study of consecutive unselected patients admitted to 60 representative cardiac or general ICUs in France with ADHF. In order to estimate the total death rate attributable to the disease data on all patients who died during transportation or upon a visit to the emergency department (ED) with the diagnosis of ADHF was collected.
Methods: Enrolled patients were hospitalized with signs and/or symptoms compatible with the diagnosis of ADHF. Short term mortality was assessed 28 days after admission. Among the 60 participating hospitals, 34 agreed to collect data on all patients who died during transportation or upon a visit to the ED with the diagnosis of ADHF.
Results: Among the 599 patients admitted alive, ADHF diagnosis was confirmed in 581 patients. They were aged 73 [25-98], 59% were men, 66% had a history of CHF and 41% history of ischemic heart disease. Main etiologic factors were myocardial ischaemia (59%), valvular disease (21%), hypertrophic or hypertensive cardiopathy (13%). Characteristics of the 34 centers participating to the registry were comparable to characteristics of all 60 participating centers. Patients who died before admission were older (77 ±13 y) than patients admitted alive, but had similar gender and ADHF etiology distributions. In patients admitted alive, 4-week mortality was 28%. Including pre-admission deaths, calculated total 4-week mortality was 41%.
Conclusion: Mortality in ADHF patients who needed admission to cardiac or general ICUs is indeed much higher than reported so far. Actually, considering patients who died before they could be admitted, total mortality was dramatically higher (41%). Our results emphasize the need for developing new therapies and guidelines for the management of patients with ADHF starting at the pre-admission phase.

P510 Prevalence and characteristics of heart failure with preserved systolic left-ventricular function in the real world: results of the Israel 2003 national heart failure survey

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Background: Left ventricular (LV) systolic function may be preserved in pts with clinical heart failure (HF) and HF is then due to predominantly diastolic dysfunction. We undertook a nationwide survey to examine the prevalence and characteristics of pts hospitalized for heart failure with preserved LV systolic function.
Methods: We conducted a prospective 2 month national survey of 4102 consecutive HF patients admitted to 93/98 internal medicine and 24/25 cardiology departments in all 25 public hospitals in Israel. Echocardiographic LV function measurements were available in 1427/2046 pts in whom HF was the primary diagnosis and reason for admission. Preserved LV systolic function was defined as an LV ejection fraction (EF)>40%.
Results: Pts with HF and preserved LV function were older, more often female, more were obese and most had systemic hypertension (Table). LV dimensions were smaller (LVED 43±16 vs 51±20 mm, p<0.0001) and EF higher (52±19 vs 27±7%, p<0.0001) in pts with preserved LV. Heart rate on admission was lower (85±20 vs 88±21 bpm, p=0.01) and systolic blood pressure higher (155±34 vs 138±31 mmHg, p<0.0001). Drug therapy of preserved LV pts included a lesser usage of digoxin, diuretics, ACE-inhibitors, beta blockers and greater use of calcium antagonists (all p<0.05). Hospital mortality was slightly lower (3.7% vs 5.1%, NS).

Patient data

	Reduced systolic LV function	Preserved systolic LV function	p value
N	758 (53%)	669 (47%)	
Age (yrs)	72±12	75±11	<0.0001
Female gender	242 (32%)	412 (62%)	<0.0001
Systemic hypertension	489 (65%)	525 (79%)	<0.0001
Diabetes mellitus	365 (48%)	295 (44%)	0.13
Obesity	153 (20%)	198 (30%)	<0.0001
Hospital mortality	39 (5.1%)	25 (3.7%)	0.20

Clinical characteristics of pts hospitalized for heart failure with preserved systolic LV function

Conclusions: This observational nationwide HF survey showed that: 1. Preserved LV systolic function was present in 47% of pts hospitalized for HF, 2. Pts with preserved LV were older, often female, obese and with systemic hypertension in 80%. 3. Hospital mortality was marginally but not significantly lower than in pts with reduced systolic function.

P511 The mitral L wave and mitral annular L′ wave in left ventricular hypertrophy: association with markers of diastolic dysfunction and increased heart failure events

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Purpose: To determine the tissue Doppler and clinical correlates of mid-diastolic transmitral flow (L wave) detected by conventional Doppler echocardiography in pts with left ventricular hypertrophy (LVH).
Methods: In consecutive pts with echocardiographic LVH and normal LV ejection fraction, conventional Doppler echocardiography and tissue Doppler imaging (TDI) of mitral annular motion were performed. Pts were followed for heart failure (HF) episodes requiring hospitalization.
Results: Of 177 pts, 34 (19%) had an L wave while 53 (30%) had a mid-diastolic (L') wave on TDI (52 at the lateral annulus, 34 at the septal annulus and 33 at both annuli). The L' wave was detected in 100% of cases with an L wave. Parameters of LV filling for pts with both L and L' waves (group I), only L' wave (group II) and neither L nor L' wave (group III) are shown (Table I). Group I was associated with more abnormal indexes of diastolic function and filling pressure. Group II had values intermediate between groups I and III. Over a follow-up period of 12 months,

Table I

Parameter	Group I (N=34)	Group II (N=19)	Group III (N=124)	p value (ANOVA)
Indexed left atrial volume (cm^3/m^2)	34.7	25.3	22.6	<0.001
Mitral E/A ratio	1.3	0.9	0.9	<0.001
Isovolumic relaxation time (ms)	84	90	94	0.041
Pulmonary venous systolic to diastolic velocity ratio	1.1	1.5	1.6	<0.001
Pulmonary venous A duration (ms)	160	138	137	<0.001
Mitral E/E' (septal annulus)	12.2	9.5	9.0	<0.001
Mitral E/E' (lateral annulus)	11.0	8.1	7.7	<0.001
Pulmonary artery systolic pressure (mmHg)	43	35	34	<0.001

11 pts were hospitalized for HF. The L wave was associated with increased risk of HF (hazard ratio [HR] 4.7, p=0.011), even after adjustment for clinical risk factors (HR 4.2, p=0.026). The HR for L' wave was 3.9 (p=0.03).
Conclusions: The mitral L wave is associated with a mid-diastolic L' wave on TDI, appears to be a marker of raised LV filling pressure and predicts HF events in pts with LVH. The L' wave is discerned more frequently than the L wave and may be an earlier and more sensitive marker of diastolic dysfunction.

P512 The restrictive pattern of left ventricular filling is a poor prognostic predictor in patients with diastolic heart failure

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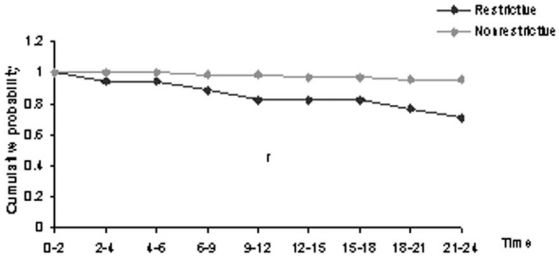
Purpose: This study has been undertaken to study if the restrictive pattern of left ventricular filling is a good predictor of a poor prognosis in patients with diastolic heart failure as in those with systolic heart failure.
Methods: We analyzed the relation of transmitral flow patterns and cardiac mortality in 86 consecutive patients with congestive heart failure symptoms and a normal or nearly normal systolic function (EFLV $>$ 45%). Transmitral flow was obtained from the apical four-chamber view between the tips of mitral leaflets. The patients were assigned to two groups according to E/A ratio and deceleration time of the E wave: a nonrestrictive group (68 patients) with E/A$\leq$1 or E/A=1 to 2 and deceleration time $\geq$150 ms, and a restrictive group (18 patients) with E/A$\geq$2 or E/A=1 to 2 and deceleration time $<$150 ms. The endpoints for follow up were death or the time of study closure.
Results: Of 86 patients with diastolic heart failure included in this study, 8 died during a mean follow-up period of 22$\pm$5 months: 5 with sudden death and 3 because of aggravation of heart failure. The cummulative cardiac survival determined by the actuarial curves was 95% at 1 year and 90% at 2 years. The cardiac survival rate in the nonrestrictive group at 1 year was 98.5% vs 83% in the restrictive group, respectively and at 2 years was 95.5% vs 71%, respectively. The comparison of two last curves was calculated with log-rank test. From this comparison results that the survival is lower in patients with restrictive pattern (p$<$0.005).



Actuarial curve.

Conclusion: The restrictive pattern of left ventricular filling is a poor prognostic predictor of cardiac death in patients with diastolic failure.

P513 Diastolic wall motion abnormality after acute myocardial infarction: clinical implications, relation to neurohormonal activation and prognostic importance

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Purpose: Left ventricular (LV) diastolic dysfunction precedes systolic dysfunction in the ischemic cascade. Therefore, regional diastolic function may be a more sensitive marker of myocardial ischemia than regional systolic function. We evaluated clinical implications, relation to neurohormonal activation and prognostic value of regional diastolic wall motion abnormality in a consecutive series of patients with first acute myocardial infarction (AMI).
Methods: Two-dimensional and Doppler echocardiography was performed in 149 consecutive patients with first AMI within 24 hours of admission to the coronary care unit. Segmental analysis of Color Kinesis images was used to evaluate the magnitude and timing of regional endocardial wall motion during ventricular ejection and filling. The area of diastolic and systolic wall motion abnormality was expressed as percentage of the LV cavity using a 16-segment model. Blood samples were collected in 126 consecutive patients (83%) 3 days after AMI for assessment of N-terminal pro brain natriuretic peptide (NT-proBNP). Angiography was performed in 106 patients (71%) 39$\pm$22 days after admission for AMI. A coronary stenosis with a $>$66% luminal narrowing was considered significant. The primary study end-point was cardiac mortality or hospital readmission due to congestive heart failure (CHF).
Results: The study included 149 patients with a mean age of 67$\pm$11 years. In the study population, the area of diastolic wall motion abnormality was 40,3% and the area of systolic wall motion abnormality was 19,5% (p$<$0.001). The area of diastolic wall motion abnormality was significantly associated with NT-proBNP (r=0.67, p$<$0.001) and angiographic severity of coronary artery disease (r=0.59, p$<$0.001). During follow-up of median 27 months, 25 patients died of cardiac causes and 9 patients were readmitted to hospital for CHF. In Cox regression analysis, the area of diastolic wall motion abnormality was an independent predictor of the composite end-point (p=0.001) after adjustment for age, Killip class, systolic and diastolic function. In that model neither ejection fraction (p=0.28) nor wall motion score index (p=0.23) provided any additional information.
Conclusions: Diastolic wall motion abnormality exceeds systolic wall motion abnormality after AMI and provides additional clinical and prognostic information to conventional systolic and diastolic measures in patients after first acute myocardial infarction.

P514 Diastolic dysfunction of the left ventricle at high altitude – just a phenomenon of interventricular interaction?

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Background: Diastolic dysfunction of the left ventricle (LV) at high altitude has been described and is supposed to derive from interventricular interaction due to acute pulmonary hypertension. However, this has not yet been investigated. We, therefore, studied diastolic function of the LV at low (490m) and at high altitude (4559m) and its relationship to pulmonary artery pressure (PAP) increase and changes in dimensions of right-sided cardiac cavities.
Methods: A total of 37 healthy subjects were included in this study. Of these, 28 had a history of high altitude pulmonary edema (HAPE), which is associated with pulmonary hypertension when exposed to high altitude. Subjects susceptible to HAPE were randomly assigned to placebo (n=9) and to prophylactic therapy (n=19) starting on the day before ascent to test the effects of medical treatment on diastolic function of the LV in association with changes in pulmonary pressure. Echocardiography was performed at low altitude $<$1 month prior to the ascent and after an overnight stay at high altitude (4559m). Diastolic function of the LV was assessed by transmitral inflow pattern and pulmonary venous flow, systolic PAP was estimated from pressure gradient of tricuspid regurgitation (dPTR).
Results: In the entire group of investigated subjects, PAP increased significantly at high altitude (dpTR 38$\pm$12 vs 19$\pm$5mmHg, p$<$0.001), ranging from 18 to 74mmHg. The heart rate adjusted ratio of early to atrial transmitral filling decreased significantly (1.58$\pm$0.37 to 1.31$\pm$0.32, p$<$0.001), while atrial reversal of pulmonary venous flow increased (23$\pm$4 to 27$\pm$7cm/s, p=0.01). The diameter of the right atrium showed a small increase (41.0$\pm$5.7 vs 38.2$\pm$6.5mm, p=0.02) and the right ventricular diameter also tended to enlarge (36.7$\pm$4.5 vs 35.3$\pm$3.9mm, p=0.1). There was no significant correlation between changes in PAP and diastolic function of the LV. Changes in dimensions of right-sided cardiac cavities and diastolic function of the LV did not correlate either. Moreover, therapy in HAPE susceptible subjects lowered PAP increase (15.8$\pm$11.3 vs 26.7$\pm$11.4mmHg, p$<$0.05), but diastolic function of the LV did not change accordingly.
Conclusion: Interventricular interaction does not appear to be the primary mechanism of diastolic dysfunction of the left ventricle observed at high altitude.

P515 Pseudonormalization of the transmitral pulsed Doppler pattern during the Valsalva manoeuvre – A/e' as new discriminative index

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The Valsalva manoeuvre (VM) has been frequently suggested as a useful method in the evaluation of the left ventricular (LV) grade II global diastolic dysfunction (DDII), through the inversion of a pseudonormalized ratio between the transmitral diastolic early (E) and late atrial (A) filling waves by pulsed Doppler. The purpose of our study was to evaluate the sensitivity and specificity of the E/A inversion during VM in LV DDII patients (pts) and its correlation with the mitral annulus motion, evaluated by Doppler tissue imaging (DTI). Using the European Society of Cardiology echocardiographic criteria for DDII diagnosis, we studied a group of 44 DDII pts (DDII group), 27 male, mean age 59$\pm$14 years old, and compared it with a control group (N group), 33 healthy individuals, 17 male, mean age 36$\pm$9 years old. Using transmitral pulsed Doppler analysis, we quantified the maximal diastolic velocities of the transmitral flow (E and A waves-cm/sec), the pulmonary venous systo-diastolic flow (S, D and Ar waves-cm/sec), and the first aliasing flow propagation velocity of the LV inflow by M-mode color Doppler (FPV$<$45 cm/sec for LV DDII). Using DTI, we measured the maximal systolic (s'), rapid filling (e') and atrial (a') diastolic velocities (Vmax-cm/sec) in 4 points of the mitral annulus: adjacent to the interventricular septum (P1), lateral (P2), inferior (P3) and anterior (P4) LV myocardial walls. VM was performed with several measurements of the previous parameters at the point of their maximal shift.
Results: 4 pts in the DDII group were excluded by degradation of the acoustic window during VM. The sensitivity and specificity for the inversion of E/A during VM in the identification of LV DDII were 88% and 57%, respectively. With ROC curve analysis the most discriminative index for DDII diagnosis was A/e' $>$4.06 in P2 during VM (area under ROC curve [AUROC]=0.883 [0.78, 0.84]). During VM

we obtained a significant increment in AUROC (0.77 vs. 0.88; p=0.006). Considering A/e' >4.06 pre-MV and during MV, the sensitivity and specificity for LV DDII diagnosis were 62%,78% and 85%,78%, respectively.
Conclusions: The inversion of a pseudonormalized pulsed Doppler E/A ratio during MV has a high sensitivity but low specificity to make it useful in the clinical practice. The A/e' ratio cut-off value >4 during MV is a new, highly discriminative index, that can be used for the diagnosis of LV grade II diastolic dysfunction, in the presence of a pulsed Doppler pseudonormalized E/A ratio.

P516 Decreased regional diastolic function in individuals with left ventricular hypertrophy measured by tagged magnetic resonance imaging. The MESA study

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Impairment of diastolic function is considered to be the mechanism of heart failure (CHF) in patients with preserved systolic LV function. Left ventricular hypertrophy (LVH) is thought to be a risk factor for this CHF that may begin as a regional process. Therefore, we investigated whether regional LV diastolic function measured by MRI tagging is altered in participants of the Multi-Ethnic Study of Atherosclerosis (MESA) with LVH.
Methods: MESA is an observational prospective study of men and women from 4 ethnic groups with no history of symptomatic cardiovascular disease. 218 participants were studied by MRI tagging strain rate, a novel index of myocardial function based on the rate of myocardial contraction and relaxation. LV mass index (LVMI) was determined from untagged images. Tagging analysis was performed by Harmonic Phase Imaging (HARP). Circumferential systolic and diastolic strain rate were measured in the mid-wall layer of the septum and anterior wall at mid LV level.
Results: Systolic and diastolic strain rates were obtained in 96% and 76% of all segments respectively. Systolic strain and strain rate measures from patients with LVH were not significantly different from the normal group. Regional systolic strain and strain rate measures from participants with LVH were not significantly different from those with non-LVH. However, stepwise regression analysis demonstrated that the magnitude of early relaxation (diastolic strain rate) is inversely proportional to LV mass ($p<0.01$). Regional diastolic strain rate was significantly reduced in LVH participants ($1.6\pm0.6\ s^{-1}$) (n=30) compared to the non-LVH group ($2.1\pm1.1\ s^{-1}$, $p<0.05$) (n=188) regardless of age or gender.
Conclusion: The present study demonstrates that LV diastolic function is decreased in asymptomatic individuals with LVH with preserved systolic function. It also demonstrates the ability of MRI tagging with HARP to measure and analyze myocardial strain rate in a large population study. Asymptomatic individuals with LVH and diastolic dysfunction may be at greater risk to develop CHF with preserved systolic function than those with LVH alone.

P517 Does pulmonary function affect Doppler indices of diastolic function?

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Background: Early diastolic velocity of the mitral annulus (Ea) assessed by pulsed tissue Doppler imaging (TDI) has been used to evaluate diastolic function of the left ventricle (LV). The purpose of the study was to investigate whether there is an influence of pulmonary function on Ea in patients with reduced pulmonary function, as assessed by spirometry and lung diffusion capacity.
Methods: 52 subjects (aged 60-79 years) recruited from general practice with dyspnea at exertion and ratio of forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) < 70% or lung diffusion capacity <5% percentile of the predicted normal value were studied. All subjects underwent physichal examination, echocardiography and lung function tests. Lung diffusion capacity was assessed in 26 subjects. Echocardiography was performed according to standard protocol including an assessment of Ea (cm/s) by TDI in the lateral mitral annulus.
Results: In a linear regression analysis, the only independent significant predictor of Ea was FEV1/FVC (p =0.027). The following parameters were included in the model: age, gender, heart rate and wall motion index. A significant negative correlation was observed between Ea and FEV1/FVC (r =-0.33; p =0.018), and a significant positive correlation was found between Ea and FVC (r =0.39; p =0.005).
Conclusion: In subjects with reduced pulmonary function, Ea is influenced by the ratio of FEV1/FVC, irrespective of age, gender and other variables. As suggested pathophysiologic mechanism, reduced pulmonary function could conceivably affect diastolic function of the LV through an interference with the right side of the heart.

P518 Improvement of the restrictive pattern of left ventricular filling with infusion of levosimendan in patients with severe heart failure

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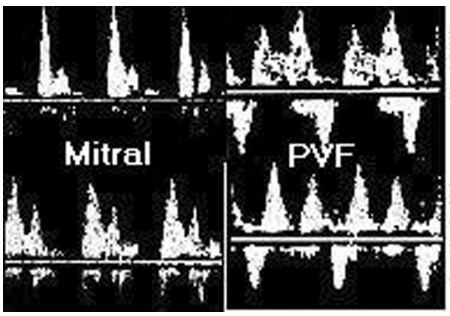
Background: Restrictive pattern of left ventricular (LV) filling is often appeared in patients with severe heart failure (HF). Although the hemodynamic effects of levosimendan were studied, the effects of levosimendan on LV filling pattern have not been investigated.
Methods: Pulsed wave Doppler mitral (transthoracic) and pulmonary venous flow (PVF, transesophageal) velocity curves were recorded in 30 patients with a restrictive pattern of LV filling with NYHA class III or IV HF who had a pulmonary capillary wedge pressure (PCWP) > 18 mm Hg and a cardiac index (CI) < 2.4 L min^{-1} m^{-2} and received 0.1 $\mu g\ kg^{-1}\ min^{-1}$ infusion of levosimendan for 24 hours. Atrioventricular coupling was defined as the ratio, Ai/(Ai+ARi) of the integrals of A wave of tranmitral flow velocity and atrial reversal (AR) of PVF velocity.
Results: Levosimendan caused significant ($P<0.001$) increases in stroke volume (from 46±4 to 57±4 ml) and CI (from 1.9±0.3 to 2.5±0.3 L min^{-1} m^{-2}) and decreases in PCWP (from 21±1 to 15±1 mm Hg). The E wave decreased (from 96±7 to 71±5 cm/s) and the A wave increased (from 40±4 to 46±4 cm/s). Moreover deceleration time was increased (from 112±7 to 189±14 ms). The S wave of PVF was increased (from 38±3 to 60±3 cm/s) and the AR was decreased in amplitude (from 36±2 to 29±2 cm/s) and duration (from 175±10 to 162±12 ms). All changes were significant ($P<0.001$). Using stepwise linear regression analysis we found that LV stroke volume was determined by the Ai/(Ai+ARi) ratio, R=0.684, $P<0.001$.



Conclusions: Levosimendan improved the restrictive pattern of LV filling leading to an increase in the left atrial forward ejection into the LV associated with a decrease in backward flow volume into the PVs. Consequently LV stroke volume was increased.

P519 "Pure" diastolic heart failure and left ventricular force-frequency relationship during exercise -echocardiography

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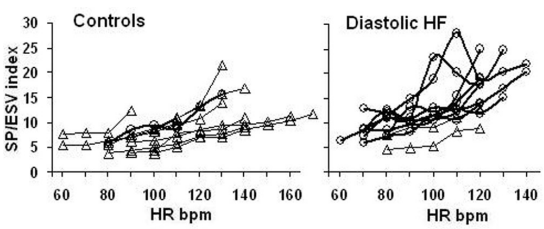
Background: Left ventricular (LV) diastolic dysfunction is an increasingly recognized mechanism of heart failure, but normal systolic function is usually defined on the basis of a crude index of resting function such as ejection fraction. Latent occult LV dysfunction can be better identified through non-invasive assessment of force-frequency relationship (FFR) during exercise-echo.
Aim: To assess whether patients with diastolic heart failure show blunted FFR during exercise.
Methods: We enrolled 11 control normotensive subjects (Group 1) and 10 uncomplicated hypertensive patients meeting European Society of Cardiology criteria for diastolic dysfunction (Group 2, all New York Heart Association class II; LV ejection fraction >45%, Isovolumic Relaxation Time >100 msec and/or E/A ratio<1 and Deceleration Time >220 msec). To build the FFR, the force was determined as the ratio of the systolic pressure (SP, cuff sphygmomanometer)/end-systolic volume index (ESV, biplane Simpson rule/body surface area).
Result: The slope value of FFR was comparable between the 2 groups (Group



1= 15.7±10.6 × 10^{-2} vs Group 2 = 18.6±8.6 × 10^{-2}, p=ns). A biphasic profile in the FFR ramp, with an initial bump followed by a later steep rise during exercise, was observed in 1/11 controls and 8/10 patients (9 vs. 80%, p<0.00001): see figure.

Conclusion: Patients with criteria of diastolic heart failure have an intact LV contractility reserve as noninvasively assessed by FFR during exercise. However, a peculiar biphasic profile of FFR can be observed only in a subset of patients with diastolic dysfunction and might be a clue to the identification of underlying subtle initial systolic dysfunction.

P520 Effect of volume reduction on diastolic function: evaluation in haemodialysis patients

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Purpose: Evaluation of left ventricular diastolic function is routinely performed using Doppler mitral inflow velocities and pulmonary venous inflow. Recently mitral annulus velocities assessed by Tissue Doppler Imaging (TDI) and Color M-mode Doppler flow propagation velocity proved to be efficient. Load dependence of these last methods is unclear. To evaluate these different parameters in changing load conditions we studied diastolic function in patients undergoing haemodialysis.

Methods: Nineteen patients on chronic haemodialysis (M:10, W:9, age: 62,7±14,4 ys), without known heart disease, had a complete echocardiogram during the previous hour and at the end of their haemodialysis session. Echocardiography evaluated left ventricular dimensions, volumes, left atrial dimensions, pulsed Doppler assessment of mitral inflow and pulmonary venous flow, TDI on septal and lateral mitral annulus and color M-mode on mitral flow. Blood pressure, heart rate and weight were measured at the beginning and at the end of haemodialysis. Parameters were analysed using T Student test.

Results: After haemodialysis no significant differences were found on blood pressure and heart rate. A mean weight loss of 3 kg (1,4-4,5) was obtained. Doppler mitral inflow showed a decrease of early diastolic velocity E (88,4±23,2 vs. 65±16,2; p: 0,000001) and of E/A ratio (1,01±0,31 vs. 0,75±0,28; p: 0,001). Pulmonary vein flow velocities also decreased significantly (S: 57,67±13 vs. 45,4±12, p: 0,0003; D: 46,39±12,32 vs. 34,22±7,4, p:0,0002; A: 30,25±5,16 vs. 27,4±3,62, p:0,04). TDI septal diastolic E' velocity decreased (7,83 cm/sec± 2,47 vs. 6,22±1,84, p:0,01) as well as lateral E' velocity (9,6±3 vs. 7,9±2,8, p: 0,06) and septal E'/A' ratio (0,74±0,17 vs. 0,63±0,2, p: 0,02). Color M-mode velocity did not change remaining abnormal (47,6±13,6 vs. 46,6±15,21, p:0,68).

Conclusions: The study confirms the preload dependence of Doppler mitral inflow. Fluid loss caused a reduction of E/A ratio; this fact could probably mean that some patients had a pseudonormal diastolic pattern in the initial evaluation. Pulmonary vein flow was as well load dependent but could confirm diastolic function improvement with the reduction of the atrial reverse component after dialysis. TDI was partially load dependent but allowed an accurate diastolic evaluation (E'/A' < 1 before and after dialysis). Color M-mode proved to be completely load-independent and feasible. All these methods should be used routinely in these patients in order to achieve precise information on diastolic function.

P521 The role of interleukin-6 and tumour necrosis factor-alpha in the acute decompensation of heart failure

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Purpose: Citokins plays an important but not completely understood role in the development of heart failure (HF). We studied the levels of citokins interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) and their relation to the features during acute decompensation of HF.

Methods: Forty-nine patients with decompensated HF and left ventricular ejection fraction (LVEF) ≥ 0.45 were included. Mean age was 53.3 years, 35 (71.4%) were man. Blood samples to determination of IL-6 and TNF-alpha were obtained during the first 24 hours. Daily weight, urinary volume, signs and symptoms of heart failure, discharge or death were recorded. Plasmatic norepinephrine (PNE) was acessed to confirm the degree of sympathic activation and severity of the disease.

Results: Shock was present in 29 patients (59.2%), the mean LVEF was 0.33±0.06, PNE ranged from 190 to 2854 pg/mL (mean 864.1±591.0), and hospital mortality was 32.6%. There was a wide range in the levels of IL-6 and TNF-alpha, but IL-6 level was significantly higher in patients with PNE ≥ 700 (p= 0.008), and TNF-alpha level was related to death (p=0.01). In patients with TNF-alpha > 8 pg/mL, the RR to death was 3.75 (IC 95%, 1.0-14.0). Patients with PNE ≥ 700pg/mL, RR for death was 5 (IC 95%, 1.3-19.5).

Citokins levels, norepine and death

	Death			PNE ≥700		
	Yes (n=16)	No (n=33	p	Yes (n=23)	No (n=23)	p
IL-6 (pg/mL)	14.9	11.3	0.45	17.3	7.9	0.008
TNF-alpha (pg/mL)	21.2	8.5	0.01	13.5	13.0	0.87

Conclusions: In patients with acure decompensation of HF, IL-6 is related to sympathic activation and TNF-alpha is related to hospital mortality. IL-6 and TNF-alpha are not related to the occurrence of cardiogenic shock or hospital stay.

P522 Matrix metalloproteinase 2 is expressed in the heart of patients with congestive heart failure

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Background: Cardiac remodeling plays an important role in the progression of cardiovascular diseases. The matrix metalloproteinases (MMPs) are an endogenous family of proteolytic enzymes implicated to contribute to left ventricular remodeling. It is generally assumed that in patients with congestive heart failure (CHF) MMPs are, at least partially, released by the heart, however this has never been investigated in humans. In addition, compared to healthy controls, only elevated levels of MMP9 but not MMP2 were found in venous plasma of patients with CHF.

Methods: Patients with CHF as determined by Dyspnoe NYHA II-III and a left ventricular ejection fraction (LVEF) of 40% or less, as assessed by echocardiography, were included in the study. Patients were on optimized standard therapy for CHF including beta-blockers, diuretics and ACE inhibitors or angiotensin II receptor blockers. Right heart catheterization was performed twice within three month. Blood was collected at the coronary sinus, the pulmonary artery and the cubital artery before and after 20 minutes of a peripheral venous infusion of icatibant (0.75 ug/kg/min), a selective bradykinin B2 receptor antagonist. Soluble MMP-2 in plasma was determined by enzyme linked immunosorbent assay (ELISA).

Results: Patients (n=10) were on average 56 ± 10.7 years old and had a mean LVEF of 28.3 ± 8.1%. Acute blockade of the bradykinin B2 receptor by icatibant had no influence on MMP2 levels (998 versus 964 ng/ml, n=17, p=0.35). MMP2 levels measured in the coronary sinus (998 ± 189 ng/ml) were slightly but significantly higher than levels measured in the cubital artery (964 ± 189 ng/ml, n=20, p=0.025). When MMP2 levels in the coronary sinus and the cubital artery, measured after icatibant treatment were also included in the analysis (n=37), mean levels were 982 ± 195 ng/ml and 950 ± 192 ng/ml respectively and significance increased to p=0.0016, corroborating the finding of elevated MMP2 levels in the coronary sinus.

Conclusions: Despite the fact that levels of soluble MMP2 in venous blood are similar in patients and in healthy controls, patients with CHF have levels of MMP2 that are significantly higher in the coronary sinus than in the cubital artery, indicating increased expression of MMP2 in the coronary vascular bed.

P523 The relationship of chemical markers to skeletal muscle strength, volume, and body fat in heart failure patients

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Background: Measurements of functional capacity, neurohormonal parameters, and proinflammatory cytokines such as soluble tumor necrosis factor-alpha receptors (TNFR-1 and TNFR-2) are established parameters to evaluate the severity of chronic heart failure (CHF). Leptin, the product of an obesity gene, has been associated with energy expenditure and weight regulation. However, the correlations of these chemical markers to skeletal muscle strength, volume, and body fat in heart failure patients are still not fully clarified.

Aim: This study was designed to evaluate the relationships of chemical markers to the skeletal muscle strength, volume, and body fat in patients with CHF.

Methods: Subjects comprised 19 CHF patients (17 males and 2 females, mean age of 59.8 years). Skeletal muscle volume and body fat were obtained using electrical impedance analysis (BIA: ART HAVEN 9 C.O.) prior to the CPX. Maximal knee extension strength (PT), an index of muscle strength, was measured by the Biodex. Plasma concentrations of TNFR-1, -2, Leptin, brain natriuretic peptide (BNP), and atrial natriuretic peptide (ANP) were measured. The obesity index (body mass index/22) was used as the parameter of body weight loss.

Results: Obesity index was significantly correlated with total muscle volume (r=0.66) and fat volume (r=0.89). Total muscle volume showed significant negative correlations with TNFR-1 (r=-0.528, p<0.05) and TNFR-2 (r=-0.618, p<0.01). Among individual muscles measured, the femoral muscle volume also showed significant negative correlations with TNFR-1 (r=-0.676, p<0.05) and TNFR-2 (r=-0.762, p<0.001). Total muscle volume and PT were not correlated with any of the other all-chemical markers. The body fat volume showed a significant positive correlation only with leptin (r=-0.822, p<0.0001). ANP and BNP were unassociated with all of these peripheral factors.

Conclusion: Body weight loss correlated with decreases in both the skeletal muscle and fat volume. These results suggest that proinflammatory cytokines reflect the severity of skeletal muscle damage. In contrast, leptin seems to reflect energy expenditure and weight regulation (cardiac cachexia), while the neurohormonal parameters (ANP, BNP) seem to reflect central alterations.

P524 Influence of long-term implication of losartan in combination with bisoprolol on endothelial dysfunction and hyperinsulinaemia in patients with stable angina pectoris

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Hyperinsulinaemia and endothelial dysfunction play important role in cardiovascular diseases. It has been shown that hyperinsulinaemia results in decreased endothelium-dependent vasorelaxation. It is important to develop effective treatment strategies.
The aim of the study was to assess effects of losartan in combination with bisoprolol on endothelin-1(ET-1) and insulin (IN) levels of in patients (pts) with stable angina pectoris.
Methods: 185 pts with stable angina pectoris were studied in a double blind, placebo controlled study. 95 pts received losartan (the average daily doses were 68,2±3,4 mg) and bisoprolol (the average daily doses were 9,6±2,9 mg) and 83 pts received placebo during 6 months. Plasma ET-1 and serum IN levels were determined by radioimmunoassay.
Results: In the placebo group baseline ET-1 level was 24,8±0,9 pg/ml, IN-232,6±15,7 pmol/l; in the group of losartan and bisoprolol treatment baseline ET-1 level was 25,9±0,8 pg/ml, IN - 246,7±12,8 pmol/l. After 6 months of therapy the ET-1 levels did not change in the placebo group (23,4±1,2 pg/ml, p>0,05) and decreased in the group of losartan and bisoprolol (15,3±0,7 pg/ml, P<0,001); IN levels did not change in the placebo group (243,5±10,8 pmol/l, p>0,05) and decreased in the group of losartan and bisoprolol (135,2±7,5 pmol/l, P<0,001).
We revealed that ET-1 levels strongly positively correlated with levels of IN before (r=+0,53; P<0,05) but not after therapy with losartan and bisoprolol (r=+0,17; p>0,05). These results suggest important role of hyperinsulinaemia in the impairment of endothelial function in pts with stable angina pectoris. Administration of losartan and bisoprolol lowered endothelial vasoconstriction and hyperinsulinaemia.
Thereby, favorable changes in haemodynamics and increase in exercise performance due to losartan and bisoprolol treatment of pts with stable angina pectoris may be explained by their influence on ET-1 and IN levels, resulting in the endothelial function improvement.

P525 Effect of telmisartan losartan and lisinopril on insulin sensitivity in hypertensive patients with and without insulin resistance

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Aim: to compare the effect of telmisartan, losartan and lisinopril on insulin sensitivity in hypertensive patients with and without insulin resistance.
Methods: after a four-week placebo period 56 mild to moderate hypertensive patients (DBP > 90 mmHg < 105 mmHg), 25 of them with normal insulin sensitivity (HOMA-I < 2.5) and 31 with impaired insulin sensitivity (HOMA-I > 2.5) where randomized to receive losartan 50 mg o.d. or telmisartan 80 mg o.d. or lisinopril 20 mg o.d. for 6 weeks in 3 cross-over periods each separated by a two-week wash-out period (3x3 latin square). At the end of the placebo running period and of each treatment period BP was measured and insulin sensitivity was assessed by the euglycemic hyperinsulinemic clamp and was expressed as the amount of glucose infused during the last 30 min of the clamp (GIR).
Results: all the drugs significantly reduced blood pressure with no difference among the three treatments. In patients with normal insulin sensitivity GIR did not change with any drug. In patients with impaired insulin sensitivity GIR was significantly increased by lisinopril (from 5.97±0.51 to 7.93±0.64 mg/min/kg, p < 0.01) and by telmisartan (from 6.14±0.53 to 7.22±0.61 mg/min/kg, p < 0.05) but not by losartan (from 6.05±0.54 to 6.42±0.58 mg/min/kg, N.S.).
Conclusions: these data suggest that: 1) anti-hypertensive drugs acting at the RAS level have different effects on insulin sensitivity in function of the characteristics of the studied population 2) drugs belonging to the same class of the angiotensin II antagonists may differ in their ability to improve insulin sensitivity. It could depend on chemical structure, pharmacodynamics and pharmakinetics of the different drugs.

P526 Diabetes mellitus worsens the prognosis for congestive heart failure patients with preserved systolic function

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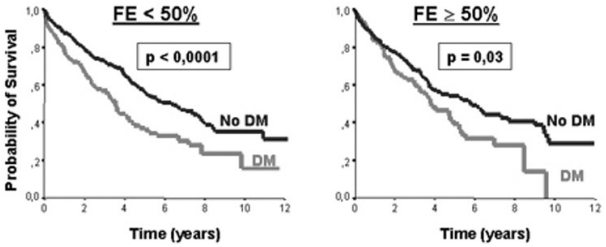
Diabetes mellitus has been found to be independently associated with higher mortality in numerous clinical studies of patients with congestive heart failure (CHF). However, few of these studies have distinguished between CHF patients with and without deteriorated systolic function. This study aimed to determine the effect of diabetes on survival in both these groups of CHF patients.
We studied the 1252 CHF patients, aged 69.0 ± 11.7 years, who were admitted to the Cardiology Service of a tertiary hospital between January 1st 1991 and December 31st 2002 and whose left ventricular systolic function was evaluated echocardiographically while hospitalized. 767 (61.3%) were men, 693 (55.4%) were hypertensive, 616 (49.2%) exhibited ischaemic cardiopathy, 152 (12.1%) presented radiological signs of alveolar oedema, and 522 (41.7%) were in NYHA class IV. 335 (26.8%) were diabetic. Left ventricular systolic function was deteriorated in 754 (60.2%) and preserved in 498 (39.8%).
Diabetes was significantly associated with shorter survival among both patients with deteriorated systolic function (median survival 3.5 ± 0.3 years as against 6.3 ± 0.7 years; p < 0.0001) and patients with preserved systolic function (median survival 3.8 ± 0.7 years as against 5.8 ± 0.7 years; p = 0.03).



Survival curves of FE < 50% and FE > 50%.

Conclusion: diabetes mellitus worsens the prognosis of both CHF patients with preserved systolic function and those with deteriorated systolic function.

P527 Correlation of obesity and mortality in patients admitted for heart failure

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Introduction-Aim: Many studies have shown the role of obesity in the development of Heart Failure (HF). However the impact of obesity on the prognosis of patients admitted for HF has not been widely studied. The aim of this study was to investigate the role of obesity in the prognosis of patients with HF.
Methods: In our study we included 842 patients (525 men-317 women), who were admitted in the cardiology department of our hospital due to HF during the period 1998-2002.We estimated the Body Mass Index (BMI) of the patients and used the basic blood tests at the admission. The heart U/S results were available approximately for the 70% of the patients. Using the BMI as grouping criterion, the patients were assigned into 3 groups: lean (BMI<25 kg/m^2, approximately 30% of the total), overweight (BMI: 25 kg/m^2 –30 kg/m^2, 30% of the total) and obese (BMI>30 kg/m^2, 40% of the total).
Results: Regarding the distribution of the patients into BMI-groups, we found: 404 patients (48% of the total) with HF due to ischemic cardiopathy, 328 patients (39%) due to dilated cardiomyopathy and 110 patients (13%) due to other causes (valvular disease, cardiomyopathy etc) or due to unknown causes. The overweight and the obese patients had much higher incidence of diabetes mellitus and hypertension and also worse lipid profile. During the one-year follow-up 255 deaths occurred (30.28% of the study population), 164 of which occurred in the group of ischemic patients (40.59% of all ischemic patients) and 91 in the group of non-ischemic patients (27.74% of all non-ischemic patients)
Conclusions: In this study we found no correlation of obesity with increased mortality in patients with HF. Further studies are needed in order to clarify the role of obesity in patients with HF as well as the overall effect of weight-loss on the prognosis of those patients.

P528 Right ventricular myocardial dysfunction associated with obesity

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Right ventricular dysfunction in overweight subjects is usually ascribed to co-morbid disease. We used tissue Doppler and strain imaging to identify whether RV dysfunction was associated independently with weight in 97 overweight (BMI 25-29.9) or obese (BMI>30) subjects and 20 controls with no co-morbidities. Obese subjects with BMI>35(gr IV) had reduced RV function evidenced by reduced myocardial early diastolic peak velocities (em) (p<0.001) and systolic velocities (sm) (p<0.001). Similar but lesser degrees of reduced systolic function were present in mildly obese (BMI 25-29.9, gr II) and moderately obese (BMI 30-35, gr III) groups evidenced by reduced RV em and sm. (p<0.05) Subgroup comparison also demonstrated differences in RV em, sm between the severely vs. mildly and moderately obese groups (<0.05).

	BMI<25 (gpI)	BMI25-29.9 (gpII)	BMI30-35 (gpIII	BMI>35 (gpIV)	p (ANOVA)
RV sm	10.4±1.8	8.2±2.8	8.0=2.6	5.8±2.8	<0.001
RV em	-10.7±2.8	-8.4±3.0	-8.1±2.7	-6.3±3.1	<0.001

Overweight subjects without overt heart disease have right ventricular dysfunction. On multivariate regression analysis, these changes were shown to be independent to blood pressures, age, gender and increased left ventricular mass. Subgroup analysis in the obese pts did not demonstrate association of these changes with duration of obesity, presence of sleep apnea and insulin sensitivity.

P529 ACE inhibitor treatment in hypertensive diabetic patients prior to acute myocardial infarction may reduce hospital morbidity and mortality

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The aim of the study was to determine whether administration of ACE inhibitor therapy prior to acute myocardial infarction (MI) is related to infarct size, hospital cardiovascular morbidity and mortality and exercise capacity in hypertensive diabetic patients.
Methods: Study population consisted of 146 consecutive patients (pts) with arterial hypertension and diabtes type 2 admitted with a diagnosis of acute MI. Outcome data were compared between groups of patients receiving ACE inhibitor therapy at least three months prior to infarction (ACEI group) and those who were not (non ACEI group).
Results: Ninety-six (66%) were receiving prior ACE inhibitor therapy. There were not significant differences in regard to age, sex, site of infarct, aspirin therapy, in two groups. Patients in ACEI group experienced smaller MI size, determined by peak creatine kinase elevation ($P<0.02$), and by wall motion score (14.5 ± 2.1 vs 15.6 ± 1.9; $P<0.005$) than pts in non ACEI group. Left ventricular ejection fraction was bigger in ACEI group than in non ACEI group (45.8 ± 8.1 vs $42.2 \pm 7.3\%$; $P<0.01$). In patients receiving ACE inhibitor therapy prior to acute MI, hospital cardiovascular events were less frequent than in those who were not: ventricular fibrillation (8% vs 16%), heart failure (19% vs 24%), re-infarction (8% vs 12%), recurrent angina (13% vs 18%), vascular death (8% vs 12%). Workload on predischarge bicycle stress echocardiography was significantly higher (65.3 ± 17.1 vs 57.1 ± 16.2 W, $P<0.05$), and duration of test significantly longer (10.5 ± 4.1 vs 8.2 ± 3.6 min, $P<0.01$) in ACEI than in non ACEI group.
Conclusion: Our data showed that hypertensive diabetic patients who experience an acute MI, those receiving prior ACE inhibitor therapy have smaller infarct size, better global left ventricular function, less hospital morbidity and mortality and better exercise capacity. Thus prior ACE inhibitor therapy have cardioprotective effects in hypertensive diabetic patients with acute myocardial infarction.

P530 Ischaemia modified albumin to detect microvascular angina in patients with Syndrome X

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Purpose: The demonstration of myocardial perfusion abnormalities and a relative reduction in coronary flow reserve in at least a proportion of patients with cardiac syndrome X (SX) supports the hypothesis that myocardial ischemia may be responsible for at least some of the observed clinical features in this group. We hypothesised that under conditions of myocardial stress such as dobutamine infusion, a proportion of patients with SX develop myocardial ischaemia which may be detected by elevated levels of a novel biochemical marker of ischaemia, Ischemia Modified Albumin(IMA).
Methods: Three groups of patients underwent dobutamine stress echocardiography; 10 patients with documented coronary artery disease (CAD), 7 patients with SX and 7 patients with atypical chest pain, thought to be non-ischaemic in origin (ATCP). Blood was drawn at baseline for Ischemia Modified Albumin (IMA), hs CRP and Brain Natiruretic Peptide (NT-BNP). At cessation of stress, approximately 20 minutes to 1 hour following peak stress, a second sample was drawn for IMA.
Results: 50% of the CAD patients had typical angina during stress. None of the patients in the SX and ATCP group had regional wall motion abnormalities at peak stress, compared to 6 of 10 patients with CAD. Median hsCRP levels were higher in patients with ATCP (5.2 mg/ml 95% Confidence Interval 0.2-11.1) compared to patients with SX 2.0mg/ml (95%CI 1.0-3.2) and CAD 4.2mg/ml (CI 0.7-7.6). Median NT-BNP levels were higher in patients with CAD, compared to the other two groups. Median IMA levels in the SX group was 58.4 U/L (95%CI 40-81) pre stress which increased to 72.6 (CI 65-82), p=0.02. Baseline median IMA levels in the ATCP group was 71.7 U/L (CI 58-89), which elevated to 87.5 U/L (CI 79-97) following stress, p=0.001. Baseline median IMA levels in the CAD group was 70.4 (CI 50-83) pre stress which increased to 93 (CI 69-107) post stress, $p<0.0001$.
Conclusions: The elevation of IMA in a number of patients with microvascular angina is novel and confirms the hypothesis that myocardial ischaemia exists in a proportion of these patients and undoubtedly contributes to their symptoms of chest pain.

P531 Myocardial 99mTc tetrofosmin single-photon emission computed tomography may underestimate myocardial viability compared to 18f-fluorodeoxyglucose imaging

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Aim: 99mTc labeled tracers are successfully used in the clinical evaluation of myocardial viability, however their diagnostic accuracy for this purpose remains controversial. The aim of this study is to assess the accuracy of 99mTc tetrofosmin single-photon emission computed tomography (SPECT) in detecting myocardial viability compared to 18F-fluorodeoxyglucose (FDG) SPECT imaging.
Methods: A total of 133 consecutive patients (112 men, mean age 60 ± 9 yr) with ischemic cardiomyopathy (mean left ventricular ejection fraction $25\pm7\%$) underwent resting 2D echocardiography to identify dysfunctional myocardial tissue. Resting dual-isotope 99mTc tetrofosmin/18F-FDG SPECT was performed to detect myocardial viability. Dysfunctional myocardium with a $\geq$50% tracer uptake was considered viable. A standard 16-segment model of the left ventricle was used to relate the echocardiographic and SPECT images, and 4 major regions were considered: anterior, septal, lateral, and inferoposterior.
Results: 2D echocardiography showed that 1649 of 2128 (77%) segments were dysfunctional. Using a treshold of 50% tracer uptake, 741 (45%) dysfunctional segments were viable according to 99mTc tetrofosmin, whereas 773 (47%) dysfunctional segments were viable on 18F-FDG SPECT. A total of 93 segments were nonviable on 99mTc tetrofosmin and viable on 18F-FDG SPECT. When 4 major regions were separately analyzed, 79 of the 93 (85%) 99mTc tetrofosmin-nonviable and 18F-FDG-viable segments were located in the inferoposterior and septal regions.
Conclusion: Resting 99mTc tetrofosmin SPECT is safe and practical for routine assessment of viability in patients with ischemic cardiomyopathy. However, underestimation of viability may occur compared to 18F-FDG SPECT, especially in the inferoposterior and septal regions.

P532 Synergistic effect of the ET-1 and ET-A receptor polymorphisms in patients with left ventricular dysfunction

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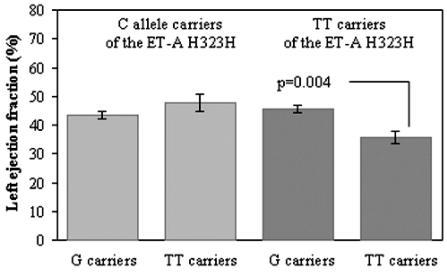
Background: The endothelin (ET) system plays a central role in the control of myocardial function its pathophysiology.
Aim: To explore whether genetic variations of ET-1 Lys198Asn and its receptor ET-A H323H could influence left ventricular (LV) systolic performance.
Methods: We studied by PCR analysis 175 patients with LV dysfunction (LV ejection fraction <45% assessed by echocardiography) and 207 subjects free of cardiovascular disease. Causes of LV dysfunction included coronary artery disease (n=151) and idiopatic (n=24).
Results: The ET-1 Lys198Asn polymorphism was significantly associated with the presence of LV dysfunction (GG: 52%, GT: 38.3%, TT: 9.7% vs GG: 60.9%, GT: 36.2%, TT: 2.9%, LV dysfunction group vs controls, respectively, p=0.01). On the contrary, the ET-A H323H variant was equally distributed among groups (p=0.94). With respect to G allele carriers, TT homozygotes of the ET-1 Lys198Asn polymorphism were not at increased risk of LV dysfunction by multivariate analysis, (OR=2.3, 95% CI, 0.7-7.4, p=0.15). However, there was a marked increased in the risk of LV dysfunction among persons who were homozygous TT for both variants in comparison to G and C simultaneously carriers of the ET-1 Lys198Asn and ET-A H323H polymorphisms, respectively (adjusted OR=23.2, 95% CI, 2.3-237, p=0.0007). Moreover, among TT carriers of the ET-A H323H variant, TT homozygotes of the ET-1 Lys198Asn polymorphism displayed a significantly higher left ventricular ejection fraction in comparison to G allele carriers (Figure).



Conclusions: The ET-1 Lys198Asn and ET-A H323H polymorphisms seem to act synergistically to increase the risk of development of LV systolic dysfunction suggesting that this genetic variant could be involved in the pathogenesis of heart failure.

P533 Endothelin-1 enhances dendritic cell adhesion to murine endothelial cells: role of ET-A and ET-B receptors

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The potent vasoconstrictor endothelin-1 (ET-1) is involved in endothelial dysfunction and has been shown to be released by inflammatory cells in the atherosclerotic plaque. ET-1 may regulate adhesion and migration of dendritic cells (DC), the most important immune-stimulating cells with potential impact in atherogenesis. The aim of the present study was to characterize the role of ET-1 and ET-A/ET-B receptor antagonists on autologous DC-EC interaction.

Methods: Mouse endothelial cells (EC) and/or pre-stained mouse DCs (C57BL/6-myeloid-DC) were separately stimulated for 24 h with different doses of ET-1 (1 pM- 5 uM). A following co-incubation for 4 h under continuous shear stress was performed. DC-EC adhesion was quantified using a fluorescent reader. ET-1 triggered DC-EC interaction was investigated before and after treatment with the specific ET-A receptor antagonist BQ-123 (100 nM) and the ET-B receptor antagonist BQ-788 (100 nM).

Results: ET-1 induced DC adhesion was dose-dependently enhanced (0.01 uM to 1 uM; 29 - 47% increase in adhesion compared to non-stimulated controls; $p<0.05$). Receptor binding studies (Western Blot) revealed the presence of ET-A and ET-B receptors on DC. The ET-1 effect on DC-EC adhesion could be partially blocked by pre-incubating DCs with the ET-A receptor antagonist BQ-123 (-25% change compared to ET-1 alone; $p<0.05$) and by the ET-B receptor antagonist BQ- 788 (-40% change compared to ET-1 control; $p<0.05$). When stimulating DC and EC with ET-1, a dose-dependent biphasic effect on DC adhesion was detectable (1pM to 10 nM reduced DC adhesion up to -27%). High-dose ET-1 (0.1-1 uM) enhanced DC adhesion up to 12% ($p< 0.05$), which was completely reversible by concomitant ET-A and ET-B receptor blockade ($p< 0.01$). Finally, we demonstrated that human DCs by themselves produce ET-1 under hypoxic conditions and under stimulation with TNFa (60-100% change to non-stimulated DCs; $p<0.01$).

Conclusions: The results of this study suggest that adhesion of DCs on autologous ECs is dose-dependently enhanced by ET-1. ET-1 is stimulating DC adhesion via ET-A and ET-B receptors on DCs. Proatherogenic conditions are increasing ET-release from human DCs. ET-antagonists may be of therapeutic value for reducing DC adhesion. Impairing DC adhesion may reduce vascular inflammation and atherogenesis.

P534 Myocardial fibrosis and heart failure

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Myocardial fibrillar collagen synthesis and degradation is a continous turnover which can lead to myocardial fibrosis due to increased intersticial and perivascular deposition. This process has been observed in humans with arterial hypertension and may promote abnormalities of cardiac function. However little information is provided about this changes in patients with heart failure and left ventricular dysfunction versus normal systolic function.

Methods: We studied a cohort of 70 patients (35 with heart failure and left ventricular dysfunction; 35 with heart failure and normal systolic function (FE>45%) and the control group consisted of 30 subjects. Serum concentrations of procollagen type I C-terminal propeptide (PIP) and C-terminal telopeptide of collagen type I (CITP), markers of collagen type I synthesis and degradation respectively, were measured by radioimmunoassays after a hospitalization due to heart failure. We excluded patients with conditions associated with alterations in serum levels of fibrillar collagens such as renal insufficiency, liver dysfunction, any autoinmune process, alterations in bone metabolism o vast wound.

Results: Patients with heart failure presented higher levels of PIP than control group ($140 \pm 56{,}38$ vs $113{,}66 \pm 36{,}6$ μgr/L)(p=0,01) but there were no differences in CITP levels ($2{,}89 \pm 2{,}37$ vs $2{,}26 \pm 1{,}7$ μgr/L). PIP and CITP mean values in the three different groups did not reach significance difference ($141{,}85 \pm 68{,}8$; $138{,}17 \pm 40{,}83$; $113{,}66 \pm 36{,}66$ μgr/L and $3{,}19 \pm 2{,}64$; $2{,}60 \pm 2{,}06$; $2{,}26 \pm 1{,}7$ μgr/L respectively). Patients with heart failure and normal systolic function were older (70,3 vs 63,8 years; $p<0.001$), they were more likely to be women (68 vs 45%; $p<0.001$) or hypertensive (91 vs 48% $p<0.001$) than patients with heart failure and left ventricular dysfunction.

Conclusions: Patients admitted with heart failure presented higher levels of fibrillar collagen type I synthesis (PIP) but not degradation (CITP) with respect to control group. There were no differences of fibrillar collagen type I synthesis and degradation between heart failure and left ventricular dysfunction versus normal systolic function.

P535 Dose-dependent effects of sildenafil on brachial artery hyperemic response in heart failure patients: relation with peak vo2 improvement

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Background: Sildenafil is a new challenge in the pharmacotherapy of CHF patients. It is unknown whether an increase in NO availability as induced by PGE5 inhibition translates into an improvement in exercise peak VO2 and whether this effect may be: a) endothelium-mediated and b) dose-dependent.

Objectives: To investigate the effects of sildenafil on endothelial function of forearm vessels and their potential role in improving exercise performance and exercise blood flow redestribution in stable CHF.

Methods: 10 stable HF patients (NYHA class II to III) treated with ACE-inhibitors and beta-blockers were randomly assigned to receive placebo or sildenafil (25 and 50 mg) according to a double-blind, crossover design. The flow-dependent endothelial-mediated brachial artery vasodilating response to distal circulatory arrest was explored by Doppler- ultrasound imaging (dual crystal Doppler system, 8 MHz transducer).

Peak VO2 and the linear relationship of VO2 changes vs work rate (delta VO2/delta WR), an index of exercise peripheral blood flow distribution, were assessed by cardiopulmonary exercise testing (cycle ergometry ramp protocol), in the baseline and after drug randomization.

Results:

	Placebo	Sildenafil (25 mg)	Sildenafil (50 mg)
Brachial artery diameter (mm)	3.8±0.2	3.9±0.1	4.1±0.1 *
Brachial hyperemic flow (mL/min)	420±100	470±100	530±90 *
peak VO2 (ml/min/kg	16±4	17±3	19±4 *
delta VO2/delta WR	0.9±0.06	1.0±0.07	1.10±0.06 *

*:$p<0.05$ vs Placebo

Changes in peak VO2 and delta VO2/delta WR after 50 mg sildenafil were inversely related with those in brachial flow ($r = 0.53$, $p< 0.01$; $r =0.73$, $p<0.001$).

Conclusions: In CHF, sildenafil induces a dose-related effect on endothelial function associated with a significant amelioration in peak VO2 and exercise blood flow distribution (delta VO2/delta WR). Long-term use of sildenafil as an adjunctive therapy in stable CHF patients seems a promising opportunity.

P536 Strength training does not reduce depressed mood in heart failure patients – a randomised study

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Depressed mood is common in chronic heart failure (CHF) patients (pts) and appears to be a powerful independent predictor of mortality in cardiac pts. We hypothesised that a structured, resistance exercise programme, while improving strength and endurance, might reduce the severity of depressed mood.

Methods: 45 CHF pts (mean age 65 yrs, male 39, female 6, ischaemic 27, non-ischaemic 18, LVEF 28 ± 7%), after baseline testing, were randomised to 3 mths of resistance exercise training (EX) thrice per week (22 pts, VO2peak 15.1 ± 3.4, BMI 28.6) or control group (CON) continuing with usual activities (23 pts, VO2peak 16.3 ± 5.0, BMI 27.4). Training alternated upper and lower body exercise, predominantly using graduated hydraulic resistance. Depressed mood was assessed using the Cardiac Depression Scale (CDS), anxiety using Spielberger's state anxiety (ANX), CHF global quality of life using the Minnesota Living with Heart Failure Questionnaire (LWHFQ) and strength with isokinetic dynometer (MERAC), averaging torque for 2 upper trunk and 2 lower trunk patterns of strength. Normal data was expressed as mean ± SD and between group differences analysed by ANOVA and paired t-tests, associations using Pearson correlation.

Results: Four EX and 2 CON pts were subsequently withdrawn. In spite of significant gains in strength in EX pts from 85 ± 24 to 103 ± 30 newton metre (EX vs CON, $p < 0.005$) and VO2peak (EX vs CON, $p < 0.05$), there was no greater reduction in CDS for EX compared with CON ($p = 0.69$). Both groups demonstrated non-significant trends towards lower CDS over 3 mths from the high baseline of 87.3 ± 25.0 to 82.7 ± 22.8, possibly from the marked increase in patient contact during the study. There were no differences between groups in either ANX or LWHFQ and no improvement in either group over time.

Baseline CDS did not predict the change in strength ($r = 0.19$) or VO2peak ($r = 0.08$). If the very depressed pts (15 pts had CDS > 100) were excluded, lower baseline CDS (less depression) was associated with more strength gain ($r = 0.51$, $p = 0.015$).

Conclusion: Resistance exercise training does not appear to reduce depressed mood in CHF patients.

P537 Echocardiographic indexes of right ventricular function, hemodynamic response to exercise and functional capacity in patients with dilated cardiomyopathy: a retrospective study

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Objective: To determine whether rest echo derived measurements of right ventricular (RV) function predict hemodynamic response to exercise and exercise tolerance in patients with dilated cardiomyopathy referred for cardiac transplantation.
Design: retrospective evaluation of RV echocardiographic parameters, rest and exercise right heart catheterisation (RHC) during cardiopulmonary exercise testing. The following RV echo variables were considered: Tricuspid annular plane systolic excursion (TAPSE), RV area fractional shortening (RVFS), RV diastolic diameter (RVDD).
Statistical methods: linear regression models and multivariate regression analysis.
Subjects: 149 patients (male 127; 72 with coronary artery disease, 68 with idiopathic dilated cardiomyopathy, 9 with valvular disease) with left ventricular (LV) end diastolic diameter index >26 mm and ejection fraction <40%. At the time of RHC all patients were in stable clinical condition, and had been on maximized oral therapy for at least two weeks; systolic pulmonary pressure was <40 mmHg and right atrial pressure <12 mmHg at rest.
Results: Multivariate regression analysis gave TAPSE and RVDD as independent predictors for worse cardiac output at rest (r=0.33, p=0.004 and r=-0.21, p=0.022 respectively) and during exercise (r=0.33, p=0.015 and r=-0.25, p=0.05); for worse cardiac index at rest (r=0.30, p=0.002 and r=-0.27, p=0.007) and during exercise (r=0.31, p=0.012 and r=-0.29, p=0.017). Lower TAPSE also predicted lower stroke volume at rest (r=0.39, p=0.003) and higher pulmonary vascular resistance during exercise (r=-0.29, p=0.017).
Peak oxygen consumption did not correlate with any RV echocardiographic index.
Conclusions: rest echocardiographic indexes of right ventricular dysfunction (lower TAPSE and higher RVDD) predict a poorer hemodynamic response to exercise in patients with dilated cardiomyopathy and congestive heart failure.

P538 Improved left ventricular systolic function after pharmacologic facilitation of coronary intervention in acute myocardial infarction

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Facilitation of percutaneous coronary intervention (PCI) with combined thrombolytic therapy (reduced dose fibrinolytic and full dose platelet GP IIb/IIIa inhibitor) is a new approach to treat patients (pts) with acute myocardial infarction (AMI). Facilitated PCI (FPCI) is assumed to cause better salvation of the myocardium by inducing early, full and permanent reperfusion.
The objective of this study was to compare regional and global contractile function in cohort of patients treated for ST-elevation AMI with FPCI (Gr A) (1/2 dose fibrinolytic drug-Actylise + full dose antiplatelet drug -Abciximab + transport to cathlab + coronary angiography + immediate PCI if needed) or Primary PCI (PPCI) (Gr B) (transport to cathlab + coronary angiography + PCI ± Abciximab, given based on operators consideration).
Data of 159 consecutive patients (pts)(66% males, 34% females, mean age 56,84 ± 9,9 years) were analyzed. 109 pts treated with FPCI, 50 pts treated with PPCI. Pts with cardiogenic shock before treatment iniciation were excluded. Echocardiography was performed 4 days and 6 months after AMI.
We found that in Gr A, during the follow-up period there was an improvement in: left ventricular ejection fraction (LVEF) (from 58,5±8,5 to 61,1±10,1; p<.005); wall motion score index (WMSI) and infarct related artery WMSI (IRAWMSI) from 1,44±0,31 to 1,27±0,33 and 1,87±0,47 to 1,49±0,49 respectively (p<.001). Meanwhile, in Gr B there was a significant decrease in LVEF (from 55,3±9,1 to 52,8±11,9;p<.05) and non-significant change in WMSI and IRAWMSI.
Gr A had in comparison with Gr B higher LVEF at follow-up (61,1±10,1 vs. 52,8±11.9; p<.005); lower WMSI and IRAWMSI at baseline (1,44±0,33 vs. 1,56±0,35; p< .05) and (1,85±0,48 vs. 1,98+0,52; p<.05) respectively and at follow up(1,28±0,34 vs. 1,51±0,38; p<.001) and (1,49±0,52 vs. 1,89±0,59; p<.001)respectively.
Conclusion: Treatment of ST-elevation acute myocardial infarction with facilitated PCI improved early and late left ventricular systolic function when compared to primary PCI.

P539 Post-systolic thickening is prevented by late preconditioning: a sonomicrometry study in conscious dogs

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Purpose: Postsystolic wall thickening (PSWT) relates to the myocardial thickening that occurs after the aortic valve closure. PSWT has been extensively reported during ischemia-induced myocardial dysfunction. However, the extent and evolution of the magnitude of PSWT during late preconditioning has not been described.
Methods: Seven dogs were chronically instrumented to measure (sonomicrometry) systolic wall thickening (SWT) and PSWT of the posterior wall. A 10-min occlusion of the left circumflex coronary artery (CAO) was performed (day 0) and repeated 24h later (day 1).
Results: At day 0, CAO markedly decreased SWT (-103%) and induced a subsequent myocardial stunning. Conversely, CAO induced a dramatic increase in PSWT during the first hours of reperfusion, demonstrating a symmetrical evolution vs SWT. At day 1, SWT was similar to day 0 at baseline but PSWT was reduced (-66%). During CAO at day 1, the decrease in SWT was similar to day 0 but the impairment of myocardial function during reperfusion was less severe, indicating delayed preconditioning. Throughout reperfusion at day 1, PSWT was significantly smaller than the corresponding one at day 0 (–49%). Interestingly at day 1, the SWT to total WT ratio was significantly increased at baseline and during reperfusion as compared to day 0, indicating that a greater part of total WT occurred during ejection.
Conclusions: During and after CAO, regional systolic wall motion is altered with a simultaneous decrease in SWT and increase in PSWT. Furthermore, PSWT is dramatically reduced in the preconditioned state, characterizing a myocardial contractile protective adaptation.

P540 Altered right ventricular homeometric and heterometric autoregulation in the failing canine heart

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Objective: Increased right ventricular afterload is a common problem in various heart diseases. This study was performed to determine the effects of an acute increase of right ventricular afterload in normal and failing canine hearts.
Methods: In 6 animals heart failure was induced by arterio-venous shunts for 3 months. 6 sham-operated animals served as controls. Heart rate, RV systolic and end-diastolic pressure (RVSP, RVEDP), and enddiastolic volume (RVEDP) and pressure-volume loops (conductance-catheter) were recorded. The slope of the end-systolic pressure-volume relationship (ESPVR) and preload recruitable stroke work (PRSW) were calculated as a load-independent index of myocardial contractility. Afterload increase was induced by constriction of the pulmonary artery with an increase in RVP to 35 and to 50 mmHg, respectively.
Results: The induction of volume-overload heart failure resulted in a significant increase of RVEDP (12.7±1.7 vs. 6.9±1.4 mmHg, p<0.05) and RVEDV (39.3±2.3 vs. 33.6±3.0 ml, p<0.05). Baseline ESPVR (1.47±0.24 vs. 1.53±0.32 mmHg/ml) and PRSW (13±4 vs. 13±2 kerg) did not differ. Moderate afterload increase to RVP=35mmHg led to a similar increase in ESPVR and PRSW at unchanged RVEDP and RVEDV. At an afterload of RVP=50 mmHg ESPVR (1.62±0.38 vs. 2.99±0.29 mmHg/ml, p<0.05) and PRSW (15.5±2.1 vs. 39.2±4.8 kerg) was significantly lower and RVEDP (16.3±1.9 vs. 8.5±1.9 mmHg, p<0.05) was significantly higher in the heart failure group.
Conclusions: Volume overload heart failure per se does not impair right ventricular contractility. However the inotropic adaptation (homeometric autoregulation) to an increased afterload is limited which is partly compensated by the Frank-Starling mechanism (heterometric autoregulation).

PULMONARY CIRCULATION

P541 Clinical assessment of the positive inotropic effect of prostacyclin analogs in patients with pulmonary arterial hypertension: an ultrasonic strain/strain rate study

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Since the 1990's a number of prostacyclin (PC) analogs have been introduced into the clinical management of patients with pulmonary arterial hypertension (PAH). The clinical observations show that PC increases the cardiac output in patients with PAH. This might be related with PC effect on the RV contractility that has not yet been clinically evaluated. Recently the ultrasound-based regional one-dimensional deformation parameters, Strain (S) and Strain Rate (SR), have been

introduced into clinical practise and have been shown to reflect myocardial contractile properties. They have also been used to quantify regional RV contractile function.
Study aim: To evaluate the role of the new deformation indices in detecting changes in RV regional systolic function in patients with PAH receiving PC (Group I) and to compare these findings with both those not receiving treatment (Group II) and healthy controls.
Methods: 25 patients with PAH were studied: 14 Group I (7M/age 49±14 y) and 11 Group II (5M/age 51±15 y). Data were compared with that from 37 Controls. Standard TTE, blood pool Doppler and 2-D colour Myocardial Velocity Imaging examinations were performed. RV free wall (FW) longitudinal deformation was measured for the two morphologically distinct segments: 1) basal smooth and 2) apical trabecular.
Results: Ultrasound estimated systolic pulmonary artery pressure (PAP - 93±23 mmHg Gr. I/89±22 mmHg Gr. II) and other characteristics (age, 6 minutes walking test) did not differ between patient groups. Mean RV FW regional peak systolic S and SR values are shown in Table 1.

Table 1

	SR 1/s		S %	
	Basal	Apical	Basal	Apical
Group I (n=14)	-2,3±0,9	-2,0±1,5†	-27±13*	-20±13†*
Group II (n=11)	-2,2±0,8	-0,8±1,1*	-26±13*	-7±13*
Control (n=37)	-2,9±1,0	-2,6±0,9	-43±11	-41±11

† $p < 0,01$ (vs. Group II); * $p < 0,01$ (vs. Control).

Conclusions: 1) S/SR indices showed significant differences in regional RV deformation between the patients and healthy controls; 2) at the same level of PAP both S and SR measured in the apical RV FW portion could detect partially restored RV regional function in patients receiving PC and therefore could be used as a new non-invasive approach in monitoring PC therapy.

P542 Flat force-frequency relationship during exercise predicts stress-induced pulmonary hypertension

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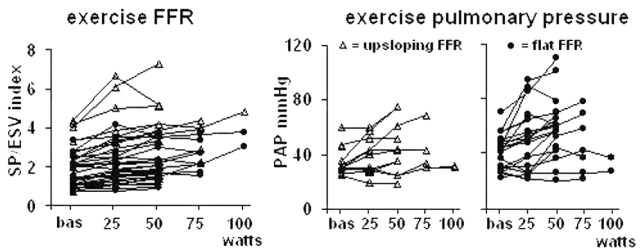
Background: Force-Frequency relationship (FFR) is a theoretically and methodologically robust method for the assessment of left ventricular contractility and can be assessed non invasively during exercise echo. Increased pulmonary artery pressure (PAP) during maximal exercise might represents lack of exercise contractility reserve in patients with resting left ventricular dysfunction.
Aim: To assess the feasibility of a totally noninvasive estimation of FFR and of Doppler derived PAP during exercise stress in the echo lab in patients with severe left ventricular dysfunction.
Methods: We enrolled 35 consecutive patients (age 62±8 years, ejection fraction=31±7%, EDV=193±61 ml) referred for exercise stress echo. Systolic PAP was derived from the tricuspid regurgitating jet velocity. 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).
Results: 22 patients had an abnormal flat-downsloping, and 13 a normal upsloping FFR (figure), in spite of comparable resting ejection fraction (29±8 vs 32±7%, p=ns). Baseline pulmonary artery pressure was higher in flat FFR (41+13 vs 31+11 mmHG, $p<0.05$) and peak stress pulmonary hypertension (PAP >45 mmHg) was present in 76% of pts with flat-downsloping, vs 38% of pts with upsloping FFR, $p<0.05$).



Conclusions: A totally noninvasive estimation of force-frequency relation is feasible during exercise stress in the echo lab. It unmasks a substantially heterogeneous contractile response in patients with similar values of conventional indices of left ventricular function. Lack of contractility reserve is significantly associated with stress induced pulmonary hypertension.

P543 Plasma brain natriuretic peptide levels predict the functional capacity of patients with severe pulmonary hypertension better than echocardiographic parameters of right ventricular function

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Background: The aim of the study was to define whether the plasma levels of brain natriuretic peptide (BNP) and the ultrasound evaluation of right ventricular (RV) performance may predict functional capacity in patients with severe pulmonary hypertension.
Methods: In 48 patients with primary or selected forms of non primary pulmonary hypertension, plasma BNP levels were measured and the following echocardiographic parameters of RV performance were assessed: tricuspid annular plane systolic excursion (TAPSE), RV area change, Tei index, peak systolic velocity and peak strain in both basal and medium segments of the RV wall. Functional capacity was assessed by means of the 6 minutes hall walk test (6MWT).
Results: Thirteen patients were unable to walk a distance greater than 150 m during the 6MWT. At univariate analysis, plasma BNP levels above 276 pg/ml and TAPSE below 15 mm significantly discriminated patients with a low exercise capacity (area under the receiver operating characteristic curve = 0.80, 95% confidence intervals 0.66-0.90 for BNP and 0.64, 95% confidence intervals 0.49-0.77 for TAPSE). At multivariate analysis only plasma BNP levels above 276 pg/ml was related to the distance covered during the 6MWT.
Conclusions: In patients with severe pulmonary hypertension, high plasma BNP levels are a stronger predictor of impaired functional capacity than any echocardiographic indicator of RV dysfunction.

P544 Correlations between echocardiographic and hemodynamic parameters in primary pulmonary hypertension: a Doppler tissue imaging study

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Background: Right heart catheterisation (KT) is often necessary for the management of pts with primary pulmonary hypertension (PPH). Some Doppler tissue imaging (DTI) derived parameters have shown interesting correlations with hemodynamic measurements in various types of pts and could avoid repeated invasive investigations in pts with PPH.
Aim of the study: To study the potential help of DTI in the hemodynamic evaluation of pts with PPH in comparison with KT.
Methods: We studied 18 pts with PPH (5M/13F, 49±14 yrs). They all underwent complete echocardiography and KT with measurement of right ventricular ejection fraction (RVEF) by thermodilution technique in a delay no longer than 48 hours. From apical 4C view, we recorded long-axis myocardial motion within the RV septal (sep) and lateral (lat) walls, 1 to 2 cm away from the level of valvular annulus and measured maximal (max), mean (mn) velocities, time-velocity integrals (TVI) of systolic (S) and protodiastolic (E) myocardial motion waves, and isovolumic contraction and relaxation times (ICT and IRT).
Results: Main results of KT were the followings: mean PAP: 53±9 and syst PAP: 83±15 mm Hg, RAP: 8.7±3.8 mm Hg, cardiac index: 2.2±0.5 l/mn/m^2, PVR: 1025±271 dynes s cm^{-5}, RVEF: 19±6%.
At echo, syst PAP was 84±17 mm Hg and cardiac index 2.1±0.6 l/mn/m^2; the ratio of RVOT TVI to maximal velocity of tricuspid regurgitation correlated well with haemodynamic PVR (r= 0.747, p0.005).
DTI showed an increased in both sep and lat (120±42 ms) IRT but no correlations were found between IRT and PAP values in those pts with high levels and narrow range of PAP values. Ratio of tricuspid flow to lat E waves correlated weakly with right atrial pressure (r=0.49, p=0.05). Sep and lat S mn correlated significantly with cardiac index (respectively r=0.682, p=0.02; r=0.595, p=0.012) and PVR (r=-0.53, p=0.03; r=-0.66, p=0.005). RVEF was better correlated with sep S TVI (r=0.81, $p<0.001$) than with lat S max (ns) or lat TVI (r=0.53, p=0.04). It also correlated with lat ICT (r=-0.545, p=0.04).
Conclusion: DTI allows an easy echocardiographic approach of RV hemodynamics in pts with PPH. VTI of systolic septal motion is well correlated with RVEF, thereby showing the importance of ventricular interdependence and the role of septal longitudinal shortening in determining RV ejection. Some previously described DTI parameters such as IRT and tricuspid E/lat E failed to be enough differential in that selected population.

P545 A novel tissue Doppler index of right ventricular contractility as prognostic factor in pulmonary hypertension

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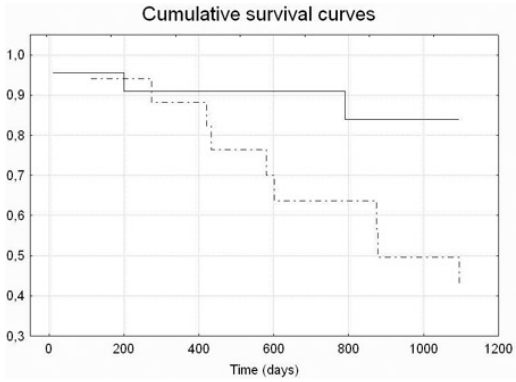
The function of hypertrophic right ventricular (RV), which is the main prognos-

tic factor in severe pulmonary arterial hypertension (PAH) is particularly difficult to assess non-invasively. Myocardial acceleration during isovolumic contraction (IVA) obtained in tissue doppler imaging (TDI) have been recently shown as a load-independent non-invasive index of RV elastance in animal model. The aim of our study was to assess the utility of IVA as an index of RV contractile function in the prognostic evaluation of PAH patients.

Material and methods: 40 patients mean age 41,6 ±14 with severe PAH (mean PAP 62mmHg ±18,3mmHg) were assessed and followed for up to 36 months. Echocardiographic examination and TDI were performed on the day of diagnostic right heart catheterization. Signals of TDI were recorded from tricuspid annulus at the free wall of RV in four- chamber apical view and IVA was measured as described in published data. We compared IVA in survivors and non-survivors groups. According to ROC analysis the optimal cut-off value of IVA in the selections of deaths was assessed.

Results: The mean value of IVA was 3.26 m/s2 ±1,19. IVA was significantly decreased in non-survivors vs survivors (2,57 m/s2 ±0,78 compared to 3,57 m/s2 ±1,2). Value of IVA 3m/s2 significantly (p=0,02) differentiated survivors from non-survivors (at picture solid line –IVA <3m/s2, dashed line >3m/s2). This value of IVA reached 90% negative predictive value (NPV) for death.



Cumulative survival curves.

Conclusion: Easily and quickly obtainable non-invasive TDI parameter- myocardial acceleration during isovolumic contraction reflects depressed RV contractile function and is related to prognosis in PAH. Whether successful treatment or progression of the disease may be monitored by following the eventual changes in IVA requires further studies.

P546 Role of pravastatin in preventing and reversing monocrotaline-induced pulmonary hypertension in rats

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Recent studies suggest that simvastatin attenuates and reverses pulmonary vascular injury in a rat model of pulmonary arterial hypertension (PAH) induced by monocrotaline (MCT). However, there have been no precise reports on the different kinds of statins on pulmonary vascular pathobiology in MCT-induced PAH.The present study was designed to examine the role of pravastatin in preventing and reversing MCT-induced PAH in rats. Rats were injected with 40 mg/kg of MCT subcutaneously and randomized to either 250mg/kg/day of pravastatin or placebo for 3 weeks. Animals treated with MCT and survived for 3 weeks were assigned to either pravastatin or placebo for next 3 weeks. We also assessed the prophylactic treatment effects of 100mg/kg/day of pravastatin for 2 weeks followed by MCT and pravastatin for 3 weeks. Pravastatin immediately following MCT and its prophylactic treatment markedly attenuated PAH with severe pulmonary vascular remodeling and prolonged survival rate ($p < 0.001$). eNOS expression on the endothelium of the pulmonary arteries was significantly decreased in the placebo group, but it was prevented after pravastatin. Enhanced expression of P-selectin on the endothelium of the pulmonary arteries and marked accumulation of CD45-positive leukocytes and proliferating cell nuclear antigen-positive leukocytes in the lung tissue of the placebo group were significantly attenuated in the pravastatin group. Late treatment with pravastatin did not palliate PAH nor improved survival. Thus, pravastatin prevented development of PAH and pulmonary vascular remodeling and prolonged survival in rats. These effects were associated with marked improvement of pulmonary vascular endothelial dysfunction and activation and anti-inflammatory and anti-proliferative effects in the lung tissue. In contrast, pravastatin failed to reverse established PAH. This study may provide an insight into therapeutic strategy of statins in pulmonary arterial hypertension.

P547 Tadalafil and dexamethasone prevent pulmonary hypertension in high-altitude pulmonary oedema susceptible subjects

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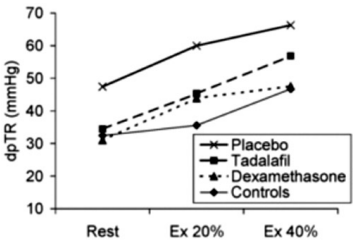
High altitude pulmonary edema (HAPE) is associated with pulmonary hypertension during hypoxemia. Insufficient NO production may contribute to it. Other mechanisms such as inadequate alveolar clearance of sodium and water are claimed to cause HAPE. Thus, we investigated if tadalafil (tadal; acting on cGMP) and dexamethasone (dexa; influencing alveolar fluid clearance) reduce pulmonary pressure at high altitude.

Methods: 23 healthy subjects with history of HAPE were randomly assigned to tadal 10mg bid (n=7), dexa 8mg bid (n=9), or placebo (n=7) starting the day before ascending in <24h to 4559m. 7 non-HAPE susceptibles served as controls. Doppler-echocardiography (pressure gradient of tricuspid regurgitation [dpTR]) was performed at low altitude (490m) <1month prior to ascent and after an overnight stay at 4559m at rest and 2 different workloads (20% and 40% of peak exercise capacity on bicycle).

Results: At 490m, dpTR did not differ between HAPE susceptibles and controls (rest mean 19±5mmHg). At 4559m, there was an increase of dpTR in all subjects at rest, highest in placebo treated HAPE susceptibles (27±11mmHg, $p<0.05$ vs. controls). Increase of dpTR was lowered by dexa ($p<0.05$) and comparable to that seen in controls (14±9mmHg; controls: 16±7 mmHg, $p>0.1$). In HAPE susceptibles on tadal, the increase also tended to be smaller (18±14mmHg, p=0.09 vs placebo) and did not differ from controls ($p>0.1$). During exercise, dexa normalised the pathological PAP increase seen in HAPE susceptibles, whereas tadal was less effective (figure).



Pulmonary pressure at high altitude.

Conclusion: At high altitude, dexa may be used to normalise pulmonary pressure in HAPE susceptibles, both at rest and during exercise. Prevention with tadal is equally effective at rest, but slightly less effective during exercise.

P548 Chronic pulmonary hypertension in high-altitude residents with re-entry pulmonary oedema, a special form of high-altitude pulmonary oedema

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Background: High altitude pulmonary edema (HAPE) usually occurs in susceptible subjects 24h after a fast climb to an altitude > 3000m above sea level. It is associated with exaggerated hypoxia-induced pulmonary hypertension related to endothelial dysfunction and decreased alveolar fluid clearance related to impaired alveolar transepithelial sodium transport. Re-entry pulmonary edema is a particular form of lung edema affecting healthy asymptomatic high-altitude residents returning home after a sojourn (> 1 week) at low altitude. The pathogenetic underlying mechanisms have not been studied and might be different from those involved in HAPE.

Hypothesis: Re-entry pulmonary edema is associated with persistent pulmonary hypertension in high-altitude dwellers.

Methods: 21 young (age: 16±3 years, age±SEM) healthy asymptomatic Bolivian residents of La Paz (3600m) who experienced at least one episode of re-entry pulmonary edema and 19 healthy age-matched (13±1 years) Bolivian without a history of re-entry pulmonary edema despite repeated sojourns at low altitude were included. Systolic pulmonary-artery pressure (echocardiography), arterial oxygen saturation (SaO2), and plasma concentrations of nitric oxide (NOx) and endothelin-1 were measured.

Results: Re-entry edema-prone subjects had a roughly 66% higher "usual" systolic pulmonary-artery pressure (37±2 mmHg) than the control group (22±1 mmHg) ($p<0.0001$). This exaggerated hypoxic pulmonary vasoconstriction was not related to more severe hypoxemia (SaO2: 91±1 vs 91±2%, re-entry edema-prone vs control group, p=0.74) or endothelial dysfunction as assessed by NOx (28±3 vs 27±3 umol/l, p=0.88) and ET-1 (3.0±0.2 vs 2.9±0.2 pg/ml, p=0.71) plasma levels.

Conclusion: Young, apparently healthy, re-entry pulmonary edema-prone high-altitude dwellers have a chronically elevated pulmonary artery pressure. These findings provide the first evidence that re-entry pulmonary edema represents a marker of chronic pulmonary hypertension.

P549 Isobaric and isometric pulse analisys of the pulmonary artery function: role of smooth muscle activation in acute hypertensive states

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Acute pulmonary hypertension (PH) may arise with or without smooth muscle (VSM) tone increase. Our aim was to determine how VSM activation (VSMA) affects both the conduit and wall buffering functions of the pulmonary artery (PA) during PH states.
Methods: We recorded pressure and diameter in 6 sheep to assess elastic (E) and viscous (V) PA wall parameters during control (CTL) and 3 states of acute PH: passively induced (PA mechanical occlusion, PPH), actively induced (intravenous phenylephrine, APH), and a combination of both (APPH). To evaluate VSMA, isobaric (PPH vs APH) and isometric (CTL vs APPH) analyses were made. We assumed the PA to be a low pass filter (cutoff frequency, fc=E/V; constant gain in dynamic range=1/E). The local wall cushioning function (WCF) as V/E^2 and the conduit function (CF) through the characteristic impedance (Zc) were evaluated.
Results: (see table): VSMA isobarically improve CF, due to arterial vasoconstriction (reduction of E). The increase in WCF implies that whereas compliance (1/E) participates in the cushioning of the pulsatility, V, related to VSMA independently of the pressure level, contributes in reducing the dynamic range by attenuation of high frequencies. Compared to passive isometric state (CTL), VSMA (APPH) showed high Zc with no significant change in WCF, even at the highest pressure level.

Hemodynamic and mechanical parameters.

	CTL	PPH	APH	APPH
SP	19±7	30±11 a	27±8 a	38±9 abc
DP	11±6	15±6 a	13±7	17±7 ac
SD	23.8±2.3	24.7±2.1 a	23.6±2.1 b	24.4±2.1 ac
DD	22.6±2.4	23.6±2.2 a	21.6±2.6 ab	22.5±2.5 bc
Zc	656±350	801±310 a	486±373 b	728±492 ac
E	5.5±1.2	9.3±3.5 a	6.4±1.2 b	7.9±1.6 ac
V	4.9±0.6	4.7±0.5	7.6±0.7 ab	7.6±0.6 ab
fc	18±3	33±12 a	13±2 ab	16±3 bc
WCF	1.8±0.8	0.7±0.5 a	2.0±0.6 b	1.3±0.4 bc

Means±SD. $p<0.05$ vs CTL (a), vs PPH (b), vs APH (c). SP, DP, SD and DD: systolic and diastolic pressures (mmHg) and diameters (mm). Zc (dyn s cm^{-5}), E (mmHg/mm), V (10^{-2} mmHg s/mm), fc (Hz), WCF (10^{-3} s cm^2/dyn).

Conclusions: VSMA during acute PH states could be considered as a compensating mechanism for the deleterious effects of high pressure.

P550 GTP cyclohydrolase I deficiency results in oxidative stress and pulmonary hypertension

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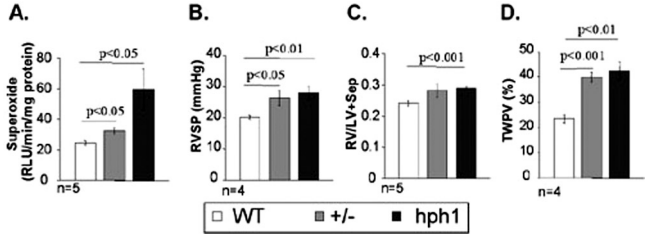
GTP Cyclohydrolase I (GTPCHI) is the rate-limiting enzyme in the synthesis of tetrahydrobiopterin (BH4), a co-factor for nitric oxide synthase (NOS). Without BH4, NOS produces superoxide instead of nitric oxide (NO). NO deficiency and oxidative stress have been implicated in the pathogenesis of pulmonary hypertension and vascular remodelling.
Aim: We examined for the effects of lung BH4 deficiency on oxidative stress and the pulmonary vasculature, using the hph1 mouse mutant which has constitutive GTPCHI deficiency.
Methods: We studied wild type (WT), heterozygous (+/-) and hph1 littermates. Lung GTPCHI mRNA levels were measured by rtPCR, and BH4 levels by differential iodine oxidation and HPLC. Superoxide was measured in lung homogenates with 5μM lucigenin chemiluminescence. Right ventricular systolic pressure (RVSP) was determined by closed-chest cardiac puncture. Right ventricular (RV) and left ventricular (LV+S) wet weights were measured, and lung sections were prepared in paraffin and stained with alpha smooth muscle actin antibody and elastin.
Results: Lung GTPCHI mRNA levels were reduced in +/- and hph1 (48±5% and 23±2% of WT, $p<0.001$). Lung BH4 levels were also reduced in +/- and hph1 (1.54±0.49 and 0.62±0.08 vs WT 3.94±0.54 pmoles/mg protein, $p<0.01$). Superoxide levels were higher in +/- and hph1 (Fig. A). RVSP, RV weights and percentage of lung thick-walled peripheral vessels (TWPV) were higher in hph1 (Figs. B to D).
Conclusions: GTPCHI deficiency in the hph1 mouse results in BH4 deficiency, leading to higher oxidative stress, pulmonary hypertension, vascular and right ventricular remodelling. These data reveal a new causative mechanism for pulmonary hypertension, and has important therapeutic implications.



P551 Splenectomy: a strong risk factor for pulmonary hypertension in thalassemic patients

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Background: Pulmonary hypertension was previously reported as a common cardiovascular manifestation in thalassemic patients. It is especially apparent in splenectomized patients. However, the association between splenectomy and pulmonary hypertension remains uncertain.
Method: We performed transthoracic echocardiography in 68 thalassemic patients (32 splenectomized and 36 non-spenectomized).
Pulmonary artery pressure was estimated by measuring the systolic transtricuspid pressure gradient of tricuspid regurgitation and adding to right atrial pressure, which was estimated by response of inferior vena cava to deep inspiration.
Pulmonary hypertension was defined as systolic pulmonary artery pressure of more than 35 mmHg. Status of splenectomy and other clinical data of the pulmonary hypertensive patients and those with normal pulmonary pressure were compared. Multivariate regression analysis was used to search for potential risk factors.
Results: There were 29 patients with and 39 patients without pulmonary hypertensive patients there were significantly higher number of nucleated red blood cells and platelet count. The prevalence of splenectomy in patients with pulmonary hypertension is higher than in those without (75.8 percent vs 25.6 percent, odds ratio 9.1, 95% CI 3.0-27.7). With multivariate analysis, splenectomy stood out as the only factor significantly related to pulmonary hypertension.
Conclusion: Our findings indicated that splenectomy is a strong risk factor for pulmonary hypertension in thalassemic patients.

P552 Multi-stage risk stratification for in-hospital overall mortality in pulmonary embolism

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Background: Pulmonary embolism (PE) presents high mortality rates, thus risk stratification in different moments is critical to guide the strategy for treatment.
Purpose: To determine the association between clinical and laboratory variables with overall mortality using a stepwise multi-stage approach to patients with PE.
Methods: A multicenter cohort involved 727 patients (57,9% female; age 69±16 years) admitted to tertiary hospitals in Brazil between Jan/98 and May/03 with the diagnosis of PE confirmed by: pulmonary angiography, helical computer tomography, magnetic resonance, echocardiography (ECHO), lung scan or venous duplex-scan with thrombus and clinical manifestation of PE. Additonal exams encompassed electrocardiogram (ECG), chest x-ray, creatinophosphokinase MB fraction (CKMB), troponin I (TnI) and ECHO. Data were submitted to univariate analysis and those variables with $p < 0.20$ entered logistic multivariate models considering intra-hospital overall mortality as the dependent variable. Three separated models were built including the following independent variables: model 1. clinical variables; model 2. same as model 1 plus right ventricular overload in ECG and alterations in x-ray; model 3. same as model 2 plus elevated CKMB, elevated TnI, and right ventricular dysfunction in ECHO. $P < 0.05$ was considered significant for odds ratios (OR) in all multivariate models.
Results: The multivariate models identified the following variables to be significant in predicting mortality: model 1- age > 40 years old (OR 1.02; CI95% 1.00-1.04), cor pulmonale (OR 2.51; CI95% 1.21-5.21), chest pain (OR 0.60; CI95% 0.38-0.95), arterial hypotension (OR 3.19; CI95% 2.00-5.09), and cyanosis (OR 1.79; CI95% 1.12-2.88); model 2- age > 40 years old (OR 1.02; CI95% 1.01-1.04), cor pulmonale (OR 2.66; CI95% 1.22-5.80), arterial hypotension (OR 3.09; CI95% 1.86-5.14), cyanosis (OR 1.81; CI95% 1.09-3.01), and alterations in x-ray (OR 2.43; CI95% 1.52-3.86); model 3- age > 40 years old (OR 1.03; CI95% 1.01-1.06), cor pulmonale (OR 2.98; CI95% 1.30-6.82), arterial hypotension (OR 3.17; CI95% 1.83-5.49), alterations in x-ray (OR 2.14; CI95% 1.30-3.54), and right ventricular dysfunction in ECHO (OR 1.91; CI95% 1.30-3.54).
Conclusion: This multi-stage approach allowed for the identification of clinical

and laboratory variables associated indepedently with overall mortality in a stepwise manner since the initial evaluation of the patients with PE. The practical usefulness of this approach in the clinical setting remais to be tested.

P553 Biomarkers strategy of risk stratification in patients with acute pulmonary embolism

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Objective: Pulmonary embolism (PE) can cause right ventricular strain and in some cases a myocardial injury. Brain natriuretic peptide (BNP) released from overloaded ventricles and troponin (realsed as the consequence of myocardial necrosis), can be helpful in the evaluation of prognosis in acute PE (APE). There are limited data on their simultaneous application for the prediction of short term prognosis in APE. We tried to assess optimal strategy using serum NT-proBNP together with cardiac troponin T (cTnT) in the prediction of the mortality and the serious adverse events (SAE) in APE.
Material and Methods: We evaluated 63 patients (21M, 42F, aged 65±17 years) with APE proven by high probability lung scintigraphy or spiral CT. On admission blood samples were collected for NT-proBNP and cTnT (Roche, ECLIA).
Results: 87% pts were anticoagulated, while 13% pts received also thrombolysis. 12 pts died during hospitalization (9 APE related deaths, 2 fatal bleedings, and 1 death due to cancer), 20 pts experienced in hospital SAE (at least one of: death, thrombolysis, cardiopulmonary resuscitation, intravenous use of catecholamines). Serum NT-proBNP concentration was higher in survivors than in PE related deaths (median 2305 pg/ml (range: 16-33340) vs 15862 pg/ml (950-60958), p<0,001). Serum NT-proBNP and cTnT were higher in patients with SAE than in pts with uncomplicated clinical course (median 11939 pg/ml (range: 16-27752) vs 10678 pg/ml (414-60958), p<0,001 and mean±SD 0,13±0,15 ng/ml vs. 0,05±0,11 ng/ml, p=0,02, respectively). Although elevated serum levels of NT-proBNP identified all PE related deaths and all pts with SAE (NPV 100%) (table), this biomarker showed only low PPV for both endpoints. However, additional cTnT assessment markedly improved PPV with still acceptable NPV.

	Positive test, all pts	PE related deaths positive test, N=9	SAE positive test, N=20	PPV/NPV for PE related deaths	PPV/NPV for SAE
NT-proBNP>400 pg/ml	50/63 pts (79%)	9/9 (100%)	20/20 (100%)	18%/100%	40%/100%
cTnT>0,05ng/ml	24/63 pts(38%)	8/9 (89%)	14/20 (70%)	33%/97%	47%/85%
cTnT>0,05ng/ml when NT-proBNP>400 pg/ml	22/50 pts (44%)	8/9 (89%)	14/20 (70%)	36%/96%	64%/79%

PPV – positive predictive value; NPV - negative predictive value

Conclusion: Serum NT-proBNP and cTnT may be elevated in patients with APE. Normal values of serum NT-proBNP indicate good, while elevated cTnT suggest worse prognosis. It seems that strategy based on clinical application of both biomarkers improves risk stratification in APE.

P554 Clinical usefulness and prognostic value of elevated cardiac troponin-I levels in acute pulmonary embolism

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Background: Right ventricular myocardial ischemia and injury contribute to right ventricular dysfunction and failure during acute pulmonary embolism. The objective of this study was to evaluate the clinical usefulness of cardiac troponin I (cTnI) in the assessment of right ventricular involvement and short-term prognosis in acute pulmonary embolism.
Methods: Thirty-eight patients with acute pulmonary embolism were included in the study. Clinical characteristics, right ventricular involvement, and clinical outcome were compared in patients with elevated levels of serum cTnI versus patients with normal levels of serum cTnI.
Results: Among the study population (n = 38 patients), 18 patients (47%) had elevated cTnI levels (mean ± SD 1.6 ± 0.7 ng/mL, range 0.7-3.7 ng/mL, median, 1.4 ng/mL), and comprised the cTnI-positive group. In the other 20 patients, the serum cTnI levels were normal (< or =0.4 ng/mL), and they comprised the cTnI-negative group. In the cTnI-positive group (n = 18 patients), 12 patients (67%) had right ventricular dilatation/hypokinesia, compared with 3 patients (15%) in the cTnI-negative group (n = 20 patients, P =.004). Right ventricular systolic pressure was significantly higher in the cTnI-positive group (51 ± 8 mm Hg vs 40 ± 9 mm Hg, P =.002). Cardiogenic shock developed in a significantly higher number of patients with elevated serum cTnI levels (33% vs 5%, P =.01). In patients with elevated cTnI levels, the odds ratio for development of cardiogenic shock was 8.8 (95% CI 2.5-21).
Conclusions: Patients with acute pulmonary embolism with elevated serum cTnI levels are at a higher risk for the development of right ventricular dysfunction and cardiogenic shock. Serum cTnI has a role in risk stratification and short-term prognostication in patients with acute pulmonary embolism.

P555 Brain-type natriuretic peptide or Troponin measurement for identifying sub-massive pulmonary embolism?

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Purpose: Measurement of B-type natriuretic peptide (BNP) and cardiac troponin (Tn) recently showed prognostic value in acute pulmonary embolism (PE). Our aim was to specify the respective value of these markers to diagnose acute right ventricular (RV) overload as well their prognostic value in acute PE.
Methods: patients admitted for acute and severe PE were consecutively studied. Patients with shock on admission were excluded. At admission, Doppler-echocardiographic examination was recorded and blood samples were obtained for blinded measurement of BNP (Triage®) and Tn I (N < 0.10µg/l). Acute RV overload was diagnosed when at least 2 echographic criteria were present: RV dilation (RV/LV ratio > 0.5), hypokinesis of the RV free wall, interventricular septal bulging in LV and tricuspid regurgitant velocity > 2.5 m/sec. Patients with evidence of chronic pulmonary hypertension (> 3.7m/sec) or LV dysfunction were excluded. In-hospital events were recorded.
Results: among the 50 included patients (63±19 years), evidence of echographic RV overload was observed in 23 patients and in-hospital events (late circulatory failure) occurred in 6 patients. BNP levels significantly increased in patients with RV overload (135 ± 107 vs 432 ± 296pg/ml, p < 0.001); area under ROC curve was 0.87 (sensitivity and specificity at 79% for BNP level at 200pg/ml). TnI were not significantly different in the two groups (0.14 ± 0.48 vs 0.38 ± 0.53µg/l, p = 0.16). In addition, BNP levels were significantly higher in patients with subsequent in-hospital events (614 ± 508 vs 270 ± 211pg/ml); BNP level of 300pg/ml predicted adverse outcome with sensitivity and specificity of 100% and 71% respectively.
Conclusion: during acute PE, BNP measurement is a highly sensitive marker of the RV overload with prognosis significance. BNP appears more relevant than TnI measurement to stratify these patients.

P556 The hemodynamic evaluation of inhaled aerosolized iloprost in heart transplant candidates with pulmonary hypertension

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Introduction: Secondary pulmonary hypertension (PH) in patients (P) with left heart failure is associated with increased mortality. Prior to heart transplantation (HTX) the information on the pulmonar- vascular response (PUVResp) to vasodilator exposure is of great importance for the management of postoperative (po) right-heart failure. In contrast to the frequently used vasodilators, such as nitric oxide (NO), oxygen (O) and nitroglycerin (N), there is no valid information on the efficacy and safety of the aerosolized stable prostaglandin analog iloprost (ILO) for testing the PUVResp.
Methods: In 30 HTX candidates (54+12 years) with dilated (n=14) or ischemic (n=16) cardiomyopathy (EF<25%) and PH, the PUVResp was tested with O/N (6l/min oxygen/10min + 0.8mg s.l. N) and ILO after 20 min. of washout (inhalation; 10mg/5 min., Nebutek IR) The Measurement of hemodynamics (H) was performed by using a femoral artery catheter and a pulmonary artery catheter (Swan-Ganz-Catheter; cardiac output measurements by Fick techniques).
Results: In comparison to the baseline values the inhalation of ILO lowered the specific pulmonary parameters, such as the transpulmonary gradient (TPG) (14.6 ± 5.7 mmHg vs. 9.5 ± 3.71 mmHg; p<0.0001), the mean pulmonary-artery pressure (mPAP) (36.3 ± 7.1 mmHg vs. 30.07 ± 8.1; p<0.001) and the pulmonary-vascular resistance (PVR) (305.8 ± 111.2 dyn s cm^{-5} vs. 192.7 ± 61.4 dyn s cm^{-5}; p<0.0001). The mean TPG and PVR with ILO were significantly lower than with O/N (9.5 ± 3.71 mmHg vs. 12.2 ± 4.8 mmHg and 192.7 ± 61.4 dyn s cm^{-5} vs. 245.4 ± 102.7 dyn s cm^{-5}, p< 0.001, respectively). The reduction of TPG and PVR to < 12mmHg and < 250 dyn s cm^{-5}, respectively, as the most positive predictive values for the PUVResp prior HTX was obtained in 28 (94%) patients with ILO vs. 21 (70%) with O/N (p<0.01). In contrast to O/N, ILO lowered sligthly the mean arterial pressure and systemic resistance and increased the left ventricular stroke volumen (p<0.05). Side effects of ILO were flush (25%) and headache (10%).
Conclusion: Inhalation of ILO is significantly more effective highly than conventional application of O/N in reducing critical parameters of PUVResp prior to HTX. With a responder rate of 97% in PUVResp testing, ILO-inhalation is a promising alternative for the management of po. right heart failure instead of NO with a non-responder rate of more than 20%.

P557 Emergency room triage of clinically stable patients with acute pulmonary embolism by bedside brain natriuretic peptide testing

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Right ventricular dysfunction (RVD) is a major prognostic indicator in clinically stable patients with acute pulmonary embolism (PE). The aim of the present study

was to investigate the value of rapid bedside testing for brain natriuretic peptide (BNP) levels in the identification of RVD in clinically stable patients with acute PE.
Methods: Consecutive patients with a first documented episode of PE diagnosed with spiral CT scan. All patients underwent echocardiography, and rapid BNP measurement within 1 h since the admission following the suspicion of PE. Acute RVD was diagnosed in the presence of objective echocardiographic criteria. Exclusion criteria were: hypotension and/or shock on admission, history of chronic heart failure (CHF) or ejection fraction $< 40\%$, or chronic cor pulmonale, plasma creatinin level > 1.5 mg/dL.
Results: Between june 2003 and july 2004, 61 patients were enrolled in the study. Thirty-five patients presented with RVD (57%) and 26 without (43%). Eleven patients (18%) with RVD had subsequent shock; of these, 7 patients underwent successful reperfusion, the remaining 4 patients (7%) died. No patient without RVD had subsequent clinical deterioration and all were discharged from the hospital. The mean BNP value was higher in patients with clinical deterioration than in patients without (950±314 pg/mL vs 296±353 pg/mL; $p<0.001$); no difference was found in patients who died versus those who survived the hospital stay (796±310 pg/mL vs 399±429 pg/mL; p=0.07). A value of BNP < 100 pg/mL was the more accurate cut-off to exclude the presence of RVD, with a sensitivity of 97% and a negative predictive value of 96%.
Conclusions: Rapid BNP testing is a useful supplementary tool for detecting RVD in clinically stable patients with acute PE. A BNP level < 100 pg/mL excludes with high accuracy patients with RVD at risk of complicated in-hospital course.

P558 Long-term follow-up after acute pulmonary embolectomy

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Background: The management of patients with acute massive pulmonary embolism remains difficult, particularly when circulatory shock is present or thrombolysis is contraindicated. Urgent pulmonary embolectomy is one of very few options but it is still the subject of controversial discussion regarding indications, operative technique, and prognosis.
Methods: In this retrospective investigation we evaluated the indications, results, long-term health status and cardiopulmonary function in all 24 consecutive patients (mean age 52±2 years) who underwent acute pulmonary embolectomy with cardiopulmonary bypass from 1976 until 2001. In all survivors, clinical examination, chest X-ray, lung scanning, pulmonary function testing inclusive lung diffusion capacity, and echocardiography was performed, on average 15 years after the operation.
Results: Most patients were preoperatively in strongly compromised hemodynamic condition (7 were preoperatively resuscitated). In 2 patients, embolectomy was performed on the basis of clinical diagnosis alone. Intraoperative mortality was 12.5% and overall hospital mortality 16.7%. Univariate analysis showed that false preoperative diagnosis, shock, the need for preoperative resuscitation, and long bypass-time (>60 min) were predictive factors for mortality. Severe complications occurred in two patients: one patient recovered fully after rethoracotomy because of cardiac tamponade, and one patient died of sepsis.
During follow-up no cardiovascular mortality, heart failure, respiratory failure and no pulmonary hypertension occurred. All patients were in NYHA classes I and II after a mean of 15 years. Even without vena caval interruption, recurrent embolic episodes were extremely rare. No late clinical symptoms related to embolectomy were observed. Pulmonary and right ventricular function at follow-up was normal or near normal in all survivors.
Conclusions: Pulmonary embolectomy on cardiopulmonary bypass remains an adequate therapy in patients with acute massive PE and failure or strong contraindication to thrombolytics. The long-term outcome shows excellent survival and low morbidity. Long-term survivors of pulmonary embolectomy enjoy normal cardiac and pulmonary function.

THROMBOSIS

P559 Effects of a high clopidogrel loading dose on platelet response and interindividual variability during coronary stenting

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Purpose: A 300 mg clopidogrel loading dose (LD) is currently used to reduce the early risk of stent thrombosis. Since there is a variable degree of platelet inhibition among individuals and a significant number of clopidogrel non responders in the early hours after coronary stenting (CS) using this treatment regimen, a higher LD has been suggested to optimize antiplatelet effects. The aim of the study was to compare platelet function in patients undergoing CS receiving a 300 mg or 600 mg clopidogrel LD assessing and the number of clopidogrel responders/non responders and interindividual variability in platelet inhibition.
Methods: The study included 50 patients undergoing CS treated with either a 300 mg (n= 27) or 600 mg (n=23) clopidogrel LD followed by a 75 mg daily dose. ADP (2 μM) induced glycoprotein (GP) IIb/IIIa activation and P-selectin expression were assessed at baseline and 4, 24, and 48 hours following clopidogrel LD. All patients were on aspirin (100 mg/d) and those receiving GP IIb/IIIa inhibitors were not included. Interindividual variability in platelet inhibition was defined by the coefficient of variability (CV=SD/mean; significant when >0.25). An adequate clopidogrel response was defined as a degree of platelet inhibition $>30\%$ compared with baseline values.
Results: A more intense and rapid inhibition of platelet activation was achieved using a 600 mg compared to a standard 300 mg clopidogrel LD during the first 48 hours after CS ($p<0.001$ by MANOVA for both GP IIb/IIIa activation and P-selectin expression); significant differences ($p<0.05$) were observed at 4 hours and maintained (with similar degrees of platelet inhibition) at 24 and 48 hours. Overall, a 600 mg clopidogrel LD increased the number of clopidogrel responders when considering GP IIb/IIIa activation (83% vs 48%, p=0.04 at 4 hours; 83% vs 44%, p=0.02 at 24 hours; 83% vs 74%, p=0.75 at 48 hours) and P-selectin expression (96% vs 63%, p=0.02 at 4 hours; 91% vs 67%, p=0.07 at 24 hours; 87% vs 45%, p=0.003 at 48 hours). However, a 600 mg LD was not associated with a reduction in interindividual variability of platelet response as the CV was >0.25 at all study time points.
Conclusion: The use of a 600 mg clopidogrel LD during CS optimizes platelet inhibitory effects early after intervention and may thus provide a more effective protection against early thrombotic complications.

P560 CLOpidogrel, upstream TIrofiban, in cath-Lab Downstream Abciximab in non-ST elevation acute coronary syndrome. The CLOTILDA Pilot study

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Purpose: This multicenter, prospective, randomized trial was performed to determine whether glycoprotein IIb/IIIa inhibitor Tirofiban (T) administered usptream, reduced peri-procedural myonecrosis in patients with non ST elevation Acute Coronary Syndrome (nSTEACS)undergoing early percutaneous coronary intervention (PCI) and treated with aspirin, heparin ev and 300mg clopidogrel (C) at least six hours before angiography. Patients randomized to C only, may receive glycoprotein IIb/IIIa inhibitor abciximab before or during PCI.
Methods: The Pilot Study reported the clinical, angiographic and biochemical findings of the first consecutive 200 patients enrolled from November 2002 to January 2004; of these, 100 patients were assigned to receive T and 100 to receive C only. Quantitative CK-MB and Troponin I (Tn I) were measured at admission, at 6, 12, 24 hours during the first day, then once daily, immediately before coronary angiography and at 6, 12, and 24 hours after PCI.
Results: Between the two groups (T vs C) there were no differences in clinical (age 66±11 vs 67±13 yrs; renal failure 11% vs 12%, diabetes 26% vs 17%, ejection fraction 49±9% vs 49±10%), ECGgraphic (ECG changes on admission 74% vs 70%), angiographic (multivessel disease 65% vs 66%, TIMI flow 0-1 on the culprit vessel 21% vs 17%, visible thrombus 55% vs 56%) and biochemical findings (at admission: TnI positive 62% vs 54%, mean TnI 1.4±3 vs 2.2±7 mg/L, mean CK-MB 11.3±22 vs 11.3±27 mg/L; at peak: mean TnI 10±17 vs 11.2±7 mg/L, mean CK-MB 37.1±55 vs 34.9±46 mg/L). PCI was performed in 67 patients of T group and 58 of C group. Abciximab was administered in 14 patients of C group. After PCI TIMI flow 2-3 was obtained in 95% of pts in the T group and in 91% of pts in the C group (NS). No significant differences were observed in the number of pts with elevation (or re-elevation) of CK-MB (18% vs 17%) and CK-MB > 3 normal values (9% vs 10%). Mean values of CK-MB peak were also similar between groups (10.8±18 vs 7.9±15 mg/L).
Conclusion: these data suggest that upstream T administration in pts with nSTEACS, does not result in a reduced extent of myonecrosis after PCI as compared to standard treatment including clopidogrel.

P561 Impact of glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes without ST-elevation in the "real world"

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Introduction: Glycoprotein IIb/IIIa inhibitors (GPI) represent a major advance in the treatment of acute coronary syndromes (ACS) without ST-elevation, as it was demonstrated in several randomized clinical trials. However, their real impact in an unselected population of ACS patients is still poorly documented.
Aim: To evaluate, in a population of patients admitted with ACS without ST-elevation, the impact of GPI therapy in the in-hospital clinical outcome.
Population and Methods: Retrospective analysis of a nationwide database containing data from 7067 patients, admitted for ACS in Coronary Care Units or Cardiology wards since January 2002; 3871 patients were found to be admitted for ACS without ST-elevation and had data regarding in-hospital therapy. This subpopulation was then divided into two groups, as they had (Group A: n=1252) or had not (Group B: n=2619) received GPI. Both groups were analyzed regarding demographic, epidemiological and clinical data (see table).
Results: Patients treated with GPI had a higher risk profile, with a higher inci-

dence of previous revascularization and a more adverse coronary anatomy (left main and/or 3-vessel disease - 24% versus 14%; p<0.05). Although GPI-treated patients had a worse clinical profile and an higher incidence of non-ST elevation myocardial infarction (NSTEMI) (71% versus 59%; p<0.05), they had a lower in-hospital mortality (3% versus 5%; p=0.03) - see table. A multivariate analysis showed that this was mainly due to a lower incidence of LV dysfunction (p=0.029).

Groups/Parameters	Group A (GPI)	Group B (without GPI)	p
Male Gender	71%	65%	<0.05
Hypercholesterolemia	51%	43%	<0.05
Smoking habits	26%	17%	<0.05
Previous PCI	10%	8%	<0.05
NSTEMI	71%	59%	<0.05
Unstable angina	29%	41%	<0.05
Left main and/or 3-vessel disease	24%	14%	<0.05
In-hospital Mortality	3%	5%	0.03

GPI and non-ST elevation ACS

Conclusions: Even in an unselected ACS without ST elevation patient population, the use of GPI in this setting is associated with a better in-hospital mortality.

P562 Low molecular weight heparins are associated with a reduced inflammatory response in non-ST elevation acute coronary syndromes as compared to unfractionated heparin

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Low molecular weight heparins (LMWH) have been reported to improve the outcome of non-ST elevation acute coronary syndromes (ACS) compared to unfractionated heparin (UFH). Increased levels of interleukin 6 (IL-6), C-reactive protein (CRP) and Von-Willebrand factor (vWf) have been associated with poor outcome of ACS patients.
We assessed the anti-inflammatory effects of LMWH and UFH in patients who were randomized to dalteparin, enoxaparin or UFH in the ARMADA study.
Methods: The study included 136 patients of which 89 received LMWH (dalteparin in 45 and enoxaparin in 44 patients) and 47 UFH. Blood samples were drawn at randomization (T1) and 48 to 120 hours after the start of the drug treatment (T2). We studied the changes (T2-T1) in IL-6, CRP and vWf antigen concentrations.
Results: The levels of all markers were comparable between the 2 LMWH groups which were merged together. At T1, the levels of CRP and vWf were comparable between the LMWH and UFH groups but Il-6 levels were significantly higher in the UFH group (12.5±16.9 vs 6.7±10.3 pg/ml, p=0.02). The changes in the levels of markers are summarized in the table.

Changes in the levels of marKERS

	LMWH (n=89)	UFH (n=47)	p
Delta IL-6 (pg/ml)	-2.7±9.3	-9.5±16.2	0.002
Delta CRP (mg/l)	4±20	16±37.1	0.02
Delta vWf (%)	28.6±39.3	82.2±37.6	<0.0001

Delta=T2-T1

Conclusions: Despite a significant reduction in the levels of the early marker IL-6 in the UFH group, semi-late markers CRP and vWf increased significantly more in such patients as compared to those treated by LMWH. These results suggest a more important and long lasting anti-inflammatory effect of LMWH compared to UFH. The pleïotropic effects of LMWH may participate in the improved outcome of ACS with such molecules.

P563 Use of low-molecular-weight heparin in percutanous coronary intervention in clinical practice in Germany – results of the ALKK-PCI registry

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Background: Low-molecular weight heparin (LMWH) is recommended in patients with unstable angina pectoris and non-ST-elevation myocardial infarction. However, little is known about the use in PCI. Therefore the aim of this study was to investigate frequency and complication rate of the use of LMWH in PCI in German interventional institutions participating in the ALKK registry (Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte).
Methods: The ALKK performs an ongoing registry of quality control in interventional cardiology. Data of 72 hospitals perfoming PCI were collected consecutively by a standardized data form in a data center. Between january and october 2003 a total of 43452 were registered.
Results: The mean age of patients was 66 years (59/74). 73% were male, 19.4% were diabetics (table).

	LMWH	UH	p-value
Indication for PCI			
n	2610	40842	
stable angina	1089 (5.9%)	17487 (94.1%)	
unstable angina/NSTEMI	641 (6.6%)	9025 (93.4%)	
STEMI	350 (4.8%)	6932 (95.2%)	
Complication rates			
death (%)	9 (0.35%)	248 (0.63%)	0.09
myocardial infarction (%)	10 (0.39%)	175 (0.44%)	0.7
stroke (%)	0	23 (0.06%)	0.2
severe bleeding (%)	8 (0.31%)	122 (0.31%)	0.96

Use and complication rate of low-molecular-weight-heparin (LMWH) and unfractionated heparin (UH) in PCI

Conclusion: The use of low-molecular-weight heparin in PCI is low with 5-6.5%, independently of the indication. There was no difference in severe bleeding complication rates after using LMWH compared to unfractionated heparin. The rate of ischemic complications was simular. We conclude that LMWH is an alternative to unfractionated heparin in PCI.

P564 Rapid attainment of reliable anti-xa levels with combined intravenous and subcutaneous enoxaparin in acute coronary syndromes; the PEPCI PRE study

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Introduction: Combined therapy with 30 mg of intravenous enoxaparin followed by 1 mg/kg subcutaneous q 12 hours has been shown to be safe and effective in the treatment of acute coronary syndromes (ACS) with a conservative management strategy. The early transition of such patients to percutaneous coronary intervention (PCI) requires the rapid attainment of reliable and stable drug levels.
Methods: Forty ACS patients (28 males) age 63±11 years and weighing 84.8±14.2 kg were treated with the above combined intravenous and subcutaneous enoxaparin regimen prior to planned invasive management. Blood samples for anti-Xa activity were obtained at 5 minutes as well as at 2, 4, 6 and 8 hours post drug initiation. For comparison anti-Xa levels were determined at the same time points in ten additional patients with ACS who were at steady state having received at least five doses of 1 mg/kg of subcutaneous enoxaparin q 12 hours.
Results: Anti-Xa levels at 5 minutes post drug initiation were in the range presently targeted for PCI (0.5 to 1.8 IU/ml) in all forty patients with a mean value of ± 1.22±0.20 IU/ml. Anti-Xa levels then remained stable for the next eight hours and were comparable to those in patients at steady state (1.05±0.19 versus 1.10±0.14 IU/ml, p=ns).
Conclusion: The combination of 30 mg/kg of intravenous enoxaparin followed by 1 mg/kg subcutaneously in patients with ACS results in the rapid attainment of reliable and stable anti-Xa activity comparable to that in patients at steady state. Anti-Xa levels are in the range presently targeted for PCI within five minutes of enoxaparin initiation and remain so for at least eight hours.

P565 Value of low molecular weight heparins in the treatment of acute coronary syndromes in the daily clinical practice

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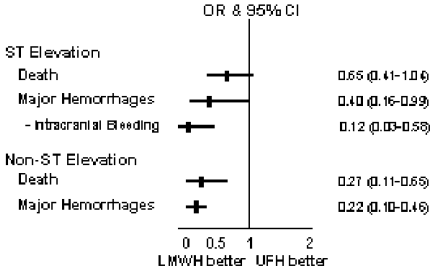
Introduction: In patients (Pts) with acute coronary syndromes (ACS) the antithrombotic therapy is a corner stone of the treatment and low molecular weight heparins (LMWH) have appeared as an advantajous alternative to unfractionated heparin (UFH) in clinical trials. Nevertheless, their benefit in the daily clinical practice is uncertain.
Purpose: To evaluate the efficacy and the safety of LMWH, compared to UFH, in the entire spectrum of ACS.
Methods: A national registry of ACS collected data from 6792 consecutive Pts since January 2002, in all the 53 cardiology departments available in the country. LMWH or UFH were used exclusively in 2003 Pts with ST elevation (Elev) and in 2941 Pts with non-ST Elev ACS. In-hospital rates of death or major hemorrhages were compared between LMWH and UFH, in a logistic regression model with propensity analysis.
Results: LMWH was exclusivelly used in 1403 Pts (70%) with ST Elev and in 2609 Pts (88.7%) with non-ST Elev ACS. In the ST Elev cohort, LMWH were more frequently used in older Pts (67±14 vs 62±13 years) and in Pts with Killip class >I (24% vs 19%), but the anterior location of ST elevation was more frequent in Pts treated with UFH (52% vs 43%). In non-ST Elev ACS, the use of LMWH was also more frequent in older Pts (68±12 vs 64±12 years) and in Pts with Killip class >I (25% vs 17%), but UFH was more frequently used in diabetics (36% vs 28%) and Pts with ST depression (51% vs 39%).



Odds ratio of adverse events.

Conclusions: In the present national registry of ACS, LMWH was the predominant anti-thrombinic therapy. The safety of LMWH was superior to UFH in the entire spectrum of ACS. The efficacy of LMWH was significantly superior to UFH in Pts with non-ST Elev ACS and borderline superior in Pts with ST Elev ACS.

P566 Antiplatelet therapy of acute coronary syndromes with percutaneous coronary intervention: are aspirin and clopidogrel sufficient?

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Background: Inhibition of platelet aggregation plays a crucial role in the treatment of acute coronary syndroms (ACS). For oral treatment ASA and Clopidogrel are available and both drugs are strongly recomended in the ACS treatment guidelines. However, data regarding the efficacy of both substances, when meassured by platelet aggregation, were only drawn from healthy individuals with only slighty activated platelets. Thus it is uncertain if we can render these data to pat with ACS.
Methods: 20 consecutive pat with NSTEMI (confirmed by TnT) who underwent early stent implantation were included into the present study. All the pat received a loading dose of 300mg Clopidogrel and 250 mg ASA in combination with weight adjusted enoxaparin. Pat who received GPIIb/IIIa inhibitors were not included in this trial. 24(±2) hours after application platelet inhibition was studied by light transmittance aggregometry (Born) in platelet rich plasma. Aggregation was recorded as the maximum percentage change in light transmittance from baseline, using platelet poor plasma as a reference. ASA resistance was prospectivly defined as platelet aggregation >30% after induction with 0,5 mg/ml arachidonic acid and clopidogrel resistance as platelet aggregation > 30% after induction with 20μmol ADP.
Results: 30% of pat (6/20) with ACS and stentimplantation did not show a significant inhibition of platelets despite the recommended loading dose of 300 mg clopidogrel (absence of clopidogrel effect). 10% of the pat (2/20) did not show a significant ASA effect. 1 pat did not show either an effect of ASA or clopidogrel on platelet aggregation.
Conclusion: 1.In ACS patients the inhibition of platelet function with ASA and clopidogrel has great interindividual variability. Nearly 40% of pat. show inadequate platelett inhibition 24 h after clopidogrel and ASA administration.
2.This underlines the need of well validated bed side platelet monitoring to identfy drug non respondors
3.Wether the efficacy of clopidogrel can be increased by given a higher loading dose is currently an issue of further studies.
4.The insufficient effect of ASA and clopidogrel in a significant number of ACS patients emphasize the need of GPIIB/IIIa inhibitors in the ACS setting.

P567 Underutilization of oral anticoagulation for atrial fibrillation in survivors of acute myocardial infarction influences long-term mortality

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Background: Oral anticoagulation (OAC) treatment is generally recommended in patients with atrial fibrillation (AF) and coronary artery disease. We investigated the prescription of OAC in patients discharged alive with atrial fibrillation after an acute myocardial infarction (AMI) and the influence of OAC treatment on 1-year mortality.
Methods: Prospective cohort study using data from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) on patients admitted to the coronary care units of 72 Swedish hospitals 1995-2001. All 11141 patients with first registry-recorded AMI who were discharged with atrial fibrillation were included. 1-year mortality data were obtained from the Swedish National Cause of Death Register.
Results: Only 21%(n=2384) of the patient were prescribed OAC while 79% (n=8757) were not. At 1 year unadjusted mortality was 26% (2301 deaths) in the no-OAC group and 20% (481 deaths) in the OAC treated group. Also in Cox regression analysis adjusting for 36 confounding factors OAC treatment was associated with reduction in 1-year mortality (relative risk, 0.66; 95% confidence interval 0.57-0.76; P<0.001) in hospital survivors of AMI with AF. This reduction of mortality was similar among all subgroups based on age, sex, baseline characteristics, previous disease manifestations, and medications.
Conclusions: In daily clinical practise OAC is only given to a minority (21%) of AMI patients with AF despite that OAC is associated with a 34% relative reduction in 1-year mortality. The results emphasise the importance of OAC treatment for AF after AMI.

P568 Flow cytometric assessment of VASP phosphorylation: an index of the efficacy of clopidogrel in patients with atherothrombotic diseases

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Introduction: Clopidogrel is an effective antiplatelet agent widely used in the prevention of thrombotic complications in atherosclerotic diseases and interventional cardiology. It is a prodrug which must be metabolised in the liver to acquire antiaggregatory properties. However, since clinical thrombosis still occurs in 5 to 10% of patients on clopidogrel while platelet aggregation remains unchanged in up to 30% of such patients, clopidogrel resistance would appear to exist. In platelets, levels of phosphorylation of vasodilator-stimulated phosphoprotein (VASP), an intracellular actin regulatory protein, are correlated with blockade of the P2Y12 receptor by clopidogrel or competitive P2Y12 antagonists and inhibition of ADP-induced platelet aggregation. The aim of this study was to use a VASP phosphorylation (VASP-P) assay to evaluate the efficacy of clopidogrel therapy for the prevention of platelet activation in patients presenting atherothrombotic diseases.
Methods: VASP-P was measured by quantitative flow cytometry using the commercial kit from Stago/Biocytex according to the method described by Schwarz et al. [Thromb Haemost 1999;82:1145]. The platelet reactivity index (PRI) was calculated from the difference in VASP-P fluorescence intensity (FI) between resting (+PGE1) and activated (+ADP) platelets according to the relation (FIPGE1-FIADP)/FIPGE1 and was expressed as a percentage. The PRI was determined in healthy donors and in patients with cardiovascular diseases treated or not with clopidogrel.
Results: The PRI was (mean ± SD) 78.3 ± 4.6% in healthy donors (n=47), 79.0 ± 4.1% in patients without clopidogrel treatment (n=34) and 60.8 ± 17.2% in patients receiving clopidogrel (n = 32) (p < 0.0001). In the clopidogrel group, the PRI was nevertheless widely dispersed (from 6.6 to 85.8%) and 34% of these patients had a PRI equivalent to values in healthy donors or patients not receiving clopidogrel.
Conclusion: One third of our patients under clopidogrel therapy displayed no inhibition of platelet activation, possibly due to interindividual differences in liver metabolism and to drug dosage. Whether these "unprotected" patients are more susceptible to recurrent ischemic complications will now be investigated in follow-up studies.

P569 Additional platelet inhibition achieved with a 600 mg loading dose in patients with chronic clopidogrel therapy

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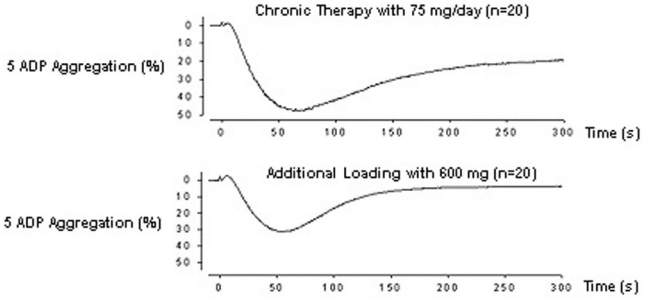
Background: It is not known whether in patients on chronic clopidogrel therapy (75 mg/day) administration of a 600 mg loading dose results in additional platelet inhibition.
Methods and Results: Patients (n=20) treated with clopidogrel (75mg/day) for at least 4 weeks and scheduled for coronary artery stenting were included. As controls served patients (n=10) scheduled for coronary stenting who were not on clopidogrel therapy. Citrated blood for optical aggregometry (stimulation with 5 and 20 μM ADP) was collected immediately before administration of a 600 mg loading dose and 6 hours post loading in all patients. Results for maximal aggregation are displayed in the table for clopidogrel and control groups. The figure shows averaged aggregometry traces of the 20 patients with chronic clopidogrel therapy before and after additional loading with 600 mg. Additional loading results in a pronounced reduction of ADP-induced aggregation.



	Before Loading	after Laoding	P
5 ADP clopidogrel	52.4±13.8	32.9±12.2	<0.0001
20 ADP clopidogrel	68.3±14.4	49.0±16.3	<0.0001
5 ADP controls	93.1±9.1	49.5±19.4	<0.0001
20 ADP controls	102.8±5.3	66.7±16.3	0.0002

Conclusion: Administration of a 600 mg loading dose results in a significant increase in platelet inhibition in patients already on chronic clopidogrel therapy.

P570 Thrombotic risk: the distinction between clopidogrel responsiveness and post-treatment platelet reactivity

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Background: The relative inhibition of pretreatment platelet reactivity (PreTR) is the most common estimate of the antithrombotic effect of clopidogrel and is a measure of drug responsiveness. However, "responsive" patients (pts) may remain with high Post-treatment reactivity (PostTR) and thus have elevated thrombotic risk.
Methods: Platelet reactivity was determined by aggregation (5 and 20μ M ADP) in 62 patients undergoing elective stenting at baseline and at 5 days post-procedure. All pts were on aspirin (325 mg) and received 300 mg clopidogrel immediately post-stenting and 75 mg qd. PreTR was divided into low, moderate, high tertiles. Non-responders (NR) were defined as < 10% relative inhibition of baseline aggregation; semi- responders (SR) as 10-30%; and responders (R) >30%.
Results: PreTR tertiles by 5μM ADP were: low (47 ± 9%); moderate (64 ± 4%), and high (78 ± 6%) and by 20μM ADP were: low (66 ± 15); moderate (85 ± 3%) and high (96 ± 3%). 8 pts were NR; 18 were SR; and 36 were R. Responsiveness directly correlated with PreTR: 86% of R had moderate or high PreTR whereas 75% of NR had low PreTR (Table). Despite being more responsive, 16% of pts with high PreTR and 17% of pts with moderate PreTR remained with moderate Post TR.

Responsiveness

	NR (n=8)	SR (n=18)	R (n=36)
Pre TR (5μ M ADP)			
High (n=19)	0	3 (5%)	16 (28%)
Moderate (n=23)	2 (3%)	6 (10%)	15 (24%)
Low (n=20)	6 (10%)	9 (15%)	5 (8%)

Conclusion: Being "responsive" to clopidogrel does not always equate with low final platelet reactivity. "Responsive" patients with persistently reactive platelets may remain unprotected. Measures of final post-treatment platelet reactivity are more appropriate than relative inhibition to assess thrombotic risk.

P571 Clopidogrel in unstable angina patients who would have been excluded from randomized pivotal trials

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Objectives: We describe the characteristics and examine the efficiency and safety of Clopidogrel in unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI) patients who would have not been eligible in the Cure trial and for all the patients treated according to the Cure trial.
Background: It is not known whether the benefit shown with clopidogrel in the selected population of pivotal trials can be extended to the real world.
Methods and Results: All patients with UA/NSTEMI are anticoagulated with subcutaneous enoxaparin associated with a loading of 500 mg aspirin and 300 mg clopidogrel. Among 517 consecutive patients, we identified 117 patients who would have not been eligible for the Cure Trial according to the 4 major exclusion criteria including heart failure (n=60) recent stroke (n=40), severe co-morbid condition (n=27), contraindications to clopidogrel or ASA (n=4). These excluded patients were older, had a lower creatinine clearance, had more frequently a past-history of CABG or a diagnosis of non-Q MI on admission. Moreover, excluded patients had a lower ejection fraction (48% vs 55%, p<0,001), a higher TIMI risk score (3.27%vs 2.80%, p=0.0016), a longer hospitalisation duration (3.93 days ± 2.83 vs 3.11 days ± 1.64; p<0.0001) and a higher rate of diabetes (31.6% vs 21.7%, p<0.05). The use of GPIIb/IIIa inhibitors was similar in the two groups (41% vs 43%, p= NS). Finally, excluded patients underwent less frequently PCI than cure-like patients (56% vs 68%, respectively, p=0.01). Excluded patients had a non significant increase of major bleeding at 30 days as compared to cure-like patients (5.1% vs 2.7%, respectively, p=NS). As expected, the rate of major coronary events at 30 days (myocardial infarction and death) was higher in excluded patients (14.5% vs 4.5%, p=0.0013). When considering common exclusion criteria of antithrombotic trials including severe renal failure, there was still no significant difference in the rate of major bleeding (5.62 vs 2.24, p=0.06), although the number of excluded patients rose up to 160. Independent predictors of death or MI at 30 days were heart failure on admission (O.R:2.7,p=0.0010), ST depression on the qualifying ECG (O.R:4.75, p<0.0001) and age (O.R:1.22, p=0.02). Correlates for bleeding at 30 days were age(O.R:1.32,p=0,002) and hypertension(O.R:2.76,p=0,02).
Conclusion: Patients who do not fit the enrolment criteria of antithrombotic trials have higher risk baseline characteristics for both bleedings and ischemic events. In these patients, the use of clopidogrel provides no significant excess of bleeding.

P572 A randomized trial comparing 30 vs. 180 days of clopidogrel in patients who received a bare coronary stent. The Random Argentine Clopidogrel Cardiology Society (RACS) study

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Background: The optimal duration of treatment with clopidogrel after PCI with stent placement remains controversial.
Methods and Results: RACS is a prospective randomized, non-blinded study of 2230 patients (pts) undergoing PCI who were randomized after successful bare stent placement to 30 vs. 180 days of clopidogrel. Pts were eligible if they had presented with an ST elevation MI, acute coronary syndrome, or stable angina (CSA). The 1o end point was a composite of death, MI, stroke, and TVR at 90 and 180 days, and 1 year. The study has 80% power to detect a 21% reduction in events between 30 days and 6 months, assuming a 12 month event rate of 23,4% in the group receiving therapy for 30 days, with significance at the 0.05 level. Baseline clinical characteristics revealed no differences between the groups in terms of age, gender, previous history, risk factors, or incidence of diabetes; 69,5% presented with an ACS, 15,7% an MI at study entry. At hospital discharge and 30 days there were no differences between groups in the frequency of death, MI, or stroke.
The outcome between 30 days and 6 months among the 909 pts who have completed 6 month follow-up is presented in the table.

Events	30 days n=453 p.	180 days n=456 p.	Odds Ratio (95% CI)	P value
Death	2,65% (12 p.)	0,88% (4 p.)	0,33 (0,09 -1,09)	0,047
AMI (Non Fatal)	2,20 % (10 p.)	1,53% (7 p.)	0,69 (0,24 - 1,99)	NS
Stroke	0,22% (1 p.)	0%	–	NS
TVR	4,42% (20 p.)	3,29% (15 p.)	0,74 (0,35 - 1,53)	NS
MACE	8,17% (37 p.)	4,60% (21 p.)	0,54 (0,30 - 0,97)	0,027

Conclusions: This interim analysis reveals that the reduction in events among pts treated with long-term clopidogrel has reached statistical significance. Complete follow-up at 1 year will be presented.

P573 S 18886, a new specific TP-receptor antagonist, is safe and as effective as aspirine in inhibiting platelet aggregation in patients with peripheral arterial disease

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Background: S 18886 is a new specific antagonist of thromboxane A2 and prostaglandins endoperoxyde receptors (TP-receptor) acting both on the thrombus and the vessel wall. S 18886 has an antiplatelet activity associated with additional properties such as an improvement of endothelial dysfunction demonstrated in clinical studies and antiatherosclerotic activity demonstrated in experimental studies.
Methods: International, double-blind, controlled study in patients with peripheral arterial disease, randomised for 12 weeks to compare 5 oral dosages OD of S 18886 (1; 2.5; 5; 10; 30 mg) versus acetylsalicylic acid (ASA) 75 mg.Platelet aggregation (centralised reading by an independent Committee) induced by U 46619 7μM (thromboxane A2 analogue), Arachidonic Acid (AA) 1mM, Collagen 2μg/ml, adenosine diphosphate (ADP) 5 μM, were performed 24h-post dose.
Results: 435 patients were randomised: 79% of male, mean age of 67 ± 10 years, mean ankle brachial pressure index at inclusion of 0.67 ± 0.15. No relevant difference between treatment groups was observed for baseline characteristics.
S 18886 dose-dependently inhibited ex vivo platelet aggregation when measured 24 h post-dose after 12 weeks. S 18886 shows a powerful inhibition of platelet aggregation induced by U 46619 and AA, and a moderate platelet inhibition induced by collagen and ADP. These effects were similar to that of aspirin. Doses μ5mg per day induce a platelet inhibition by more than 80% when induced by U 46619 and arachidonic acid. When compared to aspirin, no increase in the number of

Platelet aggregation at W12 (Mean (SD))

	S 18886					ASA
	1.0 mg (n=61)	2.5 mg (n=50)	5.0 mg (n=56)	10 mg (n=53)	30 mg (n=60)	75 mg (n=41)
U 46619	45.8 (36.4)	25.0 (33.5)	2.3 (4.0)	3.3 (10.2)	4.6 (14.8)	84.4 (10.3)
Arachidonic Acid	41.8 (35.2)	24.5 (29.5)	12.0 (14.4)	12.0 (11.4)	13.8 (18.4)	12.3 (12.6)
Collagen	72.9 (16.9)	64.6 (23.1)	52.7 (22.7)	49.3 (19.5)	48.2 (22.0)	52.0 (27.2)
ADP	70.8 (11.6)	67.0 (15.4)	65.8 (14.7)	64.0 (11.3)	67.1 (15.5)	65.8 (14.8)

bleedings was observed with S 18886 without significant dose/effect relationship. Biological data did not show any significant modifications.
Conclusion: S 18886, a new once daily oral and specific TP-receptor antagonist, is safe and at least as effective as aspirine from in inhibiting platelet aggregation in patients with peripheral arterial disease.

P574 Platelet function analyser is useful to assess the effect of different aspirin doses

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Purpose: To check the reproducibility of the platelet function analyser (PFA-100) in assessing the effect of aspirin, and to ascertain if aspirin resistance can disappear by increasing the dose.
Methods: Epinephrine closure time was measured by PFA in 46 patients (64±9 years, 37 men) on two occasions several months apart. They were taking aspirin (50 to 300 mg/day) for primary (6 patients) or secondary (40 patients with ischemic heart disease) cardiovascular prevention. Ninety-two different analyses were performed. The same dose was given to 18 patients throughout the study, and it was increased in 28 after the first analysis (in 22 cases due to aspirin resistance). The normal epinephrine cartridge closure time (ECT) was <161 sec. The maximal value measured was 300 sec. Patients were resistant to aspirin if ECT was <161 and responders when it ranged from 161 to 300 sec.
Results: In the whole group of patients the first aspirin dose was 156±73 mg and the second 236±76 ($p<0.001$). Mean ECT was 177±67 sec with the first dose and 237±75 with the second ($p<0.001$). No significant relationship was found between aspirin dose and ECT with the first or with the second dose. Resistance to the first dose was found in 22 (48%) patients and to the second dose in 12 (26%). Eleven of 22 (50%) patients resistant to the first dose became responders to a higher one. Only 1 of 22 (5%) patients who responded to the first dose, became resistant after increasing it. In 13 of the 18 (72%) patients who received the same dose there was no substantial difference between the two ECTs. However, five (28%) of these 18 patients who were resistant to the first dose, became responders to the same dose on another occasion.
Conclusions: ECT measured by PFA-100 was reproducible in 72% of patients taking aspirin when the same dose was given. Although there was no dose-response relationship in the whole group, half of the patients who were resistant to the first dose, became responders to a higher dose. It means that analytical resistance may be due to insufficient dose in 50% of cases.

P575 Aspirin resistance is related to ischaemic heart disease, male gender and tobacco

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Purpose: To study the prevalence of aspirin resistance in a number of stable patients taking this drug for cardiovascular prevention and to know if it is associated with different variables.
Methods: Platelet function was studied in 196 patients (144 men) aged 33 to 84, mean 63±9, with the platelet function analyser (PFA-100). They were taking aspirin (100 to 300 mg/day) for cardiovascular prevention. The reason was ischemic heart disease (IHD) (n=126), hypertension (41), and others (29). The normal epinephrine cartridge closure time (ECT) was <161 sec The maximum value measured was 300 sec. SPSS package was used for statistical analysis. A multivariant analysis could not be performed due to insufficient number of patients.
Results: In the entire group of patients aspirin dose ranged between 100 to 300 (156±83) mg/day and ECT between 72 and 300 (223±78) sec. Aspirin resistance (ECT <161 sec) was found in 31%. No significant correlation was found between ECT and age or aspirin dose/m^2. The qualitative variables: gender, ischemic heart disease (IHD), tobacco and diabetes were analysed in order to find a possible relation with aspirin resistance. Most patients were men (144), non-smokers (168) and had IHD (126). Diabetes, present in 64 of them, had no relation with aspirin resistance. The relative risk (RR) of resistance in men with vs without IHD was 2.3 ($p = 0.023$). No women with IHD had resistance. Among patients with IHD the RR of smokers (those who smoked in the last 12 months) vs non-smokers was 1.85 ($p = 0.03$). Among smokers the RR of patients with vs without IHD was 3.84 ($p = 0.09$).
Conclusions: Resistance to aspirin occurred in 31% of our patients, most of them men with IHD. Gender (men), IHD and tobacco are interrelated with aspirin resistance. Further studies with a greater number of patients are necessary to ascertain which of the three factors is the main factor responsible.

P576 Effect of dual antiplatelet therapy on platelet activation in patients with acute coronary syndromes in the presence of elevated serum soluble CD 40 Ligand

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Activated platelets as well as plaque inflammation participate in the pathogenesis of unstable angina or non ST elevation myocardial infarction (ACS). Serum soluble CD 40 ligand (sCD-40L) reflects both platelet activation and inflammation which are involved in ACS. Furthermore, an increase risk for adverse outcome has been observed in patients (pts) with ACS if soluble CD40L is elevated (>5.0 μg/L). While aspirin is an effective therapy for UA the addition of clopidogrel an ADP receptor inhibitor of platelets, further improves clinical outcome. However, soluble P-selectin (s-PS), a marker of platelet activation has not been predictably altered.
Aims: We evaluated the effect of clopidogrel on s-PS in association with sCD-40 L levels in pts with UA.
Methods: From 80 consecutive pts who were admitted for UA, 40 pts (mean age 70±4 years, 33 males, 7 females) were randomized to receive aspirin (325 mg, daily) and clopidogrel (300 mg loading dose followed by 75 mg daily) (group: Asp+Clop), and 40 pts (mean age 67±6 years, 31 males, 9 females) to receive aspirin (group: Asp), additionally to usual medical therapy. Blood samples were collected at 0, 8, 48 hours and on day 6. sCD-40 L and s-PS were determined by enzyme-linked immunosorbent assay.
Results: Pts on Asp+Clop compared to pts on Asp alone had at baseline similar clinical characteristics. Overall, s-PS levels were similar among the two groups at 0, 8 and 48 hours and at day 6 (Asp+clop vs Asp: 55.6±23 vs 53.75±22.9 ng/ml p=0.4, 52.41±16 vs 54.14±20 ng/ml p=0.5, 50.17±13.7 vs 60.8±37.9 ng/ml p=0.1, 50.53±17.5 vs 54.64±18.97 ng/ml p=0.4). When the effect of clopidogrel on s-PS was examined in relation to sCD-40 L serum levels, pts with high levels of sCD-40 L above 5.0 μg/dl) had a significant increase in s-PS at 8 hours, if they received Asp only (48±12 to 69.41±21 ng/ml, p=0.047), and levels of s-Ps were greater than in pts on Clop+Asp (Clop+Asp vs Asp: 43.6±10 vs 65.41±11 ng/ml, p=0.01). This difference was not maintained at 48 hours and 6 days.
Conclusions: In pts with UA and high sCD-40 L, treatment with Asp+Clop is better than Asp alone in prohibiting early P-selectin elevation. This could be related to the greater intensity of platelet activation and inflammation in pts with ACS and higher sCD-40L levels.

P577 Angiotensin-(1–7) improves platelet responsiveness to anti-aggregatory effects of nitric oxide

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We have previously shown that ischaemic heart disease is associated with platelet nitric oxide (NO) resistance, i.e. hypo-responsiveness to the anti-aggregatory effects of NO donors such as sodium nitroprusside (SNP) and nitroglycerine. NO resistance is partially due to the increased generation of superoxide radical (O2-) by NAD(P)H oxidase, for which angiotensin (Ang) II is a major stimulant. Furthermore, Ang II has been reported to potentiate platelet aggregation. Recently, Ang-(1-7) was identified as a vasodilator and possible physiological antagonist of Ang II. In the current study, we examined the effects of Ang-(1-7) on impaired platelet responsiveness to NO.
Methods: In 10 patients with acute coronary syndromes (unstable angina pectoris or non-Q-wave acute myocardial infarction), we assessed effects of Ang-(1-7) in concentrations 0.01-1μM on whole blood platelet aggregation induced by the thromboxane A2 analogue U46619 (1-3μM) and its inhibition by 1-10μM SNP.
Results: Platelets from these patients showed greater aggregability and lesser responsiveness to SNP than those from normal subjects. Ang-(1-7) did not significantly affect responses to U46619, but potentiated inhibition of aggregation by SNP, further decreasing the extent and velocity of aggregation. With both parameters, NO-potentiating effects of Ang-(1-7) revealed bell-shaped concentration-response curves, with maximal responses at 0.1μM. Thus, mean platelet responsiveness to SNP increased from 22±9% inhibition of aggregation in the absence of Ang-(1-7) to 53±7% with 0.1 μM Ang-(1-7) ($p<0.001$). Furthermore, Ang-(1-7) produced a parallel decrease in velocity of aggregation, from 73±7% to 42±6% ($p<0.001$) of control velocity with SNP and SNP/Ang-(1-7) respectively.
Conclusion: Ang-(1-7) markedly potentiates platelet responsiveness to NO, and thus ameliorates platelet NO resistance. The effect of Ang-(1-7) on platelets resembles that documented previously in vasculature, showing similar concentration-response characteristics. The cellular mechanisms underlying this effect (and analogous vascular effects) remain to be elucidated.

P578 Platelet microparticle mediate monocyte arrest on inflammatory activated endothelium by deposition of RANTES (CCL5)

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Background: Activation of platelets results in release of alpha-granular products including platelet chemokines like RANTES and in the formation of PMP. Recent

studies reported that immobilized platelet RANTES triggers monocyte recruitment on activated endothelium and is involved in atherogenesis and restonosis. In our study we tested whether RANTES is stored in PMP and whether PMP promote adhesive monocyte-endothelium interaction by deposition of RANTES.
Methods and Results: Using ELISA we detected that PMP store substantial amounts of RANTES, indicating that RANTES is packed into PMP during vesiculation. Immunofluorescence of microvascular endothelium (HMVEC) perfused with PMP revealed that PMP deposit RANTES on activated endothelium in flow. RANTES immobilization after static PMP incubation or after PMP supernatant perfusion was distinctly lower, despite a 3-fold higher RANTES concentration in PMP supernatant compared with PMP. This indicates that effective RANTES delivery is a flow dependent process requiring PMP. In addition, we detected rolling and shear-resistant adhesion of PMP to HMVEC, but no direct colocalization of RANTES and firmly arrested PMP, suggesting that transient interactions are sufficient for RANTES deposition. Preperfusion of PMP resulted in a significant increase of monocyte arrest to activated HMVEC. Pretreatment of monocytes with the receptor antagonist Met-RANTES inhibited increased monocyte arrest, revealing a major contribution of RANTES-receptors and their ligands in that process. We next explored the involvement of various PMP adhesion receptors in RANTES deposition. Blockade of P-selectin and to a lesser extent GP Ib or JAM-1 on PMP significantly reduced RANTES deposition, subsequent monocyte arrest and PMP adhesion. Interactions of these adhesion receptors may thus represent a prerequisite for deposition of RANTES by governing sufficient contact with HMVEC in flow. In contrast, blockade of GP IIb/IIIa significantly diminished RANTES immobilization and monocyte arrest, but not PMP adhesion, suggesting a dissociation of PMP adhesion and RANTES immobilization and prompting the notion that a signaling mechanism involving GP IIb/IIIa may be necessary for RANTES transfer during transient PMP interaction.
Conclusion: PMP mediate deposition of RANTES to activated endothelium and subsequently trigger monocyte arrest in flow, whereby transient PMP-endothelium interactions are sufficient and necessary for RANTES transfer by PMP. This provides a novel mechanism by which platelets may support monocyte recruitment in atherosclerosis and inflammation.

P579 Identification of the amino acid residues of the platelet GPIb essential for the von Willebrand factor binding by the clustered charged-to-alanine scanning mutagenesis

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At the site of vascular injury, von Willebrand factor (VWF) mediates platelet adhesion to subendothelial connective tissue through binding to N-terminal domain of the alpha chain of platelet glycoprotein Ib (GPIbalpha). To elucidate the molecular mechanisms of the binding, we have employed charged to alanine scanning mutagenesis of the soluble fragment containing the N-terminal 287 amino acids of GPIbalpha. Sixty-two charged amino acids were changed singly or in small clusters and thirty-eight mutant constructs were expressed in the supernatant of 293T cells. Each mutant was assayed for binding to several monoclonal antibodies for human GPIbalpha and for ristocetin-induced and botrocetin-induced binding of ^{125}I-labeled human VWF. Mutations at Glu128, Glu172 and Asp175 specifically decreased both ristocetin- and botrocetin-induced VWF binding, suggesting that these sites are important for VWF binding of platelet GPIb. Monoclonal antibody 6D1 inhibited ristocetin- and botrocetin-induced VWF binding and a mutation at Glu125 specifically reduced the binding to 6D1. In contrast, antibody HPL7 had no effect for VWF binding and mutant E121A reduced the HPL7 binding. Mutations at His12 and Glu14 decreased the ristocetin-induced VWF binding with normal botrocetin-induced binding. Crystallographic modeling of the VWF-GPIbalpha complex indicated that Glu128 and Asp175 form VWF binding sites and the binding of 6D1 to Glu125 interrupts the VWF binding of Glu128 but HPL7 binding to Glu121 has no effect on VWF binding. Moreover, His12 and Glu14 contact with Glu613 and Arg571 of VWF A1 domain whose mutations had shown similar phenotype. These findings indicated the novel binding sites required for VWF binding of human GPIbalpha

P580 Heterophilic interactions of PF4 and RANTES promote RANTES-triggered monocyte arrest on endothelium

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Background: The chemokines platelet factor 4 (PF4) and RANTES are both secreted by activated platelets and are known to influence multiple cell types and biological processes. For instance, PF4 inhibits proliferation of hematopoietic progenitor cells and angiogenesis. Like other chemokines, PF4 binds cellular proteoglycans, such as heparin and chondroitin sulfate but also interacts with heparin-binding proteins, such as VEGF or antithrombin. It has been shown that PF4 binds to IL-8 with high affinity and thereby abrogates IL-8 signals in hematopoietic progenitor cells. Platelet-derived RANTES is involved in atherogenic and neointimal recruitment of monocytes, however little is known about a modulation of RANTES functions by interaction with PF4.
Methods and Results: Here we show that co-treatment of PF4 inhibits the adhesion of IL-8-stimulated monocytic cells (MM6) on human umbilical vein endothelial cells (HUVEC) under physiological flow conditions. In contrast, the arrest of monocytes triggered by treatment with soluble RANTES was strongly enhanced by addition of PF4. Beyond the known binding to IL-8, ligand blots revealed the binding of PF4 to RANTES and other CXC-chemokines. Flow cytometric analysis of monocytes preincubated with RANTES or PF4 showed an immobilization of each chemokine on the cell surface which was additive for the combination of both chemokines. Incubation of monocytes with the supernatants of activated platelets containing both RANTES and PF4 showed increased arrest on HUVEC that could be blocked by the RANTES antagonist Met-RANTES.
Conclusions: Platelets as a source of secretory products modulating inflammatory processes play a crucial role in atherosclerosis. Similar to the supernatant of activated platelets, pre-treatment of monocytes with a combination of both RANTES and PF4 leads to enhanced arrest on endothelial cells. A possible mechanism may be the formation of heterophilic interactions between RANTES and PF4 resulting in increased binding to the monocyte surface.

P581 Inhibition of platelet-leukocyte interactions: a potential anti-inflammatory effect of Clopidogrel

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Purpose: Clopidogrel prevents atherothrombosis and its clinical manifestations by blocking P2Y12, the ADP receptor that mediates an important platelet activation-amplification loop. We investigated whether this effect results in a reduced capacity of platelets to interact with polymorphonuclear (PMN) leukocytes, which could substantiate anti-inflammatory properties of clopidogrel.
Methods: Platelet-PMN interaction was studied by flow cytometry, using cells from mice untreated or treated with clopidogrel p.o., 25 mg/kg twice a day for two days plus a 25 mg/kg dose one hour before obtaining blood for the experiment on day 3.
Results: In PRP challenged either by ADP (8 μM) or arachidonic acid (0.5 mM), clopidogrel reduced the percentage of P-selectin expressing platelets from 16% to 1.2% or 77.8% to 15.3%, respectively. In washed platelets activated by ADP (8μM), clopidogrel significantly reduced the percentage of P-selectin expressing cells from control values of 11.5$\pm$7.9% to 2.8$\pm$1.1%. The dose-dependent increase of P-selectin expression induced by thrombin, was also significantly lower in clopidogrel-treated platelets vs controls (11,3$\pm$3, 37.0$\pm$6.7, 68.1$\pm$9.0, vs 22.6$\pm$7.3, 74.0$\pm$7.2 and 84.0$\pm$5.4 at 0.06, 0.125 and 0.25 U/ml, respectively). Platelet-PMN adhesion was measured by double color flow cytometry. The numbers of platelets recruited by 100 PMN in mixed cell suspensions from clopidogrel-treated mice vs control mice, were 80$\pm$11, 109$\pm$10 and 154$\pm$27 vs 129$\pm$8, 221$\pm$26, and 300$\pm$42 in unstimulated, ADP (8μM) or thrombin (0.125 U/ml)-activated cells, respectively. As a further index of PMN activation we evaluated reactive oxygen species (ROS) in PMN loaded with the fluorescent probe DCFDA, by flow cytometry. Coincubation of PMN with ADP (8μM) or thrombin (0.125U/ml)-activated platelets increased 2-5 fold the production of ROS. This stimulation was abolished in mixed cell suspensions from clopidogrel-treated animals.
Conclusions: Clopidogrel reduces P-selectin expression, platelet-PMN adhesion and platelet-dependent ROS production. Prevention of platelet-leukocyte interaction by clopidogrel may reduce the inflammatory component at the site of vascular lesion.

P582 Connective tissue growth factor is stored in human platelets: possible implications for thrombosis and atherosclerosis

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Background: Connective tissue growth factor (CTGF) is over-expressed in wound healing, fibrosis and advanced atherosclerotic lesions. Platelets adhere to CTGF, suggesting that this protein may be involved in the formation of platelet-rich thrombi at the sites of tissue injury or atherosclerotic plaque rupture. Since platelets contain a wide array of biologically active proteins, we investigated the presence, the localization and the release of CTGF from these cells.
Methods and Results: Human platelets obtained from healthy donors were washed and stimulated with thrombin or ADP. Following incubation, proteins from un-stimulated and stimulated cell lysates and the supernatants were analysed by Western blotting. The experiments showed that un-stimulated platelets contain considerable amounts of CTGF, whereas no CTGF was detectable in platelet-poor plasma. To determine the localization of CTGF, the platelets were treated with 50-100 μg/mL of heparin, which is known to bind CTGF. There was no difference between supernatant content of CTGF in control and heparin-treated samples, indicating intracellular storage rather than extracellular association of CTGF with the membranes. To elucidate the origin of CTGF in platelets, immunohisto-

chemical analysis of human bone marrow sections was performed. The analysis showed that although CTGF protein was abundantly expressed by several cell populations in bone marrow, it was not present in detectable amounts in the cytoplasm of platelet-producing megakaryocytes, except for the weak staining near the cell membranes. This finding suggests that CTGF presence in platelets is a result of endocytosis from extracellular environment in bone marrow.
Agonist-stimulation of platelets resulted in a significant release of CTGF from the storage granules, with thrombin at 0.1 U/mL being a more potent activator than ADP at 20 μmol/L. To determine whether aspirin, which inhibits platelet activation by suppression of thromboxane A2 synthesis, can prevent the release of CTGF, the cells were incubated with thrombin or ADP in the presence or absence of 1 mmol/L of aspirin. The agonist-dependent CTGF secretion was significantly inhibited by aspirin.
Conclusions: CTGF is stored in normal human platelets, and can be released upon platelet activation. The novel information provided by this study may help to achieve more thorough understanding of CTGF-platelet interdependence and CTGF involvement in thrombosis and atherosclerosis.

P583 Persistent production of thromboxane A2 in patients chronically treated with aspirin

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Purpose: It has been recently observed that a certain number of patients chronically treated with aspirin show a reduced sensitivity to its clinical efficacy. Whether the mechanism accounting for such a reduced sensitivity depends on cyclooxygenase (COX)-1, COX-2 or both is still unclear.
Methods: We enrolled 196 patients taking aspirin (100-330 mg/day) with a history of coronary heart disease, cerebrovascular disease, or with one or more risk factors for atherothrombosis in which we studied collagen-induced platelet aggregation and thromboxane (Tx)B2 production. In a subgroup of 96 patients the mechanism leading to TxB2 production was also investigated by adding in vitro a TxA2 receptor antagonist (13-Azaprostanoic acid), aspirin or a COX-2 inhibitor (NS-398).
Results: We found a positive statistically significant correlation between collagen-induced TxB2 formation and platelet aggregation in the whole population. In the 96 patients (median value of TxB2= 40.3 pg/108 cells) 13-Azaprostanoic acid significantly inhibited platelet aggregation without affecting TxB2 production. The addition of aspirin significantly reduced TxB2 production in patients with TxB2 values above the median as compared to control, although only by 72.9%. In the same population also NS-398 caused a significant, although lower, reduction of collagen-induced thromboxane B2 production (44.3%) that was associated with the inhibition of platelet aggregation. Notably, the combined use of these drugs caused an inhibition of thromboxane B2 formation of 90.5%.
Conclusion: Chronic treatment with aspirin is associated with a persistent production of thromboxane, that enhances platelet response to agonists. COX-2 over expression and incomplete COX-1 inhibition seem to be involved in this phenomenon. Albeit the relationship between persistent TxA2 production and cardiovascular events was not investigated, our findings have a potential impact in the management of aspirin-treated patients. Persistence of thromboxane production with ensuing normal platelet aggregation clearly implies that patients potentially at risk of cardiovascular events are not on adequate antithrombotic treatment and should be therefore considered for alternative antiplatelet approaches.

P584 Role of P2Y receptors in agonist-induced tissue factor expression by platelets

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Recent data indicate that human platelets contain Tissue Factor (TF), one of the major determinants of the activation of coagulation cascade. We have shown that intraplatelet TF can be exposed on the membrane by platelet agonists such as ADP, TRAP and tromboxane A2 mimetic U46619. ADP-induced platelet activation, leading to aggregation and other functional responses, is initiated by the platelet P2Y1 receptor and amplified in a synergistic manner by the platelet P2Y12. In addition, these two receptors play an important role also in platelet activation induced by agonists other than ADP.
Aim: In the present study we investigated whether agonist-induced TF expression on platelet surface is mediated by concomitant signaling through co-activation of both receptor subtypes.
Methods: Platelet-associated TF was measured by flow cytometry using a specific monoclonal anti human TF antibody in whole blood (WB) and in platelet rich plasma (PRP) obtained from healthy subjects.
Results: ADP (10 μmol/L) incubated for 15 minutes in WB or PRP induced a consistent expression of TF (+170±40% versus unstimulated platelets, $p<0.01$). The selective P2Y1 receptor antagonist MRS2216 (50 μmol/L) inhibited membrane-associated TF as well as P-selectin expression by 60±9% both in WB and in PRP, whereas the selective P2Y12 receptor antagonist AR-C69931MX (0.5 μmol/L) almost completely inhibited ADP-induced TF as well as P-selectin expression (-95±10%). Similarly U46619 (1 μmol/L)-induced TF expression was almost abolished by AR-C69931MX, while MRS2216 only diminished it. By contrast MRS2216 and AR-C69931MX inhibited TRAP-induced TF translocation only by 20±7 and 45±10% respectively. These results suggest a predominant role of P2Y12 in mediating ADP-induced platelet-associated TF expression. Experiments performed with platelets from a patient with selective congenital P2Y12 deficiency confirmed the contribution of this receptor in agonist-induced TF expression since no expression of the protein in response to ADP, and only a little increase in response to TRAP (+130%) was observed.
Conclusions: These findings indicate that antagonist of P2Y12 significantly reduces platelet-associated TF expression; this may further strengthen the therapeutic benefits of a selective inhibition of the P2Y12 receptor.

P585 A new definition of aspirin resistance by platelet function analyzer-100 and its predictors

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Aspirin (asa) resistance has been described as having a normal closure time (CT) by PFA-100 assay despite confirmed treatment without knowing the pre-asa CT. However, there is no standard definition of asa resistance by PFA-100, with a variety of cutoff values having been used. We consider that the definition of asa resistance by PFA-100 must be done according to the comparison of post-asa CT with the pre-asa CT.
Methods: One hundred eighty-four patients with diagnosis of stable coronary artery disease or diabetes mellitus were prospectively included. Blood samples were drawn before and after the seven days of asa therapy. An individual was labeled as asa resistant if his post-asa CT was not above two standard deviation from his pre-asa CT, where the standard deviation was calculated from the baseline CTs of the study population. Asa resistance was also defined as having a normal post-asa CT (<193 s) regardless of pre-asa CT.
Results: The baseline CTs ranged 73 to 202 s, (mean 128.8±30.2, median 128 s) in the study population. Univariate analyis showed that there was no relation between baseline CTs and any of the variables analyzed, which were age, gender, diabetes, hypertension, smoking, serum cholesterol level, hematocrit and platelet count. At the end of one week of asa administration, CT increased to a mean of 260.4±64.5 s (range 84-300). According to our definition, 28 (15.2%) of 184 patients were asa resistant. Asa resistant patients were more likely to be men or smoker and less likely to be diabetics or hypertensive. Univariate analysis indicated that asa resistance was closely associated with gender (p=0.0115, DM (p=0.0058), smoking (p=0.0496) and hypertension (p=0.0210). Multivariate analysis identified diabetes(p=0.0158) as the only significant independent predictor for the presence of asa resistance. Thirty-four of 184 patients (18.5%) classified as asa resistant according to the second definition. There was a discordance between the two definition of asa resistance in 8 patients. Seven patients without asa resistance were classified as asa resistant by the post-asa CT <193 s criteria. Only one patients with asa resistance was classified as asa responsive by the post-asa CT <193 s criteria.
Conclusion: We proposed an alternative definition of asa resistance by PFA-100 method. Our results suggested that definition of resistance as post-asa CT <193 s may overestimate the prevalence of asa resistance. Nevertheless, definition of asa resistance by PFA-100 must be standardized and its utility as a predictor of cardiovascular events needs to be investigated.

P586 The matrix-metalloproteinase ADAM15 mediates platelet adhesion to endothelial cells

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Pericellular proteolysis plays a crucial role in thrombosis in arteries and microcirculation. ADAM15 belongs to the family of membrane-bound metalloproteinases that is characterized both by proteinase and disintegrin activity and is widely expressed in various cell types including endothelial cells. Previously, a RGD-motif within the ADAM15 molecule has been recognized to interact with beta3-integrins. The aim of the present study was to evaluate the role of ADAM15 for platelet adhesion and activation. Platelet adhesion to immobilized ADAM15 was characterized both under static and dynamic conditions using a parallel-plate-flow perfusion chamber. The expression of ADAM15 on endothelial cells and the effect of the substance on platelet secretion was examined by flow cytometry. Simulating arterial shear rates, platelets (1×10^8/ml) were perfused over endothelial monolayers infected with adenoviral vectors, expressing ADAM15 or a GFP-expressing control virus. We found that immobilized ADAM15 specifically mediates platelet adhesion under both static and high shear rate conditions. This effect was reduced by the GPIIb-IIIa inhibitor c7E3, but not by the αVβ3 inhibitor LM609 (static adhesion (adherent cells per 10 mm^2: control 460±58 c7E3, 203±45, LM609 464±32). Flow cytometry studies showed, that ADAM15 is surface expressed on endothelial cells and upregulated on TNFa-/INFg-activated cells. Platelet adhesion and

thrombus formation on ADAM15-GFP expressing endothelial cells was significantly increased compared with control infected cells (9,7±4,1 vs 50,8±33,7; $p<0.05$). Interestingly, on cells expressing an ADAM15 receptor with a defect metalloproteinase domain stable and large thrombus formation was significantly attenuated. Furthermore, coincubation of platelets with ADAM15 showed a dose-dependent increase in CD62P and CD40L secretion. We conclude that ADAM14 mediates platelet adhesion and activation on inflammed endothelial cells. This interaction is mediated through the platelet GPIIb-IIIa receptor and induces platelet activation and secretion. ADAM15-dependent platelet adhesion may play a critical role in the pathophysiology of thrombosis and inflammation.

P587 Increased potential for thrombin generation in patients with premature myocardial infarction and their offspring: a two-generation study

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Whilst plaque rupture is the initiating event leading to a myocardial infarction (MI), the extent of the haemostatic response may determine the extent of thrombus formation and hence the clinical outcome. This may be particularly important in patients who have suffered a MI at an early age when the atherosclerotic burden is relatively low. Thrombosis is a consequence of thrombin generation, which is driven by the activation of coagulation by tissue factor (TF). A measure of the overall thrombotic potential may be obtained from the Endogenous Thrombin Potential (ETP). 162 individuals with an MI under the age of 50 years were compared with 180 age/sex-matched controls with no family history of CHD. In addition 25 young healthy adult males with a two generational family history of premature MI were compared with 25 age/smoking status matched healthy males with no family history of MI in the preceding two generations. Blood samples collected into citrate were analysed for ETP by a modification of the method of Hemker et al (Thromb Haemostas 1993;70:617-24), measuring total thrombin generation with a chromogenic substrate (Pefachrome-TG; 5mM). Endogenous TF activity in the plasma was measured in a chromogenic assay for FXa generation. Mean ETP was significantly higher in the MI cases than the controls (119±37 vs 102±23%; $p<0.0001$). Similarly, the ETP in the healthy sons of premature MI patients was higher than in the individuals with no family history (117±21 vs 98±19%; p=0.004). Levels of "blood borne" TF activity were significantly higher in the MI cases compared to the controls (11.4±7.8 vs 9.4±6.6pM; p=0.0063) but a similar difference was not seen in the younger cohorts (16.9±6.6 vs 16.2±7.3; p=0.7). In the older subjects ETP was correlated with plasma TF levels (r=0.32; $p<0.0001$). ETP was also correlated with the level of plasma fibrinogen in both cases (r=0.44; $p<0.0001$) and controls (r=0.22; p=0.0036) and with LDL in the cases (r=0.24;p=0.0098) but not in the controls (r=0.04; p=0.6). These data suggest an increased tendency to generate thrombin associated with premature MI, which may be linked to increased circulating levels of TF. Increased ETP is also seen in healthy individuals with a strong family history of premature MI, suggesting a possible genetic link.

P588 Heparin-induced thrombocytopenia is common and associated with poor outcomes, yet uncommonly evaluated and detected: preliminary results of the multicentre CATCH registry

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Patients with acute coronary syndromes (ACS) are usually treated with unfractionated heparin (UFH) or low molecular weight heparin, and clinical trials have shown that thrombocytopenia (TCP)is relatively common and associated with worse outcome. However, large-scale systematic data on incidence, diagnostic serology and outcome are unavailable.

Methods: We aimed to determine the incidence, evaluation and outcome of HIT by establishing a comprehensive registry of patients treated with heparin and with suspected HIT, including TCP (platelets $<150{,}000/mm^3$ or >50% reduction from baseline) developing in cardiac care unit (CCU), or ordering of testing for HIT. Electronic data capture was used at 50 US sites.

Results: Data from 03/2003 to 02/2004 are available for 660 CCU patients. In-hospital evaluation and outcomes are shown (Table 1). Primary reasons for hospitalization were the spectrum of ACS, cardiac surgery and congestive heart failure (CHF). The majority received IV UFH; 12% had received heparin within 3 months pre-admission. In 11% of cases a GPIIb/IIIa inhibitor was used before TCP had occurred.

Conclusions: Preliminary data demonstrate that: 1) Cardiac patients who develop thrombocytopenia have frequent arterial thrombotic events, mainly myocardial infarction as well as CHF and high in-hospital mortality; 2) Timely evaluation, recognition, and documentation of HIT is lacking.

Table 1. Thrombocytopenia in CCU patients

HIT suspected	20.8%
Days after thrombocytop. med (25th, 75th)	2 (1, 5)
Serologic Testing for HIT	15% (5% Pos.; 10% Neg.)
Days after thrombocytop. med (25th, 75th)	3 (2, 6)
Hematology Consult	10.5%
Days after thrombocytop. med (25th, 75th)	4 (2, 9)
Final Diagnosis of HIT	7.2%
Myocardial Infarction/Reinfarction	26.4%
Stroke/Transient Ischemic Attack	3.2%
Arterial Embolism	1.4%
Deep Vein Thrombosis	2.8%
Congestive Heart Failure	21.2%
Death	6%

P589 Selective Inhibition of cyclooxygenase-2 enhances platelet vessel-wall interactions in hamster arterioles in vivo

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Purpose: Selective inhibitors of cyclooxygenase-2 (Cox-2) are reported to cause cardiovascular side effects by exerting prothrombotic effects in patients at risk. However, direct proofs for prothrombotic effects of selective Cox-2 inhibitors are lacking. We investigated, whether selective inhibition of Cox-2 could increase platelet vessel wall interactions (PVWI) in the microcirculation in vivo.

Methods and Results: Adhesion of fluorescence-labelled human platelets was monitored by intravital microscopy in arterioles of hamsters (dorsal skinfold chamber). Firm platelet adhesion to the vessel wall as well as transient PVWI (derived from platelet flow velocities) were analysed using digitalized images. Additionally, in vitro adhesion of activated platelets to human umbilical vein endothelial cells was monitored under shear stress (16dyn/cm^2).

Intraperitoneal injection of the selective Cox-2 inhibitor NS-398 (0.5mg/kg) or inhibition of endothelial NO-synthase (N-nitro-L-arginine, L-NA, 100μmol/L) increased firm platelet adhesion to the vessel wall (NS-398: 10,2±4,1 platelets/mm^2, n=7, $P<0.05$; L-NA: 12.9±2.7 platelets/mm^2, n=6, $P<0.01$) when compared to control conditions (0.9±0.9 platelets/mm^2, n=7), without causing thrombus formation. Similar results were obtained in vitro. In addition, there was significant enhancement of transient PVWI in NS-398 and L-NA treated animals. Intravenous aspirin (5mg/kg) significantly decreased PVWI (n=4) and prevented the effect of NS-398 (n=4). Enhanced PVWI following NS-398 treatment was furthermore prevented when platelets had been pretreated with iloprost (1nmol/L, n=4).

Conclusions: Selective inhibition of Cox-2 increases platelet interaction with the vessel wall and enhances firm platelet adhesion without causing arteriolar thrombosis in healthy hamsters. Diminished endothelial antiplatelet properties after inhibition of Cox-2 may trigger thrombotic events in patients at risk.

P590 Vasoconstrictors in acute coronary thrombi

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Background and Objective: Acute coronary syndrome is characterized by compromised flow at the epicardial and microvascular levels. Thrombectomy in ST-elevation myocardial infarction (STEMI) has been shown to protect the coronary microvasculature from distal embolization and improve ST-segment resolution. Following the hypothesis that thrombus constituents contribute to microvascular dysfunction, we analyzed the vasoconstrictor composition of acute coronary thrombi.

Methods: Acute coronary thrombi were harvested from consecutive patients (n=26) with the X-Sizer Catheter System Thrombus Removal Device (EndiCOR Medical Inc., ev3) in the course of acute coronary angioplasty for STEMI 6±4 hours after symptom onset. A panel of potent coronary vasoconstrictors was measured in patient peripheral blood and thrombi.

Results: Acute coronary thrombi contained 181,3±167,5 fmol/mL endothelin, equal to a 450-fold enrichment in thrombi compared with patient plasma (0,4±0,3 fmol/mL endothelin; $p<0.0001$). Serotonin and noradrenalin concentrations in acute coronary thrombi were 1964,1±1699,1 ng/mL and 5303,0±2696,0 pg/mL compared with 38,4±48,3 ng/mL ($p<0.0002$) and 354,0±178,2 pg/mL ($p<0.0002$) in plasma. The angiotensin-II concentration was 260,2±400,7 pg/mL in thrombi and 128,1±151,2 pg/mL in plasma (p=0.7).

Conclusions: Acute coronary thrombi contain high levels of vasoconstrictors, endothelin showing the highest gradient between peripheral plasma and coronary thrombus. The data underscore the importance of distal protection. Endothelin-receptor antagonists may become important new tools for STEMI treatment.

P591 Effects of a dimeric, soluble form of glycoprotein VI on platelet adhesion following vascular injury in vivo

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Background and Aims: The adhesion of platelets to the vascular wall essentially contributes to the process of arterial thrombosis. The glycoprotein VI (GPVI) acts as the major platelet collagen receptor and mediates platelet adhesion to the injured vessel wall in vivo. In our present study, we generated a soluble dimeric form of GPVI and assessed its effects on platelet adhesion in vitro and in vivo.
Methods and Results: We fused the extracellular domain of GPVI with the human immunoglobulin Fc domain to obtain a soluble form of GPVI (GPVI-Fc). In vitro the soluble form of GPVI, GPVI-Fc, specifically bound to immobilized collagen with high affinity. Binding of GPVI-Fc to collagen was inhibited competitively by soluble GPVI-Fc, but not control Fc lacking the external GPVI domain. This indicates that GPVI-Fc binds collagen specifically. To determine the effects of GPVI-Fc on cell adhesion dynamics we performed in vitro adhesion studies using GPVI transfectants or washed human platelets. We show that GPVI-Fc inhibits the adhesion of CHO cells that stably express human GPVI and of platelets on collagen under shear conditions in vitro. In addition, GPVI-Fc significantly attenuated thrombus formation under shear in a parallel plate flow chamber model. Finally, to test the effects of GPVI-Fc in vivo, arterial thrombosis was induced in the mouse carotid artery and platelet-vessel wall interactions were visualized by intravital fluorescence microscopy. Infusion of GPVI-Fc but not of control Fc virtually abolished stable arrest and aggregation of platelets following vascular injury. Importantly, GPVI-Fc but not control Fc was detected at areas of vascular injury.
Conclusion: These findings further substantiate the critical role of the collagen receptor GPVI in the initiation of thrombus formation at sites of vascular injury and identify soluble GPVI as a promising anti-thrombotic strategy.

P592 Atorvastatin improves endothelial function and affects thrombosis/fibrinolysis system in patients with congestive heart failure

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Congestive heart failure (CHF) is characterised by endothelial dysfunction and increased thrombogenecity.
Aim: We investigated the effect of atorvastatin on endothelial function and on plasma levels of antithrombin III (ATIII), proteins C and S, factors V and VII, von Willebrand factor (vWF), tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1) in patients with CHF.
Methods: Thirty-five patients with CHF (NYHA II-IV) were randomized to receive atorvastatin 10mg/day (n=17) or no statin (n=18) for 4 weeks. Forearm blood flow was measured by venous occlusion strain-gauge plethysmography. Endothelium dependent dilation (EDD) and endothelium independent dilation (EID) were expressed as the % change of flow from baseline to the maximum flow during reactive hyperemia or after sublingual nitroglycerin administration respectively. Plasma levels of thrombosis/fibrinolysis components were determined with ELISA.
Results: Atorvastatin improved EDD (42.44±4.5 to 83.7±8.5%, $p<0.01$), decreased plasma levels of tPA (15.5±2.2 to 12.3±1.6 ng/ml $p<0.05$), ATIII (82±3 to 74±4%, $p<0.05$), prtC (88±6 to 64±6%, $p<0.01$), fV (126±8 to 95±7%, $p<0.01$) and PAI-1 (3.02±0.39 to 1.96±0.34 IU/L, $p<0.05$), while it did not affect EID (65±8 to 53±6% p=ns) and levels of fVII (81±8 to 66±7% p=ns), vWF (135±13 to 123±19% p=ns) and prtS (93±5 to 95±8% p=ns). EDD and EID remained unchanged in controls (from 48±5 and 67±8 to 45±5% and 61±7% respectively p=ns for both). In control group, no significant change was observed in levels of ATIII (85±4 to 88±3%,p=ns), prtC(84±6 to 84±5%,p=ns), fV(131±10 to 122±9%,p=ns), fVII(78±12 to 69±9%,p=ns), vWF (151±19 to 135±38%, p=ns), prtS (100±8 to 96±6%, p=ns), tPA(13.2±1.5 to 11±2 ng/ml, p=ns) and PAI-1(2.64±0.38 to 3.25±0.34, p=ns).
Conclusions: Short-term treatment with atorvastatin improves endothelial function and reduces plasma levels of tPA, PAI-1, antithrombin III, protein C and factor V, in patients with CHF, suggesting that atorvastatin may affect the expression of both endothelium- and liver-derived components of thrombosis fibrinolysis system, beyond its effect on vascular endothelium in these patients.

P593 The thrombus becomes stiffer in the first 3 hours: in vivo assessment with palpography

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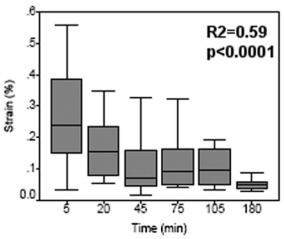
Vulnerable plaques can lead to thrombus development, which may cause acute coronary syndrome. The age of a thrombus cannot be assessed in vivo with currently available imaging methods. It is well accepted that a thrombus stiffens over time, nevertheless less is known about the time course of this process especially in the early phase of development.
Palpography - an IVUS based technique- assesses the mechanical properties of tissue and can be used to measure the stiffness of thrombi in vivo. We hypothesize that the thrombus organization starts early after introduction and stiffness is increasing over time.
Methods: In 7 anesthetic and surgical prepared pigs thrombus formation was introduced in both femoral arteries by applying electrical DC current (9 mA, 9 V) to the outer vessel wall. The current caused a vessel injury with the signs of endothelial erosion. Over this erosion a parietal thrombus was formed, which left a lumen through which the blood pressure could act as the force to strain the thrombus. Ten thrombi were formed, while in 4 cases the process failed. Palpograms were recorded at 6 time points after thrombus introduction (5, 20, 45, 75, 105, 180 min) and processed as previously described.
Results: Initially thrombi are soft and stiffened in the first 20 minutes with a strain reduction of about 50% (see figure). Further stiffening took considerable more time, but could be observed to the end of the experiment. The relation between the time and strain is highly significant (R^2=0.59; $p < 0.0001$).



Conclusion: This is the first time the in vivo development of a thrombus in an artery could be monitored with special emphasis on the organization of the thrombus. A vast parts of the organization process take place within 20 min after thrombus introduction.

P594 Effects of G894T polymorphism on endothelial nitric oxide synthase gene, on endothelial function, thrombosis/fibrinolysis system and inflammatory process in young myocardial infarction survivors

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Genetic polymorphism G894T on endothelial nitric oxide synthase (eNOS), has been associated with increased risk of myocardial infarction (MI). However, its effects on endothelial function, thrombosis/fibrinolysis system and inflammatory process remain unknown.
Purpose: We investigated the effect of G894T polymorphism on endothelial function, thrombosis/fibrinolysis and inflammatory markers in young MI survivors.
Methods: This study enrolled 60 young patients with a history of premature MI (45.2±4.2 years old). All patients were in stable clinical condition for at least one year before recruitment. Endothelial function was evaluated in the forearm using venous occlusion strain-gauge plethysmography. Endothelium dependent dilation (EDD) and endothelium independent dilation (EID) were expressed as the % change of forearm blood flow from rest to the maximum flow during reactive hyperemia or after sublingual nitroglycerin administration respectively. The G894T polymorphism on eNOS gene was determined by polymerase chain reaction (PCR), while plasma levels of plasminogen activator inhibitor (PAI-1), von-Willebrand factor (vWF) and interleukin 1b (IL-1b) were measured with ELISA.
Results: Patients were divided into groups according to genotype. Twenty patients were 894G homozygotes, 31 were heterozygotes and 9 were 894T homozygotes. EDD was significantly higher in 894GG (113.1±14.5) compared 894GT (39.8±5.2%, $p<0.01$) or 894TT(41.1±3.3%, $p<0.01$). VWF was significantly higher in 894GT (65.5±2.5%) or 894TT(57.7±3.2) compared to 894GG (50.4±3.5%,$p<0.05$ for both). Carriers of the T allele had significantly lower EDD ($p<0.01$) and higher levels of vWF ($p<0.05$) compared to 894G homozygotes. Plasma levels of PAI-1 and IL-1b were not significantly different between 894T carriers (35.4±4.9ng/ml and 0.86±0.12 pg/ml) and 894G homozygotes (37.2±6.6 mg/dl and 0.84±0.13pg/ml respectively, p=NS for both).
Conclusions: Carriers of the 894T allele appear to have blunted endothelial function and higher levels of von Willebrand factor one year after an incident of premature myocardial infarction. Therefore, G894T polymorphism on eNOS gene may affect endothelial function and thrombosis, in patients with premature myocardial infarction.

P595 Interindividual variability in response to clopidogrel in patients with coronary artery disease

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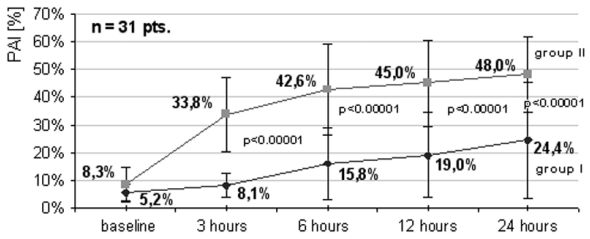
Background: Addition of clopidogrel to aspirin reduces the risk of ischaemic com-

plications in patients (pts.) with atherosclerosis. However there's a little data about variability of patient's response to this treatment in terms of platelet activity.
Methods: Thirty one consecutive pts. with stable angina pectoris referred to elective percutaneous coronary intervention, treated with aspirin were enrolled in the study. Fresh whole blood samples were obtained and platelet aggregation inhibition (PAI) was measured using point-of-care assay at baseline, 3, 6, 12 and 24 hours (h) after receiving of loading dose of clopidogrel (300 mg). Inhibitory response to treatment with clopidogrel (dPAI) was defined as absolute change of PAI from baseline to mentioned time points. We divided pts. into two groups according to median dPAI at 3 h after administration of loading dose of clopidogrel. Group I: 15 pts. with dPAI =< 10%, Group II: 16 pts. with dPAI > 10%.
Results: There was no differences between both groups in baseline PAI (5.2 ± 3.2% vs. 8.3 ± 5.8%, p=NS). Pts. with a lower response (Group I) to loading dose of clopidogrel at 3 h have got significantly lower PAI at all time points. Comparison of PAI in time between the two groups is shown in figure. PAI at 24 h strongly correlated with dPAI at 3 h (r=0.60).



Conclusions: Determination of PAI helps to identify group of pts. resistant to treatment with clopidogrel. Early identification of such group using point-of-care whole blood assay is possible and may be required to optimize effects of antiplatelet treatment. Failure to achieve adequate PAI after the initiation of clopidogrel therapy warrants further investigation because it may be associated with increased rates of adverse cardiac events during follow-up.

P596 Platelet microparticles reflect platelet activation despite aspirin use in unstable coronary disease

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Purpose: Activation and apoptosis of blood cells and endothelial cells, both accompanied by microparticle formation, underlie the development of atherosclerosis as well as thrombus formation in atherosclerotic disease. Microparticles from myocardial infarction patients induce endothelial dysfunction. Therefore, we characterized circulating microparticles in patients with stable angina, peripheral arterial disease, myocardial infarction, as well as in older (age and sex matched) and young healthy subjects.
Methods: Microparticles were isolated from plasma, and stained with cell-type specific monoclonal antibodies plus annexin V. In addition, platelet microparticles (CD61- and annexin V positive) (PMP) were triple-stained with either anti-P-selectin or anti-CD63. Soluble P-selectin and parameters of coagulation (F1+2, TAT), and inflammation (CRP) were determined.
Results: No differences between groups were observed in the total numbers or cellular origin of circulating microparticles. However, compared to young healthy subjects, older healthy subjects showed elevated numbers of P-selectin (p=0.028) but not CD63 (p=0.791) exposing PMP. Stable angina patients and older healthy subjects had comparable numbers of P-selectin (p=0.821) and CD63 (p=0.744) exposing PMP. In contrast, patients with peripheral arterial disease, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction had elevated numbers of P-selectin (p=0.07, p=0.007, and p=0.045, respectively) and CD63 (p=0.041, p=0.001 and p=0.049, respectively) exposing PMP compared to the older healthy subjects. CRP levels were higher in older than young healthy subjects (p=0.006), and in peripheral arterial disease patients (p=0.005) and non-ST-elevation myocardial infarction (p=0.001) but not in stable angina (p=0.345) and ST-elevation myocardial infarction patients (p=0.545), when compared to the older healthy subjects. Previous aspirin use did not influence P-selectin or CD63 exposure in both myocardial infarction groups. The numbers of PMP exposing P-selectin or CD63 highly correlated (r=0.581, p<0.001). In contrast, no correlations were found between these microparticle subpopulations and soluble P-selectin. F1+2 and TAT were comparable in all groups.
Conclusions: Progression of atherosclerosis is reflected by elevated CRP levels as well as elevated numbers of circulating microparticles from activated platelets, but progression to unstable disease (i.e. myocardial infarction) is primarily reflected by extensive platelet activation, despite anti-platelet therapy.

P597 Sildenafil Citrate (Viagra®) does not reverse endothelial dysfunction in patients with coronary heart disease

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Purpose Endothelial dysfunction is an independent predictor of cardiovascular events and may be due to a reduction in nitric oxide (NO) bioavailability. The fibrinolytic factor, tissue plasminogen activator (t-PA), is released from the endothelium and plays a critical role in preventing acute thrombotic events. Phosphodiesterase (PDE) inhibitors may augment NO dependent pathways. We hypothesised that sildenafil citrate, a selective PDE type 5 inhibitor, would improve endothelial vasomotor and fibrinolytic function in patients with coronary heart disease.
Methods: In a randomised double-blind placebo controlled cross-over study, sixteen male patients with coronary heart disease and eight matched healthy men received intravenous sildenafil or placebo. Bilateral forearm blood flow and fibrinolytic parameters were measured using venous occlusion plethysmography and blood sampling in response to intra-brachial infusions of acetylcholine, substance P, sodium nitroprusside and verapamil.
Results: Compared to healthy controls, patients with coronary heart disease exhibited impaired endothelium dependent vasodilator responses to acetylcholine (P=0.005) but not to sodium nitroprusside. Mean arterial blood pressure was reduced in both patients and controls (92 ± 1 to 82 ± 1 and 94 ± 1 to 82 ± 1 mmHg respectively, P<0.001 for both) during sildenafil infusion. Sildenafil increased vasodilatation with the direct NO donor sodium nitroprusside (P<0.01) but did not alter the response to acetylcholine, substance P or verapamil in patients or controls. Substance P caused a dose-dependent increase in plasma tissue plasminogen activator antigen concentrations (P<0.01) that was unaffected by sildenafil in either group.
Conclusions: Sildenafil does not improve peripheral endothelium-dependent vasomotor or fibrinolytic function in patients with coronary heart disease or matched healthy controls. We would therefore question whether PDE5 inhibitors are likely to have major secondary preventative benefits in patients with coronary heart disease. Future work is needed to explore other novel therapeutic applications of sildenafil and to develop PDE inhibitors that may be more selective for the vascular endothelium.

P598 Phosphodiesterase type 5 inhibition with sildenafil preserves endothelial function during smoking

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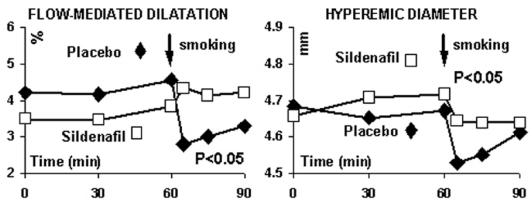
Purpose: Smoking induces an acute impairment in endothelial function. Sildenafil (Viagra©) is an effective drug for erectile dysfunction which acts by inhibiting breakdown of c-GMP through selective phosphodiesterase type 5 inhibition. The purpose of this study was to examine whether phosphodiesterase type 5 inhibition by sildenafil abrogates acute smoking-induced endothelial dysfunction.
Methods: We studied 14 healthy volunteers (age 34±4 years) without known cardiovascular risk factors except for smoking. The subjects smoked one standard cigarette (0.9 mg nicotine) on 2 separate occasions, one with sildenafil (50 mg) and one with placebo according to a randomized, double-blind, crossover, fashion. Endothelial function was evaluated with flow-mediated dilatation (FMD) of the brachial artery after reactive hyperemia induced by cuff occlusion using high-resolution ultrasonography (10.5 MHz).
Results: Sildenafil abrogated the decrease in FMD of the brachial artery that was induced acutely by smoking (left figure). This was associated with no reversal effect of sildenafil on smoking-induced decrease in resting brachial artery diameter (by 0.08 mm for both the sildenafil and placebo sessions, P<0.05 for both) and with a partial reversal of the smoking-induced decrease in hyperemic brachial artery diameter (right figure).



FMD and hyperemic diameter.

Conclusions: Phosphodiesterase type 5 inhibition by sildenafil protects from endothelial dysfunction that is induced by smoking acutely. In addition, this finding provides new insights into the overall cardiovascular profile of the drug.

P599 Short-term sibutramine therapy improves flow-mediated endothelium-dependent vasodilation of the brachial artery in obese patients with coronary artery disease

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Background: Obesity is becoming increasingly common and a major public health problem worldwide. Obesity is also independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries. Sibutramine, a serotonin and norepinephrine transporter blocker, is widely used as an adjunctive obesity treatment, however, its impact on endothelial function in obese coronary artery disease (CAD) patients has not yet been investigated.
Methods: We prospectively assessed the impact of oral sibutramine 10 mg/day therapy on endothelium-dependent brachial artery flow-mediated dilation (FMD) and endothelium-independent nitroglycerin (NTG)-mediated vasodilation, using high resolution linear array ultrasound in 15 consecutive obese non hypertensive stable CAD patients (10 men, mean age 66±11 years, mean left ventricular ejection fraction 42±9%) at baseline and after 4 months, and compared them to 15 age- and sex-matched obese CAD controls. Patients from the two study groups were instructed to follow the American Heart Association Step 1 diet and at baseline their lipoproteins were within the recommended National Cholesterol Education Program guidelines.
Results: Sibutramine significantly improved brachial artery endothelial function compared to controls. Patients from the sibutramine group reduced 10.6±1.2% of initial body weight compared to only 2.2±1.3% in the control group ($p<0.05$). Mean blood pressure and heart rate did not change significantly compared to baseline and no significant adverese events were noticed during the 4-month follow up in the two study groups.

	Baseline Baseline %FMD	4-month %FMD	Baseline BMI (kg/m^2)	4-month BMI (kg/m^2)
Sibutramine (n=15)	5.3±3.0*	8.9±2.4*	32.2±2.9	28.9±3.2
Controls (n=15)	5.6±3.2	5.2±3.6	31.9±2.5	31.2±3.0
p-value	0.55	0.01	0.66	<0.05

Values are expressed as mean±SD; %FMD=change from baseline in brachial artery diameter caused by FMD; BMI=body mass index; *p=0.02.

Conclusion: Short-term therapy with the antiobesity drug sibutramine, in addition to adjunctive diet and lifestyle therapy, significantly improves endothelial function assessed by brachial artery FMD in non-hypertensive stable CAD patients, suggesting a mechanism whereby sibutramine may benefit obese CAD patients.

P600 Improvement of endothelial function by treatment with recombinant granulocyte colony stimulating factor

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Experimental studies have shown that granulocyte colony stimulating factor (GCSF) may modulate arterial vascular tone via endothelial receptors or indirectly by release of other cytokines. We examined the effects of GCSF administration on arterial endothelial function in vivo.
Methods: We studied 32 women with surgically excised breast cancer (stage II-IIIA) who were scheduled to receive a 5 day course of s.c. recombinant human GCSF (5μg/kg), o.d. to prevent neutropenia after adjunctive chemotherapy. B-mode and Doppler brachial artery ultrasonography was used to assess flow-mediated, endothelium-dependent dilatation (FMD%) and nitrate-mediated, endothelium-independent dilatation (NMD%) of the brachial artery in all patients. Measurements were performed at baseline before chemotherapy (FMD, NMD 0), before (FMD, NMD 1) and 2 hours (FMD, NMD 2) after the first s.c. injection of GCSF and at the end (FMD, NMD 3) of a 5-day treatment with daily s.c. administration of GCSF. White cell blood count (WBC - mm^3) was also assessed at the above time periods (0,1,2,3).
Results: There were no differences between baseline FMD (FMD0)and FMD before the first GCSF injection (FMD1) (p=ns). Analysis of variance showed that FMD significantly increased 2 hours after the first GCSF injection (FMD2) and remained improved at the end of GCSF treatment (FMD3) compared to FMD before treatment(FMD1) ($P<0.05$,table). NMD remained unchanged throughout the study. After chemotherapy, WBC (WBC1) was reduced compared to baseline (WBC0) but was significantly increased after the first injection of GCSF (WBC2) and remained within normal limits at the end of GCSF treatment (WBC3) (table, $p<0.05$).
Conclusion: Treatment with GCSF improves endothelium-dependent dilatation of the brachial artery whereas does not affect endothelium-independent dilatation of the artery in vivo. Our findings suggest that treatment with GCSF stimulates endothelial function and thus, may be used to facilitate neovascularisation of the infracted region during procedures of myocardial regeneration in patients with heart failure.

Time periods	0	1	2	3
FMD (%)	4.9±3.2	4.3±3.3	6.2±3.4	5.7±2.8
NMD (%)	15.8 ±7.3	14.9±8	13.3±4.1	14.5±4.5
WBC (mm^3)	7.4±2.3	6.1±2.5	7.4±2.9	4.3±3.2

$p<0.05$, for FMD(1) vs FMD(2) and FMD(3)

P601 Improvement of endothelial function caused by carvedilol in patients with coronary artery disease

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Purpose: At present time it is well established that endothelial dysfunction is independent factor of increased risk of cardiac events. That is why use of drugs, which improve endothelial function, is preferable. Carvedilol is beta-blocker with antioxidant properties. In experimental model it decreases levels of endothelin. We examined its possibility to improve endothelial function in patients with coronary artery disease (CAD).
Methods: We examined 26 patients with CAD including 12 patients with prior myocardial infarction. Control group consisted of 14 sex and age matched subjects. Endothelium-dependent and endothelium-independent dilation of brachial artery were assessed by high resolution ultrasound during reactive hyperemia and after sublingual administration of 0.0005 g nitroglycerine. Blood samples were taken from cubital vein before and after two month of treatment by carvedilol (50 mg daily).
Results: Carvedilol improved endothelium-dependent dilation from 4.55±0.7% to 7.8±0.8% ($p< 0.05$) after two month of treatment. Nitroglycerine-induced vasodilatation was unchanged. After treatment with carvedilol level of endothelin-1 significantly decreased from 17.9±2.3 pg/L to 15.3±0.6 pg/L ($p<0.05$). Carvedilol reduced parameters of oxidative stress - activity of superoxide dismutase increased from 1319±230 U/L to 1715±184 U/L ($p<0.05$), and concentration of malonic dialdehyde decreased from 12.6±1.0 mmol/L to 7.9±1.5 mmol/L ($p<0.05$).
Conclusion: Improvement of endothelial function induced by carvedilol may have two explanations: reduction of parameters of oxidative stress and decreasing of endothelin-1 concentration. Administration of cardvedilol may be useful for patients with CAD.

P602 The endothelin-1 receptor antagonist bosentan protects from ischaemia/reperfusion-induced endothelial dysfunction in humans in vivo

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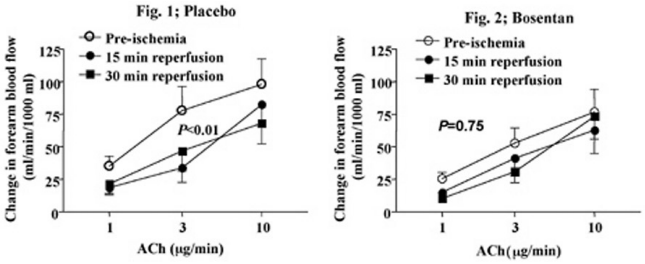
Purpose: Endothelial dysfunction develops early during reperfusion of a previously ischemic area and may be of importance for the extent of the ischemia/reperfusion injury. Endothelin-1 (ET-1) receptor antagonism protects from myocardial ischemia/reperfusion injury in animal models. The present study investigated whether oral administration of the dual ETA/ETB receptor antagonist bosentan protects against ischemia/reperfusion-induced endothelial dysfunction in humans.
Methods: Forearm blood flow was measured with venous occlusion plethysmography in 13 healthy male subjects. Forearm ischemia was induced for 20 min followed by 60 min reperfusion. Using a cross-over protocol the subjects were randomized to oral administration of 500 mg bosentan or placebo two hours before ischemia on two separate occasions. Endothelium-dependent and -independent vasodilatation was determined by intra-brachial infusion of acetylcholine and nitroprusside, respectively, before and after ischemia.
Results: Compared to pre-ischemia, endothelium-dependent increase in forearm blood flow was significantly impaired at 15 and 30 min of reperfusion when the subjects received placebo ($P < 0.01$; Fig. 1). When the subjects received bosentan the acetylcholine-induced increase in forearm blood flow was not significantly affected by ischemia/reperfusion (Fig. 2). Endothelium-independent vasodilatation was not affected during reperfusion.



ET blockade & reperfusion.

Conclusions: These results demonstrate that the dual ETA/ETB receptor antagonist bosentan significantly attenuates ischemia/reperfusion-induced endothelial

dysfunction in humans in vivo. This suggests that bosentan may be useful as a therapeutic agent in the treatment of ischemia/reperfusion injury in humans.

P603 The TP receptor antagonist S 18886 improves endothelial dysfunction on a long-term basis in atherosclerotic patients

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Background: S18886, a specific TP (thromboxane A2 -prostaglandin endoperoxide, PGG2-PGH2) receptor antagonist, has been shown to improve endothelial function in addition to its long term antithrombotic properties. In this study, we evaluated chronic and dose-dependent effects of S 18886 on platelet aggregation and endothelial function in patients with severe atherosclerosis.
Methods: 48 patients with severe carotid artery atherosclerosis treated with 300mg aspirin/day were evaluated in a randomized double-blinded study. Patients were randomly assigned to placebo or one of the three S18886 doses tested (2.5, 5, and 10 mg) for 14 days. Endothelial function, platelet aggregation and S18886 kinetics were evaluated before treatment, 1 hour after the first oral dose at day 0 and 1 hour after the last oral dose at day 14.
Results: Flow mediated vasodilation (FMD) was significantly improved ($p<0.001$) after 2.5, 5 and 10 mg S 18886 intake at day 0 (respectively $+2 \pm 1.1\%$, $+1.4 \pm 0.6\%$, $+1.3 \pm 0.5\%$) as compared to placebo ($+0.2 \pm 0.3\%$). This improvement persisted ($p<0.001$) at day 14 ($+2.3 \pm 1.0\%$, $+1.3 \pm 1.0\%$, $+1.5 \pm 0.7\%$) in response to 2.5, 5, and 10 mg S 18886, respectively while no change occurred in response to placebo ($0.1 \pm 0.4\%$). Platelet aggregation in response to U46619 (specific TP receptor agonist) was completely inhibited 2 hours following 2.5, 5, and 10 mg S 18886 intake. FMD and platelet aggregation data were correlated to plasma concentrations of S 18886.
Conclusions: these results demonstrate the long-lasting efficacy of S 18886 in improving endothelial function in patients with atherosclerosis, already treated with aspirin. Each 2.5, 5, and 10 mg dosage may be used in future trials to evaluate the potential clinical interest of this drug in the treatment of severe atherosclerosis.
Keywords: Thromboxane, endothelium, atherosclerosis disease, vasodilation

P604 Administration of a low-dose combination of perindopril and indapamide improves conduit artery endothelial function in essential hypertension

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The effect of a fixed-dose combination of an angiotensin converting enzyme inhibitor (ACEI) and a diuretic, with potential synergistic effects on conduit artery endothelium, has never been assessed in human.
Thirteen untreated hypertensive subjects were explored, two hours after acute administration of a placebo (Plac), a low-dose of fixed-combination of perindopril-indapamide (D1: 2 mg/0.625 mg) and a double-dose of this combination (D2: 4 mg/1.25 mg) during a double-blind, randomized, cross-over study, and were compared to 13 controls matched for age, sex and BMI. Mean arterial pressure (MAP, Dinamap), radial artery diameter (RAD, echotracking) and flow (RAF, Doppler) were measured at baseline and during radial artery endothelium-mediated flow-dependent dilatation (FDD) induced by post-ischemic hyperemia (PIH, wrist occlusion, 10 min). PIH was characterized by peak flow (PF) and duration of hyperemia (t1/2, time to return to 50% of peak). Endothelium-independent dilatation was assessed by glyceryl trinitrate (GTNspray: 0,3 mg).
In hypertensive subjects, compared to controls, baseline RAF and RAD, PF and GTN responses were similar whereas MAP was increased (mean±SEM, 115±3 vs. 90±3 mmHg, $p<0.05$) and t1/2 was decreased (11.1±1.9 vs. 17.2±2.2 sec, $p<0.05$). FDD was altered (RAD increase: 203±14 vs. 304±15 10-3mm, $p<0.001$). Compared to Plac, perindopril-indapamide administration did not modified baseline RAF and RAD, PF and GTN responses. Only D2 decreased MAP (Plac: 115±3; D1: 115±4; D2: 108±4 mmHg; D2 vs. Plac and D2 vs. D1, both $p<0.05$; D1 vs. Plac, NS) and increased t1/2 (Plac: 11.1±1.9; D1: 8.7±1.5; D2: 13.0±1.9 sec; D2 vs. Plac and D2 vs. D1, both $p<0.05$, D1 vs. Plac, NS). Conversely, D1 and D2 increased FDD (MAP and PF as covariates in the analysis; Plac: 203±14; D1: 218±22; D2: 227±23 10^{-3} mm; D1 vs. Plac, $p<0.05$; D2 vs. Plac, $p<0.01$; D1 vs. D2, NS).
These results demonstrate that acute administration of low-dose combination of perindopril-indapamide, in essential hypertensive patients, improves conduit artery endothelial function independently from blood pressure reduction, suggesting a direct mechanism of action of this combination on conduit artery endothelium that could be of interest for vascular protection and decrease in cardiovascular morbidity in these patients.

P605 Endothelial nitric oxide synthase is essential for statin induced improvement of endothelial progenitor cell mobilisation, left ventricular function and survival after myocardial infarction

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Background: HMG-CoA reductase inhibitors (statins) have been shown to prevent LV remodeling and, at the same time, enhance endothelial NO production and reduce NO inactivation by radicals. Reduced endothelial nitric oxide (NO) availability has been implicated in the pathophysiology of heart failure. We therefore hypothesized that atorvastatin treatment may exert beneficial effects in heart failure post-myocardial infarction (MI) by enhancing endothelial bioavailability of nitric oxide; if so, atorvastatin would not exert beneficial effects in mice lacking endothelial nitric oxide synthase (eNOS).
Methods and Results: Wild type (C57Bl/6) and eNOS-deficient mice were subjected to ligation of the left coronary artery and randomised to treatment with vehicle (V) or atorvastatin (Ator; 50 mg x kg-1; qd by gavage) for 4 weeks beginning on day 1 after MI. In WT mice post-MI, Ator improved endothelium-dependent, acetylcholine-induced vasorelaxation of thoracic aortic ring segments (Ator vs V: max. $97 \pm 11\%$ vs. $24 \pm 5\%$; $p<0.01$), mobilisation of endothelial progenitor cells (>200% by FACS analysis and culture for 7 days), neovascularisation of the infarct border, LV function (by echocardiography; fractional shortening; Ator vs V: 18 vs. 10%; $p<0.05$), reduced interstitial myocardial fibrosis and dramatically improved survival (Ator vs V: 80% vs. 46%; $P<0.01$; n=75). In contrast, ator did not affect mobilisation of endothelial progenitor cells, myocardial neovascularisation, LV function, interstitial fibrosis or survival in eNOS deficient mice post-MI (48% vs. 44%; n.s.; n=42).
Conclusions: These findings demonstrate that atorvastatin improves endothelial function and promotes mobilisation of endothelial progenitor cells, myocardial neovascularisation, LV-function and survival post-myocardial infarction by an eNOS dependent mechanism consistent with the notion that preservation of endothelial eNOS activity is a principle and important mechanism of the beneficial effects of statins postmyocardial infarction.

P606 Improved endothelium-dependent vasodilatation by endothelin receptor blockade in patients with atherosclerosis on treatment with angiotensin-converting enzyme inhibitor

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Purpose: Enhanced expression of endothelin-1 (ET-1) and angiotensin II in atherosclerosis may contribute to endothelial dysfunction, which is associated with increased risk of events in patients with coronary artery disease. The objective of the present study was to test the hypothesis that dual ETA/ETB receptor antagonism improves endothelium-dependent vasodilatation (EDV) in atherosclerotic patients on treatment with angiotensin converting enzyme inhibitor.
Methods: EDV and endothelium-independent vasodilatation were determined in 37 patients with atherosclerosis by infusion of acetylcholine and sodium nitroprusside, respectively, during measurement of forearm blood flow (FBF) with venous occlusion plethysmography. The patients were then randomized to treatment with ramipril 10 mg o.d. (n=21) or placebo (n=16) for three months after which FBF was re-evaluated.
Results: A 60 min intra-arterial infusion of the ETA receptor antagonist BQ123 and the ETB receptor antagonist BQ788 (both 10 nmol/min) increased basal FBF by 42±4% ($P<0.001$) and enhanced EDV. Acetylcholine 10 and 30 μg/min increased FBF by 74±10 and 75±10 before vs. 103±12 and 115±13 ml/min/1000 ml following ET receptor blockade ($P<0.001$). Following three months ramipril treatment, ET receptor blockade still enhanced EDV in both groups ($P<0.001$; Fig.1).

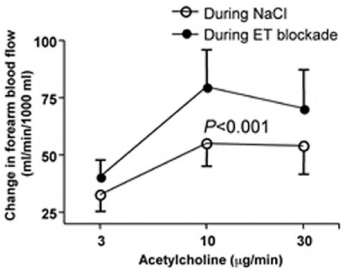

Fig. 1. ET blockade and ramipril.

Conclusions: Dual ETA/ETB receptor blockade improves endothelial function in patients with atherosclerosis, in addition to exerting direct vasodilator effects. These effects were observed also on treatment with ramipril suggesting that ET receptor blockade may have important therapeutic effects when added to ACE inhibition in these patients.

CORONARY PLAQUE IMAGING

P607 Detection of high-intensity transient signals by Doppler ultrasound during percutaneous coronary interventions

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Introduction: After percutaneous coronary interventions (PCI), a reduced coronary flow velocity reserve (CFVR) is frequently observed. Coronary microembolism may account for these observations. Brief, high-intensity transient signals (HITS) in the Doppler velocity spectrum correspond to microemboli in the cerebrovascular circulation. The aim of this study was to validate an intracoronary Doppler ultrasound device for HITS detection in the coronary circulation and to assess the incidence of HITS during PCI.
Methods: In vitro, we observed a close correlation between particle count and number of HITS detected by the intracoronary 0.014" Doppler wire (R= .97, P <.001). The clinical study included 31 patients (age 62±11 years; 22 men, 9 women) with coronary artery disease, treated with balloon dilatation and stent implantation for a single vessel stenosis. In these patients HITS were detected during PCI in 84% (26/31). We found a high reproducibility (R= .99, P <.001) and interobserver agreement (R= .85, P <.001) of HITS count. The number of HITS after stent implantation was significantly higher than after balloon dilatation (11±7 vs. 2±4, P <.001). Postprocedural CFVR was <2.0 in 55% of all patients after balloon dilatation, and <2.0 in 24% after stent implantation. The number of HITS after stent implantation did not significantly differ in patients with CFVR <2.0 in comparison to CFVR ≥2.0 (12±8 vs. 11±7, P =NS).
Conclusions: Using an intracoronary Doppler ultrasound device, embolic particles can be detected as HITS. Coronary microembolism is very common in patients during PCI, especially after stent implantation. However, the incidence of HITS does not explain a reduced CFVR after PCI.

P608 The ultrasound attenuation behind coronary atheroma predicts embolic complication during percutaneous intervention

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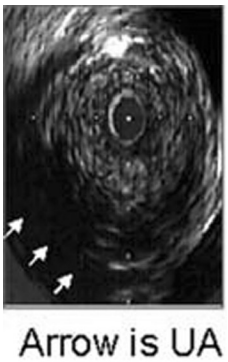
Objective: During intravascular ultrasound (IVUS) image analysis, a marked decrease of the back echo resulting failure of measurement (i.e.,ultrasound attenuation: UA) are sometimes experienced even in the absence of calcification deposit within a coronary atheroma. This study investigated the frequency and clinical relevance of UA phenomenon.
Methods: Among 1,156 patients who received percutaneous coronary intervention (PCI) between March 2000 and December 2003, a total of 648 patients who underwent IVUS before or during the early phase of PCI were examined. The clinical characteristics of patients in whom UA was observed and the features of their lesions were investigated.



Attenuation.

Results: Among the 648 patients examined, the UA was observed in 70(10.8%)patients, including 34(48.6%) patients with stable angina pectoris and 37(51.4%) patients with acute coronary syndrome. The UA rate in each of these groups of patients were 7.6% and 16.8%, respectively, indicating a higher frequency acute coronary syndrome. UA was the most frequently observed at a proximal lesion (42.9%) characterized by positive remodeling (97.1%), nearby calcification (90.0%). With regard to the outcome of treatment and the hospital prognosis of lesions associated with at UA, up to 24.2% showed slow flow during PCI, 4.3% of patients showed major advanced cardiovascular events in the early phase of treatment and hospital prognosis.
Conclusion: The cause of UA remains unknown, although it has been suggested that the phenomenon is caused by early intra-atheroma bleeding or by calcification. Considering that UA was observed in almost 10% of patients undergoing PCI and that it is likely to affect coronary flow during treatment, further evaluation of this phenomenon seems to be necessary.

P609 Influence of statin on the prevention of coronary atherosclerosis progression in the left main coronary artery (lmt) assessed by serial intracoronary ultrasound

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Recent clinical studies of HMGcoA reductase inhibitors (statins) have clearly demonstrated the clinical benefit of statin treatments in the prevention of major coronary events. We hypothesized that statin therapy would induce favorable morphological changes in early phase of the statin administration. Intracoronary ultrasound (IVUS) could be useful to detect this early plaque change. We prospectively performed serial IVUS examinations (pre, post and follow-up) for the LMT lesion in 110 patients with successful coronary intervention (PCI) for either left anterior descending coronary artery (LAD) lesions or left circumflex coronary artery (LCX) lesions. Patients with Total cholesterol <240mg/dl and low-density lipoprotein (LDL) cholesterol <130mg/dl were assigned to statin group (pravastatin; 78 patients, simvastatin 32 patients) or non-statin group. Patients with severe LMT disease and acute myocardial infarction were excluded from the study. Follow-up IVUS examinations were performed at 8±3 months after the PCI. Lumen area (LA), vessel area (VA) and plaque burden (plaque area = VA minus LA) were measured.
Results:

	Non Statin (n=59)	Statin (n=51)	p
Age (years)	64±11	62±10	ns
Male (%)	87	78	ns
DM/HT/Smoking (%)	40/52/31	43/59/30	ns
Total Cholesterol reduction (mg/dl)	5±25	27±42	<.05
% Diameter Stenosis of LMT	26	23	ns
IVUS measurements of LMT (mm^2)			
Plaque burden pre (mm^2)	11.5±3.5	11.2±3.6	ns
Plaque burden follow-up (mm^2)	11.7±3.6	10.0±3.4	<.05
Changes of plaque burden (follow-up minus pre, mm^2)	0.2±2.3	-1.2±2.3	<.05

Conclusion: Whilst baseline clinical and angiographic features were similar between two groups, significant reduction of total cholesterol and plaque burden in the LMT were observed in the stain therapy group in comparison with the non statin group. Statin therapy would convey favorable morphological changes in relatively early phase of the administration in the mild to moderate atherosclerosis.

P610 Correlation between morphological and functional characteristics of culprit atherosclerotic plaques of human coronary arteries

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In unstable syndromes there are distinct morphological and functional characteristics in the culprit lesions, mainly due to the inflammatory activation. Aim of the study is to investigate whether there is correlation between these characteristics in culprit lesions assessed by intravascular ultrasound (IVUS) and coronary thermography, respectively.
Methods: Fifty-five consecutive patients were studied, suffering from unstable angina (UA)(n=29) or chronic stable angina (CSA)(n=26). All patients underwent IVUS examination and coronary thermography. The lumen area (LA), the external elastic membrane area (EEMA), and the plaque area (PA) were measured at the lesion and at the reference site. Remodeling index (RI) was defined as the ratio of the lesion to the reference EEMA. Positive and negative remodeling were defined as indices of >1 and < 1, respectively. Temperature measurements were performed at the lesion and at the proximal vessel wall and the temperature difference was assigned as DT.
Results: Patients of both groups had similar demographic and angiographic characteristics. RI was significantly greater in the UA group compared to the CSA group (1.14±0.46 versus 0.87±0.19,P=0.01). Patients with UA had increased DT compared to patients with CSA (0.30±0.25°C versus 0.12±0.09°C,P=0.001). Patients with positive remodeling had increased DT compared to those with negative remodeling (0.33±0.26°C versus 0.11±0.07°C,P<0.0001). Patients with positive remodeling and UA had increased DT compared to those with positive remodeling and CSA (0.42±0.27°C versus 0.17±0.13°C;P=0.02)(Table). Statistical significance in DT was not achieved between UA and CSA groups with negative remodeling (Table). There was a good correlation between DT and RI (P=0.001,R=0.43).

Table 1. DT by Remodeling Index arm and type of syndrome

	Positive Remodeling (n=26)	Negative Remodeling (n=29)	P-value
UA (n=29)	0.42 ± 0.27°C (n=17)	0.14 ± 0.06°C (n=12)	0.016
CSA (n=26)	0.17 ± 0.13°C (n=9)	0.09 ± 0.07°C (n=17)	0.05
P-value	0.02	0.08	

Conclusion: The present study showed a correlation between atheromatous plaque morphological and functional characteristics. This association of remodeling with culprit plaque temperature provides new insights regarding the involvement of inflammation in acute coronary syndromes.

P611 Influenza virus directly infects the atherosclerotic plaques of apo E deficient mice and can be cultured in high titers from the aortic plaques

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Several infections have been linked to atherosclerosis, however none of them could have been cultured from plaques and treatment or vaccination for them have failed to reduce cardiovascular events. New data suggest that influenza can trigger acute coronary syndromes and influenza vaccination markedly reduces the risk of cardiovascular events. We investigated if the influenza virus can directly infect the plaques.

Methods: We infected apo E deficient atherosclerotic mice (mean age 20 month) with influenza A/HK/68 virus (lethal doze 50). We used both intravenous (I.V., via the retro-orbital sinus plexus) and intranasal (I.N., natural route of infection) methods for inoculating mice in 4 separate experiments. Homogenized tissues from lung, heart, and aorta were cultured for influenza virus. We used the standard titration method using Madin Darby canine kidney cells. Virus presence was determined by observing virus-induced cytopathic effects and confirmed by adding chicken erythrocytes. We performed immunofluorescence (IF) studies using mouse monoclonal antibody to the nucleoprotein (NP) of influenza A viruse and C3 complement. We ran RT-PCR assays using primers specific for influenza A nucleoprotein. H&E and CD68 and CD3 staining (for macrophages and T lymphocytes) were employed for histopathologic examinations.

Results: Immediately (5 seconds) after infection, we could culture the influenza virus from the blood, lung, aorta, and heart of the apo E deficient mice. On day 3 after I.N. infection, the virus could not be cultured from either of tissues. On day 7 (and until day 10 in increasing titer), we were able to culture the virus from lung (titer: 6.8 $\pm$0.9 log10/50 μL), heart (4.4$\pm$0.8), and aorta (5.9$\pm$0.8), but not from the blood (0). The titers were even higher in IV infection. Our culture data were paralleled by positive immunofluorescence for influenza antigens and positive RT-PCR assays for influenza NP gene. Plaque infection was associated with deposition of C3 complement and massive infiltration of inflammatory cells (e.g. macrophages and T cells) in the plaques.

Conclusion: We have shown (by viral culture, RT-PCR, and immunofluorescence) for the first time that influenza virus directly infects and resides in the atherosclerotic plaques. This infection is associated with pro-inflammatory changes in the plaque. Further studies are needed to fully assess the values of vaccination and/or use of antivirals to prevent cardiovascular events.

P612 Prognostic value of carotid plaque presence and morphology in hospitalized cardiological patients

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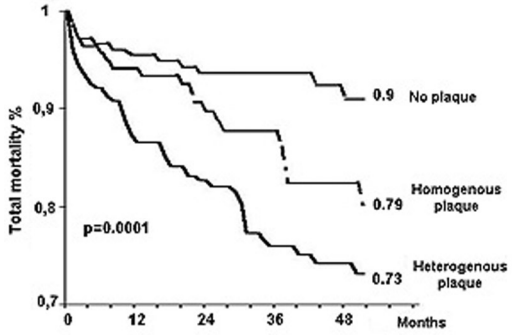
Background: Carotid plaque severity and morphology can affect cardiovascular prognosis.

Aim of study: To evaluate the importance of echographically assessed carotid artery plaque geometry and morphology as predictors of death in hospitalized cardiological patients.

Methods: 541 hospitalized patients admitted in a cardiological division (age=66$\pm$11 years, 411 men) were studied by ultrasound Duplex carotid scan and followed up for 33$\pm$16 months. According to American Society of Radiology recommendation, echo evaluation assessed: 1) severity, (normal, $<$50% stenosis, 50-69% stenosis, $>$70%, near occlusion, occlusion); 2) morphology (as homogeneous or heterogeneous).

Results: 361 patients showed carotid stenosis (67% with $<$50% stenosis, 18% with 50-69% stenosis, 9% with $>$70% stenosis, 4% with near occlusion and 2% with total occlusion). During the follow-up there were 83 all-cause death (15% of the total population). Using Cox's proportional hazard model, age (RR 1.06, 95% CI 1.03-1.09, p= 0.0000) and the presence of a heterogeneous plaque (RR 1.64; 95% CI, 1.22 to 2.19, p= 0.001) were independent predictors of death. Outcome was best in patients without plaque, intermediate in patients with homogeneous plaques and worst in patients with heterogeneous plaques (90% vs 79% vs 73%, p=0.0001) (figure).



Conclusions: In hospitalized cardiological patients, ultrasound-based assessment of carotid plaque presence and morphology are independent predictors of death.

P613 Vulnerable plaque diagnosis by a self-contained intravascular magnetic resonance imaging probe: proof of concept

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Objectives: Plaque rupture initiates intravascular thrombosis and is associated with an acute coronary syndrome. Early detection of vulnerable lesions may allow for preventive therapy. We developed a novel self-contained intravascular magnetic resonance imaging (MRI) catheter, capable of imaging the arterial wall without the need for external magnets or coils. The current study correlated findings obtained from MRI imaging with histology from human aortas and coronary arteries obtained at autopsy.

Methods: A self-contained MR probe was integrated within the tip of a coronary catheter providing cross-sectional MR imaging of the arterial wall with a radial resolution of 250 mm and lateral resolution of 600 nm. This novel device generates high-resolution tissue characterization, differentiating between necrotic core, macrophages and fibrous tissue, thereby allowing for the identification of potential vulnerable plaques, The tissues for analysis included 16 aortic arch specimens and 18 proximal and mid coronary intermediate lesions defined as 30-60% in severity by ex-vivo angiography. All tissues were analyzed histologically, using hematoxilin & eosin, Movat's pentachrome staining and CD-68 immunohistochemistry (for the presence of macrophages). A vulnerable plaque was defined as a thin fibrous cap atheroma with a fibrous cap $<$75μ thick.

Results: The 16 aortic lesions included 4 ulcerated, 2 vulnerable plaques, 2 fibrous cap atheromas, 2 intimal xanthomas, and 6 adaptive intimal thickenings. The correct MRI diagnosis was obtained in 15 out of 16 lesions (95%). The 18 coronary lesions included 3 vulnerable plaques, 7 fibrous cap atheromas, 4 fibrocalcific plaques, 2 intimal xanthoma, 1 adaptive intimal thickening and 1 plaque rupture. MRI diagnosed coronary lesions correctly in 16 out of 18 cases. The sensitivity was 100% and the specificity was 89% for the detection of vulnerable plaque.

Conclusions: Plaque interrogation using a novel self-contained intravascular MRI catheter successfully identified lipid-rich vulnerable plaques. This may be a promising technology to diagnose thin cap fibroatheromas, the major pathologic substrate for myocardial infarction and acute coronary syndromes.

P614 Does optical coherence tomography provide accurate measurements of atherosclerotic plaque components?

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The ability of Optical coherence tomography (OCT) to measure plaque components has not yet been investigated. Aim of the present in vitro study was to compare OCT with histology to determine whether OCT is able to identify lipid/necrotic pools and calcific deposits and provide relevant measurements. Methods. Nineteen coronary artery segments from different autopsy cases were imaged with OCT Light Lab catheters at a 0.5 mm/s speed. Calcific deposits were defined by OCT as well-delineated echolucent areas, while lipid pools were defined as areas of decreased signal density and more heterogeneous backscattering than fibrous tissue. To match histopathologic and OCT cross-sections, vessels were divided into consecutive 3 mm-long segments. Then, samples were fixed with 10% buffered formalin, processed for histopathologic study, serially cut and stained with Movat penthacrome method. Thickness of fibrous cap, lipid pool and calcific deposits was calculated by OCT and corresponding hystology as average of measurements obtained every 2 mm.

Results: Histopathology revealed 15 intra-plaque lipid lakes and 11 calcific deposits which were properly identified by OCT. In total 62 measurements of fibrous cap and lipid pool thickness and 55 measurements of calcium thickness were obtained. Thickness measurements obtained with hystology and OCT were the following: fibrous cap 0.21 $\pm$ 0.26 mm vs 0.23 $\pm$ 0.26 mm (p=NS); lipid pool 0.33 $\pm$ 0.16 mm vs 0.31 $\pm$ 0.14 mm (p=NS); calcium 0.47 $\pm$ 0.18 mm vs 0.48 $\pm$ 0.19 mm (p=NS). Highly significant correlations between histology and OCT measurements were found for the 62 measurements of fibrous cap and lipid pools thickness (r =0.95 and 0,92) and for the 55 measurements of calcium thickness r =0.95 ($p < 0.05$ in all)

Conclusions: OCT provides accurate measurements of plaque components such as fibrous cap, lipid pools and calcific deposits and is therefore a promising technique to study vulnerable plaques.

P615 Human Macrophages express the spezific lymphatic VEGF-receptor Flt-4 and its signaling induce apoptosis in macrophages in vitro and in unstable atherosclerotic plaques

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Introduction: Neointimal angiogenesis is a important process in the progression and destabilization of atherosclerotic plaques. Angiogenetic growth factors (GF) and their receptors (R) obelong into the VEGF family are known main players in this process. In contrast to the VEGF-Rs Flt-1 and FLK-1, the role for VEGF-R3 (Flt-4), specific for lymphatic endothelium (LyEC) and a feature of tumor vasculature, has not been characterized in detail so far.
Methods and Results: Carotid endartherectomie specimens derived from 10 patients with unstable carotid plaques were stained for Flt-4 and VEGF-D. Interestingly, macrophages (Ma) (stained by galectin-3) in inflammatory perivascular regions expressed Flt-4 as well as VEGF-D. In vitro studies could demonstrate, that freshly isolated human monocytes (Mo) and cultured Ma expressed the specific mRNA for the active long and the inactive short form of Flt-4.The protein expression for Flt-4 in Mo/Ma could be demonstrated by immunohistochemisty. In addition, nonstimulated human Mo express the ligands for Flt-4: VEGF-D and C. In contrast to VEGF-C, the Mo production of VEGF-D mRNA could be stimulated under hypoxic conditions (1% O2; $p<0.01$). To investigate the functionality of Ma-FLT-4 expression, Ma were stimulated with VEGF-D. No stimulation or downregulation could be demonstrated for IL-8, MCP-1, VEGF-A, -C, -D and Flt-1. Interestingly, there was a highly significant upregulation for the proapoptotic enzyme activated caspase-3 (for 50ng/ml VEGF-D: 62 ± 22, 33 ± 12 per cent of control, 12 and 24h, respectively). Immunohistochemical studies of advanced human carotid atherosclerotic plaques confirmed the coexpression of Flt-4 and activated caspase-3 by Ma.
Conclusion: These results reveal that human Mo/Ma stained positive for VEGF-D and the spezific lymphatic endothelial receptor Flt-4. The activation of the VEGF-D-Flt-4 signaling in Mo/Ma may stimulate the apoptotic process and thus may play a role in plaque neoangiogenesis and Mo/Ma survival in plaque inflammation.

P616 Brain impairment due to cerebral embolization during left-heart catheterization

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Purpose: Left-heart catheterization with coronary angiography and angioplasty is an invasive examination which carries a potential risk for cerebral complications. During advancement guide-wires and catheters may cause fragmentation of atherosclerotic plaques and subsequent embolization to the brain. The aims of this study were to determine the frequency of cerebral microemboli during left-heart catheterization and to assess any evidence of acute cerebral morphological changes, or clinical or cognitive impairment. We also assessed if cerebral embolization was more harmful to patients with pre-catheterization cerebral white matter lesions.
Methods: We prospectively assessed patients with angina pectoris who underwent elective left-heart catheterization with transradial or transfemoral access. Transcranial Doppler monitoring for cerebral microemboli was performed on both middle cerebral arteries during the catheterizations. Cerebral magnetic resonance imaging (MRI) with diffusion-weighted sequences, clinical neurological and neuropsychological assessments were carried out one day preceding and one day following the catheterizations.
Results: A mean number of 880 (range 73-2502) cerebral microemboli were detected in 44 patients. The post-catheterization cerebral diffusion-weighted MRI showed new white-matter lesions in five (12.2%) of 42 patients, which correlated with a higher mean number of microemboli ($p=0.031$) and with a higher mean number of coronary arteries with significant atherosclerosis ($p=0.034$). Patients who had a pathological pre-catheterization cerebral MRI deteriorated significantly at the post-catheterization neuropsychological examination when compared with those who had a normal or a borderline pre-catheterization MRI. Three patients experienced a transient cerebral deficit.
Conclusions: A high number of cerebral microemboli are generated during catheter advancement, contrast agent injection and catheter flushing in left-heart catheterization. These emboli may cause acute cerebral morphological changes, and clinical as well as cognitive impairment. The presence of pre-catheterization cerebral white matter lesions seems to dispose for acute post-catheterization cognitive impairment.

P617 Can coronary anatomy predict the presence of renal artery stenosis in patients with coronary artery disease?

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Background: The prevalence of renal artery stenosis (RAS) in patients undergoing cardiac catheterization has been estimated to be in the range of 5 to 20%. Recently, it was found that the presence of significant RAS is a strong independant predictor factor of mortality in patients with coronary disease.
The aim of our study was to determine the prevalence of angiographically significant RAS and its relationship with predictor factors, especially coronary anatomy outcome.
Methods: We prospectively studied the prevalence of renal artery stenosis in 200 consecutive patients with a significant coronary artery disease (luminal diameter narrowing$>$ 50%). Abdominal aortography followed cardiac catheterisation. An angiographically significant RAS was defined by a narrowing of the lumen $>$ 50%. One hundred sixty nine of these patients were male(85.5%), 32% had hypertension, 44% were diabetics and 54.5% had two or more vessel diseases.
Results: 85.5% of the patients in this study were males, 32% had hypertension, 44% were diabetics and 54.5% had two or more vessel disease. 18 patients (9%) had a significant RAS. All these RASs cases were unilateral and one was a total occlusion. Patients with RAS were older (65 ± 8 vs 58 ± 9 years, $p=0.002$), had higher history of hypertension (55.5% vs 30.3%, $p=0.03$) and more extend coronary artery disease($>$2 vessel diseases)(38.9% vs 17.8%, $p=0.033$). Although, we found no significant difference in the mean serum creatinine, diabetes mellitus and glomerular filtration rate. Results from the multivariable logistic analysis revealed that age$>$65 years(odds ratio, 6.64; 95% CI, 2.2, 19.9) and three-vessel coronary artery disease (odds ratio, 3.14; 95% CI, 1.1, 9.3) are independent predictors of RAS. In a patient with mulitvessel disease the positive and negative predictive values of detection RAS was 0.18 and 0.92, respectively.
Conclusion: this study suggests that the prevalence of atherosclerotic RAS in a 65 years old patient with three vessel coronary artery disease was 38.5%. In this group, abdominal aortography should be systematicaly considered.

P618 Clinical benefits of rotational coronary angiography versus traditional coronary angiography: reduction in patient radiation exposure, contrast agent use and procedure time

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Background: Coronary artery disease is traditionally diagnosed on single plane angiography systems by obtaining multiple xray images in different views, each with an injection of contrast medium. We tested the benefits of Rotational Coronary Angiography (RCAG) as compared to Traditional Coronary angiography (TCAG) using InnovaSpinTM, a new rotational acquisition technique optimized for cardiac imaging on the digital flat panel system (GE InnovaTM 2000).
Methods: Patients scheduled for coronary angiography (excluding - patients with creatinine $\geq$1.5, age $<$ 25 and $>$ 70) in Dec'03 were selected to undergo both TCAG and RCAG. The hospital ethics committee approved the study and informed consent was obtained from all patients. All diagnostic angiographies were performed as per set protocol. Patient Dose Area product (PDAP), Volume of Contrast Used, Procedure Time, Xray Acquisition time and Number of sequences were recorded for each session. The angiograms were assigned to 3 independent reviewers to assess the information obtained.
Results: 53 cases were enrolled with mean age: 54 yrs, mean height: 162.6 cm, mean weight: 64 kg and % M/F gender ratio of 81/19. No contrast or radiation induced complications were noted. Results in Table 1.

Table 1

	Traditional Technique (Mean/Median)	InnovaSpin Technique (Mean/Median)	p value	% Savings
Patient dose area product (PDAP) (cGy cm^2)	6859	2981	0.0001	56.5
Vol. of contrast used (cc)	34.66	18.06	0.0001	47.9
Procedure time (min)	5.55	3.57	0.0001	35.7
Xray sequence acquisition time (sec)	40	19	0.0001	52.5
No. of sequences	9	3	0.0001	66.7

Conclusion: Significant savings ($p<0.05$) were found in PDAP, Volume of Contrast Used, Procedure Time, Xray Acquisition time and Number of sequences using RCAG compared to TCAG. No lesion was missed using RCAG. In addition, eccentric lesions, ostial lesions, collaterals and vessel relations were better profiled with RCAG.

P619 Radial versus femoral approach for percutaneous coronary procedures: a meta-analysis of randomized trials

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Purpose: The radial approach for percutaneous coronary procedures has been increasingly used in alternative to the femoral access. Several trials have compared these two approaches with somewhat inconclusive results. A metaanalysis was performed to compare transradial and transfemoral approach in terms of clincal and procedural outcomes.
Methods: MEDLINE, CENTRAL and conference proceedings from major cardiologic associations were searched. Random-effect odds ratios (OR) for failure of the procedure (crossover to different entry site or impossibility to perform the planned coronary procedure), entry site complications (major hematoma, vascular surgery or arteriovenous fistula) and major adverse cardiovascular events (MACE) defined as death, myocardial infarction, emergency revascularization or stroke, were computed for the longest available follow-up.
Results: Twelve randomized trials (3224 patients) were included in the analysis. The risk of MACE was similar for radial versus femoral approach (OR 0.92 [95% confidence interval (CI) 0.57-1.48], p=0.7). Instead, radial access was associated with a significantly lower rate of entry site complications (OR 0.20 [0.09-0.42], $p<0.0001$), even if at the price of a higher rate of procedural failure (OR 3.30 [1.63-6.71], $p<0.001$). Heterogeneity tests were not statistically significant, except for procedural failure (p=0.044). Dividing the studies in two subgroups according to the year of publication (before and after 1999), heterogeneity regarding procedural failure was no more present (p=0.38 for older studies; p=0.73 for recent studies) and more recent trials showed no significant difference in terms of procedural failure between radial and femoral access (OR 1.39, 95% CI 0.78-2.47, p=0.3), whereas a strong difference was present in the older trials (OR 6.02, 95% CI 3.07-11.79, $p<0.0001$). Sensitivity and sub-group analysis yielded results comparable to the overall analysis.
Conclusions: Radial approach for coronary procedures appears as a very safe alternative to femoral access, as testified by similar MACE rate. Moreover, radial access virtually eliminates local vascular complications, thanks to a straightforward and time-sparing hemostasis technique. However, gaining radial access requires higher technical skills in comparison to femoral access, thus yielding an overall lower success rate. Nonetheless, a clear ongoing trend to equalization of the two procedures in terms of procedural success is evident onthrough the years, probably due to technological progress of the materials and increased operator experience.

P620 Complex diagnostic procedures are associated with significantly high radiation doses to patients during cardiac catheterisation

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Background: Cardiac catheterisation is a widely performed procedure. Ionising radiation during these procedures results in an increased risk of radiation induced effects. Cardiac investigations vary in their complexity according to the information being sought. Exposure time and radiation risks of such procedures are not fully documented. An estimation of the effective dose (ED) can be obtained from the measurements of the dose-area product (DAP). Published reports state an estimate of 2.5% per Sievert lifetime risk of fatal cancer for a population between the ages of 40 and 60 years.
Aims and methods: A retrospective analysis of adult cardiac procedures was carried out in a regional cardiothoracic unit to determine the DAP, ED and estimated risk of malignancy. We compared 7 diagnostic groups (Table 1). Dose-area product meter (Diamentor PTW, Freiberg) attached on the X-ray unit (Philips Polydiagnost C2 image intensifier system) was used for the estimation of the radiation dose received by the patient during the procedures.
Results: A total of 4,706 different procedures were studied (Table 1). Average age and weight of the patients were 60.9 years and 79.5 kgs respectively.

Table 1

Groups	Number	Screening time	DAP	ED	Risk
Group 1 (Coronary angiography)	549	248±325	15.7±13	3.4	0.008%
Group 2 (Coronary angiography + left ventriculography - LHC)	3528	200±243	16.8±9	3.7	0.009%
Group 3 (Right heart catheterisation + LHC)	217	524±387	28.8±15	6.3	0.015%
Group 4 (Left ventriculography + aortography)	11	437±470	26.5±11	5.8	0.014%
Group 5 (LHC + aortography)	168	416±424	26.5±14	5.7	0.014%
Group 6 (LHC + graft study)	189	700±518	31.3±14	6.8	0.0175%
Group 7 (LHC + aortography + graft study)	44	721±355	39.9±18	8.6	0.0215%

Screening time (seconds), DAP (Gy/Cm2), ED (mSv) and estimated risk (%) of malignancy for diagnostic cardiac imaging [Mean±SD]

Conclusions: Cardiac angiographic procedures other than a straightforward investigation of native coronaries ± left ventriculography are associated with significantly high radiation doses. Patient exposure is particularly high in those undergoing graft studies (p=0.0001).

P621 Frequency of vasospastic angina in patients with normal coronary arteries

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Aims: About 10 to 20% of patients referred to cath lab for angina have normal coronary angiography, and they are "diagnosed" of noncoronary thoracic pain. Our aim is to ascertain the proportion of these patients who could be properly diagnosed if intracoronary ergonovine test were routinely performed, and to find possible clinical and analytical differences between those with positive and negative ergonovine test.
Methods: A total of 162 patients (aged 54±11 years, 109 men) with angina underwent ergonovine test after exclusion of significant coronary lesions. Calcium channel blockers were withdrawn for the previous 48 hours and nitroglycerin was not given before angiography. Intracoronary ergonovine was injected in progressively increasing doses of 1, 5, 10 and 30 μg each minute. According to Maseri criteria, a test was positive in case of: a) complete or subtotal occlusion of some segment of a coronary artery, with or without detectable stenotic plaque; b) segmental reduction of at least 50% of the diameter of an angiographically normal coronary segment. Spasms may be focal or diffuse. Clinical and analytical data such as sex, age, hypertension, diabetes mellitus, smoking habit and cholesterol levels were also analyzed. Possible differences in these variables between patients with positive and negative ergonovine test were studied.
Results: Ergonovine test was positive in 85 patients (53%). Positivity was more frequent in males than in females (62% vs 34%, $p<0.001$) and in smokers than in nonsmokers (66% vs 37%, $p<0.001$). Patients with positive ergonovine test had higher levels of total cholesterol and lower levels of HDL cholesterol than those with negative tests (225±43 vs 211±41 mg/dl, $p<0.05$) and (43±12 vs 50±17 mg/dl, p =0,02) respectively.
Conclusions: Intracoronary ergonovine test allowed us to diagnose vasospastic angina in 53% of patients with nonsignificant coronary lesions. Vasospasm is more frequent in males, smokers and those with higher total cholesterol and lower HDL. If it is not routinely performed, many patients with thoracic pain are misdiagnosed of noncoronary pain.

P622 Long-term follow-up of patients undergoing intravascular ultrasound-guided treatment for angiographically indeterminate left main coronary artery disease

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Purpose: Reliable assessment of lesions in the left main coronary artery (LMCA) by coronary angiography is often difficult. Intravascular ultrasound (IVUS) provides useful information for angiographically indeterminate lesions. Based on a previous study with IVUS measurements of patients with angiographically normal LMCA, a recommendation was established at the Mayo Clinic in 1994 that all patients with angiographically indeterminate LMCA lesions undergo IVUS, and revascularisation be performed when minimum lumen area (MLA) < 7.0 mm^2. The aim of this study is to assess the efficacy of this strategy.
Methods: The patient population was composed of 221 patients who underwent IVUS for angiographically indeterminate LMCA lesions from December 1994 to September 2002. Follow-up was obtained through questionnaires and review of hospital charts.
Results: The patients were divided into two groups according to MLA. Group 1 (MLA < 7.0 mm^2) consisted of 75 patients, and group 2 (MLA ≥ 7.0 mm^2) of 146 patients. No complications occurred during IVUS procedures. LMCA revascularisation (coronary artery bypass surgery and percutaneous coronary intervention) was performed in 77.0% of group 1, and deferred in 79.6% of group 2. Follow-up was available for 81.9% of patients. Major adverse cardiac events (MACE), consisting of acute myocardial infarction, target vessel revascularisation and cardiac death, for patients who underwent revascularisation in group 1 and those who were treated medically in group 2 were similar in both groups (see table).

	MLA < 7 mm^2	MLA ≥ 7 mm^2
Mean follow-up (years)	2.7 ± 1.9	3.4 ± 2.0
Acute myocardial infarction	8.7%	4.2%
Target vessel revascularisation	0%	10.5%
Total death	8.7%	10.5%
Cardiac death	6.5%	2.1%
MACE	15.2%	16.8%

Conclusions: IVUS is a safe and accurate tool to assess angiographically indeterminate lesions of the LMCA. Furthermore, our data suggests that an IVUS-guided strategy with deferral of revascularisation for patients with a MLA ≥ 7 mm^2 appears to be safe.

P623 Risk factors for atherosclerosis and carotid plaque phenotype

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Background: Atherosclerotic plaque phenotype is reported to be associated with the presentation of clinical symptoms. Inflammatory atheromatous lesions are considered more unstable compared with fibrous collagen rich lesions. Aim of this study was to examine the relationship between risk factors for atherosclerosis and carotid artery plaque characteristics.
Methods: A total of 214 patients, men (68,7%) and women aged 41-89 years, underwent endarteriectomy of the carotid artery. Plaques were examined semi quantitatively on the presence of fat, smooth muscle cells (SMC), macrophages (MAC), calcifications and collagen. The degree of stainings for SMC, MAC, calcifications and collagen were categorized as; no, minor, moderate or heavy. Fat was categorized as no fat, $<$40% fat or $>$40% fat of total plaque area. All patients filled in questionnaires including questions concerning life style, medication and risk factors. Risk factors that were considered in this study were diabetes, alcohol consumption, smoking, hypercholesterolemia, gender and hypertension.
Results: Diabetes, smoking, alcohol consumption and hypertension revealed no significant associations with plaque phenotype(for all differences in stains among groups $p>0.10$). Female gender was associated with less fat ($p=0.001$), a tendency towards less calcification ($p=0.065$) and a SMC dominance ($p=0.037$). Surprisingly, hypercholesterolemia was associated with less fat in the plaque ($p=0.085$) and a SMC dominant plaque ($p<0.001$). This observed plaque phenotype in hypercholesterolemia, could not be explained by statin use, since this was not associated with a fibrous plaque phenotype.

Results gender and hypercholesterolemia

	Hypercholesterolemia (n=122)	No hypercholesterolemia (n=75)	Female (n=67)	Male (n=147)
MAC	15/35/31/19	20/36/27/16	26/32/30/12	15/36/28/22
SMC	4/30/39/27	3/42/28/27	2/24/40/34	4/41/31/24
Fat	24/51/25	24/39/37	36/49/15	20/40/40
Collagen	0/19/46/33	0/27/48/25	0/21/39/39	0/23/49/26
Calcifications	30/21/25/24	28/23/28/21	37/13/22/27	25/26/29/21

% of lesions revealing no/minor/moderate/heavy staining. For fat: fibrous/fibroatheromatous/atheromatous

Conclusion: In carotid plaques, female gender and hypercholesterolemia are associated with a more fibrous plaque phenotype.

ENDOTHELIAL FUNCTION

P624 The tyrosine phosphatase SHP-1 regulates endothelial NAD(P)H-Oxidase activity by inhibiting PI3-Kinase

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Purpose: An NAD(P)H-Oxidase is a major source for endothelial superoxide (O2-) production. However, signalling pathways leading to activation of the enzyme are poorly characterised. We investigated, whether the tyrosine phosphatase SHP-1 (SH2-domain containing phosphatase 1) acts as an upstream regulator of endothelial NAD(P)H-Oxidase.
Methods and Results: Inhibition of SHP-1 ($n=32$, $p<0.01$), or its degradation using antisense- (AS, $n=36$, $p<0.01$), or siRNA-technology ($n=8$) doubled O2- production in a time- and dose-dependent manner ($p<0.01$) in human endothelial cells (HUVEC). Simultaneous inhibition of NAD(P)H-Oxidase (gp91ds-tat) prevented this effect ($n=9$, $P<0.01$). NAD(P)H-Oxidase activity was doubled, when HUVEC were transfected with SHP-AS ($n=9$, $p<0.01$). SHP-1 AS induced tyrosine phosphorylation of p85, the regulatory subunit of phosphatidyl-inositol-3-Kinase (PI3K, $n=6$, $p<0.05$), an event known to activate PI3K upstream of rac1. Inhibition of PI3K by Wortmannin (10ng/ml) prevented the enhanced O2- production after SHP-1 AS treatment ($n=6$, $P<0.01$), confirming the involvement of PI3-kinase. Intravascular in vivo magnetofection of SHP-1 AS into hamster femoral arteries markedly increased production of reactive oxygen species within the vessel wall as assessed ex vivo ($n=4$).
Conclusions: SHP-1 activity decreases NAD(P)H-Oxidase dependent O2- production. SHP-1 thus exerts an antioxidative function and diminishes enhanced endothelial O2- production.

P625 HMG-CoA reductase inhibition by cerivastatin inversely regulates expression of LOX-1 and eNOS

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Background: Lectin-like oxidized LDL receptor (LOX-1) was initially identified as a receptor for oxidized LDL (ox-LDL) in endothelial cells. Expression of LOX-1 is increased in endothelial dysfunction and atherosclerosis and can be regulated by different inflammatory mediators, e.g. tumour necrosis factor-alpha (TNF-alpha), interleukin-6 and ox-LDL. Both clinical and experimental data support the hypothesis that inhibition of HMG-CoA reductase by statins directly influences the beginning and progression of atherosclerosis. As endothelial dysfunction and atherosclerosis are associated inter alia with a decrease in expression of endothelial nitric oxide synthase (eNOS) we investigated the modulation of the expression of LOX-1 and eNOS by cerivastatin in venous endothelial cells.
Methods: Total RNA was isolated from cultivated human venous endothelial cells, which have been activated with TNF-alpha, by standard procedures. Expression of eNOS and LOX-1 mRNA was determined by real time PCR, protein expression of eNOS was assessed with a monoclonal antibody by Western blotting. Cells treated with culture media but without TNF-alpha and cerivastatin were used as controls.
Results: TNF-alpha increased the expression of LOX-1 mRNA (10.7 fold vs. control) whereas the expression under simultaneous treatment with 10 nM cerivastatin almost dropped down to the base level (2.9 fold vs. control). In contrast to that cerivastatin increased the expression of eNOS mRNA dose-dependently. Protein expression of eNOS was augmented as well. The effects mediated through cerivastatin could be abolished through incubation of the cells with 100 nM mevalonate (LOX-1 13.5 fold, eNOS 0.4 fold vs. control). Treatment with either farnesyl pyrophosphate (15.5 fold vs. control) or geranylgeranyl pyrophosphate (12.6 fold vs. control) reversed the decrease of LOX-1 mRNA expression induced by cerivastatin, too.
Conclusion: Cerivastatin improves the expression of eNOS and reduces the expression of LOX-1 in vitro through inhibition of HMG-CoA reductase, respectively. These results support a pleiotropic protective effect of cerivastatin on venous endothelial cells.

P626 Dissecting the differential effects of low and high doses of proteasome inhibitors on endothelial cells: endothelial adaptation versus apoptosis

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Purpose: We have recently shown that low-dose proteasome inhibition enhances expression and activity of endothelial NO synthase (eNOS) in primary endothelial cells, and improves endothelial function in aortic rings (Stangl et al., FASEB J. 18, 272-279; 2004). These apparently beneficial effects of proteasome inhibition on endothelial cells were observed with low doses of proteasome inhibitors, which were non-toxic to the cells. In contrast, high doses of proteasome inhibitors induce apoptosis in various cell types including endothelial cells. In order to understand the underlying mechanisms for these differential effects, we analyzed cellular effects of low and high doses of proteasome inhibitors on endothelial cells by expressional profiling using Affymetrix chips and BD Powerblots.
Results and Discussion: Primary human endothelial cells were treated with different doses of two specific proteasome inhibitors, the aldehyde inhibitor MG132 and its boronate derivate MG262, for 24 hours. XTT-tests and caspase-activation assays confirmed that low doses of proteasome inhibitors (70 nM MG132 and 4 nM MG262) were non toxic to the cells, while higher doses (200 nM MG132 and 10 nM MG262) activated several caspases and induced about 40% cell death. Both, low and high doses, induced cell cycle arrest, which was accompanied by upregulation of p21. Expressional profiling using Affymetrix chips revealed a specific transcriptional response to proteasome inhibition, which involved either up or downregulation of several hundred genes. The number of genes regulated more than twofold by low doses of proteasome inhibitors was about 4 fold lower than with high doses (138 versus 735 genes). Expressional changes of some of these genes were confirmed by real-time RT-PCR and BDPowerblot analysis. Interestingly, we observed pronounced regulation of genes involved in endothelial activation, in particular upregulation of anti-oxidants and downregulation of MCP-1 and HMG-CO-A-reductase. The pattern of genes regulated by proteasome inhibition resembled transcriptional regulation induced by shear stress.
Conclusion: We propose that low doses of proteasome inhibitors induce a transcriptional response in endothelial cells which resembles endothelial adaptation and does not affect cell viability. This transcriptional response might protect endothelial cells against various forms of stress as suggested for shear stress.

P627 Cardiotrophin-1 induces interleukin-8 in human umbilical vein endothelial cells

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Background: Cardiotrophin-1 (CT-1) is a member of the interleukin-6 (IL-6) superfamily. Elevated CT-1 plasma concentrations are found in patients with chronic heart failure (CHF). Interleukin-8 (IL-8) is member of the C-X-C chemokines. It was shown that IL-8 concentrations in patients with CHF gradually increases with an increase in NYHA functional class. Because IL-8 is produced by a varity of cells including endothelial cells we addressed the question wether CT-1 is able to induce IL-8 in human umbilical vein endothelial cells (HUVEC).
Methods: IL-8 mRNA was determined by RT-PCR, IL-8 protein concentration in the supernatant of HUVEC with ELISA. Inhibition of STAT3 phosphorylation was done by piceatannol, blockade of phosphoinositide 3-kinase (PI 3-kinase) by wortmannin, of proteinkinase MEK by PD098059 and proteinkinase C (PKC) by staurosporin.
Results: CT-1 increased IL-8 expression in HUVEC in a time and dose-dependent manner. Using 100 ng/ml CT-1 IL-8 mRNA increased gradually reaching a maximum after 6 to 8 hours, decreased afterwards and was sightly increased after 24 hours. The maximal increase after 8 hours was 2,5±0,7 fold compared to control. We could also show that IL-8 induction is concentration dependent. Maximal IL-8 levels were reached with 100 ng/ml CT-1. CT-1 caused also an increase of soluble IL-8 in the supernatant of HUVEC. Maximal IL-8 concentration was found after 12 hours (2,6±0,7 fold increase compared to control), but IL-8 concenration was still elevated after 24 hours. Piceatannol, wortmannin, PD098059 and staurosporin had no effect on the CT-1 induced IL-8 mRNA induction indicating that STAT3 phosphorylation, PKC, PI 3-kinase and MEK are not involved.
Conclusion: CT-1 can induce IL-8 in HUVEC in a time and concentration dependent manner both on mRNA and protein level. So far the pathway responsible for the CT-1 induced IL-8 expression is not obvious. In CHF CT-1 seems to induce IL-8 production in endothelial cells and this may explain in part the finding that increased IL-8 concentrations are found in CHF patients.

P628 Deletion of p66shc gene protects against oxidative stress-induced endothelial dysfunction in type I diabetes mellitus

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Background: The p66shc protein controls cellular responses to oxidative stress. Mice lacking p66shc (p66shc-/-) have increased resistance to reactive oxygen species (ROS) and a 30% prolonged life span.Enhanced production of ROS has been recognized as the major determinant of hyperlgycemia-induced endothelial dysfunction. The present study was designed to investigate whether the inactivation of p66shc protein is protective against oxidative stress-induced endothelial dysfunction in an experimental model of type I diabetes mellitus.
Methods and Results: p66shc-/- and wild-type (WT) mice were both treated with streptozotocin (STZ, 200 mg/kg, i.p.). Following STZ injection, diabetic mice were sacrificed after 4 weeks (mean glycemic levels: 400±50 mg/dl). Aortic rings were suspended for isometric tension recording. Endothelium-dependent, nitric oxide (NO)-mediated relaxation to acetylcholine (10^{-9}-10^{-5} mol/L) was impared in WT, but not in p66shc-/- diabetic mice. To determine whether candidate mechanisms of oxidative stress resistance might explain the preserved NO bioavailability in p66shc-/- diabetic mice, we assessed the expression of oxidative stress responsive enzyme heme-oxygenase-1 (HO-1) and manganese superoxide dismutase (MnSOD) by Western blot analysis. Protein expression of HO-1 and MnSOD decreased by 40% and 35% in diabetic WT, but remained unchanged in p66shc-/- diabetic mice vs placebo treated mice (n=5, $p<0.05$). This finding was also confirmed by HO-1 activity assay. Accordingly, the levels of protein and lipid peroxidation measured by thiobarbituric acid reactive substances (TBARS) assay were lower in p66shc-/- diabetic compared to WT mice (n=3, $p<0.05$).
Conclusions: p66shc-/- mice, unlike WT, are resistant to hyperglycemia-dependent, ROS-mediated endothelial dysfunction by virtue of an unaltered expression of antioxidant defence mechanisms. Our results suggest that the p66shc is part of a signal transduction pathway also relevant to endothelial integrity and may represent a novel target to prevent diabetic vascular complications.

P629 Endothelial dysfunction in rats with heart failure is improved by treatment with the eNOS transcription modulator S2431

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Nitric oxide (NO) derived from the endothelial NO synthase (eNOS) is a key regulator of vascular homeostasis. In heart failure NO-bioavailability is reduced. Therefore, we investigated the influence of treatment with the eNOS transcription modulator S2431 (Aventis) on endothelial function in rats with heart failure after myocardial infarction.
Coronary ligation (MI) or sham-operation (sham) was performed in male wistar rats. Starting on the 7th postoperative day animals were randomly selected for a 9 week treatment with the eNOS transcription enhancer S2431 (25 ppm in standard rat chow) or with placebo. Only animals with large MIs (>40% of left ventricle) were included in the study. Acetylcholine-induced endothelium-dependent vasorelaxation was blunted in isolated thoracic aortae from placebo-treated MI rats compared with sham animals (Rmax 49±4% vs. 75±3%, $p<0.01$). Endothelium-independent relaxation induced by sodium nitroprusside was similar among the groups. Superoxide anion production (measured by lucigenin [5 μmol/l]-enhanced chemiluminescence) was significantly elevated in rats suffering from heart failure (235±22 cpm/mg) compared to sham animals (94±13 cpm/mg). Treatment with the eNOS transcription modulator S2431 improved acetylcholine-induced relaxation in MI rats (Rmax 65±5%, $p<0.05$ vs. placebo). Furthermore, the ratio of phospho-eNOS/eNOS protein was increased by S2431. In addition, the elevated vascular superoxide anion production was reduced by treatment with S2431 (135±27 cpm/mg, $p<0.05$ vs. placebo).
In conclusion, treatment with the eNOS transcription modulator S2431 improves endothelium-dependent relaxation and reduces vascular superoxide anion production in heart failure after myocardial infarction.

P630 Endothelial beta3-adrenoceptors mediate the NO-dependent vasorelaxation of human and rat coronary microvessels in response to the third-generation beta-blocker, nebivolol

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Background: The therapeutic effects of non-specific beta-blocking agents is often limited by vasoconstriction, justifying the interest for molecules endowed with ancillary vasodilating properties. Nebivolol is a selective antagonist at the beta1-adrenoceptor (AR) that releases the vasodilator, Nitric Oxide (NO) through incompletely characterized mechanisms. We identified endothelial beta3-adrenoceptors in human coronary resistance arteries and hypothesized that nebivolol exerts a partial agonist effect on these beta3-AR to mediate NO- and endothelial-dependent relaxation.
Materials and Methods: Human and rat cardiac coronary resistance microarteries (70-170 μ diameter) were mounted in dual glass micropipettes chambers in no-flow state and constant pressure for vasomotion analysis by videomicroscopy. In addition, calcium transients and NO release were measured in cultured endothelial cells with an amperometric electrode and Fura-2 fluorescence, respectively. Phosphorylation of eNOS was measured in the same cells with phospho-specific antibodies. In endothelial cells, nebivolol (1-10 μM) increased NO release to 117 ± 38 nmoles/μg prot (at 10 μM; n=3) in a L-NAME-inhibitable fashion (26.5 ± 4.3 nmoles/μg prot; $P<0.05$). In parallel, Threonine 495 on eNOS was dephosphorylated (n=3; $p<0.05$) and Ca fluorescence increased by 91.8 ± 23.7% (n=4-11). Pre-treatment with the beta1-2 antagonist, nadolol, had no effect on the Ca signal increase with nebivolol, whereas bupranolol, a combined beta1-2-3 antagonist, significantly blunted the effect ($P<0.05$). Nebivolol evoked a dose-dependent relaxation of rat microvessels (max 86 ± 6% of PGF2alpha pre-contracted tone, at 10 μM) that was sensitive to NOS inhibition, unaffected by nadolol, but prevented by bupranolol ($P<0.05$; n= 3-8). Importantly, the relaxation to nebivolol was blunted in microvessels from mice genetically deficient in beta3-AR. In human coronary microvessels, nebivolol (10 μM) also induced a relaxation (max 71 ± 5% of ET-1 pre-contracted tone) that was dependent on a functional endothelium, insensitive to nadolol and reproduced with the beta3-preferential agonist, BRL37344 (all $p<0.05$). In human microvessels, beta3 AR expression was identified in endothelial cells by immunohistochemistry and laser capture/PCR.
Conclusion: These data demonstrate that nebivolol dilates human coronary resistance arteries through an agonist effect on the endothelial beta3AR to release NO. This property may prove particularly beneficial for the treatment of ischemic and failing cardiac diseases.

P631 Differential effects of selective COX-2 inhibitors on endothelial function in salt-induced hypertension

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In view of the ongoing controversy of potential differences in cardiovascular safety of selective COX-2 inhibitors (coxibs), we compared the effects of two different coxibs and a traditional NSAID on endothelial dysfunction, a well established surrogate of cardiovascular disease, in salt-induced hypertension.
Methods and Results: Salt-sensitive (DS) and salt-resistant (DR) Dahl rats were fed a high-sodium diet (4% NaCl) for 56 days. From days 35 to 56, diclofenac (6 mg/kg/d; DS-diclofenac), rofecoxib (2 mg/kg/d; DS-rofecoxib), celecoxib (25 mg/kg/d; DS-celecoxib) or placebo (DS-placebo) were added to the chow. Blood pressure increased with sodium diet in the DS-groups which was more pronounced after diclofenac and rofecoxib treatment ($p<0.005$ vs DS-

placebo), but was slightly decreased by celecoxib ($p<0.001$ vs DS-placebo). Sodium diet markedly reduced NO-mediated endothelium-dependent relaxations to acetylcholine (ACh, 10^{-10}-10^{-5} mol/L) in aortic rings of untreated hypertensive rats ($p<0.005$ vs DR-placebo). Relaxation to ACh improved after celecoxib ($p<0.005$ vs DS-placebo and DS-rofecoxib), but remained unchanged after rofecoxib and diclofenac treatment. Vasoconstriction after NOS inhibition, indicating basal NO release, with Nù-Nitro-L-Arginine-Methyl-Ester (L-NAME, 10^{-4} mol/L) was blunted in DS rats ($p<0.05$ vs DR-placebo), normalized by celecoxib, but not affected by rofecoxib or diclofenac. Indicators of oxidative stress, 8-isoprostane levels, were elevated in untreated DS rats on 4% NaCl (6.55±0.58 vs 3.65±1.05 ng/ml, $p<0.05$) and normalized by celecoxib only (4.29±0.58 ng/ml).
Conclusion: These data show that celecoxib, but not rofecoxib or diclofenac, improves endothelial dysfunction and reduces oxidative stress, thus pointing to differential effects of coxibs in salt-sensitive hypertension.

P632 Mice with a knockout for inducible nitric oxide synthase are protected from metabolic but not vascular dysfunction on an obesogenic diet

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Obesity an independent risk factor for development of atherosclerosis is associated with abnormalities of insulin action and endothelial function. We have previously shown that wild type C57BL/6 mice fed a high fat diet, develop metabolic and vascular insulin resistance within 4-8 weeks compared to chow-fed controls. Basal NO production was significantly increased in the vasculature of obese mice mediated by iNOS expression as shown by RT-PCR. The aim of this study is to explore the metabolic and vascular effects of obesity in mice with a knockout for inducible nitric oxide synthase (inos K.O).
Male C57BL/6 mice and iNOS K.O mice on a similar background were fed an obesogenic diet (35% fat/carbohydrate) from weaning until 8 weeks. Body weight, glucocompetence, systolic blood pressure and vasomotor responses in aortic rings ex-vivo were assessed after 4 and 8 weeks of feeding. Glucose and Insulin tolerance test were performed in conscious mice following intra-peritoneal glucose (1mg/kg) or insulin injection (0.75u/kg). Blood pressure was measured by tail cuff method. Dose response curves were plotted for vasoconstriction to phenylephrine (PE) before and 30 minutes after exposure to L-NMMA (a non-specific NOS inhibitor) and insulin (2 hours,0.1units/ml). Similar dose response curves to acetylcholine (Ach 1nM-10μM) were performed before and after exposure to catalase (1250units/ml), an enzyme that dismutes H2O2.
Both wild type and iNOS K.O mice developed comparable degrees of obesity (29±0.4 vs 28±0.5g, p=N.S) and hypertension (123±0.4 vs 122.5±0.9 mmHG, p=N.S)at 4 weeks. Glucocompetence was significantly better in the iNOS K.O mice (% Fall in blood glucose after i.p insulin: 68±2.6 vs 55±0.6, $p<0.01$) suggesting that iNOS may play a key role in impaired insulin signalling during obesity. Vascular response to insulin an effect mediated by NO release, was lost in wild type mice at 8 weeks but preserved in the iNOS K.O mice (% Change in PE E-max after insulin preincubation, +11.2±5.5 vs -20±7.7, $p<0.01$). Basal NO production was significantly lower in iNOS K.O mice than wild type mice fed the high fat diet (%Change in PE E-max after LNMMA, 57.7±21 vs 135±13.2,$p<0.01$). Endothelial dysfunction was unmasked by catalase in both groups (% Change in PE E-max after catalase, -14.9±3.8 vs -15.3±2.8, p=N.S)
These results suggest that iNOS may play a key role in impaired insulin actions in both skeletal muscle and the vascular wall in diet-induced obesity. Despite being protected against impaired insulin action, inos K.O mice had blunted Ach response compensated for by production of H2O2.

P633 Divergent effects of different beta-blockers on endothelial nitric oxide-mediated vasorelaxation in atherosclerotic rabbits

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The effects of beta-blockers on endothelial dysfunction in atherosclerotic diseases remain unclear.
Aim: To compare the effects of carvedilol, propranolol, metoprolol and atenolol on nitric oxide (NO)-mediated endothelial dysfunction in atherosclerotic rabbits.
Methods: Rabbits were randomized into the 5 groups (n=6): hyperlipidemic diet only (hyperlipidemic control, HC) or hyperlipidemic diet supplemented with propranolol (nonselective beta-blocker, 10mg/kg/d), metoprolol (selective beta1-blocker, 10mg/kg/d), atenolol (selective beta1-blocker, 20mg/kg/d), or carvedilol (nonselective beta-blocker and antioxidant, 10mg/kg/d). After treated for 1 week, they underwent balloon injuries and remained on their respective diets for the further 10 weeks. 6 sham untreated rabbits received normal diets (normal control, NC). At the end of the trial, lipids and lipid peroxides (LPO) contents in serum, nitric oxide (NO) levels in plasma, acetylcholine (ACh)-stimulated endothelium-derived NO release, ACh-induced endothelium-dependent relaxation and dihydroethidium staining for superoxide in aortic segments were tested. Endothelial NO synthase activity and mRNA expression were also measured.
Results: In HC group, total cholesterol, triglycerides and LPO levels in serum, NO levels in plasma, basal NO production and superoxide production in aortic tissues significantly increased, whereas ACh-stimulated NO release, and endothelial NO synthase activity and mRNA expression in aortic tissues decreased compared with those in NC group (all $P<0.01$). Treatment with carvedilol, but not propranolol, metoprolol or atenolol, markedly reduced serum LPO and arterial superoxide levels, and increased ACh-stimulated NO release and endothelial NO synthase activity ($P<0.05$). Relaxations to ACh were diminished in atherosclerotic control (8.1±4.1%) compared with normal control rabbits (55.1±2.2%;$P<0.01$), and were improved only in carvedilol-treated group(16.5±6.0%; $P<0.05$). Serum lipid levels and aortic endothelial NO synthase mRNA expression did not change significantly in all of the drug-treated groups (P=NS).
Conclusion: This study suggests carvedilol treatment would improve NO-mediated endothelial function in atherosclerotic rabbits by restoring endothelial NO availability and antioxidant activity. These beneficial effects of carvedilol are not shared by other beta-blockers such as propranolol, metoprolol or atenolol.

P634 The relationship between severity of coronary artery disease and endothelial dysfunction

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Objective: In this study, the relationship was evaluated between flow-mediated dilation (FMD) and nitrate-induced dilation (NID) of brachial artery and severity of coronary artery disease.
Methods: Study group was consisted of sixty-four patients with angina pectoris who had established coronary artery disease documented by coronary angiography (Group I), twelve patients who had normal coronary arteries with abnormal exercise test (Group II) and eighteen healthy subjects who had normal exercise test. FMD and NID were calculated as the percent change in diameter compared to baseline of brachial artery. According the angiographic findings, Group I patients were divided into two subgroups as single or multi vessel disease. Results were compared among the groups.
Results: FMD was significantly lower in Group I and II than in Group III. NID was significantly higher in Group II and III than in Group I. FMD was not different between Group I and II. However, NID was significantly higher in Group II than in Group I. Table 1 shows FMD and NID values in all groups. In Group I, sixteen patients had single vessel and fourty-eight patients had multi vessel disease. Although NID was not different between these subgroups (10.2±3.9 and 9.9±4.1 respectively, $p>0.05$), FMD was significantly higher in patients who had single vessel disease than in patients had multi vessel disease (7.9±2.3 and 4.3±3.1 respectively, $p<0.001$).

Table 1

	Group I (n=64)	Group II (n=12)	Group III (n=18)	p1	p2	p3
FMD (%)	5.6±4.6	6.1±5.2	14.2±3.6	0.798	0.0001	0.0001
NID (%)	10.1±4.4	18.6±5.4	20.8±6.2	0.0001	0.0001	0.805

FMD and NID values in all groups. p1 compared Group I and II, p2 for Group I and III, p3 for Group II and III.

Conclusion: Abnormal FMD of the brachial artery is related to severity of coronary artery disease and it may be a marker for progressive course of the disease. Normal NID of the brachial artery suggests that possible deficiency in the endogenous nitric oxide activities in patients with angiographically normal coronary arteries and abnormal exercise test.

P635 Aldosterone-induced vasculopathy occurs after both high and low salt diets

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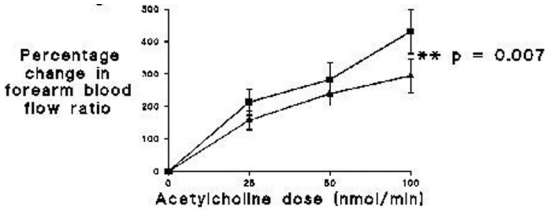
Experimental data suggest that the adverse vascular effects of aldosterone only occur with concurrent high salt intake. We wished to establish if this was also true in man. Ten, healthy, male volunteers were randomized to a week of high or low salt intake in a double-blind, crossover fashion. At the end of each week a twenty-four hour urinary sodium collection was made and various blood work performed. Acetylcholine-induced, endothelial-dependent vasodilatation was assessed by forearm venous occlusion plethysmography and QT dispersion was calculated from a twelve lead electrocardiogram. Acetylcholine-induced vasodilatation and QT dispersion were measured before and during intravenous aldosterone infusion at 12 pmol/kg/min. Aldosterone significantly blunted acetylcholine-induced vasodilatation following both high and low salt intake (p=0.023 and 0.007 respectively - see figure).
High salt intake did not worsen acetylcholine-induced vasodilatation compared to low salt intake. Both high salt intake and aldosterone significantly increased QT dispersion compared to low salt intake (46.77±6.00ms vs. 55.13±7.29ms, p=0.009 and 46.77±6.00ms vs. 65.14±19.89ms, p=0.011 respectively). There was no additive effect of salt and aldosterone on QT dispersion. Our results suggest that aldosterone does not require concurrent high salt intake to produce its undesirable effects on the vasculature in man. We provide tentative evidence that aldosterone blockade may be beneficial regardless of salt status. In the clinical



Forearm blood flow response to acetylcholine before (■) and during (▲) aldosterone infusion after low salt diet.

situation, loop and thiazide diuretics that reduce salt load actually cause RAAS activation and therefore increase aldosterone concentration. Our results suggest that patients taking these drugs would still benefit from aldosterone blockade despite low salt status.

P636 Flow-mediated dilation of the brachial artery does not predict cardiovascular events in a large patient population

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Background: Brachial artery flow-mediated vasodilation (FMD) has been associated with coronary risk factors and the presence of coronary artery disease (CAD). Recent studies have suggested that FMD is predictive for cardiovascular events. Few data exist, however, in a large non-selected patient group. The aim of this study was to determine the relation of FMD with cardiovascular events in patients admitted for invasive evaluation of chest pain.
Methods: In 398 consecutive patients (age 54±9 years) undergoing coronary angiography (CA), FMD and nitroglycerin-mediated vasodilation (NMD) were measured using high-resolution ultrasound (13 MHz) by an observer blinded to CA diagnosis. 315 patients had CAD (>30% diameter stenosis in at least 1 major vessel) and 83 patients had smooth coronaries (non-CAD). Patients were divided into 2 groups according to their FMD value: FMD above the median of 7.6% (group 1) and FMD<7.6% (group 2). After a mean follow-up of 39±12 months, cardiovascular events (hospitalization due to worsening angina with proven ischemia; CA with progression of disease; revascularization; myocardial infarction; cardiac death) were documented by phone calls to the patients, followed by review of hospital records for verification.
Results: Baseline characteristics (age, number of risk factors, presence of CAD, body mass index, plasma lipid values, blood pressure) were similar between groups. No difference was found in the number of cardiovascular events between groups (n=20 in group1, n=24 in group 2; NS, log-rank test). Also, when patients were divided according to their NMD, the number of cardiovascular events was similar between patients above vs. below the median value. On multivariate Cox regression analysis including age, number of risk factors, presence of CAD, brachial artery diameter and FMD, only presence of CAD (odds ratio=6.6; p=0.01) remained significantly associated with cardiovascular events.
Conclusion: In this large patient population admitted for evaluation of chest pain, endothelial function did not predict long-term (up to 4 years) cardiovascular events. The association of FMD and CAD may be more complex than previously reported in smaller studies. The clinical importance of a single FMD measurement should be reassessed.

P637 Impact of aging on coronary endothelial function

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Purpose: Aging has been postulated to be one of the major risk factors for endothelial dysfunction. However, only a few studies have investigated the relationship between aging and coronary endothelial dysfunction in humans. We therefore examined this relationship in patients with normal coronary arteries.
Methods: One hundred eighteen patients (74 men and 44 women, mean age of 59 yrs, range 30-80 yrs) with chest pain and angiographically normal coronary arteries were enrolled. Patients with vasospastic angina or previous history of myocardial infarction or heart failure were excluded from the present study. Acetylcholine (ACh, 3 and 30 μg/min) and nitroglycerin were infused into the left coronary ostium over 2 min. Diameter of the proximal segment of the left anterior descending coronary artery was measured by quantitative angiography. Coronary blood flow (CBF) was calculated by quantitative angiography and Doppler flow velocity measurements. The changes in coronary artery diameter and CBF in response to drug administration were expressed as percent change from baseline value. Coronary flow reserve (CFR) was also calculated as the ratio of coronary flow velocity after an injection of adenosine triphosphate (20 μg) to baseline value.
Results: Values are expressed as mean±SEM. Age was inversely correlated with ACh-induced increase in CBF (3 μg/min: 48.3±4.6%, r = -0.209, p = 0.0231; 30 μg/min: 134.7±9.8%, r = -0.234, p = 0.0106), but was not correlated with ACh-induced change in coronary artery diameter (3 μg/min: 0.5±0.6%; 30 μg/min: -1.7±0.8%, both NS) or CFR (3.45±0.10, NS). Multivariate regression analysis demonstrated that age was one of the factors negatively associated with ACh-induced increase in CBF (p = 0.0108, r^2 = 0.422).
Conclusions: These findings suggest that age is inversely correlated with coronary endothelial function at the level of resistance vessels, but not at that of conduit vessels in patients with chest pain and normal coronary arteries. In coronary arteries, aging may be principally responsible for microvascular endothelial dysfunction, at least in the type of patient we examined.

P638 Dark chocolate improves endothelial function in healthy individuals

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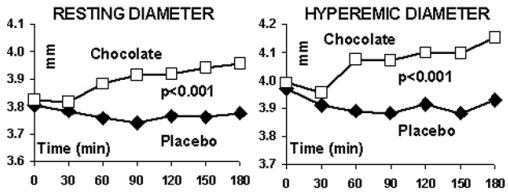
Purpose: Recent studies highlight the favorable effects of dark chocolate on the antioxidant status, mainly attributable to its polyphenol content. Endothelial function is an independent prognosticator of total cardiovascular risk. Aim of the present study was to examine the effects of dark chocolate on endothelial function.
Methods: We studied in two different days 16 healthy volunteers (29±2 years, 11 men) in a randomized, single-blind, crossover fashion (eating 100 gm of dark chocolate 74% rich in cocoa and sham eating). Endothelial function was evaluated with flow-mediated dilatation (FMD) of the brachial artery after reactive hyperemia induced by cuff occlusion of the forearm, using high-resolution ultrasonography (10.5 MHz, Sonos 5500). Scans were performed before and up to 3 hours after eating, at 30 min intervals.
Results: Ingestion of dark chocolate led to a significant increase in both the resting (F=7.2, p<0.001) and the hyperemic brachial artery diameter (F=8.3, p<0.001) throughout the whole duration of the study, when compared with sham eating (figure). FMD also increased, peaking at 60 min after eating (increase by 1.41%, p<0.05).



Resting and hyperemic diameter.

Conclusions: Ingestion of dark chocolate rich in cocoa flavonoids is associated with an acute beneficial effect on endothelial performance of healthy subjects. This finding provides further insights into the favorable effects of chocolate into the cardiovascular system.

P639 Endothelial dysfunction in human coronary arteries is related to low shear stress

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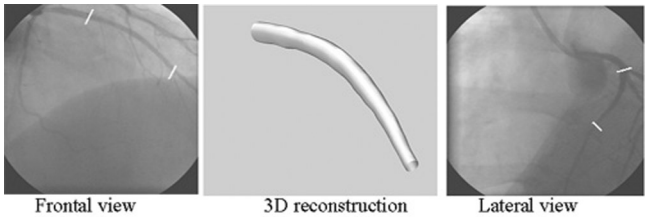
Atherosclerotic plaques are observed at low shear stress areas in the arterial tree. Endothelial dysfunction is presumed to be a precursor of atherosclerotic plaque formation. The aim of our study was to investigate in patients whether local endothelial dysfunction is related to low shear stress.
Methods: In 7 patients treated for coronary artery stenosis using stent implantation, endothelial function was assessed by acetylcholine (ACH)provocation using a selective intracoronary infusion of 10^{-8} M. The arterial response distal from the stent was measured by biplane contrast angiography and filming a calibration cube enabled to record the 3D imaging geometry. After tracing the lumen contours in the angiograms of the arteries distal from the stent, the lumen was 3D reconstructed (see figure). Computational fluid dynamics in these 3D reconstructions applying patient specific flow and viscosity, delivers local shear stress. As



total shape of the artery changes by ACH provocation, changes in geometry were assessed by determination of the change in local shear stress.
Results: Average shear stress at baseline was 1.5±0.6 Pa. In general, ACH induced vasoconstriction leading to increase in shear stress by 32% ($p<0.05$). Comparing regions experiencing low (shear stess<1.3 Pa) versus normal to high shear stress at baseline showed that vasoconstriction was restricted to the low shear stress regions. Shear stress increased by 52% in these regions. These data imply local endothelial dysfunction at low shear stress areas.
Conclusion: 3D reconstruction of human coronary arteries from biplane contrast angiograms allows 3D study of local endothelial function. For the first time, we showed in vivo that local endothelial dysfunction is associated with low shear stress areas.

P640 Does reactive hyperaemia measured by Laser-Doppler in cutaneous microcirculation reflect endothelium-depedent vasodilation?

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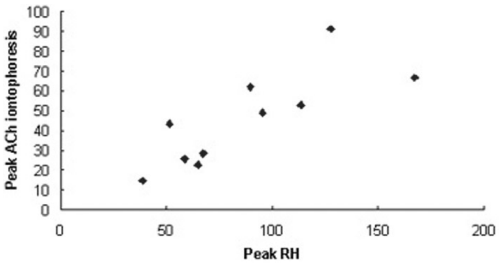
Objective: Reactive hyperaemia (RH) is commonly used to evaluate endothelial vasoreactivity in the brachial artery using ultrasonography. Laser-Doppler (LD) devices combined to RH may be useful to study endothelial vasoreactivity in cutaneous microcirculation.
Methods: We compared response during RH and after acetylcholine (ACh) and sodium nitroprusside (SNP) iontophoresis in cutaneous microcirculation of the hind paw of 10 wistar rats (322 ± 8 g). LD was used to measure cutaneous blood flow during all the procedure.
Results: Cutaneous blood flow values expressed in perfusion units (PU) were 25.86 ± 2.16 PU at baseline and 87.44 ± 12.53 PU at the peak during RH. Before ACh iontophoresis, baseline values were 20.64 ± 5.10 PU and peak values after ACh iontophoresis were 45.64 ± 7.50 PU. Before SNP iontophoresis, baseline values were 16.57 ± 2.77 PU and peak values after SNP iontophoresis were 85.07 ± 9.13 PU. A highly significant correlation between RH and ACh iontophoresis peak values was found (see figure, r=0.804, p=0.003) while no correlation was found with SNP. After administration of L-NAME, a NO synthase inhibitor, peak during RH was reduced to 50.31 ± 18.51 PU and after ACh iontophoresis to 15.32 ± 5.40 PU. No correlation was found any more between both values.



Conclusions: This study shows a good correlation between peak values of cutaneous blood flow during reactive hyperaemia and acetylcholine iontophoresis but not after L-NAME administration, suggesting that cutaneous blood flow variations measured by Laser Doppler during reactive hyperaemia may be an interesting tool to evaluate endothelial vasoreactivity.

P641 Vascular inflammatory effects of intra-arterial tumour necrosis factor-alpha in patients with coronary heart disease: impaired vasodilatation and enhanced endogenous fibrinolysis

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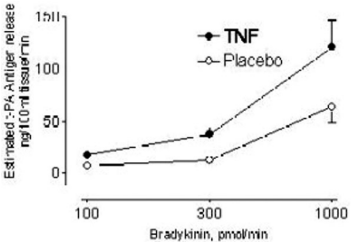
Purpose In order to explore the link between vascular inflammation and atherothrombosis, we investigated the effect of direct intra-arterial infusion of the cytokine tumour necrosis factor-alpha (TNF-alpha) on endothelial vasomotor and fibrinolytic function in patients with coronary heart disease (CHD).
Methods: Twelve male patients with stable CHD receiving standard antiplatelet and lipid lowering agents attended on two occasions. Each subject received an intra-brachial infusion of TNF-alpha (80 ng/min for 60mins) or saline using a randomised double blind cross over study design. Blood flow and plasma tissue plasminogen activator (t-PA) were measured in both arms using venous occlusion plethysmography and blood sampling during intra-brachial bradykinin, acetylcholine and sodium nitroprusside infusions.
Results: There was no change in temperature or white cell count during either visit. TNF-alpha caused a significant rise in plasma t-PA antigen concentration without affecting resting blood flow. TNF-alpha pre-treatment: impaired acetylcholine and nitroprusside induced vasodilatation ($P<0.001$ for both); augmented the bradykinin induced rise in plasma t-PA antigen (18.0±2.1 versus 23.3±2.5 ng/ml for peak response) and doubled estimated net t-PA antigen release (P=0.005 for both).



Conclusions: In patients with CHD, acute vascular inflammation impairs vasomotor function but enhances endothelial t-PA release. Increased local t-PA release may be a 'protective' response to cytokine mediated pro-coagulant arterial injury. Our results might also explain why higher t-PA antigen concentrations positively and independently predict future coronary events and provide a rationale for the link between inflammation and acute coronary thrombosis.

P642 Effect of the asp298 variant of endothelial nitric oxide synthase on patients with early coronary artery disease in a Turkish population

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Introduction: Several studies have shown that the polymorphisms of the eNOS gene are associated with hemodynamics. We investigated the relationship between premature coronary artery disease (CAD) and Glu298Asp polymorphism of the eNOS gene.
Methods: The eNOS gene polymorphism was analysed in 115 Turkish patients with a diagnosis of premature CAD and 83 control subjects. The eNOS Glu298Asp polymorphism was determined by polymerase gene reaction and restriction fragment length polymorphism.
Results: The patients group showed an increase frequency of the T allele compared to controls (0.308 versus 0.156, p=0.00). There was a significant association between the TT genotype and premature CAD [eNOS TT vs TG and GG; OR= 17.000 (CI 95% 3.952-73.125, P=0.0001)]. The patients with eNOS TT genotype had 15 fold risk of CAD compared with the control group [OR= 15.356(CI 95% 3.262-77.289, p=0.001)]. In addition, the family history of premature CAD, smoking, diabetes, obesity, dyslipidemia and eNOS TT genotype were independent risk factors of CAD.
Conclusions: These data suggest that eNOS TT genotype may have predisposing effects on premature CAD and eNOS may be one of the independent factors on premature CAD.

P643 Coronary endothelial dysfunction: more than just a matter of traditional risk factors

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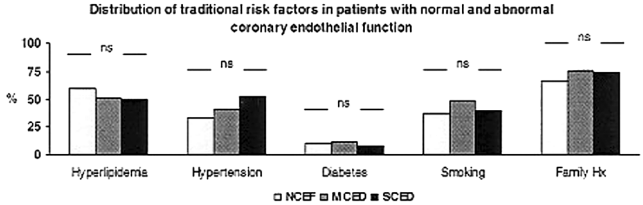
Background: Endothelial dysfunction represents an early stage of atherosclerosis. Although all traditional cardiovascular risk factors may be associated with endothelial dysfunction, not all subjects with such risk factors develop atherosclerotic disease. To further assess the role of traditional cardiovascular risk factors for the pathogenesis of endothelial dysfunction, we assessed the risk factor profiles of patients with normal and abnormal coronary endothelial function.
Methods and Results: Risk factor distribution was determined in 94 patients without obstructive coronary artery disease undergoing coronary endothelial function testing with intracoronary injection of acetylcholine (Ach). Patients were divided by their coronary blood flow response to Ach as having normal coronary endothelial function (NCEF; change in CBF >50%; n=39), mild coronary endothelial dysfunction (MCED; change in CBF 0-50%; n=25), or severe coronary en-



Traditional risk factor distribution.

dothelial dysfunction (SCED; change in CBF <0%; n=30). Groups did not differ in age, sex, or cardiovascular medication. Average number of risk factors was similar among the groups (NCEF: 2.2±0.2; MCED: 2.3±0.3; SCED: 2.1±0.2). There was no difference in the proportion of traditional risk factors between individuals with normal coronary endothelial function and those with coronary endothelial dysfunction (figure).

Conclusions: The present study demonstrates that traditional risk factor profiles do not necessarily differ between individuals with normal and abnormal coronary endothelial function. These findings suggest a variable endothelial susceptibility of individual patients to cardiovascular risk factors and underscore the importance of yet-unknown factors for prevention and promotion of coronary endothelial dysfunction.

P644 Abnormal velocity and time to peak brachial artery dilation in patients with coronary artery disease and hypertensive subjects: assessment by vascular ultrasound image analysis

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Background: Ultrasound measurement of flow mediated dilation (FMD) of the brachial artery during post occlusive reactive hyperaemia is currently the most used technique for assessment of endothelial dysfunction (ED). FMD is reduced in hypertensives and coronary artery disease (CAD) patients, but it is not known whether time and velocity to peak dilation and duration of the vasodilator response are also altered in these patients. We investigate these variables using a newly validated vascular ultrasound image analysis (VIA).

Methods and Results: Brachial artery FMD, velocity and time to peak dilation and total duration of the vasodilator response were assessed in 17 hypertensives, 18 CAD patients and 17 healthy controls using a technique that automatically and continuously measures artery diameter on-line throughout the study. FMD was higher in healthy controls (7.05±3.42%) compared to hypertensives (4.09±2.16%, p=0.004) and CAD patients (3.20±1.72%, p<0.001). Velocity to peak dilation was higher in controls (5.56±2.32 μm/s) than in both hypertensives (2.35±1.22 μm/s, p< 0.001) and CAD patients (3.75 ± 2.47 μm/s, p= 0.045). Time to peak dilation (70.5±21.6 s) was longer in hypertensives than in CAD patients (40.5±8.2 s)(figure 1); (p<0.001) and controls (45.9±11.1 s); (p<0.001). CAD patients had a shorter vasodilation response period (102.4±20.4 s) than either hypertensives (157.3±39.1 s, p<0.001) or controls (132.1±26.6 s, p=0.014).

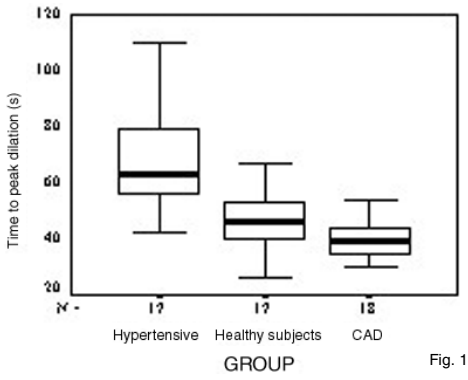

Fig. 1. Time to peak in groups.

Conclusions: Hypertensives and CAD patients showed both reduced brachial artery vasodilator capacity and impaired velocity to peak dilation after post-occlusive reactive hyperaemia. VIA allows identification of new markers of ED that may have clinical relevance.

P645 Microalbuminuria is closely associated with increased plasma levels of C-reactive protein in untreated essential hypertensive subjects

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Purpose: Inflammatory processes are related with unfavourable cardiovascular outcome and atherosclerosis. In this study we sought to determine the possible relationship between high-sensitivity C-reactive protein (hs-CRP) and urinary albumin excretion rate (UAER), another index of increased cardiovascular risk, in essential hypertensive patients.

Methods: The study population consisted of 47 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension [32 men, mean age=49 years, office blood pressure (BP)=146/96 mmHg]. On the basis of the mean UAER of three non-consecutive 24h urine samples, the patients were divided into two groups: patients with microalbuminuria (MA) (mean UAER=20-200 mg/24h) and patients without MA (mean UAER<20 mg/24h). Moreover, venous blood samples were drawn for estimation of lipid profile and hs-CRP, according to established techniques.

Results: For the pooled population, body mass index (BMI) was 27.63±3.5 kg/m^2, UAER was 21.98±10 mg/24h, total cholesterol was 231±41 mg/dl, triglycerides were 136±73 mg/dl, low-density lipoprotein cholesterol was 151±34 mg/dl and plasma levels of hs-CRP were 1.79±0.93 mg/l. According to the echocardiographic examination, left ventricular mass index was 105.5±23 g/m^2, relative wall thickness was 0.41±0.06 and left atrial diameter was 3.6±0.42 cm. Patients with MA (n=16) were matched for demographics with those without MA (n=31). Microalbuminurics had increased left ventricular mass index (by 11 g/m^2, p<0.05), 24-h systolic and diastolic BP (by 7 and 5 mmHg, respectively; p<0.05). In both groups, hs-CRP was associated with BMI (r=0.37, p<0.01), 24-h systolic BP (r=0.41, p<0.01), 24-h diastolic BP (r=0.47, p<0.001) and UAER (r=0.51, p<0.001). In addition, UAER was correlated with office systolic BP (r=0.29, p<0.05), 24-h systolic BP (r=0.41, p<0.001), ambulatory pulse pressure (r=0.39, p<0.01) and left ventricular mass index (r=0.32, p<0.05). Furthermore, patients with MA exhibited higher levels of hs-CRP (by 0.75 mg/dl, p<0.05), compared to normoalbuminurics.

Conclusions: In uncomplicated newly diagnosed essential hypertension, hs-CRP seems to constitute an emerging marker of subclinical vascular dysfunction, even at the level of renal glomerulus. The estimation of plasma hs-CRP levels, in conjunction with UAER measurement, may contribute to better cardiovascular risk stratification in this setting.

P646 Prognostic value of neopterin levels in treated hypertensive patients with chest pain but without obstructive coronary artery disease

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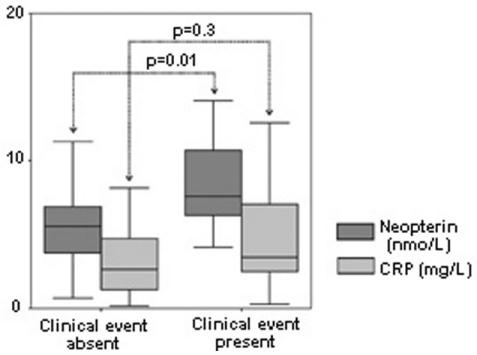
Purpose: Serum neopterin, a pterydine derivative secreted by activated macrophages, is a prognostic marker in patients with coronary artery disease (CAD). We assessed the prognostic value of C-reactive protein (CRP) and neopterin serum concentrations in hypertensive patients with angina but without obstructive CAD.

Methods: We studied 58 patients from a series of 260 consecutive patients. These were patients referred to our Unit for diagnostic coronary angiography. All had exertional stable angina and a positive exercise test response or reversible myocardial perfusion defects on cardiac scintigraphy. For the purpose of the present study, we selected treated hypertensive patients (mean age 61±10 years, 75.9% men) who had typical angina and coronary artery stenosis <50% diameter reduction. The study primary end-point was the composite of non-fatal myocardial infarction, readmission to hospital with unstable angina and cardiac death.

Results: Nine patients (15%) had at least one of the events comprised in the combined study end-point during the one year follow-up. Patients who suffered adverse events during follow up had significantly higher neopterin levels (7.6 [5.7-11.75] vs 5.4 [3.6-6.9]; P=0.01) than patients without events. CRP levels were also higher in patients with events (3.5 [2.3-9.1] vs 2.6 [1.2-4.7]; P=0.3) compared to patients without, but the difference did not reach statistical significance (figure). Multiple logistic regression analysis revealed that serum neopterin (OR: 1.5; CI 95% 1.1 to 1.9; P=0.01) was an independent predictor of future cardiac adverse events.



Conclusions: Our results suggest that neopterin may be useful to identify individuals who are at a higher risk among patients with hypertension, stable angina and non obstructive CAD.

P647 Celecoxib improved blood pressure indices in older hypertensives with osteoarthritis

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Osteoarthritis (OA) and hypertension are the most prevalent medical conditions associated with aging. COX-2 selective inhibitors have been shown effective in the treatment of OA with less GI (COX-1) related effects compared to conventional NSAIDs. Whether these differences could also impact on cardiovascular functioning and concomitant HT is unclear. The purpose of this study was to evaluate the effect of a 16 week treatment of either a COX-1 selective inhibitor (naproxen) or a COX-2 selective inhibitor (celecoxib) on left ventricular diastolic function (LVDF), arterial compliance (AC) and blood pressure (BP) in older hypertensives with OA.

Methods: Fifteen older hypertensives with OA have participated in the study. Seven subjects were randomized to naproxen (NG) (500mg/d) and eight subjects were randomized to celecoxib (CG) (200mg/d). Before, 4 weeks and 16 weeks after the randomization, measures of LVDF [early filling flow velocity (E), late filling flow velocity (A), E/A ratio, isovolumic relaxation time (IVRT) and deceleration time (DT)] and AC using VingMed-5 cardiac imaging system, BP, and VO2max determined by exercise treadmill test were assessed at rest. 24h ambulatory BP was also recorded using a Spacelabs ABPM.

Results: At baseline, there were no significant differences in subject's characteristics, clinic BP, E, E/A, IVRT, DT, AC, VO2max and 24h BP indices except A (CG: 0.85±.04, NG: 0.68±.06, $p<.05$) between the groups. At 4 week, mean SBP, mean DBP, percentages of SBP above 140 mmHg and of DBP above 90 mmHg in 24h BP were significantly lower in CG than those in NG (134.0±3.0 vs 143.8±.5 mmHg, 72.1±3.5 vs 86.8±2.2 mmHg, 35.8±8.2 vs 7.4±8.6%, 9.9±3.3 vs 47.4±9.0%, $p<.05$, respectively). Mean DBP and percentages of DBP above 90 mmHg in 24h BP were still lower in CG than in NG at 16 week (75.3±3.8 vs 87.1±2.6 mmHg, 13.3±6.1 vs 44.9±7.1%, $p<.05$, respectively). Clinic DBP tended to be lower at 4 week and was lower in CG than in NG at 16 week (74.6±2.9 vs 84.5±0.8 mmHg, $p<.05$). In CG, clinic DBP was lower at 4 week than at baseline and remained lower at 16 week (82.3±3.1, 73.7±3.6, 74.6±2.9 mmHg, $p<.05$, respectively). Within each group and between the groups, no changes were observed in LVDF indices except A at 16 week (CG: 0.86±.05, NG:0.66±.07, $p<.05$), AC and VO2max throughout the study.

Conclusion: these data suggest that a COX-2 selective inhibitor may be preferable in terms of blood pressure control to older hypertensives with OA.

P648 Subclinical inflammation and early renal dysfunction: a graded relationship between C-reactive protein and urinary albumin excretion rate in essential hypertensive subjects

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Purpose: To investigate whether high-sensitivity C-reactive protein (hs-CRP), is associated with urinary albumin excretion rate (UAER), an emerging marker of increased cardiovascular risk, in essential hypertensive patients.

Methods: The study population consisted of 47 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension [32 men, mean age=49 years, office blood pressure (BP)=146/96 mmHg]. UAER was determined in three non-consecutive 24h urine samples. Moreover, venous blood samples were drawn for estimation of lipid profile and hs-CRP, according to established techniques. All subjects were divided into three groups according to hs-CRP values: Group A (hs-CRP<1.62 mg/l), group B (hs-CRP=1.63-3.02 mg/l) and group C (hs-CRP>3.02 mg/l).

Results: For the pooled population, body mass index (BMI) was 27.63±3.5 kg/m^2, UAER was 21.98±10 mg/24h, total cholesterol was 231±41 mg/dl, triglycerides were 136±73 mg/dl, low-density lipoprotein cholesterol was 151±34 mg/dl and plasma levels of hs-CRP were 1.79±0.93 mg/l. According to the echocardiographic examination, left ventricular mass index (LVMI) was 105.5±23 g/m^2 and relative wall thickness was 0.41±0.06. Patients in group A (n=23) compared to subjects in group B (n=19) and C (n=5) had lower office systolic BP (143.6±8.9 mmHg vs 145.8±11.4 mmHg vs 157±4.4 mmHg, $p<0.05$ for all cases) and lower diastolic BP levels (95.7±6.2 mmHg vs 96±4.9 mmHg vs 102±4.4 mmHg, $p<0.05$ for all cases). Moreover, LVMI was more increased in group C than in group B and A (125.2±13 g/m^2 vs 107.9±24 g/m^2 vs 97.7±20 g/m^2, $p<0.05$ for all cases). Furthermore, patients in group C exhibited higher levels of UAER compared to group B and A (36.2±6.9 mg/24h vs 21.55±6 mg/24h vs 19.24±10 mg/24h, $p<0.05$ for all cases). In the entire population, hs-CRP was associated with BMI (r=0.37, $p<0.01$) and UAER (r=0.51, $p<0.001$). In addition, UAER was correlated with office systolic BP (r=0.29, $p<0.05$) and LVMI (r=0.32, $p<0.05$).

Conclusions: hs-CRP seems to constitute an emerging marker of subclinical vascular dysfunction, even at the level of renal glomerulus. The estimation of plasma hs-CRP levels, in conjunction with UAER measurement, may contribute to better cardiovascular risk stratification in this setting.

P649 The alteration of circulating matrix metalloproteinase and their inhibitors in gestational hypertension

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Background: Arterial invasiveness and growth are dependent on successful extracellular matrix (ECM) breakdown, which may be abnormal in gestational hypertension(GH). We hypothesised abnormalities in circulating Matrix metalloproteinase-9 (MMP-9) and tissue inhibitors of metalloproteinases-1&-2 (TIMP-1&2) in patients with GH, when compared to normotensive normal pregnancies(NP) and healthy non-pregnant controls(HC).

Methods: Circulating plasma MMP-9,TIMP-1&-2 were measured by ELISA in 23 women with GH (29(23-35)yrs), 30 NP (28-25-32)yrs) and 28 HC (33(27-37)yrs),matched for age, gestational age and parity.

Results: Levels of circulating MMP-9, TIMP-1&2 and the MMP-9/TIMP-1 & MMP-9/TIMP-2 ratios were significantly different between the three groups (Table). Post hoc Tukeys analysis($p<0.05$), demonstrated that the significant differences were as follows: for MMP-9 and TIMP-1 between HC and NP; for TIMP-2 between HC and NP, and NP and GH; for MMP-9/TIMP-1 and MMP-9/TIMP-2 between HC&NP and the latter group & GH group. Within the GH group, MMP-9 and the MMP-9/TIMP-1 ratio correlated negatively with age (r= -0.581, p=0.004 and r= -0.563, p=0.005 respectively) and levels of diastolic blood pressure (r = -0.432, p=0.040 and r= -0.461, p=0.027 respectively). Using a multiple regression analysis, only age independently correlated with circulating levels of MMP-9 (p=0.010), however neither age nor levels of diastolic blood pressure had any effect on the MMP-9/TIMP-1 ratio. The MMP-9/TIMP-2 ratio correlated negatively with levels of diastolic blood pressure (r= -0.453, p=0.030).

Table (Data as Median (IQR)

	Non Pregnant (n=28)	Normotensive Pregnant (n=30)	Gestational Hypertension (n=23)	p
MMP-9 (ng/ml)	153 (61-218)	210 (119-281	160(105-215)	0.026
TIMP-1 (ng/ml)	197(173-228)	180(145-196)	195(175-220)	0.006
TIMP-2 (ng/ml)	140(105-168)	138(110-174)	180(120-220)	0.007
MMP-9/TIMP-1	0.66 (0.35-1.06)	1.30(0.81-1.81)	0.81(0.46-1.27)	0.001
MMP-9/TIMP-2	1.13(0.56-1.68)	1.38(1.17-1.96)	0.84(0.53-1.46)	0.008

MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase

Conclusion: We demonstrate altered MMP/TIMP ratios in maternal blood during GH. These observations suggest pregnancy related changes in ECM turnover. Given the importance of changes in ECM composition to vascular and cardiac structure in hypertension we suggest that these observations may be central to the pathophysiology of human GH.

P650 Platelet P-Selectin and plasma levels of circulating cytokines in young patients with mild essential hypertension

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The role of inflammation for the development of vascular damage in atherosclerosis has been increasingly acknowledged during recent years. In this setting animal models have revealed the important role of platelet p-selectin on progression of atherosclerosis. P-selectin mediates rolling of monocytes on activated endothelium, the first step in the cell adhesion cascade. Although, these observations have stimulated research on the role of vascular inflammation in patients with essentiall hypertension (EH), the overall contribution of inflammation in EH, one of the leading cardiovascular risk factors, is far from being clear. Therefore, the present pilot study was designed to examine the role of platelet P-selectin and various inflammatory mediators in an early state of arterial hypertension in young patients without signs of target organ damage.

Methods: Fifteen patients with mild essential hypertension (33.8±7.3 years, systolic blood pressure(SBP): 143.8±10.5 mmHg, diastolic blood pressure (DBP):88.2±11.1 mmHg, mean arterial pressure (MAP) 106.6±10.4 mmHg) and 15 healthy controls (31.7±10.6years) were examined. Blood was drawn from a peripheral vein and one part immediately fixed with 1% paraformaldehyde, incubated with anti-P-selectin and platelets thereafter analysed by flow cytometry. The other part was used for measuring MCP-1, hsCRP, IL-6, TNFalpha, IL-10 levels via EIA.

Results: EH patients showed significantly enhanced expression of platelet P-selectin (17.2±5.4 vs. 10.6±4.2 mean fluorescence intensity [MFI], $p<0.001$). P-selectin expression positively correlated with MAP.(r=0.58, $p<0.001$) Furthermore patients with mild EH had significantly enhanced plasma levels of hsCRP(2.7±3.8 vs. 0.6±0.9 mg/L, $p<0.01$), Interleukin-(IL)-6 (1.4±0.7 vs 0.6±0.3 pg/mL, $p<0.001$), TNFalpha (2.8±0.7 vs. 2.4±0.4 pg/mL, $p<0.05$) and MCP-1(291.3±100.7 vs. 214.3±8.3 pg/mL, $p<0.05$). IL-6 levels positively correlated with hsCRP levels (r=0.80, $p<0.001$) and mean arterial pressure (MAP) (r=0.68, $p<0.01$)

Conclusions: This pilot study demonstrates that in an early state of EH, inflammatory mechanisms are already activated. Beside proinflammatory cytokines, platelets seem also to play an important role in mediating inflammation in the

progression of EH. It is possible that these mechanisms may play a pathogenic role in mediating target organ injury. However further investigations need to be done to clarify the role of an early anti-inflammatory therapy in patients with mild to moderate EH to alleviate hypertensive target organ damage.

P651 One-week administration of vitamin C attenuated the increase of vascular oxidative stress in spontaneously hypertensive rats without modifying the arterial pressure

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Purpose: Increasing evidences suggest that oxidative stress (OS) may contribute to the development of vascular diseases such as hypertension. The aim of this study was to appreciate the effect of a short-term vitamin C-enriched diet on 1) hemodynamic function and 2) vascular OS in normotensive and hypertensive rats.
Methods: At 12 weeks of age, spontaneously hypertensive rats (SHR, n=20) and normotensive Wistar Kyoto male rats (WKY, n=20) were used. Ten animals in each group (SHR and WKY) received or not 5g/kg/day vitamin C in drinking water for 7 days. Mean arterial pressure (MAP) and heart rate (HR) were measured in anesthetised rats. After sacrifice, thoracic aortas were excised. Reactive oxygen species (ROS) were assessed 1) by electron spin resonance (ESR) spectroscopy with a spin probe (CP-H, 1 mM), 2) by chemiluminescence evaluating NADPH oxidase activity (lucigenin, 0.5 μM), and 3) by histochemistry using an oxidative fluorescent probe (DHE, 5 μM). Aorta sections were immunolabelled for matrix metalloproteinase-1 (MMP-1) and monocytes chemoattractant protein-1 (MCP-1). Red picrosirius polarisation was used to estimate aorta collagen content.
Results: The SHR rats showed significant increases of MAP and HR. However, the treatment with vitamin C did not induce changes in cardiovascular parameters. ROS levels were higher (25-30%) in hypertensive rats as compared to control, assessed with CP-H oxidation (14.1 $\pm$ 0.9 vs. 10.5 $\pm$ 1.2 AU/mg; $p<0.01$), with chemiluminescence (2081.1 $\pm$ 182.7 vs. 1295.4 $\pm$ 190.4 Area under curve/mg; $p<0.01$) and with DHE (7.2 $\pm$ 0.6 vs. 5.3 $\pm$ 0.5% fluorecence/mm^2; $p<0.01$). Moreover, one-week vitamin C in drinking water prevented these increases in SHR rats. Semi-quantitative scores of MMP-1 and MCP-1 expression were higher in SHR than in WKY rats (respectively, 1.6 $\pm$ 0.2 vs. 0.6 $\pm$ 0.1, $p<0.001$; 1.5 $\pm$ 0.1 vs. 0.8 $\pm$ 0.1, $p<0.01$). MMP-1 augmentation was correlated with a decrease in collagen content in SHR (7.3 $\pm$ 1.6 vs 24.2 $\pm$ 5.6% collagen/unit area, $p<0.001$). The vitamin C-treatment did not change arterial inflammation (MCP-1) and collagen accumulation.
Conclusion: Increased NADPH oxidase-driven O2°- production in SHR aortas was normalised by a short period of treatment with vitamin C, without modifications of the MAP. Therefore, while in SHR an oxidative overactivity can be detected, a short term antioxidant treatment with high doses of vitamin C is not sufficient to reduce the MAP. Thus, OS appears to be one of the factors implicated in the etiology of genetic hypertension.

P652 Oxidative stress in patients with essential hypertension

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Background: Oxidative stress (OS) is implicated in endothelial dysfunction, atherosclerotic plaque formation and activation and in vascular and target organs lesions in arterial hypertension (HT). The implication of OS in progression of HT and its complications are yet little studied.
The aim to study plasma parameters of OS in patients with HT with or without complications.
Methods: We studied 118 pts (age 40-69 years) with HT (HT total group) (JNC 7 classification), 35 pts without complications (HT-C group) and 83 pts with target organ damages (HT+C group) and 15 healthy pts (age 42-58 years) (C group) free of antioxidants or beta-blocker agents. Blood samples were drawn to determine plasma prooxidants (lipid peroxides (nmol/l)-LPx), polymorphonucleare leukocytes activation index-LAI)) and antioxidants (thiol compounds-SH (nmol/l), total antioxidants capacity-AO (u/l). Statistical analysis - student t test.
Results: The parameters of OS were (tabel)

Results: The parameters of OS were:

Group	LPx	p	LAI	p	SH	p	AO	p
C	2.47		24.39		413		23.71	
HT total	4.62	0.00001	44	0.00001	342	0.00001	15.97	0.00001
HT-C	4.2	0.00001	43	0.00001	357.92	0.00001	16.96	0.00001
HT+C	4.87	0.00001	45.21	0.00001	332.39	0.00001	15.37	0.00001

LPx=lipid peroxides (nmol/l), LAI=polymorphonucleare leukocytes activation index, SH=thiol compounds(nmol/l), AO=total antioxidants capacity(u/l), p=HT total, HT-C, HT+C vs. C.

Conclusions: 1. The results suggest that HT is a disease with a state of continuum OS. 2. HT is characterized by important increase of ROS production from activated polymorphonucleare leukocytes and decrease of plasma antioxidants by consumption. 3. OS is probably an important factor in progression of HT and its complications.

MYOCARDIAL DISEASE

P653 Carvedilol improves left ventricular function in murine Coxsackievirus-Induced acute myocarditis with reduced myocardial inflammation and a modulated immunresponse

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Introduction: Proinflammatory cytokines like interleukin-1b and TNF-a induce the expression of matrix metalloproteinases that play a crucial role in myocardial remodeling. In addition, beta-adrenergic receptor stimulation by catecholamines influences the production of cytokines heralding the possibility of modulating cytokine production by beta-adrenergic blockers.
Methods: Coxsackievirus B-3 infected and non-infected BALB/c mice (each n=30) were analyzed on day 10-post infection (each n=10). Carvedilol (5mg/kg/12h) and metoprolol (15mg/kg/12h) were administered orally (5mg/kg/12h) for nine days starting from 24h after infection (n=20) and sham-infection (n=20) Hemodynamic parameters were measured in anesthetized, artificially ventilated and closed-chest animals and the mRNA abundance of MMP-8, MMP-9, IL-1b, TNF- a. TGF-b and CVB-3 were analyzed by RT-PCR. Furthermore CD3+, CD4+ and CD8+ infiltrations were measured in cryo-sections.
Results and Discussion: Hemodynamic evaluation revealed a significant improvement of left ventricular function 10 days post infection in carvedilol treated mice. Compared to controls IL-1b, TNF-a and TGF-b mRNA abundance were elevated significantly (240%*, 200%*, and 161%*) in the infected myocardium. Myocardial MMP profiles in the infected mice presented a significant up regulation of MMP-8, MMP-9 (160%*, 340%*). Additionally infected mice showed significantly elevated infiltrations with CD3+, CD4+ and CD8+ cells (730%*, 1110%*, 380%*). Carvedilol attenuated over-expression of myocardial interleukin-1b significantly in the infected mice with a trend in TNF-a. Myocardial mRNA abundance of MMP-8 was significantly reduced, while there was only a trend of reduction in MMP-9 mRNA abundance in response to carvedilol treatment. Carvedilol showed a representative reduction in the CD4+ cells with a trend of up regulation in the CD8+ cells. In addition, there was a significant correlation between IL-1b mRNA abundance and hemodynamic parameters as well as between IL-1b, MMP-8 mRNA abundance and CD4+ cell infiltration. (*$p<0,05$ versus Kontrolle (ANOVA-Test))
Conclusion: The reduced expression of proinflammatory cytokines, MMPs and the beneficial effect to the immunresponse may contribute to reduced matrix degradation with a consecutive improved structural integrity of the heart with improved hemodynamic function. This beneficial effect of a carvedilol treatment might be due to the wide range of biological activities besides the antiadrenergic potential (anti inflammatory, anti fibrotic, anti oxidative, immunmodulative).

P654 Angiotensin receptor subtypes are divergent expressed during acute phase of murine viral myocarditis

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Introduction: Heart failure is associated with a high expression of catecholamines and angiotensin. Angiotensin has different effects on receptor subtypes. The AT1 receptor transmits proliferation of cells, extracellular matrix turnover, inflammatory response and oxidative stress. Angiotensin effects on AT2 receptor subtype are regeneration, apoptosis and antiproliferation. The distribution of receptor subtypes during the acute and chronic phase of viral myocarditis is still unknown.
Methods: Therefore 4 weeks old male SWR/J mice were infected intraperitoneally with 5 x 105 PFU CVB3 (n=30) or sham-infected (n=30). The examination time-points were 4, 7 or 28 days after infection (each n=10). In all mice LV function (LVsP, dP/dt max) was evaluated by invasive measurement (tip catheter). The mRNA expression of angiotensinogen and the angiotensin receptor subtypes AT1a, AT1b and AT2 were analyzed by semiquantitative RT-PCR.
Results: During the acute phase of viral myocarditis angiotensinogen and AT1b receptor are significantly altered with the highest expression on 7th day p.i. while AT1a and AT2 receptor subtypes are downregulated. Markable the expression of AT1b is significantly correlated with angiotensinogen expression ($r^2 > 0,8$). On 28th day p.i. all parameters are nearly normalized compared to control mice.

mRNA-profiles

groups	Angiotensinogen	AT1a receptor	AT1b receptor	AT2 receptor
control	0,83±0,15	1,37±0,23	0,74±0,14	1,39±0,19
infected (4th day)	1,63±0,29*	0,78±0,19*	1,69±0,25*	1,02±0,18*
infected (7th day)	2,14±0,19*/**	1,03±0,16*/**	1,97±0,20*/**	0,66±0,08*/**
infected (28th day)	1,14±0,15*/**	1,15±0,14**	1,15±0,12*/**	1,51±0,15**

*$p<0,05$ vs control, **$p<0,05$ vs infected 4th day p.i. (ANOVA)

Conclusion: During acute phase of murine viral myocarditis angiotensin receptor subtypes are divergent regulated with a predominance of AT1b receptor. There-

fore angiotensin seems to influence inflammation and oxidative stress mostly at the AT1b receptor subtype in acute myocarditis.

P655 The treatment of coxsackievirus B3 infected mice with the soluble coxsackie adenovirus receptor CAR4/7 leads to a reduction in the myocardial virus titer

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Purpose: Soluble coxsackie adenovirus receptors (CAR) have antiviral effects on coxsackievirus B3 (CVB3) infection in vitro. We analyzed the impact of the soluble CAR isoform, CAR4/7, on the CVB3 infection in murine myocarditis.
Methods: CVB3 infected and uninfected Balb c mice were daily treated with 200μg CAR4/7. The myocardial CVB3 titer was determined by plaque forming assay seven days after infection. In addition, the grade of inflammation was analyzed by hematoxylin-eosin staining and the production of CAR-specific antibodies was tested by ELISA.
Results: The treatment with CAR4/7 led to a significant reduction of the CVB3 titer in the heart of infected animals (group 3, table 1). In contrast, the grade of inflammation was remarkably increased in CAR4/7 treated, infected mice (group 3) compared to untreated mice (group 2). CAR4/7 injection, however, did not cause myocardial inflammation in control animals (group 4). CAR4/7 treatment led to a production of CAR-specific antibodies that was higher in uninfected than in infected animals. These antibodies were reactive against normal heart tissue, but their production did not result in a myocardial infiltration with lymphocytes in uninfected mice.

Table 1

	Virus titer ($\times 10^6$pfu/mg)	Grade of inflammation	CAR antibody titer ($\times 10^3$)
Group 1 (-CVB3/- CAR4/7)	n.d	n.d.	n.d.
Group 2 (+CVB3/-CAR4/7)	4.9±0.9	1.5±0.17	n.d.
Group 3 (+CVB3/+CAR4/7)	2.0±0.5*	2.6±0.17**	47.6±19.5
Group 4 (-CVB3/+CAR4/7)	n.d	n.d.	152.8±19.1**

Data are shown as mean±SEM; n.d. = not detectable; pfu = plaque forming units; *p<0.05; **p<0.002

Conclusions: The antiviral effect of CAR4/7 treatment might be caused by the production of CAR4/7-specific antibodies that bind to myocardial CAR and prevent virus attachment to the myocytes and/or by the induction of an enhanced cellular immune response clearing the virus from the tissue. CAR4/7 might also bind to CVB3 and to membranous CAR and inhibit thereby the infection of the myocytes.

P656 Persistently coxsackievirus-infected CD4+ T cells may sustain ongoing enteroviral myocarditis

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Purpose: In permissive immunocompetent mice coxsackievirus B3 (CVB3) is known to induce chronic inflammatory heart disease, which is consistently associated with virus persistence. The pathogenic mechanisms leading to morbidity are still controversially discussed. In particular, it is not known whether, in addition to infected myocytes, infected immune cells play a role in maintenance of chronic enterovirus-mediated myocarditis.
Material and Methods: An adoptive cell transfer model was used to analyze the role of virus-infected splenocytes in enterovirus myocarditis. Splenocytes from CVB3-infected BALB/c mice were transferred into syngenic T and B cell deficient SCID mice. Furthermore, T cell hybridomas were generated to investigate their viral or autoimmune antigen specificity.
Results: In this study we demonstrate that transfer of splenocytes from acutely as well as from persistently CVB3-infected donor mice results in heart muscle infection and chronic inflammation in host SCID mice. In situ hybridization and nested PCR assays revealed CVB3 RNA in transferred cells as well as in spleen and heart tissue of recipient SCID mice, indicating a sustained infectivity of CVB3 in chronic disease. The analysis of several hundred T cell hybridomas showed no evidence for the induction of an autoreactive T cell response against heart muscle-specific antigens such as myosin. In contrast, we isolated several T cell hybridomas which were CVB3-infected and displayed a MHC-dependent specific activity against viral antigens. These T cells were found to be CD4 positive and they expressed a Th1-cytokine profile.
Conclusion: Our results indicate an important role of activated, persistently CVB3-infected CD4+ T helper cells in the pathogenesis of chronic enterovirus myocarditis. These CD4+ T cells serve as viral reservoir, release inflammatory cytokines and thereby contribute to the development of ongoing viral myocarditis.

P657 Virus receptor traps, express coxsackievirus and adenovirus receptor and the decay-accelerating factor, can block coxsackievirus infection in vitro

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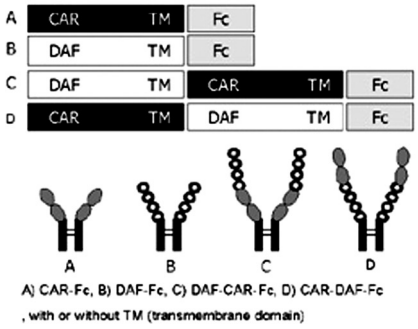
Coxsackievirus B3 (CVB3) is a major cause of viral myocarditis. It recognizes CAR receptor and DAF co-receptor proteins to facilitate infection. Protein-based agents, such as soluble receptors or monoclonal antibodies to tumor necrosis factor, and the interleukin-1 receptor antagonist, that block the action of cytokines have substantially improved treatment in autoimmune diseases and viral myocarditis. A novel cytokine trap provides both receptor chains in a dimeric configuration that resembles the two chains of extracellular cell surface receptor. The two chains of the trap are linked by fusion of the complement binding domain of IgG1.
Methods and Results: Using this concept of cytokine trap, we cloned cDNA sequences, encoding the extracellular domains of CAR and DAF fused to the Fc portion of human IgG1 (with or without transmembrane domains), into plasmid vector pCK. Four different virus receptor traps, CAR-Fc, DAF-Fc, CAR-DAF-Fc and DAF-CAR-Fc were generated to test whether the traps can neutralize the myocarditic strain (Woodruff strain, H3) of CVB3 and 6 serotypes of CVB. Using western blot, we could detect the secreted proteins of four different structures in the supernatants of transfected 293T cells. The H3 viruses were neutralized by the CAR-Fc, CAR-DAF-Fc, DAF-CAR-Fc traps, but not by DAF-Fc. Both traps with or without transmembrane domains could neutralize H3 virus. CAR-Fc dimer neutralized all serotypes of CVB1-4, 6. CAR-DAF-Fc and DAF-CAR-Fc traps neutralized CVB2, 4, 6, but not CVB1, 3 and 5.



Structures of virus receptor traps.

Conclusion: The virus receptor traps may be a novel therapeutic agent for active myocarditis if given early viremic phase, although more studies are needed to determine its mechanism and efficacy in vivo.

P658 Modulation of doxorubicin-induced cardiac dysfunction in toll-like receptor-2 knockout mice

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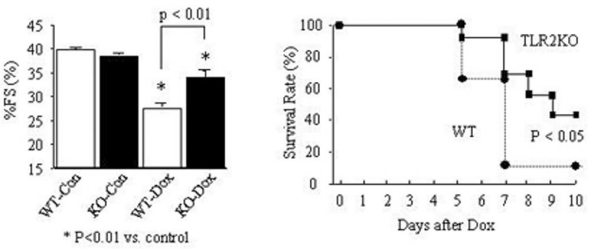
Background: Toll-like receptors (TLRs) are members of the interleukin-1 receptor family and involved in the responsiveness to pathogen-associated molecular patterns. Recent studies have demonstrated that TLRs are activated by endogenous signals such as heat shock proteins and oxidative stress, which may contribute to myocardial infarction and congestive heart failure. Oxidative stress is one of the major factors for doxorubicin-induced cardiac dysfunction. Thus, we hypothesized that TLRs contributed to the pathogenesis of doxorubicin-induced cardiac dysfunction.
Methods and Results: Doxorubicin-induced cardiac dysfunction was induced by a single injection of doxorubicin (Dox, 20 mg/kg) intra-peritoneally in wild type (WT) mice and TLR-2 knockout (KO) mice. Myocardial lipid peroxidation was significantly increased after Dox-treatment, but no significant difference was found between WT and KO mice. However, NF-kB activation and production of pro-inflammatory cytokines after Dox were suppressed in KO mice compared to WT



mice ($P<0.01$). Five days after Dox injection, left ventricular dimensions at end-diastole was smaller and fractional shortening was higher in KO mice compared with WT mice ($P<0.01$). Numbers of TUNEL positive nuclei and Dox-induced caspase-3 activation were less in KO mice than in WT mice ($P<0.01$). Consequently, survival rate was significantly higher in KO mice than in WT mice 10 days after Dox injection (46% vs. 11%, $P<0.05$).

Conclusions: These findings suggest that toll-like receptor-2 may play an important role in the regulation of inflammatory and apoptotic mediators in the heart following doxorubicin treatment.

P659 Arrhythmogenic right ventricular cardiomyopathy causing sudden cardiac death in boxer dogs

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Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary and familial heart muscle disease associated with substantial cardiovascular morbidity and high risk of sudden death in the young. Efforts to discern the relevant mechanisms have been impaired by the absence of a suitable animal model.

Methods and Results: ARVC was clinically suspected in 23 boxer dogs (12 male; 4.5 to 13.7 years old, mean, 9.1±2.3 years) based upon a clinical phenotype that included ventricular arrhythmias of RV origin (n=19, 83%), sudden death (n=9, 39%), syncope (n=12, 52%), or right heart failure (n=3, 13%). Six dogs shared similar pedigrees. Right ventricular enlargement or aneurysms occurred in 10 (43%). Striking histopathological abnormalities were present in each boxer dog but not in controls,including severe RV myocyte loss with replacement by fatty (n=15, 65%) or fibrofatty (n=8, 35%) tissue. Focal fibrofatty lesions were also present in both atria (n=8) and the left ventricle (LV) (n=11). Fatty replacement occupied substantially greater RV wall area in ARVC dogs than controls (40.4±18.8% versus 13.8±3.4%, respectively)($P<0.001$); residual myocardium was correspondingly reduced (56.6±19.2% versus 84.8±3.8% in controls)($P<0.001$). MRI demonstrated bright anterolateral and/or infundibular RV myocardial signals, confirmed as fat by histopathology. Myocarditis appeared in the RV (n=14, 61%) and LV (n=16, 70%) in each dog with sudden death, but not in controls. Familial transmission was evident in 10 of the 23.

Conclusions: We describe a spontaneous animal model of ARVC and sudden unexpected death in the boxer dog that closely resembles the human disease. Characterized by ventricular arrhythmias, sudden death, fatty or fibrofatty myocardial replacement, apoptosis, and myocarditis, this canine model should facilitate investigations into complex clinical and pathophysiologic mechanisms of ARVC and sudden death in humans.

P660 Proteasomal impairment by truncated myosin binding protein C: a novel pathogenic mechanism of familial hypertrophic cardiomyopathy?

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Introduction: Mutations of the cardiac myosin binding protein C (MyBP-C) gene are a frequent cause of familial hypertrophic cardiomyopathy (FHC). Most mutations result in variable degrees of truncation. This study analyzed the impact of two representative MyBP-C mutations on protein and mRNA expression, the ability to incorporate into the sarcomere and the involvement of cellular protein degradation pathways.

Methods and Results: Cardiomyocytes from neonatal rats were infected (MOI 5) with recombinant adenovirus encoding wildtype (wt) or mutant cMyBP-C (M6 [insertion/deletion in exon 33]: 3% truncation; M7t [skipping of exon 6]: 80% truncation; all mutations identified in patients with FHC), and Northern and Western blot analyses were performed 48 h later. Although adenoviral mRNA expression of wt and mutant MyBP-C was similar in all groups, protein levels of truncated M6 and M7t MyBP-C were markedly reduced by 30±4% (n=10, $p<0.05$) and 89±5% (n=10, $p<0.05$), respectively, compared to wt. Treatment with the lysosomal inhibitor bafilomycin A1 (50 nM) had only minor effects whereas treatment with proteasome inhibitors MG132 (50 μM) or lactacystin (25 μM) raised protein expression of M6 and M7t to wt level (n=5, $p<0.05$). Immunostaining showed correct incorporation of wt protein into the A-band. In contrast, M6 integrated poorly into the A-band, while M7t misintegrated into the Z-disc. In addition, M7t, but not wt or M6, showed intracellular ubiquitin-positive deposits. Monitoring proteasomal activity in living cardiomyocytes by co-infection with a recombinant adenovirus encoding a fluorescent substrate of the proteasome (Ub-DsRed) revealed a significant impairment of proteasomal function in cardiomyocytes expressing the truncated MyBP-Cs. Quantification by immunoblotting and FACS analysis revealed an increase in Ub-DsRed by 107% (n=5, $p<0.05$) for the mutant M6 and 246% (n=5, $p<0.05$) for M7t when compared to wt.

Conclusions: The loss of C-terminal domains of the MyBP-C not only alters its sarcomeric incorporation, but also accelerates its degradation by the ubiquitin/proteasome system (UPS). This experimental finding may explain the absence of mutant MyBP-C protein despite the presence of the mutant mRNA in endomyocardial biopsies from FHC patients. Moreover, we demonstrate that depending on the nature/degree of truncation, mutant MyBP-C significantly impairs the proteolytic capacity of the proteasome. Considering the important role of the UPS in a variety of cellular processes, a sustained impairment of this system by mutant MyBP-C may contribute to the pathogenesis of FHC.

P661 Differential regulation of metabolic genes in a transgenic rat model of hypertrophic cardiomyopathy

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Autosomal-dominant inherited hypertrophic cardiomyopathy (HCM) is associated with myocardial hypertrophy, diastolic dysfunction and an increased risk of sudden death. While multiple mutations in contractile proteins have been associated with the disease, the pathogenesis of HCM is still poorly understood. Recently, it has been suggested that inefficient energy utilization could be the common molecular pathway of HCM-associated mutations. In order to establish an in vivo model for the disease, we have previously generated transgenic rats expressing a truncated human cardiac troponin T (DEL-hTNT) molecule. This animal model displays characteristic features of HCM, including diastolic dysfunction and ventricular arrhythmias. In addition, transgenic hearts revealed metabolic dysregulation with significantly elevated myofibrillar ATP-consumption.

To identify the molecular pathways underlying this phenotype we now performed transcriptional profiling with cDNA-microarrays (Rat-Unigene-1, containing 27.000 cDNA-clones). Differential regulation was subsequently verified by real-time-PCR. DEL-hTNT-transgenic rat hearts showed a significant induction of the ATP-synthase F0-complex compared to non-transgenic littermattes (+170%). Furthermore, GLUT-4 (+175%), the M- (+100%) and B-Isoform (+127%) of creatine kinase as well as malatdehydrogenase (+136%) were significantly induced. Similarly, genes critical for energy supply from fatty acid oxidation, such as CD36/FAT (+95%), CPT-1 (+400%) and CPT-2 (+250%), were found upregulated. In contrast, the mitochondrial ATPase-inhibitor was significantly downregulated (-56%) in DEL-hTNT- transgenic rats. Moreover, the expression of several regulators of mitochondrial function and biogenesis was altered, including the peroxisome-proliferator-activated receptors (PPAR)-alpha (+79%) and PPAR-gamma (+87%), as well as Uncoupling-Protein 2 (+184%).

The differential regulation of metabolic genes in DEL-hTNT transgenic hearts thus most likely represents a compensatory mechanism for the observed increase in myofibrillar ATP-consumption. Since ATP-synthesis is already markedly induced under resting conditions, it is conceivable that cardiac energy supply becomes limiting during exercise, ultimately resulting in diastolic dysfunction and ventricular arrhythmias, two hallmarks of the HCM phenotype.

P662 L-type calcium channel inhibitor diltiazem prevents diastolic dysfunction and stress-induced cardiac decompensation in a mouse model of familial hypertrophic cardiomyopathy

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The cardiac troponin T (TnT) I79N mutation has been linked to familial hypertrophic cardiomyopathy. To investigate the effect of this mutation on left ventricular (LV) function, we determined LV pressure-volume relationships in transgenic mice expressing the human wild type (Wt) or the human mutant TnT (I79N).

Methods: Using a micro-conductance catheter LV function was determined under basal and stress conditions (0.25 mg/kg isoproterenol i.p.). After V. cava occlusion endsystolic and enddiastolic pressure volume relationships were obtained (ESPVR; EDPVR). Using the same protocol LV function 4 weeks after an intervention with the calcium channel inhibitor diltiazem was additionally investigated in an extra set of I79N mice.

Results: Basal conditions: I79N mice showed increased systolic function compared to Wt: EF:63.3±.4.3* vs. 51.1±5.0%; SV:35±3.2* vs. 27.1±1.6μl; CO: 16950±1300* vs. 12119±1027μl/min; Volume endsystolic: 26.5±2.3* vs. 32.7±2.3μl; * $p<0.05$) without differences in HR, LVP and ESPVR. Volume dependent diastolic pressure indices as LVEDP were unchanged, but the volume independent EDPVR slope was increased (0.5±0.1* vs. 0.3±0.03; * $p<0.05$. Diltiazem led to a reduction in EDPVR (0.16±0.05).

Stress conditions: HR (654±21 vs. 625±25 bpm) and LVP (159.9±8.6 vs. 169.5±11.3mmHg; $p<0.05$) response was similar in all groups, but the systolic function of I79N mice decreased compared to Wt(EF: 25.1±5.5 vs. 51.7±8.4%; SV: 14.0±3.3 vs. 22.17±4.4μl; CO: 8916±1832 vs. 13915±1558μl/min; Ves: 42.2±3.6 vs. 25.8±5.6μl and ESPVR slope 2.35±0.6 vs. 5.08±1.1; $p<0.05$). Diastolic indices demonstrate diastolic dysfunction in I79N compared to Wt

(LVEDP: 17.1±2.2* vs. 8.4±2.2mmHg; p<0.05). The significantly increased EDPVR (1.1±0.3 vs. 0.37±0.2; p<0.05) indicates cardiac stiffness worsened under beta-adrenergic stimulation. Diltiazem prevented the reduction in SV (22.8±3μl), CO (14046±1885μl/min) and the rise in LVEDP (6.1±1.4)without influencing HR.
Conclusions: I79N TnT mice show an increased cardiac stiffness under basal conditions, and a diastolic dysfunction leading to decompensation under stress. Diltiazem prevents cardiac decompensation and offers an effective therapy option in this model.

P663 Depressed left atrial function in b-thalassemia major with normal systolic and diastolic left-ventricular function

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Secondary hemochromatosis in patients with b-thalassemia major (b-thal) leads to left ventricular (LV) systolic and diastolic dysfunction. Supraventricular arrythmias are also frequent in the natural history of the disease. We tested the hypothesis that left atrial (LA) dysfunction presents early, before presentation of ventricular dysfunction.
Methods: We studied 29 consecutive b-thal patients, with normal LV systolic and diastolic function (LV ejection fraction>55%, E/A mitral inflow ratio<2 & pulmonary venous flow systolic fraction >0.5 & E mitral/E annulus(TDI)<8) assessed by a thorough Echocardiographic-Doppler and TDI study 2-4 days following transfusion. Fifteen normal volunteers served as controls. Apical 4 &2 chamber views were used to calculate LA volumes using the length-area formula at end systole(LAVmax), at the end of P wave (LAVp) and end diastole(LAVmin). Total Emptying Volume(TEV: LAVmax-LAVmin), Passive Emptying Volume (PEV: LAVmax-LAVp) and Active Emptying Volume (AEV: LAVp-LAVmin) were calculated as well as Total (TEF:TEV/LAVmax), Passive (PEF:PEV/LAVmax) and Active (AEF:AEV/LAVp) Emptying Fractions. A 24 hours ECG Holter recording obtained and blood was collected for pro-ANP (1-98)measurements from all patients and controls.
Results: There was no statistical difference between the 2 groups in age, LV dimensions and ejection fraction, mitral inflow E/A wave ratio,mitral E wave deceleration time, pulmonary venous flow S/D wave ratio and systolic fraction, and Emitral/E annulus ratio. LA volumes were increased (LAV max 36±7 vs 29±6 ml/m^2 bsa, p<0.05, LAV p 22±7 vs 17±5 ml/m^2, p<0.05, LAV min 16±5 vs 10±4 ml/m^2, p<0.01) and TEF & AEF were decreased (56±11 vs 65±10% and 29±11 vs 42±9% respectively, p<0.05 for both.
Pro-ANP levels were higher in b-thal group (2097±1562 vs 830 ± 394 fmol/ml, p<0.01) In b-thal group short runs of atrial fibrillation detected in 3/29 and frequent premature supraventricular beats in 8/29 vs 0/15 and 2/15 in controls respectively(p<0.01 and p<0.05). AEF remained lower (31±12 vs 42±9%, p<0.05) and pro-ANP higher (2122±1453 vs 830±394 fmol/ml, p<0.01)in the pts group without atrial fibrillation detected.
Conclusion: Cardiac hemochromatosis seems to lead in LA mechanical dysfunction and electrical instability even before presentation of ventricular dysfunction.

P664 Prognosis in idiopathic dilated cardiomyopathy: has it improved in tertiary referral centres over the last 10 years?

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Current medical and non medical therapies (use of beta-blockers, more frequent implantation of cardioverter defibrillator (ICD), biventricular pacing) have improved the overall prognosis in heart failure. It is unclear whether prognosis was improved in the particular setting of patients (pts) with idiopathic dilated cardiomyopathy (IDC) seen in tertiary referral centers.
Methods: In 201 pts with IDC (normal coronary angiography in all pts; age 51±12 years) prognosis was evaluated on 2 periods: 1986-1994 (period A, n=96) and 1995-2003 (period B, n=105).
Results: Compared to period A, pts in period B had larger LV end diastolic diameters (66±9 vs 68±9 mm, p=0.04), lower LV ejection fractions (36±12 vs 30±10, p=0.0002) and higher pulmonary capillary wedge pressures (12±9 vs 16±8 mm Hg, p=0.001). ACE inhibitors use was markedly increased in period B (34% vs 78%, p=0.0001) as was use of beta-blockers (15% vs 40%, p 0.0002). Amiodarone use was similar (21% vs 26%, p=NS) and use of class 1 antiarrhythmic agents was reduced (17% vs 6%, p=0.03). Five patients in each period received an ICD for sustained VT/VF and 4 patients in period B received biventricular pacing. With a follow-up of 51±42 months, 28 pts suffered cardiac death (15 progressive CHF, 13 sudden deaths) and 11 had sustained ventricular tachycardia (VT) or resuscitated ventricular fibrillation (VF). Rate of cardiac death (figure) was unchanged in the 2 periods, as was the occurrence of major arrhythmic events.

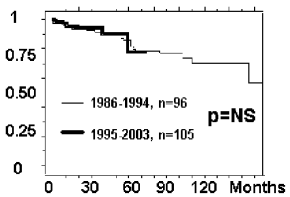

Fig. 1. Cardiac death in IDC, 1986-2003.

Conclusion: Despite the improvement in medical strategy in heart failure and its recognized efficacy, the prognosis of pts with well characterized IDC was unchanged in tertiary referral centers in the recent years. The recruitment of more severe pts might explain these results.

P665 Mode of death in idiopathic dilated cardiomyopathy. Analysis of the timing of a competitive risk

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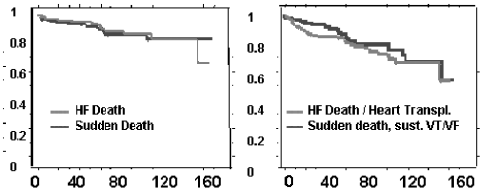
It has been suggested that the risk of sudden death in heart failure (HF) was influenced by NYHA class and was more marked in the early phase after diagnosis. This may have some interest in the choice of the use of prophylactic therapy against major arrhythmic events. It remains unclear whether this is also true in the particular setting of patients with idiopathic dilated cardiomyopathy (IDC).
Methods: In 201 patients with IDC in sinus rhythm (normal coronary angiography in all patients; age 51±12 years) The risk of cardiac death due to HF and of sudden death were evaluated separately.
Results: With a follow-up (FU) of 51 ± 42 months, 29 patients suffered cardiac death (15 progressive CHF, 14 sudden deaths), 12 had sustained ventricular tachycardia (VT) or resuscitated ventricular fibrillation (VF) and 19 underwent heart transplantation. Rate and timing of death related to HF or sudden death were similar (figure). Results were similar when we compared separately 1) HF events = death due to HF or heart transplantation and 2) Major arrhythmic events = sudden death or occurrence of sustained VT/VF (figure). NYHA class significantly influenced occurrence of HF death (class 1 to 4: 2%, 3%, 13%, 36% during FU, p=0.001) and HF events (4%, 16%, 27%, 55%, p=0.0001) but not sudden death (4%, 4%, 13%, 9%, p=0.18) nor major arrhythmic events (6%, 13%, 19%, 18% during FU, p=0.19).



Cardiac death and major events in IDC.

Conclusion: There was no clear difference in the timing of major events related to HF or major arrhythmic events in this series of well characterized IDC. Risk of arrhythmic events was similar in NYHA class 2 to 4. Therefore, prophylactic use of therapy such as implantable cardiac defibrillator should not be influenced by the NYHA class nor the duration of evolution of the disease.

P666 New evidence of link between sudden death, effort-induced polymorphic ventricular arrhythmias and ARVD2 in a family carrying a novel mutation in cardiac ryanodine receptor gene

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Cardiac ryanodine receptor (RYR2) gene mutations have been associated with Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) or Arrhythmogenic Right Ventricular Cardiomyopathy type 2 (ARVD2).
Purpose: To investigate the molecular pathogenesis of ARVD2 through the study of one family carrying a novel mutation in RYR2 gene.
Methods: Clinical evaluation and genetic analysis were performed on the family composed by 10 members of a 17-year-old boy who died suddenly. All family members underwent 12 lead ECG, Holter ECG, signal averaged ECG, 2-D and Doppler echocardiogram, and exercise stress test. RYR2 coding sequence was screened for mutation by direct sequencing. A complete necropsy of the index case was performed.
Results: Clinical findings were normal in all family members, with exception of the mother and sister of the index case who presented effort-induced ventricular arrhythmias in apparently normal hearts. DNA analysis demonstrated a novel mutation in RYR2 gene in the index case, in his mother and his young sister. Detailed histological, histochemical and ultrastructural analysis of the heart of the index case revealed myofiber damage and loss in the right ventricle. Both anterior and posterior right ventricular myocardium showed fatty and fibro fatty-replacement, focally involving the entire wall thickness. These findings were consistent with a mild form of arrhythmogenic right ventricular cardiomyopathy.

Conclusions: This study provides new evidence of link between sudden death, effort-induced polymorphic ventricular arrhythmias, ARVD2 and RYR2 mutation. Clinical diagnosis of structural alterations of right ventricle in living subjects remains still an open issue.

P667 Analysis of hypertrophic cardiomyopathy associated with Wolff-Parkinson-White syndrome

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Background: Molecular genetic studies revealed that mutations in the PRKAG2 gene that encodes the gamma2 regulatory subunit of AMP-activated protein kinase can cause autosomal dominant Wolff-Parkinson-White syndrome associated with hypertrophic cardiomyopathy. Recent studies revealed that PRKAG2 mutations cause myocardial metabolic storage disease, in which hypertrophic cardiomyopathy, ventricular pre-excitation and conduction system defects coexist. However, incidence of hypertrophic cardiomyopathy in patients with sporadic Wolff-Parkinson-White syndrome confirmed by electrophysiological study is not clear.
Methods: We have evaluated 65 patients (37 males, 28 females, age 49 $\pm$ 16 years) with isolated Wolff-Parkinson-White syndrome confirmed by electrophysiological study. Clinical evaluation, echocardiography, and electrophysiological study were performed in all the patients. Maximal wall thickness greater than 13 mm and absence of hypertension or other structural heart disease is considered as hypertrophic cardiomyopathy.
Results: Eighteen (16 males, 2 females, age 60 $\pm$ 10 years) of 65 patients had left ventricular hypertrophy by echocardiography. Eight patients of these 18 had hypertension, and 1 had aortic stenosis due to bicuspid aortic valve. Other 9 patients (8 males, 1 female, age 56 $\pm$ 10 years) who had unexplained cardiac hypertrophy were diagnosed as hypertrophic cardiomyopathy. The maximal left ventricular wall thickness was ranging from 13 to 21 mm (15 $\pm$ 3 mm) in these 9 patients with hypertrophic cardiomyopathy associated with Wolff-Parkinson-White syndrome. The locations of accessory pathways were confirmed during electrophysiological study. Left antero-lateral accessory pathway was observed in 2, left antero-septal wall pathway in 1, left postero-lateral wall pathway in 2, left lateral wall pathway in 1, right anterior wall pathway in 1, and right postero-medial wall pathway in 2. There was no significant difference in the locations of accessory pathway between hypertrophic cardiomyopathy patients and others. Two patients without cardiac hypertrophy had congenital heart anomaly, one had atrial septal defect and another had Ebstein's anomaly.
Conclusions: Hypertrophic cardiomyopathy was found in 9 of 65 patients (14%) with sporadic Wolff-Parkinson-White syndrome confirmed to have accessory pathway by electrophysiological study. There was no correlation between location of accessory pathway and coexistence of hypertrophic cardiomyopathy.

P668 Electroanatomic right ventricular voltage mapping combined with endomyocardial biopsy increases accuracy in diagnosing arrhythmogenic right ventricular cardiomyopathy/dysplasia

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Electroanatomic voltage mapping has been demonstrated to identify low-voltage areas ("scars") that correspond to regions of transmural loss of myocardium with fibrofatty replacement in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). We assessed whether electroanatomic characterization of the right ventricle by voltage mapping combined with endomyocardial biopsy (EMB)enhances accuracy for diagnosisng ARVC/D. Twenty-six consecutive patients (11 males and 5 females, aged 31$\pm$13) who fulfilled the Task Force diagnostic criteria for ARVC/D after "non-invasive" clinical evaluation, underwent further "invasive" evaluation by electroanatomic voltage mapping of the right ventricle and EMB in order to validate the diagnosis. Areas of relatively low-voltage ($<$2.0 mV) or low-voltage ($<$0.5 mV) were mapped with a high point density (148$\pm$27) to delineate their extent and borders. In 16 patients (62%) the diagnosis of ARVC/D was confirmed by abnormal voltage maps showing 2$\pm$0.8 low-voltage areas greater than 1 cm squared in area which correlated with histopatologic evidence of fibrofatty replacement at EMB. Bipolar electrograms recorded from low-voltage regions were fractionated and showed prolonged duration and delayed activation. The other 10 patients (38%), had a normal voltage mapping with homogeneously preserved electrogram voltage ($>$2 mV). Patients from this latter subgroup, significantly more often had histopatologic evidence of myocarditis according to Dallas criteria (p=0.005), as well as negative family history (p=0.01) and negative programmed ventricular stimulation (p=0.008). There was not difference between the two subgroups of patients with regard to age, sex, disease duration, ECG changes, and right ventricular abnormalities at echocardiogram and/or MRI, and left ventricular involvement. During a mean follow-up of 31 $\pm$8 months, all patients with normal voltage mapping remained stable on antiarrhythmic therapy, although 9 of 16 patients with abnormal voltage mapping required implantation of a defibrillator due to life-threatening ventricular arrhythmias (p=0.01). In conclusions, electroanatomic voltage mapping of the right ventricle in conjunction with EMB enhanced diagnostic accuracy of ARVC/D and identified a subset of patients without regional fibrofatty myocardial atrophy who had histopathologic evidence of myocarditis and a better "arrhythmic" outcome.

P669 Natural course of arrhythmogenic right ventricular dysplasia-cardiomyopathy – a registry of 313 patients

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For several years attempts are made to provide data on the natural course of arrhythmogenic right ventricular dysplasia-cardiomyopathy (ARVD/C). In a multicenter registry since 1988 313 patients with the diagnosis of ARVD/C according to ISFC/ESC criteria were included. A follow-up was performed by questionaires and telephone interviews with regard to mortality, sudden cardiac death (SCD), syncopes, heart failure and risk factors of SCD.
Results: Overall mortality was 2.9% (n=9) due to SCD in 1.6% (n=5), heart failure in 1% (n=3) and postoperative complications after heart tramsplantation in 0.3% (n=1). Risk factors of SCD were LV dysfunction in 4 cases (80%), syncopes in 5 cases (100%) and positive family history in one case (20%). In three other families SCD without definite diagnosis occurred, events in family members with clinical diagnosis of ARVD/C did not happen. Risk factors of aborted SCD in 21 patients (7%) were LV dysfunction (43%) and syncopes (38%). 77 patients (25%) suffered from non-documented palpitations, 70 patients were completely asymptomatic from arrhythmogenic events (22%). Atypical chest pain was present in 132 cases (42%). Syncopes occurred in 45 cases (14%) due to VT's in 19 cases (42%), AV block in 6 cases (13%) and undocumented mechanisms in 20 cases (44%). Symptoms of heart failure were present in 12 cases (4%).
Conclusions: ARVD/C is characterised clinically by multiple findings with an overall good prognosis. Risk factors of SCD are LV dysfunction and syncopes, a family history plays a less important role than in other forms of cardiomyopathy.

P670 Desmosomes in arrhythmogenic right ventricular cardiomyopathy: an ultrastructural investigation of intercalated discs on endomyocardial biopsy

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Background: Mutations of genes encoding intercalated disc (ID) proteins, ie plakoglobin and desmoplakin, have been found to account for both autosomal recessive and dominant inherited forms of arrhythmogenic right ventricular cardiomyopathy (ARVC). Both proteins are constituents of desmosome (D) that links the intermediate filaments network and play an important role in maintaining myocardial integrity under mechanical stress. Thus D abnormalities have been postulated to represent an ultrastructural marker of ARVC.
Material and Methods: 21 patients (10 M and 11 F, mean age 24,5$\pm$14 yrs) with an in vivo diagnosis of ARVC according to the task force criteria underwent right ventricular endomyocardial biopsy (EMB). Familiarity was present in 8 (38%). Sex and age matched EMB from pts with dilated cardiomyopathy were also evaluated. Ten EMBs from donor hearts for cardiac transplantation served as controls. EMB samples were fixed in Karnowsky/osmium tetroxide, embedded in Epon 812 and observed under a Hitachi electron microscope. IDs were evaluated in terms of convolution index, D and nexus length (micron), D and nexus percent ID length, and D and nexus number per ID unity length (10 micron). Moreover, D gap size and internal and external plaques were assessed.
Results: No major differences were found in terms of convolution index in ARVC vs dilated cardiomyopathy vs controls (2,9 vs 2,79 vs 2,7, p=NS). Mean D length, the percent D/ID length, the D number/ID unity length were higher in ARVC and dilated cardiomyopathy as compared to controls (3,38$\pm$1.47 vs 2,67$\pm$1,02 vs 2,2$\pm$0,89; 10% vs 9% vs 4%; 0,33$\pm$0,17 vs 0,37$\pm$0,11 vs 0,22$\pm$0,08, all p value $<$0.01). In ARVC, 75% presented abnormally located D and 32% pale internal plaques; widening was not visible at D level. Nexus was observed at ID more rarely in ARVC and dilated cardiomyopathy than in controls (21% vs 20% vs 75%), with a lower mean length (0,34$\pm$0,15 vs 0,40$\pm$0,15 vs 0,58$\pm$0,38, p=0,05). No correlation was found between age and any of the ultrastructural parameters investigated.
Conclusions: ARVC shows at ultrastructural level D abnormalities consisting of increased D length and number, without ID convolution changes and D gap widening. Genotype-phenotype correlation is warranted in order to establish differences among ARVC pts with and without gene mutations encoding D proteins.

P671 Isolated non-compaction of the ventricular myocardium in adults

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Background: Isolated noncompaction of the ventricular myocardium (INVM) was reported as a rare congenital cardiomyopathy predominantly found in children. INVM is characterised by thickened noncompacted myocardium and

persistence of deep intertrabecular recesses. Very few series of adults with this condition have been reported. Here we present a series of 10 adults, including two families.
Method: Patients were identified over a 12 month period in two community-based Adult Cardiac Practices. In the two families with INVM, family screening was offered after detection of the index case. All cases were verified by two independent cardiologists.
Results: Patients (5 males and 5 females) range from 13-69 years of age. Presenting symptoms included dyspnoea, thromboembolism, palpitations, syncope and cardiac arrest. Echocardiography demonstrated noncompaction of the left ventricular (LV) apex in all, with variable involvement of the periapical, inferior or lateral walls. One subject had predominant involvement of the right ventricle whilst her son had features of hypertrophic cardiomyopathy. One family which was characterised by facial dysmorphism and variable severity of INVM was notable for the correlation between the extent of INVM and associated LV systolic dysfunction among affected family members. Three affected patients had previously been misdiagnosed as having dilated cardiomyopathy, apical hypertrophy, or apical thrombus rather than INVM.
Conclusions: INVM is an important condition, which can present in adulthood with life-threatening complications. INVM is easily misdiagnosed and is of variable severity among individuals within affected families.

P672 Remodeling of gap junctions in Naxos disease: a potential mechanism of lethal arrhythmias in arrhythmogenic right ventricular cardiomyopathy

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Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) due to a deletion in plakoglobin (Naxos disease) is 100% penetrant by adolescence and is associated with high incidence of lethal ventricular arrhythmias. Plakoglobin is an intracellular protein involved in mechanical cell-cell adhesion (adherens junctions and desmosomes) at myocardial intercalated discs where the electrical coupling (gap junctions) is mainly served by connexin43 (Cx43). We tested the hypothesis that defective mechanical coupling may lead to altered electrical coupling causing intramyocardial conduction defects and ventricular arrhythmias.
Methods: Expression of plakoglobin, Cx43 and other intercellular junction proteins was studied by immunohistochemistry as well as immunoblotting and electron microscopy in myocardium of four patients with Naxos disease. Cardiac tissues were obtained at clinical (n=3) or pre-clinical (n=1) stage of ARVC.
Results: Expression of mutant plakoglobin and Cx43 was significantly reduced in right and left ventricular myocardium of all patients. Plakoglobin also failed to localize properly at intercellular junctions. Elecrton microscopy revealed smaller and fewer gap junctions. Other intercellular mechanical junction proteins as N-cadherin, desmoplakin-1 and desmocollin-2 were found to localize properly at intercalated disks.
Conclusions: In Naxos ARVC, a genetically determined defect in mechanical cell-cell junctions presumably results in early remodeling of gap junctions and defect in electrical coupling. Subsequent development of pathologic changes in myocardium with a pre-existing electrical coupling defect could create a potentially lethal arrhyhmogenic substrate.

P673 Proinflammatory and immunoregulatory pericardial cytokines in neoplastic, autoreactive, and viral pericarditis

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Background: The role of cytokines in the pathogenesis of pericarditis is not fully understood. To elucidate this issue we have analyzed proinflammatory interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha as well as the immunoregulatory cytokines (transforming growth factor (TGF)-beta1, and interferon (IFN)-gamma) in pericardial effusion and serum of patients with pericarditis and in pericardial fluid of bypass surgery patients.
Methods: Pericardial fluid was analyzed in the total of 60 patients (Group 1: 39 patients with pericarditis and large or moderate PE, undergoing pericardiocentesis, 64.1% males, 57.3±18.1 years, 43.6% neoplastic, 41.0% autoreactive, and 15.4% viral) or after sternotomy (Group 2: 21 bypass surgery patients, 42.9% males, 67.2±7.4 years). All patients underwent a comprehensive clinical, laboratory, and echocardiographic assessment. In addition to pericardiocentesis, all patients from group 1 underwent pericardioscopy (flexible endoscope AF 1101 BI, Karl Storz, Germany), and pericardial/epicardial biopsy. Selected patients with clinical indications of myopericarditis underwent also cardiac catheterization and endomyocardial biopsy (n=23/39). Pericardial fluid samples were promptly aliquoted, frozen, and stored at -70°C. The cytokines were estimated using quantikine enzyme amplified-sensitivity immuno-assays (R&D Systems, MN). Pericardial cytokines in group 1 were compared with serum levels and with pericardial cytokines in group 2.
Results: IL-6 was significantly increased in PE vs. serum in all forms of pericarditis (except in autoreactive) and increased in comparison to pericardial fluid of by-pass surgery patients. TNF-alpha was increased only in PE of patients with viral pericarditis in comparison to Group 2. TGF-beta1 was strikingly lower in the PE than in the serum of all pericarditis patients. However, TGF-beta1 levels in PE were significantly higher in Group 1 than in Group 2, except in viral pericarditis. IFN-gamma levels did not significantly differ between PE and serum or in comparison to Group 2.
Conclusions: The pattern "high TNF-alpha/low TGF-beta1" was found in viral pericarditis and low IL-6 in autoreactive PE. Different etiologies of pericardial inflammation did not influence the IFN-gamma levels.

P674 Hyperimmunoglobulin treatment is effective in CMV myocarditis – a controlled treatment trial

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Background: Treatment of virus-postive myocarditis is an unresolved problem. We therefore carried out a controled trial with 35 cytomegalovirus (CMV) positive myocarditis patients having an lymphocytic infiltrate(>14 leukocytes/mm^2) and a positive in situ hybridization and/or PCR for CMV-DNA in the endomyocardial biopsy with CMV hyperimmunoglobulin (CMVhIg).
Methods: 18 pts received 2ml/kg i.v. for 3 and 1ml/kg for 2 additional 2 days alternately.
Results: An elimination of cellular infiltrates was seen in 14 out 18 pts (P<0,01) and of CMV-DNA 13 out of 18 pts (p<0.01), which went along with a significant improvement of the at least one NYHA class(15/18) and normalized EF(15/18) of the patients in the treatment group. The control group (n=17, CMV-DNA i.s.- or PCR-positive myocarditis, no CMVhIg) demonstrated spontaneous improvement by 1 NYHA class or more in 3 out 17 pts and by EF in 7 out of 18 pts. A spontaneous resolution of the infiltrate occurred in 4/17 and negativity of CMV-DNA in 3/17. Comparing the 2 groups the effect of treatment was striking (p<0.05 for elimination of CMV and infiltrate and improvement of 1 NYHA-class). Because of the potential risk of HIV or hepatitis infection with plasma products serum titers of cardiotropic viruses were analysed before and after treatment. All treated patients had high CMV-IgG titers before treatment, which increased during therapy, IgM antibodies were detectable only in 3 pts initially. Only transiently rising titers for CVB in 2 and for influenza in one case as passive transfer were seen. No infection of HIV or hepatitis A,B,C and D were found.
Conclusion: CMV-hIg treatment eliminates CMV-DNA and inflammatory cells effectively from the myocardium. CVB, HIV and hepatitis infection could be excluded after therapy with CMV-hIg.

P675 Biopsy-proven myocarditis: prognostic relevance of clinical and etiopathogenetic features at diagnosis

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Acute myocarditis (My) may be idiopathic, viral and/or immune; frequency of these forms and prognosis are ill defined.
Purpose: We assessed frequency of My forms and prognostic significance of clinical and etiopathogenetic features at diagnosis (dgn), including histology, viral genome and anti-heart autoantibodies (AHA).
Methods: We studied 149 My patients (pts), 94 males, aged 36 ± 18 years, 86 in NYHA I-II, 63 III-IV, follow-up (f-u) 34 ± 39 months. Left ventricular ejection fraction (LVEF) by 2-dimensional echocardiography (2-D echo) and at cardiac catheterization (CC) were 43 ± 15% and 47 ± 19% respectively. Coronary angiogram was always normal. On endomyocardial biopsy (EMB) 83 pts had active, 66 borderline My (Dallas criteria) (138 lymphocytic, 5 giant cell, other in 6). AHA were detected by indirect immunofluorescence on human myocardium and skeletal muscle. Polymerase chain reaction (PCR) was used to detect viral genome on EMB. Features at dgn, including AHA and PCR, were included in both univariate and Cox regression analysis for death or transplantation.
Results: At f-u 106 pts were alive, 23 dead or transplanted, 20 lost; 101 pts were in NYHA I/II, 5 in III, with LVEF of 56 ± 11%. Actuarial survival (Kaplan Meier) was of 79% at 3 years and was lower (p=0.007) in giant cell My. AHA were found in 60/109 (55%); in 25/95 (26%) pts PCR was positive for virus. My was autoimmune, with negative (neg) PCR, positive (pos) AHA in 47% of pts, viral (pos PCR, neg AHA) in 9%, viral and immune (pos PCR, pos AHA) in 12%, idiopathic and/or cell-mediated (neg PCR, neg AHA) in 32%. By univariate analysis AHA was associated with higher RV systolic pressure (p=0.04); positive PCR with worse NYHA (p=0.01), longer symptom duration (p=0.003), higher mean right atrial pressure (mRAP) (p=0.008) and lower LVEF (p=0.02). Univariate predictors of death/transplantation were: NYHA II-IV (p=0.003), presentation with LV dys-

function (p=0.002), higher mRAP (p=0.0001), lower LVEF at CC (p=0.0001) and 2-D echo (p=0.001). Independent predictors of increased mortality risk were right ventricular end-diastolic pressure >5mmHg (RR 5.9, p=0.02) and LVEF <41% (RR 10, p=0.03), but not AHA or PCR.
Conclusions: In biopsy-proven My the degree of biventricular dysfunction at dgn was the main independent negative predictor in the mid-term. AHA identified immune-mediated My in at least 2/3 of cases. The potential role of etiology (e.g. viral vs immune) as additional independent predictor remains to be clarified in the long-term.

P676 Autoantibodies against beta1-adrenergic receptor in sera of patients with peripartum cardiomyopathy: functional characterisation

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Background: Peripartum cardiomyopathy (PPCM) is a disorder of unknown etiology characterised by acute onset of heart failure in the peripartum period. Although rarely observed in western countries, PPCM has an incidence of 1:1000 in South African women. Agonist-like autoantibodies (AAB) have been shown to activate the beta1-adrenergic receptor (beta1-AR) cascade in cardiomyocytes inducing a long-lasting stimulatory effect which results in harmful adrenergic overdrive. AAB against beta1-AR may play a role in the pathogenesis of dilated cardiomyopathy (DCM). The prevalence of beta1-AR in patients with PPCM is unknown.
Methods: AAB against G-protein coupled receptors were measured in serum samples from 10 PPCM patients, 10 DCM patients, and 5 healthy controls from South Africa. Spontaneously beating cultured neonatal rat cardiomyocytes were used as a "bioassay".
Results: Sera of all PPCM and DCM patients investigated had AAB directed against the beta1-AR - healthy controls did not. The agonistic effect was dose-dependent and specifically blocked by beta1-AR antagonists. The effect was neutralized by peptides corresponding to the first or second extracellular loop of the human beta1-AR. Sera of PPCM patients contained exclusively AAB against the second extracellular loop, while sera of DCM patients contained AAB against the first (30%) and the second extracellular loop (70%). The identified AAB epitopes (RAESDE and DEARRCY) on the second extracellular loop of the PPCM patients differed from that of the DCM patients (ARRCYND and PKCCDF). AAB of PPCM patients were identified as immunoglobulins of the IgG2 and IgG3 subclasses. AAB against the second extracellular loop of DCM patients were subclassified as immunoglobulin G2. DCM AAB and PPCM AAB caused a long-lasting agonistic effect without down-regulation of beta1-AR response. Moreover, AAB prevent desensitisation of the receptor during co-incubation with the beta-adrenergic agonist isoprenaline.
Conclusion: 1. Agonistic beta1-AR agonist-like autoantibodies of PPCM patients may play a role in the pathogenesis of PPCM, similar as the AAB in DCM patients. 2. The identified AAB epitopes (RAESDE and DEARRCY) on the second extracellular loop of PPCM patients differed from those of DCM patients (ARRCYND and PKCCDF).

P677 Circulating tenascin-c levels are increased in patients with idiopathic dilated cardiomyopathy

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Background: It is suggested that tenascin-C, an extracellular matrix glycoprotein, contributes to the development of myocardial remodeling in idiopathic dilated cardiomyopathy (DCM). However, it remains unclear whether circulating tenascin-C levels are increased in DCM.
Methods and Results: We measured serum tenascin-C levels using an enzyme immunoassay kit in 31 patients with DCM (26 men and 5 women, mean age of 63±17 years) and compared the levels with left ventricular (LV) function and levels of brain natriuretic peptide (BNP), cardiac troponin T (a marker of ongoing myocardial damage) and procollagen type III amino-terminal peptide (PIIINP; a marker of collagen synthesis). We also measured serum tenascin-C levels in 20 age- and sex- matched controls. Patients with DCM had a higher tenascin-C level than control individuals (68.5±32.5 versus 39.9±13.7 ng/ml, P=0.0005). Serum tenascin-C levels were increased according to NYHA functional class (r=0.53, P=0.004) and correlated negatively with LV ejection fraction (r=-0.48, P=0.006) and positively with LV end-systolic diameter (r=0.40, P=0.03) as well as BNP levels (r=0.61, P=0.0002). Levels of tenascin-C were higher in patients with detectable cardiac troponin T (>0.01 ng/ml) than in those without it (98.8±26.6 versus 56.1±26.1 ng/ml, P=0.0003). Serum tenascin-C and PIIINP levels positively correlated (r=0.37, P=0.04).
Conclusions: Serum tenascin-C levels are increased in proportion to the severity of LV dysfunction in patients with DCM. The associations of serum tenascin-C levels with serum troponin T and PIIINP levels suggest that increased levels of serum tenascin-C indicate ongoing replacement fibrosis following myocardial damage in DCM.

P678 Danons disease as a cause of hypertrophic cardiomyopathy: a systematic genetic screening

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Background: Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease caused by mutations in sarcomeric genes. However, extensive genetic screening failed to identify a mutation in about 1/3 of cases. One possible explanation is that other diseases, caused by other genes, may mimic HCM.
Objective: To investigate the possible involvement of Danon's disease, an X-linked lysosomal disease associated with left ventricle hypertrophy, in a large population of patients with HCM.
Methods: A population of 197 index-cases was considered; 124 were subsequently excluded because of a mutation in sarcomeric genes, and 23 because of autosomal dominant inheritance. Fifty index-cases were therefore included in the molecular analysis (direct sequencing) of the LAMP-2 gene responsible for Danon's disease.
Results: Two new mutations leading to premature stop codons were identified in patients who developed severe heart failure (<25y.): 657C>T and 173_179del. The prevalence was therefore 1% of the total population (2/197) or 4% of enrolled index-cases (2/50). Interestingly, Danon's disease was responsible for half of the cases (2/4) with HCM and clinical skeletal myopathy, but was not involved in isolated HCM (0/41).
Conclusions: Danon's disease may be involved in patients previously diagnosed as HCM. A diagnosis strategy is proposed. To distinguish HCM from Danon's disease is important because the clinical evolution, prognosis, mode of inheritance, and therefore genetic counseling, are very different.

P679 Clinical and morphological evolution of MYBPC3-related hypertrophic cardiomyopathy: evidence of an association with systolic dysfunction and end-stage progression

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Purpose: We studied the clinical and genetic features of hypertrophic cardiomyopathy (HCM) caused by mutations in the Cardiac Myosin-Binding Protein C gene (MYBPC3) in 124 consecutive, unrelated patients with HCM. More than 200 mutations in nine different genes encoding sarcomere proteins have been identified in HCM patients. Mutations in MYBPC3 the represent the cause of HCM in about 15% of familial cases; studies on Japanese and French families have shown that HCM caused by MYBPC3 mutations may have a delayed onset and is usually benign. However, genotype-phenotype relationship in other populations remains unclear.
Methods: All 35 exons of MYBPC3 were screened by DHPLC followed by automatic sequencing. The diagnosis was based on two-dimensional echocardiographic identification of a hypertrophied, non dilated left ventricle, in the absence of another cardiac or systematic disease capable of producing the magnitude of wall thickening evident.
Results: Overall, we identified 22 MYPC3 mutations in 19 patients (a 15% prevalence). Fifteen mutations (68%) were novel (IVS18+1C>T, A522T, V771M, E165D, ins/del exon 25, V189I, G531R, D786Y, R273H, E334K, R470W, Y340X, A693S, IVS12+1G>A, IVS24-2A>G) and not detectable in 100 normal controls, thus excluding the possibility of polymorphisms; three patients (16%) had two mutations affecting MYPC3, a condition termed compound heterozygosis; specifically, these were A522T with V771M, E334K with R470W, and D786Y with A693S. Average age at diagnosis in the 19 patients was 41.3±14.6 years; 8 (42%) were female. Echocardiographic features and outcome were variable, and ranged from mild hypertrophy with total lack of symptoms to severe hypertrophy with severe outflow obstruction, to end-stage progression, to cardiac arrest. Of note, evidence of systolic impairment (ejection fraction <0.50) was present in a high proportion of patients (n=5, 23%; p<0.05 versus the overall study group).
Conclusions: In a regional HCM population from Central Italy, MYBPC3 mutations were common (15% of unrelated patients); were associated with a broad spectrum of clinical and echocardiographic manifestations, with a high prevalence of systolic impairment; and had different mechanisms (missense, nonsense, insertion/deletion, splice-site). Most of the mutations were novel including those found in the three patients with compound heterozygosis.

P680 Assessment of coronary microvascular function in patients with tako-tsubo-like left ventricular dysfunction (transient left ventricular apical ballooning)

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Background: Tako-tsubo-like transient left ventricular (LV) dysfunction is charac-

terized by acute onset and reversible LV wall motion abnormalities without significant stenosis on coronary angiography. The precise mechanism of this syndrome is still unclear, but coronary microvascular dysfunction has been reported to be one of the possible mechanisms of this syndrome. The purpose of this study was to evaluate coronary microvascular function by measuring coronary flow velocity (CFV) pattern and CFV reserve (CFVR), using Doppler guidewire, in patients with tako-tsubo-like LV dysfunction.
Methods: We examined 11 consecutive patients (10 women and 1 man; mean age, 71 ± 11 years old) who were diagnosed to be tako-tsubo-like LV dysfunction according to the following criteria: 1) LV wall motion abnormality at the apex on left ventriculography; 2) ST-segment elevation or T-wave abnormality at least 2 leads on the ECG; 3) no prior history of myocardial infarction; 4) normal coronary angiogram. We excluded patients with subarachnoid hemorrhage, pheochromocytoma crisis, atrial fibrillation, severe valvular heart disease and post-tachycardia condition. Immediately after admission and 3 weeks later, left ventriculography and coronary angiography were performed. After LV apical wall motion abnormality and normal coronary angiogram were confirmed, CFV was recorded at the middle portion of the coronary artery with a 0.014-inch Doppler guidewire at rest and during hyperemia induced by an intravenous injection of 0.15mg/kg/min adenosine 5'-triphosphate.
Result: LV ejection fraction improved dramatically during follow-up period (47 ± 9 versus 65 ± 11%, $p<0.001$) mainly due to reduction of LV end-systolic volume (36 ± 9 versus 23 ± 11 ml, $p<0.05$). Deceleration time of diastolic CFV (DDT) and CFVR increased in all cases during follow-up period (457 ± 178 versus 882 ± 211 msec, $p<0.0001$ and 1.7 ± 0.5 versus 2.6 ± 0.6, $p<0.0001$, respectively). DDT in the acute phase was correlated with the LV ejection fraction and LV end-systolic volume index at 3 weeks later ($r=0.82$, $p=0.01$ and $r=0.85$, $p<0.01$, respectively).
Conclusion: Transient coronary microvascular dysfunction demonstrated by rapid DDT and restricted CFVR might be considered to be a main mechanism of tako-tsubo-like transient left ventricular dysfunction. DDT in the acute phase can predict the recovery of LV function.

P681 Effects of autoantibodies from patients with dilated cardiomyopathy by immunoadsorption on neonatal rat cardiomyocytes

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Immunoadsorption (IA) has been shown to induce hemodynamic improvements in patients with idiopathic dilated cardiomyopathy (DCM, n=7) at Sahlgrenska University Hospital. However, the mechanism for this improvement remains to be elucidated.
Aim & methods: The present study was aimed to investigate the effects of autoantibodies from patients with DCM by IA on cultured neonatal rat cardiomyocytes. The beta-1 adrenoceptor (beta-1 AR) and M2 muscarinic receptor (M2R) autoantibodies from column eluents (CE) were determined by enzyme-linked immunosorbent assay (ELISA). MTT assay was used for the detection of Complement
-Dependent Cytotoxicity (CDC) by CE (IgG 1mg/ml) on neonatal rat cardiomyocytes. IgG from healthy blood donors was used as control group. Apoptosis was detected by Annexin V test and TUNEL test. Chronotropic effect on cultured neonatal cardiomyocytes was also measured.
Results: In CE, the frequency of occurrence of beta-1 AR and M2R autoantibodies was 43% and 29% respectively. With complement and IgG, the CDC killing rate for neonatal cardiomyocytes was 23.2% higher in DCM group than that in control group (39.5±6.5% vs. 16.3±8.9%, $p<0.05$). Meanwhile, complement alone did not reduce the viability of cardiomyocytes (MTT OD value: 0.212±0.024 vs 0.212±0.013 in PBS control, $p>0.05$). Neither CE from patients nor control IgG increased the lactate dehydrogenase (LDH) releasing in the supernatant without complement (0.265±0.025 vs 0.256±0.012, $p>0.05$). Apoptotic cells was increased after incubation for 24h with CE from patients(11.2±1.0% in IgG 2mg/ml vs 3.1±0.5% in control group, $p<0.05$). With IgG (1mg/ml) from CE, 57% displayed positive chronotropic effects whereas 14% induced negative chronotropic effects. Moreover, arrhythmia was observed in 26% of tests using CE.
Conclusion: Autoantibodies removed from patients with DCM were able to induce CDC and apoptosis as well as chronotropic effects on cardiomyocytes in vitro. These mechanisms are possibly involved in the hemodynamic improvement by IA. CDC activities on cultured cardiomyocytes may act as a useful follow-up index to measured the autoimmune function of autoantibodies in CE or serum.

P682 Downregulation of full length tissue factor and its soluble isoform in patients with dilated cardiomyopathy

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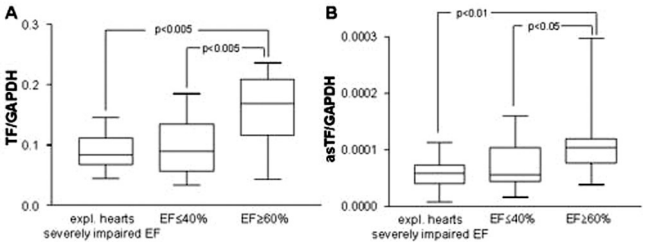
Introduction Tissue factor (TF), the cofactor of coagulation factor VII, plays a crucial role in many other fields besides hemostasis. In the myocardium, TF has been localized in intercalated discs in proximity to structural proteins responsible for maintaining cardiac muscle function. Real-time PCR was performed to investigate the expression pattern of TF and its soluble, alternatively spliced isoform (asTF) in human hearts from patients with normal and impaired ejection fraction (EF).
Methods: RNA extracted from biopsies and explanted hearts was quantified by real-time PCR (Taqman®). Patients were divided into two groups: group one (n=16) included patients with EF≥60%, group two (n=22) patients with EF≤40%. Explanted hearts from patients with dilated cardiomyopathy (DCM) were also examined (n=12). Immunohistochemistry for TF and asTF was performed.
Results: We report for the first time the identification of asTF in human hearts. Myocardial expression of TF and asTF in the biopsied DCM patients decreased both to 53.0% (Fig. 1A+B). Compared to the level in patients with normal EF, TF mRNA levels in explanted DCM hearts were also decreased to 49.5% for TF (Fig. 1A) and to 56.3% for asTF (Fig. 1B). A positive correlation was found between the TF/GAPDH mRNA ratio and the EF in the patients included ($r=0.558$, $p\leq0.001$). In addition, reduction in TF expression was associated with a redistribution of the TF antigen from the Z-bands into the cytosol of the cardiomyocytes, raising the possibility that reduction and redistribution of TF may affect cell-to-cell apposition in the myocardium.



Conclusion: Downregulation and dislocalization of myocardial TF may affect cell to cell stability and contribute to myocardial dilation and contractile dysfunction in DCM.

COMPUTED TOMOGRAPHY: IMAGING OF CORONARY ARTERIES

683 Assessment of coronary arteries and detection of severe lesions using the latest multislice detector computed tomography with 370 msec gantry rotation time

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Background: Just recently, a new multi-slice detector computed tomography (MDCT) scanner generation with 16 detector-slices and 370 msec gantry rotation time (temporal resolution: 185 msec) has become available. The aim of our study was to evaluate its feasibility, image quality and clinical accuracy in detecting coronary artery lesions.
Methods: 59 unselected, consecutive patients (pts, age:63±9 years) with clinical suspicion of coronary artery disease (CAD) referred to our institution to undergo conventional coronary angiography (CCA) were additionally studied by MDCT (Siemens Sensation 16 Speed 4D ™). Native as well as contrast enhanced scans were performed in all pts. MDCT scans were analyzed regards image quality, presence of coronary artery lesions and correct clinical diagnosis.
Results: All 59 MDCT scans showed sufficient image quality (mean heart rate after β-blockade: 57±10[40-84] bpm). The mean calcium mass was 77±158 [0-853] mg/cm^3. 13 coronary segments (sgts) were evaluated in each patient (total number: 767 sgts). No sgts were excluded from the analysis. A total number of 83 lesions with a diameter stenosis >50% were detected using CCA. 79/83 (95%) of these plaques could be detected by MDCT, but only 55/83 (66%) were correctly classified as severe lesions. Sensitivity, specificity, positive and negative predictive value were 93%, 96%, 69%, 99% for the detection of lesions, and for the correct quantitative classification 66%, 96%, 69%, 96%. The correct clinical diagnosis (presence or absence of CAD) could be obtained in 54/59 (92%) of all pts.
Conclusions: MDCT image quality could be furthermore improved with true 16-slices and faster gantry rotation time. This technology allows for a visualization of the entire coronary tree with sufficient image quality. Although the vast majority of significant coronary lesions can be detected by MDCT, a correct quantification of stenosis severity remains a problem. Based on our results in an unselected consecutive cohort, MDCT appears to be appropriate to exclude the presence of coronary artery disease. In case of detectable lesions, however, an invasive coronary angiography appears to be mandatory.

684 Myocardial bridges of the left anterior descending artery – diagnostic possibilities of the ECG-gated multi-slice computed tomography

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Background: Myocardial bridges are very interesting and still not thoroughly investigated cardiac anomaly. They can be observed during coronary angiography (about 1.5% of examinations) and more frequently in autopsy. The left anterior descending artery (LAD) is the vessel affected in almost all cases. The significance of myocardial bridges is still discussed- they may be clinically silent or can cause ischemic episodes or even sudden cardiac death. Identification of the presence and evaluation of the severity of myocardial bridge is of clinical importance.
Purpose: To evaluate the usefulness of ECG-gated multi-slice computed tomography (MSCT) in detection and assessment of changes accompanying the myocardial bridges in LAD.
Methods: The analysis included MSCT examinations of 142 consecutive patients with symptoms of ischemic heart disease. Angiography of the coronary arteries (MSCTA) was conducted with retrospective ECG-gating and single- and multisegment reconstruction algorithms, depending on heart rate (GE Medical Systems 8-row tomograph LightSpeed Ultra, workstation Advantage Window 4.0). The whole examination consisted of calcium score evaluation, test bolus and MSCTA with collimation 8x1.25mm (iv 120-150ml Ultravist, 4ml/s). The secondary reconstructions were performed in phases 15-85% R-R.
Results: In 12 cases of the examined group (8.5%) the myocardial bridges of LAD were detected. The length of abnormal segments was 5-55mm, the thickness of the muscular layer covering the artery 1-7mm. In 10 cases stenosis of the lumen was observed only in the systolic phase and in 4 cases the lumen compression was also found in the diastolic phase. The accompanying coronary artery changes were presented as well as protocols of multiplanar reformations, 3D volume rendering reconstructions and Advanced Vessel Analysis.
Conclusion: ECG-gated MSCT in patients with symptoms of ischemic heart disease may be a useful, non-invasive method to detect myocardial bridges in LAD and to evaluate signs and degree of lumen systolic and diastolic stenosis as well as the atherosclerotic lesions.

685 Diagnostic possibilities of ECG-gated multi-slice computed tomography in the diagnosis of coronary artery anomalies

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Anomalies of coronary arteries constitute about 0.6-1.2% of cases and up to date have been detected with the invasive method of coronarography.
The aim of the paper is to present the diagnostic possibilities of coronary artery angiography using ECG-gated multi-slice spiral computed tomography (MSCTA) as a non-invasive method of detecting and evaluating the morphology of lesions in patients with various types of coronary artery anomalies.
Material and methods: The paper presents the results of MSCTA performed in 22 patients with ischeamic heart disease symptoms, in whom coronarography or MSCTA revealed various anomalies of the coronary arteries. The CT examinations were conducted using the 8-row tomograph LightSpeed Ultra (GE). The coronary calcification index was evaluated using ECG-gated axial scanning and scanning after iv contrast medium bolus - 130-150ml (collimation 1.25mm, rotation time 0.5s and table feed 3, 3.5mm/s). Prior to examination, 17 patients were administered oral beta-blockers. The delay time was determined using the test bolus and SmartPrep technique.
Results: The paper presented the MSCTA image of particular types of anomalies: LCX arising from RCA, ectopic ostium of the trunk of the left or right artery from the opposite Valsalva sinus, separate ostium of LAD and LCX, lack of LCX and coronary fistulas and intramuscular course of the anterior descending artery. Moreover, the paper discussed the possibilities of evaluating the anomalous course of arteries and their relation to the surrounding structures of the heart as well as the detected atherosclerotic lesions in multiplanar reformations and 3D volume rendering technique, depending on the phase of the heart cycle.
Conclusions: MSCTA is a useful non-invasive method which may be used to detect and evaluate coronary artery anomalies.

686 The accuracy of 4-slice computer tomography and 16-slice computer tomography in the detection and quantification of significant (50%) coronary artery stenosis in comparison with coronary angiography

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Material and methods: Between January 2001 and January 2004, 126 patients (56 women and 70 men, mean age 62 SD 16 years) with stable effort angina were included in a prospective blinded study. All patients underwent MSCT and coronary angiography in the consecutive five to seven days. MSCT was performed on a MSCT scanner Somatom Plus 4 Volume Zoom – 90 pts (47 M and 43 W) and Sensation Cardiac 16 (Siemens, Erlangen, Germany) 36 pts (13 W, 23 M). CCA was obtained using an angiographer Coroscope (Siemens, Germany) (QCA). The quantification of stenosis by MSCT was done in each coronary segment by 2D and 3D reconstruction (curved MPR, 5 mm thin MIP, VRT). In 16 slice MSCT quantitative analysis was performed using the Vessel View software. 559 coronary artery segments were assessed by 4 slice MSCT, 225 segments by 16 slice MSCT (1,2,5,6,7,11,12). Statistical analysis: the 95% confidence intervals (CI) for the proportions were calculated using the exact binomial method.
Results: In the group of 4 slice CT 161 (28.8%) segments out of 559 had significant stenosis ($>$ 50%) as determined by CCA. The total true negative results were 323, true positive - 135, false negative - 26, false positive 75. The sensitivity and specificity were 83.8% and 81.1% respectively. The positive predictive value was 64%, negative predictive value 92.5%.
In the group of 16 slice CT 49 (21%) segments out of 225 had significant stenosis ($>$ 50%) as determined by CCA. The total true negative results were 171, true positive - 43, false negative - 5, false positive 6. The sensitivity and specificity were 89% and 96% respectively. The positive predictive value was 97%, negative predictive value 92.5%.
Conclusion: 16-slice is better than 4-slice MSCT as a tool for non-invasive detection of coronary stenosis in proximal and medial segments of the arteries. This method may be an interesting alternative in patients with high-risk angiography.

YOUNG INVESTIGATORS' AWARD SESSION – BASIC SCIENCE

688 Increased anisotropy of conduction associated with changes in Connexin43 expression and distribution following localised in situ ventricular stretch

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Background: Stretch has been implicated in the mechanism of ventricular arrhythmias in both left ventricular hypertrophy and following myocardial infarction. Connexin43 (Cx43) expression is increased by stretch in cell culture.
Hypothesis: In situ localised stretch alters local Cx43 distribution and expression, reflected in changes in the anisotropy of conduction.
Method: In 8 open chest dogs a custom built stretch device was applied to the right ventricle (RV). The four feet at the corners of a square device are attached to the RV by suction and then localised stretch applied, for 6 hours, by splaying the legs outwards increasing the diagonal distance from 1.3cm to 1.9cm. Epicardial mapping using a 320 electrode plaque with central pacing was used to map conduction in the target area before and after the stretch period. Quantitative Cx43 Western blotting and immunohistochemistry were performed on tissue from the stretched RV, unstretched RV and left ventricle.
Results: Longitudinal conduction velocity (LCV) was unchanged following stretch (57.2 ± 8.3 vs 52.1 ± 5.8 cm/s $p<0.26$), but transverse conduction velocity (TCV) was significantly reduced (37.1 ± 5.1 vs 28.3 ± 2.8 cm/s $p<0.01$). In the stretched area there was redistribution of the Cx43 labelling from the terminal intercalated disks to the lateral cell borders, with an increase in the semi-quantitative lateralisation score from unstretched RV, 1.75 ± 0.46, to 3.1 ± 1.09 in stretched RV ($p<0.02$). The distribution of Cx43 retained the normal pattern seen in adult myocardium, in all other regions. In Western analysis, stretched RV Cx43 expression showed a near-significant reduction compared to unstretched RV ($p<0.06$). In comparing RV with LV epicardium, Cx43 expression was reduced by 23% in the stretched RV (but not unstretched RV) compared to LV epicardium ($p<0.01$).
Conclusion: Localised stretch led to a reduction in TCV but not LCV, associated with Cx43 redistribution and an overall reduction in expression. This enhanced anisotropy of conduction may increase the tendency to reentry

689 Allopurinol, a xanthine oxidase inhibitor, attenuates myocardial oxidative stress and left ventricular remodeling and dysfunction after experimental myocardial infarction

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Background: Accumulating evidence suggests a critical role of increased reactive oxygen species (ROS) production in left ventricular (LV) remodeling and dysfunction post-myocardial infarction (MI). Xanthine oxidase (XO) has been identified as source of superoxide anions in cardiovascular tissue and increased expression of XO has been demonstrated in experimental and clinical heart failure. However, a potential role for LV-remodeling processes remains unclear. We therefore studied the effect of chronic XO-inhibition with allopurinol on myocardial ROS production and LV remodeling and dysfunction post-MI.
Methods: In 105 male C57BL/6 mice MI was induced by ligation of the left anterior descending artery. On day one after MI mice were 1:2-randomised to treat-

ment with allopurinol (20mg x kg-1 qd by gavage, n=35) or placebo (n=70) for 30 days. 13 sham-operated mice served as controls. Animal experiments were approved by the local animal research committee. Myocardial XO expression was determined by western blot and XO activity was analysed by electron spin resonance spectroscopy (ESR) using the spin trap CP-H. Superoxide production was measured using the superoxide dismutase-inhibitable cytochrome c-reduction assay, and dihydroethidium fluorescence staining. Echocardiography was performed before and 4 weeks after MI. Stained LV tissue sections were assessed by histomorphometry.

Results: XO-protein expression was increased by >1.4-fold in the remote LV-myocardium post-MI as compared to sham-operated mice, and XO-activity was increased (7.9±1.5 vs. 4.4±0.9nmol O2.- x μg protein-1 x min-1, $p<0.05$). In mice post-MI treated with allopurinol XO-activity of remote LV-myocardium was substantially inhibited (0.8±0.3nmol O2.- x μg protein-1 x min-1; $p<0.01$). Superoxide production was increased in remote LV-myocardium post-MI. There was a significant reduction of superoxide production in the remote LV-myocardium post-MI after allopurinol treatment. LV-end-diastolic diameter was reduced after allopurinol treatment post-MI as compared to placebo-treated mice (4.9±0.2 vs. 6.6±0.2%; $p<0,05$), and LV-ejection fraction improved (33.4±4.7 vs. 19.6±4.5%; $p<0,05$). Myocardial hypertrophy and interstitial fibrosis were reduced in the allopurinol group post-MI. The infarct size was similar in both groups.

Conclusion: This study demonstrates a novel beneficial effect of allopurinol on LV-remodeling processes after experimental myocardial infarction, which resulted in an improved LV-function possibly mediated by reduced myocardial xanthine-oxidase activity and ROS production.

690 Ablation of phospholamban in SERCA2b/b mice reverses impairment of Ca^{2+} uptake into the sarcoplasmic reticulum despite reduction in SERCA levels

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In the hearts of gene-targeted mice with a defect in the SERCA2a-specific mRNA splicing, SERCA2a is substituted with SERCA2b (SERCA2b/b); the total levels of SERCA are decreased while phospholamban (PLB) expression is increased. In SERCA2b/b the maximal sarcoplasmic reticulum (SR) Ca^{2+} uptake is reduced, but its affinity for Ca^{2+} is increased. Cardiomyocytes from SERCA2b/b have a slowed relaxation in particular at high Ca^{2+} loads. To examine the importance of the PLB upregulation, SERCA2b/b were cross-bred with PLB-/- (double knock-outs, DKO). Total SERCA levels were further reduced in DKO (SERCA2b/b -43±6%, DKO -70±3%, vs. wildtype, WT). Yet relaxation in field-stimulated DKO myocytes (0.5 Hz, unloaded shortening) was faster in DKO (Tau 39.2±3ms, $P<0.05$ n=17) than in WT (68.1±5ms, n=13) and in SERCA2b/b (88.5±8ms, $P<0.05$ n=21). Similarly, decline of Ca^{2+} transients was significantly faster in DKO (Tau of 93±7ms, compared to 297±27ms in SERCA2b/b, 225±18ms in WT). Myocyte contraction amplitudes were larger in DKO (9.6±0.8% cell length vs. 4.9±0.6% cell length in SERCA2b/b, $P<0.05$). SR Ca^{2+} content assessed with caffeine application in cells under voltage clamp was larger in DKO (198±39μM, n=8) than in WT levels (128±9μM, $P<0.05$ n=7); there were no differences in ICaL. We further examined function at markedly increased Ca^{2+} loads when Ca^{2+} removal by the Na^+/Ca^{2+} exchanger was prevented with Na^+-free internal and external solutions. Repeated depolarizing steps from -70 to 0 mV (0.25 Hz) eliciting Ca^{2+} influx via the L-type Ca^{2+} channel resulted in increasing cellular and SR Ca^{2+} loading. In DKO myocytes, relaxation time of Ca^{2+} transients increased slightly with time in 0 Na^+ (RT50=89±15ms after pulse 0 vs. 124±15ms after pulse 5, $P<0.05$), but remained significantly faster than in WT (RT50=250±13ms after pulse 5, $P<0.05$) despite intracellular [Ca^{2+}] in excess of 1200 nM. These observations are in sharp contrast to the markedly impaired SR Ca^{2+} uptake previously observed in SERCA2b/b.

Conclusions: PLB ablation can compensate for a reduction of SERCA protein by more than 50%, to the extent that relaxation rates and SR Ca^{2+} stores are increased beyond WT levels. This suggests that the modulation of SERCA by PLB is more important than the actual protein level, and supports the principle that PLB might be a major target for therapy.

691 TIMP-3 over-expression via the stent-based delivery of adenovirus inhibits neointimal formation by promoting smooth muscle cell apoptosis

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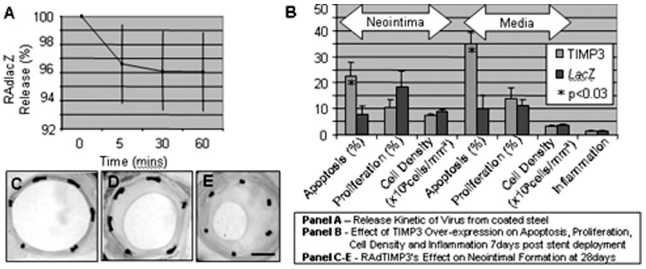
Background: Therapeutic prevention of restenosis has advanced rapidly in the last few years following the advent of drug-eluting stents. However, some doubt exists about the use of anti-mitotic agents to broadly disrupt vascular remodelling and recent reports have revealed problems regarding late acute thrombosis, delayed re-endothelisation and stent mal-apposition. Our current study investigates a biologically targeted approach to inhibiting neointima formation using a therapeutic gene, tissue inhibitor of metalloproteinase-3 (TIMP-3), delivered via an adenoviral vector carried on a commercially available 'eluting stent'.

Methods and Results: Efficient viral-stent binding and release (Panel A) combined with effective cell and tissue transfection have been confirmed invitro. Immunohistochemical analysis for TIMP3 demonstrated localised overexpression confined to sites of invivo delivery, this was associated with a significant increase in apoptotic activity but did not result in an enhanced inflammatory response or proliferative activity (Panel B). This biological effect translated into a significant reduction in neointima formation at 28 days - Neointimal Area 1.27±0.42mm^2 with TIMP3 stents (Panel C) vs. 2.62±0.69mm^2 with RAdlacZ stents (Panel E), $p<0.001$, and 2.12±0.44 mm^2 with bare stents (Panel D), $p<0.005$.



Conclusions: This is the first report demonstrating effective stent-based gene delivery producing significant inhibition of neointimal proliferation. Our results demonstrate the feasibility of gene-eluting stent technology and highlight TIMP-3 as a potential therapeutic gene.

YOUNG INVESTIGATORS' AWARD SESSION – THROMBOSIS

693 Inhibition of platelet activation in rats with severe congestive heart failure by treatment with an endothelial NO-synthase transcription enhancer

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Background: Increased risk of thrombembolic events in congestive heart failure (CHF) has been attributed to a hypercoagulable state including vascular endothelial dysfunction and reduced formation of nitric oxide (NO) as well as platelet activation. Phosphorylation of platelet vasodilator-stimulated phosphoprotein (VASP) reflects the integrity of the NO/cGMP-signalling pathway. VASP-phosphorylation also functions as a key regulator of the initial sequences of platelet activation.

Methods and Results: After experimental myocardial infarction, male Wistar rats were treated with either placebo or the endothelial NO synthase (eNOS)-transcription enhancer (S2431) for 10 weeks. Only in rats with severe CHF (LVEDP>15 mmHg), endothelial NO formation and platelet VASP-phosphorylation were significantly reduced. Platelet surface-expression of P-selectin and glycoprotein 53 were increased compared with sham-operated animals.

In CHF rats, chronic treatment with S2431 significantly enhanced platelet VASP-phosphorylation (mean immunofluorescence at Ser157: Placebo: 44.8±6.5, S2431: 64±8.1, $p<0.05$; Ser239: Placebo: 13.2±0.6, S2431: 18.1±2.5, $p<0.05$). In parallel, platelet surface-expression of P-selectin and glycoprotein 53 was reduced in the treatment group (P-selectin: placebo: 98.2±14.1, S2431: 43.2±12.4, $p<0.05$; glycoprotein 53: placebo: 14.9±1.0, S2431: 12.7±0.7, $p<0.05$).

Conclusions: Platelet activation was evident in CHF rats. Therapy with the eNOS-transcription enhancer S2431 reduced increased platelet activation in parallel to normalisation of platelet NO bioavailability.

694 Genetic regulation of the platelet ADP response

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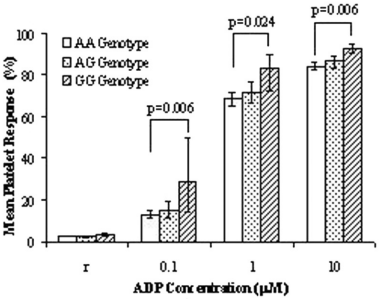
Background: The platelet adenosine diphosphate (ADP) receptors, P2RY1 and P2RY12, play a pivotal role in platelet aggregation. There is marked inter-individual variation in platelet response to ADP. The purpose of this study was to determine whether genetic variants in the P2RY1 or P2RY12 genes affect platelet response to ADP.

Methods and results: Both genes were screened for polymorphisms using direct sequencing of PCR products. Associations between selected polymorphisms and the platelet response to incremental doses of ADP (0.1, 1.0 and 10 μM), assessed by whole blood flow cytometric measurement of fibrinogen binding to activated GPIIb-IIIa, were then determined in 200 subjects. Five polymorphisms were found in the P2RY1 gene and eleven in the P2RY12 gene. All polymorphisms were silent. A P2RY1 gene dimorphism, 1622A>G, was associated with a significant (p=0.007) effect on platelet ADP response, with a greater response in carriers of the G allele (frequency 0.15). The effect was seen at all concentrations of ADP

but greatest at 0.1 μM ADP where the response in GG homozygotes was double that seen in AA homozygotes (p=0.006).



ADP response by P2RY1 1622 genotype.

Conclusions: This is the first report of genetic variation at the P2RY1 locus influencing platelet reactivity to ADP. Identification of this genotype effect partly explains the inter-individual variation in platelet response to ADP. The findings could have important clinical implications with regards to atherothrombotic risk and inter-individual variation in efficacy of certain anti-platelet agents.

695 Platelet response to dual antiplatelet treatment in type II diabetes

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Purpose: Diabetics (D) have an increased platelet reactivity and a reduced aspirin (ASA)-induced platelet inhibition. Long-term dual antiplatelet treatment (ASA + clopidogrel) is overall associated with a better outcome compared to ASA alone. If platelet reactivity continues to be increased in D compared to non-diabetics (ND) on dual antiplatelet treatment is still unknown. Thus, aim of this study was to compare platelet function in D and ND patients on sustained dual antiplatelet treatment.
Methods: A total of 110 patients (55 type II D vs 55 ND) with known coronary artery disease on sustained (>1 month) ASA (100 mg/d) and clopidogrel (75 mg/d) treatment were included. Patients were well matched for baseline characteristics. Diabetic status was defined according to WHO criteria. Platelet activation was assessed as P-selectin expression and PAC-1 binding using whole blood flow cytometry in ADP (2 μM) stimulated platelets (expressed as % of positive platelets). Platelet aggregation was assessed using light transmittance aggregometry in platelet-rich-plasma (expressed as % of platelet aggregation) stimulated with ADP (6 and 20 μM) and collagen (6 μg/mL).
Results: (mean±SD): P-selectin expression (24.4±16.2 vs 15.9±10.9; p=0.002), PAC-1 binding (39.8±21.1 vs 30.9±18.6; p=0.02), and collagen-induced platelet aggregation (42.3±17.8 vs 32.5±18.2; p=0.005) were significantly increased in D compared to ND, respectively. A positive trend in ADP-induced platelet aggregation was observed following both a 6 μM (35.6±14.4 vs 30.9±14.6; p=0.09) and 20 μM (49.4±13.2 vs 45.0±15.7; p=0.1) stimuli in D compared to ND patients.
Conclusions: Platelet reactivity persists increased in D compared to ND patients on dual antiplatelet treatment. An enhanced platelet reactivity observed in D despite the adjunct of clopidogrel on top of aspirin may continue to set D patients at an increased atherothrombotic risk.

696 "Aspirin resistance" in patients with cardiovascular disease

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Purpose: There is heterogeneity in the way patients respond to aspirin, with some suffering thromboembolic events despite treatment. We hypothesized that incomplete platelet cyclo-oxygenase (COX)-1 suppression as a consequence of COX-1 genetic variation may be responsible in some cases.
Methods: Aspirin response, determined by serum thromboxane (TX)B2 levels and arachidonic acid (AA)-induced platelet aggregation, was prospectively studied in patients (n=135) with stable cardiovascular disease on aspirin (75-300mg). Mean AA aggregation ≥20% was deemed significant (Gum et al, 2003). A serum TXB2 level >3ng/ml was associated with enhanced platelet aggregation and was thus used as a cut-off for optimal aspirin response. Patients were genotyped for five COX-1 variants (-842A>G, 22C>T (R8W), 128G>A (Q41Q), 644C>A (G213G) and 714C>A (L237M)). Haplotype frequency and effect of haplotype on both platelet phenotypes were estimated by maximum likelihood. The four most common haplotypes were considered separately and all less common were pooled.
Results: COX-1 haplotype was significantly associated with aspirin response determined by AA aggregation (p=0.004; 4 d.f.). Carriers of the promoter -842G allele, which is in full disequilibrium with a COX-1 signal-peptide variant (50C>T (P17L)) (Halushka et al, 2003), showed enhanced aggregation (see table). Serum TXB2 generation was also significantly modified by genotype (p=0.02; 4 d.f.). This effect largely reflects elevated serum TXB2 levels in all but the two commonest haplotypes (see table).

Haplotype	No agg'	Yes agg'	Low TX	High TX
ACGCC	182.4(75%)	13.0(65%)	139.4(76%)	60.6(71%)
ACGAC	25.5(10%)	1.0(5%)	19.3(11%)	5.3(6%)
GCGCC	11.7(5%)	4.0(20%)	9.3(5%)	7.3(9%)
ATGCC	12.5(5%)	1.0(5%)	8.0(4%)	5.8(7%)
Rare 'types	11.9(5%)	1.0(5%)	7.9(4%)	6.7(7%)
Total	244(100%)	20.0(100%)	184(100%)	85.7(100%)

Inferred No. of alleles among patients with no/yes AA agg' and low/high TX by haplotype

Conclusion: Genetic variability in COX-1 appears to modulate both AA-induced platelet aggregation and serum TXB2 generation. Heterogeneity in the way patients respond to aspirin may in part reflect variation in COX-1 genotype.

YOUNG INVESTIGATORS' AWARD SESSION – POPULATION SCIENCES

698 Running exercise of different duration and intensity: effect on endothelial progenitor cells in healthy subjects

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Background: Increased numbers of circulating endothelial progenitor cells (EPC) are associated with improved vascular function. The effect of physical activity on circulating EPC in healthy individuals is not known.
Methods and Results: In order to study a potential link between the extent of physical exercise and progenitor cells in humans, EPC were quantified by flow cytometry and cell culture in 19 healthy volunteers undergoing three protocols of running exercise. Intensive running, defined as 30 min at 100% of the velocity of the individual anaerobic threshold, IAT (~82% VO2max), as well as moderate running with 30 min at 80% of the velocity of the IAT (~68% VO2max), significantly ($p<0.05$) increased circulating EPC (DiLDL+/Lectin+). Similarly, flow cytometry revealed upregulation of CD34+VEGFR2+, CD34+/CD133+ and CD34/CD117+ EPC (*$p<0.05$, table). However, moderate short-term running for 10 min did not upregulate EPC counts. Serum lactate increased after intensive exercise from 1.3 ± 0.5 at baseline to 5.1 ± 1.7 mmol/l ($p<0.01$) but was not altered after moderate exercise for 30 or 10 min.

Flow cytometry (positive/100,000 events)

	CD34+/VEGFR2+		CD34+/CD133+		CD34+/CD117+	
	pre	post	pre	post	pre	post
Intensive running	21±9.2	49.3±18.6*	240.9±59	351.4±77.2	429±93	574±129*
Moderate running						
30 min	24.5±10.3	64.4±21.2*	271.6±63.4	387.9±104*	452±92	543±105*
10 min	26±12.2	27.5±11.4	277.8±44.9	295.7±45.7	452.5 ±96.7	474.2±10

Conclusions: Intensive and moderate exercising for 30 min, but not for 10 min, increases circulating levels of EPC which may represent an important beneficial outcome of physical exercise. The data support the notion that increased numbers of EPCs correlate with cardiovascular health and suggest EPC quantification as a novel surrogate parameter of vascular effects of exercising.table

699 Subgroup analyses in cardiovascular trials: why are they misleading?

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Purpose: Subgroup analyses in cardiovascular randomized controlled trials (RCTs) are commonly overused and overinterpreted. We aimed to study the uses of subgroup analyses in current cardiovascular RCTs from top medical journals.
Methods: We reviewed published main reports of parallel, phase III cardiovascular RCTs, with more than 50 patients per arm, between September 1 and November 30, 2002 from influential cardiovascular and internal medicine journals (Circulation, JACC, Am Heart J, Am J Cardiol, N Engl J Med, Lancet, JAMA, BMJ, Ann Intern Med). Information about subgroup analyses included: pre-specification, number of subgroups, use of interaction test, and, claiming and emphasis on subgroup results. We also reviewed the use of subgroup analyses between small (<300 patients) and large trials, negative and positive trials, and CONSORT (Consolidated Standards for Reporting of Trials)-adopting and non-adopting journals.
Results: We identified 35 trial reports, with a median of 769 patients (range: 103 to 67800). Two thirds (n=22; 63%) reported subgroup analyses. Of them, only 36% (n=8) fully and 14% (n=3) partially pre-specified subgroup analyses. 77% (n=17) reported 5 or more subgroups (median 10 [1 to 33]). Only 32% (n=7) used

interaction tests, 50% (n=11) used separate analyses and 14% (n=3) used both. Furthermore, 8 trials claimed differences with overall results, 7 trials showed subgroup effects in summary and/or conclusions and 9 trials gave equal emphasis to overall results. Large trials reported more subgroup effects than small trials (19/25 vs. 3/10; p=0.02), but were not powered specifically to detect subgroups effects. Positive trials reported somewhat more subgroups than negative trials and CONSORT-adopting journals reported somewhat more subgroups than non-adopting journals (not statistically significant).
Conclusions: Subgroup analyses in cardiovascular trials are frequently not pre-specified, use large number of subgroups, do not use the recommended test of interaction and are generally underpowered even in large trials. Recommendations of appropriate conduct and reporting of subgroup analyses need to be translated into current practice, since conclusions of well-performed trials may be misleading otherwise.

700 Prediction of stroke by home versus screening blood pressure measurements in relation to 2003 ESH-ESC classification: the Ohasama study

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Purpose: To compare the predictive power of self-measured blood pressure at home (HBP) and casual blood pressure (CBP) for stroke risk in relation to 2003 ESH-ESC classification (EEC).
Methods: HBP and CBP measurements were done in 1702 subjects (≥40 years) without a history of stroke, who were followed up for an average of 11 years. The subjects were classified into five risk groups according to the EEC (Table 1). Blood pressure categorization was based either on HBP or on CBP. The risk of first stroke was examined by the Cox hazards model.

Table 1. Stratification of risk

	Optimal	Normal	High normal	Grade 1	Grade 2	Grade 3
CBP-based (mmHg)	<120/80	120-129/ 80-84	130-139/ 85-89	140-159/ 90-99	160-179/ 100-109	≥180/110
HBP-based (mmHg) (mmHg)	<115/75	115-124/ 75-79	125-134/ 80-84	135-144/ 85-94	145-159/ 95-104	≥160/105
No RF	Average	Average	Average	Low	Moderate	High
1-2 RF	Average	Low	Low	Moderate	Moderate	Very High
RF>2 or DM	Average	Moderate	High	High	High	Very High
ACC	Average	High	Very High	Very High	Very High	Very High

Risk factors: Age, Sex, Hypercholesterolemia, Smoking, and Obesity. CBP: Casual blood pressure, HBP: Home blood pressure, RF: risk factors, DM: Diabetes Mellitus, ACC: associated clinical conditions.

Results: Stroke risk was linearly stepping up based on HBP as well as on CBP (Fig. 1). In terms of the magnitude of relative hazard, the predictability of HBP was higher than that of CBP.

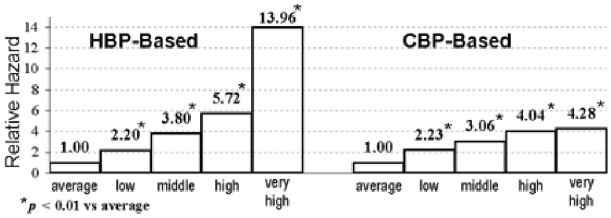

Fig. 1. First stroke risk among groups.

Conclusions: The EEC had a stronger predictive power by HBP-based than by CBP-based, suggesting the importance of hypertension management based on HBP.

701 The cost-effectiveness of screening for left ventricular systolic dysfunction in the general population and in high-risk subjects, a comparison of eight potential screening strategies

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Background: Left ventricular systolic dysfunction (LVSD) is a chronic, treatable, but often asymptomatic or misdiagnosed condition. Programmes to screen for and treat LVSD are currently being discussed, although who to screen, how to screen, and the cost-effectiveness of screening is yet to be established.
Methods: Accordingly, 1392 members of the general public and 928 high-risk subjects (any of ischaemic heart disease, hypertension, diabetes mellitus, heavy alcohol use, peripheral vascular disease and cerebrovascular disease) ≥45 years old were randomly selected from 7 representative general practices. Attending subjects underwent an ECG, N-terminal pro-brain natriuretic peptide (NTpBNP) serum levels and traditional echocardiography (TE) examination. 562 consecutive subjects also underwent hand-held echocardiography (HE) examinations. The screening characteristics and cost-effectiveness (cost per case of LVSD diagnosed) of 8 strategies to predict LVSD (Left ventricular ejection fraction <45% on TE) were compared: TE in all (Strategy 1); ECG then TE in abnormals (Strategy 2); NTpBNP then TE in abnormals (Strategy 3); NTpBNP and ECG then TE if either abnormal (Strategy 4); NTpBNP and ECG then TE if both abnormal (Strategy 5); HE then TE in abnormals (Strategy 6); ECG then HE in abnormals then TE in abnormals (Strategy 7); NTpBNP then HE in abnormals then TE in abnormals (Strategy 8).
Results: 1205 subjects attended. 96% of subjects with LVSD in the general population had identifiable risk factors. All screening strategies assessed gave excellent negative predictive values (minimum 99% in the general population, minimum 97% in high-risk subjects). Screening high-risk subjects was more cost-effective than screening the general population. Strategy 1 was least cost-effective. NTpBNP screening was more cost-effective than ECG screening. No cost-savings were seen combining ECG and NTpBNP data. Strategies 2, 3, 6 and 8 gave cost-savings of up to 63%, 80%, 76% and 88%, respectively, compared to Strategy 1 in screening the general population and up to 44%, 57%, 61% and 73%, respectively, in screening high risk subjects. Strategy 8 was the most cost-effective strategy.
Conclusions: This study supports the development of community-based screening programmes to screen for LVSD in high-risk members of the community, using natriuretic peptide levels with or without hand-held echocardiography to stratify those who should be referred for hospital-based traditional echocardiography. Such programmes would be cost-effective and miss few cases of LVSD in the community.

YOUNG INVESTIGATORS' AWARD SESSION – CLINICAL SCIENCE

703 Long-term cardiovascular consequences of angina: 20 year follow-up of more than 15,000 middle aged men and women (the Renfrew-Paisley study)

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Background: Although angina is a common condition there are few studies which have examined its natural history. We have examined the long-term cardiovascular consequences of angina in a very large UK epidemiological study.
Methods: Between 1972 and 1976, 15,406 men and women aged 45-64 years, living in the two industrial towns of Renfrew and Paisley in the West of Scotland underwent comprehensive cardiovascular screening. We report all deaths and hospitalisations for cardiovascular reasons occurring over the subsequent 20 years according to baseline Rose angina score. Rose positive angina was defined as definite angina, grade I or II, on a Rose angina questionnaire.
Results: At baseline screening 669 (9.5%) men and 799 (10.6%) women had Rose positive angina. Case-fatality for those with Rose positive angina was 67.6% in men and 43.2% in women at 20 years compared to 45.3% and 30.4% in those without angina (p<0.05). 43.7% of men and 23.3% of women with Rose postive angina had a fatal or non-fatal AMI compared to 24.4% and 12.4% of those without angina (p<0.05). 70.7% of men and 49.8% of women had a cardiovascular hospitalisation or death compared to 48.3% and 33.4% without angina (p<0.05). The adjusted risk of cardiovascular events (death or hospitalisation) at 20 years in patients with a positive Rose angina score corrected for other risk factors in a comprehensive multivariable analysis, is shown in the table.

Adjusted risk* of cardiovascular events

	Men - Rose positive	Women - Rose positive
Any death	1.4(1.2-1.5)	1.2 (1.1-1.4)
Any CV event	1.6(1.5-1.8)	1.5 (1.3-1.7)
CV death	1.7(1.5-1.9)	1.4 (1.2-1.7)
Any AMI	1.8(1.6-2.1)	1.7 (1.4-2.0)
Non-fatal AMI	1.8(1.5-2.2)	1.9 (1.5-2.3)
Heart Failure	1.6(1.2-2.2)	2.0 (1.5-2.7)

*hazard ratio (95% confidence intervals) relative to patients without a positive Rose angina scoreAMI = acute myocardial infarction CV = cardiovascular Event = death or hospital admission

Conclusions: Though often regarded as a relatively benign condition, angina in middle age markedly increases the risk of death, myocardial infarction, heart failure and other cardiovascular events over the next 20 years.

704 Long-term prognostic value of dobutamine stress echocardiography in septo and octogenarians

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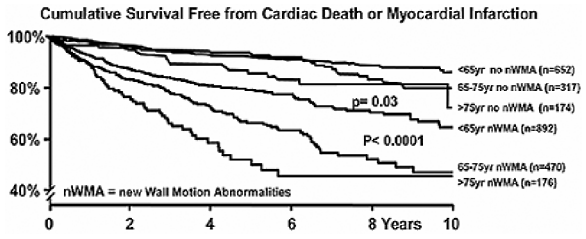
Purpose: Dobutamine stress echocardiography (DSE) has an incremental prog-

nostic value in the general population. However, its use to predict late cardiac events in the very elderly is ill defined.
Methods: Patients were divided into three groups (<65, 65-75, >75 years). All patients underwent DSE (up to 40 mg/kg/min) for evaluation of coronary artery disease, using a 5-point 16 segment score. Patients were evaluated for the presence of rest wall motion abnormalities and stress induced new wall motion abnormalities. A combination of cardiac death and nonfatal myocardial infarction was used as endpoints for the present study. Event-free survival of different age groups was compared using Kaplan Meier method. Multivariable Cox regression analysis was used to adjust for important clinical risk factors.
Results: The mean age of the study population was 61 years (range 14-92yrs), 994 (29%) patients between 65-75 years and 440 (13%) were over 75 years. New wall motion abnormalities were present in 1608 (45%) patients. Cardiac arrhythmias and severe hypotension during DSE occurred in respectively 171 (5%)and 33(1%); there was no relation with age. During a mean follow-up of 6.5 years 586 (17%) patients experienced cardiac death or nonfatal myocardial infarction. Kaplan Meier survival curves showed no difference in the prognostic value of DSE in relation to age (see figure). Multivariate analysis showed male gender, (HR: 1.3 [1.1-1.6]), heart failure (HR: 2.2 [1.8-2.7]), smoking (HR: 1.3 [1.1-1.5]), diabetes (HR: 1.6 [1.3-2.0]), and stress induced ischemia (HR: 2.3 [1.8-2.8]) as independent predictors of late cardiac events.



Kaplan Meier curves.

Conclusions: DSE has long-term prognostic value in elderly patients over 75 years of age.

705 Should nocturnal systolic blood pressure be treated in patients with dysautonomia-related orthostatic hypotension? Insight from a prospective survival study

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Introduction: The predictive value of nocturnal blood pressure (BP) has been established in hypertensive patients. Patients with dysautonomia and orthostatic hypotension (OH) often present with abnormal circadian BP variation. The purpose of this study was to investigate the prognostic value of ambulatory BP monitoring on cardiovascular mortality in these patients. This pilot study is the first step of an interventional trial designed to assess the impact of controling nocturnal BP on cardiovascular mortality in patients with dysautonomia related-OH.
Methods: We prospectively enrolled patients with dysautonomia and OH defined as a decrease in systolic blood pressure of at least 20 mm Hg during active standing. All patients, initially underwent an ambulatory blood pressure monitoring. Informations about gender, age, smoking habits, drug regimens, cardiovascular history were collected. We recorded cardiovascular (CV) events (CV and non CV death, CV morbidity) during scheduled follow-up visits and phone interview. The primary outcome was cardiovascular mortality. Deaths not related to CV disease were censored.
Results: 74 patients were included [39 men (52.70%), mean age: 69.1±10.8 years]. Etiologies of dysautonomia were Parkinson's disease (n=26, 35.1%), multiple system atrophy (n=19, 25.7%), pure autonomic failure (n=13,17.6%), diabetic autonomic neuropathy (n=10, 13.5%), Lewy bodies disease (n=5,6.76%) or amyloid polyneuropathy (n=1,1.4%). The duration of follow-up was of 49.6±36.4 months during which 11 CV deaths (14.9%) and 10 non cardiovascular deaths (13.5%) occurred. Baseline 24-hour systolic blood pressure (141.7±26.0 versus 130.0±13.9 mm Hg, p=0.03) and nocturnal systolic blood pressure (145.0±24.6 versus 130.8±16.9 mm Hg, p=0.01) were statistically higher in patients who died from CV complications than in survivors. Based on Cox analysis and after adjustment for age, sex and previous cardiovascular events, an increase of 10 mm Hg in nocturnal systolic blood pressure led to an increase of 43% in the risk of cardiovascular mortality (95% confidence interval [11-77]).
Conclusion: This study shows for the first time that elevated nocturnal systolic blood pressure in patient with OH and dysautonomia is independently, continously and significantly associated with an increase in CV mortality. Further studies are needed to assess the beneficial effect of decreasing nocturnal blood pressure in these patients.

706 Randomized comparison between stent and balloon in patients with STEMI undergoing primary angioplasty of small vessels. A substudy of the Zwolle-6 randomized trial

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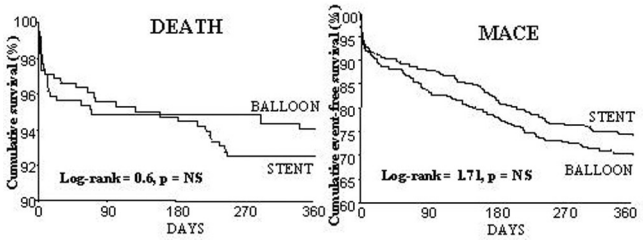
Purpose: In the Zwolle 6 randomized trial, 1683 patients with STEMI were randomized, before angiography, to stent (S) or balloon (B), without any exclusion criteria. In this study we present data form the subanalysis in patients with small vessels (< 3.0 mm).
Methods: In a total of 798 patients treated by primary angioplasty the culprit lesion was located in a small vessel (S = 387 and B = 411). The primary endpoint was major adverse cardiac events (MACE) (death, reinfarction, and/or reintervention at 1-year).
Results: The cross-over rates from B to S and S to B were 22.6% and 19.6%, respectively. No difference was observed in 1-year mortality and MACE (figure).



Conclusions: Our study is the first randomized trial comparing stenting and balloon angioplasty in a large cohort of unselected, consecutive patients with STEMI. This subanalysis shows that routine stenting does not improve clinical outcome in patients with small vessels undergoing primary angioplasty for STEMI.

NEW PREVENTION STRATEGIES

729 Type 2 diabetes mellitus – a preventable risk factor for coronary heart disease. How important is leisure time physical activity? The MONICA/KORA Augsburg Cohort Study

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Purpose: The presence of diabetes is considered a coronary heart disease (CHD) equivalent and is associated with a 10-year risk of more than 20% for developing a major coronary event, a risk that is equal to that of persons with established CHD. Therefore, prevention of type 2 diabetes is of particular importance. In the present study we investigated whether and in what dimension leisure time physical activity can reduce the risk of type 2 diabetes mellitus in men and women from the general population.
Methods: The study sample included 4,070 men and 4,036 women aged 25 to 74 years who participated in one of the three MONICA Augsburg surveys between 1984 and 1995, and who were free of diabetes mellitus and CHD at baseline. Leisure time physical activity (four levels), other life style factors as well as other CHD risk factors were measured at the baseline examination. Incident cases of type 2 diabetes were assessed using a follow-up questionnaire in 1998. The relative hazard rates associated with leisure time physical activity were calculated using multivariable Cox regression.
Results: During an average follow-up of 7.4 years there were 145 incident cases of diabetes among men and 82 among women. In both sexes, high leisure time physical activity (leisure time physical activity more than 2 hours per week during the whole year) was associated with a reduced risk of type 2 diabetes mellitus. After adjustment for confounding factors, the hazard ratio in high active men was no longer significant (HR 0.83; 95% confidence interval (95% CI); 0.50-1.36). Contrary, high active women had the lowest risk of type 2 diabetes even after multivariable adjustment (HR 0.24; 95% CI; 0.06-0.98). In subgroup-analysis, the protective effect of physical activity was significant in women with a BMI < 30 kg/m^2 (HR 0.30; 95% CI 0.12-0.78) only, this association lost significance in women with a BMI ≥ 30 kg/m^2 (HR 0.88; 95% CI; 0.43-1.82) after multivariable adjustment. Furthermore, when comparing active obese women with active non-obese women, active obese women had an 18-fold higher incidence of type 2 diabetes in comparison to active non-obese women.
Conclusion: These findings suggest that women generally profit more from leisure time physical activity than men. In particular, in obese women diabetes and CHD could be prevented if they could reduce their weight to a BMI < 30 kg/m^2 in addition to regular leisure time activity.

730 A randomised non-pharmacological intervention study for prevention of ischaemic heart disease. Inter99

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Objectives To evaluate the effect of a population based screening and non-pharmacological intervention for prevention of ischaemic heart disease (IHD) using modern educational and behaviouristic methods.
Methods: The study population comprises 61,301 persons. Of these a random sample of 13,016 persons were invited for a risk assessment for development of IHD by means of a computer program (PRECARD®). The remaining 48,285 served as reference population and were not invited. According to predefined criteria participants were classified into a high risk and a low risk group. The 13,016 persons were a priori randomised to receive a low intensity intervention or a high intensity intervention. Intervention focused on smoking cessation, increase in physical activity and change in diet. Interventions were made in three waves (at base line, after one year, and after three years). Spontaneous changes in lifestyle in the reference population were monitored by questionnaires at base line and after one, three and five years to a random sample of the reference population. Effects were calculated as change in lifestyle habits, biological risk factors, and absolute risk of IHD.
Results: A comparison between the high and low intensity intervention group and between the intervention groups and reference population after one year is presented. Participation rate at base line was 52% (N=6,784). A total of 60% fulfilled the criteria for lifestyle intervention and had a health counselling talk. In the high intensity intervention group nearly half accepted group based intervention during a 6 months period. A total of 62% of the high risk population was re-examined after one year. Significant more persons in the intervention groups stopped smoking compared to the reference population. Systolic blood pressure, LDL-cholesterol, and estimated total risk of IHD decreased significantly in the high intensive intervention group compared to the low intensive intervention group ($p<0.05$). Changes in BMI, waist circumference, and total cholesterol all showed a non-significant trend in favour of the high intensity intervention group.
Conclusion: There is a marked need for lifestyle counselling in the population. The present study shows a positive effect of population based screening and intervention after one year when modern educational and behaviouristic methods are used.

731 Primary prevention of cardiovascular disease: a cost-effectiveness comparison

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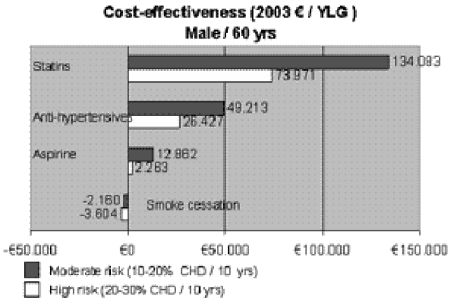
Coronary heart disease prevention modifies different risk factors by evidence-based interventions. However, while these interventions are proven effective for almost all populations, resources are limited and priority setting is mandatory.
Aim: To evaluate and compare the cost-effectiveness of four different risk lowering treatments (smoking cessation, antihypertensive treatment, aspirin and statin therapy) in primary prevention of coronary heart disease (CHD) for male populations at different ages and levels of risk.
Methods: Using data from the Original Framingham Heart Study and the Framingham Offspring study, we built life tables to model the benefits of the four risk lowering interventions. At baseline patients were classified by level of absolute risk of CHD (based on the Anderson Formulae) and age. Effects and costs of the interventions were based on the literature and projected over a 10-year time horizon. Cost-effectiveness ratios were calculated using a third party payer perspective.
Results: The most cost-effective treatment is smoking-cessation therapy, representing savings in almost all situations. Statins therapy is the least cost-effective treatment (ranging from 73971 to 190276 euros per year of life gained) even if off-patent costs are included in the model (29772 to 82067 euros per year of life gained). Aspirin was the second most cost-effective intervention (2263 to 16949 euros per year of life gained) followed by antihypertensive treatment (26427 to 75403 euros per year of life gained).



Cost-effectiveness of primary prevention.

Conclusions: A cost-effective strategy should offer first smoking cessation therapy for smokers and aspirin for all levels of risk. Antihypertensive therapy is efficient over a wide range of risk. Statins are to be saved for populations at higher levels of risk.

732 Heart failure results in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

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Purpose: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) provided an opportunity to examine the relative benefit of chlorthalidone (C), lisinopril (L) and amlodipine (A) in preventing HF in 33,357 high risk hypertensive patients.
Methods: ALLHAT was a double-blind, randomized clinical trial in high risk hypertensive patients aged $\geq$55 years. HF was designated a priori as a secondary outcome and reported by investigator. All HF (treated, hospitalized, and fatal) and the subset hospitalized/fatal HF were examined. Cox regression was used to examine HF overall and during and after the first year of the trial.
Results: See Table. For both HF endpoints, L and A had twofold greater rates during the first year compared with C ($p<.001$). After the first year, rates were similar in L and C whereas A continued to have 20% higher rate than C ($p<.001$). Approximately 10% of participants entered ALLHAT not on prior antihypertensive drugs. There was no significant interaction between use of prior medications and treatment group differences for HF in the first year. Blood pressures (BP) were equal at baseline (146/84 mm Hg) and at one year were 137/79, 139/79, 140/80 mm Hg in C, A, and L, respectively. At one year, the percentages of patients in whom open-label step-up drugs had been added were as follows in C, A, and L, respectively C diuretic (5, 8, 7), calcium channel blockers (5, 5, 7), ACE inhibitors (5, 5, 5), and atenolol (12, 17, 20).

Table 1. Relative Risks by Time Period

Comparison	Outcome	Overall RR (95% CI)	Baseline to Year 1 RR (95% CI)	> Year 1 RR (95% CI)
L vs C	All HF	1.20 (1.09, 1.34)	2.22 (1.75, 2.82)	1.04 (0.92, 1.17)
	Hosp./Fatal HF	1.11 (0.99, 1.24)	2.08 (1.58, 2.74)	0.96 (0.85, 1.10)
A vs C	All HF	1.38 (1.25, 1.52)	2.32 (1.83, 2.94)	1.22 (1.10, 1.37)
	Hosp./Fatal HF	1.35 (1.21, 1.50)	2.22 (1.69, 2.91)	1.22 (1.08, 1.38)

Conclusion: 1) Risk of either HF outcome was dramatically decreased for C vs A or L during the first year. 2) Risk of HF after year one for C was similar to L but decreased compared with A. 3) Use of prior medication did not influence treatment effects during the first year. 4) BP differences and concomitant medication use are unlikely to explain HF differences seen in the first year. 5) Diuretics are superior to ACE inhibitors or calcium channel blockers in the prevention of HF in patients with hypertension.

733 Use of waist circumference as an indicator of cardiovascular risk in a menu-based programme of cardiac rehabilitation

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Background: Diet plays an important role in the prevention and management of coronary heart disease (CHD) and may account for up to 30% of deaths from CHD. Body mass index (BMI) has traditionally been used to assess obesity as a risk factor for CHD but fails to take account of body composition and distribution of body fat. As one of the best correlates of visceral adipose tissue, waist circumference measurements are advocated as an alternative and more effective measure of CHD risk.
Purpose: To evaluate change in dietary behaviours, weight, BMI, and waist circumference 12 weeks following initial dietary intervention as part of a menu-based cardiac rehabilitation programme in the west of Scotland.
Methods: Weight, height, waist circumference and dietary intake were measured in 40 patients referred to the dietitian during phases one to three of cardiac rehabilitation (27 male, 13 female, mean age 61.2 years, age range 46-82 years). Dietary intake was assessed using the Health Education Board for Scotland's healthy eating food frequency questionnaire. All measurements were taken during the patient's first dietetic consultation and 12 weeks later. T-tests identified changes over time.
Results: Dietary habits significantly improved over the 12 weeks. There was a significant decrease in the unhealthy habits score (18.7$\pm$7.0 to 11.6$\pm$5.1) and a significant increase in the healthy habits score (27.1$\pm$7.8 to 33.5$\pm$8.1). There were no significant changes in either body weight (79.1$\pm$10.6 kg vs. 78.2$\pm$10.5 kg) or BMI (29.0$\pm$4.2 kg/m^2 vs. 28.6$\pm$3.9 kg/m^2), however, waist circumference decreased significantly (96.9$\pm$10.2 cm to 91.6$\pm$10.1 cm). The number of patients who fell within the healthy range for waist circumference increased from 8 at baseline to 23 at 12 weeks.
Conclusions: Cardiac rehabilitation with dietary intervention was associated with positive changes in dietary behaviour and decreases in waist circumference independent of any change in BMI or weight. Waist circumference measurements may be a more sensitive measure of change in cardiovascular risk compared to weight and BMI and therefore represent an important addition to assessment.

734 The effect of adherence to the Mediterranean diet on the severity and prognosis of acute coronary syndromes: the Greek study of ACS (The GREECS)

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Objective: We sought to investigate the effect of adherence to the Mediterranean diet on the severity and short-term prognosis of acute coronary syndromes.
Methods: From October to December 2003, 546 patients from 7 major hospitals in Greece and with a discharge diagnosis of acute coronary syndromes were enrolled into the study. Of them, 75% were men (65 ± 11 years old) and 25% were women (71 ± 13 years old). Adherence to the Mediterranean diet was based on a diet score (range 0 – 55) that evaluated the inherent characteristics of this diet through a validated food frequency questionnaire. Higher values of this score indicate greater adherence to this traditional diet. Cox proportional hazard models were applied to evaluate the diet score on the 30-day outcome of cardiovascular events (death or hospitalization due to CVD), after adjusting for several potential confounders.
Results: Patients with myocardial infarction had lower diet score as compared to patients who had unstable angina (n = 386, 23±7 vs. n = 160, 29±9, p = 0.002). An inverse association was observed between the diet score and Troponin I levels (r = -0.12, p < 0.001) and white blood cell counts (r = -0.16, p = 0.01). Moreover, the diet score was inversely associated with the 30-day risk of events (relative risk per 10 unit increase = 0.81, 95% CI 0.69 – 0.94), after adjusting for the type of syndrome and several potential confounders. Thrombolysis appears to be protective in those who were in the highest quartile of the diet score (relative risk = 0.55, 95% CI 0.36 – 0.78), but not in those who were in the lowest quartile (relative risk = 1.06, 95% CI 0.2 – 23.1), after various adjustments made.
Conclusion: Our findings may state a hypothesis for lower risk of cardiac events in patients who adopted the Mediterranean diet and had an acute coronary syndrome. Moreover, greater adherence to this diet seems to be associated with less severe coronary syndrome.

WOMEN, MEN AND CARDIOVASCULAR DISEASE

735 Sudden cardiac death in young women: are there gender differences in cardiovascular substrates?

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Background: Sudden cardiac death (SCD) in the young is due to a wide spectrum of either congenital or acquired cardiovascular substrates. However, no study specifically addressed their prevalence and characteristics in a female population.
Material and Methods: A consecutive series of natural SCDs occurring in people <35 year of age was evaluated. Cerebral and respiratory causes and sudden infant death syndrome (<1 year of age) were excluded. Clinical data, circumstances of death, gross and histologic findings were reviewed to assess any difference among male and female SCD victims.
Results: 400 consecutive cases of SCD in the young have been collected in the time interval 1980-2003. They were 277 males (69%) and 123 females (31%), mean age 25±8 vs 22.5±9, p=0.02. As far as the pathophysiologic mechanism, SCD was mechanical more in females than males (9% vs 4.5%). Myocarditis, arrhythmogenic right ventricular and hypertrophic cardiomyopathies showed an almost equal prevalence as a cause of SCD in both sexes (14%, 13% and 9% in male vs 20%, 12% and 8% in females, p=NS). Atherosclerotic coronary artery disease was almost exclusive of the male sex (23% vs 3%, p<0.0001), whereas acquired non-atherosclerotic coronary artery disease did affect mainly the females subgroup (6% vs 1%). Moreover, the prevalence of mitral valve prolapse was higher in females than males (15% vs 5%, P=0.01). SCD remained unexplained in 6% of males and 10% of females. Competitive sport activity was more frequent in males than females (18% vs 4,8%, p=0.008). Noteworthy, 10% of women who were in the reproductive period died suddenly in the peripartum
Conclusions: SCD in women is not a rare event, since one third of juvenile victims are female. Major causes are represented by subtle substrates such as myocarditis and mitral valve prolapse. No sex difference has been found as far as the prevalence of inherited cardiomyopathies. Peripartum period represents a peculiar trigger of SCD in women with underlying cardiovascular substrates.

736 Is the female gender an idependent predictor of adverse outcome after percutaneous or surgical revascularization? A report from the Arterial Revascularization Therapies Study (ARTS)

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Background: Previous studies have shown that women (W) undergoing coronary revascularization procedures have a higher incidence of in-hospital mortality and morbidity than men (M). To determine whether W have an unfavorable long-term outcome after percutaneous (PCI) or surgical (CABG) coronary interventions compared with M, we evaluated patients (pts) undergoing revascularization within the Arterial Revascularization Therapies Study (ARTS).
Methods: We prospectively evaluated 1205 pts with angina or silent ischemia and multi-vessel (MV) disease randomized to PCI or CABG of whom 283 (23%) were W. The clinical presentation, in-hospital morbidity and mortality, and the freedom from major adverse cardiac and cerebrovascular events at 3- years were evaluated.
Results: W were older (65±8 vs 59±10 years, p<0.001), with a higher prevalence of hypertension (59% vs 40%, p<0.001), hypercholestelolemia (71% vs 54%, p<0.001), family history for coronary artery disease (52% vs 37%, p<0.001) and stable angina (64% vs 57%, p=0.03) than M, but had a lower incidence of history of myocardial infarction (35% vs 46%, p<0.001) or current smoking (18% vs 30%, p<0.001). The presence of unstable angina, the extent of coronary artery disease and the location of the stenosis was similar in W and M. W assigned to CABG received the same number of arterial conduits and had similar number of distal anastomoses compared to M (1.1±0.6 vs 1.2±0.6 and 2.6±1.0 vs 2.8±1.1 respectively, NS). In hospital mortality for CABG pts was higher in W compared to M (4.1% vs 0.4%, p<0.005), while bleeding complications were higher at PCI (7.2% vs 0.2% p<0.01). Pts assigned to PCI had no differences in in-hospital mortality (W:2.2%, M:0.6%, p:NS).At an average of 3 years follow-up the survival without death/cerebrovascular accident/myocardial infarction/revascularization was similar in M and W. (M: PCI=66.2%, CABG=83.9%; W: PCI = 64.5%, CABG=81.4%).
Conclusion: The 3 year outcomes of W with MV disease undergoing coronary revascularization are similar to those in M. Despite the similarity in long-term outcomes, there are several gender-specific differences in clinical characteristics and risk factors profile resulting in higher in-hospital complications in W.

737 Effects of female sex and age on early mortality in aortocoronary bypass surgery

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Objectives: We aimed to determine the interaction between sex and age in early mortality after coronary artery bypass surgery and to analyze which variables affect mortality in a sex- and age-specific manner.
Methods: An in-hospital mortality analysis of 17 528 consecutive patients operated on between 1993-2001 in the German Heart Institute Berlin was performed.
Results: Women had a 1.5-fold (p<0.001) higher age dependent early all-cause mortality after CABG than men. Women under 50 years had a 2.4-fold (p<0.02) higher mortality rate, whereas women over 80 years had a mortality comparable to that of age-matched men. Female sex was independently associated with all-cause mortality (HR 1.24, CI 1.008-1.516, p=0.042). Using the area under the receiver operating command curve to determine the optimal cut-off value for age revealed that women under 70.5 years have an independent overmortality compared to age-matched men (HR 1.33, CI 1.008-1.758). Older women had the same mortality risk as older men (HR 1.16, CI 0.861-1.559, p=0.334). Risk factors were age- and sex-dependent; numbers of diseased vessels and previous myocardial infarction were more important in women.
Conclusion: Female sex is an age-dependent risk factor for early mortality after CABG. Clinical parameters as yet unknown contribute to the overmortality in women.

738 Why do women have an increased mortality after coronary surgery? Analysis of clinical, angiographic and surgical variables in relation to in-hospital mortality in a multicentre registry

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Women have higher in-hospital mortality than men after coronary artery bypass surgery (CABG). Women may have more co-morbidities or more technical problems related to small arteries during the procedure.
Objective: 1-To compare clinical, angiographic and surgical variables between women and men to explain different early mortality.2- Analyze if gender is an independent predictor of in-hospital death.
Methods: ESMUCICA was a prospective multicenter CABG registry performed among 12 hospitals in Argentine between the years 2000 and 2002. Selected centers had to accept external monitoring and electronic case reports forms for every cardiac surgery. For the present study all 3209 isolated & consecutive CABG patients were included. There were 2475(82%) men and 554(18%) women. Bivariable and logistic regression analysis were performed.
Results: Women were older (66±9 vs. 62±10 years, p=0.001), had smaller body surface (1.71±15 vs. 1.95±15 m^2, p=0.001), had more diabetes (32 vs.24%, p=0.001), more hypertension (76 vs. 66%, p=0.001), progressive angina (40 vs. 31%, p=0.005), Parsonnet Index >10 (83 vs. 34%, p=0.001); and less prior myocardial infarction (22 vs. 34%, p=0.006), left ventricular dysfunction (23 vs. 30%,

p=0.001) and chronic pulmonary disease (5 vs. 11%, p=0.001). Women had more 1 or 2 vessel disease (36 vs. 30%, p=0.02) and no differences in left main and 3-vessel disease. Women had more urgent surgery (45 vs. 34%, p=0.007), off-pump surgery (35 vs. 25%, p=0.006) and less arterial grafts (1.39 vs. 1.69, p=0.001), on-pump time (105 vs. 110 min., p=0.001) and total surgical time (245 vs. 257 min., p=0.006). Women had more peri-operative acute myocardial infarction (7 vs. 4.5%, p=0.01), low cardiac output (15 vs. 10%, p=0.01) and in-hospital mortality (6.7 vs. 4.4%, p=0.003).
Independent predictors for in-hospital mortality were: urgent surgery (OR 1.8, 95% CI 1.28-2.56, p=0.001), left ventricular dysfunction (OR 1.7, 95% CI 1.39-2.13, p=0.001), off-pump surgery (OR 1.7, 95% CI 1.13-2.66, p=0.01), age (OR 1.5, 95% CI 1.28-1.86, p=0.0001) and body surface area (OR 0.64, 95% CI 0.43-0.98, p=0.04) (ROC 0.74).
Conclusion: Women had increased mortality after coronary surgery because of a worse clinical profile. They had similar or better angiographic characteristics. Surgical times in women were shorter not suggesting more technical problems. Female gender was not an independent predictor for in hospital death.

739 Diabetes mellitus, clinical presentation and outcome in men and women with ACS. Data from the euro heart survey ACS

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Background: Diabetes mellitus (DM) is associated with poor outcome in men and women with coronary disease. Few studies have investigated interactions between sex and diabetes with respect to clinical presentation and hospital outcomes in acute coronary syndromes (ACS).
Aim: To study the clinical presentation and hospital mortality among men and women with ACS and DM.
Methods: We analysed 10253 patients (3329 women) with a discharge diagnosis of ACS in the Euro Heart Survey ACS. Of the women, 28% had DM and of the men 20%.
Results: Fewer DM men presented with ST-elevation ACS, compared to non-diabetic men (age-adjusted odds ratio 0.79 (0.70-0.89)). In contrast, among the women, there was no difference in the proportion of ST-elevation-ACS between DM and non-DM patients (OR 1.09 (0.93-1.27)). However, when differences in smoking, hypertension and prior disease were taken into account, DM was associated with increased risk of presenting with ST-elevation-ACS in women (OR 1.28 (1.09-1.51)), whereas the decreased risk in men was no longer significant (OR 0.91 (0.80-1.03)). There was a significant interaction between sex, DM and presenting with ST-elevation-ACS (p=0.0004). Of the women with DM, 8.6% died in hospital, compared to 4.9% among women without diabetes (age-adjusted OR 1.73 (1.28-2.32)) with corresponding mortality rates among men with and without DM of 4.8% and 4.0%, respectively (OR 1.08 (0.81-1.43)); p for DM-sex interaction 0.025.
Conclusion: DM in women with ACS is associated with higher risk of presenting with ST-elevation-ACS and of in-hospital mortality, whereas DM in men with ACS is not associated with increased risk of either. These findings suggest a differential effect of DM on the pathophysiology of ACS based on the patient's sex.

740 Endothelial function predicts future development of coronary artery disease in women with chest pain and normal coronary angiograms

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Background: Prognosis of women with chest pain and angiographically normal coronary arteries is believed to be totally benign. Previous studies, however, did not account for the decade or so delay in development of coronary artery disease that women may experience.
Methods: This study assessed long-term follow-up of 42 women with de novo angina, evidence of reversible myocardial perfusion defects on single emission computed tomography, and normal coronary angiograms. At recruitment, all women underwent endothelial function testing (intracoronary acetylcholine) during catheterization. Patients were followed-up for more than 10 years. Angiography was repeated at the end of the follow-up in 37 patients.
Results: At recruitment, 22 patients developed diffuse vasoconstriction during acetylcholine in absence of identifiable focal coronary spasm (acetylcholine-positive group). The remaining 20 patients showed vasodilation (acetylcholine-negative group). At the end of follow-up, in acetylcholine-positive group, 1 patient developed cardiac death, 13 still complained of chest pain, and 8 had remission of symptoms. In acetylcholine-negative group all patients showed a complete resolution of chest pain starting from 6 to 36 months after baseline assessment. Single emission computed tomography was repeated in all survivors. In acetylcholine-positive group, it showed reversible perfusion abnormalities in 15 patients (13 symptomatic and 2 asymptomatic). Perfusion abnormalities were in the same myocardial segments showing reduced uptake at enrollment. The severity of uptake reduction in each myocardial region was not significantly changed from baseline (3.4±0.5 versus 3.6±0.5). In acetylcholine-negative group, single emission computed tomography did not show reversible perfusion abnormalities. Angiography showed development of coronary artery disease in the 13/17 patients of the acetylcholine-angina group and confirmed normal appearing coronary arteries in all acetylcholine-negative group patients.
Conclusions: In women with angiographically normal appearing coronary arteries, persistence of pain over the years often relates to development of coronary artery disease. Endothelial dysfunction in a setting of normal coronary arteries is a sign of future development of atherosclerosis.

MULTIPLE USES OF MYOCARDIAL DEFORMATION ASSESSMENT BY ECHOCARDIOGRAPHY

741 A new method to define end-systole in dyskinetic myocardium – a useful tool in strain Doppler analysis

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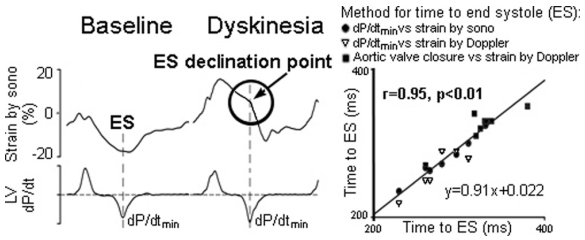
Introduction: Measurement of myocardial velocities and strain in different cardiac phases provides important diagnostic information. One limitation of the cardiac phase analysis, however, is uncertainty regarding timing of end-systole (ES). We became aware that dyskinetic segments in moderately ischaemic myocardium have a sudden rapid decrease in strain near ES. In the present study we investigate if this strain declination point is a marker of ES.
Methods: In 7 anaesthetized dogs we measured LV pressure and myocardial long axis strain by SDE and by sonomicrometry as reference method. Ischaemia was induced by LAD occlusion. ES, identified by the declination point in strain by sonomicrometry (Figure) and SDE, respectively, was compared to ES defined by dP/dtmin. In 8 patients with acute myocardial infarction ES by SDE were compared to ES defined by aortic valve closure.
Results: In dyskinetic segments that were partly active, ES as defined by SDE and by sonomicrometry correlated very well with ES defined by dP/dtmin (r=0.99, p<0.01 and r=0.94, p<0.01, respectively). In patients, ES by SDE correlated well with ES defined by aortic valve closure (r=0.90, p<0.01) (Figure). Normal and passive strain traces did not have a consistent strain declination point at ES.



Conclusions: In dyskinetic myocardium that is partly active ES corresponds to a sudden rapid decrease in strain. This temporal relationship is probably explained by the ES sudden drop in wall tension in non-ischaemic myocardium, which allows sudden contraction in partially active ischaemic segments. Since patients with myocardial infarction usually have some regions with moderate ischaemia, the methodology is expected to work in most patients.

742 Impact of global left ventricular deformation on myocardial velocities during isovolumic contraction

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Background: Myocardial isovolumic contraction (IVC) velocities by Tissue Doppler imaging (TDI) have been proposed as important markers of cardiac function. There is, however, limited understanding of the physiologic meaning of IVC velocities. We investigate the hypothesis that IVC velocities may be a result of changes in ventricular shape and torsion during early systole. Another potential mechanism is that IVC velocities represent wall oscillations related to the first heart sound.
Methods: In 5 anesthetized dogs instrumented with multiple ultrasonic crystals we measured myocardial segment length, long- and short-axis diameters and ventricular torsion in 3 planes between apex and base. In 2 dogs we recorded intracardiac phonocardiography. Myocardial velocities were measured by TDI.
Results: In each experiment the LV long-axis increased during IVC and the long-/short-axis ratio increased from 1.17 to 1.24 (p<0.05), indicating more ellipsiodal shape. However, the rate of LV elongation did not correlate with anterior wall IVC velocity by sonomicrometry or TDI (r=0.17 and 0.09, respectively). There was substantial LV torsion during IVC, and torsion decreased from apex towards LV

equator. This was in contrast to peak IVC velocity that tended to be higher at the equator than at the apex ($p<0.05$) and base (ns). Systolic ejection velocities decreased from base towards equator ($p<0.05$) and from equator to apex ($p<0.05$). Phonocardiography showed that the spike of first heart sound occurred immediately prior to peak IVC velocity.
Conclusions: The shift to a more ellipsiodal shape of the LV during IVC did not contribute to IVC velocities. Furthermore, the distribution of IVC velocities, with a peak at the LV equator where torsion is minimal, does not support the notion that torsion accounts for peak IVC velocities. Therefore, most likely IVC velocities are generated in part by local fiber shortening, and potentially the most rapid velocity components represent oscillations with same etiology as the first heart sound.

743 Diastolic deformation measured by strain echocardiography provides information on myocardial stiffness: implications for the assessment of myocardial viability

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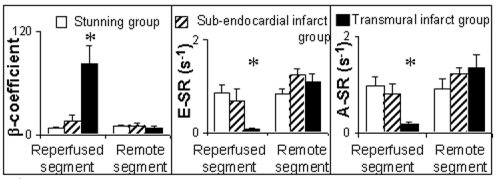
Background: In this study, we compared longitudinal diastolic deformation to myocardial stiffness, using an open-chest swine model of acute myocardial infarction (MI).
Methods: Left anterior descending coronary artery was occluded for variable duration (20-180 min) to induce either stunning, subendocardial MI, or transmural MI (n=18; 6 pigs/group). Reperfusion was allowed for 120 min. Sonomicrometry- and tissue Doppler-derived longitudinal strain rates (SR) and strain as well as systolic shortening were measured in the ischemic (anterior) and remote normal (inferior) myocardium. Myocardial stiffness was measured from exponential relationship: LV pressure = a $*$ exp(beta $*$ segment length) by varying preload (caval constriction and saline infusion). Transmural extent of necrosis was quantified by triphenyl-tetrazolium chloride staining.
Results: (mean SE): Infarct transmurality was 0% in stunning, 18 7% in subendocardial MI, and 97 2% in transmural MI groups. Increases in myocardial stiffness (beta-coefficent) in transmurally-infarcted walls were associated with markedly reduced late diastolic strain and SR during both early (E-SR) and late (A-SR) filling phases (figure). Conversely, myocardial walls with subendocardial MI or stunning had relatively preserved stiffness and E-SR and A-SR. Systolic SR (7 1%, 13 4%, and 7 1% from baseline; respectively) and shortening (<10% from baseline in all) were depressed at reperfusion in all ischemic segments. Tissue Doppler-derived data showed similar differences.



*P < 0.01 infarcted vs. remote segments or other groups

Conclusions: Preserved diastolic deformation early after reperfusion for acute MI discloses presence of viable, compliant tissue, even when systolic function has not yet recovered. These results are consistent with our previous findings for radial deformation.

744 Validation of a new approach for quantifying myocardial deformation based on automated anatomical regional tracking of gray scale data

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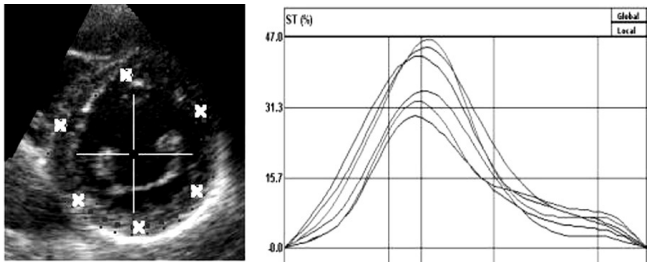
Background: Strain and strain rate imaging (SRI) are new tools for the quantitative analysis of regional myocardial function. The current implementation of the technique is based on myocardial velocity imaging (MVI), that requires manual tracking of the region of interest (ROI), which is a time-consuming post-processing step. This currently limits its widespread applicability in routine clinical practice. In order to overcome this limitation, a new tool has been developed that measures myocardial deformation by automatic ROI tracking performed on 2D grayscale (GS) images, significantly reducing post-processing time.
Aim: To validate this new method for quantifying regional deformation against conventional technique.
Methods: GS images were acquired (GE Vivid7; 50-80 Hz) in both Sax and apical 3-CH views in 20 normals using second harmonic imaging and processed using the new tool in a prototype software (EchoPAC 2D Strain) to extract radial (R) and longitudinal (L) myocardial velocity and strain curves (fig1). The same parameters were extracted using conventional SRI techniques by acquiring the corresponding MVI data sets (> 150Hz) and analyzing them using dedicated software (SPEQLE). The correlation between both methods was expressed using the correlation coefficient (CC).
Results: The CC for peak systolic velocity and strain were respectively 0.61 (L), 0.84 (R) and 0.70 (L), 0.77 (R). Average time to analyse each patient data was 5 min (new tool) versus 25 min (SPEQLE).



Conclusions: A good correlation was found between the GS deformation estimation and color Doppler based MVI measurements. The advantage of the new technique was that analysis time was reduced by a factor of five. This new tool should make ultrasound deformation imaging more clinically applicable.

745 Myocardial systolic dysfunction as early sign of cardiac involvement in asymptomatic patients with systemic sclerosis: a strain and strain rate tissue Doppler analysis

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Background: Systemic sclerosis (SSc) is a multisystem disease characterized by widespread vascular lesions and fibrosis of skin and distinct internal organs. We sought to clarify whether myocardial strain Doppler or strain rate were able to detect early regional myocardial systolic dysfunction before the onset of cardiac symptoms in patients with SSc.
Methods and results: 25 healthy subjects and 23 age- and sex-comparable (56.3±8.2 y; 20 female) patients affected by SSc underwent clinical examination, serological tests, high-resolution chest-TC, standard Doppler echocardiography, Tissue Doppler, strain and strain rate imaging (SR) at the basal, mid, and apical left (LV) and right (RV) ventricle in apical views. Patients were classified as having either diffused (11 pts) or limited (12 pts)SSc. The cutaneous involvment was classified by the modified Rodnan Skin Score (mRSS) into high mRSS (score > 10) and low mRSS (score < 10). By chest-TC, 11 patients showed interstitial pulmonary fibrosis. ANA immunofluorescence detected anti-centromere antibodies in 8 patients, and anti-topoisomerase I in 15 cases. By standard Doppler echo, tricuspid annular plane systolic excursion (TAPSE), LV mass index, LV fractional shortening, and LV ejection fraction were comparable between the two groups, while RV end-diastolic diameter was increased in SSc ($p<0.01$). Doppler tricuspid inflow peak E and E/A ratio were slightly decreased in SSc ($p<0.01$), while systolic pulmonary pressure was increased ($p<0.0001$). With the use of pulsed TD, no significant differences in myocardial systolic function were evidenced between the two groups. Conversely, basal peak systolic RV SR (l/s) was significantly reduced in patients with SSc with respect to controls (-0.76±0.3 vs -2.0±0.4, respectively. $p<0.001$). Furthermore, RV basal strain demonstrated statistically significant differences between the 2 groups (-8.0±5% in SSc vs -19±4% in controls; $P<0.001$). By stepwise forward, multiple linear regression analysis, pulmonary systolic pressure ($p < 0.0001$) and pulmonary fibrosis ($p < 0.001$ were the only independent determinants of RV basal SR
Conclusions: Systemic sclerosis is characterized by an early impairment in systolic function at a time when fractional shortening, TAPSE and LV ejection fraction remain normal. This abnormality precedes the onset of symptoms and can be detected by strain and SR but is not apparent by TD imaging. Therefore Strain analysis may represent a useful tool for the non-invasive follow-up of SSc patients, better selecting patients with early RV systolic impairment.

746 Validation of a new ultrasound method for measuring myocardial strain combining speckle tracking and tissue Doppler imaging

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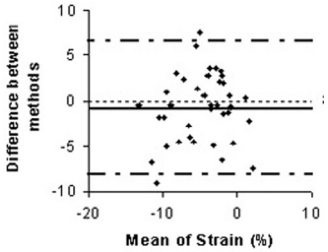
Purpose: Ultrasound tissue Doppler (TD) based estimates of myocardial strain in the left ventricle are limited by angle dependency. We have developed a new ultrasound application combining TD and speckle tracking (ST) to find the two-dimensional motion of points of myocardium, and thus be able to calculate strain in the myocardium lying between. Our aim was to validate this application against sonomicrometry.

Methods: In three anaesthetized dogs four pairs of ultrasonic crystals were implanted along the left ventricular long axis in the middle segments of the septal, lateral, inferior and anterior wall. Directly following sonomicrometry recording, apical ultrasound TD images with underlying greyscale were recorded of the same segments with a Vivid 7 scanner (GE Vingmed Ultrasound, Norway). Recordings were done at baseline, during saline loading and LAD occlusion.
Results: Strain could be measured in 39 of 44 segments using the TD/ST application. Strain calculated from the TD/ST-application was not different from strain measured by sonomicrometry (5,1±4,5 vs. 4,3±4,1%, resp., p=0,2). The 95% limits of agreement were -6,5 to 8,1% (Bland-Altman plot in figure). The correlation between the two methods was r=0,62 (p<0,01). Segment length was 20±5 mm.



Bland-Altman plot.

Conclusion: The new application combining speckle tracking and tissue Doppler imaging showed good agreement with sonomicrometry, and the agreement was in the same range as what has previously been reported for tissue Doppler based strain estimation. The application seems to have potential in reducing angle dependency of ultrasound myocardial strain estimates.

COMMUNICATION IN VASCULAR SMOOTH MUSCLE CELLS

747 T-cadherin expression in vascular cells correlates with cell cycle progression and functions in promotion of proliferation

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Purpose: In vascular tissue the progression of atherosclerosis, restenosis and tumour neovascularization is attended with marked increase in T-cad levels on the surface of EC and SMC. We hypothesize that there is a positive correlation between T-cad expression and abnormal vascular cell motility and growth, and that T-cad might be involved in regulation of vascular cell phenotypic modulation. The purpose of this study was to examine the relationship between expression of T-cad and vascular cell proliferation.
Methods and results: Specifically, we have analysed how T-cad levels change during the progression of the cell cycle, and whether overexpression of T-cad influences vascular cell growth rates. Cultures of human umbilical vein endothelial cells (HUVEC) and rat and human aortic smooth muscle cells (rSMC and hSMC) were used. T-cad was overexpressed in HUVEC and hSMC using an adenoviral expression system. In cultures released from G1/G0 synchrony parallel Western blot analysis of T-cad and cell cycle phase specific markers (p27Kip1, cyclin D1, E2F1, PCNA, cyclin B) showed increased T-cad protein levels subsequent to entry into early S-phase with sustained elevation through S- and M-phases of the cell cycle. T-cad was increased in G2/M-phase (colchicine) synchronized cultures. In FACS-sorted cell populations expression of T-cad in S- and G2/M-phase was higher than G1/G0-phase. HUVEC and hSMC overexpressing T-cad exhibited increased proliferation as assessed in enumeration, DNA synthesis and cell cycle progression assays. After release from G1/G0 synchrony HUVEC overexpressing T-cad exhibit more rapid entry into early S-phase, and increased cell cycle progression was confirmed by FACS analysis after double staining with propidium iodide and BrdU.
Conclusion: Taken together the findings support that in vascular cells T-cad is dynamically regulated during the cell cycle and that its expression functions in the promotion of proliferation.

748 Integrin-linked kinase is increased in intimal thickening and modulates cell-matrix and cell-cell interactions

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Proliferation and migration of vascular smooth muscle cell (VSMC) plays a key role in intimal thickening during atherosclerosis and restenosis after angioplasty and stent placement. Cell-matrix and cell-cell contacts may modulate VSMC proliferation and migration. Integrin-linked kinase (ILK) is a ubiquitously expressed protein serine/threonine kinase that has been implicated in cell-matrix and cell-cell signaling pathways. In this study we assessed the expression of ILK in the first wave of proliferation and migration and during intimal thickening in balloon injured rat carotids using immunocytochemistry and Western blotting (n=4). Expression of ILK was dramatically increased in the first 48 hours after balloon injury of rat carotids coinciding with induction of medial VSMC migration and proliferation. Furthermore, the expression of ILK was greatly increased in the intima at 10 days after injury (n=4). Similar findings were observed in a human saphenous vein model of intimal thickening (n=6). To directly examine the role of ILK, cultured human VSMCs were infected with 300 plaque forming units per cell of an adenovirus (RAd ILK-KD) to express a kinase deficient ILK (ILK-KD) and compared to VSMCs infected with a control virus (RAd Lac-Z). Cell proliferation assessed by tritiated thymidine incorporation was significantly reduced by 33±6% in cells over-expressing ILK-KD compared to VSMC infected with control virus at 42 hr after infection (n=3, $p<0.05$). Furthermore, cell number was significantly reduced by 48±7% in cells over-expressing ILK-KD compared to controls at 90 hr after infection (n=3, $p<0.05$). Wounding assays illustrated VSMC migration was significantly reduced by 9.5±2.4 fold following over-expression of ILK-KD compared to control infected cells at 42 hr after infection (n=4, $p<0.05$). Over-expression of ILK-KD dramatically reduced cell-matrix contacts assessed by immunocytochemistry for the focal adhesion protein, paxillin, cleavage of phosphorylated FAK and disorganization of alpha-actin stress fibres at 42 hr after infection. Furthermore, disassembly of cell-cell contacts as assessed by Western blotting and immunocytochemistry for beta-catenin and N-cadherin occurred in cells at 42 hr after infection with RAd ILK-KD (n=3).
Our data suggests that inhibition of ILK disrupts the cell-matrix contacts via focal adhesions and cell-cell junctions by modulating beta-catenin and N-cadherin levels and results in the inhibition of proliferation and migration. We suggest that ILK plays a central role in promoting intimal thickening by increasing VSMC proliferation and migration.

749 Lysyl oxidase downregulation by LDL in endothelial cells requires LDL internalization and processing

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Extracellular matrix (ECM) plays a key role in the development of the atherosclerotic process. One of the enzymes involved in ECM maturation is lysyl oxidase (LOX) whose expression/activity is decreased by LDL in the vascular wall (ATVB 2002; 22:1409).
Purpose: To analyze the molecular mechanisms involved in LOX downregulation by LDL.
Methods: RT-PCR assays were developed to determine LOX mRNA levels in porcine aortic endothelial cells (PAEC) and human LDL receptor (LDL-R)-deficient fibroblasts. LOX activity was evaluated by a high-sensitivity fluorimetric assay. Expression levels of GRP78, marker of endoplasmic reticulum (ER) stress, were analyzed by Western-blot.
Results: LDL-mediated LOX downregulation was not observed in LDL-R deficient fibroblasts suggesting the involvement of LDL-R on this effect. In addition, LOX mRNA downregulation was abrogated in the presence of chloroquine, an inhibitor of lysosomal processing. LDL lipid extracts or fatty acids only caused a little decrease of LOX mRNA levels not comparable to LDL effects. Inhibition of pertussis toxin-sensitive G proteins did not abrogated the LDL-mediated reduction of LOX. On the other hand, LDL bioactive components such as Sphingosine-1-P or C2-Ceramide did not alter LOX expression. Although tunicamycin, an ER stress inducer, decreased LOX activity, GRP78 protein levels were not modified by LDL, thus this treatment did not cause ER stress.
Conclusion: LOX downregulation by LDL seems to be independent of cell signalling pathways activated by bioactive LDL components but dependent of LDL internalization and lysosomal processing. These findings suggest that LOX downregulation and hence ECM proatherogenic permeability changes are LDL-Apo-B dependent and may provide a new therapeutic antiatherogenic target.

750 Resistin promotes smooth muscle cell proliferation through activation of the ERK1/2 pathway

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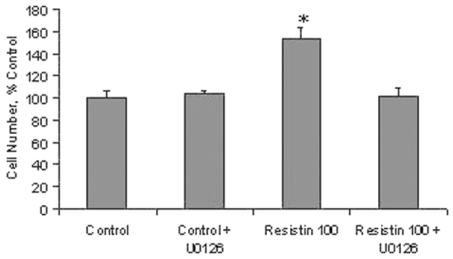
Resistin is a novel adipokine and its biological role in humans is unclear; however, plasma resistin concentrations are elevated in patients with type 2 diabetes. Restenosis is a major complication of PTCA, expecially in patients with type 2 diabetes. Proliferation of smooth muscle cells (SMCs) is a key event in this process.
Purpose: To assess whether resistin could induce SMCs proliferation and to study the mechanisms whereby resistin signals in SMCs.
Methods and Results: 24 hour-serum starved human aortic SMCs were stimulated with increasing concentrations (10, 25, 50, and 100 ng/ml) of resistin for 48 hours. Cell proliferation was induced by resistin in a dose-dependent manner as assessed by direct cell counting (maximum 1.5-fold over medium alone at 100 ng/ml). To investigate the molecular mechanisms involved we assessed whether this phenomenon was the result of activation of the extracellular signal regulated kinase (ERK) pathway. SMCs were stimulated with resistin (100 ng/ml) and pro-

cessed for total protein isolation at baseline (no stimulation), and after 10, 15, 60 and 180 min following stimulation. Transient (10-15 min) phosphorylation (activation) of the p42/44 MAP Kinase (ERK1/2) was shown by immunoblotting. To better define the role of pERK in SMC proliferation, SMCs were preincubated with U0126 (10 μM), a specific inhibitor of ERK phosphorylation; SMCs were stimulated with Resistin and proliferation and ERK phosphorilation evaluated. The resistin-induced SMCs proliferation and the ERK1/2 activation were both suppressed by pretreatment with the U0126.



Conclusions: We provide the first evidence that resistin, a novel adipokine, activates ERK and causes HASMCs to proliferate, suggesting a novel link between type 2 diabetes and restenosis.

751 Profilin is expressed in human atherosclerotic plaques and induces proliferation and migration of vascular smooth muscle cells

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Profilin is an ubiquitously expressed protein characterized by the ability to sequester actin monomers. In addition, it interacts with signaling molecules like vasodilator-stimulated phosphoprotein (VASP). Under some pathological conditions like experimental glomerulonephritis it is secreted into the extracellular space and induces cellular responses on mesangial cells. We have recently demonstrated that profilin levels are increased in the aortic endothelium of diabetic rats and that profilin overexpression triggers indicators of endothelial dysfunction downstream of LDL signaling. We now investigated profilin expression in human atherosclerotic plaques and evaluated atherogenic cellular effects on vascular smooth muscle cells (VSMCs).
Immunostaining of coronary arteries from 5 patients with coronary heart disease (CHD) showed profilin expression in atherosclerotic plaques but not in the normal vessel wall. Stimulation of quiescent VSMCs with profilin (10^{-7}M) in vitro led to phosphorylation of specific intracellular signaling cascades like extracellular-regulated kinase (Erk 1/2), p70S6 kinase and Akt within 10-15 minutes. Furthermore, profilin induced DNA synthesis in VSMCs in a dose-dependent manner, as BrdU incorporation increased to 163.4 ± 4.5% and 170.4 ± 7.4% upon stimulation with profilin at 10^{-7}M and $^{10-6}$M, respectively, compared to unstimulated control cells (both $p<0.05$). Chemotaxis assays, performed using a modified Boyden chamber, also demonstrated a dose-dependent increase in VSMC migration upon profilin stimulation (10^{-9} to $^{10-6}$M) within 5 hours to 141 ± 2.4% (10^{-8}M), 159 ± 8% (10^{-7}M), and 190 ± 22% (10^{-6}M) versus non-stimulated controls (all $p<0.05$). Preincubation with the PI 3-kinase inhibitor wortmannin (100 nM) led to complete inhibition of profilin-induced Akt phosphorylation and abolished DNA synthesis, whereas the MEK inhibitor PD 98059 (10 μM) completely inhibited profilin-induced Erk phosphorylation in VSMCs.
We demonstrate that profilin is expressed in human atherosclerotic plaques, whereas it is not detected in normal vessel wall. Furthermore, profilin induces atherogenic cellular effects in VSMCs such as proliferation and migration. These data implicate that profilin may be involved in the pathogenesis of atherosclerosis and may thus represent a novel therapeutic target.

752 Calpain activation counteracts mechanically-induced apoptosis of vascular smooth muscle cells in vitro and after angioplasty in vivo

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Background: Exposure of the vessel wall to intense mechanic force causes rapid onset of apoptosis of vascular smooth muscle cells (VSMC) within the media, thereby initiating chronic remodeling processes. Although involvement of the cysteine protease calpain in apoptosis has been suggested, its role in mechanic stress-induced programmed cell death remains obscure. We hypothesized that calpain is a regulator of apoptosis of VSMCs exposed to mechanic stress in vitro and in vivo after ballon angioplasty.
Methods and Results: Rat VSMC were subjected to cyclic-stretch (0.5 Hz at 125% resting length). After 24 h apoptotic nuclei had increased from 3±1% to 11±3% as measured by dUTP-biotin nick end labeling (TUNEL). Beginning at 8 h, p53 and p21Cip1 expression as well as Bax/bcl-2 ratio increased as determined by immunoblot. Within 15 min of stretch calpain activity was upregulated 2.4±0.4 fold (n=6, $P<0.001$) as measured by the fluorigenic calpain substrate SLLVT-AMC. Inhibition of calpain activity by PD150606 or calpeptin dramatically augmented stretch-induced p53 and p21Cip1 expression and Bax/bcl-2 ratio. Stretch-induced apoptotic rate was further increased to 35±4% and 30±6% of cells ($P<0.01$) respectively. The p53 inhibitor pifithrin was able to prevent increased p21Cip1 expression, Bax/bcl-2 ratio and apoptotic rate (8±2%) induced by calpain inhibition. These in vitro results were transferred into the rat model of carotid artery dilatation: Ballon injury resulted in an increase of apoptotic nuclei from 0.2±0.2 to 12.3±2.2% of medial cells within 12 h (TUNEL). Intravenous pretreatment of the animals with the calpain inhibitor calpeptin (250 μg/kg) resulted in a further significant increase of apoptotic nuclei to 20.2±3.3%. As well, medial cellularity was found significantly reduced from 316±24 (undilated control) to 263±20 cells 24 h after ballon injury. Calpeptin treatment further augmented this cell loss to 198±20 cells, n=6, $P<0.05$).
Conclusion: Calpain counter-acts mechanically-induced excessive VSMC apoptosis in vitro and in vivo presumably through prevention of p53 upregulation. Therapeutic modulation of calpain activity may represent a novel strategy to influence vascular remodeling processes through targeted induction of apoptosis (for the prevention of restenosis) or inhibition of apoptosis (to allow positive remodeling of vein grafts).

OXIDATIVE STRESS AND THE ENDOTHELIUM

767 The multidrug resistance protein 1 mediates cell survival under oxidative stress

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Atherosclerotic plaques develop preferably in regions exposed to oscillatory shear stress such as arterial branch points. Oscillatory shear has been connected with endothelial dysfunction, increased reactive oxygen species (ROS) and apoptosis. One of the major cellular oxidant defense systems involves the redox couple of reduced and oxidized glutathione (GSH/GSSG). It has been shown that exposure to ROS decreases levels of intracellular GSH and this is due to active transport out of the cell. We therefore sought to identify the transport protein and to determine if export of GSH or its oxidized form GSSG under oxidative stress affect endothelial cell survival.
We exposed human aortic endothelial cells (HAECs) to oscillatory or laminar shear for up to 16 hours and measured GSH/GSSG or its product disulfide (DS) by HPLC. These measurements revealed an active transport of GSSG by the multidrug resistance protein 1 (MRP1), which we found to be strongly expressed in HAECs and mouse aortas by Western Blot. Inhibition of MRP1 by MK571, a specific pharmacologic inhibitor, or downregulation by siRNA both efficiently prevented this export. To examine if inhibition of MRP1 modifies the cellular survival we exposed HAECs to shear and measured the rate of apoptosis via caspase 3 activity and annexin V expression. Inhibition of MRP1 resulted in a 50% reduction in apoptosis under oscillatory shear. To confirm these findings in vivo we used DOCA salt hypertensive mice, an animal model of oxidative stress, and measured the release of GSSG dependent DS from the endothelium in mouse aortas by HPLC. We found 2-fold enhanced levels of DS in DOCA salt aortas compared to control animals and were able to inhibit the observed export by incubation with MK571. MRP1-/-mice showed drastically reduced levels of DS and no increase under DOCA salt hypertension compared to controls. TUNEL staining of the aortas revealed an increased rate of apoptosis under DOCA salt hypertension compared to control and MRP1-/-DOCA salt hypertensive animals. In addition endothelial dependent vasorelaxation was significantly less impaired in MRP1-/-DOCA mice vs. DOCA salt controls.
In summary our findings identify a novel mechanism of oxidative stress management in endothelial cells and may provide a new therapeutic target.

768 Regulation of endothelial xanthine oxidase expression and activity by angiotensin II: impact on endothelial function

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Introduction: Angiotensin II (ang II) induced vascular superoxide production may contribute to endothelial dysfunction and atherosclerosis.We have recently reported that xanthine oxidase (XO) activity, a major vascular superoxide forming enzyme system, is increased in patients with coronary disease (CAD) and relates inversely to endothelial function.We therefore hypothesized that angII may be important in regulation of vascular XO and determined the effect of ang II on endothelial XO expression and XO-mediated superoxide production in vitro and its relevance for endothelial dysfunction in patients with coronary disease.

Methods: Time and dose dependent expression of xanthine oxidase in response to angII (10^{-7}mol/l) was determined in cultured bovine aortic endothelial cells (BAECs).The effect of the XO inhibitors oxypurinol and tungsten, on ang II-stimulated superoxide production was analyzed by electron-spin-resonance spectroscopy (ESR) using the spin trap CP-H.Furthermore,the effect of vascular xanthine oxidase inhibition (oxypurinol;600μg x min-1;i.a.) in vivo on flow-dependent, endothelium-mediated vasodilation (FDD) of the radial artery was analyzed before and after 4-weeks treatment with the AT-1 receptor antagonist losartan (50 mg bid) in 10 patients with coronary disease.
Results: Ang II substantially increased XO protein expression and potently stimulated superoxide anion formation in cultured BAECs (4.4±0.4 vs. 1.5±0.2 nmolO2-/μg protein;p<0.01).Both, ang-II stimulated endothelial XO expression and superoxide anion formation were completely abolished by co-treatment with the AT1-recepetor antagonist losartan (1.6±0.3nmol O2-/μg protein;p<0.01), whereas the AT2 receptor antagonist PD 123319 had no effect (4.3nmolO2-/μg protein;n.s.).Importantly, two specific XO inhibitors (oxypurinol and tungsten; both 10^{-6}mol/l) markedly inhibited angII-stimulated superoxide production in cultured BAECs (oxypurinol:2.5±0.2 vs.4.4±0.4;tungsten 2.7±0.1 vs.4.4±0.4 nmol O2-/μg protein;each p<0.01). In vivo, oxypurinol improved FDD in patients with CAD by more than 50% (5.2±1.1 vs. 8.8±1.2%; p<0.05) before AT-1 receptor blocker treatment, while having no effect after 4 weeks of losartan treatment (10.8±0.7 vs. 10.9±0.9%), suggesting that ang II is critically involved in regulation of vascular XO activity in vivo.
Conclusions: These findings suggest that ang II is a potent regulator of XO protein expression and activation in endothelial cells via the AT1-receptor.AngII induced upregulation of xanthine oxidase appears to contribute to endothelial dysfunction in patients with coronary disease.

769 Evidence of a functional role in vivo in humans of the T242C p22phox SNP on forearm blood flow responses of hypertensive patients

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Background and Aim: Genetic factors and superoxide anion (O2°-) affect endothelial (E) function. A C242T single nucleotide polymorphism (SNP) on exon 4 of the NAD(P)H oxidase p22phox subunit gene substitutes His-72 to Tyr residues at a heme-binding site and may modulate NAD(P)Hox activity and vascular O2°-generation.
Design and Methods: We compared E-dependent (EDV) and E-independent (EIV) vasodilatation across p22phox genotypes in 228 subjects, 165 uncomplicated essential hypertensive patients (PH) and 63 healthy normotensive subjects (NT). EDV and EIV was assessed as the forearm blood flow response to acetylcholine (ACH; 0.15, 0.45, 1.5, 4.5, 15 μg/100 ml/min) and sodium nitroprusside (SP, 1, 2, 4 μg/100 ml/min), respectively. We evaluated the impact of the p22phox SNP on NO-mediated EDV and on ROS-induced NO breakdown with the NOS inhibitor N(G)-monomethyl-L- arginine (L-NMMA, 100 mg/100 ml/min) or vitamin C (2.4 mg/100 mL ml/min), respectively. Melting curve analysis of amplicons from fluorescent SNP specific probes was used for genotyping.
Results: There were (p=0.02) less TT homozygous in PH (11%) than in NT (25%). EDV was lower in PH than in NT (p<0.001), and in patients with than without family history of hypertension. The C242T SNP affected EDV, but not EIV, by interacting (p=0.001) with gender and age. NO inhibition did not unveiled any SNP effect on EDV. By contrast, TT homozygous PH patients, but not NT subjects, showed a blunted response to vitamin C compared to the other genotypes.
Conclusions: These results indicate a functional role in vivo in humans of the T242C p22phox SNP on EDV, likely by altering vascular O2°- production.

770 Beneficial effect of folic acid on endothelial dysfunction after acute myocardial infarction

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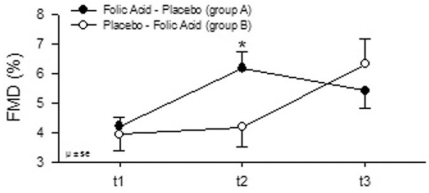
Background: Endothelial dysfunction is one of the consequences of ischemia/reperfusion (IR)-injury after an acute myocardial infarction (AMI). Recent in vitro and in vivo experiments demonstrated a beneficial effect of folic acid (FA) on IR-induced injury.
The mechanisms of action of FA are multiple. FA not only lowers total homocysteine (tHCY), it also enhances the bioavailability of tetrahydrobiopterin, it directly interacts with eNOS and it has antioxidant and antithrombotic capacities.
Material en methods: A randomized, double-blind crossover study was performed in 30 patients with AMI. In group A, FA(10mg/d) was administered for 6 w, followed by a washout period (2 w) and by a placebo period (6w). Group B received first the placebo, thereafter FA. Endothelial function was assessed by flow-mediated dilation (FMD), using high-resolution ultrasound at t1(basal), t2(week 6) and t3(week 14).
Results and Conclusion: FMD values at t1, t2 and t3 for group A and B are demonstrated in the figure. There was a significant difference in FMD between both groups at t2 (p=0.031, Mann-Whitney). FMD in group A decreased when giving placebo, but this was not significant.



Basal tHCY-levels were comparable among the groups (group A: 15.1±1.1 μmol/L, group B: 13.5±1.3 μmol/L; p=0.52, Mann-Whitney). There was no correlation between differences in tHCY and in FMD at t1-t2 for group A (Spearman rho=-0.21, p=0.40) and t2-t3 for group B (rho=-0.07, p=0.85). Repeated measures ANOVA indicated a significant interaction effect (p=0.001), demonstrating the different behaviour between the groups over the time. Using tHCY as a covariate in this analysis didn't abolish the interaction-effect (p=0.002), indicating that the beneficial effect of FA on FMD in AMI is independent of tHCY.

771 Red wine and grape juice reverse human endothelial dysfuncion independently of lipid effects

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Background: Although red wine (RW) may reduce cardiovascular risk the mechanisms remain poorly defined. Since endothelial dysfunction is a key event in coronary artery disease (CAD), we investigated whether RW and grape juice (GJ) could correct it in hypercholesterolemic individuals.
Objective: To compare the effect of RW and GJ upon vasodilatory function, ICAM-1 and VCAM-1, platelet aggregability and lipids.
Methods: Flow-mediated dilatation (FMD) as well as endothelium independent vasodilatation (NT) were measured in the brachial artery using high-resolution ultrasonography, with 7.5 MHz transducer. We studied 16 hypercholesterolemic patients (pts), without other risk factors. There were 8 men and 8 women, whose age was 52±8 years (mean±SD). Pts were randomized to either RW (250 ml/day) or GJ (500 ml/day) for 14 days, and then crossed over, with equal wash-out periods; hence each pt received both treatments.
Results: At baseline, total plasma cholesterol was 262.2±36 mg/dl, LDL 181.2±29 mg/dl, HDL 57.2±16 mg/dl, tryglicerides 121.1±49 mg/dl, Lp(a) 35.5±34 mg/dl, Apo(A1) 1.5±0.3 mg/dl and Apo(b) 1.3±0.3 mg/dl. VCAM-1 averaged 363.2±127 ng/ml and ICAM-1 140±47 mg/ml. FMD increased significantly with both GJ and RW (table). Endothelium-independent dilatation also increased significantly after RW, but not with GJ. ICAM-1 decreased with GJ only (140±47 vs 115.2±21; p<0.05) but VCAM-1 was unaffected. No significant alterations were observed in plasma lipids, and platelet aggregability with either RW or GJ.

	Baseline	GJ	Baseline	RW
% FMD	10.9±7.4%	16.9±6.7%*	10.1±6.4%	15.6±4.6%*
%NT	19.8±8.7%	18.0±9.4%	17.0±8.6%	23.0±11.9%*

*p<0.05; n=16

Conclusions: Both RW and GJ similarly improved FMD in pts with persistent hypercholesterolemia. Hence, FMD improvement is independent of alcohol and lipids; it is probably due to flavonoids. Endothelial protection is one mechanism by which RW and GJ reduce cardiovascular risk.

772 Rosuvastatin and oxidative stress induced by nitrate tolerance

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Background: Nitrate tolerance is associated with an enhanced superoxide anion production and could be attenuated by statins as they interact with the two main (eNOS and NAD(P)H oxidase) pathways involved in this oxidative stress.
Methods: 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 nitroglycerin (NTG 50 mg/kg/d, sub-cutaneous injections b.i.d.); group 2 received only NTG (50 mg/kg/d, b.i.d. for 3 days) and group 3 served as control. 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 O2- production (counts/10s/mg) was assessed by lucigenin chemiluminescence technique.
Results: 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); O2- 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) and O2- production was decreased: 208±19 (n=6, P<.05 vs group 2). In addition, before NTG exposure, rosuvastatin treatment decreased p22phox (the essential NAD(P)H subunit) abundance in aortic wall and NAD(P)H oxidase activity. In contrast, this treatment did not alter either eNOS abundance or the basal release of endothelium-derived NO.
Conclusion: Long-term rosuvastatin treatment protects against nitrate tolerance by counteracting NTG-induced increase in O2- production in the rat aorta. This protection seems to involve a direct interaction with the NAD(P)H oxidase pathway rather than an upregulation of the eNOS pathway.

IMPROVING RISK STRATIFICATION BY NUCLEAR CARDIOLOGY

794 Extensive left ventricular remodeling does not allow viable myocardium to improve in left ventricular ejection fraction post-revascularization and is associated with worse long-term prognosis

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Background: Extensive left ventricular (LV) remodeling may not allow functional recovery post-revascularization, despite the presence of viable myocardium.
Methods and Results: 79 consecutive patients with ischemic cardiomyopathy (LVEF 29±7%) underwent surgical revascularization.
Before revascularization, viability was assessed by metabolic imaging with F18-fluorodeoxyglucose and SPECT. LV volumes and LVEF were assessed by resting echocardiography. LVEF was re-assessed by echocardiography, 8-12 months post-revascularization. Three-year clinical follow-up (events: cardiac death, infarction and hospitalization for heart failure) was also obtained.
49 patients had substantial viability; 5 died before re-assessment of LVEF. Of the remaining 44 patients, 24 improved >5% in LVEF after revascularization, whereas 20 did not improve in LVEF. LV end-systolic volume was the only parameter that was significantly different between the groups (109±46 ml for the improvers vs 141±31ml for the non-improvers, P<0.05). The change in LVEF post-revascularization was linearly related to the baseline LV end-systolic volume, with a higher LV end-systolic volume associated with a low likelihood of improvement in LVEF post-revascularization. During the 3-year follow-up, the highest event-rate (67%) was observed in patients without viable myocardium with a large LV size, while the lowest event-rate (5%) was observed in patients with viable myocardium and a small LV size. Intermediate event-rates were observed in patients with viable myocardium and a large LV size (38%), and in patients without viable myocardium and a small LV size (24%).
Conclusion: Extensive LV remodeling prohibits improvement in LVEF post-revascularization and affects long-term prognosis negatively, despite the presence of viability.

795 Prognostic value of left ventricular cavity dilatation during 99mTc-tetrofosmin exercise myocardial scintigraphy for predicting coronary events

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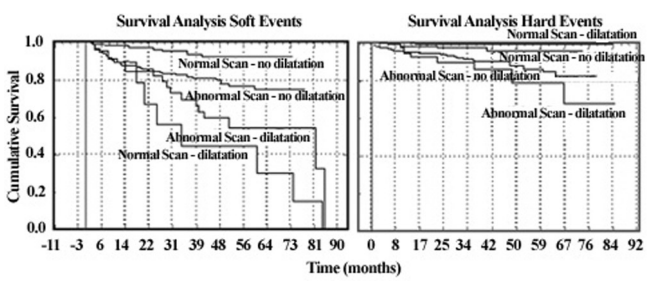
Transient of fixed left ventricular (LV) dilatation during myocardial scintigraphy has been associated with multivessel disease, and may be an independent prognostic marker in addition to perfusion defects. The aim of the present study was to assess the predictive value for future cardiac events of LV dilatation during 99mTc-Tetrofosmin exercise SPECT myocardial perfusion imaging in addition to perfusion defects. The study included 546 consecutive patients, 440 without LV dilatation and 106 with transient or fixed LV dilatation who underwent SPECT imaging with 99mTc-Tetrofosmin after exercise testing. Follow-up, defined as the time from scanning until a hard event (myocardial infarction and cardiac death) or soft event (hospitalization for heart failure, unstable angina or coronary revascularization) or patient response, lasted up to 84 months (median 39). An ischemic scintigraphic perfusion score, which takes into account both the extent and severity of abnormal perfusion defects both at rest and after stress, was calculated to estimate the severity of perfusion abnormalities. Statistical analysis using the Kaplan-Meyer survival curves showed a significant difference in event free survival for both hard and soft events (p<0.05 and p<0.0001. respectively) between patients with normal scan with no LV dilatation, normal scan with LV dilatation, abnormal scan with no LV dilatation and abnormal scan with LV dilatation as shown in the figure. The group with the highest risk for both hard and soft events had a LV dilatation.



In conclusion, transient or fixed LV dilatation are commonly seen during 99mTc-Tetrofosmin exercise SPECT myocardial perfusion imaging and are useful predictors of cardiac events.

796 Rest myocardial perfusion imaging in the identification of acute coronary syndromes

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Background: Chest pain in patients presenting to the emergency department remains a major challenge. One of the goals in the management of these patients is the rapid identification of an acute coronary syndrome. Myocardial injury is associated with elevated blood levels of troponin and occurs in higher risk patients. The purpose of this study was to evaluate rest myocardial perfusion imaging (RMPI) in the identification of acute coronary syndromes (ACS).
Methods: Patients (pts) with ongoing chest pain or an episode of pain in the last six hours, without a history of myocardial infarction and haemodinamically stable, were enrolled in this study. After clinical evaluation, a blood sample was drawn for assessment of troponin I. Values above 0,20 ng/ml, were considered positive. A second assessment of troponin was performed four hours later if the first result was negative or inconclusive. RMPI was performed after the first blood sample was drawn. Tomographic images were acquired after an injection of 15 mCi of 99mTc-tetrofosmin and were analyzed regarding the presence of perfusion defects (abnormal rest perfusion).
Results: One hundred and seven patients were included in the present study, 77 males (72,0%) and 30 females (28,0%). Their mean age was 62,1 ± 12,4 years. Thirty-four patients (31,8%) were diagnosed with an ACS by elevation of troponin I; the first assessment of troponin was positive in 19 (55,9%) of these pts. RMPI was abnormal in 68 pts (63,6%) and 33 of those pts had an ACS (97,1%) with elevated troponin (p<0,0001). Nineteen (26,0%) of the 73 patients without elevated troponin I were eventually identified as having a significant underlying coronary artery disease. RMPI was abnormal in 16 (84,2%) and normal in 3 (15,8%) of these patients (p= 0,0002).
Conclusions: Rest myocardial perfusion imaging identified 97,1% of patients with an acute coronary syndrome (elevated troponin I) while the initial Troponin was positive in only 55,9% of the patients. Rest myocardial perfusion imaging was abnormal in 92,5% of patients with an acute coronary syndrome or/and the diagnosis of significant coronary artery disease. Although a sensitive marker of risk, Troponin needs more than one assessment to identify patients with myocardial injury and this introduces a delay in diagnosis and early treatment. Rest myocardial perfusion imaging is useful in the management of patients with chest pain, especially when the other exams are inconclusive or negative and follow-up evaluations are indicated.

797 Prognostic value of myocardial perfusion imaging in symptomatic and asymptomatic patients after percutaneous coronary intervention

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We previously reported on a similar rate of ischemia by myocardial perfusion imaging (MPI) in a cohort of symptomatic and asymptomatic patients after stenting percutaneous coronary intervention (PCI). The aim of this study was to evaluate the prognostic value of MPI in predicting major adverse cardiovascular events (MACE) after PCI in these patients.
Methods: In 2003 we presented a group of 337 patients after PCI (all underwent stenting), and performed stress MPI that has been followed-up for 12±2 (8-16) months to determine the presence of MACE (cardiac death, myocardial infarction, PCI or CABG). All clinical, risk factors for CAD, stress and perfusion variables were included in the univariate analysis.
Results: MACE were presented as follow: cardiac death in 9 (2.9%), myocardial infarction in 12 (3.9%), PCI in 36 (11.8%) and CABG in 16 (5.3%). Of note MACE rate was similar in symptomatic and asymptomatic patients [32/186 (17%) vs. 19/119 (16%), p=NS].
The results of clinical and MPI variables are presented in Table 1.
In multivariate analysis, presence of ischemia was the most important independent predictor of MACE (odds ratio 7.45, CI 95%2.95-18.8, p<0.001).
Conclusion: The presence of myocardial ischemia by MPI performed after PCI

Table 1

	MACE n=51 (%)	No MACE n=252 (%)	p value
Age	64.7±12.0	64.2±11.2	NS
Men	38 (74.5)	177 (70.2)	NS
S/P MI	17 (33.3)	101 (40.1)	NS
Hypertension	28 (54.9)	148 (58.7)	NS
Diabetes Mellitus	18 (35.3)	59 (23.4)	NS
Smoker	6 (11.8)	42 (16.7)	NS
Dyslipidemia	36 (70.6)	139 (55.2)	0.04
Symptomatic Patients	33 (64.7)	162 (64.3)	NS
Positive Ergometry	13/28 (46.3	55/129 (42.6)	NS
METs	9.0±2.7	9.4±2.7	NS
Ischemia	46 (90.2)	126 (50.0)	<0.01
Degree of Ischemia	1.76±0.76	1.4±0.5	0.03

predicts worse outcome during 1 year of follow-up in both symptomatic and asymptomatic patients.

798 Impaired microcirculation in reperfused territory precedes restenosis after direct stenting for acute myocardial infarction

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Purpose: Association of impaired microcirculation in the reperfused territories on target lesion restenosis following direct stenting for acute myocardial infarction (AMI) is unknown. Therefore, we performed 15O-water positron emission tomography (15O-water PET) and follow-up coronary angiography (CAG) in patients with AMI who underwent successful direct stenting.
Methods: In 20 patients with AMI (age 60±12 yrs: 13 men), direct stenting was performed within 8 hours after the onset. 15O-water PET was performed at 3 to 4 weeks from the onset, in which myocardial blood flow was measured at rest and during hyperemia induced by adenosine triphosphate (160μg/kg/min). Myocardial flow reserve (MFR) was calculated as the ratio of myocardial flow during hyperemia to that at rest in the reperfused territories and normal control territories. The first follow-up CAG was performed within 1 week after the PET study, and the second follow-up CAG was performed 5 to 8 months after the onset.
Results: No patient demonstrated restenosis in the treated artery at the first follow-up CAG that was performed within 1 week after the PET study. However, at the second CAG, restenosis occurred in 10 patients (Group A) while the treated lesions in the other 10 patients (Group B) remained free from restenosis. In the Group A, MFR in the reperfused regions was 2.44±1.25, which was similar to that in control regions (2.54±0.79, NS). However, in the Group B, MFR in the reperfused regions was significantly lower than that in normal control regions (2.02±0.28 vs. 2.67±0.54, $p<0.05$) despite the absence of angiographical restenosis
Discussion and Conclusion: Thus, significant association existed between microcirculatory reserve in reperfused territory at subacute phase and future restenosis of the culprit artery after direct stenting for AMI. It is speculated the sustained endothelial dysfunction or proinflammatory cytokine production at the target lesions at subacute phase may both accelerate local neointimal proliferation and limit microcirculatory vasodilator response in the distal regions.

799 Impact of viability assessment by positron emission tomography in non-revascularized patients with ischaemic dysfunctional myocardium

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Objective: Viability as detected by positron emission tomography (PET) is a well known important independent variable associated with outcome in patients with depressed left ventricular function. Revascularized patients do well, whilst patients that are not revascularized do poor. Nevertheless there is a lack of data on the relation between the extent of the mismatch area and cardiovascular risk in a large patient population with long term follow up. Our aim was 1. to evaluate the prognostic value of a viability pattern in a large not revascularized population of patients with ischemic cardiomyopathy undergoing a PET study. 2. to evaluate the impact of the extension of the mismatch area on prognosis.
Methods: 261 patients with ischemic cardiomyopathy and depressed left ventricular ejection fraction underwent positron emission tomography for assessment of viability and prospective follow-up.
Results: 94 patients were revascularized and excluded by the present analysis. The remaining 167 patients were not revascularized and represent our study population. Univariate predictors of death in the study population were age, diabetes, smoking habits, previous AMI, presence of LBBB, angiographic triple vessel disease and presence of a mismatch pattern at PET. Multivariate analysis selected age (p=0.005), left bundle branch block (p=0.001), and mismatch at PET (p=0.001) as independent prognostic indicator. An 8% increase in mismatch determined a 36% increase in risk. Cut-off analysis shows a non-significant effect on risk having a mismatch between 0-20 compared with 0 (HR 0.97, 95%CI 0.46-2.05), whereas the effect is significant for values above 20 (HR 3.21, 95% CI 1.38-7.49).
Conclusions: In non-revascularized patients with ischemic cardiomyopathy detection of viable myocardium with positron emission tomography identifies a group of patients at high risk of death in the follow-up. This risk is directly correlated with the extension of the mismatch area for values above 20%.

PATHOPHYSIOLOGICAL ASPECTS OF RESYNCHRONISATION THERAPY

817 Biventricular pacing reverses left ventricular non-uniform workload and remodeling induced by left bundle branch block

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Purpose: Clinical trials indicate that biventricular pacing (BiVP) can reduce left ventricular (LV) dilatation in patients with heart failure and left bundle branch block (LBBB). We investigated to what extent LBBB leads to abnormal contraction and ventricular remodeling and whether BiVP can reverse these processes.
Methods: In 14 dogs LBBB was induced by RF-ablation and divided into a group with 16 weeks (n=8) and a group with 8 weeks of LBBB followed by 8 weeks of BiVP (n=6). LV end-diastolic volume (EDV) and wall mass of the septum and LV lateral wall (LVLat) were measured biweekly by 2D-echocardiography. LV midwall systolic circumferential shortening (CSsys, MR tagging) and myocardial blood flow (MBF, fluorescent microspheres) were measured before (Baseline) and after 8 and 16 weeks of LBBB and after 8 weeks of BIVP.
Results: (table) LBBB reduced LV dP/dtmax by 22±15%* below Baseline while BiVP increased it by 12±7%** above LBBB level. During LBBB CSsys and MBF were decreased in the septum and increased in the LVlat, indicating nonuniform workload distribution. Values after 8 and 16 weeks of LBBB were similar(data not shown). BiVP restored regional CSsys and MBF to Baseline. LBBB gradually increased LV EDV and LVlat wall mass, indicating LV dilatation and asymmetric hypertrophy. Eight weeks of BiVP reversed LV EDV and LVlat wall mass to Baseline, indicating reversal of LV dilatation and regional hypertrophy.

BiV pacing during LBBB

(n=6)		LBBB	BiV
CSsys	LVLat	172±24%*	91±9**
	septum	14±5%*	114±16**
MBF	LVLat	71±10%*	95±10%**
	septum	122±13%*	101±23%**
wall mass	LVLat	128±17%*	113±11%**
	septum	106±14%	107±14%
LV EDV		128±20%*	108±14%**

Values are expressed as % of Baseline and were obtained after 8 weeks of LBBB and 8 weeks of BiVP. * And ** =$p<0.05$ compared to Baseline and LBBB, respectively.

Conclusion: This is the first evidence that biventricular pacing corrects the nonuniform LV workload distribution, the reduction in contractility, as well as the LV remodeling, induced by LBBB.

818 What is the best ultrasound modality to evaluate mechanical asynchrony in patients with biventricular pacemaker for dilated heart failure? Preliminary results from the EVER-PACING study

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Background: Cardiac resynchronization therapy (CRT) is now used for treatment of dilated heart failure with left bundle branch block but the best index to assess mechanical ventricular asynchrony has not been established. To address this topic the multicenter 1-year follow-up EVER-PACING study has been designed. Preliminary data relative to the acute patient evaluation are presented here.
Methods: Thirty-seven patients (mean age 68±8 years, 27 males) with dilated cardiomyopathy, NYHA class III-IV, left ventricular ejection fraction (LV-EF) <35%, QRS>120 ms were studied before the implantation of the biventricular pacemaker and at predisharge. The following ultrasound parameters were evaluated: LV end-diastolic and end-systolic volume (EDV, ESV, ml), LV-EF (%), Doppler dP/dt (mmHg/s), color Doppler area (cm^2) and CW Doppler duration (ms) of mitral regurgitation (MR). Four ultrasound indexes of mechanical asynchrony were also calculated: conventional Doppler interventricular delay (Qa-Qp, ms), M-mode peak septal to posterior wall motion delay (SPWMD, ms), tissue Doppler standard deviation of 12 time-to-peak systolic LV myocardial velocities (DTI-SD, ms), and

standard deviation of 4 time-to-peak systolic LV myocardial strains (Strain-SD, ms). Differences between variables were evaluated by the Student t-test.
Results: See table. Feasibility and reproducibility were significantly higher for Qa-Qp and Strain-SD and lower for SPWMD and DTI-SD.

Parameter	Pre-CRT	Post-CRT	P	Parameter	Pre-CRT	Post-CRT	P
EDV	239±72	224±67	< 0.001	MR dur	436±140	369±143	< 0.001
ESV	185±60	160±51	< 0.001	Qa-Qp	57±26	32±20	< 0.001
EF	23±7	28±6	< 0.001	SPWMD	184±89	46±84	< 0.001
dP/dt	494±205	701±187	< 0.001	DTI-SD	58±22	39±20	< 0.001
MR area	9±6	6±5	< 0.001	strain-SD	103±6	70±4	= 0.022

Conclusions: Indexes of both interventricular (Qa-Qp) and intraventricular (SPWMD, DTI-SD, Strain-SD) mechanical asynchrony are acutely reduced by biventricular pacing, with simultaneous reduction of LV volumes and MR and increase of global systolic LV function. Feasibility and reproducibility, however, are higher for Qa-Qp and Strain-SD. These two indexes, therefore, could be both used for evaluation of mechanical inter and intraventricular asynchrony in clinical practice.

819 Biventricular pacing reduces interstitial remodelling, tumour necrosis factor-alpha expression, and apoptotic death in human chronic heart failure

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Recent data from the COMPANION trial have for the first time documented that cardiac resynchronization therapy with biventricular pacing (CRT) increases survival in patients with advanced chronic heart failure. Despite this will lead to a steady increase of biventricular device implantation, little is known regarding the cellular and molecular underpinnings of CRT. To this aim, we performed endomyocardial biopsies in 8 patients, aged 62±8, with dilated cardiomyopathy before and 6 months after the implantation of a biventricular pacing device. Clinical status, left ventricular (LV) architecture and function were assessed as well as myocardial ultrastructure, tumor necrosis factor-alpha expression, and apoptotic index.
CRT improved clinical status as shown by a significant reduction of the score on the Minnesota living with heart failure questionnaire (+24%), 6-minute walked distance (+13%) and total exercise time (+14%) (all p<.05 vs. baseline). This was associated with reverse LV remodeling substantiated by LV volumes and mitral regurgitant area reductions. Direct examination of myocardial tissue revealed a significant decrease of collagen volume fraction from 24% to 18.2%, tumor necrosis factor-alpha expression (-40%), and apoptotic index (-23%), with increased capillary density (+11%) after 6 months of biventricular pacing (all p<.05 vs. baseline). We provide the first evidence of reduced interstitial remodeling, tumor necrosis factor-alpha expression and apoptosis by CRT, all factors that may underlie its beneficial effects on heart failure progression and survival.

820 3D-electroanatomical mapping in heart failure patients with right bundle branch block

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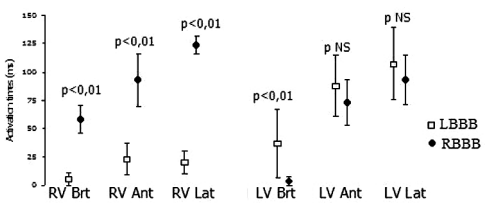
Purpose: The sequence of right (RV) and left ventricular (LV) activation in patients (Pts) with heart failure (HF) and right bundle branch block (RBBB) has not been characterized yet. We characterized endocardial RV and LV activation sequence in HF Pts with RBBB using 3D electroanatomic mapping system (3D-Map) in order to provide the electrophysiological background that is needed for better understanding which Pts will most likely benefit from cardiac resynchronization therapy (CRT) and for eventually identifying optimal pacing site(s).
Methods: Using 3D-Map, RV and LV activation sequences were studied in 6 HF Pts with RBBB, and were compared with those of 60 HF Pts with left BBB (LBBB) matched for age, gender, cardiomyopathy etiology, coronary involvement, and QRS duration.
Results: The vast majority of RBBB Pts had coronary artery disease involving the left anterior descending artery. Clinical and hemodynamic profile was significantly worse in the RBBB group compared to LBBB group. According to 3D-Map analysis RBBB Pts showed significantly longer delays of RV endocardial breakthrough (Brt), significantly longer activation times of the anterior (Ant) and lateral (Lat) RV regions and of total RV compared to LBBB Pts. Delay of LV Brt was significantly shorter in RBBB Pts, while activation times of the Ant and Lat LV regions and of total LV were not significantly different between the two groups (graph).



Activation times.

Conclusions: Pts with RBBB, compared to those with LBBB, have greater right-sided delay, while the degree of LV conduction delay is similar. The assessment of such electrical abnormalities is facilitated by 3D-Mapping and may be useful to understand how CRT should best be delivered in this group of Pts.

821 Comparative assessment of right, left and bi-ventricular pacing in patients with permanent Atrial fibrillation

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Purpose: Pacing from the apex of the right ventricle is sub-optimal as it provides non physiologic asynchronous contraction and detrimental remodeling. Purpose was to test the hypothesis that left ventricular (LV) and biventricular (BiV) pacing are superior to right ventricular (RV) apical pacing in patients undergoing AV junction ablation and pacing for permanent atrial fibrillation.
Method: Prospective randomized, single blind, 3-month cross-over comparison between RV and LV pacing (phase 1) and between RV and BiV pacing (phase 2) performed in 56 patients (70±8 years, 34 males) affected by severely symptomatic permanent atrial fibrillation, uncontrolled ventricular rate or heart failure. Primary endpoints were quality of life and exercise capacity.
Results: Compared with RV pacing, the Minnesota LHFQ score improved by 3% and 9% with LV and BiV pacing respectively, the NYHA class score by 5% and 7%, the 6 min walking distance by 9 (+3%) and 14 (+4%) meters (no statistical difference). Similar results were observed in patients with or without systolic dysfunction and/or native left bundle branch block. Compared with pre-ablation measures, the Minnesota LHFQ score improved by 37%, 38% and 48% with RV, LV and BiV pacing respectively, the NYHA class score by 21%, 25% and 30%, the 6 min walking distance by 37 (13%), 46 (16%) and 65 (22%) meters (all differences p<0.05). The Specific Symptom Scale, the Karolinska questionnaire and the clinical event occurrence gave similar results.
Conclusions: Rhythm regularization achieved with AV junction ablation improved quality of life and exercise capacity with all modes of pacing. LV and BiV pacing provided no significant additional favorable effect compared to RV pacing. This effect seems to be equal in patients with both depressed and preserved systolic functions and in those with and without native left bundle branch block.

822 Quantitative assessment of intraventricular asynchrony with real-time 3D echo in patients with narrow QRS complexes: is it possible to identify a new target group for resynchronisation therapy?

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Purpose: Patient selection for cardiac resynchronisation therapy (CRT) relies on prolonged QRS duration, but this has been shown to be a poor marker for intraventricular asynchrony. Real-time 3D echo (RT3DE) can quantify mechanical asynchrony and possibly identify a new target group for CRT.
Methods: 65 patients with left ventricular ejection fraction < 40% underwent ECG, 2D and RT3D echo. QRS duration and 2D echo parameters of left ventricular function and asynchrony were measured (FS, LVEF, MPI, SPWMD). RT3DE datasets were analysed offline to produce time-volume curves for global and regional LV volumes. An asynchrony index (AI) was defined as the standard deviation of the time to minimum volume for each segment. Previous data showed the AI in patients with normal LV function to be 4.2±1.7. Subjects with AI greater than 2 standard deviations (>7.6) were considered to have significant asynchrony.
Results: 32 patients (49.2%) had QRS duration > 120 ms. No correlation was found between the asynchrony index and QRS duration (r = 0.03). There was no significant difference in the AI between patients with broad or narrow QRS complexes (13.2±8.1 vs. 12.1±6.7 respectively, p = NS). There was a good negative correlation between the AI and LVEF regardless of QRS duration (r = 0.59 for narrow QRS vs. 0.67 for broad QRS complexes). 11 patients (16.9%) with narrow QRS complexes had significant mechanical asynchrony. There was poor correlation between AI and 2D parameters of asynchrony (SPWMD: r = 0.19, MPI: r = 0.21).

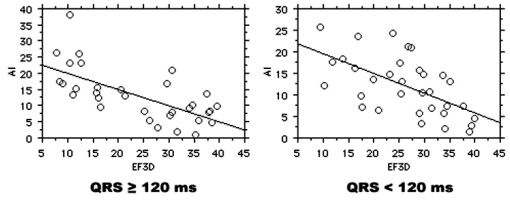

Fig 1. Asynchrony in wide and narrow QRS.

Conclusion: This study shows that mechanical asynchrony is increasingly prevalent with worsening systolic function, independent of QRS duration. A significant group of patients with QRS < 120 ms was identified that may potentially benefit from CRT.

DETERMINANTS AND PREVENTION OF POST MYOCARDIAL INFARCTION LEFT VENTRICULAR REMODELLING

823 PET imaging of bone marrow cell homing after intracoronary transfer in patients following acute myocardial infarction

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We have recently shown that intracoronary transfer of autologous bone marrow cells (BMCs) significantly enhances left ventricular ejection fraction recovery in patients after acute ST-elevation myocardial infarction (BOOST trial). By using ex-vivo 18F-FDG radio-labeling and PET scanning, we have now determined the fate and tissue distribution of BMCs after intracoronary transfer in patients after STEMI. Six male patients (36-61y) with large STEMI and successful acute percutaneous coronary intervention (PCI) of the culprit vessel (4 LAD, 1 LCX, 1 RCA) were included in the study. After providing informed consent, patients underwent bone marrow (131±11ml) harvest 8±2 days after PCI. Nucleated BMCs were enriched by 4% gelatin-polysuccinate sedimentation and were transplanted the same day. The final cell preparation contained 25±7x108 nucleated BMCs. Prior to transplantation, 5% of the final cell preparation were radio-labeled by 18F-FDG (13-27MBq) by incubation in an insulin and potassium containing phosphate buffer. Labeled cells were purified by sequential centrifugation steps (the purified cells contained <0.5% free FDG). Cell viability after radio-labeling and purification was 97±2%. The labeled cells were then combined with the non-labeled cells (95% of the final cell preparation) and infused into the infarct-related coronary artery through the central lumen of an over-the-wire balloon catheter (same protocol that was used in the BOOST trial). One hour after intracoronary application, all patients underwent 3D static whole body PET scanning (dedicated full ring scanner Ecat Exact 47, Siemens/CPS). In 3 of the 6 patients, one half of the labeled cells were injected via an antecubital vein under simultaneous dynamic 3D PET recording, prior to intracoronary infusion of the second half of the labeled cells. In all 6 patients, radio-labeled BMCs showed a typical distribution into spleen, liver, and bone marrow (>90% of total radioactivity). After selective intracoronary infusion, 0.8-4% of the total activity were detected in the infarcted myocardium. After peripheral intravenous application, no significant myocardial uptake was evident. The enrichment in the infarcted area by selective intracoronary application was more than 15-fold higher as compared to peripheral application. As shown by PET imaging in the present study, autologous BMCs home to the infarcted area after selective intracoronary infusion in patients recovering from an acute STEMI. Intravenous cell delivery in contrast, does not appear to be a suitable route for BMC transfer after myocardial infarction.

824 The effect of valsartan, captopril, or both on left ventricular size and function following high-risk MI: the VALIANT echo study

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Purpose: To determine whether the angiotensin receptor blocker valsartan, alone or combined with the ACE inhibitor captopril, is more effective than captopril alone at attenuating ventricular remodeling after MI.
Methods: VALIANT enrolled patients with left ventricular systolic dysfunction (EF <40%), heart failure (HF), or both on average 4.5 days post-MI. Patients were randomly assigned to receive captopril, valsartan, or captopril plus valsartan. Echocardiograms were obtained at baseline (mean 5.0±2.5 days; n=605), at 1 month (n=544), and at 20 months (n=428). Ventricular contours were digitized in a core lab by 1 blinded observer. Intra-observer reproducibility, assessed by blinded repeat analysis, was 3.2%. LV volumes, areas, and EF were calculated by using biplane method of discs.
Results: Baseline measures of end diastolic volume, EF, and infarct segment length were similar across all treatment groups and were each predictive of total mortality, development of HF, or the combination of death, HF, or MI (table). Changes in end diastolic volume from baseline to 20 months in the captopril, valsartan, or combination arms were similar (2.5±16.9mL vs 2.7±18.4mL vs 2.0±17.7mL, p=0.94) as were changes in EF (2.6±7.2% vs 1.9±7.8% vs 1.3±6.6%, p=0.30). Of patients who survived to 20 months, those with interim nonfatal CV events had increased end diastolic volume (7.4±21.7mL vs 1.6±16.8mL, p=0.018) and decreased EF (-0.35 vs 2.3, p=0.008).
Conclusions: Captopril, valsartan, and their combination have similar effects on changes in ventricular size and function after MI.

Baseline Measure	Total Mortality	Death or HF	Death, HF, or MI
EF (per 5 unit decrease)	1.40 (1.21,1.66)	1.43 (1.25,1.81)	1.39 (1.22,1.56)
End diastolic volume (per 10mL increase)	1.07 (1.01,1.13) p=0.015	1.09 (1.05,1.14)	1.08 (1.04,1.12)
Infarct segment length (per % infarct size)	1.15 (1.08,1.23)	1.17 (1.11,1.23)	1.15 (1.09,1.21)

Values are hazard ratios [95% CI]. Unless otherwise indicated, p<0.0001.

825 Human atrial natrieuretic polypeptide protect against left ventricular remodelling in the patients with acute anteroseptal MI. Eprospective randomized trial evaluated by 99mTc-tetrofosmin QGS

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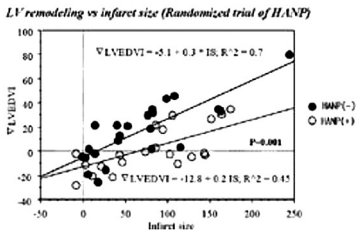
Background: The aim of this study is to demonstrate HANP administration combined with acute revascularization prevent LV remodeling independent of myocardial salvage.
Methods: Consecutive 44 patients with acute anteroseptal myocardial infarction who were successfully revascularized by primary stenting, were randomly assigned to either continuous infusion of HANP at a dose of 0.025 μg/kg/min for 3 days, or saline. Myocardial salvage, infarct size, and LV volume was assessed by 99mTc-tetrofosmin imaging.
Results: No differences in patients backgrounds were observed. HANP suppressed LVEDVI increase in comparison with placebo (HANP: 3.2±16.8 control: 16.0±23.4 p<0.05) with no difference in salvage index(HANP: 55.6±24.9% control: 55.5±34.1%). The relationship between the infarct size and delta-LVEDVI were shown in the figure.



HANP and remodeling.

Conclusion: This study clearly demonstrate that HANP can suppress LV volume expansion despite no differences of infarct size.

826 Transcoronary origin of circulating apoptotic endothelial cells in patients with acute coronary syndromes

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Plaque rupture and endothelial erosion represent the pathomorphological substrate of acute coronary syndromes (ACS). Numbers of circulating endothelial cells (EC) are increased in patients with acute coronary syndromes and after myocardial infarction. A possible explanation may be the detachment of apoptotic endothelial cells from the vascular wall in the setting of vascular inflammation. We, therefore, characterised the fraction of circulating apoptotic mature endothelial cells from blood of patients with ACS. In order to detect the origin of these cells, we simultaneously took selective blood samples from the femoral artery and vein, great cardiac vein (GCV) and the aortic root.
Circulating mature endothelial cells were defined as negative for the leukocyte marker CD45 and double-positive for the endothelial markers CD146 and vWF. These CD45-CD46+vWF+ cells were analysed for their apoptosis ratio by means of annexin V-staining using FACS analysis.
Numbers of circulating apoptotic endothelial cells in the peripheral blood of patients with ACS (n = 28; 5.7/μl [1.9 - 28/μl]) were elevated fourfold compared to healthy controls (n = 33; p<0.05) and twofold compared to patients with stable angina (n = 44; p=0.06). In a subgroup of patients with ACS (n=8), in whom selective blood sampling was performed, a significant transcoronary increase of apoptotic EC by 52% ([18 - 274%] p<0.05) was found in the GCV. Furthermore, all three patients with negative troponin showed a transcoronary increase of apoptotic EC. In contrast, no such gradient was found in patients with stable coronary artery disease (CAD; n= 20). Localisation of stenosis had no influence on transcoronary gradients in patients with chronic CAD. No difference of numbers of circulating apoptotic endothelial cells was found in probes taken from the femoral artery or vein.
The increased occurrence of circulating endothelial cells in ACS is related to augmented apoptosis of endothelial cells, detached from the vascular wall. The significant transcoronary gradient of mature apoptotic endothelial cells in patients with ACS documents for the first time the pathophysiological role of endothelial erosion in the coronary circulation in vivo.

827 Clinical relevance of circulating granulocyte macrophage colony stimulating factor in acute myocardial infarction and postinfarction cardiac remodeling

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Background: We have found elevated plasma granulocyte- macrophage colony stimulating factor (GM-CSF)in advanced heat failure secondary to ischemic cardiomyopathy. However, no in vivo data exist about the relationship of circulating GM-CSF and soluble adhesion molecules ICAM-1 and VCAM-1 (sICAM-1 and sVCAM-1) with the severity of AMI as well as the pathophysiologic events of postinfraction left ventricular (LV) remodeling process.
Methods: To clarify the role of GM-CSF in AMI, plasma levels of inflammatory markers were determined in 41 AMI patients (all received reperfusion treatment) by ELISA assays serially during the first week of hospitalization and one month after the hospital admission. Patients (n=20) with uncomplicated AMI (Killip class I) were classified as group A, patients (n=21) with AMI complicated by heart failure manifestations (Killip classes II and III) were classified as group B, while 20 age- and sex-matched volunteers were used as healthy controls. LV dimensions, volumes and ejection fraction (LVEF)were estimated by echocardiography.
Results: A sustained increase of circulating GM-CSF, sICAM-1 and sVCAM-1 was observed only in the group B of AMI patients during the first week of the study course. Patients of group B exhibited significantly higher peaks of GM-CSF ($p<0.01$), sICAM-1 ($p<0.05$) and sVCAM-1 ($p<0.01$) than patients of group A and healthy controls ($p<0.001$). In group B, significant correlations were observed between the peak of GM-CSF levels and the peak of serum creatine kinase-MB (r=0.42, $p<0.05$), white blood cell counts (r=0.67, $p<0.001$) and LVEF (r=-0.51, $p<0.01$). At one month follow-up, patients (n=17) with severe post-infarction LV dysfunction (LVEF-<35%) exhibited significantly higher levels of GM-CSF (21.8±1.5 vs 11.7±0.9 pg/ml, $p<0.001$), sICAM-1 (331.4±18.4 vs 201.3±12.1 ng/ml, $p<0.001$) and sVCAM-1 (748.4±34.7 vs 512.9±18.8 ng/ml, $p<0.001$) than did the other patients (n=24) without this condition (LVEF>35%). Significant correlations were observed between GM-CSF levels and LV end-diastolic volume index (r=0.55, $p<0.001$) or LV end-systolic volume index (r=0.49, p=0.001), as well as plasma sICAM-1 (r=0.69, $p<0.001$).
Conclusions: We have found a significant elevation of plasma GM-CSF and soluble adhesion molecules during the course of AMI, with the highest values in patients with AMI complicated by heart failure manifestations and severe left ventricular dysfunction. GM-CSF may orchestrate inflammatory and cellular interactions during the LV remodeling process by upregulating cellular adhesion molecules and other inflammatory substances.

828 Usefulness of coronary flow velocity reserve to predict long-term left ventricular remodelling after primary angioplasty. An echocardiographic study

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Purpose: Coronary flow velocity reserve (CFVR) measured by transthoracic Doppler echocardiography (TTDE) proved to be useful to predict short-term systolic function recovery after primary angioplasty. However, the influence of CFVR on long-term ventricular remodelling needs to be determined.
Methods: We studied 45 patients (57±16 years, 80% men) who suffered a first anterior acute myocardial infarction, without complications, and were successful treated with primary angioplasty. Ejection fraction, end-diastolic volume and end-systolic volume were measured by TTDE at discharge (EF1, EDV1, ESV1) and after 1 year (EF2, EDV2, ESV2). Increments of these values were calculated. CFVR was measured in the left anterior descending artery by TTDE (Philips Sonos 5500) using a 12 MHz transducer. Dipyridamole (0.84 mg/kg) was used as vasodilator. An echo-contrast agent (SonoVue) was administered to all patients. Group I (n=30) was constituted by patients with CFVR $\leq$1.7 and group II (n=15) by patients with CFVR >1.7.
Results: The median follow-up was 497 days. Differences between groups are shown in Fig. 1.

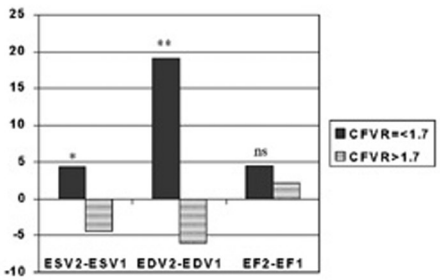

Fig. 1. *p=0.05; **p=0.003; ns= not significant.

Conclusion: CFVR influence left ventricular remodelling. Ventricular dilation is predicted for an impaired CFVR. However, long-term systolic function is not modified by an impaired CFVR.

ABLATION OF ATRIAL FIBRILLATION: FROM SOURCE TO SUCCESS

831 Atrial conduction in patients prone to paroxysmal atrial fibrillation

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Background: Although conduction velocity slowing is considered to contribute towards the development of atrial fibrillation (AF), prolongation of p-wave duration and intra-atrial conduction delay with premature atrial stimuli in patients with paroxysmal AF remains the only evidence of such conduction abnormalities. The techniques used in these studies indicate that the global atrial activation time is altered but this may be due to changes in the pathways of activation and not necessarily alteration in the rate of electrical propagation.Wavefront propagation velocity (WPV) can only be measured if the time interval and distance are known between two points, which are connected by a line perpendicular to the direction of activation of the wavefront. We hypothesize that slowing of atrial WPV occurs in patients with AF.
Methods: Patients with paroxysmal AF and control patients with left-sided accessory pathways but no history of AF were recruited. Carto© maps of both atria were carried out during sinus rhythm (SR) and pacing at 600ms cycle length.(CL) 3D isochronal activation maps were analysed. Multiple triads of points were analysed with a mathematical function incorporating Cartesian and trigonometric equations, in order to calculate the WPV specifically in the direction of propagation. Absolute effective refractory period (AERP) was measured at 3 sites, at 600 and 500ms. The dispersion and adaptation of AERP were calculated. The mean SR CL during mapping was recorded. All measurements were taken prior to ablation.
Results: 14 patients with paroxysmal AF and 13 control patients with no history of AF were recruited, of which 12 AF patients and 10 control patients had left atrial mapping. There was no difference in age or baseline SR CL between the two groups. Patients with AF had a slower right atrial conduction velocity (62.7 ± 9.4 vs 74.1 ± 10.7 cm/s during SR, p=0.03 and 68.4 ± 12.7 vs 83.8 ± 16.2 cm/s during pacing, p=0.004) but no difference in left atrial conduction velocity.(71.8 ± 7.4 vs 69.1 ± 9.8 cm/s during SR, p=ns and 69.1 ± 17.3 vs 69.4 ± 12.2 cm/s during pacing, p=ns) There was increased dispersion of refractoriness (40 vs 7 ms at 600ms CL, p=0.01 and 43 vs 14 ms at 500ms CL, p= 0.01) but no difference in absolute refractoriness nor in adaptation to a shorter CL.
Conclusion: Our results suggest that right and left atria may have different roles in the development of AF with left atrial triggers contributing to the initiation of AF whilst changes in right atrial WPV contributing to the myocardial substrate that predisposes to paroxymsal AF.

832 Comparison between anatomical and integrated approach for pulmonary veins ablation

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Pulmonary vein (PV) disconnection by catheter radiofrequency (RF) ablation has been reported to cure atrial fibrillation (AF). Different techniques have been proposed. With an anatomical approach circumferential RF lesions are created around all PVs ostia, without electrophysiological confirmation of PVs disconnection. Aim of this study was to compare the outcome of a pure anatomical with an integrated approach (anatomical and electrophysiological).
Methods: Fourty three consecutive patients (pts) affected by drug refractory AF, were assigned to two different approaches. Group A consisted in 21 pts (20 male, 1 female, mean age 53±9.9 years) affected by paroxysmal (12), persistent (5) and permanent (4) AF that underwent PVs ablation by means of a pure anatomical approach. Group B consisted of 22 consecutive pts (19 male, 3 female, mean age 51 ± 10 years) affected by paroxysmal (16), persistent (3) and permanent (3) AF that underwent RF ablation of PVs by means of an integrated approach. In all pts RF ablation was performed with Carto system in order to anatomically create circumferential lines around each PV. In Group B pts the persistence of PV potentials was then assessed with a decapolar circular catheter. If PV potentials persisted, RF pulses were delivered targeting the electrophysiological breakthroughs to disconnect PVs.
Results: Total procedure duration, fluoroscopy time, and RF delivery time were similar in both groups: 227±43, 56±23 and 45±22 minutes (group A), 234±30, 53±18 and 39±12 minutes (Group B) respectively (ns). One pericardial effusion occurred after the procedure in group B. After 9.7 ± 5.6 months, 10 pts (48%) of group A and 18 pts (82%) of group B were in stable sinus rhythm ($p<0.05$). Of group A all sinus rhythm pts were on anti arrhythmic drugs, while of Group B 9 sinus rhythm pts (50%) discontinued all drugs after 6 months. Two Group A pts (9.5%) and 3 Group B pts (14%) required two procedures (ns).

Conclusions: PVs ablation by means of an anatomical and electrophysiological integrated approach seems more effective than a pure anatomical RF ablation approach. Electrophysiological confirmation of PVs disconnection could be an useful successful marker of RF treatment of AF.

833 Adenosine test predicts acute recovery of left atrial to pulmonary vein conduction after electrical isolation of the pulmonary veins

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The electrical isolation (EI) of the pulmonary veins (PVs) from the left atrium (LA) is a curative treatment for pts with atrial fibrillation (AF). Adenosine (ADE) administration may transiently or permanently restore LA-PV conduction after PV EI. We prospectively investigated the usefulness of ADE-test in predicting acute recovery of LA-PV conduction (occurring before the end of the procedure) in 23 consecutive pts (19 m, mean age: 53±12 yrs) with drug-refractory (> 2 antiarrhythmics) paroxysmal AF submitted to PV EI.
Methods and Results: PV EI was obtained by selective, low-energy (30W, 50 C°), radiofrequency current (RFC) applications delivered at the atrial aspect of the PV ostium in correspondence of the LA-PV conduction breakthroughs indicated by a 64 pole "basket-shaped" catheter (Constellation 8031, Boston Scientific) inserted within the target PV. ADE-test (12 mg i.v. bolus) was performed 10 min after each successful PV EI. Spontaneous recovery of LA-PV conduction was assessed by re-inserting the reference catheter within all targeted PVs before the end of the procedure (waiting period after each PV EI > 20 min). Overall, 74 PVs were successfully isolated and in 21 of them (28%) ADE-test resulted in transient LA-PV conduction recovery. Spontaneous recovery of LA-PV conduction was observed in 7 PVs (9%), and it occurred more frequently in positive ADE-tests (24% vs 3.8%; p <0.03). Sensitivity and specificity of ADE-test were 71% and 76%, respectively. All spontaneously re-conducting PVs were successfully re-isolated by additional RFC delivery at the residual LA-PV conduction breakthrough(s).
Conclusions: Spontaneous LA-PV conduction recurrence in the acute phase after PV EI is relatively uncommon and it can be predicted by ADE-test. These findings have practical implications when PV EI procedures are performed.

834 Detailed analysis of recurrent atrial fibrillation episodes after percutaneous left atrial substrate modification

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Background: Treatment of atrial fibrillation (AF) by percutaneous placement of linear and circular ablation lines does not necessarily result in an immediate complete freedom of AF. Due to the modification of the AF substrate a stepwise decrease in the duration of the individual AF episode may result over time after ablation.
Methods: 100 patients with paroxysmal (n=80) and persistent (n=20) AF underwent a left atrial ablation with placement of circular lesions around left and right pulmonary veins (PV) as well as linear lesions between left and right PV and from left PV to the mitral annulus, using the CARTO system. The PV were completely isolated in less than 20% of the circular lesions. Follow-up was based on recurrent 7-day-ECGs (total analysis of 54.201 hours of ECG recording). Duration of AF episodes was classified into 3 different groups: A=30sec-2h, B=2h-24h, C≥24h.
Results: For patients with paroxysmal AF prior ablation, the distribution of AF episodes into the 3 duration groups was: 73% A, 24% B, 3% C. During follow-up that distribution changed substantially: 85% A, 12% B, 3% C immediately after ablation; 85% A, 13% B, 2% C after 3 months; 86% A, 10% B, 4% C after 6 months.
For patients with persistent AF prior ablation, the distribution was: 0% A, 6% B, 94% C. During follow-up that pictured changed significantly: 71% A, 15% B, 14% C immediately after ablation; 90% A, 8% B, 2% C after 3 months; 93% A, 5% B, 2% C after 6 months.
Conclusions: In case of AF recurrences the duration of individual AF episode decreased significantly during follow-up after ablation, indicating a substrate modification effect instead of a trigger elimination. Importantly, both patient groups with paroxysmal and persistent AF before ablation developed primarily very short episodes (< 2 h), whereas long episodes (> 24 h) became rare. This may have an impact on anticoagulation regimen in the future.

835 Limited pulmonary vein disconnection vs electroanatomical encircling in atrial fibrillation ablation. Is it wise to use an individualized approach?

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Two different techniques are being used in atrial fibrillation ablation (AF): Pulmonary veins (PV) disconnection (D), or electroanatomical encircling of the PV (EAE). However there are very limited data comparing the results of both techniques.
Objectives: The aim of the study was to analyse the results of an strategy based on the selection of the ablation method according to the patient condition.
Methods: The study included 66 consecutive patients, with refractory AF. A group of 38 pts with presumed focal AF (runs of atrial tachycardia at the Holter recording), underwent a limited PVD procedure using a Lasso Catheter, isolating only PV with electrical activity (mean 1.9±0,8 PV per patient). Another group of 28 pts without evidence of focal origin, were submitted to an extensive ablation by EAE using a CARTO mapping system. A Holter recording was performed at 1, 3 and 6 months, and a magnetic resonance imaging (MRI) of PV and an echocardiogram were obtained at 6 months. No patient was lost during a mean follow up of 6.7±4 months. Antiarrhythmic drugs were discontinued after 3 months in sinus rhythm. Ablation was considered successful when there were no documented recurrences of AF.
Results: There were no differences in age, gender, atrial diameter between both groups. However, there were more pts with structural heart disease among EAE group (50% vs 26% p<0.05), and the proportion of persistent AF was higher among the EAE than in the PVD (43% vs 10%, p<0.05). furthermore, 2 pts of the EAE group had permanent AF. Total procedure duration was 106±34 min for PVD vs 148±42 min for EAE (p<0.05). PVD patients received less radiofrequency energy: 626±319 sec vs 2650±853 sec for EAE p<0,05. However fluoroscopy time was longer in PVD (50±20 min vs 34±15 min for EAE p<0.05). Two patients of the PVD group had a coronary air embolism and one patient of the EAE group had a transient ischemic attack, all resolved spontaneously. At MRI, there were 4 assymptomatic PV stenosis among the PVD vs none in the EAE group. There were no differences in efficacy in paroxysmal AF between both techniques (PVD 71% vs EAE 71%), However the PVD was less effective than the EAE in pts with persistent AF (25% vs 67% p<0.05). Two patients with unsuccessful PVD were submitted to EAE with good result.
Conclusions: A limited PVD achieve a good result in patients with focal paroxysmal AF. A more extensive ablation procedure may be used in patients without evidence of focal origin, persistent AF or failures of PVD.

836 Myocardial crossing fibres between the venous orifice of the pulmonary veins: relevance for catheter ablation in atrial fibrillation

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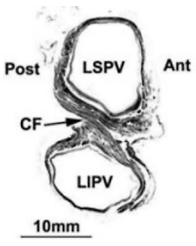
Introduction: Previous anatomic studies showed the complex arrangement of the myocardial tissue on the pulmonary veins (PV) with the evidence of muscle fibres oriented in circumferential, longitudinal and oblique directions.
Methods: We have examined the orientation of the myocardial fibres at the venoatrial junction in 96 PV from 24 normal human autopsied hearts (52±18 years, 17 males). Disections of the subepicardial myofibres arrangement were observed in 12 hearts and histological cross-sections in the remaining 12 specimens.
Results: In all heart a sleeve o atrial myocardial fibres extended into the walls of the PV. These muscular fibres encircling the venoatrial junctions especially in the posterior region of the left atrium. At the ostium of the PV were usually loop-like extensions from the atrial longitudinal fibres and became circular at varying distances into the venous walls. However local variation were found with subendocardial fibres following their longitudinal orientation from the atrium into the wall of the PV. At the junction of the PV with the left atrium we found myocardial fibres crossing the isthmus between the superior and inferior venous orifice of the PV. Histological sections showed crossing fibres (CF) in the left-PV in 5 hearts (41%) and in the right-PV in 3 hearts (25%). The CF runs along the posterior wall of the superior PV crossing through the interpulmonary isthmus to the anterior margen of the inferior PV in 5 hearts (figure). Reverse orientations (from anterior to posterior PV wall) was observed in other 3 hearts.



Crossing fibres in PV.

Conclusions: The evidence of myocardial CF between the interpulmonary isthmus may set the scene for electrical connection between PV. These anatomic finding may have clinical implication for local PV isolation.

HEART FAILURE WITH PRESERVED SYSTOLIC FUNCTION: WHATS NEW?

846 Increased prevalence of diastolic dysfunction in healthy hypertensive females

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Purpose The incidence of hospitalizations for heart failure with preserved systolic function is higher in females compared to males. In contrast, hospitalizations for heart failure with left ventricular dysfunction is more prevalent in males. This difference might be related to age and/or to the higher incidence of atherosclerosis in males. We aimed to investigate the prevalence of diastolic dysfunction in healthy hypertensive females compared to males.
Methods: A total of 177 elderly patients older than 60 years (53% male, 47% female) with untreated hypertension (SBP 160 > mmHg and/or diastolic > 95 mmHg) were recruited from a population survey. Patients did not have any signs or evidence of cardiovascular disease. Left ventricular dimensions, wall thickness, peak early (E), atrial (A) diastolic filling velocities and deceleration time (DT) were measured by echocardiography. Atrial and B-type natriuretic peptides (ANP and BNP) were measured in all patients. Diastolic dysfunction was defined as an E/A-ratio < 1 and/or a DT <120 or >220 ms.
Results: Overall, diastolic dysfunction was present in 159 of the 177 healthy hypertensives (90%). We found no differences in age, systolic and diastolic blood pressure between males and females. The prevalence was higher in females compared to males (98% vs. 83%; p = 0.0016). After adjustment for possible confounders such as age, systolic and diastolic blood pressure, body mass index, left ventricular wall thickness, and left ventricular mass index, females had a significantly increased risk for diastolic dysfunction (OR 8.1; p = 0.007). In addition, both ANP and BNP were higher in females compared to males. Multivariate analysis demonstrated that female gender was significantly related to the level of ANP (p = 0.008) and BNP (p = 0.0003).
Conclusions: Echocardiographic evidence of diastolic dysfunction was found in 90% of healthy hypertensive patients. Female gender was significantly related to both echocardiographic evidence of diastolic dysfunction and increased levels of ANP and BNP. These gender differences were independent of age, blood pressure, left ventricular dimensions and left ventricular mass index.

847 Brain natriuretic peptide as a marker of diastolic dysfunction in the general population: importance of left ventricular hypertrophy

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BNP is a marker of systolic left ventricular dysfunction (LVD) and congestive heart failure and has recently been suggested as a marker of diastolic dysfunction (DD). To assess the usefulness of BNP for the detection of DD, we examined 1678 subjects within a population-based survey (MONICA Augsburg) and determined LV systolic and diastolic function and mass. Diastolic abnormality was considered when Doppler criteria were pathological. Diastolic dysfunction was considered in the presence of diastolic abnormality with left atrial hypertrophy and/or intake of diuretics.
BNP (Shionogi) was increased in subjects with diastolic dysfunction (mean 20.3 ± 4.7 pg/ml vs control 9.6 ± 0.5 pg/ml, p < 0.001), but to a lesser extent than in left ventricular hypertrophy (LVH)(mean 37.3 ± 49.1 pg/ml, p < 0.001 vs control) or systolic dysfunction (mean 76.2 ± 23.2 pg/ml, p < 0.001 vs control). In univariate analysis, age, BMI, systolic blood pressure, left atrial size, LV mass index, diastolic dysfunction and EF displayed a significant correlation with BNP (p < 0.001). However, LV mass index displaced diastolic dysfunction as a significant predictor of BNP in multivariate analysis. In a subgroup analysis stratified to LV hypertrophy, the highest BNP concentrations were found in subjects with diastolic dysfunction and concomitant LVH (mean 47.3 ± 21.4 pg/ml, p < 0.05 vs control), while those individuals with sole diastolic abnormality displayed BNP concentrations at the control level (mean 9.7 ± 1.7 pg/ml).
Increased BNP concentrations in subjects with diastolic dysfunction appear to be mainly a result of a concomitant LVH, which is a known strong predictor of BNP. Population-wide screening for diastolic dysfunction cannot be recommended with BNP.

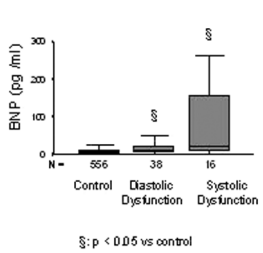

Fig 1. LVD vs DD.

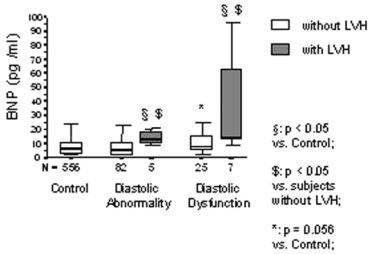

Fig 2. DD +/- LVH.

848 Is circulating tissue inhibitor of metalloproteinase-1 elevation associated with impaired diastolic relaxation in patients with hypertension?

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Backgorund: Hypertension(HBP), hypertensive heart disease and left ventricular (LV) hypertrophy are integral to diastolic heart failure. Tissue inhibitor of metalloproteinase 1 (TIMP-1) is linked to extracellular matrix(ECM) fibrosis. We studied the link between circulating TIMP-1, matrix metalloproteinase 9 (MMP-9) and resting echocardiographic LV filling.
Methods: Circulating MMP-9 and TIMP-1 levels were measured in citrated plasma by ELISA in 74 patients with HBP (58 male, age 58±11yrs) and 34 controls (23 male, mean age 53±13years)(Table). All had confirmed normal short axis systolic contractility.
Results: MMP-9 and TIMP-1 were higher in the hypertensive group (Table). Within the hypertensive cohort, only TIMP-1 correlated with left ventricular mass (r=0.271, p=0.024), left ventricular mass index (r=0.323, p=0.007) and tissue Doppler parameters of diastolic dysfunction (e' (r= - 0.338, p=0.005), and e/e' (r=0.334, p=0.005).

Table (Data as Mean (SD) or Median (IQR)

	Controls (n=34)	Hypertensives (n=74)	p
SBP (mmHg)	126(13)	150(26)	<0.0001
DBP (mmHg)	79(8)	88(14)	<0.0001
LVMI	64(48-79)	80(63-98)	0.0055
E (m/s)	0.71(0.15)	0.81(0.15)	0.004
A (m/s)	0.66(0.12)	0.81(0.16)	<0.0001
E/A	1.10(0.94-1.23)	1.00(0.85-1.16)	0.229
e'	0.12(0.09-0.14)	1.00(0.85-1.16)	0.0017
a'	0.09(0.05-0.10)	0.09(0.08-0.11)	0.123
e'/a'	1.20(1.00-1.80)	0.88(0.71-1.05)	<0.0001
e/e'	6.54(4.75-7.14)	8.89(7.55-10.75)	<0.0001
MMP-9 (ng/ml)	41(35-91)	70(49-120)	0.0039
TIMP-1 (ng/ml)	305(238-380)	380(280-550)	0.0054

SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricular mass index; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase

Conclusion: TIMP-1 is thought to increase tissue concentrations of collagen type I by preventing its breakdown by MMPs. Our findings therefore add weight to a hypothesis suggesting that TIMP-1 may be a key mediator of left ventricular diastolic dysfunction by affecting ventricular ECM structure.

849 Neurohumoral correlates of markers of collagen turnover in heart failure with preserved systolic function

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Background: Plasma concentrations of the amino-terminal propeptide of type III procollagen (PIIINP) are known to reflect cardiac extracellular matrix turnover (ECM) in patients with heart failure and reduced ventricular systolic function (HF-RSF). Plasma PIIINP concentrations have not been described in patients with preserved systolic function (HF-PSF). We have also examined the relationship between plasma PIIINP concentration and neurohumoral activation in heart failure (HF).
Methods: We studied 219 patients with an emergency admission for HF. Venous blood was collected during admission for measurement of PIIINP, aldosterone (aldo) and B-type natriuretic peptide (BNP). All patients underwent echocardiography.
Results: The mean age of patients was 76 years and 57% were women. The table shows plasma PIIINP and neurohumoral concentrations. Median PIIINP was higher in the HF-RSF group (p=0.024); 54% HF-RSF and 38% HF-PSF group had an elevated PIIINP. BNP was also more markedly elevated in HF-RSF. Median aldo did not differ between the two groups: 20% HF-RSF and 18% HF-PSF had an elevated aldo. Overall, PIIINP correlated weakly (r=0.23) but significantly (p=0.001) with BNP but did not correlate with aldosterone.

Neurohumoral markers of ECM in HF-PSF

Plasma Factor * Median (IQR)	Normal Range	HF-PSF (n = 137)	HF-RSF (n=82)
PIIINP ug/L	6.7	5.9 (5.1 - 7.8)	7.2 (5.5 - 8.3)
BNP pg/ml	<70yr >61 ≥70yr >68	205 (66 - 595)	839 (289 - 1278)
Aldo ng/100ml	≤20	9.0 (4.4 - 17)	9.4 (4 - 17.9)

Comparison of neurohumoral markers of extracellular matrix turnover between heart failure with reduced systolic function (HF-RSF) and heart failure with preserved systolic function (HF-PSF)

Conclusion: There is biochemical evidence of ECM turnover in patients with HF-PSF. This does not appear to be related to increased circulating aldosterone.

850 Elevated serum C-reactive protein level is a risk factor for left ventricular diastolic abnormality: a community-based study

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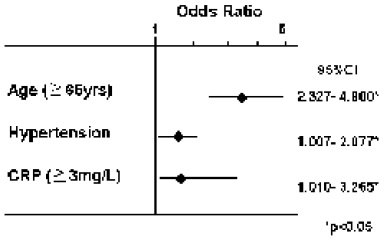
Background: To clarify the prevalence of and risk factors for preclinical left ventricular systolic dysfunction (LVSD) and diastolic abnormality (LVDA) in our population, we have performed left ventricular functional evaluations in combination with cardiovascular risk assessment in a community-based population.
Methods: The study was carried out in a sample of 1,057 randomly selected subjects from the general population (age 40-79 years, mean 60 years). Doppler echocardiography, blood tests, ECG and demographic measurement were completed in all subjects. Subjects were excluded if they were shown to have atrial fibrillation and/or unclear echocardiogram. The remaining 982 subjects (men = 466, women = 516; mean age 60 years) were included in the analysis. LVSD was defined by left ventricular EF. LVDA was defined by age-dependent partition variables of E/A and deceleration time.
Results: When LVSD was defined as EF $\leq$ 50%, the prevalence was 1.2%. In contrast, LVDA was common (17%) in this population. The risk factors for LVDA were examined by a multivariate logistic analysis using risk assessment data. We found that serum CRP $\geq$ 3 mg/L (odds ratio=1.45; $p < 0.05$), age $\geq$ 65 years (odds ratio = 3.34; $p < 0.01$), and hypertension (odds ratio = 1.45; $p < 0.05$) were significant predictors of LVDA.



Risk factors for diastolic abnormality.

Conclusion: When compared with published data based on western populations, although the prevalence of LVSD was lower in our population, the rate of LVDA was comparable. In addition, the presence of elevated serum CRP level independently contributes to impairment of left ventricular relaxation.

851 Incidence of preserved left ventricular function and determinants of short-term mortality in patients with acute heart failure: the EFICA study

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Introduction Patients with acute decompensated HF (ADHF) have life threatening symptoms and high mortality rate. The prevalence of preserved left ventricular (LV) systolic function in such patients and its influence on outcome remain poorly defined. EFICA (Epidémiologie Francaise de l'Insuffisance Cardiaque Aiguë), is a prospective observational study of ADHF undertaken to investigate the clinical and etiologic features, practical management and outcome in 60 representative ICUs in France. Because echocardiography is standard practice in France, we were able to collect data on left ventricular function in a very large proportion of our patient population.
Methods: Enrolled patients were hospitalized with signs and/or symptoms compatible with the diagnosis of ADHF. Analysis were performed using the logistic model and Odds Ratio (OR).
Results: Among the 599 patients included, ADHF diagnosis was confirmed for 581 patients. They were aged 73 [25-98], 59% were men, 66% had a history of CHF and 41% history of ischemic heart disease. Main etiologic factors were myocardial ischaemia (59%), valvular disease (21%), hypertrophic or hypertensive cardiopathy (13%). Echocardiography data was available in 437 patients with estimation of LVEF in 365 of them. LVEF was $<$ 35% in 45%, within the range of 35-50% in 33%and $>$50% in 21% of those patients. Preserved LV function (LVEF$>$45%) was present in 27% of all patients, in 18% of patients admitted with and in 30% without cardiogenic shock. It was most frequent (80%) in patients presenting with pulmonary edema and a history of hypertension and/or hyertrophic cardiopathy. The 28 days mortality rate was 27%. Factors independently associated with high mortality were: cardiogenic shock (OR=5.2, n=29%), co-morbidity (OR=4.9, n=51%), renal failure on admission (OR=1.9, n=52%), myocardial ischaemia on ECG (OR=1.8, n=29%), diastolic BP $<$70mmHg (OR=1.4, n=45%), and with low mortality were: hypertrophic and/or hypertensive cardiopathy (OR=0.35, n=13%), diastolic PB $>$95 mmHg (OR=0.35, n=15%), and obesity (OR=0.55, n=22%). LVEF in itself did not influence short-term outcome.
Conclusion: ADHF cannot be regarded as one entity. Our study identified major determinants of short-term mortality. ADHF with hypertrophic and/or hypertensive cardiopathy carries the best prognosis. ADHF occurs frequently in patients with preserved LV systolic function. This was particularly true in patients presenting with hypertensive pulmonary edema.

DIAGNOSIS AND EVALUATION OF HEART FAILURE – STILL A CHALLENGE IN THE EVERYDAY CLINICAL PRACTICE

852 How useful is the 12-lead electrocardiogram for the evaluation of patients with suspected heart failure? Data from the EuroHeart Failure Survey

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Background: The 12-lead ECG is considered a valuable tool for the exclusion of heart failure but there are relatively few data on large unselected cohorts of patients with suspected heart failure in which to test this hypothesis. Also, ECGs have usually been reported as normal or abnormal using non-standard interpretation and with no attempt to grade the severity of ECG abnormalities or of the conditions being diagnosed.
Methods: The EuroHeart Failure survey screened consecutive deaths and discharges during 2000-2001 predominantly from medical wards over a 6-week period in 115 hospitals from 24 countries belonging to the ESC, to identify patients with known or suspected heart failure. 10,701 patients were enrolled, a 12 lead ECG obtained from 9,800 and 5,828 had an objective assessment of cardiac function. ECGs were read in a central laboratory and classified as having no, minor or major abnormality. Patients were classified as having no detectable cardiac abnormality, left ventricular (LV) diastolic dysfunction, systolic dysfunction (SD) or valve disease, each of which was assessed as mild, moderate or severe.
Results: 55.0% of patients had moderate or severe cardiac disease in one or more of the above categories and 36.5% had moderate or severe LVSD. Only 73 ECGs (1.3%) were entirely normal; 19 (26%) of these patients had evidence of moderate or severe cardiac disease although only 8 (11%) had LVSD. 739 (12.7%) ECGs were considered mildly abnormal and of these 304 patients (41%) had moderate or severe cardiac disease, mostly LVSD. 5,016 (86%) patients had a major abnormality on their ECG and of these 3,377 (67%) had moderate or severe cardiac disease, mostly LVSD. A QRS $>$120msec was present in 2,443 (42%) cases and increased the probability of finding a moderate or severe cardiac abnormality from 55% to 71% and included only 386 (16%) patients without a major cardiac abnormality. QRS prolongation was superior to classification by the presence or absence of major abnormalities or anterior Q-waves (post-test probabilities of 60% and 62% respectively) for the detection of major cardiac abnormalities or LVSD.
Conclusion: In patients with a hospital admission for suspected heart failure, a normal ECG is uncommon even in if cardiac dysfunction is absent and does not exclude serious structural heart disease. QRS duration is a simple quantifiable ECG measurement that appears to provide useful diagnostic information. ESC guidelines on the diagnostic use of the ECG should be reviewed.

853 Brain natriuretic peptide and symptoms as markers of severity in patients with chronic heart failure: Val-HeFT data

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Purpose: Elevated levels of BNP have proved to be diagnostic of heart failure (HF), and prognostic of outcomes. However, BNP is not abnormally elevated in all patients (pts) with HF, and therefore, cannot replace symptoms (SYM) in the clinical evaluation. This study analyzed how BNP reflects the severity of SYM and its relation to mortality in a clinical trial population.
Methods: Baseline SYM of effort, rest and nocturnal dyspnea, orthopnea and fatigue were graded and grouped into: Absent, Minimal (absent and +/++), Severe (present and +++/++++), Moderate (combination of Minimal and Severe), and compared to baseline BNP (Shinogi) above and below the median of 97pg/ml, and to mortality during a mean follow-up of 23 months.
Results (table): Fewer SYM were associated with a higher % of normal BNP values, and more SYM, with a higher % of elevated BNP values. High BNP levels

BNP, symptoms and mortality

Symptoms	N	%	%	Median BNP (pg/mL)		Mortality (%)		
		<97	≥97	<97	≥97	<97	≥97	All pts
Absent	70	57	43	35	198	7.50	20.00	12.86
Minimal	1403	54	46	40	214	10.32	21.17	15.32
Moderate	2762	47	53	41	245	12.91	28.29	21.00
Severe	70	41	59	24	506	20.69	53.66	40.00
All pts analyzed	4305	50	50	40	237	12.00	26.53	19.33

generally increased with the severity of SYM, but did not discriminate between minimal to moderate SYM. Normal BNP levels did not discriminate between pts with or without SYM. Over 40% of pts with moderate to severe SYM had BNP values below the median value. Mortality in pts with BNP values below the median was lower than in pts with BNP above the median for equivalent severities of SYM.
Conclusion: In patients with chronic heart failure and structural heart disease, symptoms and BNP levels should be considered concurrently in weighing the prognosis of patients in heart failure.

854 The electrocardiogram in diagnosis of heart failure due to left ventricular systolic dysfunction – is advice from guidelines flawed?

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All Guidelines and NICE guidance for the diagnosis and management of heart failure due to LVSD suggest that if an ECG if normal then LVSD is very unlikely. Such conclusions are dependent on case selection and the prevalence of LVSD in the population studied. Our experience in assessment of patients with suspected LVSD in primary care is that this statement is not always accurate. Furthermore there are difficulties in interpretation of ECG data by GPs in particular.
Methods: All patients referred to a GP led one-stop diagnostic clinic for suspected HF had a clinical assessment and a 12 lead ECG performed by experienced technicians. All had full echocardiography by a British Society of Echocardiography accredited technicians. Left ventricular function was assessed by "eyeball" assessment, Simpson's rule and wall motion index. The ECGs were independently assessed by 2 experienced clinicians and classified as normal or abnormal if Q waves, T wave changes, axis deviation, bundle branch block, left ventricular hypertrophy or atrial fibrillation (Minnesota criteria) were present. Where discrepancy existed (8 ECGs) these were reviewed by both clinicians and agreement on classification achieved.
Results: 217 consecutive patients attending the first year of our clinic (January – December 2002) were included in the study. 84 (37.7%) were male. Mean age was 72.9 with a range of 35-94. 82 (37.8%) had LVSD and 135 (62.2%) had normal systolic function.

ECG	LVSD	
	Yes	No
Normal	18	84
Abnormal	64	51

Sensitivity = 78%; Specificity = 62%; Positive predictive value = 55.7%; Negative predictive value = 75%.

Of the 18 patients with LVSD who had a normal ECG 4 had severe, 2 moderate and 12 mild systolic dysfunction
Conclusions: Other researchers have previously shown that significant LVSD can be present in the presence of a normal ECG. Our study supports this statement. If current guidance was adhered to in referral of patients for echocardiography 18 (22%) of patients with LVSD would have been missed. Previous studies that suggested that a normal ECG effectively rules out LVSD may not have been representative of the type of patients referred by GPs with suspected HF. A "real life" study of 800 patients is underway to investigate the role of ECG and NT pro-BNP in triage of patients with suspected HF by GPs.

855 Poor sensitivity of weight and brain natriuretic peptide changes in predicting clinical deterioration of heart failure

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Background: Daily weight monitoring and BNP assessment have been advocated by guidelines to alert impending clinical deterioration in chronic heart failure.
Aims: This study assesses the sensitivity and specificity of different absolute and relative criteria of BNP increase and weight gain in the prediction of clinical deterioration.
Methods: Patients with unscheduled attendance to the HF service with suspected clinical deterioration were prospectively assessed. The attending cardiologist adjudicated on the presence of clinical deterioration of heart failure. The sensitivity and specificity of reported weight gain for predicting clinical deterioration using absolute (2 kg gain and 1kg gain) and relative (2% gain and 1% gain) criteria were evaluated. In addition we assessed the sensitivity and specificity of BNP increase from stable baseline value for predicting clinical deterioration using absolute (100 pg/ml gain and 50 pg/ml gain) and relative (20% gain and 10% gain) criteria.
Results: One hundred and eight episodes of deterioration in 59 patients (72.4 $\pm$ 8.0 years, 67% male, 68.6% ischemic, 77.1% systolic dysfunction) were included in the study. Ninety-nine episodes were confirmed clinical deterioration with weight increase from 75.6 $\pm$ 16.5 kg to 76.8 $\pm$ 16.8 kg and BNP increase from 406 $\pm$ 414 pg/ml to 789 $\pm$ 855 pg/ml (both $p<0.001$). Weight or BNP did not change in the 9 episodes judged not to be clinical deteropration of HF. The sensitivities and specificities of our absolute and relative criteria are presented in the table.

Sensitivities and specificities

Weight	Sensitivity	Specificity	BNP Increase	Sensitivity	Specificity
2 kg increase	42	100	100 pg/ml	55	67
1 kg increase	54	100	50 pg/ml	62	56
2% increase	42	100	20%	54	56
1% increase	56	89	10%	58	56

Conclusions: These data demonstrate that weight increase and BNP increase in isolation may not be sensitive in assessing clinical deterioration in heart failure. These observations need to be emphasized in patient education and to physicians involved in assessment of heart failure patients. Most importantly, these findings underline the continued preeminence of careful clinical assessment in assessing potential clinical deterioration.

856 Misdiagnosis or diastolic dysfunction explaining heart failure symptoms

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Background: The diagnosis of heart failure (HF) in routine clinical practice is unreliable, mainly due to the low specificity of symptoms. The goal of this study was to assess how often symptoms suggesting HF in the absence of left ventricular systolic dysfunction are attributable to diastolic HF and how often alternative causes can be identified.
Methods: We designed a cross-sectional study with the main goal of determining the prevalence of HF in a community sample of adults living in Porto. Participants were asked about symptoms suggesting HF, and a clinical examination, ECG, spirometry and echocardiogram were performed. Seven hundred participants have been evaluated (280 men and 420 women, aged 69.5$\pm$11.8 years). Personal history of coronary heart disease (CHD) was defined as previous myocardial infarction or angina according to self-reported information, Rose's questionnaire and/or pathological Q waves on ECG. Obesity was defined as body mass index $\geq$30kg/m^2. Exertion dyspnea was attributed to HF in the presence of left ventricular systolic dysfunction, moderate-severe valvular disease or atrial fibrillation. In participants without any of these abnormalities, symptoms were attributed to lung disease if there were moderate to severe obstructive or restrictive changes on spirometry. In the absence of HF and lung disease as defined, symptoms were attributed to obesity or CHD. The characteristics of symptomatic participants in which none of these diseases were identified were compared with those of each of the previously defined groups as well as those of the asymptomatics.
Results: Overall, 250 (35.7%) participants declared exertion dyspnea and/or tiredness, leading to mild-moderate functional limitation. In 24 (9.6% of symptomatic subjects) these symtoms were attributable to HF; in 101 (40.4%) to lung disease, in 47 (18.8%) to obesity and 14 (5.6%) to CHD without systolic dysfunction. Only 64 symtomatic subjects were left and the clinical, analytical and echocardiographic characteristics (including parameters of transmitral flow to study patterns of left ventricular filling) of these were in general more similar to those of the asymptomatics than any of the other groups.
Conclusion: In most participants who reported symtoms compatible with HF on the questionnaire but who did not have systolic dysfunction, valvular disease nor atrial fibrillation, it was possible to identify alternative explanations for those symptoms. Therefore, before attributing them to diastolic HF, it is mandatory to search for these alternative causes and as far as possible correct them.

857 Rapid brain natriuretic peptide test and Doppler echocardiography: a cost-effective screening for early diagnosis of heart failure

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Background: The onset of symptoms is a critical point in the natural history of heart failure(HF).Conventional diagnostic methods such as echocardiography have established utility for the detection of impaired left ventricular ejection fraction (LVEF) however this test is not available for routine diagnostic screening. Brain natriuretic peptide (BNP) has emerged as an important diagnostic serum marker in congestive HF.
Methods: We prospectively evaluated whether the combination of BNP measurements and echocardiography would effectively stratify patients with new symptoms in a cost-effective heart failure program based on the cooperation between hospital cardiologists and primary care physicians. BNP plasma level was measured by means of the "Triage BNP System" (Biosite Diagnostic). Standard echocardiography was performed and left ventricular systolic/diastolic function was assessed.
Results: 357 pts (mean age 74$\pm$11,female 50%,NHYA class 2.9$\pm$0.8,atrial fibrillation 20%,COPD 12%, renal impairment 6%)were referred to the HF clinic by 100 general practitioners (GPs). Mean BNP concentration was 469 $\pm$ 505 pg/ml in the 240 pts diagnosed compared with 43$\pm$105 pg/ml in the 117 without heart failure. HF pts were grouped into diastolic dysfunction (BNP: 373 $\pm$ 335 pg/ml), systolic dysfunction (BNP: 550 $\pm$ 602 pg/ml), and both systolic and diastolic dys-

function (BNP: 919 ± 604 pg/ml). The optimal BNP cut-off level, identified by receiver operating characteristic analysis (AUC 0.95), was >80 pg/ml with a sensitivity of 84% and a specificity of 91%, with a net saving of 31% of total costs, without compromising the diagnostic accuracy.

ROC analysis/BNP cut-off

BNP (pg/ml) (study group %)	Sensitivity %	Specificity %
30 (24%)	99	71
50 (32%)	93	85
70 (38%)	87	89
80 (40%)	84	90
100 (43%)	80	91
120 (46%)	76	92

Conclusions: Blood BNP concentrations, in patients with symptoms suspected by a general practitioner, can play an important role for diagnosing and stratifying pts into risk groups of cardiac dysfunction.

NOVEL THERAPEUTIC STRATEGIES IN CHRONIC STABLE ANGINA

876 Long-term safety and antianginal efficacy of the If current inhibitor ivabradine in patients with chronic stable angina. A one-year randomised, double-blind, multicentre trial

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Background: Ivabradine, is a novel selective and specific inhibitor of the If current in the sinus node. Previous reports demonstrated anti-ischemic and anti-anginal effects similar to the beta blocker atenolol. The objective of the present study was to assess the long-term safety and antianginal efficacy of two doses of ivabradine.
Methods: 386 patients with a ≥3-month history of chronic stable angina and documented CAD were randomised double-blind to two parallel-groups receiving either ivabradine 5 mg bid (n=198, group 1) or ivabradine 7.5 mg bid (n=188, group 2) for twelve months. Concomitant medication including AAS, serum lipid lowering agents, long acting nitrates or dihydropyridine calcium channel blockers were authorised during the study. Safety was assessed on reported adverse events in follow-up visits at 1, 3, 6, 9 and 12 months. Mean treatment time on the study drug was 10.4 ± 3.6 months/pat. Antianginal efficacy was based on the reduction in the number of angina attacks per week reported in patient's diary from M0 to M12.
Results: Ivabradine was safe and well tolerated throughout the study duration. Transient visual symptoms, (phosphene like), mostly of mild intensity where the most frequently reported adverse events, but lead to treatment withdrawal in only 4 patients (1 in group 1, and 3 in group 2).
Resting heart rate was reduced 10 bpm in group 1 (from 71 to 62 bpm) and 12 bpm in group 2 (71 to 59 bpm) at the end of treatment. Only in 3 cases (0,8%, all from group 2) sinus bradycardia was the cause of treatment withdrawal. At M12 uncorrected QT was increased consistently with the reduction in heart rate while corrected QT (QTc) was unchanged. No ECG abnormality was detected in this study.
The number of angina attacks per week showed a significant reduction at M12 as commpared to M0: -1.9 ± O 4.8 (95%CI [-2.6; -1.3]) and -1.2 ± O 4.1 (95%CI [-1.9; -1.2]) with ivabradine 5 and 7.5 mg bid, respectively.
Conclusion: In this one-year double-blind trial ivabradine was shown to be safe and well tolerated at the usual recommended doses of 5 and 7.5 mg bid for the treatment of stable angina. Both doses of ivabradine demonstrated relevant antianginal efficacy in patients with documented CAD and chronic stable angina stable angina treated with concomitant anti-anginal medications.

877 Arandomized, double-blind, placebo-controlled, Phase 2 study: the efficacy of fasudil in patients with stable angina

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Background: Fasudil, an orally available rho-kinase inhibitor, selectively inhibits coronary arterial vasoconstriction and may modify other processes causing myocardial ischaemia.

Objective: To evaluate the effectiveness of fasudil in the treatment of stable angina. Favourable safety and tolerability are reported separately.
Methods: In a Phase 2, multicentre, double-blind, placebo-controlled, randomized trial, the effects of fasudil were evaluated on total exercise duration, time to onset of myocardial ischaemia (≥1 mm ST-segment change), Canadian Cardiovascular Society (CCS) class and quality of life measures in patients with stable angina. Patients with objective evidence of coronary artery disease were required to have reproducible baseline exercise test times and exercise-induced ST segment depression ≥ 1 mm. A total of 84 of the 206 patients screened met entry criteria and were randomized 1:1 to placebo or fasudil. Anti-anginal medications were limited to nitroglycerin prn and monotherapy with either a beta- or calcium-channel blocker. Other cardiovascular medications including aspirin, statins and ACE inhibitors were allowed. After a 3-week washout period, fasudil or matching placebo was force-titrated from 20 mg tid to 80 mg tid with 20 mg tid increments every 2 weeks. Final efficacy measures were obtained after 8 weeks.
Results: At study end, exercise duration 1 hour post-dosing was increased by 1.97 min (118.4 sec) in the fasudil group and by 1.43 min (86.1 sec) in the placebo group (both p<0.001 vs baseline but p=ns between groups). Time to onset of myocardial ischaemia was increased by 2.87 min (172.1 sec) in the fasudil group and by 0.73 min (43 sec) in the placebo group (RR=0.45, p=0.012). The percentage of patients with ≥ 1 CCS class improvement showed a positive fasudil dose-dependent trend(p=ns). No significant differences between groups in the weekly frequency of angina attacks or use of nitroglycerin were observed, but positive trends in the physical limitation and treatment satisfaction scores of the modified Seattle Angina Questionnaire (SAQ) were observed with fasudil treatment.
Conclusions: This Phase 2 dose-finding trial demonstrated that titrating fasudil to 80 mg tid over 8 weeks improved time to exercise-induced myocardial ischaemia compared to placebo in stable angina patients. Favourable trends in exercise time, CCS class and SAQ scores were also observed. Thus, fasudil is promising as a new therapy for myocardial ischaemia.

878 Antianginal and antiischaemic effects of the If current inhibitor ivabradine compared to amlodipine as monotherapies in patients with chronic stable angina. Randomised, controlled, double-blind trial

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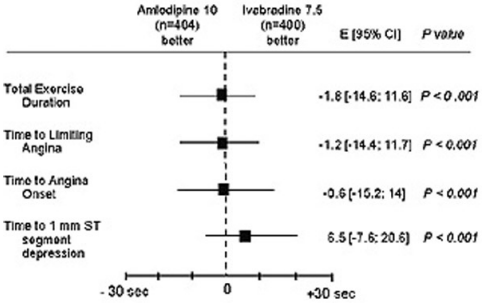
Background: Ivabradine, a novel selective and specific inhibitor of the If current in the sinus node, has previously demonstrated anti-ischaemic and anti-anginal activity in a placebo-controlled trial (Borer 2003) and similar anti-anginal efficacy than the beta-blocker atenolol (Tardif 2003). The objective of this study was to demonstrate the non-inferiority of the anti-anginal and anti-ischaemic effects of ivabradine (Iv) compared to amlodipine (Am).
Methods: In a double-blind, parallel-group, non-inferiority trial (equivalence limits of 30 sec on total exercise duration), 1195 patients with a ±3-month history of chronic stable angina and documented CAD were randomised to three groups receiving Iv 7.5 mg bid (n=400), Iv 10 mg bid (n=391) and Am 10 mg od (n=404) for three months. Patients underwent bicycle exercise tolerance tests (ETT) at randomisation (M0) and every month until the third month (M3).
Results: Total exercise duration at trough (primary endpoint) was increased from M0 to M3 by 27.6±91.7 sec, 21.7±94.5 sec with Iv 7.5 and 10 mg bid, respectively and by 31.2±92.0 sec with Am 10 mg od confirming the non inferiority of Iv vs Am (p<0.001). Time to limiting angina, time to angina onset and time to 1 mm ST segment depression were also consistently increased. In contrast, heart rate and rate pressure product were significantly more reduced with ivabradine than with amlodipine at rest and at peak exercise.



The number of angina attacks were decreased by about two thirds and the short acting nitrates consumption by about one half across the study in all treatment groups.
Conclusion: In this large 3-month double-blind controlled trial, treatment with ivabradine was shown to be as effective and safe as amlodipine in patients with chronic stable angina.

879 Immediate and long-term clinical outcome after spinal cord stimulation for refractory stable angina pectoris in patients with chronic pacemaker treatment

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Spinal cord stimulation (SCS) is a safe treatment option for patients with severe angina pectoris who are not candidates for revascularization procedures. So far, SCS has been applied in small numbers of patients in some European countries only. We report on the mid- and long-term clinical results and the reduced hospitalization frequency of patients treated with SCS.

Patients: Since January 2001, SCS was performed in 35 patients (pts.) (31 men, 4 women, age 66±8 years, BMI 26±6 kg/qm). All pts. had a history of angina pectoris grade III to IV according to Canadian Cardiovascular Society (CCS) for more than 6 months refractory to maximum medical therapy. Prior to SCS, 1.2±0.7 surgical and 1.1±1.2 catheter-based coronary revascularizations had been performed. In addition, six patients had transmyocardial laser revascularization.

Under local anesthesia, a 6- to 8-polar stimulation lead was inserted trough a needle. Correct lead positioning produces paraesthesia in the chest corresponding to the area of angina. After 3 to 5 days of successful testing stimulation the generator was implanted in the left upper abdomen.

Results: In 31 pts. angina was reduced significantly. In 3 pts. the lead was removed because of ineffectivity during the test period (n=2) or an infection (n=1). In 2 pts the leads had to be repositioned after dislocation. After two years, a persisting improvement could be observed in terms of angina and consumption of short-acting nitrates (table). The frequency of hospitalizations was reduced from 32±23 before to 4±8 days/year after SCS.

SCS	before (n=32)	after 6 months (n=26)	after 24 months (n=12)
Angina (class/n)	III/19, IV/13	0/15, I/4, II/5, III/1	0/7, I/3, II/2
Nitrates (per week/n)	> 7/20, 3-7/12	>7/0, 3-7/3, <3/8, 0/14	>7/0, 3-7/5, <3/3, 0/4

Summary: SCS has proved to be a safe procedure in patients with symptomatic angina refractory to medical therapy.

880 Percutaneous coronary intervention in chronic stable angina: is there benefit from remote ischaemic preconditioning?

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C- reactive protein (CRP) serum levels increase in acute coronary syndromes. Elevated CRP has been shown to predict adverse cardiovascular events in patients with known coronary artery disease (CAD) and in apparently healthy individuals. Furthermore, after stent implantation, elevated levels of CRP have been associated with increased probability of restenosis. Remote ischemic preconditioning (RIPC) prevents ischemia-reperfusion induced endothelial dysfunction.

Purpose: To evaluate whether elective stent implantation in patients with stable CAD causes significant increase in serum levels of CRP and whether RIPC is beneficial in this clinical setting.

Methods: In a randomized trial, 42 consecutive patients, mean aged 62.2±9.7 years with stable angina who underwent coronary angiography and had single-vessel disease were either prepared with RIPC (n=20) or not (control group, n=22) before elective percutaneous coronary intervention (PCI) with stent implantation. RIPC was induced by three 5-minute cycles of ischemia (inflation of blood pressure cuff to 200 mmHg) of both upper limbs simultaneously. Creatine kinase (CK), creatine kinase-MB fraction (CK-MB), troponin-I (TNI) and CRP serum levels were measured at baseline, 12, 24 and 48 hours after stent implantation.

Results: There was no difference between groups in baseline levels of CK, CK-MB, TNI and CRP. In the RIPC group cardiac enzymes increased significantly 24 hours after the procedure: CK was 70.2±32 ng/ml at baseline and 94.8±47.8 ng/ml 24 hours after the procedure (p=0.001), CK-MB was 0.66±0.51 ng/ml at baseline and 3.57±2.34 ng/ml 24 hours after stent implantation ($p<0.001$) and TNI was 0.033±0.04 ng/ml at baseline and 0.8±0.6 ng/ml 24 hours after the procedure ($p<0.001$). In the control group cardiac enzymes did not increase significantly. CRP increased in both groups 48 hours after stent implantation, from 3.28±2.12 ng/ml to 15.71±10.8 ng/ml ($p<0.001$, vs baseline) in the RIPC group and from 3.52±2.78 ng/ml to 14.06±11.8 ng/ml ($p<0.001$, vs baseline) in the control group.

Conclusion: CRP increases 48 hours after stent implantation in patients with stable coronary artery disease; RIPC does not prevent it. It is of interest that RIPC not only does not protect, but it increases cardiac enzymes release after PCI.

DILATED CARDIOMYOPATHY OR VIRAL MYOCARDITIS?

913 Circulating auto-antibodies to mycobacterial Heat Shock Protein 65 are increased in patients with dilated cardiomyopathy and coronary microvascular dysfunction

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Background: Low titers of auto-antibodies against Heat Shock Proteins (HSP), a family of intracellular proteins with well known cytoprotective functions, can be normally found in human peripheral circulation. However, high titers of auto-antibodies to various members of the HSP60 family can be demonstrated in patients with ischemic heart disease and have been pathogenetically associated with inflammatory processes involving the coronary vasculature. Few data are available on the presence of these auto-antibodies in non atherosclerotic cardiac diseases such as Dilated Cardiomyopathy (DCM) where functional abnormalities of the coronary microcirculation have been recently demonstrated.

Methods: To this purpose, serum levels of anti-HSP60 and anti-mycobacterial HSP65 antibodies were measured by ELISA in 54 patients with DCM without overt heart failure (6 in NYHA I and 48 in class II, LVEF% 37.0±10.2, mean±SD) and in 22 healthy controls. The coronary microvascular function was assessed in patients by rest/stress Positron Emission Tomography myocardial blood flow (MBF) study. The levels of IL-6 were measured as marker of inflammation by high-sensitive enzyme immunometric assay.

Results: DCM patients showed reduced MBF both at rest (0.68±0.20 ml/min/g, mean±SD) and during dipyridamole stress (1.62±0.70 ml/min/g, mean±SD) indicating abnormal coronary microvascular function. Auto-antibodies to HSP65 and to HSP60 were increased in DCM patients as compared with controls. While this difference was highly significant for anti HSP65 titers (118.3±9.6 vs 57.1±4.8, mean±sem, p= 0.0001) it was not significant for anti-HSP60 (30.6±4.7 vs 17.4±2.8 μg/ml, mean±sem, p=0.08). IL-6 levels were significantly increased in DCM patients as compared with controls (2.0±0.33 vs <0.5 pg/ml, mean±sem, $p<0.001$).

Conclusions: The presence of high titers of circulating anti-HSP65 auto-antibodies and increased levels of IL-6 in patients with DCM and coronary microvascular dysfunction suggests a possible involvement of autoimmune reactions to HSPs in the coronary vessel wall in the pathogenesis of this non-atherosclerotic cardiac disease.

914 Antiviral interferon therapy in DCM patients with viral persistence

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Background: Myocardial persistence of various cardiotropic viruses are a possible cause of dilated cardiomyopathy (DCM). The treatment of heart failure is symptomatic so far. In this pilot study, we analyzed whether an immunomodulatory therapy with interferon-beta (IFN-b) is save in DCM patients, effective with respect to virus clearance, and prevention of progression of left ventricular (LV) dysfunction.

Methods: In addition to conventional heart failure medication including digitalis, diuretics, ACE-inhibitors, beta-blockers and spironolactone, 38 DCM patients (age: 54±11 years; history of symptoms: 46±27 months; LVEF: 41.1±11.1%) with persistence of enteroviral (EV, n=17), adenoviral (ADV, n=7), Parvovirus B19 (PVB19, n=6), human Herpes virus 6 (HHV6, n=3) genomes or co-infections with PVB19+HHV6 (n=5) were treated with 18 mio. IU IFN-b/week subcutaneously for 24 weeks. Viral genomes were amplified in endomyocardial biopsies by nested polymerase chain reaction (nPCR) before and after interferon treatment. LVEF was determined by LV angiography, and LV diameters by echocardiography, respectively.

Results: Cardiac specific adverse side effects were not observed. After 24 weeks of IFN-b treatment, viral genomes were eliminated in 33/38 patients (87%). 68% of patients improved regarding the NYHA classification. While complete virus elimination was achieved in all patients with EV, ADV and PVB19 monoinfections, viral elimination was observed only in 1/3 (33%) patients with HHV6 and in 3/5 (60%) patients with PVB19 and HHV6 co-infections. LVEF improved from 40.5±12.1% to 50.8±13.3% ($p<0.001$) in patients with virus elimination, while LVEF did not improve in patients with virus persistence (45.0±7.3% to 42.4±12.0%). These findings were independent of the duration of symptoms before IFN-b treatment.

Conclusions: Antiviral IFN-b treatment is a save therapy in DCM patients with chronic LV dysfunction and biopsy proven viral persistence. The efficacy of IFN-b for improvement of LVEF strongly depends on the elimination of viral genomes, which can be achieved primarily in patients with EV, ADV and PVB19 monoinfections. In contrast, DCM patients with HHV6 persistence, especially in cases of co-infections with PVB19, only partially respond to IFN-b treatment favorably.

915 Relationship between circulating levels of angiogenic factors and matrix metalloproteinases in patients with dilated cardiomyopathy

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Background: Increased myocardial activity of matrix metalloproteinases (MMPs) is largely responsible for left ventricular (LV) remodeling in clinical and experimental forms of dilated cardiomyopathy. Vascular endothelial growth factor (VEGF) is a major angiogenic factor, and interleukin (IL)-4 is an unique cytokine with an angiogenic effect. These angiogenic factors regulate MMP expression in the human tissue. This study was designed to evaluate the relationship between circulating levels of angiogenic factors and MMPs in patients with idiopathic dilated cardiomyopathy (DCM).
Methods: We studied 28 patients with DCM in New York Heart Association functional class II or III, who had been treated with spironolactone, angiotensin II type-1 receptor blockers, and beta-blockers. Fifteen age-mached healthy subjects with no cardiac disease served as normal control. Serum levels of VEGF, IL-4, MMP-2, -3, and -9 were measured using enzyme-linked immunosorbent assay.
Results: Serum levels of VEGF, MMP-2, -3, and -9 were significantly higher in patients with DCM than in control subjects (all $p < 0.05$). Serum IL-4 levels were significantly lower in patients with DCM than in control subjects ($p = 0.012$). In patients with DCM, there was a significant correlation between levels of MMP-9 and VEGF ($r = 0.682$, $p = 0.005$). In addition, the levels of MMP-9 negatively correlated with levels of IL-4 ($r = -0.536$, $p = 0.039$).
Conclusions: Our results demonstrate a close association between serum levels of angiogenic factors and MMP-9 in patients with DCM. Thus, the alterations of circulating levels of VEGF and IL-4 may be closely related to cardiac matrix degradation during LV structural remodeling in DCM.

916 Fractaline expression in myocarditis and dilated cardiomyopathy – possible role for the determination of inflammatory acuity

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Background: Intramyocardial inflammation, often evoked by cardiotropic viruses, is considered as major pathogenic condition in myocarditis and dilated cardiomyopathy (DCM). However, no inflammatory marker has been elucidated for the assessment of inflammatory acuity, yet. Fractalkine (FKN) is a chemokine, which has been shown useful for the determination of inflammatory activity in cardiac allograft rejection. We therefore investigated FKN expression in endomyocardial biopsies (EMBs) from patients with acute myocarditis and DCM.
Methods & Results: FKN immunoreactivity detected by the EnVision® technique was quantified by digital image analysis (DIA; unit: area fraction/AF) in EMBs from n=15 patients with the tentative clinical diagnosis of acute myocarditis (n=5 females; mean age: 31±12 years; history of symptoms <15 days) and DCM (n=10; n=4 females; mean age: 47±10 years; history of symptoms >6 months). EMBs from healthy donor hearts (n=7) were used as controls. Based on the 90% percentile calculated from the FKN statistical distribution in controls, an FKN-AF >0.1% was considered significantly increased. FKN immunoreactivity was not different between controls and DCM EMBs ($p > 0.05$), and no DCM case supervened this statistical limit of baseline FKN immunoreactivity (mean FKN-AF: 0.02%±0.02%). In contrast, 6/15 (40%) of the EMBs from the acute myocarditis cohort demonstrated significantly enhanced FKN expression (mean FKN-AF: 0.3%±0.2%). FKN expression was expressed by endothelia, in perivascular regions and partially also by cardiomyocytes.
Conclusions: Our data demonstrate for the first time FKN expression in the setting of acute myocarditis. However, FKN expression is exclusively expressed during this very acute phase, and does not persist up to the stage of low-grade inflammation present in DCM. Therefore, FKN might be a useful diagnostic target for the determination of inflammatory stage in myocarditis patients.

917 Cardiovascular magnet resonance assessment of human myocarditis; a comparison to histology and molecular pathology

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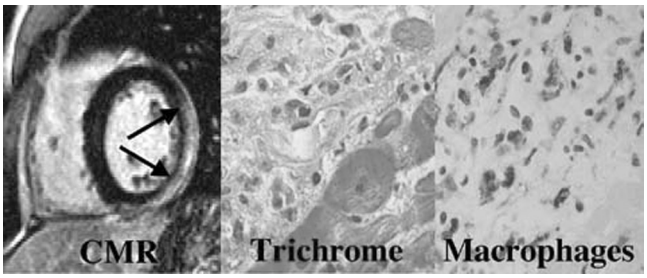
Background: Active myocarditis can occasionally lead to sudden death (SD) in young adults and 10% of all patients (pts) may develop chronic dilated CMP. Since the initial onset is difficult to recognize clinically and the diagnostic tools available are unsatisfactory, new strategies to diagnose and monitor myocarditis are needed.
Methods: Cine and contrast MR imaging (CMR) was performed in 32 pts who were diagnosed with myocarditis by clinical criteria. To determine whether CMR visualizes areas of active myocarditis, endomyocardial biopsies (EMB) were taken from the region of contrast enhancement (CE) and submitted to histological, immunohistological and molecular pathological analysis. Follow-up CMR (FU) was performed 3 months later.
Results: HE was present in 28 pts (88%) and was mostly seen originating from the epicardial quartile of the wall, most frequently located in the lateral free wall. In the 21 pts, in whom EMB was obtained from the region of CE, active myocarditis was found in all except two (PVB 19, n=13; HHV 6, n=6). Conversely, in the remaining 11 pts in whom EMB was not taken from CE active myocarditis was found in one case only (HHV 6). At follow-up the amount of CE decreased from 9±11% to 3±4% (FU) of LV mass as the LVEF improved from 47±19% to 60±10% (FU) and the end-diastolic volume decreased from 174±80 ml to 133±47 ml (FU).



Conclusion: CE is a frequent finding in the clinical setting of myocarditis and is associated with active inflammation defined by histology and immunohistology. Myocarditis occurs predominantly in the lateral free wall, originating from the epicardial quartile of the myocardium. CMR is a powerful tool to diagnose and monitor human myocarditis.

918 intramyocyte detection of epstein barr virus genome by laser capture microdissection in patients with inflammatory cardiomyopathy

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Background: Epstein Barr virus (EBV) is an ubiquitous human herpesvirus associated with myocarditis in up to 6% of patients (pts) with infectious mononucleosis. The relationship between EBV and myocarditis in absence of an acute viral infection is still unclear. We sought to investigate the role of EBV in myocarditis using laser capture microdissection for the detection of the virus genome in endomyocardial biopsy tissue.
Methods: Among 193 patients with histologic and immunohistochemical diagnosis of myocarditis, 43 (22%) had a myocardial viral infection detected by PCR and RT-PCR on frozen endomyocardial biopsies. Nine of them (21%) (39±12 ys) were positive for EBV. Laser capture microdissection was performed on 5 μm thick paraffin sections (3-4 biopsies of 3-5 mm^3 each/patient) stained with CD45RO. Lymphocytes and myocytes were microdissected and analyzed separately by PCR analysis on DNA extracted from the collected cells. Peripheral blood samples from all patients were investigated for the presence of EBV genome, anti EBV viral capside antigen (VCA) IgM/IgG and anti EBV nuclear antigen (EBNA) IgM/IgG antibodies. Blood samples and surgical biopsies from pts with positive and negative EBV serology were used as controls.
Results: In all patients the clinical manifestation of myocarditis was heart failure (NYHA class III-IV, EF=29±5%). No patient had systemic evidence of EBV infection. The EBV genome was detected in myocytes and absent in infiltrating lymphocytes in all cases. PCR analysis was negative for the presence of EBV in the peripheral blood in 8 of the 9 pts. Serologic tests showed a positivity for anti-VCA and anti-EBNA IgG and were negative for IgM. EBV genome was absent both in myocardial samples and in the blood of controls.
Conclusions: Laser capture microdissection allowed to identify intramyocyte EBV genome in 21% of pts with inflammatory cardiomyopathy. EBV localization suggests its possible causal role in myocarditis and claims for an antiviral and/or immunostimulating therapy.

MODERATED e-POSTERS II

BRUGADA SYNDROME

P955 Prevalence of fluctuations of typical electrocardiogram changes in Brugada syndrome: implications for correct phenotyping and risk stratification

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Brugada syndrome is characterized by an incomplete right bundle branch block, ST-segment elevations in V1-V3 and the risk of sudden cardiac death. It is known, that these ECG changes can transiently normalize. The index ECG is an important parameter for the risk stratification and in asymptomatic patients it often leads to further investigations. So transient non-diagnostic ECGs might lead to underdiagnosis of Brugada syndrome or incorrect risk stratification. Therefore, we prospectively studied the prevalence of diagnostic and non-diagnostic ECGs in consecutive patients diagnosed with Brugada syndrome with focus on the likelihood of transitions between diagnostic and non-diagnostic ECGs.
Patients and Methods: In 21 Patients diagnosed with Brugada syndrome 151 ECGs (Median 7) were obtained during a mean follow-up of 7±10 months. The first documented ECG was defined as index ECG. Each ECG was classified as diagnostic or non-diagnostic and as Brugada-type I, II or III according to the criteria of the Brugada Consensus Conference.
Results: 8 patients had a diagnostic, i.e. type I, index ECG, 6 had a type 2 ECG, 1 a type 3, and the remaining 6 patients had a normal ECG. All patients with a diagnostic index ECG had at least 1 non-diagnostic ECG during follow-up. 4 out of 13 patients with a non-diagnostic index ECG (type II, III or normal) showed transiently diagnostic (type I) ECGs during follow up. Of note, VF was inducible in 7 out of 8 patients with a type I index ECG and transient non-diagnostic ECGs. In 3 out of 4 patients with a non-diagnostic index ECG and transient diagnostic ECGs VF was inducible and 1 patient had previous syncope.
Conclusions: 1) Due to the high prevalence of fluctuations from diagnostic to non-diagnostic ECGs or vice versa, one ECG cannot exclude the diagnosis of Brugada syndrome. 2) For correct phenotyping and risk stratification of patients diagnosed with Brugada syndrome repetitive ECG registrations are necessary.

P956 The association of two benign polymorphisms H558R and Q1077 on SCN5A gene leads to a loss of Na^+ channel function and cause brugada syndrome

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Background: Brugada syndrome (BrS) is a cardiac hereditary disease characterized by right bundle branch block, ST segment elevation in the right pericardial leads V1 through V3 on the surface ECG and may lead to sudden death. About 20% of the patients with BrS exhibit mutations in the SCN5A gene encoding the alpha-subunit of the human cardiac voltage-dependent Na^+ channel known as hNav1.5. The aim of this study was to examine the SCN5A gene for mutations in a family with BrS clinical phenotypes and to characterize the effect of these mutations on the channel function.
Methods: To uncover BrS clinical phenotype, Pronostyl test was performed on the patient and his twin brother according to common guidelines. Genomic DNA was extracted from whole blood of BrS patient and his family. The coding exons of SCN5A gene were amplified using the Polymerase Chain Reaction (PCR) and directly sequenced using the automatic sequencer. The presence of two polymorphisms H558R and Q1077 were confirmed in BrS patient using automatic sequencing. The hNav1.5/H558R/Q1077 mutant was constructed in vitro using site directed mutagenesis, mutant channels were expressed in the tsA201 human cell line and studied using the patch clamp technique, Immunofuorescence and confocal microscopy.
Results: Two benign polymorphisms in SCN5A gene, H558R and Q1077, were identified in the index patient. The polymorphisms are localized respectively in the DI-DII and DII-DIII linker regions of the hNav1.5 sodium channel. H558R was absent in the asymptomatic twin brother. The ECG of the index patient showed a BrS type 1 ECG phenotype, under Pronostyl test. The brother's ECG was not typical for BrS, and the Pronostyl test did not unmasked a type 1 ECG phenotype. Currents density were measured from tsA201 cells transfected with the double mutation and showed about 70 to 80% reduction in Na^+ current amplitude without significant alterations on its biophysical properties, indicating an evident loss of functional Na^+ channels. No syncopes had been observed in the patient since an ICD was installed in 2001.
Conclusions: The association of the two benign polymorphisms H558R and Q1077 resulted in a reduced Na^+ channel expression. This will cause a loss of function as previously shown for other SCN5A mutations causing BrS.

P957 Clinical characteristics of patients with Brugada syndrome and negative response to flecainide but positive response to ajmaline challenge

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Background: Pharmacological challenge with sodium channel blockers is used to provoke or enhance ST-segment changes in patients with the suspicion of a Brugada syndrome. The most frequently used drug for pharmacological challenge is flecainide. Ajmaline has been demonstrated to be also very sensitive in the detection of ECG changes diagnostic of Brugada syndrome. Since ajmaline is not available in many countries, flecainide is used more frequently. A disparity of the response to both substances has already been reported. The present study describes the clinical characteristics of patients who exhibit typical ECG changes diagnostic of Brugada syndrome on administration of ajmaline but do not respond to flecainide.
Patients and methods: A total of 7 out of 22 patients with a Brugada syndrome were studied, who underwent both ajmaline and flecainide challenge and revealed a positive response to ajmaline and negative response to flecainide. Symptoms, familiy history and results of programmed ventricular stimulation were analysed.
Results: Among the seven patients who had a positive ajmaline and a negative flecainide challenge, there were 2 female and 5 male patients. VF was inducible in 4 patients, by two premature extrastimuli in 2 and by three premature extrastimuli in another 2 patients. Family history was negative in all seven patients. The clinical presentation was syncope in 3/7 patients and palpitations in one patient. 3 patients had no prior symptoms.
Conclusions: 1. In 3 patients with recurrent syncope and positive ajmaline challenge, flecainide challenge is negative. 2. Inducibility of VF is high (57%) in patients with a Brugada syndrome and a negative flecainide challenge. 3. Flecainide challenge is insufficient as a diagnostic tool in a subset of patients with a Brugada syndrome who are at an increased risk of sudden death and may therefore be followed by an ajmaline challenge, if the drug is available.

P958 Mapping and ablation in long QT and Brugada syndrome: a real option for the cardiologist?

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Background: The clinical course of inherited arrhythmogenic diseases is often characterized by polymorphic ventricular tachyarrhythmias that may lead to sudden cardiac death. Ablation has not been considered as a therapeutic option in patients with these diseases until very recently when mapping and ablation of isolated premature ventricular beats (PVCs) has been proposed as a surrogate endpoint for radiofrequency therapy based on data collected in 7 patients with long QT syndrome (LQTS) and Brugada syndrome (BrS). The presence of chronic ventricular arrhythmias is considered uncommon in patients with LQTS and BrS but conclusive data are not available. In order to assess the number of patients suitable for mapping and ablation of PVCs, we performed a targeted analysis interrogating our large database of patients with LQTS and BrS.
Methods and results: The study population included 602 patients (patients): 465 LQTS and 137 BrS. 255/602 (42%) patients presented either isolated or repetitive ventricular arrhythmias during repeated 24-hours Holter recordings. However frequent isolated ventricular beats (n= >30/hour) with or without repetitive forms (couplets or triplets) that would be amenable to be mapped were present in only 12/255 patients (4.7%), 6/12 males, mean age at diagnosis 41 ± 25 years (range 9-74 Six out of 12 patients (4 LQTS and 2 BrS) had experienced at least one syncopal event caused by ventricular fibrillation, torsade de pointes or sustained ventricular tachycardia). Ten patients had a diagnosis of LQTS and 2 of BrS. In 6 patients, premature beats originated from the right ventricular outflow tract, in 2 patients from left ventricular outflow tract and in the remaining 2 patients from the left ventricular apex. Two patients presented multiple PVCs morphologies.
Conclusions: Our findings demonstrate that patients with frequent PVCs suitable for mapping and ablation of the extrasystolic beats that triggers life-threatening arrhythmias are extremely rare (12/602 patients i.e 2.0%) among LQTS and BrS patients suggesting that this therapeutic option may have a limited role in the management of these patients.

P959 Assessment of reverse effect of isoproterenol to sodium channel blocker on inducibility of ventricular fibrillation by programmed electrical stimulation in Brugada syndrome

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Aim: This study was to assess the protective effect of isoproterenol against a pure sodium channel blocker, pilsicainide, on inducibility of ventricular fibrillation (VF) by programmed electrical stimulation (PES) in Brugada syndrome (BS).
Methods: Eleven patients with BS were performed PES at three times with following two pharmacological intervention protocol: 1) firstly PES as control, sec-

ondly PES after pilsicainide administration, and lastly PES during isoproterenol infusion (Group A, n=5); 2) firstly PES as control, secondly PES during isoproterenol infusion, and lastly PES after pilsicainide administration(Group B, n=6). Two groups were compared and assessed the number of premature stimuli to be needed to induce VF at each pharmacological intervention, and were compared coupling interval of last premature extrastimuli when VF was inducible at same steps. In group B, pilsicainide administration and PES were performed when it was confirmed that heart rate returned to the former level after isoproterenol discontinuation. We defined exacerbation when VF was inducible at less aggressive step or inducible at longer coupling intervals when VF was inducible at same steps;Improvement was defined oppositely.

Result: In group A, VF-inducibility was exacerbated after pilsicainide administration and was improved during isoproterenol infusion in all patients; Overall VF induction rates were 60%(3/5) in control, 100%(5/5) after pilsicainide administration, and 20%(1/5) during isoproterenol infusion.In group B, VF- inducibility was improved during isoproterenol infusion and was exacerbated after pilsicainide administration in all patients; Overall VF induction rates were 100%(6/6) in control, 16.7%(1/6) during isoproterenol infusion, and 83.3%(5/6) after pilsicainide administration. Comparing VF-inducibility after pilsicainide administration with VF-inducibility at control in two groups revealed a statistically significant difference in exacerbation rate [100%(5/5) vs. 33.3%(2/6), p=0.035]. However, no statistically significant difference was found between two groups for RR intervals (758.2 $\pm$ 71.9ms vs. 740.0 $\pm$ 205.9ms, NS) and ERP (207.5 $\pm$ 7.5ms vs. 208.3 $\pm$ 29.3ms, NS) measured just before pilsicainide administration.

Conclusion: VF-inducibility was exacerbated by pilsicainide and improved by isoproterenol. The effect of isoproterenol on VF-inducibility was observed not only during infusion but also after discontinuation of drug infusion even when heart rate returned to the former level, suggesting long-lasting effect of isoproterenol on the VF-inducibility in BS.

P960 Is the ventricular defibrillation threshold higher in patients with the Brugada syndrome?

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Dysfunction of the sodium current channel is responsible for distinctive electrophysiologic changes in patients with the Brugada syndrome (BS). High energy requirements for ventricular defibrillation (DF) have been reported in isolated patients with BS, but it has never been systematically studied.

Methods: The records of 32 consecutive implantable cardioverter defibrillator (ICD) recipients with the BS from 4 different centers with a similar defibrillation testing policy were retrospectively reviewed. The lowest energy tested, the highest unsuccessful energy, and the lowest successful energy for DF at ICD implantation were compared with a control group of 50 consecutive patients, who were ICD recipients and had no BS.

Results: No significant differences in the number of unsuccessful shocks (0.5$\pm$0.8 vs. 0.3$\pm$0.6), the lowest energy tested (13.5$\pm$3.0 vs. 12.9$\pm$3.7 J), the highest unsuccessful energy (13.8$\pm$3.5 vs 12.9$\pm$4.1 J), and the lowest successful energy for DF (16.0$\pm$5.3 vs. 14.2$\pm$5.6 J) at ICD implantation were found between the BS and the control groups. Failure of at least 2 maximum energy shocks and requirement of external defibrillation were found in 1 patient with the BS and in 2 patients of the control group. Patients with the BS showed a significantly higher ventricular pacing threshold (0.8$\pm$0.6 vs 0.5$\pm$0.2 V; P=0.006) and a lower R wave amplitude (10.1$\pm$4.0 vs 12.9$\pm$6.4 mV; P=0.03) than the control group.

Conclusion: This study suggests that energy requirement for ventricular DF is not significant higher in patients with BS than in patients without BS. In contrast, BS is associated with higher ventricular pacing threshold and lower R wave amplitude.

ATHEROSCLEROSIS II – BASIC SCIENCE

P961 Identification of a chromosomal locus for a rare autosomal dominant inherited form of myocardial infarction on chromosome 8q24

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Myocardial infarction (MI) is considered to be a multifactorial disease that results from an integrated vascular response to common cardiovascular risk factors. In cooperation with 17 in-hospital cardiac rehabilitation centers, we identified 124 families with at least three affected family members. Of these, 18 families with 103 living MI patients, show an autosomal dominant pattern of inheritance that cannot be explained by traditional risk factors.

Methods: A genome-wide screening in 476 probands using a modified Weber 9 screening set with 402 markers was performed in order to identify a gene locus for MI. Non-parametric multipoint analysis was carried out using GENEHUNTER and SIMWALK software package.

Results: We identified a susceptibility locus for MI on chromosome 8q24. This locus could be reproduced in three independent families. The GENEHUNTER NPL scores were 4.3, 3.9, and 1.0, respectively. In each family a four marker haplotype cosegregates with the phenotype. In this three families, analysis of traditional risk factors did not reveal differences to patients with sporadic MI, whereas female gender was significantly overrepresented (30.8 vs. 12.6% in sporadic MI; $p<0.001$).

Conclusion: In this study we identified a gene locus for a rare form of autosomal dominant inheritance of MI in three independent families. The chromosomal region 8q24 harbours interesting candidate genes that will be addressed in ongoing studies. Systematic sequencing has to be carried out in order to identify the mutation that leads to the phenotype MI.

P962 Association of hsp70-2 and hsp70-hom polymorphisms with severity of coronary artery disease in patients with chronic stable angina

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Background: Heat shock proteins (HSPs) constitute a large family of proteins that aid in a cell's response to acute stress. Previous studies have shown that a member of this family of proteins, HSP70, is involved in protection of the vessel wall against stress insults. However, no clinical data in regard to the effect of HSP70 genes on coronay artery disease (CAD) are available. We studied polymorphisms in two genes namely hsp70-2 and hsp70-Hom to assess whether they are associated with severity of CAD.

Patients: This study included 519 consecutive White patients (400 men; 119 women) of over 55 years old (mean age 65.6 $\pm$ 5.8), with typical stable exertional chest pain underwent diagnostic coronary angiography.

Methods: Angiographic vessel score (number of major epicardial vessels with significant stenosis of $\geq$70% lumen diameter) ranged from 0 to 3. Genomic DNA was extracted from EDTA-blood samples by standard techniques. hsp70-2 (A1267G) and hsp70-Hom (T2437C; Met493Thr) polymorphisms were detected using PCR and restriction digest.

Results: In our investigation the homozygous hsp70-2 polymorphism had a protective effect on the severity of CAD, which was more prominent in women than men. Women homozygous for the hsp70-2 polymorphism had significantly lower vessel score compared to women with normal genotype and carriers by 0.7 and 0.6, respectively (1.06 $\pm$ 0.75, 1.71 $\pm$ 1.05, and 1.77 $\pm$ 0.88, p=0.014 and p=0.017, respectively). Conversely, in women carrier or homozygous for the hsp70-Hom polymorphism vessel score was higher compared to women with normal genotype (mean 1.84 $\pm$ 0.9 and 1.5 $\pm$ 1.00 respectively, p=0.010). These associations were independent of traditional CAD risk factors.

Conclusions: Our data show for the first time that the genetics make up of hsp70-2 and hsp70-Hom are associated with the severity of CAD and these associations are gender dependent. This alteration of the methionine (non-polar, hydrophobic) to threonine (neutral, hydrophilic) located on the floor of the peptide-binding groove may cause reduction of the protective activity of the HSP70 protein product.

P963 Genetic polymorphism G894T on endothelial nitric oxide synthase, increases the risk for prematue myocardial infarction in young smokers

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Genetic polymorphism G894T on endothelial nitric oxide synthase (eNOS) leads to a Glu/Asp substitution on eNOS molecule and it has been associated with increased cardiovascular risk and endothelial dysfunction. However, its role in the pathogenesis of myocardial infarction (MI) remains unclear.

Aim: We investigated whether G894T polymorphism on eNOS gene is associated with the development of premature MI in young subjects.

Methods: This study enrolled 212 young patients with premature MI (46.6$\pm$5.2 years old) and 577 healthy controls (48.1$\pm$13.5 years old), derived from ATTICA cohort. The G894T polymorphism on eNOS gene was determined by polymerase chain reaction (PCR).

Results: Homozygosity for the G894T polymorphism existed in 27 MI patients (12.7%) and in 58 (10.1%) controls (p=0.281). After adjustment for age and sex, the odds ratio for MI was 1.737(95%CI: 0.777 to 3.879, p= 0.178) for 894T homozygotes and 1.059(95%CI: 0.656 to 1.710, p=0.816) for heterozygotes, in comparison to 894G homozygotes respectively. However, among young smokers, homozygosity for 894T allele was observed in 25 of 190 MI cases (13.2%) and only in 16 of 256 controls (6.3%, p=0.009), while heterozygotes were 82 of 190 (42.2%) among MI cases and 108 of 256 healthy smokers. 894G homozygotes were 83 of 190 (43.7%) among MI cases and 132 of 256 (51.5%) among healthy smokers. Furthermore, among young smokers, the odds ratio of 894T homozy-

gotes for MI was 3.555(95%CI: 1.541 to 8.201, p= 0.003) compared to 894G homozygotes and 2.986(95%CI: 1.376 to 6.481, p=0.006) compared to 894GG+GT genotypes. Furthermore, among smokers, the frequency of the T allele was 0.348 in MI patients and only 0.273 in healthy controls (p=0.015).
Conclusions: The present study supports that G894T polymorphism on eNOS gene may interact with smoking leading to premature, myocardial infarction in young smokers.

P964 The prevalance of methylene tetrahydrofolate reductase enzyme polymorphism and its association with coronary artery disease in Turkish population

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Objective: Methylene tetrahydrofolate reductase (MTHFR) is a key enzyme in the metabolism of homocystein. C677T and A1298C are two of the most important polymorphysims of enzyme. In our study, association of MTHFR polymorphism and homocystein metabolism with the incidence and severity of coronary artery disease (CAD) were determined.
Material and method: 96 patients (80 men) with CAD and 92 healthy people (36 men) were included. In both groups, homocystein, folic acid and vitamin B-12 levels were detected. C677T and A1298C polymorphisms were determined with PCR. The severity of CAD was quantified with Duke score. The findings are shown in the table.

	CAD	Control	p
Homocystein(mmol/L)	16.12±5.51	11.77±6.32	<0.001
Folic acid(ng/mL)	7.4±3.03	9.59±3.25	<0.01
Vit B-12(pg/mL)	279.4±174.27	271.3±180.9	NS
C677C	53.7%	60.9%	NS
C677T	37.9%	35.9%	NS
T677T	8.4%	3.2%	NS
A1298A	34.1%	43.5%	NS
A1298C	65.9%	56.5%	NS
677 C allell	71%	78%	
1298 A allell	67%	71%	

Results: In the CAD group homocystein levels were found significantly higher in C677T polymorphism compared to C677C ($p<0.05$). In T677T polymorphism homocystein levels were not significantly high, but in the whole study group, T677T polymorphism was associated with high homocystein levels ($p<0.05$). Folic acid levels were found significantly lower in CAD patients with CT and TT genotype compared to CC ($p<0.05$). No significant relation was detected between A1298C polymorphism genotypes and homocystein and folic acid levels. No significant relation was detected between the Duke scores and the polymorphisms.
Conclusion: In conclusion, C and A allells were found high in 677 and 1298 genes for MTHFR, no significant relation was found with CAD and T677T and C1298C genotypes, T677T genotype was associated with increased levels of homocystein and decreased levels of folic acid which might be a risk factor for CAD.

P965 The effects of synthetic peptides corresponding to MCP-1 sequences on monocytic cell migration

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Purpose: Monocyte chemoattractant protein-1 (MCP-1) is detected in human atherosclerotic lesions and its implication in atherogenesis is proved in transgenic mice. MCP-1 is also induced in myocardial infarcted area where it regulates monocyte/macrophage recruitment and thus stimulates growth factors' induced angiogenesis. Great attention is paid now to the development of therapeutic agents preventing atherosclerosis and stimulating angiogenesis, in particular to synthesis of short peptides corresponding to MCP-1 sequences. The aim of our study was to synthesize MCP-1 N- and C-terminal peptides and to analyze the effects of these molecules on spontaneous and MCP-1-stimulated monocytic cell migration.
Methods: MCP-1 structure was analyzed with "Peptide Companion" software. Peptides (12 amino acids) were synthesized by standard solid phase chemistry: #1-H-EICADPKQKWVQ-OH [1], #2-H-CQIWKQKPDLC-OH (cyclic, all A-amino acids)°, #3-H-DHLDKQTQTPKT-OH, #4-H-RRITSSKCPKEA-OH. Cell migration was analyzed in Boyden chamber with THP-1 monocytic cells and human peripheral blood monocytes obtained by Percoll gradient centrifugation.
Results: Peptides #1, #2 and #3 inhibited THP-1 cell and monocyte chemotaxis in MCP-1 gradient, while peptide #4 stimulated both spontaneous and MCP-1 - induced monocytic cell migration (table).
Conclusion: Peptide homologous to 66-77 MCP-1 C-terminus inhibits monocyte migration as well as known N-terminal fragments. Peptide homologous to 30-41 MCP-1 N-terminus stimulates cell migration. These peptides could be used as MCP-1 antagonist and agonist in vivo.
[1] J. Reckless, D. Grainger. 1999 Biochem. J. 340:803-811; J. Reckless et al., 2001 Immunology 103:1-17.

Peptide effects on cell migration.

Peptide, #	THP-1	monocytes
	Inhibition of chemotaxis to MCP-1, %	
1	55±14	8±2, n.s.
2	24±16	31±4
3	30±10	21±5
	Stimulation of spontaneous migration, %	
4	39±5	45±10
	Stimulation of chemotaxis to MCP-1, %	
4	24±9	38±15

n.s. - non-significant

P966 Toll-like receptor 2 activation of monocytes decreases adhesion to endothelial cells under flow conditions

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Purpose: Atherosclerosis is associated with an intense inflammatory response. During this response mediators like chemokines and cytokines are able to recruit leukocytes and macrophages to the site of injury. Previously, we demonstrated that peptidoglycan (PGN), a Toll-like receptor 2 (TLR2) ligand, is present in unstable atherosclerotic lesions hiding inflammatory cells. The presence of peptidoglycan was mainly observed in macrophage-rich regions. In the present study, we determined the effect of TLR2 ligands on monocyte adhesion to endothelial cell layers under flow conditions.
Methods: The TLR2 ligands used are purified Staphylococcus aureus PGN and synthetic Pam3Cys. On monocytes, activated by these TLR2 ligands, the expression of adhesion molecules CD18, CD11b and CD62L was measured by flow cytometry. Furthermore, an in vitro flow chamber model was used to study the interaction between PGN- and Pam3Cys- activated monocytes to endothelial-like cells (Chinese Hamster Ovary cells (CHO cells) expressing E-selectin, and L-cells expressing E-selectin and ICAM-1) and Human Umbilical Vein Endothelial Cells (HUVEC). The role of L-selectin on adhesion of the monocytes to the endothelial cells was evaluated by the use of a blocking antibody (Dreg56).
Results: Higher levels of the monocyte receptors CD18 and CD11b (in MFI) were expressed on monocytes activated with the TLR2 ligands compared to control monocytes (CD18; 137.0±22.4 versus 79.9±11.0, CD11b; 221.2±57.8 versus 132.1±21.9 for Pam3Cys and CD18; 126.9±22.7 versus 91.4±18.2, CD11b; 185.5±32.5 versus 94.2±16.7 for PGN), while L-selectin (CD62L) was shed from the surface after monocyte activation (10.3±2.8 versus 38.3±6.8 for Pam3Cys and 23.8±10.4 versus 47.2±5.3 for PGN). TLR2 activation resulted in a significantly reduced number of adherent monocytes to the endothelial cell layers compared to non-activated control monocytes. This suggests that L-selectin shedding results in a decrease in monocyte tethering to endothelial cells. Indeed, in the presence of an L-selectin blocking antibody adherence of control monocytes dropped to values similar to monocyte adhesion after TLR2 activation.
Conclusion: These results show that monocytes increase the expression of adhesion receptors on their surface and shed L-selectin upon TLR2 activation. Surprisingly, however, the adhesion of monocytes to endothelial cells is decreased after TLR2 activation probably due to the L-selectin shedding. Future studies will evaluate the role of CD11b, CD18 on TLR2 stimulated monocytes in the shear resistance to endothelial cells.

P967 Anti-inflammatory effects of angiotensin-II subtype 1-receptor antagonists in hypertensive patients with micro-inflammation

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Purpose: Experimental studies revealed pro-inflammatory properties of angiotensin II. We evaluated the anti-inflammatory effects of the angiotensin II subtype 1-receptor antagonist olmesartan medoxomil alone and in co-therapy with the HMG-CoA-reductase-inhibitor pravastatin in patients with essential hypertension and micro-inflammation.
Methods: We measured a panel of vascular inflammation markers including high-sensitivity C-reactive protein (hsCRP) and lipid levels during 12 weeks of therapy with olmesartan (n = 100) or placebo (n = 99) in a prospective double-blind multi-center trial. Pravastatin was added to the double-blind therapy at week 6 in both treatment arms. Blood pressure control was achieved with addition of hydrochlorothiazide to the double-blind therapy.
Results: Olmesartan treatment significantly reduced serum levels of hsCRP (-15.1%; $p<0.05$), high-sensitivity tumor necrosis factor-alpha (hsTNF-alpha; -8.9%; $p<0.02$), interleukin-6 (IL-6; -14.0%; $p<0.05$) and monocyte chemotactic protein-1 (MCP-1; -6.5%; $p<0.01$) already after 6 weeks of therapy, whereas placebo treatment had no significant effect. After 12 weeks of therapy hsCRP (-21.1%; $p<0.02$), hsTNF-alpha (-13.6%; $p<0.01$) and IL-6 (-18.0%; $p<0.01$) decreased further with olmesartan and pravastatin co-therapy, but pravastatin alone (with placebo co-therapy) had no significant effect on inflammation markers. In

contrast, addition of pravastatin lead to a significant ($p<0.001$) reduction of total and low-density lipoprotein cholesterol serum concentrations in both, the olmesartan and placebo treatment group (-15.1% and -12.1% respectively).
Conclusions: Angiotensin II-receptor blockade significantly reduces vascular micro-inflammation in patients with essential hypertension already within 6 weeks of therapy. Co-administration of pravastatin significantly reduces cholesterol levels but has no additional effect on inflammation markers.

P968 Effects of C-reactive protein on human monocyte in atherogenesis

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The contribution of an inflammatory component to atherosclerosis is now widely accepted. The acute-phase reactant C-reactive protein (CRP) has been suggested to participate to the initiation, progression and clinical complications of atherosclerosis. The mechanisms through which CRP is involved in these processes are incompletely characterized. The aim of this study is to investigate the effects of CRP on human monocytes transcriptome and proteome using oligonucleotide array technology coupled with Real Time Quantitative PCR and Cytokines Array technology.
Methods: Blood was harvested on citrate from healthy women volunteers (n = 4) and monocytes were isolated using anti-CD14 antibodies and magnetic cell sorting microbeads (Miltenyi Biotech). Monocyte purity was checked by FACS. Isolated monocytes were cultured for 20 hours in MSF medium (Invitrogen®) supplemented with 1%AB serum, before exposure to 25 μg/ml CRP for an additional 12 or 24 hours. Cultured monocytes were lysed in Trizol and mRNA extracted and amplified using the Amino Allyl Message Amp aRNA kit (Ambion®). Amplified cDNA was Cy3/Cy5 labeled and hybridized to 50 mer oligonucleotides on a custom-made MWG DNA array (MWG Biotech) representing 250 genes known to play a role in atherogenesis and inflammation. Modified expression of some genes was confirmed in Real Time Quantitative PCR. Expression of intracellular and secreted protein was measured with Human Cytokine Array (RayBiotech).
Results: Our first results indicate that monocyte exposition to CRP for 12h increases expression of several genes involved in different monocyte functions such as inflammation (IL-1 alpha, IL-1 beta, IL-6 and Gro alpha), recruitment (MCP-1 and IL-8), adherence (Int alpha 6) to endothelial cell, and thrombogenesis (PAI2). This genomic surexpression is followed by the secretion of cytokines implicated in the inflammation (Gro alpha), recruitment (IL-8), as well as angiogenesis (Gro alpha, IL-8 and HGF). Moreover, several upregulated secreted cytokines in presence of CRP are potential inducers of matrix metalloproteinases (MMP-1 and MMP-9).
Conclusion: These results suggest that CRP may have a proatherogenic effect on the monocyte, and a proangiogenic effect link to arterial remodeling leading to neovascularisation.

P969 C-reactive protein induces apoptosis in human coronary vascular smooth muscle cells

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C-reactive protein (CRP) is a prototypic marker of inflammation and an independent risk predictor of future cardiovascular events. Recent evidence suggest that CRP is also synthesized within atherosclerotic lesions by vascular smooth muscle cells (VSMC) and macrophages. Apoptosis of VSMC in atherosclerotic lesions may contribute to a weakening of the plaque texture and progression of atherosclerotic lesions by conversion from a hypercellular lesion to a more cytopenic fibrotic atheroma. In the present study, we investigated the effect of CRP on human coronary VSMC. CRP (5-20 μg/ml, 72 h) dose-dependently induced VSMC apoptosis as assessed by typical morpholocical changes, TUNEL assay and Annexin V binding (3.86 ± 0.54-fold at 20 μg/ml CRP, $p<0.05$). Pretreatment with the pan-caspase inhibitor Z-VAD-FMK (200 μmol/L) completely abolished CRP-induced cell death suggesting a caspase-mediated mechanism. To further define the molecular mechanisms of CRP induced apoptosis, a DNA microarray was employed to identify CRP-regulated genes. The growth arrest- and DNA damage-inducible gene 153 (GADD153) mRNA expression was prominently upregulated by CRP (5.71 ± 0.32-fold, $p<0.05$). As confirmed by Northern blot analysis, CRP induced a time- and dose-dependent increase in expression of GADD153, a gene involved in growth arrest and apoptosis which is regulated at both transcriptional and post-transcriptional levels. Transient transfection experiments using a GADD153 luciferase-promoter construct and mRNA decay studies revealed that CRP-induced GADD153 mRNA expression occurs primarily at the post-transcriptional level by mRNA stabilization (mRNA half-live 59 min vs 354 min). SiRNA (100 nM) specific targeting GADD153 reduced CRP-induced cell death (36.35 ± 4.2% inhibition compared to non-silencing siRNA), suggesting that GADD153 plays a causal role in CRP-induced cell death. Immunhistochemistry and immunfluorescence stainig of serial sections of human early atherosclerotic lesions and fibrous cap atheroma demonstrated the presence of DNA fragmentation (TUNEL positive cells) in areas containing VSMCs and CRP, which colocalized in cells immunopositive for GADD153. These data demonstrate that GADD153 is a CRP-regulated gene in VSMC, which plays a functional role in CRP-induced apoptosis. These findings further support the emerging hypothesis that CRP plays a direct role in the development of atherosclerosis and its thrombotic complications and constitutes a novel target for the treatment of atherosclerosis.

P970 Oxidized low-density lipoprotein as a predictor of outcome in patients with unstable coronary artery disease

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Background: Elevated plasma levels of oxidized low-density lipoprotein (OxLDL) are associated with acute coronary syndrome (ACS). The predictive value of OxLDL in these patients has not yet been established.
Methods and Results: OxLDL was measured using a commmercially available sandwich enzyme-linked immunosorbent assay (ELISA) in 433 patients with ACS. After adjustment for other predictors of risk, OxLDL levels above the median (76 U/L) were associated with a higher risk for acute myocardial infarction (AMI) (Odds Ratio (95% CI): 1.82(1.09-3.06)) within 2 years after the index event. This increased risk was associated with spontaneous MI's and not procedure-related. When patients were divided according to troponin T status, the predictive value of OxLDL was most evident in the troponin T negative group with a risk of AMI of 16.9% in patients with elevated OxLDL compared to 1.7% ($p=0.004$) in those without.
Conclusions: Elevated plasma levels of OxLDL identify patients with unstable CAD at increased risk for future MI independent of other risk variables. In particular, in patients with unstable CAD and no evidence of myocardial damage, an elevated level of OxLDL appears to predict future AMI.

P971 Antibody titers against various forms of oxidized LDL in patients with coronary artery disease are influenced by the LDL -associated PAF-acetylhydrolase activity

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Purpose: The oxidative modification of LDL induces immunogenic epitopes, many of which are due to phospholipids formed during oxidation, such as lysophosphatidylcholine (lyso-PC), platelet activating factor (PAF) and oxidized phospholipids. Lyso-PC is enzymatically generated during LDL oxidation through the hydrolysis of oxidized phospholipids by the LDL-associated PAF-acetylhydrolase (PAF-AH). The aim of our study was to evaluate the autoantibody titers against various forms of oxidized LDL (oxLDL) and oxidized phospholipids in patients with coronary artery disease (CAD).
Methods: Sixty-five patients (7 women, 58 men, mean age 62.5±9.5) and in 47 age- and sex- matched healthy volunteers (controls) participated in the study. LDL isolated from fresh plasma was oxidized in the presence of 5μl CuSO4. Three different forms of oxLDL were prepared, oxLDLL, oxLDLP and oxLDLD, i.e. at the end of lag, propagation and decomposition phase, respectively. The same forms were also prepared after previous inactivation of endogenous PAF-AH [oxLDL(-)]. Malondialdehyde-modified LDL (MDA-LDL) was also prepared and used as antigen. Autoantibody titers were measured by ELISA.
Results: CAD patients had significantly higher titers against oxLDLL (1.131 ±0.430 vs. 0.919 ± 0.271, $p < 0.004$), oxLDLP (1.467±0.727 vs. 0.941±0.284, $p<0.000$) and oxLDLD (1.217±0.385 vs. 0.963±0.348 $p<0.000$). By contrast the autoantibody titers against all forms of oxLDL(-) and MDA-LDL did not differ between CAD patients and controls. In addition, patients exhibited lower autoantibody titers against lyso-PC (0.102±0.048 vs 0.139±0.039, $p=0.0003$) compared to controls. No difference was observed in autoantibody titers against PAF and lyso-PAF between CAD patients and controls
Conclusions: These results indicate that responsible for the elevated autoantibody titers against oxLDL observed in CAD patients, is mainly lyso-PC and not the intact oxidized phospholipids, thus suggesting an important role of the LDL-associated PAF-AH in the formation of these autoantibodies.

P972 Expression and function of the liver X receptor in human vascular smooth muscle cells

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Liver X receptors (LXR alpha and LXR beta) are important regulators of cholesterol efflux and inflammatory gene expression in macrophages and synthetic LXR activators prevent the development of atherosclerosis in mice. However,

the expression and functional relevance of LXR in vascular smooth muscle cells (VSMC) has not been investigated. In the present study, we demonstrate the expression of LXR alpha in human coronary vascular VSMC using RT-PCR and immunofluorescence staining. As proliferation of VSMC is a hallmark of atherosclerosis and restenosis, we analyzed the effect of LXR activation on VSMC proliferation. The synthetic LXR agonists, T0901317 and GW3965, inhibited PDGF+insulin induced VSMC proliferation in a dose-dependent manner (84.2 $\pm$ 4.6% and 100% inhibition at 5 μM, respectively, $p<0.05$, n=3). Flow cytometry demonstrated that T0901317 and GW3965 prevented G1-S progression induced by PDGF+insulin. To elucidate the mechanisms by which LXR ligands inhibit G1-S phase transition, we examined their effect on retinoblastoma (Rb) protein phosphorylation which functions as the key switch for G1-S progression. T0901317 (0.1-5 μM) inhibited PDGF+insulin induced Rb phosphorylation (86.4 $\pm$ 6.1% inhibition at 5 μM, $p<0.05$, n=3). Both mitogen-induced degradation of p27kip1 (100% inhibition, n=3, $p<0.05$) and induction of cyclin D1 and cyclin A (97.7 $\pm$ 4.57%, 66.9 $\pm$ 3.8% inhibition, respectively, n=3, $p<0.05$) were markedly attenuated by LXR ligands. To further examine the mechanism for LXR-induced p27kip1 protein accumulation, Skp2 expression, an F-box protein that targets p27kip1 for degradation, was analyzed. T0901317 potently inhibited mitogen-induced Skp2 protein expression (92.1 $\pm$ 8.1% inhibition, n=3, $p<0.05$). Finally, adenovirus-mediated overexpression of the S phase transcription factor E2F, which is released after Rb phosphorylation, reversed the inhibitory effect of LXR ligands on S phase gene expression, indicating an E2F dependent mechanism. Thus, LXR ligands exert their antiproliferative efficacy on VSMC by targeting critical cell cycle regulators, including G1 cyclins, p27Kip1 and Rb. Skp2 as a upstream regulator of p27Kip1 degradation may play a central role for LXR-mediated inhibition of VSMC proliferation. These findings indicate a previously unrecognized role for LXR in VSMC proliferation and, therefore, LXR ligands may constitute a novel therapeutic for proliferative vascular diseases.

P973 Inhibition of collagen cross-linking by beta-amino propionitrile limits post balloon angioplasty restenosis and constrictive remodeling in the double injury rabbit model

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Background: Collagen accumulation after balloon angioplasty has already been described with a strong correlation between collagen content and the severity of restenosis. The present study was designed to evaluate the effect of inhibition of collagen cross-linking by beta aminopropionitrile (bAPN) on restenosis and arterial remodeling after balloon angioplasty in the double injury rabbit model.
Methods and Results: Atherosclerotic-like lesions were induced in femoral arteries of 22 New Zealand white rabbits by the association of air-desiccation and high cholesterol diet. One month later, balloon angioplasty was performed. In the group 1 (n=11), rabbits were fed with bAPN (100mg/kg) 7 days prior to angioplasty and for the following 4 weeks. In group 2 (n=11), rabbits were used as control. Angiography, biochemistry and histomorphometry were evaluated 4 weeks after angioplasty. bAPN significantly reduced collagen content in b APN treated rabbits in both neointima (23.0 $\pm$ 3.8% versus 29.4 $\pm$ 4.0%; p=0.0042, respectively for bAPN and control) and media (31.9 $\pm$ 2.6% versus 39.0 $\pm$ 10.1%; p=0.013, respectively for bAPN and control). Histological residual stenosis was significantly lower in group 1 than in group 2 (31$\pm$18% vs 48$\pm$25%, p=0.02). Similarly, minimal luminal diameter was higher in group 1 than in group 2 (1.6$\pm$0.5 mm vs 1.2$\pm$0.3 mm, p=0.02). bAPN promoted enlargement remodeling since remodeling index was significantly higher in group 1 than in group 2 (1.4$\pm$0.1 vs 0.8$\pm$0.1, p=0.03).
Conclusions: These findings suggest that collagen cross-linking appears as a potential mechanism of healing associated with restenosis and constrictive remodeling after balloon angioplasty in the atherosclerotic rabbit model.

P974 Decorin overexpression reduces the development of early atherosclerosis in Apolipoprotein E-deficient Mice

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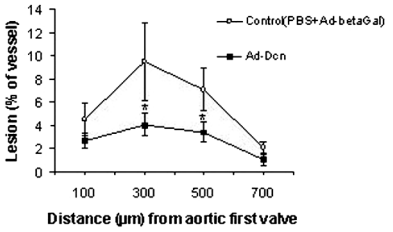
Background: Arterial proteoglycans have different effects during atherosclerosis development. Decorin is an extracellular matrix proteoglycan that regulates TGF-beta bioactivity and assists in collagen fibrillogenesis. Moreover, decorin can inhibit cell growth and migration. In this study, we investigated the effect of adenovirus-mediated overexpression of human decorin on the development of early atherosclerosis in Apolipoprotein E-deficient (ApoE-/-) mice.
Methods and results: Female ApoE -/- mice (n=20) aged 10 weeks were administered intravenously with an adenovirus (2.5×10^9 plaque-forming units) containing human decorin gene (Ad-Dcn) or beta-galactosidase (Ad-betaGal). A group of mice were infused with PBS solution. Human decorin was detected in plasma up to 4 weeks after injection, by western blot. Exogenous decorin expression was also detected in both the liver and aorta. Six weeks after adenovirus-mediated gene transfer, sections of aortic roots were stained with Oil-red-O. Plaque development was analyzed at 100, 300, 500 and 700 μm from the appearance of the first aortic valve. Measures of plaque size (lesion surface, percentage of vessel surface) were analyzed by ANOVA. No significant difference in lesion percentage was observed between beta-galactosidase-transfected and PBS-infused mice groups, therefore these two groups were pooled together (control). Decorin-trasnfected mice showed a significant reduction in atherosclerotic lesion size as compared to control group (figure), $p<0.01$).



Conclusions: Decorin overexpression can limit early atherosclerotic plaque development in ApoE -/- mice model. These findings suggest that decorin proteoglycan could have an anti-atherogenic effect.

P975 Activation of alpha v-integrin by proprotein convertase PC5 regulates VSMC functions and diversely affects integrin-signaling

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Integrin alpha v consists of a disulphide-bound 125 kDa heavy chain and 25 kDa light chain, which are cleaved from a 150 kDa precursor pro-protein. Both, MT1-MMP and proprotein convertases have been implicated in alpha v endoproteolytic activation. We have recently shown, that the proprotein convetase (PC)5 isozyme is upregulated in the neointima following balloon-injury in rodents, colocalizing with alpha v in VSMCs. In this study, we investigate the consequences of PC-inhibtion for integrin-dependent cell function and signaling in VSMCs, as well as the expression of PC5 in human atherosclerotic lesions.
Results: Reducing and non-reducing immunoblotting demonstrated, that a pharmacological PC-inhibitor and brefeldin A, which inhibits trans-Golgi trafficking, inhibit alpha v activation in VSMCs, indicating that PC-activity is required and that integrin alpha v activation occurs in the trans-Golgi network were PC5 is highly concentrated in VSMCs. In contrast, inhibition of MMP-activity with GM6001 had no effect on integrin processing. Our results were confirmed with specific PC5 antisense oligonukleotide (asODNs). PC5 asODNs inhibited VSMC adhesion on vitronectin comparable to a alpha v beta 5-blocking antibody (clone P1F6), but had no effect on VSMC adhesion to collagen I, presumtively because adhesion to collagen I is alpha 2-integrin dependent and does not require endoproteolytic activation. Furthermore, PC5 asODNs inhibited VSMC migration on gelatin- and vitronectin coated membranes. Inhibition of PC5 activity repressed adhesion-dependent FAK-autophosphorylation and subsequent Akt-activation on upon vitronectin attachment, but did not affect integrin-dependent ERK1/2 phosphorylation, indicating that the status of alpha v activation could diversely regulate integrin-dependent signaling pathways. PDGF stimulation confirmed, that signaling pathways were intact in PC-inhibited VSMCs. Immunohistochemistry demonstrated, that PC5 colocalized with alpha v in VSMCs in human atherectomy specimens (n=10).
Conclusion: The present study demonstrates, that alpha v integrin is activated by PC5 in the trans-Golgi network of VSMCs. This type of endoproteolytic activation is necessary for VSMC adhesion to vitronectin and integrin-denpendent signal transduction. The presence of PC5 in human atherosclerotic lesions indicates, that PC5 might be a novel traget to modulate integrin-VSMC-matrix interactions and signaling during atherosclerosis and restenosis.

P976 Effects of HMG-CoA reductase inhibition on endothelial function and lipid profile in HIV-infected persons on protease inhibitor-containing antiretroviral combination therapy

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Purpose: Antiretroviral combination therapy has altered cardiovascular risks and manifestations in HIV-infected persons. Protease inhibitors in particular have been linked to dyslipidemia, glucose intolerance, endothelial dysfunction and an increased susceptibility for cardiovascular diseases. Hence, the aim of this study was to evaluate the effects of pravastatin on endothelial function and plasma lipid profile in HIV-infected persons on antiretroviral therapy.
Methods: 31 HIV-infected persons on stable protease inhibitor-containing antiretroviral combination therapy for at least 4 months and plasma cholesterol >

5 mmol/L were randomly assigned to receive pravastatin 40mg daily or matching placebo for 8 weeks in a double-blind cross-over fashion. Flow-mediated vasodilation (FMD) of the brachial artery was assessed by high-resolution ultrasound at baseline and after each treatment period, and plasma lipid levels were measured.
Results: After 8 weeks of treatment, flow-mediated dilation significantly improved with pravastatin (3.2%) compared to baseline (2.0%, p=0.003), and compared to placebo (2.5%, p=0.03). Total cholesterol was reduced from 6.4 mmol/l to 5.5 mmol/L ($p<0.0001$) and LDL cholesterol from 3.7 mmol/L to 3.0 mmol/L (p=0.001). Changes in FMD were inversely related to changes in LDL cholesterol (r=0.36, p=0.014).
Conclusions: In HIV-infected persons on protease inhibitors-containing antiretroviral therapy, pravastatin improved endothelial dysfunction and the plasma lipid profile and thus, may hold the potential to reduce the cardiovascular burden in this patient group at risk.

NUCLEAR CARDIOLOGY/MAGNETIC RESONANCE IMAGING AND CARDIAC RADIOLOGY

P977 Determinants of thoracic aorta size measured by magnetic resonance imaging. Which variables should be taken into account to consider aorta as really enlarged?

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The aortic size is a basic parameter for the management and prognosis of aortic disease. The aims of the present study were: 1) to evaluate the influence of cardiovascular risk factors (CRF) adjusted by sex, age and body surface in the thoracic aorta size and, 2) to define the normal aortic diameters in the specific subgroup of healthy subjects and the influence of age, gender and body surface on such diameters.
294 subjects (208 men; 20-83 y;m:59±15) with no known aortic disease underwent MRI. Aortic diameter was determined in the 4 thoracic segments. Age, gender, body surface, smoking (42%), hypertension (51%), diabetes (21%) and atherosclerotic disease (45%) were considered. A linear regression model was built for determining both which CRFs were associated with aortic diameters in the whole population and to quantify the influence of age and body surface in the variability of such diameters in the subgroup without any CRF (n=67).
Diabetes, atherosclerotic disease and hypertension were independently associated with aortic diameters depending on the segment considered. In the subgroup without any CRF (41 men; 49±17y), age and body surface but not gender were related to the variability of aortic diameters across the 4 segments ($p<0.05$). Table shows absolute values, indexed values by body surface area and the expected increments per 10 years in the indexed aortic diameters for each segment according to our model.

Aortic diameters

	Root	Ascending	Arch	Descending
Absolute values	29.7 (3);35	30 (4.2);40	24 (4);32	21,6 (4); 30
Indexed values	17 (2.2);21	17 (3);25	13.5 (2.3);19	12 (2.4); 19
Expected increments	0.7(0.4-0.9)	1.1(0.8-1.4)	1(0.7-1.2)	1.1(1-1.3)
R=	0.58	0.7	0.72	0.81

Absolute values in mm (mean (SD);97th percentile), indexed values in mm/m^2 (mean (SD);97th P) and the expected increments in the indexed aortic diameters per 10 years in mm/m^2/10y (mean(95%IC)) for each segment. Last row shows the global linear association coefficients (R) for predicting 10-year increments in the indexed diameters according to our model.

Conclusions: normal aortic diameter values are related to body surface area and age; thus these variables should be considered to detect a truly enlarged thoracic aorta. Hypertension, diabetes and atherosclerotic disease are associated with aortic diameters.

P978 Atherosclerotic plaque detection by contrast-enhanced magnetic resonance imaging. A comparative animal study of gadofluorine and Gd-DTPA

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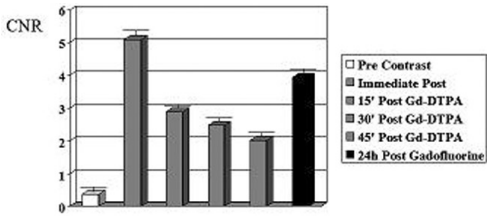
Contrast-enhanced MRI has been developed to improve signal in high resolution imaging. Recentely, the use of Gadofluorine has been shown to facilitate atheroslcerotic plaque detection. However, no study has been designed to compare the usefulness of Gadofluorine versus conventional contrast agent such as Gd-DTPA.Atherosclerotic plaques were induced by balloon injury and hypercholesterolemic diet in the aorta of 14 New Zealand White rabbits (6 controls). MRI was performed at 1.5 T, before (PRE), and after injection of Gd-DTPA, followed by Gadofluorine (next day). Because of Gadoflurine high relaxivity compared to Gd-DTPA, we injected x4 time the dose of Gd-DTPA (repectively 250μmol/kg vs 50μmol/kg). Time courses of enhancement for plaque detection were assessed after Gd-DTPA injection up to 90 minutes and 24h post Gadofluorine. A T1W GRE sequence was used (TR/TE=300/4ms; flip=20°; BW=±230; slice thickness=2.5 mm; FOV=12 cm; matrix 256x256; Nex=16). Histopathological analyses were systematically performed. Atherosclerotic plaque enhancement, 24h POST Gadofluorine, was increased by a factor 4 compared to PRE contrast imaging ($p<0.0001$). It was heterogeneous along aortic length, corresponding to plaque areas of different thickening as confirmed by histopathology. No contrast enhancement was seen in control group. Using Gd-DTPA, CNR immediately after injection (5.02±0.5 vs 0.29±0.2 ($p<0.0001$)) decreased rapidly with time (figure).



Enhancement was aspecific as indicated by contrast uptake in controls ($p<0.005$).Our study demonstrates that Gadofluorine improves plaque detection in NZW atherosclerotic rabbits compared to Gd-DTPA. The use of Gd-DTPA is not further required for plaque imaging as it enhances arterial and peripheral tissue as well without any specificity.

P979 High resolution magnetic resonance imaging of human atherosclerotic carotid lesions before and after six months of high dose atorvastatin therapy

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Background: Recent studies demonstrated that ex vivo and in vivo high resolution MRI can image and characterize atherosclerotic plaque. The aim of the study was to evaluate the effect of a high dose Atorvastatin therapy (Sortis® 40 mg/d) on lesion size in the arteria carotis communis (ACC). Patients were investigated before therapy and after six months.
Method: 24 patients (mean age 65 years; 18 males) were imaged with a 1,5 Tesla scanner (Sonata®, Siemens, Erlangen, Germany) in supine position using a conventional neck-array. Pre- and post contrast images were acquired with a gadolinium agent (0,1 mmol/kg bw) using a multislice T1w Turbo Spin Echo Sequence (TR 800 ms, TE 9 ms, FOV: 200 x 230 mm, matrix: 336 x 512), with a SLT of 2 mm positioned orthogonal to the ACC and the bifurcation. Lesion size planimetry was performed in defined positions in the distal ACC. The measurement values before/after therapy were compared. The results of plethysmographic flow measurements and the index of vessel wall elastizity were compared.
Results: All investigations were of sufficient qulity for analysis; qulaity was graded as very good in 40/48 ACC (right and left/pat.), good in 8/48. Planimetric analysis revealed an average vessel wall area before therapy of 0,53 cm^2 (±0,17 cm^2), after 6 months of therapy 0,40 cm^2 (±0,13 cm^2), that means an area reduction of 0,13 cm^2 (25%), $p<0,0001$. Accordingly the index of vessel wall elastizity improved from 16,53 (±4,36) to 21,67 (±11,56), $p<0,05$.
Conclusion: In vivo high resolution MRI is capable of identifying atherosclerotic plaque and allows to measure its size. Measurements are highly reproducible and allow follow up investigations. Atorvastatin 40 mg per day led to a significant reduction of plaque area after six months. Accordingly vessel wall elastizity improved.

P980 Significant dilation of the right ventricular outflow tract in patients with Brugada syndrome. A comparative study using magnetic resonance imaging

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Purpose: Cardiovascular magnetic resonance imaging (CMR) is a powerful diagnostic tool for evaluating cardiac structure and function. Recently, right ventricular wall motion abnormalities were described using electron beam tomography in patients with Brugada syndrome. In the present study we prospectively evaluated cardiac magnetic resonance imaging findings in patients with Brugada syndrome compared to matched controls.
Methods: CMR was performed on 15 consecutive patients with proven Brugada syndrome. MR images were acquired with a 1.5-T whole-body MR system (Magnetom Sonata; Siemens, Erlangen, Germany). For the assessment of global and regional left and right ventricular function, electrocardiographically gated cine images were obtained with a segmented true fast imaging with steady-state precession, or FISP, sequence in three long-axis views (two-, three-, and four-chamber views) and seven to 11 short-axis views 1 cm apart to cover the whole left ven-

tricle in repeated breath holds. The imaging protocol included also breath-hold dark blood prepared T1-weighted multi-slice turbo spin-echo images for the evaluation of the right ventricular anatomy and morphology. Ventricular volumes and dimensions were compared to age- and sex-matched normal volunteers.
Results: The right ventricular outflow tract area was significantly enlarged in patients with Brugada syndrome compared to controls (11 vs. 9 cm^2, p = 0.018). There was a trend to larger right ventricular end-diastolic and end-systolic volumes and lower right ventricular ejection fraction in patients with Brugada syndrome compared to controls. However, none of these differences reached significance (p=0,3, p= 0,08 and p= 0.06 respectively). There was no statistically significant difference in the left ventricular parameters between patients and controls.
Conclusions: These findings support the view that subtle structural changes, such as RVOT dilation may point to a localized arrhythmogenic substrate in patients with Brugada syndrome.

P981 Intracellular sodium magnetic resonance imaging assessment of viability after chronic infarction in rat hearts

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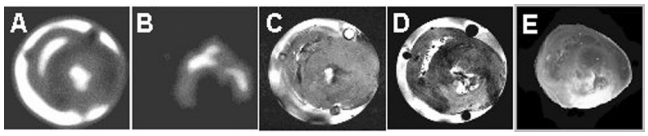
Late enhancement MRI is rapidly becoming the new gold standard for assessment of myocardial viability. However, several false positives have been reported, most likely related to edema. As an alternative we have suggested ^{23}Na chemical shift imaging (CSI) and have shown that imaging of intra- and extracellular sodium is superior to total sodium imaging in identifying the affected zone during acute zero and low flow conditions. Here we investigate the potential of ^{23}Na CSI in chronic infarcts in rat hearts induced by coronary artery ligation. Three weeks after ligation, hearts (n=4) were excised, perfused and imaged at 9.4 T by ^{1}H MRI and ^{23}Na CSI. To separate intra- and extracellular sodium resonances, the shift reagent TmDOTP was included in the perfusate. After imaging, hearts were sliced and TTC stained. Extracellular (A) ^{23}Na-image intensity in the infarct was higher than in remote tissue, 53 $\pm$ 10% vs. 39 $\pm$ 6.6%. Intracellular (B) ^{23}Na-intensity in the infarct was less than in remote tissue: 0.7 $\pm$ 0.07% vs. 1.2 $\pm$ 0.1%. Remote areas showed intra- and extracellular ^{23}Na-intensities comparable to sham hearts (n=4). The ^{1}H-image (C) did not show any abnormalities, but a contrast agent (D) clearly demarcated the infarct. The unstained area on the TTC-image (E) corresponded well with the contrast enhanced image and the intracellular ^{23}Na image.



^{23}Na and ^{1}H MRI.

These data demonstrate that intracellular ^{23}Na-imaging is a promising new tool for assessment of myocardial viability.

P982 In vivo magnetic resonance imaging of magnetically labelled human embryonic stem cells after itramyocardial transplantation

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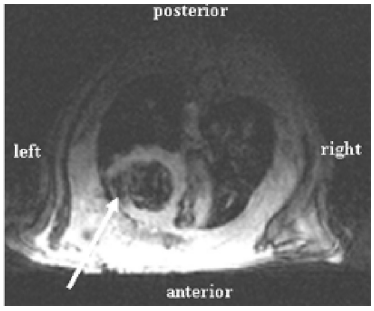
Introduction Human embryonic stem cells (hES) have emerged as a potentially new therapeutic approach for treatment of heart diseases. The aim of this study was to evaluate the feasibility of magnetic labelling and visualisation of hES with magnetic resonance imaging in vivo.
Methods: hES were established and expanded according to standard procedures. The cells were magnetically labelled by addition of SPIO (small particles of iron-oxide) agent dextran-coated ferrum-oxide particles (Endorem®) to the culture medium. Accumulation of SPIO in hES was assessed by Prussian Blue staining and electron microscopy. Viability of the cells was assessed by trypan-blue. In vivo MR imaging was performed on 2.35 T Bruker Biospec magnet. Male Sprague-Dawely rats were used. Magnetically labeled hES (~300 000) were injected into anterior LV wall. Cardiac gated gradient echo pulse was used with the following parameters, FOV = 8 cm, matrix = 256 $\times$ 192, TR 150 ms, TE 8 ms. In vivo MRI was perforemed 24 h and 5 days after the transplantation.
Results: hES appeared to be unaffected by magnetic labelling and maintained their ability to proliferate and differentiatet and in the culture. No agent for membrane permeabilisation was needed for facilitation of intracellular SPIO accumulation. Prussian Blue and electron microscopy have revealed numerous iron particles in the cytoplasm of hES. On T2- weighted images, the labelled cells have shown well-defined hyopintense areas at the site of injection in anterior LV wall both in vitro in the mouse heart (Fig. 1) and in vivo in the rat heart (Fig. 2.).



MRI of human embryonic stem cells.

Conclusions: It is feasible to magnetically label and visualise hES. MR visualisation of magnetically labelled hES may be a valuable tool for in vitro and in vivo tracking of hES.

P983 Pulmonary vein diameter reduction after radiofrequency catheter ablation for paroxysmal atrial fibrillation evaluated by contrast-enhanced three-dimensional magnetic resonance imaging

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Segmental ostial pulmonary veins (PV) electrical disconnection has been proved to be effective in totally or partially suppressing atrial fibrillation of focal origin (AF). PV stenosis have been reported as a procedure-related complication. The aim of our study was to prospectively evaluate incidence and degree of PV stenosis after AF ablation, using contrast-enhanced 3D magnetic resonance imaging (MRI).
Methods: PV electrical disconnection was performed in 24 consecutive patients (pts, mean age of 52$\pm$10 y) with the help of a 10 to 20 poles Halo catheter (15 to 20 mm in diameter), and using a 4 mm irrigated tip RF catheter. Maximal power delivery was set at $<$ or = 30 Watts with a target temperature of 45°C. MRI (1.5-T, Symphony, Siemens) was systematically performed prior to and 2$\pm$0.7 months after ablation. For 3D-MRI data acquisition and further image processing, contrast enhanced Care Bolus/FL3D-COR TMRA sequence was positioned in paracoronal orientation, and after injection of contrast agent (0,4 cc/kg body wt, Dotarem, DOTA-Gd), one breath-hold measurement was obtained. Morphology and diameter of the ostium of 96 ablated PVs were evaluated. Coronal and longitudinal diameters of the left atrium were also measured.
Results: Mean PV ostia diameters before and after ablation are displayed in the table (*p$<$0.05). PV narrowing between 10-20%, 20-30% and 30-40% was documented in 22%, 12%, 3% of the PVs and in 62%, 50%, 12% of the pts. No PV occlusion nor PV stenosis $>$ 40% was observed. At this short term follow-up, there was no significant modification of the left atrial dimensions.

	Left upper PV (mm)	Left lower PV (mm)	Right upper PV (mm)	Right lower PV (mm)
Pre-ablation	19 $\pm$ 4	17$\pm$3	20 $\pm$ 4	18 $\pm$ 4
Post-ablation	18 $\pm$ 4	15 $\pm$ 3	19 $\pm$ 4	17 $\pm$ 4

Conclusion: Systematic evaluation of PV diameter before and after AF ablation using contrast-enhanced 3D MRI technique allows slight but significant PV narrowing in more than half of the pts.

COMPUTERS IN CARDIOLOGY

P984 Trans-telephonic electrocardiography in the management of the early post-discharge phase of patients with acute myocardial infarction or unstable angina

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Aim of the research: Early post-Myocardial Infarction(MI)discharge has created a setting in which home monitoring may be of critical need.We tested telecardiology in the management of early post-MI phase.
Materials and methods: Consecutive pts who entered the ICU because of MI or unstable angina (UA) at our Hospital were randomly given or not telecardiology service (Sorin Life Watch's Call Center) for at least 20 days, until the first follow up visit. In case of need, the pt can send an ECG to the Call Center, who transmits it to our Intensive Care Unit (ICU), where the reference cardiologist adopts the appropriate procedures. At the first visit information about cardiac and non cardiac events occurring during the follow-up and quality of life are collected.
Results: Out of 85 pts randomized to telecardiology monitoring, 6 (7%) refused the service. Among the 79 pts who were provided with the device, 59 (75%) had

had an acute MI and 20 had suffered from UA. Thirtysix % of the post-MI pts and 50% of the UA pts used the device. The features of post-MI pts who used and who didn't use telecardiology are similar: 86% vs 82% male, age 60±12 vs 60±11 yrs, 48% vs 58% anterior MI, acute revascularization procedures in 76% vs 66%. At time of discharge, 52% of post-MI pts who sent ECGs and 45% of post-MI pts who didn't send any ECG had residual coronaric stenoses, left ventricular ejection fraction (LVEF) was 49±7% vs 51±7%. Among pts discharged after UA, 50% used the device and nobody reached the emergency room afterwards. Overall 31 (39%) pts sent a total of 49 ECGs. In 3 cases the pt was sent to the emergency room and 1 was admitted because of re-infarction, while the other 2 were discharged home. The other 46 cases were managed at home, thus preventing hospital admission. Fourteen (26%) of the 53 post-MI control (non telecardiology) pts had symptoms after hospital discharge and 7 referred to the the hospital or to the GP. 81% of post-MI pts who sent ECGs felt reassured by the service availability. Pts who made a minor use of the device referred to feel a poor usefulness in the service itself. Almost all post-UA pts who used the device felt reassured by its availability. 60% of post-UA pts who sent ECGs and no one of the post-UA pts who didn't send any ECG had residual coronaric stenoses at discharge.

Conclusions: telecardiology represents a useful support in the home management of cardiologic problems in post-MI/UA pts and may allow to decrease hospital readmittance. UA pts are those who seem to benefit most from telecardiology.

P985 Efficacy of a telecardiology system in the evaluation of symptoms recurrences after discharge for acute coronary syndromes. Preliminary data of a randomized controlled study

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Aims: Patients discharged after an Acute Coronary Syndrome (ACS) are at risk of early recurrence of symptoms and new cardiac and non-cardiac events. A post-discharge management program based on remote interaction with pts, using a Telecardiology system (TCS), may be helpful in the evaluation of symptoms recurrences. Aim of the present, randomised controlled study, was to compare the Usual Specialized Care (USC) and a TCS in pts discharged after an ACS. Preliminary data are reported.

Methods: Pts in USC received office visits at 15 and 30 days after discharge. In the TCS model, pts received a portable device (Card-Guard), transferring by telephone a 12-lead EKG to a receiving station, working 24/24 hours and transferred via internet to the CCU, where a cardiologist and a nurse were available for reporting and interactive consultation. Pts were asked to call the centre spontaneously, in the case of symptoms (teleassistance) and during scheduled (weekly)phone-calls(telemonitoring), followed by a 1- month visit.

Results: Data from 108 pts (mean age 61±12), enrolled during the first 5 months of the study are available. STEMI was diagnosed in 56 (51.9%) and NSTEMI in 52 (48.1%). Coronary angiography (CA) was performed in 16.7%, an elective PCI in 40.7% and an urgent PCI in 33.3%. Pts were randomised in 2 groups: 53 to TCS (GrA) and 55 to USC (GrB). Enrollment and follow-up are ongoing. Mean risk score at discharge was similar (GrA: 16,6±12,8; GrB: 15,9±12.4, p=ns). During a total of 178 phone calls, GrA pts reported symptoms in 41 (23%). Angina was the principal symptom in 14 (34%), respectively: 37% during the first 15 days and 29.4% during the subsequent 15 days. In GrB pts, during 86 visits, symptoms were reported in 41 (47.7%). Angina was present in 15 (36%), respectively 52.2% at 15th day and 22.2% at 30th day. At a 1-month follow-up there were 11 hospital re-admissions (10,1%): 3 in GrA pts (5.6%, all for angina, followed by repeated PCI in 2) and 8 in GrB (14.5%, 1 for angina, 3 for heart failure, 1 for pneumonia, 3 for gastrointestinal bleeding, associated to angina in 2).

Conclusions: The preliminary results of the present study suggest that: 1) A disease management program based on TCS may improve the quality and efficiency of care after discharge for ACS.; 2) Angina is more frequent during the first 2 weeks after an ACS discharge; 3) TCS seems to allow a better evaluation of angina recurrence and subsequent decision of appropriate re-admissions; 4) TCS also improve the identification and management of post-discharge non-coronary complications.

ECHOCARDIOGRAPHY/DOPPLER

P986 Incidence, severity, dose-dependency and evolution of valvular heart disease induced by pergolide in patients with Parkinsons disease

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Aim: Pergolide (P), an ergot-derived dopamine agonist, was introduced as an adjunctive therapy in Parkinson's disease (PD) since 1989. The aim of this study was to compare in a large population of PD patients, the incidence, the severity, and the evolution of valvular disease in patients treated with P and patients never treated with an ergot-derived dopamine agonist.

Methods: All patients with PD treated with P, Group1 (n= 49; 18 patients with high dose > 5 mg/d and 31 with low dose < 5 mg/d),and those never treated with an ergot-derived dopamine agonist, Group 2 (n= 12) were evaluated by echocardiography with special attention to the valvular status. All examinations were read blinded. A scoring system of valvular disease was introduced: score 1= proven restrictive valvulopathy (RV) (pathology+ or regression after interruption of P); score 2= important (regurgitant jet > 2/4) valvular disease suggestive for RV or restrictive tricuspid valvulopathy; score 3= mild to moderate (regurgitant jet < 2/4) RV and score 4= no RV. Tenting distance and area were measured for all mitral valves (MV). Pulmonary pressures were derived from the tricuspid regurgitant jet if present.

Results: From Group 1, 42% (n= 21/49) had at least 1 valve with a restrictive abnormality (35% MV, 14.5% AV and 12.5% TV) compared to 0% (n= 0/12) from Group 2 (p< 0,001). Tenting distance and area were higher (p< 0,005) for those MV estimated to be restrictive by the blinded reader compared to the estimated non restrictive MV of the P treated patients and of Group 2: 10.7 versus 6.4 and 5.2 mm and 2.42 versus 1.44 and 1.15 cm^2.

Proven, important or moderate (score 1, 2 and 3) RV were present in 50% of the high-dose versus 32% of the low-dose (NS) versus 0% of the control group (p< 0,001). A significant correlation existed between the tenting area's of the MV and the cumulative doses of P(y= 0,0001 x + 1,3085; p= 0,017).

From the 6 patients in whom P was stopped, 1 patient presented a regression of his mitral restrictive disease.

Systolic pulmonary artery pressures were: 40±12, 38±6 and 33±7 mm Hg(NS) in the high-dose, versus low-dose versus control group.

Conclusions: 1) Valvular heart disease is not a rare finding in patients treated with P. 2) There exists probably a dose dependency (cumulative doses) 3) Regression of valvular lesions can occur after cessation of P 4) Pulmonary pressures seems to be higher in the P group but differences were not statistical different 5) Although P remains an excellent treatment in PD, our findings suggest the necessity of a close echocardiographic monitoring.

P987 Bicuspid aortic valve in the preparticipation military screening of a large population of young males

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The majority of data regarding the prevalence of bicuspid aortic valve (BAV) come from autoptical series (reported incidence: from 0.4% to 2.25%). Since military duty is mandatory in Italy, all males aged > 17 years undergo medical screening in recruiting offices to evaluate their suitability for service. The present study is aimed to retrospectively evaluate the effectiveness of preparticipation screening strategies in detecting BAV in a large populations of male conscripts.

From 1993 to 1995, 20,946 conscripts were evaluated in 3 recruiting offices in northeastern Italy: 5,618 were referred to the Military Hospital in Verona and 1692 (8%) underwent 2D echocardiography.

In 1659 technically satisfactory echocardiograms, 167 VAB (0,8%; aged 18.4 years) were identified: eighty of these (48%) were diagnosed as having BAV de novo during the screening. BAV were normally functioning in 48 patients (29%); while 110 (66%) had regurgitation (mild in 90, moderate in 20); 8 patients had mild aortic stenosis; 3 had aortic coarctation (1 had been successfully operated). Aortic root dimensions were evaluated in BAVs and in a control group of 87 young males matched for age and body size. Aortic root was significantly (P<0.001) larger in patients than in controls at each aortic level.In normally functioning BAVs, aortic size were larger than in controls but smaller than in regurgitant BAVs.

Aortic root dimensions (mm)

	Normals (87)	BAV (167)
Anulus	22	24,6
Valsalva sinuses	27,3	32,9
Sinotubular junction	24,6	29,5
Ascending aorta	24,7	30,1

Our findings are consistent with previously reported prevalence figures demonstrating the effectiveness of military screening strategies in early detection of BAV. Moreover, our findings display an early incidence of hemodynamic impairment and confirm the notion that BAV is frequently associated with aortic root dilatation, of greater degree in patients with regurgitant than in those with normally functioning BAVs.

P988 Relations between aortic elastic properties, age and aortic diameter in bicuspid aortic valve

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Abnormal elasticity of the ascending aorta are considered a correlate of structural abnormalities of the aortic wall in patients with bicuspid aortic valve (BAV). To

verify this hypothesis, we examined the relations between age, aortic diameter, aortic stiffness and distensibility in 127 out patients with BAV [121 males; age 23±10 years, body surface area (BSA) 1.81±0.2 m^2] and in 116 control subjects matched for age, gender and body size.
Aortic root dimensions were assessed by 2D-echocardiography at four level. Aortic distensibility and stiffness were derived by M-mode evaluation of the aortic root together with blood pressure measured by cuff sphygmomanometer. Patients had significantly larger aortic size, greater peak aortic flow velocity, higher systolic blood pressure and pulse pressure than controls.
Aortic distensibility was less in BAVs (4.71±3.67 × $10^{-6}$$cm^2$ $dyne^{-1}$) than in controls (7.44±3.94 × $10^{-6}$$cm^2$ $dyne^{-1}$; P<0.001) and aortic wall stiffness index was greater in BAV subjects (7.21±4.93) than in normal group (3.57±1.88; P<0.001). Aortic stiffness and distensibility varied with age and aortic size in both patients and controls, but relations between age, aortic size and distensibility differed significantly in the 2 groups. A subgroup of BAV patients (Group A; n= 49) fell outside the range of normality of control subjects, for both distensibility and stiffness; otherwise, 125 patients (Group B) were within the 95% confidence interval of both parameters. Group A subjects had greater BSA, higher systolic blood pressure and pulse pressure than Group B patients. Importantly, these two groups had comparable aortic dimensions, indexed for BSA, at each level.
Conclusions: BAV patients have impaired elastic properties of the ascending aorta, and display altered relations between aortic distensibility/stiffness and aortic size. These findings confirm the hypothesis that load-bearing characteristics of the aortic wall are intrinsically abnormal in BAV patients.

P989 Quantitative exercise echocardiographic assessment of asymptomatic aortic valve stenosis: prognostic implications

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Background: In patients (pts) with asymptomatic aortic valve stenosis, exercise testing may help to stratify the clinical risk. However, data are limited and the role of quantitative exercise echocardiography has never investigated.
Methods and Results: Sixty-three consecutive pts with moderate to severe asymptomatic aortic stenosis who prospectively underwent quantitative echocardiographic measurements at rest and during semi-supine exercise test were followed up for 14±6.5 months. Of these pts, 26 had an abnormal response to exercise (occurrence of one or more of the following findings: angina, dyspnea, >2 mm ST segment depression, fall or small (<20 mmHg) rise in blood pressure during the test) and 18 presented cardiac events during follow-up (symptoms 2, acute pulmonary edema 2, aortic valve replacement 11, cardiac death 3). In univariate analysis, patients who had cardiac events exhibited a much higher increase in both maximum (36±15 vs 25±14 mmHg, p=0.011) and mean (25±13 vs 16±10 mmHg, p=0.00011) transaortic pressure gradients, whereas left ventricular ejection fraction (63±14 vs 69±12%, p=0.0003) and heart rate (112±21 vs 130±20 bpm, p=0.0022) reached at peak stress were lower. Change in ejection fraction (-1.1±7.7 vs 6.3±5%, p=0.001, in aortic valve area (-0.02±0.17 to 0.12±0.6 cm^2, p=0.0065) and in heart rate (39±15 vs 53±21 bpm, p=0.0013) were also weaker. These patients experienced more frequently symptoms during exercise (14/18 vs 12/45, p=0.00068). By logistic multivariate analysis, three independent predictors of cardiac events were selected stepwise: a larger increase in mean transaortic pressure gradient (p=0.011) during exercise, a lower change in heart rate (p=0.033) at peak exercise and the occurrence of symptoms during exercise (p=0.04).
Conclusions: Quantitative exercise echocardiography could be useful to identify a high-risk subset of patients with asymptomatic aortic valve stenosis and help for clinical decision making.

P990 Diagnostic and prognostic usefulness of tissue Doppler imaging in assessing myocardial function in severe aortic stenosis

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Doppler Tissue Imaging (DTI) early diastolic velocity recorded at lateral corner of annulus (EL) has been recently demonstrated to decline progressively with age and to be reduced in pathologic left ventricular hypertrophy, as well as in patients with restrictive cardiomyopathy. Recent observations suggest that (EL) can be considered a pre-load independent index of LV relaxation, such as mitral E velocity corrected for influence of relaxation (E/EL) ratio, relates well to mean pulmonary capillary wedge pressure (PCWP) and may be used to estimate LV filling pressure. Aim of present study was to assess incremental value of DTI, compared to conventional ultrasound evaluation, in assessing global diastolic and systolic function in patients with severe left ventricular hypertrophy caused by severe aortic valve stenosis. Aortic Stenotic patients (AS) were carefully selected in Cardiac Department; 35 subjects (AS: valve orifice ≤1cm^2) (10 female), mean age 71.5±5.3 and 35 healthy subjects (C) of comparable age, sex and body mass index were studied. All study subjects performed: conventional 2D-Doppler echocardiography and Doppler Tissue Imaging (DTI) at mitral annulus level, near posterior septum and lateral wall. The following were the main findings of the present study for DTI parameters: the early diastolic myocardial velocity (Em) at lateral wall and at septum level was significantly lower in AS in comparison with controls. Late diastolic myocardial velocity (Am) at lateral wall and at septum levels was significantly higher in AS in comparison with controls. Em/Am ratio both for the lateral wall and the septum was significantly lower in AS in comparison with controls. The aortic patients were divided into two groups: twenty patients who presented initial signs of congestive heart failure and a depressed left ventricular systolic function (DSF): Ejection fraction (EF) ranged 35-50% and fifteen totally asymptomatic with a normal left ventricular systolic function (NSF) (EF>50%).AS DSF group showed a significantly lower peak S velocity (DTI) in comparison with AS NSF (p<0.001) and a significantly higher E/EL (16.8±2.1) in comparison with AS NSF (6.9 ± 1.5. DTI load-independent parameters confirmed depressed systolic function and increased pulmonary capillary wedge pressure in such group of patients and have allowed a better optimizing of valvular replacement. DTI analysis could integrate conventional echo examination, allowing to obtain a more precise and relevant diagnostic and prognostic information in the work-up and care of such patients.

P991 Echocardiographic and clinical evaluation in long-term observation after small size-aortic valve replacement

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Background: The aim of our study was to evaluate the data concerning the influence of prosthesis size and type on long term left ventricular hemodynamic function and mass reduction after implantation of small-size mechanical prosthesis in aortic position.
Material and method: We studied 50 pts. 16 males, 34 females with mean age 58,6±21 years and mean LV ejection fraction 52±5%, who undergo valve replacement therapy (AVR) for isolated severe aortic stenosis. Sorin valves were implanted in 10 patients; Medtronic in 14, St.Jude in 9, Carbomedics in 2 and On-X® in 15 patients. LV mass (calculated on echocardiographic parameters), exercise capacity in NYHA class, rest and exercise transvalvular peak (PG) and mean gradient (MG), were analyzed with reference to valve type and diameter, time of operation and body surface area (BSA). Dobutamine stress echocardiography was performed in all patients to maximal dose 40μg/kg/min.
Results: In more than 75% of pts. the marked postoperative improvement of NYHA class was observed. Peak gradient as well as mean gradient decrease significantly in both groups. LV mass decreased significant in mean 3,5 years follow up observation period in On-X® valves group: from 341±56,3g to 241±4,3g (p<0,05) and non-significant in another valves types: from 310,5±43,9 to 251±34,4g.
All 19mm valves produced higher mean stress gradient in comparison to 21 and 23mm valves, especially in patients with BSA >1,7m^2 (p<0.05). Only analyzed group of On-X® valves present significant lower peak and mean stress gradient, independent on valve size and BSA. The mean value of peak stress gradient on all aortic prostheses increased between 2nd and 3rd year after implantation (p<0.05) and was almost unchanged to 4th year.
Conclusion: Good clinical outcome and left ventricular mass reduction after small-size aortic valve replacement were not correlated with high stress gradient of analyzed valves. Small size On-X® valves prostheses shown a very good performance in aortic position (EOA and EOA index) and significant LV mass regression in long term observation.

P992 "Pseudosevere" paravalvular aortic insufficiency after implantation of Shelhigh Superstentless NR 2000+ bioprosthesis

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Background: The Shelhigh Superstentless NR 2000+ bioprosthesis is a new aortic valve prosthesis with the following special properties: 1. Superstentless-Construction with a dynamic suspension of the commissures, 2. the whole surface of the prosthesis consists of biological material, fixed by glutaric aldehyde. Owing to the new architecture of this stentless valve, the level of this novel aortic valve prosthesis is higher compared with a mechanical valve or a common bioprosthesis with a traditional suture ring, when it is supraannularily implanted in a conventional manner. This accounts for the fact that a paravalvular insufficiency jet does not, as usual, parallel the left ventricular outflow tract, but instead is perpendicular to the left ventricular outflow tract (runs in parallel to the level of the valve itself).
Methods: 132 patients who received a Shelhigh Superstentless NR 2000+ bioprosthesis in aortic position between 11/2000 and 11/2003 were investigated. In order to detect paravalular regurgitations, they were routinely examined after valve replacement using color Doppler echocardiography. For a semiquantitative estimation of the severity of the paravalvular regurgitation the ratio of the diameter of the insufficiency jet on color Doppler imaging to the diameter of the left ventricular outflow tract was measured.

Results: In this particular population we detected so far three patients with paravalvular regurgitation. Using the above estimation for classification of aortic regurgitation, these three cases would have been formally classified as a severe aortic regurgitation. However, only the unusual architecture of this new type of prosthesis with a higher position of the prosthesis implies the unusual direction of the insufficiency jet which is just parallel to the valve level. Therefore, the image of a left ventricular outflow tract completely colored suggested severe aortic regurgitation, although regurgitation was only mild in two and moderate in one patient.
Conclusion: In this new type of aortic bioprosthesis, special attention has to be paid to the estimation of the degree of regurgitation. This is due to the particular architecture implying that a paravalvular insufficiency jet will be running in parallel to the valve itself. Alternative echocardiographic criteria to estimate the severity of a regurgitation should be additionally used to circumvene this problem.

P993 Can the tricuspid inflow E-wave reflect tricuspid regurgitation severity?

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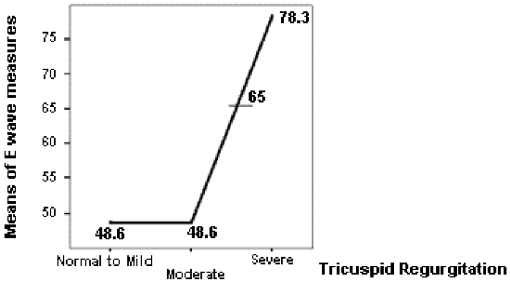
Purpose: The E-wave velocity in the diastolic mitral flow was previously shown to discriminate between severe and non-severe mitral regurgitation, in both native and prosthetic valves. This property has not been systematically tested in the tricuspid position. The Purpose of this study was to evaluate correlation between the E- wave velocity in the tricuspid valve and tricuspid regurgitation (TR) severity.
Methods: The height of the tricuspid inflow E-wave was measured in 119 consecutive patients (Age 62+16.6 years, 48% female) with good quality echocardiograms. Patients with tricuspid stenosis, trans-venous pacemakers and tricuspid prostheses were excluded. E-wave measures were taken in mid-inspiratory phase of shallow breathing. TR was quantified as normal or mild (group 1), moderate (group 2) or severe (group 3) by integrating the jet to right atrial area ratio, signs of right-ventricular volume overload, and flow patterns in the hepatic veins.
Results: There were 43 patients with mild TR, 43 with moderate TR, and 33 with severe TR. The E wave velocity was 48.6±13.8, 48.6±11.7 and 78.3±26.1 cm/s in groups 1, 2 and 3, respectively ($p<0.0001$). The mean E wave was similar in groups 1 and 2, but was significantly higher in group 3. An E wave exceeding 65 cm/s was 73% sensitive and 88% specific for the detection of severe TR, with positive and negative predictive values of 71% and 90%, respectively.



Means of E wave in TR.

Conclusions: A tricuspid inflow E-wave exceeding 65 cm/s can usefully discriminate between severe and non severe TR. This simple measure, independent of color-Doppler setting, can aid in the diagnosis or exclusion of severe TR in selected cases.

P994 The incidence and clinical significance of mitral valve prolapse in childhood and adolescence. Are we "overdiagnose" the syndrome?

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Purpose: Despite the fact that the mitral valve prolapse syndrome (MVP) has been intensivelly investigated in adults, the international bibliograrhy is poor of information in younger ages. The wide expantion of prerartipation cardiovascular screening for children and adolescents imposes the need for better knowledge of the prevalence and the clinical significance of MVP in the youngsters and by that study we try to contribute to this purpose.
Methods: 8060 children and adolescents, 4015 males and 4045 females aged 0-18 years old had been studied in preparticipation cardiovascular screening between 1990-2003. There were separated in three groups according to the age: 0-6, 7-12, 13-18 years old (3002,3820,1238 individuals). They had been all exaninated physically, by ECG and echo (2D,pulse and coloured doppler). In cases of arrythmias exercise stress testing and 24 h ecg recording had been used.
Results: 121 children and adolescents (1,5% of the studied population), 44 males and 77 females ($p<0,004$) were found to have MVP syndrome. In the age of 0-6:9 (0,3%), 7-12:53 (1,4%), 13-18:41 (3,3%) ($p<0,00001$). 21 of them (17%) referred mild and atypical symptoms. Mid systolic click was found in 60 persons (50%) and mild systolic murmur at the cardiac apex in 34 (28%). ECG'S changes only in 10(8,3%). Examination by echo revealed low severity mitral regurgitation in 32 (27%), trivial MR in 73 (60%), and no MR in 16 (13%). 10 persons (8,3%) were found to have arrythmias in ECG or 24 hour holter monitoring, the 7 of them supraventricular and the 3 ventricular arrythmias, which were disappeared during the exercise stress test. During 3-8 year follow up none had shown clinical or echocardiographical deterioration, endocarditis, embolism, syncope or therapy demanding arrytmia.
Conclusions: The MVP syndrome is of significantly lower incidence in children and adolescents in comparison to adults and appears to be increasing with age and strongly related to females. There are ECG findings in low amount. No major complications were referred in our-under study-population. The recently wide expantion of the echocardiographic evaluation of children and adolescents may lead to "overdiagnosis" of MVP.
Our results suggest that the MVP syndrome is benign in young ages and great attention is recquired in order to avoid the disclusion of young people from athletic activities and creating causeless anxiety to them and their parents.

P995 MVP as part of Don Quixote mitral valve. Is redundancy more important than billowing?

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Earlier we described association of chest pain with long nonprolapsed nonthickened anterior mitral leaflet (Don Quixote mitral valve) and hypercontractile left ventricle.
Aim: to establish whether Don Quixote mitral valve is associated with common complaints of patients with MVP syndrome - chest pain, palpitations and syncope.
Methods: Patients with any billowing of the mitral valve's leaflet in parasternal long axis (PLA) view or significant mitral annulus calcification were not included in the study. A total of 243 consecutive outpatients (mean [±SD] age, 53±17 years; 56 percent men) underwent echo examination of the heart. Blindly to referral diagnosis ratio of the length of the anterior and posterior mitral leaflets (A/P ratio) was calculated in parasternal long axis (PLA) and apical four chamber (4-CH) views. Patients with nonanginal chest pain, rapid palpitations and/or syncope formed main group (62 subjects, mean [±SD] age 42±18; 52 percent men). The other patients, including those with musculosceletal or hypertrophic cardiomyopathy's chest pain, formed control group (181 subjects, mean [±SD] age 56±17; 58 percent men).
Results: In the upper quartile of the relative length of the anterior mitral leaflet (A/P ratio) approximately one of two patients suffered from nonanginal chest pain or rapid palpitations and/or syncope, compared with approximately only 1 of 20 patients in the lower quartile (see table).

Rate of pain, palpitations or syncope

243 patients	PLA A/P ratio	4-CH A/P ratio	PLA x 4-CH A/P ratio	EF x max. A/P ratio
1. Upper quartile	47%	50%	52%	47%
2. Preupper quartile	22%**	37%^^	32%*	40%^
3. Prelower quartile	18%***	11%***	18%***	11%***
4. Lower quartile	16%***	7%***	5%***	5%***

Significance level of the difference relative to the upper quartile: $P<0.001$ - ***, $P<0.0027$ - **, $P<0.046$ - *, $P<0.1$ - ^^, $P<0.5$ - ^

Conclusions: 1. Patients with long nonprolapsed anterior mitral leaflet (Don Quixote mitral valve - A/P 4-CH ratio $\geq$4.1) suffer from nonanginal chest pain, rapid palpitations or syncope significantly more frequently than those with shorter anterior mitral leaflet. 2. Its appears that patients with MVP and redundant anterior mitral leaflet constitute extreme part of Don Quixote mitral valve and billowing of the leaflet is less important, than it's redundancy.

P996 Plasma D-dimer in correlation with hypercoagulable states in mitral valve pathology and atrial rhythm: indirect evidence for antithrombotic effect of mitral regurgitation

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Purpose: Mitral stenosis (MS) and/or atrial fibrillation (AF) are the two most common hypercoagulable states, and severe mitral regurgitation (MR) has been reported to prevent left atrial thrombus(LAT) formation and systemic embolism (SE). D-dimer has been used as a biochemical marker of maintaned fibrinolytic activity in several prothrombotic states. We aimed to assess the spectrum of prothrombotic burden in pts with mitral valve disease and/or AF using the plasma D-dimer analysis.
Methods and Results: The study population is comprised of 89 (51F,38M,mean age 38±10) pts with mitral valve disease, 21 pts with nonvalvular (NV) AF (12F, 9M, mean age 46±8)and 15 age-matched healthy controls(8F,7M,mean age 43±5). Mitral valve group was divided as pure or predominant MS (n=27), pure and severe MR (n=26), and MS concomitant with severe MR (n=36) subgroups.

Atrial rhythm was AF in 13 pts with MS, 12 pts with MR,and 19 MS+MR, and sinus in the remainder. None of the pts had any history of recent anticoagulant medication or SE. D-dimer levels tended to increase from controls to the pure MS subgroup. The highest levels of D-dimer were observed in MS with AF subgroup (527±134), and the lowest level were in controls (132±36). D-dimer levels are as follows; 386±194 in NVAF, 401±169 in MS+SR, 244±168 in MS+MR with AF, 220±117 in MS+MR with SR, 135±67 MR+AF, and 150±45 in MR+SR subgroups. Patients having MS+AF had higher D-dimer levels as compared to those in NVAF (p=0.05), MS+MR with AF (p=0.005), MS+MR with SR ($p<0.001$), and MR+AF ($p< 0.001$) subgroups. No difference was observed between NVAF and MS+SR (p=ns). Atrial rhythm showed no effect on D-dimer levels in MS+MR(p=ns) and pure MR (p=ns) subsets. MS+MR or pure MR subgroups had D-dimer levels similar to controls. Patients with NVAF had significantly higher D-dimer levels than controls (p=0.003).

Conclusion: We conclude that plasma D-dimer levels closely correlate to the procoagulant risk in mitral valve disease and NVAF. The highest levels were obtained in subsets of MS +AF and NVAF, and the lowest levels in pts with MR irrespective of the atrial rhythm. Presence of severe MR seems to decrease the D-dimer in pts with MS and/or AF to levels as low as those detected in controls. However,the validity of D-dimer as a predictor of LAT and/or SE remains to be determined.

P997 Protective effect of severe mitral regurgitation against left atrial thrombosis and embolism in mitral stenosis and/or atrial fibrillation: clinical and surgical data from 1459 patients

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Mitral stenosis (MS) and/or atrial fibrillation (AF) have been documented to be associated with the increased risks of left atrial(LA) thrombus(T) formation and systemic embolism (SE). However, both the LAT and SE have been reported to be infrequent in pts with AF in the presence of severe mitral regurgitation (MR). Despite the growing evidence suggesting the natural protective effect of severe MR against SE and LAT formation in pts with AF, indications of anticoagulation in this subset of pts with AF remain to be determined. We aimed to investigate the incidence of LAT within the main LA cavity and/or LA appendage(LAA) in pts with AF and sinus rhythm (SR) who underwent valve replacement because of the rheumatic MS and/or MR,and to assess whether severe MR prevents LAT formation and SE in pts with chronic AF. The study population comprised of 1459 pts (F 915,M 544,mean age 42±16) operated for pure or predominant MS (n= 747), pure and severe MR (n= 567), and MS with severe MR (n=145) in our institution between 1993 and 2004. Preoperative atrial rhythm was AF in 773 pts (53%), and sinus rhythm (SR) in the remainder. History of SE prior to surgery was noted in 125 (16.7%) pts with MS, in one pt with MS+MR (0.6%).Incidence of SE was higher in pts of MS with AF as compared to pts of MS with SR(26% vs 3.4%,$p<0.001$).However, none with pure MR had a history of SE. History of anticoagulation was noted in 161 pts with SE and/or LAT.Intraoperative assessment disclosed LAT in 163 pts (11%).In MS subgroup, pts with AF had a higher incidence of LAT as compared to pts with SR(32% vs 7%,$p<0.001$). In pts with MS and AF,LAT was located in LAA in 72(16.8%), in LA in 34(8%),and both in the LA and LAA in 33(7.7%) pts. In subgroup of MS with SR, LAT was found to be located in LA main cavity in 6 pts(2%),and in LAA in 17 pts(5.3%). However,LAT was not detected in pts with MS+MR and pts with severe MR,irrespective of the atrial rhythm.

We conclude that clinical and surgical data from the large group of pts support the protective effect of severe MR against SE and LAT formation in pts with MS and/or chronic AF even in the absence of anticoagulation. The management of the valvular AF and MS seems to need reconsideration in the presence of severe MR.

P998 Distinct echocardiographic features in S. aureus, S. viridans, enterococcal and S. coagulase negative infective endocarditis

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Episodes of infective endocarditis caused by S. aureus, S. viridans, enterococci and S. coagulase negative show different clinical course and outcomes in terms of morbidity and mortality.

Objective: To delineate the echocardiographic features of episodes of infective endocarditis caused by each of these microorganisms.

Methods: We studied 435 consecutive episodes (ep) of infective endocarditis; of them, 197 were caused by S.aureus, S. viridans, enterococci or S. coagulase negative. Transesophageal echocardiography (TEE) was performed in all cases. According to Duke criteria, 95.4% had definite endocarditis.

Results: There were 58 ep due to S. aureus (29.4%), 56 due to S. viridans (28.4%), 31 due to enterococci (15.7%) and 52 (26.4%) due to S. coagulase negative. Prosthetic endocarditis were more common in ep caused by S. coagulase negative. Mitral or aortic native valve involvement were more frequent in S. viridans episodes. Vegetation sizes were similar. Valve dysfunction was less severe in S. viridans episodes. Other echocardiographic characteristics are shown in the table.

	S. aureus (%)	S. viridans (%)	Enterococci (%)	S. coagulase negative (%)	p value p value
Prosthetic endocarditis	29.3	12.5	29	63.5	< 0.001
Mitral native	46.6	55.4	48.4	25	0.01
Aortic native	36.6	53.6	51.6	25	0.01
Vegetations detected by TEE	89.7	83.9	77.4	75.5	0.19
Vegetation Size $\geq$ 20 mm	11.4	16.3	18.2	27	0.46
Mobility $>$ 120°	51.5	76.5	68.8	72	0.04
Calcium echogenicity	12.5	12.5	18.8	27.3	0.11
Valve dysfunction	24.1	17.9	29	42.3	0.03
Periannular complications	32.8	30.4	25.8	38.5	0.66

Conclusions: 1) S. viridans infect native valves, with less severe valve destruction. 2) Vegetation size and density are similar regardless of causative germ. 3) Vegetations caused by S. aureus have less mobility and they are somewhat smaller. 3) Periannular complications are equally frequent. 4) S. coagulase negative more commonly involve prosthetic valves.

P999 The elderly with endocarditis have less vegetations than younger patients

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Background: Infective endocarditis appears to be increasing among the elderly. Some authors have noted a poor febrile and inflammatory responses in elderly patients with endocarditis.

Methods: We studied 435 consecutive episodes of infective endocarditis, 169 (38.8%) in patients aged $\geq$ 65 years (group I) and 266 (61.2%) in patients $<$ 65 years (group II). According to Duke criteria, 88.8% of group I and 94.2% of group II were definite episodes, the remaining were possible episodes. Vegetations were assessed by transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and pathology, either from necropsy or surgery.

Results: TTE detected vegetations in 37.3% of group I and 55.3% of group II, $p<0.001$. TEE could find vegetations in 122 episodes of group I (72.2%) and 203 of group II (76.3%), p=0.33. Vegetations were similar in size (p=0.48), mobility (p= 0.40) and echogenicity (p=0.66). Pathology was available in 221 episodes (79 in group I and 142 in group II), and vegetations were present in 54 episodes of group I (68.4%) and 115 of group II (81%), p=0.03. Using pathology as the gold standard, TEE detected vegetations in 48 of group I (88.9%) and 104 of group II (90.4%), p=0.75.

Conclusions: 1) Elderly patients with endocarditis have less vegetations than younger patients. 2) The sensitivity of TTE to detect vegetations in elderly patients is lower than in younger patients. 3) The sensitivity of TEE in the elderly is similar than in the younger age group.

P1000 Assessment of factors associated with progression of carcinoid heart disease

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Background: Few studies have demonstrated that serotonin and chemotherapy were associated with the progression of carcinoid heart disease (CHD). The aim of this prospective study was to assess the role of patent foramen ovale in the progression of CHD.

Method: In 38 consecutive patients (mean age 60 years, range 40-74, 50% women) with carcinoid syndrome, we performed 100 echocardiographic studies (mean follow-up was 24 months (range: 12-48 months)). The echocardiographic parameters were systematically assessed: 1) right-CHD, 2) left-CHD, 3) right to left shunting through a patent foramen ovale (PFO) using contrast echocardiography at rest and after cough test or Valsalva maneuver. The progression of CHD was assessed using an echocardiographic scoring system. The metabolite of serotonin (urinary 5-HIAA) and plasmatic chromogranin A have been assessed at baseline (first echocardiography) and during follow-up.

Results: At baseline, echocardiography revealed 15 pts (39%) with right-CHD and 5 pts (13%) with left-CHD (Table). At the end of follow-up, the incidence of right-CHD and left-CHD was respectively 61% (23 pts) and 34% (13 pts). The baseline and follow-up frequencies of PFO were respectively 21% (8 pts) and 42% (16 pts). The presence of PFO, the increase of the metabolite of serotonin (urinary 5-HIAA) and the increase of plasmatic chromogranin A levels were predictive factors of progression of both right- and left-CHD ($p<0.005$), but not chemotherapy (p=0.7).

	All patients	Patients with PFO	Patients without PFO	P Value*
Right-CHD – no. (%)				
– At baseline	15 (39)	5 (63)	10 (33)	0.13
– End of follow-up	23 (61)	14 (88)	9 (41)	0.004
Left-CHD – no. (%)				
– At baseline	5 (13)	4 (50)	1 (3)	0.0005
– End of follow-up	13 (34)	13 (81)	0 (0)	< 0.0001
Progression of CHD – no. (%)				
– End of follow-up	18 (47)	14 (88)	4 (18)	< 0.0001

*p value for comparison between patients with or without PFO.

Conclusion: Our data suggest that PFO is a new marker of carcinoid heart disease progression and should be systematically researched by contrast echocardiographic studies.

ATHEROSCLEROSIS II – BASIC SCIENCE

P1001 LDL receptor expression and apolipoprotein B binding capacity in patients with hypercholesterolemia caused by Cys152Trp mutation in the LDL receptor gene

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Familiar hypercholesterolemia (FH) has been evidenced to be related to genetically determined changes in low density lipoprotein receptor (LDLR). Several mutations in LDLR have been reported, but its functional and clinical importance has not been clarified.

The purpose of the study was to evaluate LDLR mutations in patients with hypercholesterolemia in a Central European population. We analyzed the LDL receptor gene using the single-strand conformation polymorphism (SSCP) and direct sequencing technique. The range of serum cholesterol and LDL-cholesterol was 250-450 and 200-400mg/dl in FH patients. In a screening of the LDLR gene mutations of 54 consecutive patients with familial hypercholesterolemia, we discovered new point mutations in 18 exon: one-nucleotide deletion (Asp2731), thirteen-nucleotide deletion (Val2734), C2623A causing Leu850Ile, T2786C, G2728A. Mutations was also located in three different exons (4,7,8); C518G causing a Cys152Trp in exon 4, T1012A causing Cys317Ser in exon 7 and T1102C causing Cys347Arg in exon 8. The mutation in exon 4 and 7 was previously reported in a compound heterozygote for familial hypercholesterolemia.

We used flow cytometry assay with an anti-LDLR monoclonal antibody to detect the LDLR ligand function. Peripheral blood lymphocytes were prepared from heterozygous patients with FH caused by Cys152Trp mutation in exon 4 LDLR and from healthy individuals. The cell were stimulated to express the maximum amount of low density lipoprotein receptor by pre-incubation in a lipoprotein deficient medium. We subsequently incubated the cells with anti- LDL receptor monoclonal antibody to measure expression LDLR on the lymphocytes surface. Then we studied binding and internalization of apolipoprotein B to LDL receptor from FH patients as compared to healthy control by flow cytometry evaluation of LDLR expression after subsequent cell incubation with apolipoprotein B in vitro.

Basal LDLR expression was 21.14 M.C.F. (mean channel of fluorescence) in healthy donors and 14.12 M.C.F. in FH patients. After lymphocyte incubation with apolipoprotein B anti-LDRL antibody binding was 15.26 M.C.F. in controls and 10.80 M.C.F. in FH patients, respectively.

We conclude, that LDL receptor from heterozygous patients with Cys152Trp mutation has significantly lower ligand function than LDLR from healthy control. The patients receptor has significantly impaired binding affinity to the apolipoprotein B than healthy donors receptor.

P1002 Relationships of promoter and coding sequence genetic polymorphisms of p22phox subunit to the vascular NAD(P)H oxidase activity

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We have previously described an association between C242T polymorphism in the p22phox, with NAD(P)H oxidase activity. As new polymorphisms are being identified across the genome, functional effects of genetic variation may be attributed to interactions between polymorphisms rather than their individual effects. Accordingly, we have now identified several new polymorphisms within p22phox promoter and coding sequence using combined WAVE gene screening and database search. We analyzed relationships between polymorphisms within p22phox and their association with NAD(P)H-dependent superoxide production (measured by 5uM lucigenin chemiluminescence) in 110 human saphenous vein segments.

We have identified 10 new polymorphisms, but we focused on 2 promoter polymorphisms [G-932A (reported recently by Moreno,2003) and C-538T in the potential transcription factor binding sites], two polymorphisms which lead to amino-acid change (defined in the databases C242T and C549T) and an A640G in 3'UTR. Close linkage disequlibrium was observed between all polymorphisms of p22phox gene apart from G-932A which seemed to be independent of the other polymorphisms. Moreover type III sums of squares ANOVA has shown that both C242T and G-932A polymorphisms were independently associated with vascular NAD(P)H oxidase activity (Table 1). Interestingly A and C alleles (respectively) were associated with increased NAD(P)H oxidase activity (339±29 for A-C haplotype vs. 260±13 for G-T RLU/s/mg; $p<0.01$).

Table 1

Polymorphism	A-932G	C-538T	C242T	C549T	A640G
F value	5,781	0,557	3,412	1,298	0,607
p value	0.004*	0,575	0,031*	0,278	0,547

Multivariate analysis of the effects of individual polymprphisms on vascular NAD(P)H oxidase acivity performed using type III sum of squares ANOVA

Conclusions: Present study identifies that both G-932A and C242T polymorphisms of p22phox are independently associated with NAD(P)H oxidase activity. Further studies identifying functionality of these polymorphisms and haplotype analysis to directly study their functional role are now needed in order to be able to judge on the usefulness of these enzymes as markers of increased susceptibility to oxidative stress.

P1003 Gene expression profiling of endothelial cells from normal and systemic sclerosis patients

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Systemic sclerosis (SSc) is a clinically heterogeneous, systemic disorder which affects the connective tissue of the skin, internal organs and the walls of blood vessels. Defective angiogenesis, resulting in tissue ischemia, is prominent in the diffuse form of SSc, but its pathogenetic basis is unknown.

We isolated microvascular endothelial cells (MVEC) from the dermis of healthy individuals (N-MVEC) and patients with diffuse SSc (SSc-MVEC) in order to identify differences in the gene expression profiling. For this purpose we used a 14,000 gene oligonucleotide array (70-mers oligonucleotide, Operon technologies). Total RNA from cultured MVEC was isolated by RNeasy Kit (QIAGEN). Pooling of MVEC total RNA from patients and controls was performed. One hundred and ninety nine genes showed altered expression levels between SSc-MVEC and N-MVEC: 153 were up-regulated and 46 were down-regulated. More than 25 of the genes (e.g. MIF, LAMR1, IL-8, CTGF, CFL1, PEA15, PGAR, KLKs, PLAT, PLAU, etc) which were differentially expressed in SSc-MVEC are directly or indirectly involved with angiogenesis. Interestingly, in contrast with the clinical data indicating a vascular desert-like pattern, many proangiogenetic genes were found to be over-expressed in SSc. These results suggest that an epigenetic event which occurs in SSc may be able to vanish the angiogenic attitude of MVEC. Preliminary data indicate that the truncation of the urokinase-plasminogen activator receptor (uPAR) in SSc-MVEC may account, at least in part, for defective angiogenesis. Since the decrease of kallikrein in SSc accounts for a weak activity of the cell-associated fibrinolytic system, which has been shown to be critical in angiogenesis, we have focused our study on the cell-associated urokinase type plasminogen activator (uPA)/uPA receptor (uPAR) system. In SSc-MVEC uPAR undergoes an epigenetic truncation between domain 1 and domain 2, a cleavage which is known to impair uPAR functions. These properties of SSc-MVEC were associated with poor spontaneous and uPA-dependent invasion, proliferation and capillary morphogenesis.

We have shown that the over-expression of MMP-12 accounts for uPAR cleavage in SSc-MVEC. These observations raise the possibility that MMP-12-dependent truncation of uPAR in SSc-MVEC vanish the pro-angiogenic attitude of endothelial cells.

P1004 Inflammation of peri-adventitial fat of human coronary arteries as a marker of plaque vulnerability. Destabilization from the outside in?

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Background: Previous work from our laboratory showed the presence of significant phagocytic activity in the aortic peri-adventitial fat of animal models of atherosclerosis (apoE-deficient mice and Watanabe rabbits), compared to only mild activity in their wild-type conterparts. In the present study we compared the adventitial fat of human coronary arteries in patients with plaque ruptures to that of patients with stable fibrocalcific plaques. We hypothesized that the macrophagic density would be much greater in the former.

Material & Methods: Thirty-one histologic sections of human coronary plaque rupture were contrasted with twenty-four cases of stable fibrocalcific plaques for the presence of peri-adventitial fat macrophages (Kp-1 positive cells). Quantitative morphometry was performed.

Results: The thirty-one plaque rupture cases had a markedly greater macrophage infiltration as evidenced by number/mm^2 peri-adventitial fat (262±209 vs. 58±51, p=0.000016). As expected, plaque rupture sections showed typical features of thin cap fibroatheroma with large lipid cores and high density of plaque macrophages that were accompanied by a significant macrophage infiltrate in the adventitia and peri-adventitial fat. S100 and Toluidine blue staining ruled out the possibility that these cells might represent dendritic cells or mast cells, respectively.
Conclusion: This study shows the presence of active macrophages in the peri-adventitial fat of human coronary arteries. These cells were present in much greater quantity in the setting of plaque rupture as opposed to burnt-out fibrocalcific plaques. There appeared to be no significant difference in macrophage density between adventitia and peri-adventitial fat. Peri-adventitial fat inflammation might play a significant pathogenic role in atherosclerosis progression and complications, possibly by contributing to plaque destabilzation from the outside in. A single study by Mazurek et al (Circulation 2003;108:2460-6), on patients undergoing elective CABG, demonstrated that the epicardial adipose tissue is a source of inflammatory cytokines. Further studies are needed in patients with unstable plaques to confirm if inflammatory cytokine production from the macrophages recruited to the peri-adventitial adipose tissue potentiate the action of those acting in the plaque, perhaps perpetuating this response in a vicious cycle pattern.

P1005 Dendritic cells of patients with coronary heart disease show an upregulation of the costimulatory molecules CD40, CD80 and CD86 compared to healthy controls

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Dendritic cells (DCs) were shown to infiltrate atherosclerotic lesions. Due to their ability of antigen uptake and presentation, DCs are extremely potent regulators of the adaptive immune system. Thus, they may play an important role in inflammatory processes in atherosclerosis. However, their exact role in the process of atherosclerosis are largely unknown. Patients with stable and unstable coronary artery disease (stCAD, unstCAD) considerably differ in their inflammatory status compared to each other or to healthy individuals. We therefore hypothesised a possible phenotypical and functional difference of immature and mature DCs (iDCs, mDCs)in every group.
Methods: Monocytes from 25 patients with stCAD and unstCAD, respectively and 25 healthy individuals were enriched from PBMC and subsequently differentiated into iDCs in medium containing IL-4 and GM-CSF. After 7 days, cells were differentiated with LPS into mDCs. Total cell numbers were counted and functionally important cell surface molecules (i.e. CD1a, CD86, CD40 etc.) were analysed unsing flow-cytometry. Significance of differences between the three groups was calculated using the Kruskal Wallis test and Post test (Dunn's multiple comparison tests).
Results: Concerning the examined co-stimulatory molecules we found a significant up-regulation for CD40 on iDCs and mDCs for stCAD and unstCAD compared to controls (iDCs: stCAD vs. instCAD vs. Controls: 15.4 ± 4.8 vs 15.2 ± 4.5 vs. 11.5 ± 3.7; p=0.04; stCAD vs. Controls: p< 0.01, unstCAD vs. Controls p< 0.01. mDCs: stCAD vs. instCAD vs. Controls: 26.6 ± 8.9 vs 25.7 ± 8.2 vs. 17.4 ± 6.7; p=0.006; stCAD vs. Controls: p< 0.001, unstCAD vs. Controls p< 0.001). For CD80 a significant upregulation was found only on mDCs of stCAD and unstCAD (stCAD vs. instCAD vs. Controls: 23.5 ± 6.3 vs 24.1 ± 4.7 vs. 18.2 ± 5.2; p=0.02; stCAD vs. Controls: p< 0.01, unstCAD vs. Controls p< 0.001). A significant upregulation for CD86 was found only on mDCs of stCAD (stCAD vs. instCAD vs. Controls: 322.5 ± 98 vs 284.4 ± 94.8 vs. 241.5 ± 115.3; p=0.04; stCAD vs. Controls: p< 0.01). For CD1a, HLA-DR no difference was detectable.
Conclusion: DCs of patients with stCAD and unstCAD show a phenotype typical for a chronical inflammatory situation. Therefore DCs are likely to play an important role in the processes of atherosclerosis.

P1006 GP91phox-dependent expression of platelet CD40 ligand

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Background: CD40 ligand (CD40L) plays a key role in the pathogenesis of aterothrombosis. CD40L expression on platelets is mediated by agonists but the underlying mechanism is still unclear.
Methods: Cytofluorimetric analysis of CD40 ligand expression was performed on washed human platelets stimulated at 37C° for 10 min with collagen and thrombin. CD40L expression was measured both in platelets from healthy volunteers-with and without the addition of antioxidants, aspirin or a phospholipase A2 (PLA2) inhibitor- and in platelets from two patiens with an inherited deficiency of gp91phox, the central core of NADPH oxidase. Immunoprecipitation analysis was also performed to deteminate wheter normal platelets showed gp91phox expression.
Results: Unlike catalas and mannitol, superoxide dismutase(SOD) significantly inhibited collagen- and thrombin-induced platelet CD40L expression in platelets from healthy subjects. Immunoprecipitation analysis also showed that platelets from healthy subjects expressed gp91phox. In two male patients with inherited gp91phox deficiency,colagen- and thrombin-stimulated patients showed almost complete suppression of superoxide anion (O2-) and CD40L expression; a similiar suppression was seen with arachidonic acid, thus suggesting a role for this pathway in agonist-induced platelet NADPH oxidase activation and CD40L expression. Likewise, incubation of platelets from healthy subjects with PLA2 inhibitor almost completely prevented agonist -induced O2- and CD40L expression.
Discussion: These data provide the first evidence that platelet CD40L expression occurs via arachidonic acid-mediated gp91phox activation.

P1007 Involvement of C-reactive protein in atherosclerosis development in ApoE*3-Leiden/hCRP transgenic mice

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Background: Inflammation has emerged as a key factor in atherosclerosis, and the acute phase marker CRP has been shown to be a strong predictor of cardiovascular events in healthy persons as well as in patients with CVD. However, it is not clear whether CRP is actively involved in the development of atherosclerosis. The purpose of this study was to investigate the involvement of the acute phase marker C-reactive protein (CRP) in the development of atherosclerosis in apolipoprotein E*3-Leiden/hCRP transgenic mice.
Methods: ApoE*3-Leiden/hCRP transgenic mice (E3L/CRP)(14 males and 13 females) were used to study the development of atherosclerosis; 14 male and 13 female ApoE*3-Leiden (E3L) transgenic mice were used as controls. The mice were given a high-cholesterol diet resulting in plasma cholesterol levels of about 15 mmol/L. After 6 - 7 months of diet feeding, atherosclerosis in the aortic root area was quantified.
Results: Cholesterol exposure did not differ significantly between groups (312 ± 31 and 325 ± 25 mmol/l*weeks for female mice; 552 ± 61 and 499 ± 96 for male mice, respectively). Atherosclerotic lesion area did not differ between E3L/CRP and E3L mice (35250 ± 31285 and 36255 ± 27482 μm^2 in female E3L/CRP and E3L mice, 26402 ± 16973 and 24776 ± 20442 μm^2 in male E3L/CRP and E3L mice, respectively). Lesion type was also assessed. Female mice had mostly type III-V lesions, whereas the males had mostly type III lesions. However, no differences were observed in lesion types between the E3L/CRP and E3L mice.
Conclusion: Since lesion area and type in ApoE*3-Leiden/CRP mice are not different from those in ApoE*3-Leiden mice, CRP does not appear to be actively involved in atherosclerosis development in hypercholesterolemic mice.

P1008 Progression of native coronary plaques and in-stent restenosis are associated and predicted by preprocedural C-reactive protein levels

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Purpose The process of progression in coronary artery disease including in-stent restenosis (ISR) and native plaques is still unclear. Aim of this prospective study was to investigate the relationship between ISR and progression of other plaques that had not undergone intervention within the same patient after stent implantation.
Methods: Baseline and follow-up (6±1 months) quantitative coronary angiography data were prospectively evaluated in 219 consecutive patients treated by single stent implantation. Herein, 219 coronary target lesions (mean diameter stenosis 74%) and 134 untreated plaques with mild to moderate narrowing (>20%) were assessed. Angiographic, procedural, clinical and biochemical determinants were assessed for prediction of ISR (>50%) and/or coronary progression (increase in stenosis >20%) after stent placement.
Results: ISR was present in 61 of 219 (28%) stented target lesions and angiographic progression in 15 of 134 (11%) primarily untreated plaques. Among angiographic, procedural and clinical determinants, only diabetes (P=0.01) and length of stenosis (P=0.02) were predictive of ISR, whereas smoking predicted plaque progression (P=0.02). As our central finding, progression of untreated plaques was found associated with presence of ISR in 12 cases compared to its absence in 3 cases (P=0.01). Remarkably, preprocedural CRP levels could discriminate both between patients with or without later progression of untreated plaques (18.3±17.9 mg/l versus 6.9±13.1 mg/l; P=0.01) and between patients with or without later ISR (11.0±16.0 mg/l versus 5.6±11.6 mg/l; P=0.02). Of note, 13 of 15 (87%) patients with angiographic progression at 6-month follow-up presented with acute coronary syndromes compared to only 46 of 204 (23%) patients devoid of plaque progression (P=0.001).
Conclusion: Progression of atherosclerosis in not previously intervened coronary plaques was more likely seen with development of target lesion ISR, clinically associated with acute coronary syndromes. Increased preprocedural CRP may identify the patient at risk for progressive coronary atherosclerosis as well as for ISR development.

P1009 Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis patients without clinically evident atherosclerotic disease

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Background: Cardiovascular disease is the most common cause of mortality in rheumatoid arthritis (RA) patients. Carotid intima-media wall thickness (IMT) increase and the presence of carotid plaques are indicators of generalized atherosclerosis.
Objective: To seek for the presence of subclinical atherosclerosis in long-term treated RA patients without clinically evident atherosclerosis or its complications and to assess whether demographic or clinical factors affect the development of atherosclerotic disease.
Methods: Forty-seven Caucasian patients fulfilling the 1987 American College of Rheumatology classification criteria for RA were recruited from our hospital. Patients were required to have been treated for at least 5 years, including current treatment with one or more disease-modifying antirheumatic drugs. Patients with diabetes mellitus, renal insufficiency, hypertension, cardiovascular or cerebrovascular disease and smokers were excluded. Forty-seven matched controls were also studied. Carotid IMT and carotid plaques were measured in the right common carotid artery. The study was performed using high-resolution B-mode ultrasound.
Results: Patients had greater carotid IMT (0.779 $\pm$ 0.164 mm) than did controls (0.699 $\pm$ 0.129 mm); (p=0.010). Sixteen (34%) patients showed carotid plaques compared with only 7 (15%) controls (p= 0.031). There was a positive correlation between the age at the time of study and the carotid IMT (OR=6.8 IC 95% [1.77-26.11]; p=0.005). Also, RA patients with carotid plaques had a significantly longer disease duration (mean: 21.0 years) and more extra-articular manifestations (63%) than those without plaques (12.7 years and 26%, respectively). Patients with carotid plaques had significantly greater carotid IMT (0.859 $\pm$ 0.116 mm) than those without plaques (0.739 $\pm$ 0.171 mm) (p= 0.014). Both age at the time of the study (OR=1.13 IC 95% [1.02-1.27]; p=0.024) and disease duration (OR=1.4 IC 95% [1.01-2.07]; p=0.05) were the best predictive factors for the development of severe morphological expression of atherosclerotic disease.
Conclusions: Long-term treated RA patients have severe subclinical atherosclerotic findings related to both age at the time of the study and disease duration.

P1010 Autoantibodies to HSP60 accelerate atherosclerosis in ApoE-deficient mice via endothelial damage

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Background: Accumulating evidence confirms the positive association between anti-heat shock protein 60 (HSP60) autoantibodies and the presence of atherosclerosis in humans. Data from epitope mapping indicate that human autoantibodies to HSP60 mainly bind to three regions of mammalian and bacterial HSP60. However, whether these autoantibodies play a causal role in the development of atherosclerosis is yet to be confirmed.
Methods and Results: In the present study, serum autoantibodies to HSP60 from patients with severe coronary heart disease were isolated by affinity chromatography, which was found to recognise both bacterial and human HSP60 as identified by Western blot analysis. When these autoantibodies were injected into the tail vein of apoE-deficient mice (10 weeks old), areas of atherosclerotic lesions in the aortic sinus and the endothelial surface of the thoracic aorta were significantly increased compared to untreated or IgG treated animals 8 weeks after injection. There was no significant difference in blood cholesterol levels between treated and untreated controls. Interestingly, administration of mouse monoclonal antibody II-13, recognising amino acid residues 288 to 366 of HSP60, which is also a binding site for human autoantibodies, effectively induced atherosclerotic lesions in apoE-/- mice, but lesions were not induced by another anti-HSP60 antibody ML-30. Immunohistological analysis revealed that the ratio of smooth muscle cells and macrophages in antibody-induced lesions was similar to that of untreated controls. Furthermore, II-13 injection to mice resulted in endothelial cell damage as evidenced by patchy detachment of cells expressing TIE2-LacZ marker gene, which was followed by cell replication as confirmed by BrdU incorporation.
Conclusions: Our findings provide the first evidence that antibodies recognising amino acid residues 288 to 366 of HSP60 induce atherosclerosis via the mechanisms of autoimmune reactions to HSP60 expressed on arterial endothelial cells.

P1011 Regulation of smooth muscle cell proliferation by the extracellular matrix:a mechanism regulating skp-2 stability via focal adhesion kinase

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Proliferation of vascular smooth muscle cells (SMCs) is important in atherosclerosis, restenosis and late vein graft failure. Availability of mitogens and interaction with the intimately associated extracellular-matrix (ECM) are important factors controlling SMC proliferation. Proliferation is negatively regulated at the level of the cell cycle by the cyclin-dependent kinase inhibitors (CDKIs) such as p27/Kip1. Levels of p27/Kip1 are dependent on mitogen stimulation and the composition of the ECM. Here we sought to further elucidate the mechanisms underlying the mitogen and ECM-dependent regulation of p27/Kip1 in SMC.
We studied the S-phase-kinase associated protein-2 (Skp-2), an F-box protein previously implicated in the ubiquitination and subsequent degradation of p27/Kip1 in fibroblasts. Skp-2 protein expression was strongly upregulated in rat aortic SMC by serum mitogens. Skp-2 function in SMCs was investigated using adenovirus vectors expressing wild-type and a dominant negative F-box deleted mutant form, DN-Skp-2. Expression of wild-type Skp-2 promoted p27/Kip1 downregulation (to 30.8$\pm$10% compared to control; p=0.0204, n=3) and enhanced SMC proliferation. Conversely, expression of DN-Skp-2 increased p27/Kip1 levels (to 156%$\pm$13.5% compared to control; p=0.0253, n=3) and inhibited proliferation. To investigate ECM-dependent regulation, we first showed that Skp-2 levels were elevated in adherent SMC but not in SMC cultured in suspension. Skp-2 protein and mRNA was also significantly lower in cells grown on type-1 collagen and laminin matrix compared to plastic or fibronectin, respectively. To investigate the underlying mechanisms, we used a recombinant adenovirus expressing a dominant-negative mutant of FAK (FAKY397F). Expression of FAKY397F inhibited FAK phosphorylation, SMC proliferation and resulted in a significant inhibition (to 15.1$\pm$2.1%, $p<0.05$, n=3) of Skp-2 expression. Interestingly, FAK inhibition did not alter Skp-2 mRNA expression, implying post-transcriptional regulation. Furthermore, treatment with the proteasome-inhibitor MG-132 blocked the downregulation of Skp-2 induced by FAK inhibition.
Taken together, this data demonstrates that Skp-2 regulates SMC proliferation at least in part by controlling the levels of p27/Cip1. Furthermore the ECM regulates SMC proliferation via FAK-dependent modulation of Skp-2 protein stability.

P1012 Role of TNF-alpha in human cardiac myofibroblast proliferation, invasion and MMP-9 secretion: inhibition by simvastatin

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Purpose: Tumor necrosis factor-alpha (TNF) plays a key role in the progression of myocardial remodeling and heart failure. During the remodeling process, activated cardiac myofibroblasts secrete matrix-degrading metalloproteinases (MMPs) and undergo increased proliferation and invasion. Statins (HMG-CoA reductase inhibitors) are cholesterol-lowering drugs that also have direct cellular effects unrelated to lipid-lowering. These pleiotropic effects may underlie their ability to reduce myocardial remodeling and heart failure mortality. In the present study we examined the ability of TNF to induce human cardiac myofibroblast proliferation, invasion and MMP-9 secretion, and investigated whether statins could directly modulate these effects.
Methods: Human cardiac fibroblasts were cultured from biopsies of right atrial appendage. Immunofluorescent characterization revealed that these cells were of a myofibroblast phenotype. Immunoblotting of whole cell homogenates was performed to investigate TNF receptor expression. Proliferation assays were performed on cells from different patients and cell number was determined over 4 days in response to TNF alone or with appropriate supplements. Myofibroblast invasion was investigated using a modified Boyden chamber assay with a Matrigel barrier, and MMP-9 secretion from these cells was quantified using gelatin zymography.
Results: Human cardiac myofibroblasts expressed both the TNF-RI and TNF-RII receptor subtypes. Exposure of cells from 41 different patients to 1 ng/ml TNF induced a mean increase in cell number of 23.1$\pm$3.9% (range 78.6-179.6, $P<0.001$). Interestingly, approximately half of these cell populations showed no proliferative response, whereas others were highly proliferative. In the Boyden chamber assay, TNF (1-10 ng/mL) induced significant ($P<0.01$) increases in myofibroblast invasion and concomitant MMP-9 secretion. Furthermore, experiments using TNF receptor-specific neutralizing antibodies showed that these cellular effects were mediated via activation of the TNF-RI subtype. Further experiments determined that simvastatin (0.1-10 μmol/l) significantly inhibited TNF-induced myofibroblast proliferation, invasion and MMP-9 secretion in a dose-dependent manner.
Conclusions: TNF increases human cardiac myofibroblast proliferation, invasion and MMP-9 secretion, all of which are significantly inhibited by simvastatin. Inhibition of cytokine-induced myofibroblast activation by statins may therefore offer a potential therapeutic strategy for the control of adverse myocardial remodeling.

P1013 Decreased extracellular matrix metalloproteinase inducer protein levels are associated with increased MMP expression after arterial injury and in atherosclerotic lesions

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Background: Increased Matrix Metalloproteinase (MMP) synthesis and activation are important features in cardiovascular diseases. Recently, a cell membrane

protein termed extracellular matrix metalloproteinase inducer (EMMPRIN) was shown to stimulate the production of several MMPs, including MMP-1, MMP-2 and MT1-MMP in oncological tissues. We studied the relationship between EMMPRIN expression and MMP activity after arterial injury and in human atherosclerotic plaques.
Methods: Twenty-five rabbits were balloon dilated unilaterally in femoral and iliac arteries and terminated at 2, 7, 14 and 28 days. EMMPRIN mRNA expression was determined by quantitative-PCR; EMMPRIN and MT1-MMP protein levels by western blotting and MMP-1 and MMP-2 activation by zymography. Contralateral arteries were used as controls. EMMPRIN levels and MMP-2 and MMP-9 activity were also studied in human atherosclerotic plaques (N=65).
Results: see table. Increased EMMPRIN mRNA levels were accompanied by increased MT1-MMP, MMP-1 and MMP-2 levels after arterial injury. EMMPRIN protein levels were decreased compared to control arteries. We confirmed that decreased EMMPRIN protein levels were associated with increased MMP activity in human atherosclerotic plaques. This might be due to cellular release of the protein for activation. Indeed, we found that EMMPRIN was released from rabbit primary adventitial fibroblasts and was present in human serum.

Days after surgery	2	7	14	28
EMMPRIN (mRNA)	1.0 ± 0.6	2.4 ± 0.6 *	2.4 ± 0.6 *	1.4 ± 0.4
EMMPRIN (protein)	2.4 ± 1.9	0.2 ± 0.1 *	0.3 ± 0.1 *	0.5 ± 0.1 *
MT1-MMP (protein)	1.6 ± 0.3	3.1 ±0.7 *	16.9 ± 8.0 *	25.1 ± 11.0
MMP-1 (protein)	0.9 ± 0.6	15.6 ± 10.2 *	22.7 ± 13.8 *	4.1 ± 2.1
MMP-2 (protein)	6.4 ± 1.4 *	10.8 ± 0.8 *	14.0 ± 0.8 *	9.5 ± 1.6 *

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

Conclusions: Increased EMMPRIN mRNA levels and decreased EMMPRIN protein levels, were associated with increased MMP levels, in both rabbit and human arterial tissue. EMMPRIN was released by vascular cells and present in the serum. This not only shows the upregulation and release of EMMPRIN in vascular tissue, but also points to a role of EMMPRIN as a potential new serum marker reflecting MMP activity in the arterial wall.

P1014 Metalloproteinase-9 and neopterin serum levels are associated with rapid coronary artery disease progression in patients with stable angina pectoris

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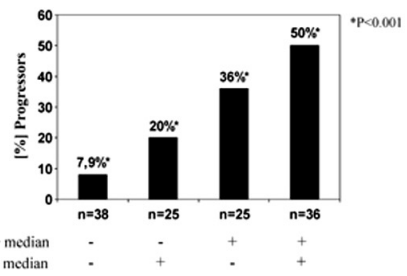
Purpose: Macrophage activation with release of matrix metalloproteinases (MMPs) has been implicated in atheromatous plaque disruption. Neopterin, an immunomodulator produced by active macrophages, is a marker of cardiovascular risk. We assessed the association between circulating neopterin and MMPs and rapid angiographic coronary artery disease (CAD) progression in patients with chronic stable angina (CSA).
Methods: We studied 124 consecutive CSA patients who were on a waiting list for coronary angioplasty (PCI). All patients underwent two coronary angiograms: the first was carried out at study entry and the second immediately prior to PCI. CAD progression was defined as: (1) ≥10% diameter reduction of a pre-existing stenosis ≥50%, (2) ≥30% diameter reduction of a pre-existing stenosis <50%, (3) progression of a lesion to total occlusion or (4) the development of a new lesion ≥30% in a previously normal segment.
Results: CAD progression occurred in 35 (28%) patients. Neopterin (8.8 nmol/l [7.6-14.6] vs 6.9 nmol/l [5.9-10.3], P=0.003) and MMP-9 (44.5 μg/l [29.1-100.6] vs 34.6 μg/l [25.8-45.4], P=0.007) levels were significantly higher in patients with rapid CAD progression compared to those without. MMP-2 levels, however, did not differ significantly between groups. Figure shows significant differences in proportions of CAD progressors among patients classified according to the medians of MMP-9 and neopterin. Logistic regression analysis revealed that neopterin (OR 5.5, CI 95%: 2.1 to 14.6; P=0.001) and MMP-9 (OR 2.7, 95% CI: 1.2 to 6.4; P=0.02) were independent predictors of CAD progression.



Conclusions: Increased circulating levels of MMP-9 and neopterin are associated to rapid CAD progression and may be markers of disease activity and cardiovascular risk.

P1015 Angiotenisin II type 1a receptor-deficiency reduced the expression of matrix metalloproteinase in atherosclerosis of apoE-deficient mice

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Background: Angiotensin II type 1 receptor may contribute to atherogenesis by facilitating the proliferative and inflammatory response to hypercholesterolemia. We reported that angiotensin II type 1 receptor (AT1)-deficiency reduced atherosclerosis, extracellular matrix (ECM) production, and oxidative stress in apolipoproteinE-defecient mice (apoE-/-). There is a possibility that decreased ECM production causes plaque instability of atherosclerosis. Therefore, we investigated whether AT1-deficiency affected plaque instability of atherosclerotic lesion using AT1a-deficient mice (AT1a-/-) and apoE-/-.
Methods: AT1a-/- crossbred with apoE-/-, and homozygous knockout mice for AT1a (AT1a-/-/apoE-/-) and wildtype mice at AT1a locus (AT1a+/+/apoE-/-) were established. Male mice were fed a chew diet and analyzed at 60 weeks of age. Atherosclerotic lesions in the aortic root were measured by a quantitative assay. Azan staining for collagen and Victoria blue staining for elastin were performed to assess the matrix production. Immunohistchemistry for matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) which related to plaque stability, and C-reactive protein (CRP) which related to inflammation, was performed.
Results: There was no significant deference in total cholesterol level between AT1a-/-/apoE-/- and AT1a+/+/apoE-/- (573.9plusminus205 vs. 527.7plusminus94.9 mg/dl). The atherosclerotic lesion of AT1a-/-/apoE-/- mice were significantly smaller than that of AT1a+/+/apoE-/- (0.75plusminus0.19 vs. 2.35plusminus0.50 mm^2, p<0.001). The amount of collagen and elastin of AT1a-/-/apoE-/- was also less than that of AT1a+/+/apoE-/-. The immunoreactivity of MMP-2, MMP-9, and CRP in AT1a-/-/apoE-/- was less than that in AT1a+/+/apoE-/-. These results suggested that the inhibition of MMP activity and CRP production by AT1a-deficiency facilitated plaque stability in atherosclerotic lesion.
Conclusion: Although AT1a-deficiency reduced ECM production, it also inhibited MMP activity and inflammation. These results support the effect of AT1 blockade on plaque stability of atherosclerotic lesion in clinical use.

P1016 Increased carotid intima media thickness in children with human immunodeficiency virus: impact of disease and protease inhibitor therapy

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Background: Protease inhibitors (PI) have significantly improved the prognosis of human immunodeficiency virus (HIV) infection in adults and in children. However, PI therapy often leads to insulin resistance and dyslipidemia which may have adverse vascular consequences. Premature atherosclerotic disease is increasingly recognized in HIV patients, but the mechanisms are unclear. In particular, it is difficult to distinguish the impact of the disease itself from the risk factor profile in adults. The purpose of this study was to determine the relative impact of HIV infection and antiretroviral therapy on early vascular disease in children.
Methods: We studied 77 HIV infected (HIV+) children (46m, 31f), aged 11.1±0.4yrs (mean±SEM) and a control group (C) of 45 healthy children (24m, 21f) aged 11.9±0.4yrs. 30 of the HIV+ children had a history of PI treatment (PI) and 47 had not received PI therapy (NPI). To characterize early structural disease, carotid artery intima media thickness (IMT) was measured using high resolution ultrasound in all subjects. Disease severity was defined according to Communicable Disease Center (CDC) Classification.
Results: IMT was greater in HIV+ children compared with C (0.67±0.01 vs 0.52±0.01mm, p<0.001). IMT increased with age in HIV+ children (0.009mm per year p<0.01) whereas no age effect was detected in the C children. Within the HIV+ group, IMT was greater in PI compared to NPI children (0.70±0.02 vs 0.66±0.001mm, p<0.05 after adjusting for age). C-reactive protein (CRP) levels were higher in the HIV+ compared to C children (median CRP 0.52 vs 0.20 mg/l respectively, p= 0.001), but increased CRP did not predict increased IMT in HIV+ or C subjects. CRP levels were similar in PI and NPI children. Total cholesterol and non-HDL cholesterol levels were higher in PI compared to NPI groups (4.56±0.17 vs 3.85±0.11mmol/l, p<0.001 and 3.19±0.18 vs 2.73±0.10 mmol/l, p=0.02 respectively) but did not independently predict IMT. CD4 cell count and CDC classification were similar in the PI and NPI children and did not predict increased IMT in these children.
Conclusion: Childhood HIV disease is associated with dyslipidemia and increased IMT, most apparent in those with exposure to PI therapy. This relationship appears to be independent of routine lipid parameters and systemic inflammation, determined by measurement of CRP. These findings suggest that close monitoring of HIV+ children, especially those on PI therapy, may be warranted to improve detection of those at high risk of premature atherosclerosis.

NUCLEAR CARDIOLOGY/MAGNETIC RESONANCE IMAGING AND CARDIAC RADIOLOGY.

P1017 Accuracy and reproducibility of acute myocardial infarct size measurements by contrast enhanced cardiovascular magnetic resonance

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There has been a growing interest in myocardial infarct (MI) size measurements as a surrogate end point for clinical trials. Currently, 99mTc-sestamibi SPECT imaging is thought to be the best available measurement tool for infarct size determination. However, there are no studies definig the reproducibility of 99mTc-sestamibi SPECT of serial imaging in patients with acute MI. Contrast enhanced CMR (ceCMR) may serve as an advantageous imaging technique for infarct size measurements. However, there has been controversy about the reproducibility and accuracy to assess acute MI using the delayed enhancement technique.
We thought to examine the accuracy and reproducibility for acute MI size measurements by ceCMR to establish the foundation for the use of this technique as an end point in clinical trials.
Fourteen dogs and 30 patients with first acute MI were studied. Dogs were examined two days after reperfused MI and the in vivo CMR images were compared to infarct size determined histologically (TTC). Images were acquired every 5 min (5-45 min post contrast agent (ca)) with 1) fixed inversion time (TI) (250 msec for 0.1 mmol/kg, 300 msec for 0.2 mmol/kg Gd-DTPA) 2) variable TI set by the scanner operator to null signal from normal myocardium. Patients with acute MI (infarct age 4.4±2.3 d, peak CK 1375±902) were scanned with a variable TI at 5 and 30 min post-ca (0.15 mmol/kg Gd-DTPA).
Results: In dogs, compared to TTC CMR infarct size using a fixed TI was 102% (±11) and 103% (±7 SD) for 0.1and 0.2mmol Gd-DPTA, resp. at 5 min post-ca, and decreased to 59% (±24SD) and 62% (±17 SD) of TTC infarct size by 45 min post-ca ($p<0.001$). For variable TI, conversely, CMR infarct size remained constant from 5 to 45 min post-ca (p=NS, 95% limits of agreement:-3.29 and 5.2% and 2.93 and 4.7% 5 and 45 min after post-ca, resp.), and never differed from true infarct size defined by TTC by more than 1.1% at any of the time points or doses (Fig.1). In patients, were observed a large range of infarct sizes (1.1%-46% of LV). The infarct size determined by ceCMR using a variable TI remained constant between 5 and 30 min post-ca (95% limits of agreement:-1.4 and 1.3% of LV Fig.2).
CeCMR measures acute MI size with an accuracy of ±3.8% of infarct size and a reproducibility of ±1.4% of LV mass if pulse sequence parameters (TI) account for clearance of the contrast agent from the myocardium. Based on these results the number of patients needed in a clinical trial to evaluate the potential efficacy to decrease MI size could be reduced 4-fold by using CMR rather than 99mTc-sestamibi SPECT.

P1018 Usefulness of myocardial delayed enhancement magnetic resonance in the diagnosis and surgical treatment of endomyocardial fibrosis

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Purpose: Endomyocardial fibrosis (EMF) is a rare restrictive cardiomyopathy, whose differential diagnosis includes cardiac diseases with apical obliteration. The treatment is fibrous tissue (FT) resection in symptomatic patients (pts). Myocadial delayed enhancement (MDE) magnetic resonance with gadolinium-based contrast (Gd) allows the detection of myocardial injury and fibrosis. Therefore, the aim of this study was to analyze the utility of MDE in patients with EMF.
Methods: We studied prospectively 24 pts (19 females, 58±11 years) with EMF, 4 (17%) with predominant right ventricular (RV) involvement, 12 (50%) with predominant left ventricular (LV) involvement and 8 (33%) with biventricular involvement. Six (25%) of these pts were submitted to resection of LV fibrosis and were analyzed by MDE pre- and postoperatively. MDE were performed in a 1.5TGE CV/I magnetic. Images were acquired after 10-20 minutes of 0.2 mmol/kg of Gd bolus. We analyzed % LV FT (%FT)= LV FT/LV mass.
Results: All surgical cases were confirmed as EMF during surgery and by pathology. Data are shown in Table. Postsurgical LV fibrosis decreased significantly (table. *$p<0.05$, pre- vs. postsurgical).

Variable	RV fibrotic mass (g)	LV fibrotic mass (g)	% LV fibrotic mass (%)
LV EMF (n=12)	–	16±7	13±7
RV EMF (n=4)	13±12	–	–
Biventricular EMF (n=8)	12±9	22±14	17±8
Pre- (n=6)	–	19±6*	25±7*
Post- (n=6)	–	14±3*	11±3*

Conclusions: MDE is useful to confirm the diagnosis of EMF by differentiating from apical thrombus, hypertrophy and tumor. MDE was able to detect and quantify the fibrous tissue in both ventricles pre- and postoperatively. Moroever, this technique provides the precise location of fibrous tissue crucial for surgical planning.

P1019 Cardiovascular magnet resonance assessment of human myocarditis; IR gradient echo compared to T1 turbo spin echo imaging protocols

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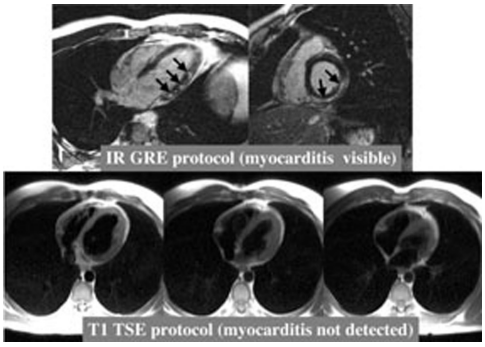
Contrast CMR using T1 TSE pulse sequences is well established for the evaluation of myocarditis. However, new IR GRE techniques increasing image contrast up to 500% and reduce artifacts. Thus, such pulse sequences may provide better sensitivity for the detection of myocardial damage in the setting of myocarditis compared to the established T1 TSE protocol.
We compared contrast CMR using new IR GRE techniques to the standard T1 TSE protocol established by Friedrich et al. in patients presenting with known (n=15) or suspected myocarditis (n=73). All T1 TSE images were evaluated by calculating relative enhancement according to Friedrich. IR GRE images were read in the AHA/ACC 17 seg model. Each segment was divided in 4 quartiles (epicardial, mid-epi, mid-endo and endocardial) and each quartile was graded as enhanced or not enhanced.
In the 15 patients with known myocarditis (biopsy) IR GRE depicted epicardial contrast enhancement (CE) in 14 patients, whereas T1 TSE detected increased signal in only six patients. Among the 73 patients presenting with clinically suspected myocarditis IR GRE revealed CE in 16 patients compared to 5 patients by T1 TSE. Thus, IR GRE imaging detected myocarditis in more patients than T1 TSE (30/88 vs. 11/88 p=0.0000008). T1 TSE imaging did not diagnose myocarditis in any case that was ruled negative by IR GRE. Areas of enhancement in IR GRE images were most frequently located subepicardial in the LV lateral wall. Conversely, CE in T1 TSE imaging was more transmurally distributed.



Contrast CMR imaging is capable of detecting myocarditis in vivo. IR GRE imaging may provide a higher sensitivity for the detection of myocarditis compared to T1 TSE imaging. The area of signal enhancement differs between IR GRE and T1 TSE protocols.

P1020 Gadolinium enhancement cardiac magnetic resonance in cardiac amyloidosis: clinical, pathophysiologic and hystologic correlations

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Gadolinium enhanced cardiovascular magnetic resonance (CMR) has been proven to be useful in non invasive assessment of myocardial substrate of hypertrophic, dilated and storage cardiomyopathies, whereas no dedicated studies are available on amyloidotic cardiomyopathy (AC). We sought to assess whether delayed enhancement (DE) occurs in AC and correlates with clinical, morphological and functional features of the disease.
Methods: Eighteen patients (62±13 years, 11 men) with AC underwent gadolinium CMR. Seven patients had familial TTR-related amyloidosis and 11 had AL amyloidosis. Myocardial histology was available in 12. DE was graded according to the number of involved segments (DE seg) and to the transmural extent of DE within each segment (DE score).
Results: DE was detected in 14/18 patients (77%), irrespectively of type of amyloidosis (TTR vs AL), TTR mutation, age and sex. Fifty four of 323 segments (16,7%) were involved, more often at midventricular level (15,7%) compared with basal (7%) and apical (5,2%) level (p=.019). The mean number of DE segments per patient was 2,8±2,7. No significant association was found between DE and left ventricular (LV) mass, left and right ventricular thickness, and histological findings. Total QRS score and Sokolow index on ECG were higher among patients with no or mild (<4 segments) DE (117±48 mV vs 83,6±24 mV, p=.047,

21±10 mV vs 13±3,5 mV, p=.018). Correlation analysis disclosed positive significant values between DE score and LV systolic volume (r=.53, p=.05) on CMR, and between DE seg and LV end-diastolic (r=.764, p=.001), end-systolic (r=.607, p=.021) LV volume and end-systolic left atrial diameter on echo (r=.581, p=.029). Segments with high DE score were more often akynetic (45% vs 18%, p=.0001).
Conclusion: Myocardial DE is common in both familial and AL cardiac amyloidosis and is probably due to non uniform expansion of infiltrated interstitium. Segmental and transmural distribution of DE is highly variable and midventricular regions are more frequently involved. DE is associated with impaired segmental contractility and larger ventricular and atrial sizes.

P1021 Prediction of post-infarction systolic function recovery. Simultaneous assessment of four indexes with cardiac magnetic resonance imaging early and late after infarction

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Purpose: To evaluate the usefulness of the four most widely used myocardial viability indexes with cardiac magnetic resonance (CMR) for predicting systolic function recovery early and late after myocardial infarction (MI).
Methods: We studied 32 patients with a first ST-elevation MI, single-vessel disease and an open infarct-related artery (TIMI 3, stent in 26 cases). At the first week (1w), using cine images and 2D True-FISP sequences, wall motion thickening (WM, mm), wall thickness (mm) and WM improvement with low-dose dobutamine (DeltaDob, mm) were quantified in all segments (s, 17 s model). After intravenous administration of gadolinium-DPTA (0.1 mmol/kg), perfusion (first-pass, scale 0 to 1) and the transmural extent of necrosis (late enhancement, %) were determined. At the sixth month (6m) CMR indexes were re-evaluated (all patients maintained an open artery). Sensitivity (S), specificity (Sp) and the area under the ROC curve (AUC) of all indexes for predicting significant improvement of WM from 1w to 6m (deltaWM >2 mm) were determined.
Results: At 1w and at 6m 496 s were properly analyzed. We focused our study on those hypo/akinetic 124 s (25%) with WM-1w <2 mm. At 6m 33 segments (27%) improved (deltaWM >2 mm). Thickness-1w >5 mm (110 s, 89%) had S 97%, Sp 14% and AUC 0.62[0.51-0.73] (p=0.04). DeltaDob-1w >2 mm (25 s, 21%) had S 40%, Sp 85% and AUC 0.62[0.5-0.74] (p=0.05). Perfusion-1w=1 (67 s, 54%) had S 85%, Sp 57% and AUC 0.72[0.62-0.81] (p <0.0001). Late enhancement-1w <50% (43 s, 35%) had S 82%, Sp 82% and AUC 0.85[0.77-0.93] (p <0.0001). AUC of late enhancement-1w was significantly better (p <0.0001) than all other indexes for predicting deltaWM >2 mm. From 1w to 6m, DeltaDob >2 mm (21% vs. 40% s) and Perfusion=1 (54% vs. 73% s) increased (p<0.0001), whereas thickness >5 mm (89% vs. 88% s) and late enhancement <50% (35% vs. 36% s) did not change. In an analysis per patients (n=32) late enhancement-1w <50% in the infarcted area had S 80% and Sp 75% for detecting significant improvement in WM of the infarcted area, and showed the best correlation with WM-6m (r=-0.79 p <0.0001).
Conclusions: Early after MI, late enhancement is the best CMR index for predicting systolic function recovery. Normal thickness and normal perfusion lack specificity, whilst contractile reserve lacks sensitivity. Perfusion and contractile reserve with dobutamine improve in the months following MI; these dynamic changes might explain their relatively low predictive value in predicting systolic recovery soon after MI.

P1022 Prediction of reversible left ventricular dysfunction in chronic ischaemic heart disease: head-to-head comparison of contrast-enhanced magnetic resonance imaging and ^{201}Tl SPECT

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Purpose: 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 predict reversibility of left ventricular (LV) dysfunction in patients with chronic ischemic heart disease.
Methods: 26 patients (pts) with LV dysfunction (EF 33±12%) were examined on a 1.5T scanner. Functional cine studies (TrueFISP) and ce images (inversion recovery Turbo FLASH) 5 min after injection of 0.15 mmol/kg Gd-DTPA were acquired. Rest-redistribution SPECT was performed according to standard protocols. 9 months after revascularization (bypass surgery: n = 16; percutaneous intervention: n = 10) pts were repeatedly examined with cine MRI. 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 < 25% 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. Moreover, LV ejection fraction (EF) for both MRI scans was determined by planimetry.
Results: 81 of 166 (49%) dysfunctional segments, which had been revascularized, showed improved wall motion with follow-up MRI. Ce MRI showed a sensitivity of 94%, a specificity of 94%, and an accuracy of 94% to detect viable myocardium, whereas SPECT a sensitivity of 86% (p=0.7), a specificity of 56% (p=0.002), and an accuracy of 68% (p=0.006). On a patient basis, increase of LVEF >5% was shown in 11 (42%) pts. Multivariate regression analysis identified the dysfunctional-but-viable myocardial ratio by MRI as the only predictor of increase in LVEF > 5% (p=0.03), whereas the equivalent by SPECT was not predictive. Receiver operator characteristics established a dysfunctional-but-viable myocardial ratio of 0.46 (sensitivity 91%, specificity 91%) by MRI, and 0.86 (sensitivity 56%, specificity 93%) by SPECT as the best discriminators. Hereby, the area under the curve was significantly larger for MRI (p < 0.05).
Conclusions: Ce MRI, especially by virtue of its superior specificity, compares favorably to Tl-201 SPECT for prediction of regional and global functional recovery in the setting of chronic myocardial ischemia.

P1023 Contrast-enhanced magnetic resonance versus thallium scintigraphy in the detection of myocardial viability – prospective comparative study

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Purpose A newer diagnostic method in the detection of myocardial viability is contrast enhanced magnetic resonance imaging (MR). The purpose of this study was to compare it prospectively to the SPECT thallium scintigraphy (Th-SPECT).
Methods: The study enrolled the patients with ischemic cardiomyopathy before elective surgical revascularization (RV). Systolic dysfunction was defined by ejection fraction (EF) of less than 45%. Contrast enhanced MR and Th-SPECT imaging, using rest redistribution, were performed before RV according to the standardized protocols. Myocardial viability was defined by Th activity of more than 50% (th-SPECT) and by the extent of contrast-enhanced tissue of no more than 75% of the segmental area (MR).
The left ventricular systolic function was assessed both by MR and radionuclide ventriculography. The check up evaluation was performed four months after RV. The improvement in global systolic function was defined by 5% increase in ejection fraction (EF) and was related to the amount of dysfunctional viable myocardium (DVM). The DVM was defined as the number of dysfunctional viable segments divided by the total number of segments in the myocardium.
Results: 25 patients were included. The mean ejection fraction before the RV was 35.4(±9.27). After RV ejection fraction improved in 13 patients. It increased from 34,6 to 45,2%. The mean DVM defined by Th SPECT and MR was 0,44±0,15 and 0,6±0,27. In patients with no change in EF the DVM determined by Th-SPECT and MR was 0,59±0,25 and 0,79±0,14. We identified no characteristics explaining the absence of improvement of EF in the second group.
The changes in regional systolic function were evaluated in total number of 654 segments that were dysfunctional before RV. The systolic function improved in 42,5% and 50,2% viable segments defined by Th-SPECT and by MR. The improvement was also apparent in 22,3% segments that were described as nonviable by Th-SPECT imaging. However, all of them showed signs of viability on MR study.
Conclusion: Contrast enhanced MR in comparison to the Th-SPECT provides more accurate visualization of the viable myocardium. However, it is not clear whether it can better identify the patients with ischemic cardiomyopathy that can profit from myocardial revascularization.

COMPUTERS IN CARDIOLOGY

P1024 Telemonitoring of home blood pressure may be useful in improving the control of blood pressure in hypertensive patients

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Objectives: Combination of self blood pressure monitoring (SBPM) at home with teletransmission facilities (TELE)may offer a more efficient approach to monitor BP over long time periods, leading also to an easier quantitative management of a large number of SBPM values and to a greater patients' compliance with treatment. Aim of our study was to investigate whether TELE-SBPM lead to a better control of high BP in general practice.
Methods: 12 General Practitioners screened 329 mild-moderate hypertensives (HT). 298 HT were recruited (58 ± 11 yrs, 54% males), in whom 24 h ambulatoryBP monitoring (M) was performed at baseline and after 6 months of follow-up, during which treatment (T) was optimized according to the assigned method of BPM. Patients were randomized to either usual care (A, n=111)or to TELE-SBPM, with (B, n=94) or without (C, n= 93)feedback-based SBPM reminding support. By

ITT data analysis we compared (ANOVA) changes in ABP and achievement of daytime ABP normalization between the 3 groups. Between-group differences in need of T changes, in quality of life (QOL) and in health care costs were also assessed.
Results: Baseline office Systolic/diastolic BP values were 149, 150 and 147/89, 89 and 89 mmHg in gruops A, B and C respectively, the corresponding daytime ABP values being 140/84, 141/83 and 138/85 mmHg. The percentage of daytime ABP normalization was higher in groups B (55%) and C (56%) than in group A (51%) ($p<0.05$, B+C vs A). There was a tendency towards less frequent changes in T in group B than in A and C (12% vs 15%, p=NS). QOL increased significanlty more in B than in A and C (+5%, vs. +1%, $p<0.05$), with a tendeny towards lower costs. No significant differences between B and C were observed with the exception of QOL.
Conclusions: TELE-SBPM led to a better control of ABP in HT than usual care, with no significant differences due to addition of SBPM tele-reminding. This was associated with an increased QOL and with a tendency towards a more regular T regimen, in spite of the relatively short follow-up. The encouraging results of this pilot study on the clinical value of TELE-SBPM would deserve to be confirmed by a larger trial.

P1025 Feasibility and clinical utility of home monitoring in patients with implantable cardioverter defibrillators

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Background: Home Monitoring (HM) has been developed to remote surveillance of patients with implantable cardioverter defibrillators (ICD) by regular automatic transmission of selected implant data to the physician. We report on technical feasibility and clinical utility of HM-ICDs.
Methods: We evaluated 16 patients (pts, 65 $\pm$ 14 years) after implant of a HM-ICD. In 13 pts a single chamber ICD (Belos VR-T, Biotronik, Germany) and in 3 patients a dual chamber ICD (2 pts Belos DR-T, 1 pts Belos A+ T, Biotronik, Germany) was implanted. The ICD transmitted automatically every 24 hours HM messages to a mobile phone which relayed them to the attending physician per fax in the form of a Cardio Report or via internet.
A patient was classified as "not successfully monitored" if (A) more than 3 contacts were necessary to maintain HM, (B) the longest interval without message exceeded 7 days.
Results: Mean follow up was 121 $\pm$ 86 days. Two patients were excluded, one pt because of dysfunction of the rechargeable battery of the mobile phone and one patient due to inability to correctly handle the system. For the remaining pts, 1425 messages were transmitted to the attending physicians. 3 patients (21%) were classified as not successfully monitored after hospital discharge due to criterion (B), none due to criterion (A). For the sucessfully monitored patients 98% of the messages were transmitted. 35 interrupts in the message sequence occurred, with 25 (71%) lasting less than 3 days, 8 (23%) lasting less than 5 days and 2 (6%) lasting less than 7 days. 8 (73%) of the successfully monitored pts had no interrupts longer than one day. 280 event reports were transmitted. 271 episodes in the VT 1 zone and 9 episodes in the VF zone were shown. In one patient an incessant ventricular tachycardia was noticed due to HM event reports resulting in immediate hospitalization of the patient.
Conclusion: Home Monitoring technology enables seamless remote monitoring for ICD patients. Monitoring may be interrupted in case of insufficient cellular phone transmission or poor patient compliance. In pts successfully supervised, HM enables a comfortable and efficient therapy surveillance providing increased patient safety.

ECHOCARDIOGRAPHY/DOPPLER

P1026 Usefulness of echocardiography in percutaneous closure of patent foramen ovale

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Background: Percutaneous closure of patent foramen ovale (PFO) is now the treatment of choice for patients (pts) who suffered cryptogenic stroke or paradoxical embolism. Echocardiography plays a major role in the diagnostic and interventional approach as well as in the follow-up of those pts.
Methods: We prospectively collected data of 50 consecutive pts (female 30%, age: 27-70y., mean 44 years) referred for percutaneous PFO closure. Forty-four pts (88%) had cryptogenic stroke, 5 pts (10%) had transient ischaemic attack and 1 pt (2%) presented with paradoxical embolism. All pts underwent transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) during work-up. Interatrial septal aneurysm (IASA) was defined as $>$ or = 15 mm excursion in TM mode. Right to left shunt (grade 3: severe, grade 2: moderate, grade 1: mild and grade 0: absent) at rest and during Valsalva manoeuvre was assessed by intravenous contrast injection (air-microbubbles) before, during and at 1, 3, 6 and 12 months after percutaneous PFO closure. PFO closure with PFO-Star in the 22 first pts (Cardiac Inc, Burnsville, MN) and Starflex occluder in 28 pts (NMT Medical Inc, Boston, MA) was achieved under fluoroscopy and systematic TEE control.
Results: Echocardiography showed an IASA in 43% of pts and an hypermobile ($>$10 mm) interatrial septum in 31% of pts. Right to left shunt during Valsalva manoeuvre was grade 2 or 3 in all pts before PFO closure. During intervention under general anesthesia, right to left shunt during Valsalva manoeuvre was underestimated in the majority of pts (65%). Echocardiography-guided device implantation revealed 1 partial expansion of the device at the wrong side of the interatrial septum in 1 pt, and motivated the device's withdraw in order to change its size in 3 pts. After a mean follow-up of 24 months, only 63% of pts with the PFO-Star occluder had grade 1 or 0 right to left shunt, but 100% of pts with the Starflex occluder had no residual shunt. There was no neurologic event or paradoxical embolism during follow-up.
Conclusion: Echocardiography plays a major role in the diagnostic evaluation, the percutaneous closure and the follow-up of pts with PFO. Echocardiography confirms that this percutaneous technique is safe and efficient. Finally, residual interatrial right to left shunt seems to be related to the closure device type.

P1027 Residual shunts after transcatheter closure of patent foramen ovale depend on occluder type: a consecutive series of 76 symptomatic patients

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Purpose Transcatheter closure of patent foramen ovale (PFO) to prevent recurrent embolic events bears a low risk and is technically feasible with high success rates. However, there is still the question of different outcome for each currently available catheter device. In the present study, we report on preliminary experience with the Amplatzer, CardioSeal and Helex occluder devices and thereby focus on acute and long-term results.
Methods: In a consecutive series of 76 symptomatic patients (31-76a) with documented PFO, of that 23 with concomitant atrial septal aneurysm (ASA), defects were occluded by Amplatzer (n=38), CardioSeal (n=23) or Helex (n=15) devices. Follow-up transesophageal echocardiography (TEE) including contrast application and subsequent Valvsalva manoeuver were performed on days 1, 7 and 28, and on months 3, 6 and 12.
Results: In all 76 patients, occluder devices were successfully implanted. In 1 case, an Amplatzer PFO occluder that had embolized into the pulmonary artery 24h post implantation was percutaneously trapped, subsequently followed by the implantation of an ASD occluder during the same procedure. Trivial residual shunts were initially seen in 15 patients (7 PFO, 8 PFO/ASA) and persisted in only 5 patients beyond 6 months without clinical signs. All patients with a initially provocable shunt soon after occluder implantation revealed a late decrease in shunt frequency. Statistical analysis did not show a relationship between shunt and defect type or size, respectively. Importantly, at day 1 complete PFO closure was achieved by the Amplatzer device in 33/38 (87%), by CardioSeal in 20/23 (87%) and by Helex in 8/15 (53%) cases. Whereas at 3 months no provocable shunt was found for 36/38 (95%) Amplatzer procedures, the corresponding data were 21/23 (91%) for CardioSeal and 9/15 (60%) for Helex occluders. At 6 months, no shunts were observed for all Amplatzer (100%), 22/23 (96%) CardioSeal and 11/15 (73%) for Helex devices. The same data were confirmed 12 months after septal occluder implantation for each device type.
Conclusion: Although residual shunts may be documented soon after device implantation, they rarely persist beyond 6 months in the vast majority of procedures. Transient residual shunting was found more frequent with PFO closure using the Helex (in up to 40-50%) than the Amplatzer or CardioSeal occluder. Clinically, these small to minimal residual shunts were not accomponied by recurrent thromboembolic events.

P1028 Assessment of the predictive value of transoesophageal echocardiography before transcatheter closure of ostium secundum atrial septal defect in adults

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Aims: The aim of the present study was to assess the diagnostic accuracy of transesophageal echocardiography (TEE) for selection of feasible patients for transcatheter closure of ostium secundum atrial septal defect (ASD), for selection of appropriately sized device.
Patients and methods: Two trained examiner selected the patients for transcatheter ASD closure after TEE. Closure was performed on 49 adult patients (38 female, 11 male, mean age 40 years (ranging 17 –70)).
Results: Amplatzer septal occluder (ASO) was successfully deployed in 41/49 patients (84%). In 38 cases with simple defect the mean size of the implanted ASO was 22 mm (ranging 13-28). The mean size of the ASD measured by TEE was 16,3 mm (ranging 8-26) and the mean stretched diameter was 20,3 mm (ranging 12-27). There was significant correlation between the ASD size by TEE and the ballon-stretched diameter (r: 0,65, $p<$ 0,001). The mean size of ASO

was 1,7 mm larger than the stretch diameter. Three patients had multiple defects, all were closed with single ASO device. A complete closure of the shunt was achieved in 2 patients with two defects. In one case with three small, closely located defects remained one trivial residual shunt. In 8 patients the closure was not attempted. Indentation of the sizing balloon could not be observed in 7 of these cases, and the intervention was not performed. In one case the device was retrieved because of inappropriate position of the ASO.
Conclusion: Our data suggest, that TEE is a moderately accurate method for screening feasible patients for transcatheter ASD closure. TEE measurements lead to a underestimation of the size of the closure device. Size of device should be selected according to stretch diameter.

P1029 Ten years follow-up after balloon pulmonary valvuloplasty in adults

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Balloon pulmonary valvuloplasty (BPV) was performed in 68 pts between 1986 and 1998. Their age ranged from 16 to 60 yrs (mean 28±12), their weight was between 43 and 99 kg (mean 64±13). 20 pts were NYHA class I, 43p-II, 5p-III. Mean pressure gradient between right ventricle and pulmonary artery (PG) measured invasively before and immediately after BPV decreased from 78±41 to 43±40 mmHg ($p < 0.0001$). Doppler echocardiographic measurement was 78±38 and 42±32 mmHg respectively ($p < 0.0001$).
During the follow-up time 3.3 to 15 yrs (mean 9.6) two pts died from extracardiac disease, 2 required surgery because of dysplastic valve, 3 were lost to follow-up. From the group of remaining 61pts, 59 are in NYHA class I, 2 are in NYHA class II. PG in these 61 pts measured by Doppler decreased from 39±31(the day after BPV) to 22±8 mmHg at follow-up ($p < 0.0001$). Reduction of PG at follow-up was due to a decrease of subvalvular muscular hypertrophy (regression of subvalvular PG on Doppler examination). Residual PG ≤30 mmHg (considered as a good long-term result) was detected in 52/61 pts; PG > 30 mmHg persisted in 9 pts: 4 of them had incomplete regression of subvalvular hypertrophy, 4 pts had dysplastic valve, in 1 pt too small balloon was used. Right ventricular hypertrophy (anterior wall thickness ≥7 mm in ECHO 2D) persists in 20 pts (including 9 pts with residual PG > 30 mmHg). Of interest, the remaining eleven pts (18%) have PG <30 mmHg. Dysplastic valve was found in 6 pts. BPV was unsuccessful in all of them. Mild pulmonary valve incompetence was found in 37 pts, moderate in 4. It did not influence right ventricular diastolic dimension. BPV was repeated in 3 pts.
Conclusions: BPV in adult patients is a safe procedure with high success rate. Good long-term results confirm that BPV should be the treatment of choice for pulmonary valve stenosis in adults. The regression of right ventricular hypertrophy is incomplete in 18% of adult patients after BPV despite low PG. It is therefore recommended to perform the procedure in childhood. Subvalvular muscular hypertrophy decreases in the majority (93%) of adult patients after successful BPV. Pulmonary incompetence does not influence clinical outcome at follow-up. BPV in patients with dysplastic valve is unsuccessful.

P1030 Mid-term effects of stent implantation for aortic recoarctation on systemic hypertension, carotid mechanical properties and pulse wave reflection

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Primary stent implantation is a diffuse technique to treat aortic recoarctation. however, the effects of aortic stenting on pressure profile, mechanical properties of great elastic vessels and pulse wave reflection have not been documented.
From 1/1/99 to 1/1/2003, 15 patients (median age and weight 17years and 56kg) underwent direct stenting of aortic recoarctation. Indications were: clinical gradient >20 mmHg (14), systemic hypertension at rest (5), systemic hypertension on effort (11). Five received anti-hypertensive treatment.
All subjects had successfull stent implantation. Mean gradient diminished from 27±10 to 4±6mmHg (p=0,0004). A correlation was found between systolic blood pressure (SBP) at rest and initial gradient (r=0.8) and between initial gradient and percent reduction of SBP at rest after stent implantation (r=-0.73). At a mean follow-up of 22±11 months all patients underwent effort test and vascular echography. SBP at rest diminished from 139.58+14.51 to 131.43+6.83 mmHg (p=0.04) and SBP on effort from 244.58+17.15 to 221.78+24.64 mmHg (p=0.018); 3 patients received an anti-hypertensive treatment.
Cross-sectional compliance and distensibility of the common carotid artery (CCA) were not significantly modified, however the CCA intima media thickness diminished from 0.64±0.07 to 0.57±0.08 mm (p=0.04) and the augmentation index diminished from 5.3±9% to –2.3±10% (p=0,012).
In conclusion, a persistent satisfactory anatomical and hemodynamic result after stent implantation in recoarctation of the aorta can diminish SBP at rest an on effort. In addition, it is a determinant of the suppression of an early reflection site of the pulse wave. Isthmus enlargement could decrease great elastic vessels wall stress, reducing arterial wall thickness.

P1031 Reliability of intraoperative transoesophageal echocardiography in the assessment of residual ventricular outflow tract obstruction

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Purpose: Despite the large use of transesophageal echocardiography (TEE) in congenital heart surgery, limited information is available regarding the correlation between intraoperative TEE assessment of residual ventricular outflow tract obstruction and postoperative transthoracic echocardiography (TTE). Studies to validate the post-bypass TEE assessment of ventricular outflow tract obstruction are necessary prior to the routine application of this technique toward intraoperative decision making. The aim of this study was to assess the reliability of the post-bypass TEE to detect residual gradients compared with the postoperative TTE in patients with ventricular outflow obstruction.
Methods: Post-bypass TEE peak systolic gradients of 129 patients, mean age of 7 years, 81 with right ventricular outflow tract obstruction and 48 with left ventricular outflow tract obstruction, were compared with the postoperative TEE within 30 days of surgery. Postoperative lesions were graded for predicted hemodynamic significance when peak systolic gradient was > 40 mmHg.
Results: In patients with left ventricular outflow tract obstruction post-bypass TEE showed mean peak systolic gradients higher than postoperative TTE (30 mmHg versus 24 mmHg p=0,014). In 75% of patients post-bypass TEE gradients were < 40 mmHg and agreed with postoperative TTE in 94%. In the remaining patients post-bypass TEE gradients were >40 mmHg and agreed with postoperative TTE in 33% (a hyperdynamic LV was observed in theses cases). In patients with right ventricular outflow tract obstruction post-bypass TEE mean peak systolic gradients agreed with postoperative TTE (28 mmHg versus 25 mmHg p=0,21). In 88% of patients post-bypass TEE gradients were < 40 mmHg and agreed with postoperative TTE in 91,5%. In the remaining patients post-bypass TEE gradients were >40 mmHg and agreed with postoperative TTE in 60%.
Conclusion: Post-bypass TEE showed to be a reliable technique to detect residual outflow tract in the majority of patients, although when considered gradients >40 mmHg, TEE suggested a greater severity of ventricular outflow tract obstruction, particularly on the left side obstructions.

P1032 Surgical repermeabilization of occluded pulmonary arteries in patients with congenital heart disease: effects on pulmonary branches growth

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This study was undertaken to determine outcomes and best strategies for treatment of occluded pulmonary branches in patients with congenital heart disease. Between 1998 and 2002, occlusion of a previously patent pulmonary branch was established in 23 patients. Data were obtained retrospectively. Diagnosis were: pulmonary atresia and ventricular septal defect in 11, tetralogy of Fallot in 6, others forms of pulmonary stenosis or atresia in 6. Median age and weight at diagnosis were 9 years (range 6 days-43 years) and 24 kg (range 2.6-60). Fourteen patients had had a previous surgery. The occluded pulmonary branch was visualized at angiography by wedge injection or injection in collateral circulation. Left pulmonary branch was occluded in 20 patients, right pulmonary branch in 3. Criteria for repermeabilization were: estimated duration of occlusion <6 months and ratio occluded/controlateral branch >0.2.
Twelve patients fulfilled these criteria and underwent pulmonary branch reconstruction at a mean interval of 2 months (range 6 days-6 months) from evidence of occlusion. Six patients had pericardial patch reconstruction, 3 termino-terminal anastomosis, 2 thrombectomy, 1 Blalock-Taussig shunt. There was 1 late death. At a median follow-up of 4 years (2 months-5 years), all patients underwent cardiac catheterization: in 8 patients the reconstructed branch was patent, in 3 re-occluded. Hypoplasia of the occluded branch was reversed in 6 patients.
Our data show that, in selected patients, reconstruction of an occluded pulmonary branch can restore pulmonary vascularisation and reverse branch hypoplasia. Strict surveillance is mandatory to prevent pulmonary branch loss.

P1033 Factors influencing vegetation size at admission in infective endocarditis

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The vegetation size has been studied as a prognostic factor in infective endocarditis. It is unclear, however, which factors are associated to vegetation size. AIM: We assesed the influence of several clinical and microbiological factors on vegetation size at admission, before the initiation of an adequate antibiotic treatment.
Methods: We studied 435 consecutive episodes (ep) of infective endocarditis.

Transesophageal echocardiography (TEE) was done in all and was used to assess the size of the vegetation.
Results: Vegetations (vg) were observed in 265 ep (60.9%) and vg size (mm) ranged from 5 to 47, mean 14.2, SD 7.7. Vg size were similar in left or right-sided ep (13.9 vs 16.2, p=0.08). Clinical course, acute or subacute (14.2 vs 11.8, p=0.90); previous empiric antibiotic treatment (13.5 vs 14.5, p=0.49); type of underlying heart disease (p=0.09) and causative microorganism (p=0.62) did not influence on vg size. Patients with only one ep had larger vg than patients with multiple ep: 14.6 vs 9.81, p=0.03. Ep with a new atrioventricular block had smaller vg than ep without this complication: 10 vs 14.5, p=0.02. Vg size was larger (16.9 vs 13.5, p=0.006) when embolisms were already present at admission. Mechanical valves had smaller vg than native and biological valves: 11.2, 14.7 and 15.1 respectively, p=0.007. Vg in ep in which aortic native valve was infected were somewhat smaller than in ep with this valve respected: 13 vs 14.8, p=0.07. Perianular complications did not have influence on vg size, p=0.37. On multivariate linear regression analysis, independent factors associated to vg size at admission were the following (mean difference; 95% confidence interval; p value): involvement of native aortic valve (-3.1; -0.8 to -5.4; p=0.01); mechanical prosthetic endocarditis (-5.2; -2.6 to -7.8; p=0.001), and embolisms present at admission (4.0; 1.7 to 6.4; p=0.001).
Conclusions: 1) Native aortic valve infection and mechanical prosthetic endocarditis are associated to small vegetations. 2) Embolic events present at admission are associated to larger vegetations. 3) Side of endocarditis, causative microorganisms and periannular complications do not influence vegetation size at admission.

P1034 Distinctive features of infective endocarditis complicated with periannular abscesses or pseudoaneurysms

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Introduction: Periannular extension of infective endocarditis (IE)- abscess, pseudoaneurysm, fistula- worsens the prognosis of patients with this disease. An abscess represents infected material contained within a fibrous cap, while a pseudoaneurysm is a cavity in communication with bloodstream.
Objective: To assess the existence of distinctive features in episodes of IE with either abscesses or pseudoaneurysms.
Methods: We analysed 347 consecutive episodes of lef-sided infective endocarditis. There were 130 ep with periannular extension of the infection. Our study group consists of 99 ep accompanied either by abscesses or pseudoaneurysms. Those patients that had both types of periannular complications have been excluded.
Results: Sixty-two ep were complicated with periannular abscesses only (group-gr- I) and 37 ep were accompanied exclusively by pseudoaneurysms (gr II). Of them, 46.8% and 45.9%, respectively, were prosthetic endocarditis, p=0.9. They were definite ep according to Duke criteria in 96.8%, gr I, and 100%, gr II, p=0.2. The frequency and type of predisposing heart conditions was similar for both groups. At admission, fever was present in in 82.3% of cases in gr I and 67.6% in gr II, p=0.09. Patients had chills in 66.7%, gr I, vs 40.7%, gr II, p=0.03. A new AV block was detected in 17.7%, gr I, and 13.5%, gr II, p= 0.5. The microbiological profile was similar in both groups, p=0.3. Detection of vegetations by transesophageal echocardiography (TEE) was comparable, p=0.7. The periannular complication was present in the first TEE in 46.8% gr I and 54.1% gr II, p=0.4. Vegetation size was $\geq$ 10 mm in 66.7% and 88.5% of ep, p=0.04. Valve regurgitation was similar, p=0.3. Mitro-aortic infections were common (35.5% and 32.4%, respectively, p= 0.75). Heart failure was present during the first week of adequate antibiotic treatment in 50.9% and 28.6%, p=0.03. Signs of infection were uncontrolled in 33.9%, gr I, and 35.1%, gr II, p=0.8. Septic shock ensued in 12.9% and 8.1%, p= 0.4. Cardiac surgery was more frequent in ep of gr I (87.1% vs 59.5%, p=0.002). Time from the first TEE study to surgery was shorter in gr I (median of 7 vs 15.5 days, p= 0.01). Mortality rates were similarly high: 40.3% and 37.8%, p= 0.8
Conclusions: in episodes of infective endocarditis complicated with abscesses, compared to those complicated with pseudoaneurysms, 1) Presentation with fever and chills is more common; 2) Microbiological pattern is similar; 3) Vegetation size is smaller; 4) Heart failure is more common; 5) Cardiac surgery is more frequent; 6) Mortality rates are similar.

P1035 A quantitive index for thoracic aorta atherosclerosis predicts coronary artery disease in patients undergoing transoesophageal echocardiogram

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Background: The relationship between thoracic aorta atherosclerosis (TAA) and coronary artery disease (CAD) has been shown by previous studies. Extent and severity of TAA as assessed by transoesophageal echocardiography (TEE) has been also associated with the severity of CAD. The aim of this study was to show the quantitative relationship between TAA and CAD in patients undergoing TEE.
Methods: We prospectively studied 246 patients (149 men, mean age 57.9$\pm$11.83 years, 97 women, mean age 56.9$\pm$12.33 years, p=0.54), who underwent TEE and coronary angiogram for different indications in our institution between October 1991 and April 1996. For each patient age, sex, standard risk factors for CAD were assessed. TEE was performed in a three-month period around the coronary angiogram. All TEE studies have been analysed and ascending aorta, aortic arch and descending aorta were graded independently as following: Normal Intima: Grade I, (points 0), Intima thickening without plaques: Grade II, (point 1), One plaque$<$3mm: Grade IIIA, (points 2), More than one plaque$<$3mm: Grade IIIB, (points 3),One or more plaque$>$3mm: Grade IV, (points 4),Large mobile or protruding plaque(s): Grade V, (points 5).
TAA grade was defined as the grade of the thoracic aortic segment with the most severe atherosclerosis. TAA burden index (TAABI) was defined as the sum of the points that have been awarded to each segment.
Results: Eighty-four pts (54 men) had CAD. When TAA was examined independently for each segment of the aorta, it was an independent factor for predicting coronary artery disease: for ascending aorta the possibility of prediction was increased 90% (odds ratio 1.90, CI 95%: 1.26-2.85), for aortic arch was tri-folded (odds ratio 3.03, CI 95%: 2.08-4.40) and for descending aorta it was increased 70% (odds ratio 1.70, CI 95%: 1.27-2.26).
ROC curve analysis showed that TAABI had the better specificity and sensitivity in predicting CAD with an area under the curve 89%. A TAABI cut-off point value more than 6 is associated with 20-fold increase of possibility of CAD existence. The specificity of TAABI value $>$6 in the prediction of CAD is 88%, the sensitivity is 81%, the positive predictive value is 77% and the negative predictive value is 90%.
Conclusion: Thoracic aorta atherosclerosis burden index is an easy to obtain by TEE parameter. A TAABI value more than 6 is an accurate index for CAD prediction implying that severe TAA is strongly related to CAD while it is rather safe to assume that patients with no TAA or mild TAA do not have angiographically significant CAD.

P1036 The reliability of transoesophageal echocardiography in patients with surgical treatment of proximal aortic dissection

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Aims: Transoesophageal echocardiography (TEE) plays central role in the diagnostic workup of aortic dissection. This retrospective study was designed to assess the reliability of TEE diagnosis in patients who underwent surgical therapy. Patients and methods: Proximal aortic dissection was diagnosed by TEE in 119 cases between 1993-2003. 95 patients with proximal dissection were analyzed retrospectively, who underwent surgery. Both TEE and surgical description results were available in only 75 out of 95 patients. The following criteria were selected for comparison: the presence of dissection, the type of dissection, the localization of intimal tears (entry/reentry), the assessment of coronary artery involvement, pericardial effusion, the mechanism of aortic regurgitation and the special forms of aortic dissection.
Results: The diagnosis and type of aortic dissection matched in all patients between TEE and surgical evaluation. In 64 patients (85%) localisation of the intimal tears was the same with both method. Tears entry was not visualized in 7 patients, false localization accured in 4. The involment of coronary arteries was assesed correctly with TEE in 66 cases (88%), in one case it could not be detected and in 8 patients the description was different from the surgical results. In 8 cases with ischaemic changes on ECG the TEE could detect the origin of the right coronary artery from the false lumen. Pericardial effusion and pericardial tamponade at the moment of the analysis was concordant in 61 patients (81%). The mechanism of aortic regurgitation was thought to be similar in 61 cases. Intramural haematoma was diagnosed in 6 cases with TEE, while only in 4 cases with surgery. In the other two patients classic dissection was found at surgery.
Conclusion: Our data confirm that TEE is a reliable diagnostic method in the diagnosis of aortic dissection. The indication for surgery proved to be correctly proposed in all cases. The reliability of description of details about dissection was between 81-88% using surgery as a reference method. The time interval between TEE analysis and surgery can influence the volume of the pericardial effusion and can explain our detected difference.

P1037 Transthoracic echocardiographic parameters for thromboembolic risk: correlation with transoesophageal velocities

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Left atrial appendage (LAA) dysfunction is an important thromboembolic risk. LAA emptying velocity (LAA eV) obtained with transesophageal echocardiography (TEE) is the most feasible, accurate and reproducible echocardiographic parameter clinically useful to study LAA function.

Aim: Aim of this study is to correlate TEE LAA eV to other echocardiographic parameters for thromboembolic risk obtained with transthoracic echocardiography (TTE), in order to find a more easily obtainable measurement with a comparable accuracy.
Method: We studied 92 patients (56 with sinus rhythm and 36 with atrial fibrillation) with clinical indication to TEE. All patients received a II harmonic TTE performed immediately prior to TEE by a different cardiologist, with a complete LAA study. The following TTE measurements were performed: 1) the TTE LAA eV, 2) the thickness change of medial LAA wall related to emptying and filling LAA phases (TTE LAA Delta) with a M-mode tracing in 2-chamber modified view, 3) the maximal LAA area, 4) the parasternal left atrial diameter (LA diam), and 5) the left ventricular ejection fraction (EF).
Results: The following table shows the feasibility of echocardiographic parameters and their correlation (r) versus the TEE LAA eV, considered as gold standard.

	TTE LAA eV	TTE LAA Delta	TTE LAA area	LA diam	EF
Feasibility (%)	80/92 (86%)	87/92 (94%)	66/92 (72%)	92/92 (100%)	92/92 (100%)
Correlation (r) vs. TEE LAA eV	0.77	0.71	0.21	0.26	0.01

Conclusions: Among those parameters obtainable with TTE predictors of thromboembolic risk, only the TTE variables of LAA function show a good correlation with the gold standard TEE LAA eV. Among these TTE variables of LAA function, the new monodimensional index TTE LAA Delta, expression of LAA contractility, showed the best feasibility.

P1038 Transoesophageal Doppler echocardiographic evaluation of the esophago-cardiac reflex in patients with angina-like chest pain

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Coronary artery disease (CAD) and gastroesophageal reflux disease (GERD) are known to be the most prevalent causes of chest pain, and therefore they frequently coexist. On the other hand, esophageal acid exposure may lead to coronary flow reduction via the esophago-cardiac reflex (ECR). The aim of the study was to investigate the presence of ECR in patients with chest pain and to establish its association with CAD, coronary spasm and GERD.
Patients, methods: 42 patients (M/F 21/21; 55{36-74) ys.) with angina-like chest pain were studied. Coronarography, upper gastrointestinal endoscopy and 24h pH monitoring was carried out in all patients. The presence of microvascular angina was proved by impaired coronary flow reserve capacity. The effect of esophageal acid stimulation (0.1 N HCl, 120m1/10min) on the coronary flow - compared to 0.9% NaCl - was measured by transesophageal echocardiography (TEE) in the proximal part of the left descending artery in a blinded manner.
Results: Esophageal acid perfusion decreased the coronary flow in 45% (19/42) of the patients representing the presence of ECR. The prevalence of significant CAD, microvascular angina, coronary spasm, and GERD were 19/42, 10142, 5142 and 17/42 patients respectively. The presence of ECR was independent of both CAD, and microvascular disease. Patients with coronary spasm, had significantly higher coronary flow reduction for esophageal acid stimulation {$p<0.001$). On the other hand the presence of ECR was associated with higher DeMeester scores ($p<0.05$) and more acid reflux episodes exceeding 5 minutes ($p<0.05$) on pH-metry.
Conclusion: Our new method appeared to be valuable tool for the establishment of ECR in patients with angina-like chest pain. Proven coronary spasm, the presence of prolonged gastroesophageal acid reflux episodes and erosive esophagitis are suspected factors playing a role in the development of linked-angina.

P1039 A modified transoesophageal echocardiografic approach allows the assessment of pressure gradient in pulmonary valve stenosis

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The accurate measure of maximal pressure gradient (MaxPG) and mean pressure gradient (MnPG) in the pulmonary valvular stenosis (PS) may be difficult during the standard transthoracic echocardiography (TTE) and require an integrated evaluation with a multiplanar transesophageal approach (TEE). We verified if a modified transesophageal aortic arch view can be used to measure the peak sistolic velocity (PSV) by continous wave Doppler through the pulmonary valve.
Methods: twenty two adult patients with isolated PS and high quality transthoracic imaging underwent a TTE and TEE in the same session. During TEE pulmonary valve and main pulmonary artery can be optimally visualized through the modified view of the aortic arch by a more cranial position of the transducer and an oblique orientation of the scanning plane (35°- 45°). Thus a long axis imaging of the main pulmonary artery permits, in this section, a good quality Doppler recording of the forward pulmonary flow. During TTE pulmonary valve and artery were viewed using parasternal and subxiphoid short axis approach.Therefore PSV, MaxPG and MnPG were calculated from the simplified Bernoulli equation during both TTE and TEE.
Results (mean ± SD):

	TEE	TTE	r value	SEE
PSV (cm/sec)	348 ± 64	335 ± 54	0.95	15
Max PG (mmHg)	50 ± 18	44 ± 15	0.92	6
Mn PG (mmHg)	32 ± 10	26 ± 12	0.90	5

An optimal visualization of pulmonary transvalvular flow can be obtained in most of patients using the modified TEE.
Conclusion: Doppler recording of pulmonary transvalvular flow during modified TEE approach is a reliable and accurate method to evaluate pressure gradient in patients with PS. The combined TTE and modified TEE analysis of the pulmonary high velocity jets can be helpful in patients with associate obstructive lesions to locate the area in which the increase in velocity occurs.

MODERATED POSTER SESSION II

EXERCISE TESTING

P1040 Assessment of relationship between non-invasive coronary flow reserve and oxygen uptake in athletes with repolarization abnormalities during exercise test

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Background: Coronary flow reserve (CFR) can be measured by transthoracic echocardiography (TTE) during vasodilator stress on mid-distal left anterior descending (LAD). Athletes (A) represent an ideal subject of investigation for this purpose. It is well known that they have higher aerobic performance (VO2max) in comparison with sedentary subjects. The aim of our study was to verify the relationship between CFR and VO2max in these subjects.
Methods: Starting from January 2002, 46 subjects (all males; age=37±8 years), 20 Athletes (A) with normal exercise test (AN),18 A with abnormal ecg exercise test (AA) and 8 normal sedentary subjects as control group (CG) were evaluated by stress echocardiography. TTE (S3-S8 probe, second harmonic 3,6-7 MHz, HP 5500-7500, Philips technology). Mid-distal LAD coronary artery was imaged from a modified apical two-chamber view. Wherever color-coded blood flow from the baseline could not be obtained, contrast enhancement with Levovist (Schering AG,300 mg/ml/m') was used. Peak diastolic coronary flow velocity of each coronary artery was recorded by pulsed Doppler under the guidance of Color Doppler flow mapping. CFR was calculated as the ratio of dipyridamole/rest peak diastolic flow velocity (0,84 mg over 6 m').
Results: Interpretable rest-peak signals were obtained in all 36 A for LAD (100%). The CFR mean value on LAD resulted as 4,5±5 (range:2,8-5,9) and the mean value of VO2max resulted as 40±6 ml/kg/m'(range:36-45 ml/kg/m'), showing an excellent linear relationship with each other (r=0.73;r2=0,53: $p<0.0001$).
Conclusion: With latest generation, high frequency, second harmonic, contrast-enhanced transthoracic echocardiography, imaging of coronary artery flow and assessment of flow reserve is highly feasible in the A for LAD. This noninvasive parameter shows a close relationship with aerobic performances in A, confirming that the VO2max represents the most powerful metabolic trigger of CFR and therefore can be proposed for a more complete functional evaluation of " the athlete's heart".

P1041 Systematic preparticipation screening leads to identification of young competitive athletes with arrhythmogenic right ventricular cardiomyopathy at risk of sudden death during sports

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Systematic monitoring of sudden death (SD) in young people of the Veneto region of Italy showed that arrhythmogenic right ventricular cardiomyopathy (ARVC) is a leading cause of athletic field deaths (24% of fatal events). The present study was designed to assess the impact of systematic preparticipation screening, in practice in Italy for more than 20 years, for detection of competitive athletes affected by ARVC and for prevention of SD. Cardiovascular causes of disqualification and follow-up were evaluated in a series of 38,273 young competitive athletes (aged 35 years or less) who underwent preparticipation cardiovascular evaluation - by history, physical examination and 12-lead ECG - from 1982 (the year of discovery of ARVC) to 2001 in Padua. Two decades of screening were compared (1982-1991 vs 1992-2001). Diagnosis of ARVC was made according to the criteria recommended by the Task Force of the European Society of Cardiology. Of 38,273 athletes, 3,597 (9.4%) were referred for further examination such as exercise stress testing, Holter monitoring, echocardiography/MRI or angiography, due to a positive initial screening, and 15 (14 males, and 1 female, aged 19 years) showed definitive evidence of ARVC (prevalence of 0.04%). Reasons for further examination was positive family history in 3, inverted T-waves beyond lead V1 in 12 (80%), and ventricular arrhythmias in 9 (60%). In all athletes definitive diagnosis relied on demonstration of right ventricular dilatation with wall motion ab-

normalities such as bulgings/aneurysms by imaging techniques.The prevalence of disqualifications due to ARVC was significantly greater (p=0.003) from 1992 to 2001 (13 of 388 athletes; 3.3%) as compared to the decade 1982-1991 (2 of 421 athletes; 0.5%). None of the 15 disqualified athletes died during a follow-up of 6.4 years. In conclusion, ARVC has been discovered only 20 years ago and initially it was either underdiagnosed or regarded with scepticism by the medical community. As a consequence, diagnosis at preparticipation cardiovascular evaluation was missed, although the majority of affected athletes had suggestive signs and/or symptoms. In the last 10 years, with increased awareness of clinical findings suggestive of ARVC, more athletes with ARVC at risk of SD during sports are now being identified by systematic preparticipation screening and this is expected to result in reduction of athletic field deaths in the near future.

P1042 Epicardial vessel remodeling associated to endurance training in middle-age normal subjects

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Prolonged endurance training has been reported to yield a large artery remodeling including an increased size of human epicardial coronary arteries. However, it is not yet clear whether this adaptation is related to an increase in left ventricular (LV) mass (physiologic LV hypertrophy), to repeated increases in coronary blood flow during increments of metabolic demand, or both.

Aim: Aim of this study was to assess, in trained subjects as compared to sedentary controls, the relationships between luminal diameter of left main coronary artery (LMA), LV mass and the maximal coronary flow increase during pharmacologically-induced arteriolar vasodilation.

Materials and Methods: 17 NC and 14 endurance athletes (A; marathon runners and triathlonists) comparable for age (47±13 vs. 46±12 years) underwent transesophageal Doppler-echocardiography. The images of the left main coronary artery (LMA) at baseline were stored on optical disk. Coronary flow velocity in the left anterior descending artery was measured at baseline and during maximal flow response to i.v. dipyridamole infusion (0.84mg/kg/8min). In digitized zoomed diastolic images, the inner contour of the proximal segment of LMA was manually delineated, and the mean diameter automatically calculated from several measurements by a computer-driven image analysis system. Reported values represent the average of measurements in five cardiac cycles. Dipyridamole-induced coronary flow increase (CFI) was expressed as the ratio of maximal and baseline coronary flow velocity. LV mass index was estimated by 2D-guided M-mode echocardiography.

Results: LV mass index and LMA inner diameter were significantly higher in A than in NC (LVMI: 72±15 vs. 38±7 g/m$^{2.7}$; LMA: 3.88±0.4 vs. 3.41±0.3 mm; $p<0.01$ for both), while CFI was comparable in both groups (3.69±0.5 vs. 3.39±0.9). LMA inner diameter was directly related to LV mass index (r=0.56, $p<0.02$) but not to CFI in NC. On the contrary, it showed a direct relationship with CFI (r=0.62, $p<0.02$) but not with LV mass in A.

Conclusion: Endurance exercise training seems to induce a favorable remodeling of coronary conductance vessels through frequent high-flow stimuli caused by a substantial increase in myocardial oxygen demand during repeated exercise load.

P1043 Exercise induced ST-segment depression with convex pattern: a marker of good prognosis

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Background: During exercise testing, ST-segment depression with convex pattern has been associated with no significant epicardial coronary artery disease on angiography, and preliminary data from our laboratory have indicated that this finding is associated with normal stress perfusion (Herdy et al. Eur Hear J 2003;24[abstract suppl]:683). However, no information is available on the prognosis of patients with exercise-induced ST-segment depression with convex pattern.

Purpose: To evaluate the long-term follow-up of patients with exercise-induced ST-segment depression with convex pattern.

Methods: From September 2001 to October 2003, 1425 exercise myocardial perfusion scyntigraphies were performed in our laboratory. One investigator prospectively identified patients who presented exercise-induced ST-segment depression with a convex pattern in 2 or more electrocardiographic leads, and another investigator evaluated the corresponding exercise 99mTc-sestamibi myocardial perfusion scyntigraphies, without knowledge of the electrocardiographic findings. All patients who presented exercise-induced ST-segment depression with a convex pattern were followed for a mean of 17.7 months (3 to 36 months) and cardiovascular outcomes, including revascularization, hospitalization, and death, were evaluated.

Results: One hundred patients (7% of all tests performed), with female predominance (53%), and a mean (±SD) age 51±8 years, presented exercise-induced ST-segment depression with convex pattern. None of these patient presented symptoms during the exercise test, and all myocardial scintigraphies presented normal perfusion. On follow-up, only one patient presented an acute myocardial infarction and one patient had unstable angina which resulted in coronary angioplasty (incidence of cardiovascular events: of 1,5% per year).

Conclusion: Exercise-induced ST-segment depression with convex pattern is associated with normal perfusion and with low incidence of cardiovascular events on follow-up, indicating that this finding should be interpreted as false positive for the diagnosis of myocardial ischemia.

P1044 Exercise testing in asymptomatic aortic stenosis patients

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Background: the usefulness of the exercise testing (ET) in asymptomatic aortic stenosis patients (pts) is under discussion. We have investigated the impact of ET results in outcome and medical decision of surgery treatment.

Purpose: 1) Determine the value of the ET in the outcome and medical decision of surgery indication in asymptomatic moderate and severe aortic stenosis (AAS)pts. 2) Evaluate the safety of the ET.

Methods: consecutive 106 p with AAS who performed a maximal ET. ET was considered abnormal if the patient had symptoms (angina, syncope or dysnea), changes in ST segment and/or fall in systolic blood pressure $>$ 10 mmHg. The follow up was done on the basis of review of the medical records, discussion with the primary care physician or telephone calling. End points were defined as death or aortic valve surgery.

Design: retrospective clinical study

Statistic: Kaplan Meier event free survival, log rank test, Cox and multiple logistical regressions.

Results: severe aortic stenosis: 90 p (84.9%), maximum systolic gradient: 82.8±24.5 mmHg, valvular area: 0.67±0.16 cm^2. There was not registered complication related to ET. The follow up was completed in 101 p (95.3%), aged 63.9 (±15.1), 65 (61.3%) male. Follow up median: 10.7 month, percentile 25-75: 4.9 – 19.4. Sixty-nine ET were abnormal. AVR was indicated in 45 p (44.5%), 35 with abnormal ET and 10 with normal ET. There were 2 (2%) sudden deaths with previous symptoms (both with abnormal ET). Kaplan-Meyer event-free survival was 24,5 ± 9,6% at 36 months.

	n	Odds ratio	95% CI	p
Abnormal ET	69 (65.1%)	3.59	1.7-7.57	0.001
Symptoms	38 (35.8%)	3.22	1.77-5.85	$<$ 0.0001
Changes in ST	44 (41.5%)	2.08	1.15-3.75	0.01
Fall in SBP	28 (26.4%)	2.77	1.2-4.3	0.01

Cox regression analysis showing end points predictors

Conclusions: ET can be applied safely in asymptomatic pts with moderate and severe aortic stenosis. The main usefulness of this test is the identification of: a) asymptomatic false pts and b) pts with abnormal response to exercise. The mentioned findings give additional information for the decision of prescribing surgery.

P1045 Spontaneous breath-by-breath variations (fast but random) in exercise VO_2 are reduced in patients with chronic heart failure

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Background: Spontaneous breath-by-breath variations in tidal volume are reported to be markedly reduced in patients with restrictive lung disease (Brack T, et al. Am J Respir Crit Care Med. 2002). Since similar lung changes are known in patients with heart failure, it can be postulated that spontaneous variations (especially "fast" components) in respiratory parameters may be reduced in these heart failure patients, thereby more readily unmasking the presence of slow periodic (not random) oscillations (OSC) during exercise, which is characteristics of severe heart failure.

Methods: In 229 patients with heart failure due to dilated cardiomyopathy (DCM, LVEF=30±11%) and 195 control subjects without cardiovascular disease, we analyzed VO2 by repeating FFT while serially shifting the time-window of 4-min every 30 sec from rest to peak exercise. From power spectrum (PS) averaged for each segment, total, low-frequency (LF, 0.5-1.25 cycle/min), and high-frequency (HF, 1.25-5.0 cycle/min) PS were compared between the 2 groups.

Results: Compared with DCM patients, control subjects had greater total-PS and HF-PS by 23% and 31%, respectively (both $p<0.001$), while LF-PS was not significantly different between the groups. HF-PS was markedly reduced in DCM patients with OSC (n=30, by -35%, $p<0.001$) compared with those without OSC.

Conclusion: Spontaneous variations ("fast" but "random") in VO2 during exercise were reduced in DCM patients, especially in those manifesting OSC. This finding suggests that these changes may contribute to more readily unmask the presence of slow periodic VO2 oscillations characteristic of those patients with heart failure.

P1046 Anaerobic capacity and maximal accumulated oxygen deficit evaluation in chronic heart failure patients: feasibility and repeatability

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Exercise tolerance of chronic heart failure (CHF) patients is usually expressed as maximal aerobic power (peak VO2). However, it is acknowledged that also anaerobic energy sources are often activated during daily physical activities. The parameter currently used to describe the maximal energy amount obtainable from anaerobic energetic system (anaerobic capacity) is maximal accumulated oxygen deficit (MAOD). Goal of this study was to evaluate feasibility and repeatability of MAOD measurement in a group of CHF patients and a group of age-matched healthy sedentary (HS) or cycling amateurs (CYCL) subjects. We studied 10 CHF patients (age 66±4 years, ejection fraction 28±9%, peak VO2 15.2±2.5 ml/kg/min), 5 HS (age 60±5 years, peak VO2 28.5±3.6 ml/kg/min), and 5 CYCL (age 60±6 years, peak VO2 38.6±4 ml/kg/min). All participants in the study underwent a basal symptom-limited ramp cardiopulmonary exercise testing (CPX), 4 submaximal constant-load CPXs at comparable relative wokloads for determination of the VO2/Watt relationship, and 3 supramaximal constant-load CPXs for MAOD measurement, whose workload was adjusted to obtain test durations of about 1, 2, and 3 minutes, respectively. MAOD was defined as the difference between predicted and measured oxygen consumption at the evaluated supramaximal workloads. One of the 3 supramaximal CPXs was randomly repeated in each patient and subject. No adverse event occurred in the evaluated groups. In CHF patients, mean supramaximal CPXs duration was 85±8 sec, 140±27 sec, and 204±41 sec, corresponding to 129±4%, 113±7%, and 101±7% of peak workload at basal CPX, respectively. Highest MAOD mean values were those of shortest supramaximal CPXs (12.3±3.4 ml/kg, equal to 46% and 44% of HS e CYCL values, respectively), with heart rate and systolic and diastolic blood pressure mean values equal to 99±6%, 100±8%, and 100±0% of basal CPX, respectively. Supramaximal CPXs repeatability was good, with intraclass correlation coefficients of 0.91, 0.97, 0.98, 0.93, and 0.92 for duration, maximal heart rate, maximal systolic blood pressure, measured VO2/kg, and MAOD, respectively. Finally, MAOD of shortest duration supramaximal CPXs was significantly related to respiratory exchange ratio values at 2 minutes during recovery after basal CPX ($r = 0.69$, $p < 0.02$) in the entire study population. In conclusion, in CHF patients measurement of MAOD is feasible and repeatable, and can be predicted by respiratory gases analysis during recovery after conventional CPX. These data may provide new insights in the pathophysiology of exercise intolerance of CHF patients.

P1047 Inspiratory muscle training improves oxygen kinetics during recovery after maximal exercise in patients with heart failure: results of a randomized and controlled trial

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Background: During the recovery period of a maximal cardiopulmonary exercise test, strength of inspiratory muscles (IM) is reduced in some patients with heart failure. This weakness of IM is associated with a prolongation of oxygen kinetics during recovery. In this study we tested the hypothesis that inspiratory muscle training (IMT) could reverse IM weakness after exercise and could improve the oxygen uptake (VO2) kinetics during recovery in patients with heart failure.
Methods: Thirty two patients with heart failure and weakness of IM (maximal inspiratory pressure < 70% of predicted) participated in the study. Patients were randomly assigned to a 12 week program of IMT (n = 16), including 7 sessions of 30 minutes per week, with weekly increments to maintain 30% of MIP, using a threshold inspiratory muscle trainer or to a control group (n=16), that performed the same program without inspiratory load. MIP was measured at rest and 10 minutes after maximal exercise before and after the program. To evaluate VO2 kinetics during recovery, before and after intervention, the slope of VO2 for the 3 minutes of the recovery period (VO2/t–slope) was calculated by linear regression. The time required for a 50% fall from peak VO2 ($T\frac{1}{2}VO2$) was also calculated.
Results: Patients had a mean (±SD) age of 58±7 years, and a left ventricular ejection fraction of 38±13%. Baseline characteristics were not different between groups before training. After IMT, there was marked improvement in MIP at rest (before: 60±9 cmH2O; after: 130±11 cmH2O) and 10 min in the recovery period (46±2 vs 116±15 cmH2O) for the intervention group and no significant change in the control group (ANOVA p = 0.0001). VO2/t-slope increased only in the trained group (before: 0.892±0.7 L/min.min; after: 1.378±0.7 L/min.min – ANOVA p = 0.001). $T\frac{1}{2}VO2$ decreased (before: 1.56±0.3 min; after: 1.04±0.16 min –ANOVA p = 0.0001) only in the trained group.
Conclusion: Inspiratory muscle training improves muscle strength at rest and after maximal exercise, as well as oxygen kinetics during recovery in patients with heart failure. These observations indicate that inspiratory muscle weakness is a reversible determinant of oxygen uptake kinetics in the recovery period in patients with heart failure.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR THERAPY

P1048 Morphology discrimination in dual-chamber defibrillators: a multicentre study

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Purpose: Morphology discrimination (MD) is a diagnostic algorithm based on QRS morphology analysis, implemented in dual-chamber ICDs from St. Jude Medical. MD is based on automatic comparison, for detected events, between each single sensed QRS complex and a previously stored patient-specific QRS template. We evaluated the contribution of MD in Specificity (SP) and Sensitivity (SE) of rhythm discrimination during spontaneous and induced arrhythmic episodes.
Methods: . All episodes detected in 58 patients (mean f-up 19±8) were reviewed and classified: SE and SP were evaluated, according to various potential diagnostic settings ('Any' or 'All' the criteria indicating ventricular tachycardia). Moreover, the ability to discriminate sinus tachycardia during exercise testing and induced atrial fibrillation (AF) were analysed (setting a cutoff =102bpm).
Results: 682 spontaneous episodes (82 ventricular tachycardia, 7 ventricular fibrillation and 593 supraventricular tachyarrhythmias) that occurred in 58 patients were considered (see Table). Overall, SE with "Any" criterion was 96,3%, while it was 76,8% with "All"; SP was 86,3% with "Any"and 96,7% with "All". MD contributed significantly to improve SE/SP balance, in comparison with no use of this discriminator (see Table). Considering 29 episodes of sinus tachycardia occurring during exercise teasting and exceeding detection cut-off, SP with "Any" criterion was 86,2% (25/29). For induced AF SP with "Any" on 19 episodes exceeding detection cut-off was 63.2% (12/19).

Sensitivity (SE) and specificity (SP) on spontaneous arrhythmic episodes

	"Any"	"All"	MD only	Without MD
SE	79/82 (96.3%)	63/82 (76.8%)	78/82 (95.12%)	64/82 (78.04%)
SP	498/577 (86.3%)	558/577 (96.7%)	550/593 (92.7%)	491/593 (82.8%)

Conclusion: In dual-chamber ICDs use of MD allows to attain an improvement in the appropriateness of rhythm discrimination. The contribution of MD results in maintainance of a high level of sensitivity in appropriate ventricular tachycardia diagnosis.Table

P1049 ST analysis in the implantable cardioverter-defibrillator: first intraoperative data of patients with and without previous myocardial infarction

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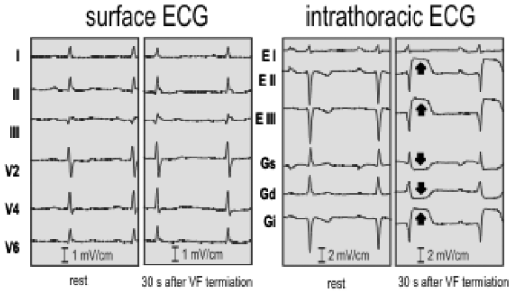
ICD systems with the possibility of analyzing and storing an ICD-based intrathoracic 6-channel ECG (IT-ECG) are under investigation. The aim of the study was the analysis of ischemia-evoked ST changes in pts with and without previous myocardial infarction (MI).
Methods: During 27 ICD implantations in pts with proven residual ischemia (thallium scintigram, 18 pts: history of MI, 9 pts: no prior MI), the IT-ECG (6 leads in ICD, Goldberger/Einthoven: RVA, VCS, ICD-casing) and the surface ECG (S-ECG) were recorded digitally (500 Hz, 12 bit) and analyzed with respect to ST deviations (ST-d) before, 60 and 240 sec after synchronized R-wave shock (RWS, impedance test shock) and after termination shock in induced ventricular fibrillation.
Results: The mean ST-d 60 sec (240 s) after RWS was 1.69±1.48 mV (0.84±0.65 mV) in the IT-ECG vs. 0.03±0.03 mV (0.02±0.02 mV) in the S-ECG ($p<0.01$). The mean ST-d after termination shock in ventricular fibrillation was 2.13±1.91 mV vs. 0.03±0.03 mV after 60 sec ($p<0.01$) and 0.98±0.75 mV vs. 0.02±0.02 mV after 240 s ($p<0.01$). Pat. with (60 sec after termination shock: IT-



ST deviations after VF termination.

ECG 1,99±1.74 mV, S-ECG 0.03±0.03mV) or without (IT-ECG: 2.42±2.37 mV, S-ECG 0.03±0.03 mV) prior MI did not differ in ST-ds.
Conclusion: Previous MI do not influence reliable and reproducible recognition of ischemic ST-d in the ICD using the intrathoracic 6-channel ECG. Recognition is also independent of localization of residual ischemia in the individual patient.

P1050 Clinical predictive factors of electrical parameters variability in DDD pacemakers

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Background: Capture Management (CM) is a Medtronic K700 and K900 pacemakers (PM) feature that automatically measures ventricular pacing threshold at predefined time intervals by automatically detecting the evoked response after a pacing stimulus. Aim of this study was to evaluate the range of variation of ventricular pacing threshold and the possible clinical predictive factors of this variation in PM implanted patients (Pts).
Methods: 182 Pts (53% M, mean age 60±28) were implanted with a K700 or K900 PM. Mean NYHA class was 1.5±0.7, 14% of Pts had atrial fibrillation (AF), 38% hypertension, 13% diabetes, 14% cardiomyophaty (CMP) and 19% were under antiarrhythmic drugs (AA-drugs). CM was programmed to automatically measure ventricular threshold every two hours. A multivariate analysis has been done with all the clinical variables to detect predictive factors for pacing parameters variations. Mean follow-up (f/u) was 8±7 months (range 1-30).
Results: Mean threshold variation was 12.9±8.3% (range 0-45). The correlation between the relevant clinical factors and the electrical parameter variations are shown in the table. Threshold and impedance variations significantly increased with age increasing. AF seemed to be a predictive factor for higher variations of atrial sensing (AS) and impedance, while CMP of threshold and AS. Females seemed to have higher variability of AS and threshold. Also ventricular lead model influenced threshold variation in our population.

	V threshold	V Impedance	V Sensing	A Sensing
Age	p<0.01	p<0.05	ns	ns
AF burden	ns	p<0.05	ns	p=0.176
CMP	p<0.05	ns	ns	p<0.05
Sex	p=0.141	ns	ns	p<0.05
Hypertension	p=0.112	ns	ns	ns
NYHA class	ns	ns	ns	p=0.121
Brady-Tachy	ns	ns	ns	p=0.112
Lead model	p<0.01	ns	ns	ns

Conclusions: Most of the Pts showed a very stable threshold. CM could be very important in older Pts with AF, CMP and hypertension.

P1051 P wave and far-field R wave analysis by automated signal processing at rest and during exercise

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Purpose: Sophisticated monitoring of atrial activity is a prerequisite for modern pacemaker therapy. Ideally, near-fields (NF) and far-field R waves (FF) ought to be distinguished by beat-to-beat template analysis of the atrial signal. A prerequisite is that NF and FF are stable under different conditions.
Methods: A Matlab®-routine was developed to analyze atrial electrograms (EGM) of 23 patients three months after implantation of a Medtronic DR353 device. Two types of atrial leads were used: the Medtronic 5068 (tip-ring spacing 17,8mm) or the 6940 lead (9,0mm). Unfiltered atrial EGMs were analyzed unipolar at rest, bipolar at rest, standing, during treadmill exercise and post exercise. The influence of interelectrode distance of the atrial bipole, lead position and sinus node disease was analyzed. Signal points above noise level were attributed to either NF or FF by their defined temporal distance. A template was created and amplitudes, widths, slew-rates and signal content were measured.
Results: NF amplitude and width was not different between unipolar and bipolar configuration, however, FF amplitude and width as well as the number of FF sensed per near NF were significantly lower in bipolar configuration. Bipolar NF and FF parameters and templates were not influenced by posture or exercise (Fig. 1). Shorter tip-ring distances of the atrial bipole, lead position and the presence of sinus node disease did not have any impact on NF and FF signal characteristics.
Conclusions: Atrial NF and FF can be automatically classified and quantified by an automated signal processing routine. Atrial signals did not change during exercise or posture which is a prerequisite for the implementation of beat-to-beat template analysis into pacemakers.

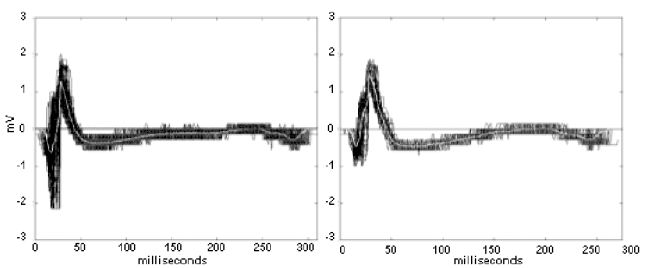

Fig. 1. Template at rest and exercise.

P1052 How to avoid inappropriate mode switch due to far-field sensing – preliminary results of the FFS-test study

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Background and objectives: Farfield-R-wave sensing (FFS) in the atrial channel is the most frequent cause for false positive mode switching (MS) in dual chamber pacemakers and may result in an inappropriate loss of AV-synchrony. Additionally, false positive MS episodes impair the reliability of MS counters used for arrhythmia diagnosis in clinical practice. Objective of the prospective randomised FFS-test study are the evaluation of the incidence of FFS and the efficacy of an optimised programming of the postventricular atrial blanking (PVAB) based on a FFS-test.
Method: At discharge, patients (pts) were randomly assigned to either receive an individually optimised PVAB or nominal PVAB (100 ms). Optimised PVAB was determined to be at least 25 ms longer than the coupling interval of atrial FFS at an atrial sensitivity of 0.1 mV. Atrial sensitivity then was programmed to 0.3 mV in both groups. False positive MS was evaluated by stored electrograms (max. 8 episodes, 6 seconds each, dual channel registration) at the 1 and 3 month follow-up.
Results: 199 pts have completed the 1 month follow-up. Mean age of pts was 70 ± 11 years, 64 were female. Indication for pacemaker implantation was sinus nodal disease (n=88), binodal disease (n=27), AV-block (n=73), and others (n=11). 101 pts were assigned to optimised PVAB, 98 pts received nominal PVAB. False positive MS occurred in 5 (5%) pts of the FFS Test group. 2 of these pts had not received optimised PVAB (e.g. due to atrial fibrillation). In the group assigned to nominal PVAB false positive MS occurred in 22 (22%) pts (p<0.001). Optimised PVAB was determined to be ≤100 ms in 45 pts, and to be >100 ms in 56 pts, with a median of 125 ms (range 85-165 ms). Amplitude of FFS potentials was between 0.2 mV and 1.0 mV (median 0.2 mV). In none of the patients false negative MS was observed.
Conclusion: Additional testing for atrial FFS and consecutive adjustment of the PVAB improves correct pacemaker function by avoiding false positive MS and improves reliability of MS counters.

P1053 More of intrinsic ventricular activation with an improved new pacemaker algorithm: search AV plus

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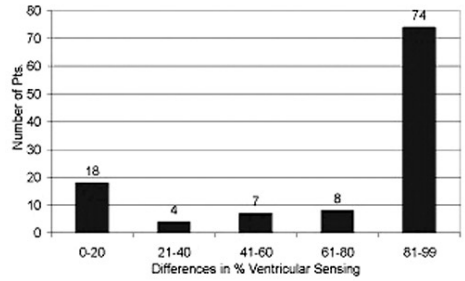
Preservation of intrinsic ventricular activation is preferable in pacemaker patients (pts) whenever possible. A new algorithm Search AV+ (SAV+), incorporated in Medtronic EnPulseTM series pacemakers offers the capability to search out for longer AV intervals (nominaly 320 ms) in pts with intermittent or intact AV conduction.
The objective of this prospective, multi-center, non-randomized clinical trial was to compare the percent ventricular sensing in pts with intact AV conduction with both SAV+ ON and SAV+ OFF.
Methods: The percent ventricular sensing with SAV+ ON and what it would have been if SAV+ had been OFF was evaluated in 194 DDD/R indicated pts via device diagnostics. The required SAV+ programming was: PAV 150 ms, SAV 120 ms, maximal increase to AV 170 ms. The SAV+ feature automatically suspended after approximately one week when no intrinsic conduction was found. The patient cohort was defined by the clinician assessment of 1:1 AV conduction via a test performed at the 2-week follow-up (f/u) visit.
Results: At the one-month f/u visit SAV+ remained ON for 100 (91%) of 111 pts with intact AV conduction. The mean percent ventricular sensing for SAV+ ON was 76.3% versus SAV+ OFF 2.8% (mean difference 73.5%, median 93.5%). The frequency distribution of the differences in percent ventricular sensing in pts with intact AV conduction is presented in the figure. SAV+ was automatically disabled in 53/83 patients without 1:1 AV conduction.In the remaining 30 pts, the mean

percent ventricular sensing was SAV+ ON = 54.1% vs. SAV+ OFF = 9.4% (mean difference of 44.7%, median 52.6%).



Conclusion: Search AV + algorithm in new EnPulse series Medtronic pacemakers substantially increases intrinsic ventricular activation and decreases the amount of unnecessary pacing.

P1054 Impact of atrial rhythm diagnostics on clinical managment: final results

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Purpose: The purpose of this multicenter registry was to investigate the impact of device diagnostics on the clinical management of patients with atrial tachyarrhythmias (AA) utilizing the Vitatron Selection AFm, a bradycardia device with sophisticated AA monitoring features.
Methods: Information on medication and device programming changes was collected at pacemaker follow-up visits. Physicians identified which changes were based directly upon the information provided in the atrial diagnostics.
Results: 282 patients (pts) were enrolled (54% female; mean age 75 $\pm$ 10 years). 269 pts had at least one follow-up with a mean follow-up of 493 days $\pm$ 252 (1 to 820) days. 195 (72%) of the patients had at least one follow-up with documented AA episodes. 194 (72%) had at least one follow-up without documented AA episodes. The AA group and No AA groups are not mutually exclusive.
Physicians identified the device atrial rhythm diagnostic information as the impetus to make the therapy changes described in the table below.
The most common pharmacological changes to treat patients who presented with AAs at follow-up were related to rate and rhythm control; the most common device programming changes were to the Lower Rate and Atrial Sensing settings.

Diagnostic Directed Therapy Changes

	Rate Control	Rhythm Control	Warfarin	Device	Total Patients with Changes
Follow-ups with AAs N=195	20% (37/195)	23% (45/195)	7% (14/195)	24% (47/195)	43%) (84/195)
Follow-ups without AAs N=194	2% (4/194)	3% (5/194)	4% (7/194)	14% (28/194)	21% (40/194)

Percentage (proportion) of patients with at least one diagnostic directed therapy change. Patients could have more than one diagnostic directed therapy change at a single visit.

Conclusion: In 41% (110/269) of all patients with at least one follow-up, and in 43% (84/195) of patients with documented AAs at follow-up, physicians utilized the atrial diagnostics available in the Selection AFm to guide therapy decisions related to ventricular rate control, sinus rhythm maintenance, anti-coagulation therapy, and device programming.

P1055 Improved detection of wide QRS for VT/SVT differentiation by the implantable cardioverter-defibrillator using leadless intrathoracic electrocardiogram

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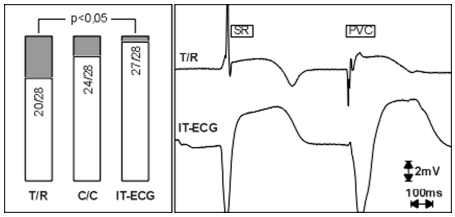
Measurement of increased QRS-width (QRSW) is an additional tool for VT/SVT differentiation in single-chamber ICDs. QRSW can be assessed from either tip to ring (T/R) or coil to active can (C/C). However, if the axis of the VT is orthogonal to T/R or C/C no increase in QRSW can be found. We recently demonstrated that using the two ICD-coils and the ICD-can for ECG derivation provides three additional intrathoracic ECG leads (IT-ECG) with similar axis as the surface leads I, II and III.
Purpose: Aim of this study was compare T/R, C/C and IT-ECG for detection of increased QRSW caused by premature ventricular complexes (PVC).
Methods: During 33 implantations of single-lead ICDs surface ECG, IT-ECG an T/R were digitally (500Hz, 12bit) recorded. Screening for PVCs was performed using the surface ECG leads. An increase in QRSW was determined for T/R, C/C and IT-ECG by comparing the PVC to the preceding sinus rhythm (SR) beat (right figure).
Results: Spontaneous PVCs were found in 18/33 pts. presenting with 28 different PVC morphologies. QRSW of the PVC was different from QRSW in SR in T/R, C/C and IT-ECG (each $p<0.001$). Mean QRSW(SR) was in T/R: 58$\pm$14ms; in C/C: 112$\pm$21ms, IT_ECG: 115$\pm$21ms (ANOVA: $p<0.001$). Mean QRSW (PVC) was T/R: 82$\pm$25ms; C/C: 164$\pm$24ms; IT-ECG: 17$\pm$25ms (ANOVA: $p<0.001$)
An increase of QRSW(PVC) of more than 20% compared to QRSW(SR) was detected in 20/28 (71%) of cases using T/R, in 24/28 (86%) using C/C and in 27/28 (96%) using IT-ECG (T/R vs. IT-ECG: $p<0.05$; C/C vs. IT-ECG: p=n.s.)



PVC shown by IT-ECG and T/R (right).

Conclusions: The intrathoracic IT-ECG provides a higher sensitivity than tip/ring for the detection of increased QRS-width of PVCs. This the IT-ECG may enhance the differentiation of SVT and VT by the QRS-width criterion.

P1056 Intracardiac impedance in biventricular electrode configuration for left ventricular volume monitoring

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Purpose: Biventricular pacing therapy plays an increasing role in the improvement of the hemodynamic state in patients suffering from chronic heart failure and conduction disturbances. The biventricular pacing electrode configuration can also be used for measuring intracardiac impedance across the left ventricle. The feasibility of determining left ventricular (LV) stroke volume and end diastolic volume changes by biventricular impedance measurements with an implantable device was investigated in an in vivo dog model. The biventricular impedance measurements were compared to right ventricular (RV)-only impedance measurement.
Methods: VVI pacing at several rates, as well as isoproterenol infusion with different dosages, was applied to alter the hemodynamic state in 6 anesthetized mongrel dogs. The impedance, the aortic blood flow measured by a transit-time flow meter, the LV pressure, the ECG and the IEGM signals were recorded during the interventions. Impedance was measured both in biventricular configuration, i.e. between RV endocardial and LV epicardial pacemaker leads, and in RV configuration, i.e. between several electrodes placed on one RV catheter. The measurements were performed after thoracotomy and AV nodal ablation. The stroke impedance (SZ), i.e., the difference between the end-systolic and end-diastolic impedance, and the end diastolic impedance (EDZ) were correlated with the LV stroke volume (LVSV), that was computed from the aortic flow integral.
Results: A significant decrease of the LVSV with increasing pacing rate was observed for all dogs (reduction to 67$\pm$11% of the LVSV at the lowest rate). The impedance measurements using only RV electrodes did not show a significant correlation with LVSV. When measuring impedance in biventricular configuration, however, the SZ showed a strong correlation with LVSV (mean r = 0.9, $p<0.001$), and was reduced to 70$\pm$20% during pacing. For the correlation EDZ vs. SV a mean r value of -0.89 was found in the same setups. Similar results were obtained during the injection of the positive inotropic drug. The LVSV increased with increasing drug dosage (increase to 189$\pm$14%). The SZ was increased to 192$\pm$19%, and there was a strong correlation between SZ and LVSV (mean r = 0.97, $p<0.001$).
Conclusions: This animal study confirms the feasibility of monitoring the LVSV and the end-diastolic LV volume by measuring the intracardiac impedance in biventricular configuration. This opens the possibility for continuous hemodynamic monitoring by implantable biventricular pacemakers and ICDs.

P1057 Home monitoring in implantable cardioverter-defibrillator therapy improves patient surveillance

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Background: Follow-up of implantable cardioverter defibrillator (ICD) patients is dependent on, and mostly restricted to regular follow-up visits at 3-months intervals. A disadvantage of these long intervals can be a delay in awareness of changes in the clinical status. The incorporation of long-range transmission capa-

bilities into ICD's (Home monitoring) may overcome this disadvantage and allows early intervention
Objectives: To study the diagnostic power and potential advantages of telemetrically transmitted data.
Methods: All patients received a single lead ICD (Belos VRT, Biotronik, Berlin, Germany)with long-distance telemetry and were included in a multi-center study. This ICD is capable of periodically transmitting therapy and status data to a dedicated patient device and then to a service center. The service center decodes the data and sends a report at specified time intervals to the physician.
Results: Up to now, 19 patients (age 61.5 SD 13 years, 4 females) have been included. Mean follow-up is 130.6 + 96 days. In 2 patients 4 asymptomatic VTs were detected in all of which ATP was successful. In one patient a rapid VT was detected in the programmed VF zone, for which a successful shock was delivered. In one patient the diagnosis of lead fracture due to Twiddler's syndrome was made. Acute impedance rise was preceded by an unexplained decrease and was followed by an urgent check-up and replacement of the lead.
Conclusions: These results demonstrate clearly the potential of the home monitoring system incorporated in ICDs. It provides the possibility for prompt reaction in response to cardiac events and system failure, especially in symptom free patients, who are not pacemaker dependent, but might rely on the integrity of an ICD system.

P1058 Home monitoring improves detection of atrial tachyarrhythmia

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Introduction: There is increasing evidence for equivalence of rate and rhythm control in pacemaker patients with paroxysmal atrial fibrillation (AF). Nevertheless, rapid reaction to the onset of AF remains a topic of high interest due to the necessity of appropriate anticoagulation. Furthermore, AF is an independent risk factor for stroke, progression of heart failure and morbidity of patients of higher age.
Methods: The European multicenter clinical trial "Home Monitoring for the management of patients with atrial tachyarrhythmia (HomePAT)" investigates the benefit of permanent remote monitoring of pacemaker patients implanted for sinus node disease. The primary endpoint refers to the optimisation of pacing and medication therapy in paroxysmal AF. The study is designed as a prospective randomised single-blinded parallel group trial. Patients (pts) who receive dual chamber rate adaptive Home Monitoring (HM) pacemakers are enrolled and followed for 6 months. Rapid detection of atrial tachyarrhythmia is enabled by daily HM transmissions of mode switch counters, which are presented to the physician for one half of the patients ("report group") and are hidden for the other half ("control group"). We present a first analysis on the feasibility of arrhythmia detection via HM.
Results: Currently, 59 pts (36 male; mean age 68.8 $\pm$ 10.1 years) have been enrolled and followed for 160 $\pm$ 59 days. Of these, 28 had presented with paroxysmal atrial tachyarrhythmia (AT) already before implant. During follow-up, 17 pts (28.8%) showed mode switch episodes longer than 12 hours in the HM counters on at least one day: 10 pts from the report group, 7 from the control group. Six of the 10 report group pts had the AT documented by standard means, too, thereof 3 without previous AT episodes. Three of the 7 pts from the control group had an additional AT documentation by standard means during routine follow-up, too, one of these without previous notice of AT. There is no significant difference between the average of the mean episode duration in pts with and without ATs previous to implant (9.2 h $\pm$ 3.1 h vs. 11.2 h $\pm$ 6.6 h), but a tendency towards reduced duration of AT episodes in pts missing AT documentation via standard means (12.1 h $\pm$ 7.7 h vs. 7.8 h $\pm$ 3.1 h).
Conclusions: First results indicate that home monitoring has the potential to improve the detection of paroxysmal episodes of atrial tachyarrhythmia. Atrial antiarrhythmic therapy might benefit from the seamless remote monitoring enabling rapid information about the patient's atrial rhythm, irrespective of episode length or symptoms.

P1059 Time duration in an implantable cardioverter-defibrillator-based automatic transtelephonic monitoring system between a ventricular tachyarrhythmia and physician notification

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Background: An issue of automatic transtelephonic monitoring in patients (pts) with implantable cardioverter defibrillators (ICD) is the rapid notification of the attending physician about a ventricular tachyarrhythmia. The aim of the present analysis was to assess in ICD pts the time duration between the occurrence of ventricular tachyarrhythmias and the availability of the corresponding ICD data to the attending physician.
Methods: The European multi-center study included 220 pts (ejection fraction 40 $\pm$ 15%) with class I ICD indications who received the single (n=201) or dual-chamber (n = 19) ICD Belos VR-T/DR-T (Biotronik). Both ICDs provide the automatic transtelephonic monitoring feature "Home Monitoring": The ICD automatically transmits daily or in case of an arrhythmic event the stored data via a modified mobile phone to an evaluation center which forwards it to the responsible physician. The time duration between an episode detected by the ICD and the corresponding notification of the physician was determined. Pts with frequent wearing of the mobile phone (Group INT) were compared to pts who placed the mobile phone as recommended beside the bed (Group CON). The former group was identified by sending messages arriving outside the standard periodic time schedule.
Results: During 274 $\pm$ 117 days follow-up, 90 (41%) pts had 1170 automatic home monitoring transmissions. Group INT consisted of 37 and Group CON of 53 pts. Clinical demographics of the two groups were not significant different from each other. Group INT had 921 and Group CON 249 transmissions. An immediate successful home monitoring transmission occurred for 527 of the 921 (57%) transmissions in Group INT and for 28 of the 249 (11%) transmissions in Group CON ($p < 0.05$). The time delay for the remaining transmissions was in Group INT $<$ 12 hours for 171 messages (19%), between 12 and 24 hours for 175 (19%), and $>$ 24 hours for 48 (5%) event messages. In Group CON the time delay for the remaining messages was $<$ 12 hours for 14 (6%), between 12 and 24 hours for 159 (64%), $>$ 24 hours for 48 (19%) event messages.
Conclusions: The data transmission with the device-based automatic transtelephonic monitoring system worked correctly. In pts who worn the mobile phone, 57% of the transmissions were immediately available for the attending physician, 95% within 24 hours. In pts who placed the mobile phone beside the bed 81% transmissions were send within 24 hours. The continuous wearing of the mobile phone can help to improve the arrhythmic monitoring in ICD pts with an automatic transtelephonic monitoring system.

P1060 Individualization of follow-up in implantable cardioverter-defibrillator patients with the help of automatic remote implantable cardioverter-defibrillator monitoring

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Integration of modern telecommunication technology in implantable cardioverter defibrillators (ICD) allows an automatic transtelephonic transmission of ICD data to the attending physician ("home monitoring").
Methods: In a European multicenter clinical trial consecutive patients with class I ICD indication received an ICD system with home monitoring (HM) technology (Belos VR-T/DR-T, Biotronik). During a 12-months-follow-up data were collected from regular clinical examinations with ambulatory ICD interrogation after 3, 6, 9 and 12 months as well as from daily and event-related automatic data transmission.
Results: A HM- ICD was implanted in 253 patients (pt). Follow-up data are yet available for analysis from 220 pt (32 female, mean age $\pm$ SD 62.3 $\pm$ 11.6 years). Nineteen pt had a dual chamber ICD, 201 pt a single chamber device. Mean follow-up was 274$\pm$117 days. The index arrhythmia was a documented ventricular tachycardia (VT) in 131 pt, a documented ventricular fibrillation (VF) in 69 pt, and others in 20 pt. During follow-up, arrhythmic events were detected in 79 pts. 47 pt had episodes defined as slow VT, 16 pt fast VT episodes, and 51 pt episodes defined as VF. In 72 pts ICD therapy was initiated. That was antitachycardia pacing (ATP) in 40 pt and shock therapy in 62 pt. The success rate for ATP was 67.3% and for shock therapy 88.1%. Daily and event related HM data revealed recurrent slow VT in 36 pt, inadequate episode detection due to sinus tachycardia in 6 pt, inadequate episode detection due to atrial arrhythmias in 12 pt and proarrhythmic effects of drug treatment in 1 pt. In all these pt, an individualized treatment was initiated by the attending physician (reprogramming in 40 pt, catheter ablation in 1 pt, alteration of drug treatment in 39 pt). The effects of therapeutic measures could be controlled by use of consecutive HM data transmissions.
Conclusion: In ICD patients, a regular and event-related automatic, transtelephonic ICD data transmission results in an immediate detection of device defined arrhythmic events. This facilitates an optimized and individualized antiarrhythmic therapy and allows a monitoring of treatment efficacy.

P1061 Telemetric homemonitoring for patients with implantable defibrillators: experiences during long-term follow-up

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Implantable defibrillators (ICD) are the therapy of first choice for patients (pts.) with survived sudden cardiac death (SCD) or sustained symptomatic ventricular tachyarrhythmias (VT). Studies as i.e. MADIT II initiated a further increase of ICD-implantations. Technical progress offers close follow up using long distance telemetry including information regarding systemstatus, episode and therapy counts via homemonitoring (HM). Since May 2002 91 pts. (age 68±15.7 years; EF 33±16.9%; CAD: n=68, dilative CM: n=19, hypertrophic CM: n=2, arrhythmogenic reght ventricular CM: n=2) received an ICD with HM (Biotronik, Germany: single chamber ICD: n=81, Belos or Lexos VR-T; dual chamber ICD: n=10, Belos DR-T). ICD-indications were SCD in 28 pts., sustained VT in 27, syncopes and inducible VT in 15 and prophylactic in 21 pts. Routine follow up (FU) was scheduled after 4 weeks, then every 3 months (mths.). HM was performed every 2 weeks and event triggered, i.e. episode detected, therapy delivered, etc., including information regarding battery status, lead- and shockimpedance, episodes (VT/VF) and therapy count (overdrive stimulation (ATP)/shock). Failure of transmission occurred in 13 pts. due to cellular net problems. Evaluation was carried out via internet. During a period of 3 to 22 mths. 5 pts. were admitted to the hospital in advance: 2 pts. with recurrent sustained VT, 3 pts. with inadequat frequent ATP due to atrial fibrillation. Data at 12 mths. presented in the table show no significant differences between FU and HM.

Data obtained at 12 mths.: HM vs. FU

n=82	HM	FU
battery [V]	6.19±0.05	6.19±0.03
leadimpedance [Ohm]	561.3±123.3	547±134.9
shockimpedance [Ohm]	57.1±9.9	56.7±11.2
VT/VF [n]	327/109	327/109
ATP/shock [n]	764/102	764/102

Conclusion: HM is feasible and save to perform close follow up regarding systemstatus, episode and therapy count. Still, 1, 3 mths. and yearly FU post implant are necessary to measure threshold and sensing values which can not be obtained by HM, yet. Decrease of out patient clinic visits, hospital stays and increase of patient comfort still offering close surveillance can be achieved via HM.

P1062 Diagnosis of syncope with the implantable loop recorder: clinical value of automatic recording features

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Background: The implantable loop recorder (ILR) is an effective tool in evaluating patients (pts) with unexplained syncope. Current ILR-devices are equipped not only with patient-activated recording of electrocardiograms (ECG) but also with automatic activation capabilities. However, the clinical value of these features critically depends on the quality of ECG recognition.
Method: An ILR was implanted in 78 conscutive pts (age: 19-85 years) with recurrent unexplained syncope. 64 pts received a device with automatic recording features (Reveal Plus 9526, Medtronic Inc.). Implant sites were chosen with respect to appropriate signal quality and stability. Auto activation parameters were set to the storage of up to 5 episodes (bradycardia <40/min; asystole >3 sec; tachycardia >165/min). Follow up was performed until arrhythmias were proven or excluded as cause of syncope or till battery depletion. A maximum of 5 episodes per patient was included into final analysis.
Results: During a mean follow up of 7 months (1-18 months) 268 automatically recorded episodes were analysed. In 216/268 episodes (81%) activation was inappropriate due to oversensing or undersensing phenomena. In 43 episodes (16%) an intermittent total loss of contact was responsible for inappropriate activation. 2 automatic recordings (1%) occurred parallel to manual activation by the patient. Arrhythmia as cause of syncope was neither proven nor excluded with automatic activation alone.
Conclusion: In clinical practice, automatic recording features are not useful due to significant sensing problems. Future devices should be equipped with more advanced sensing algorithms to support diagnosis even in pts who fail to activate the ILR manually.

P1063 Syncopal recurrences after implantation of loop recorder: absence of predictors and role of "non-diagnostic" findings at preimplantation work-up

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Implantable loop recorder (ILR) is a new tool in the diagnostic management of patients (pts) with syncope of unknown origin. However, one of its limitatins is that the recurrence rate after its implantation is low when compared with previous syncopal episodes.
We analyzed the recurrence rate, the possible predictors of recurrences as well as the findings in 45 consecutive pts (26 females, age 60.0 ± 18.2; 17-86) in which an ILR was implanted because of syncope of unknown origin between jaunary 2001 and january 2004.
The median number of previous syncopal episodes was 3 (1 - >25). Structural heart disease was present in 3 pts (2 ischemic heart disease, 1 rigth ventricular cardiomyopathy), and bundle branch block in 4 pts.
Head up tilt test (HUT) was performed in 41 pts, and was positive in 14. Electrophysiological study (EPS) was performed in 16 pts: non sustained ventricular tachyardia (NSVT) was induced in 1 pt, and no other abnormalities were found in the remaining. Holter monitoring was performed in 42 pts: in 1 pt an assymptomatic NSVT was recorded. ATP test was performed in 13 pts: 1 pt showed an asystolic pause of 7.2 sec., and it was normal in the remaining. Carotid sinus massage (CSM) was performed in 26: 1 showed an assymptomatic pause of 4.9 sec.
At follow-up 13 (29%) pts had syncopal recurrences with activation of ILR. 3 pts showed transient A-V block: 1 who had bundle branch block, 1 who had a positive HUT with transient A-V block and 1 with an assymptomatic asystolic response to CSM. 2 pts showed an asystolic pause: 1 with negative and 1 with positive HUT. 1 pt showed NSVT during syncopal recurrence (no structural heart disease, normal EPS, and assymptomatic NSVT recorded at Holter monitoring). The remaning patients were in sinus rhythm durnig syncopal recurrence. One addittional pt showed assymptomatic episodes of parosyxmal atrial fibrillation that terminated with long asystolic pauses (up to 4 sec.).
We did not find any predictor of recurrences.
These data confirm that the reccurrence rate of syncope decreases after implantation of ILR, limiting its diagnostic contribution. Prospective studies are needed to identify those patients more likely to have recurrences after implantation, and thus to benefeit more of ILR. However it must be stressed that the diagnostic contribution in those patients who have recurrences is high, not only in recognizing or ruling out an arrhythmic origin of syncope, but also in confirmig the causal relationship of some abnormal findings that are found with different tests, but that are not considered fully diagnostic.

P1064 Prospective and randomized study of patients with syncope and bundle branch block. Analysis of the usefulness of implantable Holter versus pacemaker

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Background: In patients with bundle branch block and syncope, the bradiarrhythmia may not always be the etiology of the syncope. There are scarce data about the approach and cost-efficacy of the treatment strategy: empiric pacing versus Holter implantable loop in these patients.
Material and Methods: 47 patients were analysed. 15 were excluded due to pathological findings during the study. 32 patients were randomized after the history, examination and complementary investigations, including electrophysiological study were not diagnostic of the etiology of syncope.
Results: 15 patients were randomized to pacemaker (Group I) and 17 to Holter Reveal (Group II). During a mean follow-up of 9 ± 6 months, there was no mortality. In the Group I only 1 patient had a recurrence, of vasovagal etiology. In the second group, there were 6 recurrences, 2 due to atrio-ventricular block, 1 due to ventricular tachycardia, and 3 without alterations in the stored electrogram.
Conclusions: In patients with intraventricular conduction defects and syncope of unknown origin, the use of Holter Reveal allow us to reduce the pacemaker implant in 88% of the cases.

P1065 Arrhythmias in pacemaker patients. Diagnostic value of stored electrograms

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Purpose: Stored electrograms (EGM) commonly used in ICDs now have been incorporated in new generations of pacemakers. The EGM storage help us to detect and verify arrhythmias occurring in pacemaker patients. In our study we retrieved stored EGMs from pacemaker patients for arrhythmia detection and confirmation.
Methods: We studied 23 patients (18 male), mean age 60 ± 7 years with pacemaker in whom EGMs had been recorded 3 months after implantation. The pacemakers were: DDDR n=21, VDD n=1, 1 VVIR n=1. The indication for implantation was: atrioventricular block n=14, sick sinus syndrome n=5, slow atrial fibrillation n=1 and carotid sinus syndrome n=3. Triggers for EGM recording were ventricular tachycardia (VT) or atrial tachycardia (AT) with 8 beats >150 bpm, sudden bradycardia response (SBR) with rate drop > 25 bpm and pacemaker mediated tachycardia (PMT).
Results: We retrieved and analyzed 79 EGMs: 18 VT episodes (22.8%), 31 AT episodes (39.2%), 18 SBR episodes (22.8%) and 12 PMT (15.2%). VT was confirmed in 13 (71.2%) out of 18 VT episodes, while 5 (27,8%) were false posi-

tive, 3 (16.7%) due to ventricular oversensing (noise) and 2 (11.1%) due to rapid atrial fibrillation. AT was confirmed in 14 (45.2%) out of 31 AT episodes, while 17 (54.8%) were false positive due to atrial ovesensing (noise). SBR was confirmed in 16 (88.9%) out of 18 SBR episodes, while 2 (11.1%) were false positive due to atrial ovesensing. PMT was confirmed in 10 (83.3%) out of 12 PMT episodes, while 2 (16.7%) were false positive due to sinus tachycardia. In total, 53 EGMs (67%) confirmed the detected arrhythmic event while 19 (24%) were false positive due to oversensing.
Conclusion: Stored EGMs in pacemaker patients were diagnostic for arrhythmias in 67% and false positive in 33%. The stored EGMs are useful tools for arrhyhmia detection and confirmation. Thus, they are very helpful for the evaluation of the appropriate function and programming of the pacemaker.

P1066 How long should be maintained cardiac remote telemetry?

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Background: Cardiac remote telemetry is useful for the management of patients (PP) at medium risk for developing potentially lethal arrhythmias admitted at hospital. However, no information exists concerning how long telemetry should be maintained before discarding events. In our institution, a 16-channel telemetry is controlled 24 hours a day by trained nurse.
Objectives The aim of this study was to analyze the incidence and time to potentially lethal arrhythmias since the onset of monitorization in medium-risk patients.
Methods: We included PP admitted at the hospital with the diagnosis of syncope, chest pain, sick sinus suspicion, palpitations or ECG abnormalities. We divided potentially lethal arrhythmias in ventricular tachycardia/ventricular fibrillation; extreme bradycardia (less than 30 beats per minute)/pauses longer than 5 seconds and asymptomatic ST segment persistent elevation. Data are expressed as mean $\pm$ SD (range). Differences between groups were compared using a Mann-Whitney test for non paired data.
Results: A total of 1345 cardiac telemetries TL were registered during 1 year period. The incidence of potentially lethal arrhythmias, requiring aggressive manage was 2% (27/1350). Distribution of potentially lethal arrhythmias by groups was: ventricular tachycardia/ventricular fibrillation: 6 PP (22.2%); extreme bradycardia/pauses longer than 5 seconds: 19 PP (70.4%) and asymptomatic ST segment persistent elevation: 2 PP (7.4%). There were no deaths during hospitalization. Mean time to potentially lethal arrhythmias was 2.1$\pm$2.2 days(0.5-0). Syncope was the most frequent indication for cardiac telemetry (27%). In syncope guided telemetry patients, the incidence of potentially lethal arrhythmias was 3.4%, with a mean time to event of 1.7$\pm$1.4 days (0.5-5).
Conclusions: Telemetry is very useful in the management of medium-risk patients admitted at hospital. In our experience, in PP admitted at hospital with the diagnosis of syncope, all potentially lethal arrhythmias occurred in the first 5 days of cardiac telemetry monitoring, suggesting that longer period is not required.

P1067 Development of a rechargeable implantable cardioverter-defibrillator: first results of in-vitro and in-vivo measurements

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Present ICD-systems use a conventional dry battery as energy source. Therefore most often life span of this system is determined by the capacity of the battery, which amounts depending upon demand 3-5 years. If the battery is exhausted, the entire device must be exchanged. An expensive operation with many physical and psychological risks and side effects for the patient is the consequence, which can significantly affect the quality of life. If the energy source in these systems would be rechargeable, most of these exchange operations could be omitted.
Methods: The project deals with recharging of batteries through the intact skin via a magnetic field. The aim of the study was to optimize the energy transfer through the skin into the ICD. We started with in-vitro-measurements to identify the appropriate frequency of the magnetic field. An automatic compensation of variable boundary conditions (e.g. tissue thickness) was tested. The Ventak Prizm II (Guidant, MN) widened with a receiving coil for energy transmission and a charging electronic was used as prototype. Thereafter an acute animal study (sheep) was performed to test the functionality of this modified ICD during the charging process.
Results: A large coil around the can for energy receiving was identified having the best transmitting results. The higher the field frequency the higher the absorption of the housing of the ICD that could be estimated at 16dB at 100 kHz. The optimum frequency for energy transmission is 100 kHz. There was no significant heating of tissue between both coils. Detection and therapy of supraventricular and ventricular brady- and tachyarrhythmias was feasible. No malfunction of the ICD was found.
Conclusion: Using optimized parameters, transmission of energy intended to recharge batteries of ICDs is possible without unacceptable heating of the surrounding tissue or impairment of the ICD function in the acute sheep experiment.

P1068 A preserved autonomic balance identifies among MADIT II patients a subgroup at low risk for implantable cardioverter-defibrillator discharge

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Introduction: The practical implications of the results of the MADIT II trial have raised concerns, in the US and particularly in Europe where the National Health Services are largely supposed to bear the costs of implanting an unprecedented number of implantable cardioverter defibrillators (ICDs). Indeed, by loosening the selectivity of the criteria to reduced left ventricular function only could result in many patients receiving an ICD without benefit. The identification of patients less likely to benefit from ICD implantation is one reasonable way to provide substantial cost-savings with small losses in population life expectancy.
Methods and results: The ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study showed that profound alterations in the autonomic balance, identified by baroreflex sensitivity (BRS) $<$ 3 ms/mmHg and time domain heart rate variability (SDNN) $<$ 70 ms, were significantly and independently related to cardiac mortality. We have now reanalyzed our database and we have tested the hypothesis that in patients with a left ventricular ejection fraction (LVEF) $<$ 30% (n =70, mean age 60 $\pm$ 9 years, LVEF 25 $\pm$ 4%) a well preserved autonomic balance (BRS $>$ 6 ms/mmHg, SDNN $>$ 105 ms) would predict a low rate of fatal cardiac events. During a mean follow-up of 24 months cardiac death occurred in 11 patients (16%). The distribution of deaths according to the different levels of autonomic impairment is shown in Table 1.

Table 1

	BRS $<$3	BRS 3-6	BRS $>$6	SDNN $<$70	SDNN 70-105	SDNN $>$105
Alive (N=59)	20	25	14	23	23	13
Deceased (N=11)	8	2	1	7	4	0

Conclusions: The use of autonomic markers might allow a reduction of approximately 20% (15/70 for BRS and 13/70 for SDNN) in the number of ICDs used for MADIT II-like patients. This retrospective analysis provides a useful working hypothesis and suggests the value, for patients as well for society, of quantifying prospectively the role of non-invasive autonomic parameters for the identifications of patients with depressed LVEF unlikely to benefit substantially from an ICD.

P1069 Arrhythmic events in LQTS patients with implantable cardioverter defibrillators

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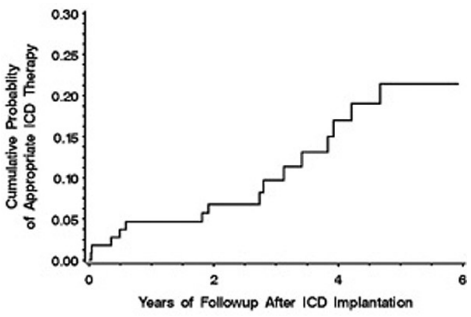
Background: Implantable cardioverter defibrillators (ICDs) are increasingly used in high-risk long QT syndrome (LQTS) patients. The aim of this study was to evaluate a long-term utilization of ICDs for terminating episodes of ventricular tachyarrhythmias in LQTS patients.
Methods and Results: Among 125 LQTS patients (101 females and 24 males), enrolled in a prospective Rochester ICD Registry, 76% of patients presented with syncope, 40% with aborted cardiac arrest, 27% hadrecurrent syncope despite beta-blockers, and 35% had sudden death in family. Data regarding appropriate and inappropriate ICD therapy were acquired during a mean follow-up of 55 months after implantation date. Figure shows a 20% cumulative probability of first appropriate ICD therapy during a 5-year period. There was one death in studied patients. Eighteen patients (14%) had at least one appropriate therapy with 6 of them having 1 therapy, 7 patients had 2-4 therapies, and 5 patients had 5 or more therapies for torsade de pointes VT or VF. Appropriate ICD therapies occurred in majority of patients despite beta-blockers. There were 3 patients with arrhythmia



Appropriate ICD therapy in LQTS patients.

storm (5, 14, and 38 shocks, respectively) successfuly treated with ICD. Inappropriate therapy was delivered in 9 (7%) patients due to inappropriate sensing or ICD/lead malfunction. Multivariate Cox analysis revealed that QTc>500 ms was the only factor associated with increased risk of arrhythmic events requiring ICD therapy (HR=3.55; p<0.05).
Conclusions: High-risk LQTS patients have a 4-5% annual rate of appropriate ICD therapy for ventricular tachyarrhythmias justifying utilization of this therapeutic modality. Longer QTc was the only clinical factor predicting arrhythmic events requiring ICD therapy in studied patients.

P1070 High incidence of adequate implantable cardioverter-defibrillator interventions in patients with hypertrophic cardiomyopathy implanted for primary prevention

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Introduction: Risk stratification of patients (pts.) with hypertrophic cardiomyopathy (HCM) and selection of candidates for ICD implantation may be difficult. A combined approach including non-sustained ventricular tachycardia (nsVT) on Holter, excessive left ventricular hypertrophy (LVH >30 mm), abnormal blood pressure response (BPR) during exercise, a family history of sudden death (SD), and recurrent syncope has been suggested to identify high risk pts. ICD implantation for primary SD prevention has been proposed if more than one of these risk factors (RF) are present.
Methods: In a cohort of appr. 900 HCM pts. 21 pts. with more than one (2-4) RF were identified. Dual chamber ICD implantation with endocardial leads was performed for primary SD prevention, allowing antitachycardia and antibradycardia pacing as well as storage of intracardiac electrograms (IEGs). We analyzed these IEGs to assess the predictive value of the proposed risk stratification algorithm.
Results: Mean age of our pts. (17 men, 4 women) was 41±14 (15-65) years, NYHA class was 2.0±0.8. Left ventricular outflow obstruction was present in 14 pts., 7 pts. including one after septal ablation were non-obstructive. A family history of SD was present in 9 pts., nsVT in 15, syncope in 10, excessive LVH in 6, and abnormal BPR in 4 cases. All pts. were on drug treatment (amiodarone in one, verapamil in two, and beta-blockers in 18 pts.). Electrophysiologic testing was performed in 20 pts., and 11 (52%) of these had inducible VT/VF.
During a mean follow up of 15 (3-29) months, 4 adequate ICD discharges in 3 pts. were documented. One pt. with 2 RF including LVH of 44 mm had 2 episodes of VF, two RF were present in other 2 pts with one event either. ICD related complications occurred in 2 pts. (inadequate ICD interventions because of sinus tachycardia, and lead malfunction with T wave oversensing in one pt. each).
Conclusions: The incidence of appropriate ICD discharges in our cohort of HCM patients considered to be at high risk and hence receiving ICD implantation for primary SD prevention was 3%/pt.-year, supporting the proposed risk stratification. ICD implantation should be strongly considered in this group.

P1071 Prevention of implantable-defibrillator shocks by cognitive behavioral therapy: a randomized controlled trial

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Background: Patients with implantable cardioverter-defibrillators (ICD) often receive adjunctive therapy to prevent frequent shocks. Although psychological stress is known to favor ventricular arrhythmic events, there is no evidence that stress management decreases ventricular electrical instability in ICD patients.
Objective: To investigate whether cognitive behavioral therapy (CBT) results in a decrease of arrhythmic events requiring ICD intervention.
Methods: Seventy of 213 consecutive ICD patients (59±10 years, 64 males) were randomly assigned to CBT (n=35) or conventional medical care (n=35). Patients who received CBT were offered 2 monthly sessions for 3 months. Psychological well-being and quality of life were assessed at baseline, 3 months and one year. Heart rate variability (HRV) was analyzed on serial 24-hours Holter recordings. The primary outcome was ICD therapy. Secondary outcomes were HRV and psychological status.
Results: Analysis was limited to patients without antiarrhythmic drugs. At 3 months, there were 15 patients in each group. None of the patients in the CBT group had experienced arrhythmic events requiring ICD intervention, as compared to 4 in the control arm (p<0.05). At 3 months, anxiety (based on the Hamilton Anxiety Rating Scale [HAM-A]) was significantly less in the CBT group as compared to the control group (HAM-A score 3.23 + 0.88 vs 6.94 + 0.8, P<0.01). At 12 months, although anxiety was still significantly lower in the CBT group (2.6 ± 1.5 versus 9.0 ± 4.3) there was no difference in the number of arrhythmic events requiring therapy between groups (2 of 10 versus 3 of 10 patients respectively). Quality of life variables did not change throughout follow-up in both groups. Among HRV indexes, only PNN 50 increased significantly in the active treatment group as compared to the control group.
Conclusion: By decreasing anxiety and possibly improving sympatho-vagal balance, cognitive behavior therapy may decrease the propensity to ventricular arrhythmias, and thus be be a potentially useful adjunct in the management of ICD patients. These effects appear however to be limited in time.

P1072 Clinical course and implantable cardioverter-defibrillator therapy in women enrolled in MADIT II

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Background: MADIT II demonstrated that ICD therapy contributes to a significant 31% reduction in the risk of mortality in postinfarction patients with EF<31%. There are limited data regarding ICD therapy in postinfarction women. The aim of this study was to evaluate the risk of cardiac events and effects of ICD therapy in women as compared to men enrolled in MADIT II.
Methods and Results: Among 1,232 patients enrolled in MADIT II, there were 192 (16%) females and 1,040 (84%) males. Women were under-represented, assuming that they usually account for 25% of patient population in most postinfarction studies. When compared to males, despite similar age distributions, females had more frequently NYHA >I (70 vs 63%; p=0.067), more frequent history of hypertension (60% vs 52%; p=0.047), less frequent CABG surgery (42% vs. 60%; p<0.001), more frequent diabetes (42% vs. 34%) and more frequent LBBB (25% vs. 17%; p=0.011). A 2-year cumulative mortality estimated from Kaplan-Meier curves in patients randomized to conventional therapy was somewhat higher in females than in males (30% and 20% respectively, p=0.17), but identical 2-year rates were found in ICD arm patients (16% in each), suggesting a possibly greater ICD benefit in females than in males. Adjusting for relevant clinical covariates and stratifying by enrollment center, the hazard ratio for ICD effect in women was also slightly lower in men (0.54; p=0.100 for women and 0.56; p=0.003 for men) but the difference is not statistically significant (p=0.77). By contrast, the 2-year probability of approrpriate ICD therapy for VT/VF was slightly lower in females than in males (21% and 28%, respectively, p=0.17). Women tended to have a higher risk of hospitalization for CHF than men (30% and 23% in both arms together, p=0.04, but with lesser difference for the endpoint CHF or death).
Conclusions: Postinfarction women with severe left ventricular dysfunction have similar, or possibly higher, risk of death than comparable men, but are underrepresented in the MADIT-II study population. ICD benefit was found to be similar or possibly better in women than in men. Hence, increased effort needs to be made to implant ICDs in eligible women following MADIT II indications.

P1073 Reasons for inappropriate implantable cardioverter-defibrillator therapies: first results of the prospective European EPICENTER registry

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Background: Inappropriate therapy for supraventricular tachycardia (SVT) is one of the most frequent complications of ICD therapy. The aim of this prospective multicenter registry is to investigate sensitivity (SEN) and specificity (SPE) of ICD therapy, and to analyze the reasons for inappropriate therapy in context with individual device programming.
Methods: In this preliminary analysis, 359 stored episodes of 75 patients (61 male, mean age 66±10 years, mean FU 77±69 days) with an EPIC single (79%) or dual (21%) chamber ICD (St. Jude Medical) have been analyzed so far.
Results: All 196 episodes of sustained ventricular tachycardia or fibrillation (VT/VF) were appropriately detected and terminated by the device (SEN 100%). Inappropriate therapies were delivered for 31 of 146 spontaneous SVT episodes (SPE 79%) in 4 patients. Only 1 of 31 inappropriate therapies (3%) was due to a false positive diagnosis of the SVT discriminators. 30 SVT episodes with a mean cycle length of 294 ±32 ms (range 210-320 ms) were detected in the VF zone of the device (cut-off 307±22 ms), in which no SVT discriminators are applied.
Conclusions: SVT discriminators should be enabled even for faster rates to avoid inappropriate therapy for rapid SVT. Therefore the VF zone needs to be programmed to higher cut-off rates (e.g. above 213 bpm) to allow discriminators to withhold inappropriate therapies.

P1074 Is it feasible to implant implantable cardioverter-defibrillators under local anaesthesia even for defibrillation test?

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The aim of this monocentric study was to compare prospectively the feasibility of implantable cardioverter-defibrillator (ICD) implantation under local anaesthesia (LA) versus short general anaesthesia (SGA) for defibrillation test (DT). We implanted ICDs in 124 pts (mean aged 61.4 ±14 years) between October 2002 and November 2003. The pts were randomised in 2 groups. In the LA group, the

implantation was made under local anaesthesia even during DT. DT was made in manual mode with a shock delivered when patient faint. In the SGA group, the implantation was made under local anaesthesia with a short general anaesthesia for DT, done in the automatic mode. Whatever the group was, the choice of FV induction mode (direct or alternating 30Hz or 50 Hz) depended on ICD's manufacturers. No T wave shocks were used in the LA group. We evaluated hemodynamics parameters during implantation (heart rate, arterial oxygen saturation, blood pression), FV induction methods, patient's pain during procedure (visual analogue scale, quality of sleep the night before, anxiety questionnary), economic parameters and complications after implantation. The defibrillation was tested by one shock at 20 J.

Results: 77 patients were included in the LA group and 47 in the SGA group. Concerning general characteristics (age, sex ratio, EF, indication of ICD) there was no difference between the two groups. Anaesthesia type did not influence the results of patients' pain evaluation. Concerning hemodynamic and economic parameters and complications, there were no difference between the two groups. The analyse of the induction's methods showed that direct current was more effective to induce FV than alternating current (30 or 50 Hz) or shock on T wave ($p< 0.05$). However direct current was a little more painfull than alternating current ($p< 0.05$). The FV duration lasted longer in the AL group 16.6 $\pm$ 4.7 seconds than in the SGA group 8.8 $\pm$ 3.7 seconds ($p< 0.05$). The mean number of shocks during procedure was not different between the two groups (1.4 $\pm$ 0.8 group AL versus 1 $\pm$ 0.2 group SGA, ns) but 16 patients needed more than one shock in the AL group versus only 2 in the SGA group ($p<0.05$). In 12 patients, a 20 J shock was not able to reduce FV: 11 patients in the AL group and 1 patient in the SGA group ($p< 0.05$). In all these patients, the lead was immediately replaced with a correct DT.

Conclusion: Thus, it is feasible to use local anesthesia for current ICD implants. It avoids general anesthesia with no painfull procedure in the great majority of patients.

P1075 Detection und termination of spontaneous atrial and ventricular tachyarrhythmias in implantable cardioverter-defibrillator patients with a history of atrial tachyarrhythmias

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Atrial tachyarrhythmias are a common co-morbidity in patients with an ICD indication. Recently introduced ICD's are equipped to independently detect and treat atrial and ventricular tachyarrhythmias. The purpose of this prospective study was to evaluate the incidence and termination of spontaneous atrial and ventricular tachyarrhythmias in patients with a history of atrial tachyarrhythmias.

Methods and Results: Eighty-nine patients (ejection fraction 45 $\pm$ 6%, 46% coronary heart disease) were included in this study and received the dual chamber ICD VENTAK PRIZM AVT (Guidant). Spontaneous atrial and ventricular tachyarrhythmia were printed and evaluated during an average follow-up period of 272 $\pm$ 72 days utilising the stored intracardiac electrogram function of the device. 19 patients (21%) presented with atrial tachyarrhythmias only, atrial and ventricular tachyarrhythmia were documented in 32 patients (36%) and 18 patients (20%) had only ventricular tachyarrhythmias. Patients with atrial tachyarrhythmias only had a total of 3274 atrial episodes; 2002 terminated spontaneously, 1264 were treated with ATP and 8 with shock therapy. ATP was successful in 735 (58%) of 1264 episodes. Patients with atrial and ventricular tachyarrhythmias had 7277 documented atrial tachyarrhythmias, 5231 terminated spontaneously, 1153 of 2009 were terminated by ATP (57.4%) and 37 by shock therapy (20 patient controlled). Atrial tachyarrhythmias identified as atrial flutter had a higher ATP conversion success rate (66.7%) than episodes defined as atrial fibrillation (26.4%). Patients with ventricular tachyarrhythmias had 667 documented episodes, 208 terminated spontaneously, 229 were terminated by ATP and 230 by shock.

Conclusions: Spontaneous atrial and/or ventricular tachyarrhythmias within the first months after ICD implantation had 77% of the patients with an ICD indication and a history of atrial tachyarrhythmias. ATP therapy terminated 58% of all atrial tachyarrhythmias successfully; ATP therapy could successfully terminate atrial flutter in 66.7% of all documented episodes. The dual chamber ICD detected, classified and terminated all ventricular tacharrhythmias appropriately.

P1076 Incidence and time to the first syncopal recurrence due to arrhythmia after an implantable cardioverter-defibrillator implantation in patients with sustained ventricular tachycardia

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Purpose: Implantation of an ICD is the first line therapy for most patients (p) presenting with syncopal monomorphic ventricular tachycardia (VT). This group of p has a high risk of arrhythmia recurrence requiring ICD therapy and a 6 month period of driving restriction is usually recommended. However, data regarding recurrence rate, mechanisms and time to the first arrhythmic syncope following ICD implantation is limited in this group of p.

Methods: Incidence and causes of syncope recurrence after ICD implantation among p with syncopal VT (Sy-VT, n=26) were compared with those found in p with clinically well tolerated VT (NSy-VT, n=50) in a cohort of p with structural heart disease and an ICD. Mean left ejection fraction was similar in both groups. (Sy-VT:34$\pm$17%; NSy-VT 35$\pm$14%; p=NS) A VT zone with a detection cycle length (CL) >280 ms and two antitachycardia pacing (ATP) schemes were programmed in all p. The first ATP scheme was: 2-3 sequences of burst pacing, 15 beats, 91% VT CL. The second ATP pacing was programmed in a non selective way (2-3 sequences. >88% VT CL).

Results: At a mean follow-up of 30$\pm$21months in the Sy-VT and 34$\pm$23 months in the NSy-VT groups, the Sy-VT group had a higher incidence (P=0.001) of syncope recurrence (7 p, 11 episodes, 27%) than the NSy-VT group (1 p, 1 episode, 2%) Syncope was associated with ICD proarrhythmia due to VT acceleration to a faster VT/VF by ATP or low/high energy shocks in 7 episodes (63%). Syncope was related to spontaneous VT and VF events in 4 episodes (36%). The average CL at initial detection was 301$\pm$38 ms and 325$\pm$25 ms for syncopal and non-syncopal episodes, respectively (P=NS)in the Sy-VT group. The median duration was 78 sec for syncopal episodes and 25 sec for non syncopal episodes (P=0.01)Median time to the first arrhythmic episode and to the syncope recurrence was 49 days and 367 days, respectively (P=0,01).

Conclusion: Syncopal recurrence due to arrhythmia is common in patients with syncopal VT. In this setting, syncope is often the result of device therapy (proarrhythmia). Because of a late recurrence of syncope in this particular group of patients, driving restrictions should be prolonged.

VENTRICULAR TACHYCARDIA

P1077 Variations of autonomic tone before the onset of repetitive monomorphic idiopathic ventricular tachycardia

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Background: Repetitive Monomorphic Idiopathic Ventricular Tachycardia (RMIVT) typically arises from the right ventricular outflow tract and is frequently induced by exercise or isoproterenol infusion. This study was designed to analyse dynamic changes in autonomic tone immediately before the spontaneous onset of RMIVT using Heart Rate Variability (HRV) indices.

Methods and Results: Holter tapes from 14 patients (6 male, 8 female, mean age 43 $\pm$ 18 yrs; mean number of VT runs per day 134 $\pm$ 213; mean VT rate 194 $\pm$ 40 bpm; median VT length 4 beats) with RMIVT were analysed. A total of 36 clusters of nonsustained episodes RMIVT preceded by at least 1 hour of sinus rhythm without VT runs were submitted to frequency-domain HRV analysis (25 min before onset of RMIVT divided into five 5-min periods; 8 min before onset of RMIVT divided into eigth 1-min periods). Analysis was performed using repeated measures ANOVA: during the 25 min preceding the onset of RMIVT, the mean RR interval decreased significantly from 767 $\pm$ 118 to 723 $\pm$ 105 ms (p= 0.015) and Low-Frequency to High-Frequency (LF/HF) ratio increased significantly from 2.24 $\pm$ 0.79 to 2.49 $\pm$ 1.0, p= 0.03). During the 8 min before onset of RMIVT the mean RR interval decreased significantly from 745 $\pm$ 118 to 718 $\pm$ 102 ms (p= 0.001) and LF-NU (LF components, normalized units) increased significantly from 205 $\pm$ 72 to 253 $\pm$ 113 ms (p= 0.014). No change was observed in HF components during the 25 or 8 min preceding the onset of RMIVT.

Conclusion: changes in HRV parameters suggest a strong and time-dependent primary activation of the sympathetic tone before the occurrence of RMIVT. Withdrawal of vagal tone does not appear to be essential to the initiation of VT clusters in RMIVT.

P1078 Long-term management of electrical storm due to amiodarone refractory ventricular tachycardia in patients with chronic heart failure: a comparison of sotalol and bepridil

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Recently, it is suggested that an incidence of electrical storm (ES) in patients (pts) with implantable cardioverter defibrillators (ICD) is approximately 10 to 30% and ES is an independent marker for subsequent death among ICD pts. Although it is reported that ES could be managed by amiodarone (AMD) and beta-blocker, a management of ES due to AMD refractory ventricular tachycardia (VT) is not known. Therefore, we evaluated whether sotalol showed effective for ES due to AMD refractory VT in pts with chronic heart failure (CHF) compared with bepridil.

Methods: Among 126 ICD pts with CHF due to impairment of left ventricular ejection fraction (LVEF<40%) in our hospital, ES, which was defined as more than 3 separate episodes of VT within 24 hours, occurred in 30 pts (24%). Although AMD was administered in all 30 pts with ES and AMD showed effective for ES in 13 of 30 pts, AMD was ineffective for ES or withdrawn because of pulmonary fibrosis in the remaining 17 pts. These 17 consecutive pts with ES due to AMD refractory VT (mean LVEF =30%) were evaluated in this study. After ES, 6 of 17

pts were initiated with bepridil and the remaining 11 pts were initiated with sotalol. When ES occurred even after the administration of bepridil or sotalol, another drug was administered in pts with ES. Mean follow-up periods were 41 months after the administration of bepridil or sotalol.
Results: Bepridil showed ineffective for ES in all 6 pts initiated with bepridil (mean dose=200 mg/day). On the other hand, sotalol showed effective for ES in 9 of 11 pts initiated with sotalol (mean dose=137 mg/day). Moreover, sotalol showed effective for ES in 5 of 6 pts refractory to bepridil. In summary, sotalol showed effective for ES in 14 of 17 pts (82%), and bepridil showed effective for ES in 1 of 8 pts (12%). Furthermore, among these 14 pts treated with sotalol in long-term management of ES, no patients developed torsades de pointes and acute exacerbation of CHF during 25 months follow-up duration.
Conclusions: These results suggest that sotalol in long-term management of ES due to AMD refractory VT in patients with CHF is effective for both VT and CHF as compared with bepridil.

P1079 AVE0118, a novel transient outward current antagonist, protects against ischaemically induced ventricular fibrillation

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Background: It is well established that the activation of the transient outward current (Ito) is largely responsible for the initial limited repolarization of the cardiac potential (phase 1). Furthermore, Ito is more abundant in epicardium as compared to the endocardium of the ventricle. Regional differences in the activation of ionic currents could occur as a consequence of myocardial ischemia. This would cause an increased dispersion of repolarization leading to reentry and ventricular fibrillation. The inhibition of Ito, therefore, may attenuate regional differences in repolarization and thereby, prevent malignant arrhythmias induced by ischemia. Recently, AVE0118, a novel drug that blocks the transient outward current (in atrial and ventricular tissue) and the ultra rapid component of the delayed rectifier current (IKur, which is only expressed in atrial tissue) has been developed. It was the purpose of the present study to evaluate the effects of AVE0118 on susceptibility to malignant arrhythmias provoked by myocardial ischemia.
Methods: Ventricular fibrillation was induced by a 2 minute occlusion of the left circumflex coronary artery during the last min of exercise in dogs with healed myocardial infarctions. The exercise plus ischemia test provoked ventricular fibrillation in nine animals. On subsequent days, the exercise plus ischemia test was repeated after pretreatment with AVE0118 (1.0 mg/kg, i.v., slow bolus).
Results: AVE0118 did not change QTc (Fridericia's correction) interval (control, 248.3 $\pm$ 7.8 vs. AVE, 252.7 $\pm$ 2.2 ms) but elicited significant (ANOVA, $P<0.05$) increases in heart rate before (control, 113.4 $\pm$ 7.0 vs. AVE, 143.4 $\pm$ 5.0 beats/min) and during exercise (control, 186.3 $\pm$ 6.4 vs. 200.1 $\pm$ 3.0 beats/min). Yet despite the increase in heart rate, AVE0118 significantly reduced the incidence of ventricular fibrillation protecting 7 of 9 animals (Fisher Exact Test, P=0.002).
Conclusions: Thus, AVE0118 was effective in the prevention of malignant arrhythmias induced by myocardial ischemia without altering QTc interval. These data suggest that the selective inhibition of the transient outward current in ventricular tissue may represent a novel antiarrhythmic intervention.

P1080 Natural antiarrhythmics: antiarrhythmic and electrophysiological effects of three polyunsaturated omega-3 fatty acids in isolated rabbit hearts

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Objectives: Polyunsaturated <omega>-3 fatty acids such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and alpha-linolenic acid (ALA) have been shown clinically to reduce the incidence of sudden cardiac death. We wanted to investigate whether these agents may affect directly the activation propagation and repolarisation pattern of the heart and act antiarrhythmically.
Methods: Isolated rabbit hearts (Langendorff) were submitted to 256 channel epicardial multielectrode mapping using 256 AgCl electrodes attached to the hearts surface allowing to monitor the cardiac activation and repolarization process in a film-like manner. After 45 min equilibration 1-20 μM either DHA, EPA, ALA or vehicle were infused intracoronarily (10 min/concentration).
Results: DHA slowed the epicardial activation wave and significantly prolonged the total activation time (TAT) from 22$\pm$3 to 35$\pm$5 ms. Epicardial potential duration (EPD)and QTc was not markedly altered while its spatial dispersion was enhanced by DHA. The beat-to-beat-variability of the breakthrough points of the activation pattern was not altered by DHA. In concentrations >10μM DHA caused significant negative inotropic and chronotropic effects. In contrast, EPA caused significant prolongation of EPD and QTc (by 15%), slightly increased dispersion, but had less effect on TAT. EPA also exhibited a significant negative inotropic and chronotropic effect. ALA exhibited smaller effects on TAT and heart rate, but as EPA prolonged QTc. Using programmed stimulation we found that DHA and EPA enhanced the threshold for elicitation of ventricular extrabeats, while ALA was ineffective. Regarding the propagation of the action potential we found that DHA significantly reduced longitudinal conduction velocity (as was previously seen with Na-channel blockers), while EPA and ALA had minor effects.
Conclusions: DHA, EPA and ALA exert direct electrophysiological effects but exhibit different profiles of action. DHA and EPA exhibited antiarrhythmic activity as assessed by programmed stimulation. While DHA shows effects similar to a class I anatiarrhythmics (affecting TAT and velocity) EPA action is similar to a class III antiarrhythmic drug (affecting QTc). Thus fish oil components exhibit direct electrophysiological and antiarrhythmic effects.

P1081 Impact of myocardial ischaemia on ventricular defibrillation threshold during chronic oral class III antiarrhythmic drugs therapy: comparison between amiodarone, dronedarone and azimilide

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Introduction: The effects of chronic oral therapy with class III antiarythmic drugs on ventricular defibrillation threshold (DFT) during ischemia are unknown. The goal of this study was to evaluate these effects under basal and ischemic conditions in a closed-chest animal model.
Methods: Azimilide (20 mg/kg/day), dronedarone (30 mg/kg/day) and amiodarone (30 mg/kg/day) was administered per os during 7 days in 15, 21, and 19 pigs respectively, while 15 pigs with no treatment served as controls. A triple-lead defibrillation system consisting of two endocardial electrodes and a subcutaneous patch was used. Ventricular fibrillation was induced by stimulation. A step-up and -down protocol was used to calculate mean DFT before and 10 minutes after coronary artery occlusion with an angioplasty ballon in the left descending artery.
Results: QT interval was significantly prolonged in the azimilide group versus control group, whether ischemia was present or not: 494 $\pm$ 47 msec vs 428 $\pm$ 52 msec (p= 0.005) and 491 $\pm$ 43 vs 403 $\pm$ 42 msec (p= 0.001), respectively. Mean blood pressure, heart rate, PR and QRS intervals did not differ between groups. DFT was not significantly different in the azimilide group versus control group before ischemia (18.8 $\pm$ 4.8 vs 20.8 $\pm$ 4.8 Joules; p = 0.33) and after ischemia (23.2 $\pm$ 3.8 vs 21.8 $\pm$ 5.2 Joules; p=0.54). Ventricular fibrillation cycle length increased significantly during ischemia in the azimilide group only (105 $\pm$ 24 vs 85 $\pm$ 13ms; p = 0.04).
Conclusion: These findings suggest that, in contrast to amiodarone, chronic oral treatment with azimilide and dronedarone does not affect ventricular defibrillation threshold at baseline or during acute myocardial ischemia, despite significant lengthening of ventricular repolarization.

P1082 Left ventricular outflow tract: a possibly underestimated source of isolated ventricular premature beats. Results of radiofrequency catheter ablation in highly symptomatic patients

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Ventricular premature beats (VPBs) with left bundle branch block (LBBB) morphology and inferior axis frequently arise from the right ventricular outflow tract (RVOT). However, at this site, disappointing results in terms of local prematurity, pacemapping and poor suppression at radiofrequency (RF) pulses are not rare. It has been proposed that in some patients (pts), these arrhythmias may arise from the left ventricular (LV) OT, but controversial results in RF transcatheter ablation (RFTCA) have been reported.
Methods: We report a single-centre experience in 18 pts, 11 males, mean age 46$\pm$12 years, markedly symptomatic for frequent VPBs (mean 23012$\pm$5320/24 h), non-responders or intolerant to common antiarrhythmic drugs (Class IC, beta-blockers). Eventual presence of organic heart disease was assessed in all pts with complete clinical screening. More specifically, in no patients arrhythmogenic RV dysplasia was evident, while coronary heart disease was diagnosed in 2 pts and hypertension in 2 pts.
Results: In no pts ventricular programmed stimulation up to three 3 beats and 3 drive cycle length, induced life-threatening arrhythmias. In 11/18 pts (61%) RFTCA was successfully performed at the RVOT, while in 7 pts RVOT mapping showed poor findings as local prematurity (5$\pm$4 ms vs 22$\pm$6, $p<0.05$) or pacemapping. In 6 of these pts, LVOT mapping showed fragmented potentials with marked local prematurity (34$\pm$15 ms) and good results at pacemapping, guiding the application of effective RF pulses. Lead V3 R/S ratio > 1 was the only ECG predictor of LV origin. VPBs disappearance was prompt in 5 pts, while in 2 pts it was preceded by short run of idioventricular rhythm. In contrast, accelerated ventricular rhythm typically heralded successful RFCA in the RVOT, thus suggesting a different underlying mechanism. All pts were discharged without drug therapy. At a mean follow-up of 9$\pm$4 month, significant VPBs recurrence (> 10% of basal VPBs) was observed in 3 pts (16%) with no difference between the two RFTCA sites.
Conclusions: In our experience LVOT was detected as a frequent site of origin of isolated VPBs, refractory to drug therapy. A LBBB morphology with inferior axis and early precordial lead transition was suggestive of LV origin. RFTCA in highly symptomatic patients was safe and associated to a favourable medium term outcome.

P1083 Non-propagated stimulus from the ablation catheter: validation of a new criterion for ablation of postinfarction ventricular tachycardia

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Conventional mapping criteria are very sensitive but little predictive for postinfaction ventricular tachycardia (VT) termination by radiofrequency (RF) application. Tachycardia termination by electrical stimulus with only local influence (non-propagated stimulus – NPS) has been reported as an accurate predictor of catheter placement at a narrow isthmus of conduction in isolated patients. However, the value of this criterion has not been prospectively evaluated.
Methods: 34 consecutive patients (32 male, 70±10 years) were prospectively included in the study. They underwent 43 procedures for postinfarction VT ablation. Twelve procedures were excluded from the study because VT intolerance, poor VT inducibility or sustainment, or drug impregnation. VT mapping and ablation was guided by conventional criteria and, whenever a RF application was planned, VT termination by NPS from the ablation catheter was attempted by single pulse stimulation scanning the whole tachycardia cycle length (CL) or by asynchronous continuous pacing at a CL longer than 600 ms during 10 seconds. Following NPS attempt, VT was reinduced, if it had been terminated, and RF was applied irrespectively of prior NPS achievement.
Results: The target VT was successfully ablated in 18 procedures. NPS terminating VT was observed in 31 and 1 sites where RF subsequently succeeded and failed to terminate VT, respectively. The target VT could be reinduced following RF termination in 17 sites showing NPS. The NPS criterion presented 66%, 98%, 97%, and 82% sensitivity, specificity, and positive and negative predictive values for VT termination by RF application, respectively. The NPS criterion also showed 78%, 82%, 41%, and 95% sensitivity, specificity, and positive and negative predictive values for VT definitive ablation, respectively. No VT acceleration or conversion to VF was observed with the NPS pacing protocol.
Conclusion: NPS is highly positive predictive and sensitive for VT RF termination and ablation, respectively.

P1084 Ablation of ventricular arrhythmia originating from purkinje fibers in patients after myocardial infarction

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Introduction: The spectrum of ventricular arrhythmias arising from the Purkinje network after myocardial infarction (MI) is unknown.
Methods and Results: 34 consecutive pts (30 male; age 63±12) undergoing ablation of drug refractory ventricular arrhythmias after MI (5 years) were studied. In each case reversible causes of arrhythmia were excluded before ablation. These arrhythmias were monomorphic VT (n= 27), polymorphic VT (n= 5), or VF (n=11). Mapping was initially performed by delineating the scar border zone using electroanatomic voltage mapping. During stable arrhythmia (or ventricular ectopy), activation mapping, entrainment mapping and mapping the earliest site of activity was used to identify the likely mechanism of the arrhythmia. During sinus rhythm, pace mapping techniques were utilized. Purkinje origin of arrhythmia was defined by a sharp spike (Purkinje) potential ventricular activation. The accuracy of mapping was confirmed by ablation.
In 11 pts Purkinje potential (PP) were observed either before ventricular ectopy or during arrhythmia: 5 presented with polymorphic VT, 1 with VF, and 5 with monomorphic VT. In all these pts arrhythmia termination or the elimination of ectopy was observed following RF applications delivered at the sites at which ventricular activation was preceded by PP; which in all but 1 case was localized to the scar border zone. There was no difference in age, duration from MI or left ventricular function. However, pts with VF or polymorphic VT all had anterior MI, while pts with monomorphic VT were more likely to have inferior or posterior MIs. 23 pts had implantation a defibrillator. At 14±4 months all pts are free of recurrent arrhythmia.
Conclusions: The Purkinje network may be responsible for multiple patterns of ventricular arrhythmias after MI: ectopy, mono/polymorphic VT, and VF. In this subset of pts with Purkinje origin of arrhythmia after MI, pts with anterior MI were more likely to present with polymorphic VT or VF.

P1085 Ablation of ischaemic ventricular tachycardia using CARTO: should mapping be performed during tachycardia or sinus rhythm?

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For ablation of ventricular tachycardia (VT) in patients with coronary artery disease a three dimensional mapping system is frequently used. Mapping is performed either during VT or sinus rhythm/pacing (SR). We compared these two mapping strategies in 94 patients using the CARTO system.
Methods and Results: VT-mapping was performed during induced stable VT (32 patients) or stable incessant VT (14 patients) with identification of the critical area of slow conduction using diastolic potentials and concealed entrainment pacing. For SR-mapping (48 patients) the following strategy was used: first pathological myocardium was identified by fragmented, late and/or low amplitude (<1.5 mV) bipolar potentials. Then pace mapping inside or at the boarder of this pathological myocardium was performed during SR in order to identify the VT exit. The catheter remained at the area with the best match between stimulated QRS and VT-QRS, ideally at a site with a long stimulus to QRS interval. Afterwards VT was induced and the critical site was confirmed by local diastolic potentials during VT and, if possible, VT termination by radiofrequency (RF) current delivery. Patients with SR map were not significantly different from patients with VT map in regard to age (65±9 vs 65±8 years), VT-cycle length (397±82 vs 419±98 msec), number of RF applications (17±8 vs 17±10 applications) and ablation result, i.e., non inducibility of any VT (69 vs 43%), inducibility of only non clinical VT (27 vs 39%), or with the clinical VT remaining inducible (4 vs 18%). However, procedure duration and fluoroscopy time were significantly shorter in the SR group as compared to the VT group (391±117 vs 460±147 min ($p<0.05$) and 21±10 vs 32±22 min ($p<0,05$), respectively).
Conclusion: When using a CARTO guided approach for VT ablation in patients with coronary artery disease, SR mapping is as successful as mapping during VT. However, ablation based on the SR map has the advantage of shorter procedure time and shorter fluoroscopy time and may therefore be considered as the mapping and ablation strategy of choice.

P1086 Monomorphic premature ventricular contractions initiate ventricular fibrillation regardless of underlying substrate

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Purpose: Monomorphic premature ventricular contractions (PVCs) in the Purkinje system have been shown to be responsible for ventricular fibrillation (VF) initiation in patients with no structural heart disease. Whether a similar mechanism is responsible for initiation of VF in other types of structural heart disease is unknown. We prospectively sought to assess the initiation pattern of VF in a heterogeneous patient population presenting with VF storm.
Methods: A case series consisting of consecutive patients presenting with electrical storm secondary to VF was compiled at four institutions. Electrical storm was defined as 2 or more documented episodes of VF within a 24 hour period. Clinical characteristics of the patients were collected prospectively. All patients were monitored continuously on multi-lead telemetry. Strips of initiation of VF were collected and analyzed.
Results: A total of 40 patients were identified. The majority (29/40) of patients had ischemic cardiomyopathy. However, 3 patients had pure valvular heart disease, 2 had idiopathic dilated cardiomyopathy, and 6 had structurally normal hearts. VF storm occurred in the setting of acute heart failure in 10/40 (25%) patients. Patients had a mean of 7.5 ± 3.0 episodes of VF. In all cases, VF was observed to be initiated by a unimorphic PVC. Mean coupling interval of the PVCs was 195 ± 45 ms. All patients except 8 ischemics and 3 normals settled with IV antiarrhythmic drug therapy or after stabilization of acute heart failure.
Conclusions: VF appears to be initiated by unimorphic PVCs in a variety of different cardiac diseases. The majority of VF storms appeared related to acute heart failure or responded to antiarrhythmic therapy.

P1087 Ventricular septal pacing reduces incidence of atrial fibrillation in dual-chamber paced patients

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Right ventricular apical (RVA) pacing has been shown to produce long-term detrimental effects on left ventricular function. We examined the incidence and frequency of episodes of atrial fibrillation (AF) in an unselected group of patients requiring a dual chamber pacemaker (DDD/R) for AV block, randomly assigned to RVA or right ventricular septal (RVS) electrode placement.
Methods: Thirty four patients (19 male), age 45-93 years, were implanted with a DDD/R pacemaker with mode switch (M/S) capability. Fourteen were paced at RVA, 21 at RVS. The number of M/S episodes (MSE), overall duration of time (%) spent in AF (MST), premature atrial contraction (PAC) data and percentage of time spent ventricular pacing was collected through pacemaker diagnostic data at 1, 6 and 12 months post implant.
Results: Data at 1, 6 and 12 months post-implant are reported as mean ± SE. Statistical analysis between groups used Mann-Whitney test and within groups was by Friedman test with Dunn's post analysis test. There was no difference between groups in AF incidence before pacing. There was a significant rise in both MSE and MST in RVA paced patients with time. No significant differences were found within the RVS group over the 12 month follow-up.

Percentage ventricular pacing showed no difference between groups at any time point (range 97.0±2.23 to 99.1±0.06%).

Table

	No. of M/S episodes		% of time M/S		PAC runs	
	RVA	RVS	RVA	RVS	RVA	RVS
1m	1.07±0.99	226±217	0.008±0.007	2.46±2.42	52170±38560	2822±2177
6m	1325±820**	24.1±11.84#	11.72±6.72*	0.08±0.05#	226500±134100	6093±5744
12m	1108±912***	951±864	10.71±5.30	1.10±0.82	924900±723900	1210±1189

= p< 0.01 compared with RVA at same time point.* = p<0.05, **= p<0.01, ***=p<0.001 compared with 1 month.

Conclusion: Pacing from the RVS results in less atrial fibrillation than traditional RVA lead placement within 6 months and this effect appears to continue to 12 month follow-up. This finding may explain some of the difficulties in demonstrating benefits of DDD over VVIR pacing in recent studies and supports the increasing use of non-RVA pacing sites.

P1088 Effects of triggered and continuous atrial pacing on AF burden and the mode of AF onset in pacemaker patients

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Atrial pacing prevents the recurrences of paroxysmal atrial fibrillation (AF). Some recent preventive pacing functions pace the atrium only after detection of specific triggers. A benefit of continuous pacing can be the prevention of sudden AF onset. The aim of the study was to compare the effects of triggered and continuous atrial pacing.

Methods: The study included 107 patients (pts) with standard pacing indications and symptomatic paroxysmal AF who had received the DDDR pacemaker Selection 9000 or Prevent AF (Vitratron). All pts were paced with triggered preventive pacing functions only (PAC-Suppression, Post-PAC Response, Post Exercise Response) and with the 3 triggered and 1 continuous pacing function in cross-over randomisation for 3 months each. Group TRI-CON was paced initially with triggered and after cross-over with continuous pacing, group CON-TRI was paced in the first 3 months with continuous and then with triggered pacing. The percentage of atrial pacing, the AF-burden, the frequency of sudden AF onsets, and the frequency of > 2 premature atrial contractions (PAC) within last 5 mim/min prior AF onset were determined. The latter two parameters were assessed from the AF onset-triggered pacemaker diagnostics.

Results: After the first 3 months atrial pacing was in group TRI-CON with 78 ± 24% lower compared to 91 ± 18% in group CON-TRI (p = 0.001). After cross-over the percentage of pacing increased in TRI-CON to 92 ± 15% and decreased in CON-TRI to 81 ± 25% (p <0.001). AF-burden was after the first randomisation in TRI-CON significant lower with 5.1 ± 11.2% compared to CON-TRI with 12.7 ± 22.8% (p < 0.05). AF-burden increased after cross-over to 9.9 ± 22.0% (TRI-CON) and decreased to 4.0 ± 6.4% (CON-TRI) (p < 0.05). The frequency of sudden AF onset was not significantly different in TRI-CON with 47 ± 40% compared to 44 ± 38% (CON-TRI) and after cross-over with 45±41% (TRI-CON) and 38±39% (CON-TRI), respectively (not significant (n.s.)). The frequency of PAC-triggered AF onset was similar in the two groups with 53±40% (TRI-CON) and 55 ± 38% (CON-TRI) and remained unchanged after cross-over with 55±41% (TRI-CON) and 62±39% (CON-TRI) (n.s.).

Conclusions: The pts had during activation of the triggered pacing functions alone a low AF-burden. The additional activation of continuous pacing increased the frequency of pacing, but also increased the AF-burden. The continuous pacing function had no specific preventive effect on sudden AF onset. The higher AF burden during activation of continuous pacing was not associated with more frequent PAC-triggered AF onsets.

P1089 The influence of atrial rhythm on AF occurrence in patients with sinus node disease and ventricular pacing system

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Results of some studies didn't show significant superiority DDD over VVI pacing mode in pts with sinus node disease during long-term FU. Retrospective analysis of medical files was performed of 225 pts (85 M, 140 F aged 34-83; aver. 64,8) which in years 1975-95 received (due to sinus bradycardia - 110 pts and braty-tachy or tachy-brady syndrome - 115 pts) VVI pacing system. The time of FU was 10-272 aver. 85,4 months.

Results: The first ECG performed during FU usually 4 weeks after implantation showed SR (with inhibition of pacemaker) in 20,4%, dissociation of atrial rhythm and ventricular pacing in 31,1%, continuous ventricular pacing with retrograde atrial activation (VA conduction) in 41,8% and AF in remained 6,7% pts. Results of the analysis of all ECG (repeated every 6 mth.) are presented in table. History of AF before implantation (tachy-brady and braty-tachy syndrome) showed to have only slight influence on AF appearance during FU.

Results of ECG files analysis

Predominant atrial rhythm during FU	Number of pts	No AF	Paroxysmal AF	Permanent AF
Sinus rhythm without V pacing	41	59%	12%	29%
V pacing, no retrograde (VA) conduction, periodically SR	45	42%	9%	49%
V pacing with retrograde atrial activation, periodically SR	33	21%	9%	70%
Only V pacing with retrograde atrial activation	93	15%	12%	73%
AF on beginning of FU	13	0%	15%	85%
Total	225	28%	11%	60%*
Last 3 ECG on the end of observation (aver. 7 years)	Age (aver. years)	Pacing period (aver. months)	Embolic complications	Death
SR (64 pts)	64,7	61,6	(5%)	(37%)
AF in one of last ECG (25 pts)	64,7	64,7	(8%)	(33%)
Permanent AF (100 pts)	66,3	98,4	(10%)	(46%)
Pacing mode was changed (36 pts)	61,0	69,9	(6%)	(22%)

*In 44 out of 136 pts after successful cardioversion pacing mode was changed.

Conclusion: Unfavorable effects of ventricular based pacing appear in most of pts with sinus node disease during long-term FU. Slow sinus rate (high percentage of ventricular pacing) and retrograde (VA) conduction seems to be most important determinants of patients lots.

P1090 A randomised study of single and dual chamber implantable cardioverter-defibrillators in detection of atrial tachyarrhythmias

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Introduction: A proposed benefit of dual chamber implantable cardioverter-defibrillators (ICDs) is the reduction in inappropriate detection of atrial tachyarrhythmias due to addition of atrial information. The purpose of this randomised study was to investigate the accuracy of single and dual chamber detection algorithms during spontaneous atrial tachyarrhythmias.

Methods: ICD candidates without indications for bradycardia pacing or resynchronization therapy were included. All received a dual chamber ICD and were randomised to programmed single (onset 16%, stability 40 ms) or dual chamber detection (onset 16%, stability 40 ms,and Afib threshold, V>A, or SMART). Stored electrograms were used using both atrial and ventricular channels. The detection results were corrected for multiple episodes within a patient with the generalized estimating equations (GEE) method.

Results: 60 patients (47 male, 58 ± 14 years, LVEF 30%) were included, 29 had single chamber and 31 dual chamber setting. A total of 578 spontaneous arrhythmia episodes (33 patients) were classified by the investigators; 329 episodes were ventricular tachyarrhythmia (28 patients). The sensitivity for detection of ventricular tachyarrhythmias was 100% for both settings. Atrial tachyarrhythmias were recorded in 249 episodes (20 patients). Detection was inappropriate for 102 atrial tachyarrhythmia episodes (41%, 13 patients). No significant difference in spontaneous atrial tachyarrhythmia detection between both groups was demonstrated (Chi-square 0.1; P = 0.73). Episodes of regular atrial tachycardia were significantly more misclassified compared to other atrial tachyarrhythmias (Chi-square 10.5; P < 0.0001). Overall, no significant difference in arrhythmia detection, atrial and ventricular, between both groups was demonstrated (Chi-square 0.2; P = 0.63).

Conclusion: The applied detection criteria in dual chamber devices do not offer benefits in atrial tachyarrhythmia detection. Atrial tachyarrhythmias with stable atrioventricular conduction remain a clinical problem in both single and dual chamber ICDs.

P1091 Single-chamber versus dual chamber cardiac pacing and arterial distensibility in patients with sinus node disease

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Purpose: It is known that blood flow influences the arterial distensibility by endothelial-dependent mechanisms. Permanent pacemaker (PM) implanation is an effective treatment of patients with sinus node disease. However, single-chamber, ventricular- based PM is associated with ventricular asynergy which may unfavourably influence the arterial distensibility by changing the pattern of blood flow in aorta. The aim of this study was to compare the effect of PM mode on the arterial distensibility.

Methods: The study population consisted of 40 pts with sinus node disease. Patients with atrial fibrillation were not included. In 20 pts VVI-PM was implanted. The remaining 20 pts – received DDD- PM. Groups were comparable according

to age, gender and hemodynamic parameters (heart rate, blood pressure). Before PM implantation, following 4 and 60 days PWV was evaluated using a computer system COMPLIOR. For automatic measurement of PWV pressure waveforms were digitized at rate 500Hz for carotid-femoral distance. 10 healthy volunteers constituted a control group.
Results: Comparison of PWV measurements between groups is shown in the table.

Pulse Wave Velocity in m/s

	Before PM implantation	4 days after PM implantation	60 days after PM implantation
VVI Group	13,0 ±1,3	14,8 ± 2,1*	14,5 ± 2,3*
DDD Group	13,3 ± 0,8	11,4 ± 1,9*	11,1 ± 2,0*
Control Group	7,0 ± 0,6	7,2 ± 0,4	7,1 ± 0,6

*p<0,01 vs initial.

Conclusions: 1. VVI pacing (in contrast to DDD) significantly reduced the distensibility of large arteries shortly after PM implantation and following 2 months. 2. VVI-PM should be avoided in pts with known diseases which usually decrease the arterial distensibility (atherosclerosis, arterial hypertension, diabetes mellitus).

P1092 Prevalence of atrial tachyarrhythmias in dual chamber paced patients with optimised programming – initial results from the PAFOS study

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Introduction: Prevention of atrial fibrillation (AF) by dynamic atrial overdrive pacing has been investigated in several clinical trials. However, the results were controversial and likely influenced by multiple factors like inappropriate Auto-Mode-Switches (AMS) due to Far Field R-Wave Oversensing (FFS), atrial undersensing during AF, potential proarrhythmic effects due to non-optimized pacemaker programming and conventional pacing. The PAFOS (Prevention of Atrial Fibrillation by optimised Overdrive Stimulation) study takes into account these influencing parameters when evaluating the effect of dynamic atrial overdrive pacing.
Method: Patients (pat) with a class I/II dual chamber pacing indication, paroxysmal/persistent AF and an implanted DDDR-pacemaker Identity DR (St. Jude Medical) are candidates for the study. After a run-in phase a two months monitoring period is started with optimized and fixed medication, adapted atrial blanking period to avoid FFS and individual AV-/PV-delay optimization. Subsequently pat are classified according to their AMS burden. Pat with an AMS burden $\geq$ 2% will be classified in study group I and randomized for 6 month to AF Suppression algorithm ON or OFF. All other pat will be monitored for 6 months in study group II with AF Suppression OFF. A first analysis of this group II has been performed.
Results: Up to date 150 pat (73 male, mean age 72,9±O7,9) have been classified. 44 pat (29%) were classified to group I with a mean AF burden of 18,3±22% (Median:11,5%), 106 pat (71%) to group II with a mean AF burden of 0.1±0,3% (Median:0%). Total mean AF burden was 5.4±14,4% (Median:0%). Mean AF-Burden in Group II increased to 2,6±12,5% (Median:0%; n=68)after 3 months and 9,3±27,3% (Median:0%; n=39) after 6 months. Analysis of the stored IEGMs shows no inappropriate AMS due to oversensing at an atrial sensitivity of 0.2mV. The AV/PV-delay optimization shows a broad variation in a range from 90-220 ms.
Conclusion: The first data indicate that the precautions of the PAFOS concept lead to reliable AMS data. Optimized medication and pacemaker programming as well as conventional pacing itself seem to contribute to the high percentage of pat with low AF-burden. However those pat also need close AF monitoring during long term follow up.

P1093 Cardiac memory leads to electrical synchronization of different regions of the ventricular myocardium

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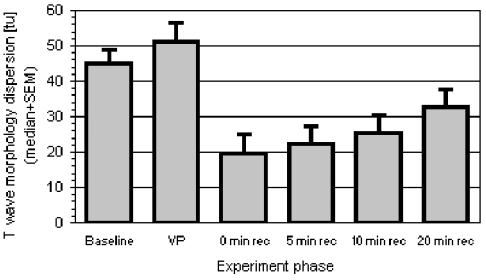
The term Cardiac Memory (CM) refers to transient changes in T wave morphology that appear after cessation of ventricular pacing (VP). It is not known whether in intact hearts in situ, different layers and regions of the ventricular myocardium react differently during CM. We therefore investigated the development of T wave morphology during CM.
Methods: We studied chronically instrumented, acutely anesthetized dogs. CM was induced by VP at 400 bpm for 120 min, followed by 20 min recovery of atrial pacing (AP) at 500 ms cycle length. Altogether, 11 experiments were available from 6 animals. Digital ECGs with limb leads I and II + 7 transmural needles were recorded at 120 min of VP, after cessation of VP, and at 5, 10, and 20 min of recovery. CM was measured as distance between the peaks of the AP T wave vector at baseline and during CM on frontal plane and decreased significantly during recovery (from 0.227±0.046 (SEM) to 0.102±0.028, $p < 0.05$) confirming the presence of CM mechanisms. Multi-lead T wave morphology was assessed by the so-called T wave morphology dispersion (TMD) that expresses the differences in T wave shapes recorded in different leads. Low values of TMD indicate spatial synchronisation of different parts of ventricular myocardium.
Results: The figure shows the development of TMD during CM. The changes during recovery were very highly significant compared to baseline (p = NS, 0.007, 0.001, 0.0009, and 0.002, at VP and 0, 5, 10, and 20 min of recovery, respectively).



Conclusion: This data analysis suggests that mechanisms of CM involve synchronisation of different regions of ventricular myocardium turning the physiologically elliptic 3D T wave loop into a spherical pattern thus causing suppression of physiologic repolarisation gradients.

P1094 Cardiac resynchronization therapy decreases the inducibility of ventricular tachycardias in patients with end-stage heart failure

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Background: Patients (pts) with heart failure and dilated cardiomyopathy are at high-risk of the occurrence of ventricular tachycardias (VT). Whether cardiac resynchronisation therapy (CRT) reduces the susceptibility to these arrhythmias is a matter of ongoing debate. In the current study, we evaluated if the inducibility of VT was reduced after 6 months of CRT in end-stage heart failure pts.
Methods and Results: Eighteen pts (15 men, age 62±11yrs) treated with a combined CRT-ICD device for end-stage heart failure (NYHA class III-IV), dilated cardiomyopathy (10 ischemic, 8 idiopathic) and wide QRS complex were included. Indications for the ICD device were out-of-hospital cardiac arrest (n=7) or VT (n=11). All patients underwent an electrophysiological (EP) study with ventricular programmed electrical stimulation (PES), both before implantation of the CRT-ICD device and after a period of at least 6 months of CRT. The PES-protocol consisted of an 8 beat drive train with basic cycle lengths of 600, 500 and 400 ms and up to 3 extra stimuli with a minimal cycle length of 200 ms. Anti-arrhythmic drug usage before CRT (sotalol n=8, amiodarone n=10) did not significantly differ from usage during long-term follow-up (sotalol n=7, amiodarone n=11).
All patients responded well to CRT with a reduction in NYHA class from 3.1±0.3 to 2.2±0.6 ($p<0.05$). Before CRT-ICD implantation, sustained VT could be induced in 15 (83%) patients. After a period of 9.3 ± 2.3 months of CRT, sustained VT was inducible in 6 (33%) patients ($p<0.01$).
Conclusion: In patients with end-stage heart failure and dilated cardiomyopathy, long-term CRT significantly decreases the inducibility of VTs, suggesting an anti-arrhythmic effect of long-term CRT.

P1095 Paired ventricular stimulation: an approach for hemodynamic stabilization of refractory ventricular tachycardia

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Purpose: Incessant ventricular tachycardia (VT) or VT storm is still a challenge for every physician. As electrical cardioversion may only transiently terminate the arrhythmia beta-receptor blockade and amiodarone infusion currently are the most efficient treatment strategies. However, it may take hours to terminate VT. Ventricular premature beats (VPB) introduced during VT at coupling intervals immediately outside the ventricular refractory period but shorter than the VT cycle-length will not generate an arterial pressure wave but prevent ventricular excitation by every 2nd VT beat. The resultant prolongation of ventricular filling time and postextrasystolic potentiation of ventricular contractile force should increase arterial pressure during VT.
Methods: In 15 patients with previously spontaneous VT/VF sustained non-syncopal VT was induced by programmed stimulation during an electrophysiological study. VPBs at short coupling intervals were then introduced from the right ventricle.
Results: Paired stimulation during VT reduced the number of arterial pulse waves by 50% and significantly increased systolic pressure (71 vs. 90 mm Hg; $p<0.001$)

and mean arterial pressure (60 vs. 72 mm Hg; $p<0.001$). Diastolic pressure rose from 54 to 60 mm Hg (p=n.s.). Even during longer episodes of VT up to 60 min. paired stimulation did not accelerate VT or induce VF in this group of patients at high-risk for ventricular arryhtmias but reduced patients discomfort during VT.
Conclusions: Paired ventricular stimulation during VT augments systolic arterial pressure by almost 30% and mean pressure by 20%. Paired stimulation may be used for hemodynamic stabilization of patients with refractory or incessant VT until other therapeutic means are coming to an effect. The algorithm may also be implemented in ICDs as therapy of last resort during incessant VT.

P1096 Pacing away from the right ventricular apex – is it practical and safe for all patients?

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We have previously shown right ventricular septal (RVS) pacing is safe and practical in patients with structurally normal hearts. This study assessed pacing the RVS compared with apical (RVA) lead placement in unselected patients requiring a dual chamber DDD/R or single chamber VVIR pacemaker for AV block.
Methods: Fifty eight patients (36 male)(mean age 74.7±11.5yrs) were implanted with either a DDD/R or VVIR pacemaker and randomised to receive either RVA or RVS lead placement. Implant electrical data, procedure and fluoroscopy times (minutes), and complications were recorded. Threshold (volts @ 0.5msec), impedance (ohms) and complication data were collected at 24 hours, 1 and 6 months post implant.
Results: At implant, fluoroscopy times in the DDD/R group were significantly longer for RVS lead placement than RVA (6.5±5.1 vs. 3.4±1.5, $p<0.05$). There were no significant differences in procedure time between RVA and RVS in either single or dual chamber groups. There were no implant complications, ventricular lead displacements or failures up to 1 month in the DDD/R group. In the VVIR group, 1 patient randomised to RVA pacing was paced at the RVS due to an unstable apical position. Two patients from the DDD/R RVA group required atrial electrode repositioning.

Table

		DDD/R (n = 48)		VVIR (n = 10)	
		RVA (n= 20)	RVS (n = 28)	RVA (n= 6)	RVS (n = 4)
Implant	Threshold	0.40 ± 0.18	0.61 ±0.20*	0.57±0.41	0.60±0.14
	Impedence	741±188	799±143	707 ± 156	851 ± 186
24 hours	Threshold	0.46±0.10	0.53±0.10	0.70±0.40	0.65±0.20
	Impedence	818±131	754±144	641±73.6	812±188
1 month	Threshold	0.67±0.51	0.75±0.53	0.90±0.56	0.71±0.23
	Impedence	774±183	744±145	658±97	866±153
6 month	Threshold	0.64 ±0.51	0.70 ±0.34	0.84 ±0.17	0.83 ± 0.17
	Impedence	761±194	761±184	681 ±134	833 ± 161

Data are mean ±SD; *p <0.05

Conclusion: RVS pacing is safe and practical for unselected patients but fluoroscopy times are slightly longer, which may relate to difficulty with placing stylet delivered leads at non-apical sites. These times should improve with greater experience, newer leads and implant systems.

HEART FAILURE: EXPERIMENTAL ASPECTS AND RISK OF INFLAMMATION

P1097 Ranolazine increases ATP synthesis in failing cardiomyocytes through stimulation of mitochondrial respiratory activity

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Background: Left ventricular (LV) dysfunction in the setting of heart failure is often attributed to myocardial energy deprivation. We previously showed that acute intravenous administration of ranolazine, a partial fatty acid oxidation inhibitor that stimulates carbohydrate oxidation, improves LV function in dogs with chronic heart failure. The mechanism(s) responsible for this hemodynamic benefit of ranolazine is not fully understood. In this study, we tested the hypothesis that, in failing cardiomyocytes, ranolazine improves myocardial energetics by enhancing mitochondrial respiration that lead to increased synthesis of ATP.
Methods: Studies were performed in cardiomyocytes isolated from the LV myocardium of 7 dogs with heart failure produced by multiple sequential intracoronary microembolizations (LV ejection fraction <30%). Cardiomyocytes were saponin skinned and mitochondrial state-III respiration (V-ADP) was measured using an oxygraph and a Clark electrode in the presence of 1 mM ADP, 5 mM malate, 5 mM pyruvate, 5 mM succinate, 1 mM ascorbate and 0.4 mM N,N,N',N'-tetramethyl-p-phenylenediamine (TMPD). Measurements were made in the absence of ranolazine (baseline) and after the addition of 1.0 mg/L of ranolazine. Mitochondrial respiration was quantified in ng atoms of oxygen/min/200,000 cardiomyocytes. Maximal ATP content (ATPmax) was measured in the presence of the same substrates as above using luciferase and a luminometer and expressed in relative light unit/sec/1000 cardiomyocytes (RLU/sec).
Results: At baseline, V-ADP was 195 ± 6 and increased significantly to 246 ± 7 after the addition of ranolazine ($p<0.05$). The increase in V-ADP following the addition of ranolazine was accompanied by a significant increase in ATPmax compared to baseline (10.7 ± 0.7 vs. 13.5 ± 0.6 RLU/sec, $p<0.05$).
Conclusions: In failing cardiomyocytes, ranolazine increases ATP synthesis through stimulation of mitochondrial respiratory activity. Increased synthesis of ATP in heart failure can alliviate the existing state of myocardial energy deprivation and, in doing so, contribute to the improvement of LV function seen following acute intravenous administration of ranolazine.

P1098 Potent cardiorenal actions in experimental heart failure with dual activation of soluble and particulate guanylate cyclases by BAY 58-2667 and brain-type natriuretic peptide: a novel therapeutic strategy

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Background: Soluble guanylate cyclase (sGC) is an important enzyme, which via cyclic guanosine monophosphate (cGMP) production mediates potent vasodilating actions in multiple vascular beds. Particulate guanylate cyclase (pGC) via cGMP results in potent renal natriuretic and diuretic actions with vasodilating properties. Importantly, sGC and pGC may in part be differentially localized which may limit maximal cGMP activating pathways with sole activation of either pGC or sGC. BAY 58-2667 belongs to the new pharmacological class of direct sGC activators that, unlike conventional nitrates, activate sGC without the development of tolerance and without cGMP-independent actions. B-type natriuretic peptide (BNP), which is a pGC activator, is natriuretic and vasodilative, but in experimental congestive heart failure (CHF) does not increase cardiac output or reduce systemic vascular resistance. We hypothesized that co-administration of BAY 58-2667 and BNP in experimental CHF would complement the beneficial cardiac unloading actions of BAY 58-2667 with the beneficial renal actions of BNP.
Methods: CHF was induced in two groups of male dogs (both N=7) by rapid right ventricular pacing at 240 beats per minute. After 10 days, cardiorenal parameters were measured in clearances at baseline and with two intravenous doses of BAY 58-2667 (0.1 and 0.3 μg/kg/min, respectively) alone or in combination with BNP (10 and 50 ng/kg/min, respectively). Clearances were compared within groups by analysis of variance for repeated measures, while groups were compared qualitatively.
Results: BAY 58-2667 alone potently ($p<0.05$) decreased mean arterial pressure, cardiac filling pressures, and systemic and renal vascular resistance, while cardiac output and renal blood flood increased. These actions occurred to a similar degree when BNP was added to BAY 58-2667. However, in addition there were significant ($p<0.05$) increases in urinary flow, urinary sodium excretion, glomerular filtration rate, and filtration fraction. Both regimens did not further activate the renin-angiotensin-aldosterone system.
Conclusion: Direct sGC activation by BAY 58-2667 has potent beneficial cardiac unloading actions in experimental CHF. While additional pGC activation with BNP does not augment hemodynamic actions with BAY 58-2667, it enhances renal function. These findings suggest that coactivation of sGC and pGC may be a beneficial and a novel strategy in the treatment of CHF.

P1099 Different binding properties of ouabain, digoxin, digitoxin, β-acetyl-digoxin and methyl-digoxin to human cardiac Na,K-ATPase isoforms

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In the human heart three isoforms of the human Na,K-ATPase (hNKA) are expressed: a1b1, a2b1 and a3b1. The NKA is the target of cardiac glycosides, which inhibit the enzyme and are used for the treatment of symptomatic heart failure and atrial fibrillation. It is unknown if different cardiac glycoside compounds have different isoform specific affinities, and if isoforms have different subcellular distributions in human cardiac myocytes.
cDNAs of human NKA a1b1, a2b1 and a3b1 were heterologously expressed in yeast cells (no endogenous NKA). Isoform specific binding of ouabain (OUA), digoxin (DIG), digitoxin (DTX), β-acetyl-digoxin (AcD) and methyl-digoxin (MeD) was assessed in radioligand binding assays using ^{3}H-ouabain (20 nM) in the absence or presence of K+ (each $n\geq5$). The subcellular localization was investigated in isolated cardiac myocytes of human atrial tissue by immunohistochemistry.
In the absence of K+, only OUA and MeD, but not DIG, DTX and AcD, had isoform specific affinities. In the presence of K+ (1mM) also DIG and AcD had isoform specific affinities (Table). The affinity ranking of the isoforms differed between the agents (Table). Immunohistochemistry showed that all isoforms are located in the

plasma membrane and in intracellular membranes, but only a1b1 and a2b1 in the t-tubuli.

KD in nM (±SEM)

	Human NKA	Ouabain	Digoxin	Digitoxin	β-Acetyl-Digoxin	Methyl-Digoxin
no K+	a1b1	13.3 ± 1.7	26.4 ± 4.8	17.1 ± 3.4	31.6 ± 2.2	16.5 ± 6.7##
	a2b1	32.8 ± 3.4**	25.7 ± 10.3	16.4 ± 5.5	26.8 ± 3.8	96.5 ± 19.3
	a3b1	16.7 ± 0.6	36.5 ± 6.8	24.5 ± 7.6	31.3 ± 5.1	56.6 ± 13.6
with K+ (1mM)	a1b1	18.9 ± 4.8	110,0 ± 3.9##	47.4 ± 10.8	49.1 ± 1.1	58.7 ± 8.0
	a2b1	n.d.	52.2 ± 1.4	32.4 ± 3.9	56.4 ± 18.5	95.4 ± 22.3
	a3b1	24.3 ± 14.6	50.0 ± 4.2	53.1 ± 11.0	95.6 ± 7.8$	75.4 ± 14.8

**P<0.01 vs. a1 and a3, ##P<0.01 vs. a2 and a3, $P<0.05 vs. a1 and a2, n.d. not determined

In conclusion, hNKA isoforms have different subcellular localizations and may serve different functions. The cardiac glycosides OUA, DIG, AcD and MeD, but not DTX, show isoform specific affinities which differ between the agents. Therefore, it may make a difference which of the compounds is used for therapy. However, to date it is still unclear which affinity profile is best for which disease.

P1100 Curcumin exerts Ca^{2+}-dependent positive inotropic effects in rabbit myocardium

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Curcumin (tumeric) possesses a wide range of pharmacological properties including antiinflammatory, anticarcinogenic and antioxidant effects. Curcumin has been reported to affect sarcoplasmatic reticulum (SR) Ca^{2+} handling through inhibition of the SR Ca^{2+} pump, reduction of slippage of the SERCA pump and inhibition of Ca^{2+} release channels. No functional effects of curcumin in cardiac tissue, however, have been reported.

Methods: We tested the effects of curcumin (3, 10 and 50 μmol/l) on isometric force (isolated trabeculae, adult rabbit hearts, 1 Hz, 37°C), $[Ca^{2+}]_i$ transients (confocal microscopy, fluo-4 fluorescence from single cardiac myocytes), SR Ca^{2+} content (rapid cooling contractures, RCC; caffeine-induced $[Ca^{2+}]_i$ transients), L-type Ca^{2+}-current (ICa,L; whole cell patch clamp), and myofilament Ca^{2+} sensitivity (skinned fibers). Effect of Curcumin (1-50 μmol/l) on SR Ca^{2+}-load was tested in isolated SR-vesicles.

Results: Curcumin exerted pronounced and long-lasting positive inotropic effects in isolated trabeculae (force increase by 50±14%, 136±46% und 180±39% at 3, 10 und 50 μmol/l; all $p<0.05$). At 50μmol/l the inotropic effect was associated with an increase in RCCs by 60±11% ($p<0.05$). Inhibition of SR function with cyclopiazonic acid (20 μmol/l) and ryanodine (1 μmol/l) almost completely prevented the inotropic effect. $[Ca^{2+}]_i$ transient amplitude increased after incubation with 1 μmol/l curcumin by ~40% which was parallelled by an ~20% increase in the caffeine-induced $[Ca^{2+}]_i$ transients. ICa,L was not affected by 1 μmol/l curcumin and decreased at higher concentrations. NCX-current was not affected at any concentration. SERCA was inhibited at a IC50 of ~20μmol/l, whereas ryanodine receptors were not affected. Myofilament Ca^{2+} sensitivity was unaltered at 1 and 50 μmol/l.

Conclusions: In rabbit myocardium, curcumin exerts Ca^{2+}-dependent positive inotropic effects which are mediated by the SR and occur despite a reduction of SERCA activity and ICa,L. The results are consistent with reduced slippage and/or increased efficiency of the SERCA pump.

P1101 Desmin storage restrictive cardiomyopathy with atrio-ventricular block is associated with desmin gene defects

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Background: Diseases causing restrictive cardiomyopathy (RCM) can be due to myocardial or endocardial disease: in the former, the most frequent cause is storage/accumulation either extracellular (amyloid) or intracellular (iron, or desmin). Desmin accumulation (desminopathy) affects both heart and skeletal muscle. Desminopathies have been causally linked to defects of desmin and alpha-B crystallin (CRYAB) genes. 13 mutations have been identified to date in the desmin gene (chr. 2q35), 12 in patients with desmin storage myopathy, and one in a familial dilated cardiomyopathy.

Methods and Results: We report four mutations, three novel and one known, in the desmin gene in four unrelated probands diagnosed with RCM plus atrioventricular block treated with pacemaker implantation. Of the four probands none had clinically overt skeletal muscle involvement at the time of diagnosis. Their heart disease had been diagnosed at the mean age of 30±11 years. The median follow-up was 60 months. During this interval, three underwent heart transplantation (HTx), one died while awaiting HTx, one progressed from NYHA class I to IV in 19 months, while one progressed from NYHA class I to II in 60 months. The diagnosis of desmin storage RCM was carried out through the electron microscopy study of the endomyocardial biopsy (EMB) and confirmed with the immunoelectron microscopy study in three of these patients. The fourth patient underwent HTx in another centre: his disease was not diagnosed at the time of transplantation. He was referred to our hospital for molecular genetic analysis following a miological evaluation with skeletal muscle biopsy, documenting a desmin accumulation eight years after HTx.

Molecular genetic analysis identified 4 mutations of the desmin gene: R16C, R406W, T453I, delGTATACCTTG splice site junction (exon 3). Screening of the Alpha-B Crystallin gene gave negative results. The disease was familial autosomal dominant in two cases, autosomal recessive in one and associated with a de novo mutation in one. Overall, 17 members of the four families underwent clinical and instrumental screening as well as molecular genetic analysis. Of the 17 members eight were affected and carried the desmin gene defect.

Conclusion: Desmin storage disease involving the heart causes a typical RCM plus atrioventricular block. Although two genes have been reported as associated with the disease, the desmin gene is the most likely candidate. The typical phenotype constitutes on easy cardiological marker for addressing these patients to EMB and molecular genetic analysis of the desmin gene.

P1102 Negative inotropic effect of sirolimus in isolated human cardiomyocytes

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Objective: Sirolimus plays an important role in preventing restenosis after coronary stenting: the RAVEL- and SIRIUS-study could demonstrate a significant decrease of restenosis-rate by the use of rapamycin-eluting stents. However, the pharmacological mechanism of rapamycin on cardiac contractility are still unknown. Therefore, we investigated the acute inotropic effects of rapamycin on enzymatically isolated human atrial cardiomyocytes. Isolated myocytes turned out to be ideal for examining inotropic effects of any substances based on the fact that diffusion barriers and the influences extracellular structures can be excluded.

Material and Methods: Right atrial myocardial tissue was obtained during routine aorto-coronary bypass surgery (n=8). The isolated cells were electrically stimulated (15V, 0.2Hz) and fractional cell shortening was measured on a stage of an inverted microscope using a video edge detecting system.

Results: In our examinations a dose-dependent decrease of fractional shortening of isolated myocytes could be documented for sirolimus-concentrations higher than 10 nM in comparison to the used solvent DMSO (negative inotropic effect of 14.3±5.6% at 10nM, 24.9±9.9% at 100nM, 25.3±11.1% at 1μM, $p<0.05$). Additionally, the diastolic cell length showed a significant decline with increasing concentrations of sirolimus.

Conclusion: The reduction of myocardial contractility caused by sirolimus can presumably be explained by an altered function of the sarcoplasmic reticulum since it is known that sirolimus destabilizes the cardiac ryanodine receptor. This leads to a decline of systolic calcium transients and to an increasing diastolic calcium leak of the sarcoplasmic reticulum. This calcium leak explains the descent of diastolic cell length.

Our results demonstrate for the first time a significant negative inotropic effect of sirolimus on isolated human cardiomyocytes which is probably caused by an altered function of cardiac ryanodine receptors.

P1103 Biventricular autocrine/paracrine systems in monocrotaline induced pulmonary hypertension

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Increasing evidence suggests occurrence of LV contractile dysfunction in pulmonary hypertension (PH) in the absence of LV overload. The role of autocrine/paracrine mechanisms on the development of such dysfunction remains largely unknown.

RV and LV hemodynamic and morphometric measurements along with evaluation of mRNA expression (RT real time PCR, normalized for GAPDH) of angiotensinogen (Agtg), ACE, aldosterone synthase (A-synt), chymase, ET-1, IGF-1 and BNP were carried in Wistar rats 4 (M4, n=7) and 6 (M6, n=7) weeks after monocrotaline injection (MCT, 60mg/kg, sc) and compared with sham (S, n=7): Additionally, immunohistochemical analysis in S and M6 allowed evaluation of expression and localization of ET-1 in those groups. Results presented as mean±SEM; $p<0.05$: * vs S, # vs M4, with mRNA data reported in Arbitrary Units of ratios.

MCT increased systolic RV pressure (S=21±1; M4=39±2*; M6=51±4*# mmHg) and RV/LV weight ratio (S=0.23±0.02; M4=0.37±0.03*; M6=0.58±0.03*#), whilst end-diastolic LV dimensions decreased (S=8.2±0.6; M4=6.9±0.7; M6=5.4±0.9* mm). LV function was impaired only in the M6 group: dP/dtmax (S=4953±550; M4=5263±393; M6=2205±272*# mmHg/s), time constant tau (S=22±2; M4=19±2; M6=27±2*# ms). MCT significantly changed gene expression of RV-ACE (S=1.0±0.1; M4=1.7±0.3; M6=9.8±1.4*#), LV-ACE (S=1.0±0.1; M4=1.9±0.1; M6=4.5±1.1*), RV-ET-1 (S=1.0±0.1; M4=0.7±0.1*; M6=3.2±0.8*#), LV-ET-1 (S=1.0±0.2; M4=0.9±0.1; M6=6.8±2.0*#), RV-BNP (S=1.0±0.3; M4=8.2±2.3*; M6=11.6±1.9*#), but not of LV-BNP or RV and LV Agtg, A-synt, chymase and IGF-1. RV mRNA levels were linearly related ($p<0.01$) with those of the LV, both for ACE (r=+0.88) and ET-1 (r=+0.71). Immunohisto-

chemical analysis detected ET-1 in the cardiomyocytes of both ventricles only in M6, which was, however, higher in LV free wall.
The present study showed that LV dysfunction in a model of selective RV overload is accompanied by biventricular activation of regulatory (ACE and ET-1) systems, while counter-regulatory BNP is selectively activated in the RV. Our results suggest that local autocrine/paracrine activation might be sufficient to induce myocardial dysfunction even in the absence of significant changes in ventricular loading conditions.

P1104 May right ventricular outflow tract pacing be an alternative for biventricular pacing?

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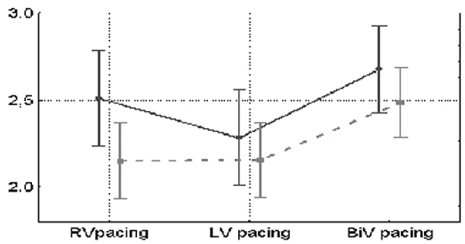
It is known, that right ventricular outflow tract pacing (RVOTp) is more beneficial than apex pacing (RVAp). There is some concern if left ventricular (LV) or RVOT pacing could be an alternative for biventrucilar pacing (BiVp). The aim: to compare acute hemodynamic effects of RVp, LVp and BiVp in pts with RV lead in RVA and RVOT position.
Methods: In 47 pts with BiVp system Cardiac Index (CI) was determined by impedance cardiography (BioZ.com; Cardiodynamics). Measurements during 5 min periods were collected and averaged, after the adaptation periods of 3 min throughout RVp, LVp and BiVp in turn. Within-subject ANOVA and post-hoc LSD test were applied.
Results: In the whole group CI was higher during BiVp than RVp and LVp as it was in the RVA subgroup. In the RVOT subgroup the difference between RVp and BiVp was not observed due to better performance of RVOT than RVA pacing (t = 2,57; p<0,02 CI). BiVp pts with RVOT RV lead location had better cardiac performance than BiVp pts with RVA lead but the between-subject comparison was not significant.

CI (l/min/m^2)	No	1) RVp	2) LVp	3) BiVp	ANOVA LSD test p<0,05
All pts	47	2,29	2,20	2,56	1-3, 2-3
RVA subgroup	29	2,15	2,15	2,48	1-3, 2-3
RVOT subgroup	18	2,51	2,28	2,68	1-2, 2-3

Within subject ANOVA p<0,0001



CI in RVOT subgroup (upper), RVA (lower).

Conclusions: RV pacing in RVOT position is superior to RVA pacing and brings similar hemodynamic effect as BiVp. RVOTp may be an alternative for BiVp at least in pts with LVp difficulties.

P1105 The mobilization of CD34+, CD117+, CXCR4+, c-met+ tissue-committed stem cells into peripheral blood in patients with acute myocardial infarction

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Bone marrow-derived adult stem cells can contribute to myocardial regeneration after ischaemic injury. Bone marrow and skeletal muscles contain a population of CXCR4+ cells expressing genes specific for early muscle-committed progenitor cells which circulate in the peripheral blood and can be mobilized by ischaemia-related inflammatory cytokines. The aim of the study was to assess the change in the number of circulating CD34+, CD117+, c-met+ and CXCR4+ tissue-committed stem cells (TCSC) and the concentration cytokines: SDF-1, G-CSF, VEGF, IL-6 and HGF in patients with AMI in comparison to stable chronic angina (SA).
Patients and methods: 56 patients with AMI (< 12 hours) and 39 with SA were enrolled. Peripheral blood samples (PBS) were drawn on admission, after 24 hours and 7 days. PBS was incubated with anti-CD34, anti-CD117, anti-c-met and anti-CXCR4 monoclonal antibodies and assayed on FACSCalibur flow-cytometer and results were expressed as the absolute number of cells per 1 μL of blood. Real-time PCR was used for detection of cardiac, muscle and endothelium specific markers.
Results: Table 1 shows the the change in the number of TCSC in PBS in AMI patients in comparison to SA patients. In logistic regression the SDF-1 levels >1000 pg/mL were the independent predictor of significant increase [> 100 cells/μL] of CD34+ cells number [OR (95%CI) 5.6 (1.4-23) p=.01]. Real-time PCR revealed that TCSC express (up to 35-fold increase) mRNA for specific cardiac (GATA4, MEF2C, Nkx2.5/Csx), muscle (Myf5, Myogenin, MyoD) and endothelial (VE-cadherin, von Willebrand factor) markers.

Table 1.

	Stable angina	AMI baseline	AMI 24 hrs	AMI 7 days
CD34+	28 (0-128)	86 (0-1190)*	72 (0-627)*	101 (0-1259)*
CD117+	356 (113-3478)	613 ((0-17190)**	518 (105-13744)	461 (125-31126)
CXCR4+	1107 (513-2149)	1486 (377-4575)*	1455 (115-5462)*	1558 (408-3987)*
c-met+	1270 (448-7463)	10225 (861-53779)*	14658 (1143-97896)*	8411 (562-111996)*
HGF [pg/ml]	213	271*	379*	220
SDF-1 [pg/ml]	2123	987*	1045**	1769*

*p<0.01; **p<0.05 vs. SA.

Conclusion: The study demonstrates in the setting of AMI a marked mobilization of circulating tissue-committed stem cells expressing specific cardiac, muscle and endothelial markers and shows that SDF-1 is an important factor influencing the mobilization.

P1106 Selective cerebral overexpression of growth hormone alters cardiac function, morphology, energy metabolism and catcholamines in transgenic mice

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Background: Growth hormone (GH) has important regulatory effects on cardiac morphology and function both during normal development as well as in pathophysiological settings such as myocardial infarction (MI) and congestive heart failure (CHF). The aims of this study were to evaluate the effects of selective overexpression of GH in the brain on cardiac morphology, function, interaction between GH and sympathetic nervous system (SNS) as well as on cardiac and brain energy metabolism.
Methods: Transgenic mice with selective GH overexpresssion in the brain under control of the glial fibrillary acidic protein promoter (GFAP-bGH, n = 15) were created and compared to genetically matched non-transgenic littermate controls (C, n = 15). Cardiac morphology and function were evaluated in vivo using transthoracic echocardiography during resting and stress conditions induced pharmacologically by dopamine (D) and isoprtenolol (ISO). Myocardial and brain energy metabolism were evaluated noninvaseively using in vivo volume-selective phosphorus magnetic resonance spectroscopy (31P MRS). Myocardial content of noradrenaline (NA) was analyzed by means of HPLC.
Results: Compared to the C animals, the bGH mice have show several differences in the cardiac phenotype. Systolic (fractional shortening) and diastolic function (E/A wave ratio) was disturbed in the GFAP-bGH mice ($p < 0.05$). During the dopamine stress, there was chronotropic insufficiency in the bGH group ($p < 0.01$) while no difference was observed in response to isoprotenolol. Left ventricular dimensions were increased in GFAP-bGH mice ($p < 0.05$). There was no difference in body weight, heart weight and brain weight. Myocardial content of noradrenaline was lower in the GFAP-bGH group ($p < 0.05$). PCr/ATP ratio was higher in the brain (2.98 ± 0.14 v. 2.15 ± 0.14, $p < 0.05$) and lower in the heart ($1,59 \pm 0,07$ v. $1,96 \pm 0,04$, $p < 0.05$) in the GFAP-bGH mice.
Conclusions: Selective cerebral overexpression of GH results in marked alterations of cardiac function, morphology and metabolism in transgenic mice. Decreased myocardial content of catecholamines in GFAP-bGH mice suggests complex interaction between GH and sympathetic nervous system that my be involved in altered cardiovascular phenotype of the GFAP-bGH mice.

P1107 Translocated Rho kinase from cytosol to nucleus interacted with p300 and subsequently upregulated c-fos, NF-kB, and b-MHC gene expression in cardiac myocytes

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A small GTPase, RhoA, participates in cytoskeletal organization and gene expression. We have previously reported that RhoA stimulates c-fos gene expression through c-fos serum response element (SRE) in cardiac myocytes (CM). Rho kinase (Rho-K) has been reported to bind with RhoA and modulate Endothelin-1 (ET-1)-induced cardiac myocyte hypertrophy. Transcriptional coactivator p300 plays an important role for transcription in CM and is known to relate cardiac myocyte hypertrophy. However nothing is known about the role of p300 in RhoA-mediated gene expression. c-fos promoter/enhancer and b-MHC promoter/enhancer linked to the luciferase reporter gene (c-fos luciferase and b-MHC luciferase, respectively) and luciferase reporter gene driven by multimerized NF-kB sites (NF-kB luciferase) were activated by dominant active type (DA) RhoA (RhoAval14), DA Rho-K (Rho-K CAT) and p300. RhoA-induced these luciferase expressions were inhibited by dominant negative type (DN) Rho-K (Rho-K RB/PH.TT) and DN p300 (p300A). Also Rho-K-induced these luciferase expressions were inhibited by p300A. The deletion and mutation analysis revealed that c-fos SRE accounts for c-fos luciferase expression by RhoA, Rho-K and

p300. Rho-K fused GFP (Green Fluorescence Protein) (GFP-Rho-K) was located in the cytosol under no stimulation. However GFP-Rho-K was translocated into nucleus by RhoAval14 stimulation. Furthermore, RhoAval14 fused GFP (GFP-RhoAval14) also translocated into nucleus. In vitro protein-protein interaction assay, 35S methionin-labeled p300 bound GST fusion Rho-K protein. Furthermore, in mammalian two-hybrid assay, Gal4-p300 (p300 fused to Gal4) and VP16-Rho-K (Rho-K fused to VP16) activated Gal4 luciferase expression, which means the possibility that Rho-K bound with p300. Finally, nuclear extracts from CM after ET-1 stimulation were immunoprecipitated using anti-p300 antibody. Not only Rho-K but SRF(Serum Response Factor) were co-immunoprecipitated with p300. These results indicated that activated Rho-K translocated into nucleus and bound with p300, subsequently c-fos gene expressions were upregulated through SRE in CM.

P1108 Alteration of sympathetic function in hibernating myocardium

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Background: Chronic left ventricular (LV) dysfunction in patients (pts) with coronary artery disease (CAD) that improves after revascularization is known as hibernating myocardium (HM). Despite a global decrease of sympathetic effectors, which occurs in heart failure secondary to an increased sympathetic stimulation, HM responds transiently to sympathomimetics such as dobutamine. We hypothesised that the beta-adrenoceptor (beta-AR) axis is functionally impaired, but still responsive in HM. To test this, we measured in vivo with positron emission tomography (PET) presynaptic norepinephrine (NE) reuptake-1 (11C-hydroxyephedrine) and post-synaptic beta-AR density (11C-CGP-12177) and correlated the results with the expression of intracellular regulators of the beta-AR signalling axis in myocardial biopsies ex vivo.
Methods: Eighteen pts with angiographically proven CAD and LV dysfunction (ejection fraction 38±11%) underwent function and viability assessment with cardiovascular magnetic resonance (CMR). PET data in pts were compared with those in 30 healthy controls. HM was defined as dysfunctional, but viable segments subtended by stenosed coronaries. During bypass surgery, myocardial biopsies were taken from HM and remote myocardium (RM) and processed for RNA extraction. Transcripts encoding beta1-AR, beta2-AR, Gs-alpha, and adenylate cyclase-6 were measured by quantitative PCR. Six months post bypass, improvement of wall motion demonstrated by CMR by at least one degree was considered significant.
Results: All biopsied hibernating segments showed significant functional improvement at 6 months follow-up. Both NE re-uptake and total (beta1+beta2) AR density in vivo were significantly reduced in pts compared to controls ($p<0.001$), with no difference between HM and RM (NE reuptake 53.4±29.7 mL/g vs 53.1±20.9 mL/g, p=ns; compared to 65.7±17.6 mL/g in controls and beta-AR density 5.53±2.06 pmol/g vs 5.69±1.81 pmol/g per g tissue, p=ns; compared to 10.5±3.76 pmol/g in controls). However, mRNA encoding beta1- and beta2-AR were reciprocally regulated (beta1-AR mRNA HM > RM; beta2-AR mRNA RM > HM, both $p<0.05$) while Gs-alpha and adenylate cyclase mRNAs were significantly reduced in HM ($p<0.05$).
Conclusion: While no differences were seen in pre-synaptic NE re-uptake and beta-AR density between HM and RM, there are significant differences in the mRNA expression of beta-AR subtypes and intracellular signalling pathway represented by Gs-alpha and adenylate cyclase. This might contribute to the dysfunction of HM in the presence of a maintained response to dobutamine.

P1109 Altered glucose metabolism during myocardial remodeling: MEF2 regulates the transcription of glucose transporter GLUT4 in cardiac myocytes

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The change in the morphological phenotype of cardiomyocytes during left ventricular remodeling is associated with resumption of a fetal pattern of gene expression, referred to as dedifferentiation. There occurs a shift from fatty acid to glucose metabolism, even at low insulin concentration, which is caused at least in part by downregulation of the insulin-sensitive glucose transporter GLUT4 and compensatory upregulation of less insulin-sensitive GLUT1.
To study the molecular mechanisms influencing expression of GLUT4, we have resorted to adult rat cardiomyocytes (ARC) in primary culture that undergo spontaneous dedifferentiation, including downregulation of GLUT4 (GLUT4 protein -47±14% on day 2). Exposure to Insulin-like Growth Factor-1 (IGF-1), and to a lesser extent to Fibroblast Growth Factor-2 (FGF-2), restored normal levels of GLUT4 expression. The effect of both growth factors was mediated by activation of the p38 MAP kinase. Transient transfection of neonatal rat cardiomyocytes (NRC) with MEK6DD, a constitutively active p38 MAPK kinase, stimulated transcription from the rat glut4 promoter. This effect was prevented by treatment with the pharmacological p38 MAPK inhibitor SB203580.
p38 MAPK activates the transcription factor Myocyte-specific Enhancer Factor 2 (MEF2), which is required for skeletal muscle and adipose tissue GLUT4 expression. We determined whether MEF2 mediates the effects of IGF-1 and FGF-2 on GLUT4 expression. Nuclear localization of MEF2, which indicates activation, was low during dedifferentiation (11% of MEF2-positive nuclei), but increased in response to IGF-1 (44%) and FGF-2 (36%). Growth factor-enhanced nuclear localization of MEF2 was reduced by treatment with SB203580. Similarly, IGF-1 and FGF-2 increased in a p38 MAPK-dependent manner the binding of ARC nuclear proteins to a consensus MEF2 binding site in the glut4 promoter. Mutation of the MEF2 binding site in the rat glut4 promoter transfected into NRC reduced both baseline and MEK6DD-stimulated transcription.
In conclusion, the transcription factor MEF2 plays a central role in transcription of GLUT4. Inactivation of MEF2 may contribute to suppression of GLUT4 during dedifferentiation of cardiomyocytes, which can be reversed by p38-mediated reactivation of MEF2.

P1110 Impact of catecholamines on SERCA2A expression: signal transduction and functional consequence

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Background: Catecholamines contribute via stimulation of a-adrenoceptors to the adaptation of the heart to increased afterload. The role and mechanisms by which this pathway increases myocardial mass has been established. The functional consequences of this hypertrophic responsiveness has not been addressed and was investigated now.
Methods: Cultured adult ventricular rat cardiomyocytes were treated with phenylephrine (PE, 10 μM), a selective a-adrenoceptor agonist. Cell function was determined after 24 h via a cell edge detection system at low (0.5 Hz) and high (2.0 Hz) beating frequencies as unloaded contraction or in presence of viscous load. Intracellular calcium concentrations were determined via fluorescence (FURA) signalling, protein expression of SERCA2A was determined by immunoblot technique and its mRNA expression by real-time RT-PCR. Activation of transcription factor NFAT was quantified by electromobility shift assays and NFAT activity was blocked by transfection of cardiomyocytes with NFAT decoys.
Results: Chronic treatment of cardiomyocytes with PE impaired cell shortening under viscous load (400 cP) at 0.5 Hz from 7.25±0.40% to 4.82±0.62%, n=12 cells, $p<0.01$). At 2.0 Hz this reduced activity was largely compensated due to increased relaxation velocity (137±15 μm/s to 181±36 μm/s, $p<0.05$). In parallel, SERCRA2A protein expression increased (2.3±0.3-fold) and mRNA expression 1.9±0.4-fold ($p<0.05$). The effects on cell activity were independent of PKC and ERK-activation and therefore not linked to hypertrophic growth. In a PKC-independent manner, PE induced an increase in diastolic cell calcium and activation of NFAT. As NFAT is known to be activated via the calcium/calcineurin pathway, this pathway was blocked more directly by addition of the calcium chelator BAPTA or cyclosporine. In both cases, induction on SERCA2A expression and increases in relaxation velocities were inhibited. Inhibition of NFAT activity with neutralizing decoys reduced SERCA2A expression with no effect of scramble decoys.
Conclusions: Under chronic stimulation of a-adrenoceptors cardiomyocytes tend to develop a functional deficit, which is partly antagonized by PE-dependent activation of the calcium/calcineurin/NFAT pathway leading to increased SERCA2A expression. This allows the cell to maintain cell function at increased afterload as mimicked by viscous load.

P1111 Intracellular calcium handling in isolated rabbit cardiac myocytes overexpressing cytoplasmic vs. nuclear CaMKIIdelta isoform

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Ca/calmodulin-dependent protein kinase II delta (CaMKIIdelta) is the predominant isoform of CaMK in the heart. We reported that overexpression of the cytoplasmic deltaC isoform in transgenic mice induces heart failure and severely alters Ca handling by increasing SR Ca leak through CaMKII-dependent ryanodine receptor (RyR) phosphorylation. Here we overexpressed CaMKIIdeltaC vs. deltaB (nuclear form) and LacZ control by adenoviral gene transfer (MOI 100, 24 h) in rabbit myocytes to circumvent possible indirect effects in transgenics and to compare the effects of different subcelluar CaMKIIdelta overexpression. Protein expression of CaMKIIdeltaC and deltaB was ~4-6-fold that of LacZ control with similar increases in phosphorylated CaMKII. When increasing stimulation rate from 0.5-3 Hz, twitch shortening in CaMKIIdeltaC transfected myocytes (n=36) decreased by 19 vs. 9% in LacZ (n=29). Relaxation measured by tau in CaMKIIdeltaC rate-dependently accelerated by 89 vs. 77% in LacZ. In CaMKIIdeltaB (n=30) vs. LacZ (n=43) there was no difference in shortening or relaxation between groups. In CaMKIIdeltaC peak Ca current (ICa) was increased by 33% (-5.3±0.4 vs. -3.6±0.4 pA/pF; $p<0.05$). [Ca]i was reduced by 27% in the face of

a 41% reduction in SR Ca load ($p<0.05$). Thus fractional SR Ca release was increased by 60% ($p<0.05$). Resting Ca spark frequency (CaSpF) was also 12% higher in CaMKIIdeltaC cells despite the lower SR Ca load, thus CaSpF normalized to SR Ca load was increased by 88% ($p<0.05$) leading to a distinct SR Ca leak. RyR phosphorylation was significantly increased, whereas FKBP-RyR interaction using co-immunoprecipitation did not show FKBP dissociation from RyR. In contrast, in CaMKIIdeltaB no significant changes for ICa, [Ca]i, or SR Ca load were found. SERCA & NCX function were not altered in CaMKIIdeltaC cells, suggesting that the altered function observed in CaMKIIdeltaC transgenics resulted from the heart failure phenotype. We conclude that the effects of CaMK overexpression on RyR function and SR Ca leak as observed in transgenic mice are mimicked by adenoviral expression in myocytes, and that CaMKIIdeltaC directly increases diastolic RyR opening and enhances E-C coupling efficacy whereas the nuclear isoform CaMKIIdeltaB exerts no functional effects.

P1112 Recovery of Ca transients, SR Ca reuptake and shortening during acidosis requires the CaMKII/PLB signaling pathway but is impaired in heart failure

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During acidosis, Ca transients ([Ca]i) are decreased and the relaxation of [Ca]i decline (tauCa) is prolonged, but later during acidosis [Ca]i and tauCa partially recover. To test whether CaMKII-dependent phospholamban (PLB) phosphorylation is required for this recovery we used cardiac myocytes from rabbits and overexpressed CaMKIIdeltaC using adenoviral gene transfer (MOI 100, 24 h). In addition, myocytes from PLB knockout (PLB-KO) and transgenic mice overexpressing CaMKdeltaC (CaMK-TG) having heart failure vs. wild-type (WT) mice were investigated. Twitch shortening was recorded at 1 Hz during control conditions (pH 7.4) and acidosis (pH 6.5). [Ca]i was measured using indo-1 and fluo-3, SR Ca content was assessed using caffeine contractures (10 mM). CaMKII was inhibited using KN-93 (1 μM). During the initial phase of acidosis (1-4 min) in WT mouse (n=8), [Ca]i decreased from 1.8 ± 0.2 to 1.1 ± 0.1 F/F0 ($p<0.05$) and relaxation prolonged ($p<0.05$). Later during acidosis (6-12 min), [Ca]i and relaxation partially recovered by ~50%. KN-93 completely prevented this recovery of [Ca]i and tauCa^{-1} during late acidosis in WT. In PLB-KO mouse myocytes (n=11) [Ca]i decreased during early acidosis from 2.9 ± 0.3 to 1.3 ± 0.2 F/F0 ($p<0.05$) and tauCa^{-1} decreased from 10.5 ± 0.6 to 7.6 ± 0.7 s^{-1} ($p<0.05$). However, [Ca]i and tauCa^{-1} did not recover during late acidosis. Parallel results were seen for shortening and caffeine contractures. In freshly isolated rabbit myocytes (n=10), recovery of shortening during late acidosis (by 53%) and [Ca]i (by 55%) as well as relaxation parameters were prominent and could be inhibited using KN-93 ($p<0.05$) similar to WT mouse. In contrast, when overexpressing CaMKIIdeltaC acutely by 4-5 fold in rabbit myocytes (n=5), there was an increased recovery for shortening (77 vs. 58%), [Ca]i (65 vs. 57%), and improved relaxation (by ~10%) vs. LacZ control (n=5). In CaMK-TG myocytes (n=7; chronic CaMKIIdeltaC overexpression) the ability to recover during late acidosis was impaired vs. WT (n=5) myocytes. Shortening in CaMK-TG increased from 4.69 during early acidosis to 6.41% RCL) during late acidosis whereas shortening only increased from 4.41 to 5.58% RCL in CaMK-TG. We conclude that CaMKII and PLB are crucial to the recovery of [Ca]i and relaxation during acidosis. Moreover, PLB phosphorylation by CaMKII leading to enhanced SR Ca uptake plays an important role in limiting the decline in [Ca]i (and contraction) during acidosis. However, in our heart failure model overexpressing CaMKIIdeltaC, where PLB and SR Ca ATPase expression is reduced, recovery during acidosis is impaired.

P1113 Do the changes in expression of sarcoplasmic reticulum Ca^{2+} ATPase and Na^{+}–Ca^{2+} exchanger protein levels modify the natural course of left ventricle dysfunction?

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Reduced contraction and slowed relaxation are the central features of the failing heart. Both have been attributed to changes in Ca^{2+}-ATPase of the sarcoplasmic reticulum (SERCA 2) and Na^{+}/Ca^{2+} exchanger (NCX) expression. In human subjects however, the influence of the expression changes on the natural course of left ventricle dysfunction is unknown. The purpose of our study was to estimate the impact of the alteration in SERCA 2 and NCX expression on the grade and course of left ventricle dysfunction in volume overload.

The study group was composed of 36 patients, (mean age 62 years), with heart failure due to volume overload secondary to severe mitral regurgitation. On echo exam following abnormal parameters were observed: left ventricle (ESVI 51, SE $\pm$ 5.4 ml/m^2, EDVI 123 ml/m^2, SE $\pm$5.2; SVI 72 ml/m^2, SE $\pm$ 3), left atrium (60 mm, SE $\pm$ 0.2), systolic pulmonary pressure (sPAP 47 mmHg, SE $\pm$ 4). All subjects had normal coronary angiograms. The increase in BNP (pg/ml - 144, SE $\pm$ 23), noradrenaline (pg/ml - 568, SE $\pm$ 44), TNFalfa (pg/ml - 24, SE $\pm$ 2.1.) and its soluble receptors sR1 (ng/ml - 1.3, SE $\pm$ 0.08) along with sR2 (ng/ml - 2.65, SE $\pm$ 0.15) were discovered.

During mitral valve replacement specimens from the anterior papillary muscle of left ventricle were obtained. The expression of SERCA2 and NCX on protein levels were determined by Western blot.

By discriminant analysis according to ESVI the patients were divided into two groups: A (n = 19 pts) ESVI $<$ 55 ml/m^2; B (n = 17 pts) ESVI $>$ 55 ml/m^2.

Both groups do not significantly differs in gender, mean age and period of disease course. The group B revealed reduced expression of SERCA 2 and normal expression of NCX in contrast to group A where normal expression of SERCA2 with increased expression of NCX were observed. Group B in comparison to group A besides the most severe left ventricle dysfunction (ESVI - ml/m^2 - 82, SE $\pm$ 13 vs. 38, SE $\pm$ 2, respectively, $p < 0.005$; EDVI - ml/m^2 - 148, SE $\pm$ 12 vs.112, SE $\pm$ 4, respectively, $p< 0.005$), presented greater neurohumoral activation: BNP (pg/ml - 240, SE $\pm$ 45 vs. 96, SE $\pm$ 22, $p < 0.005$), noradrenaline (pg/ml - 748, SE $\pm$ 80 vs. 481 SE $\pm$ 45, respectively $p < 0.005$), TNFalfa (pg/ml - 35, SE $\pm$ 3 vs.18, SE $\pm$ 1.8, respectively, $p < 0.001$).

In homogenous group of patients with heart failure due to volume overload, we found the association between two distinct phenotypes (changes in expression of SERCA 2 and NCX) and the grade of left ventricle dysfunction. The phenotypic changes may affect the natural course of left ventricle dysfunction secondary to mitral valve dysfunction.

P1114 Regulation of melusin differentiates molecular pathways of pressure and volume load induced cardiac hypertrophy

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Background: Melusin, an intracellular partner of integrins, is necessary for pressure-induced left ventricular hypertrophy (LVH) and prevents cardiac dilatation during chronic pressure overload by specifically sensing mechanical stress. However, melusin is not involved in angiotensin-II and norepinephrin mediated hypertrophy and thus may be a useful marker to differentiate different forms of hypertrophy. In order to characterize differences between LVH induced by pressure and volume load at a molecular level, we measured the expression of melusin together with a number of hypertrophy associated genes in both conditions.

Methods: We quantitated melusin mRNA and protein in hearts from rats subjected either to aortic banding (AoB) or aorto-caval shunt (Shunt). MRNA for the renin-angiotensin (RAS) and endothelin (ET) system (AT1, ET1, ETRA, ETRB, ECE1), hypertrophy associated growth factors (TGFbeta1, CTGF, ITGbeta1, OPN), collagen (Col1, Col3) and matrix metalloproteinases and their inhibitors (MMP2, MT-1 MMP, TIMP1-4) were determined by Real Time PCR in the same samples (TaqMan). GAPDH served as external control.

Results: We found a significant upregulation of melusin mRNA and melusin protein in AoB, but not in Shunt animals. In contrast, most other genes were regulated in both conditions. The most striking differences between AoB and Shunt were found for CTGF which was upregulated 15-fold in AoB and 5-fold in Shunt, for OPN (8-fold in AoB, 5-fold in Shunt), and TIMP-1 (7-fold in AoB and 4-fold in Shunt). In contrast, Shunt animals showed a more severe upregulation of the neurohormonal parameters belonging to the RAS and ET system compared to AoB- AT1, ETRA and ETRB were increased 3.2-, 3.4- and 3.3-fold in Shunt and 1.81-, 1.9- and 2.3-fold in AoB.

Conclusion: So far, melusin is the only stress protein to be upregulated only in AoB but not in Shunt. In contrast, the myocardial RAS and ET systems were much stronger activated by volume load than by pressure load. Melusin might be a key factor that contributes to the different phenotype of concentric and excentric LVH in AoB and Shunt.

P1115 Downregulation Erb2 and Erb4 Receptors in patients with congestive cardiomyopathy and in patients with pressure overload hypertrophy due to aortic stenosis is related to diastolic load

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Background: Neuregulin-erbB signaling promotes cell survival and growth. In model of LV hypertrophy (H) due to aortic stenosis (AS), transition to failure was associated with downregulation of erbB2 and erbB4 receptors. However, the regulation of erbB receptors in human LVH or failure is unknown. Note, use of erbB2 antibodies in breast cancer women resulted in higher incidence of congestive heart failure (CHF). Therefore, we investigated LV myocardial expression of erbB2 and erbB4 receptors in patients (pts) with LVH due to AS and pts with CHF due to idiopathic congestive cardiomyopathy (CCMP).

Methods: LV biopsies were obtained perioperatively in 8 AS pts, and in 5 pts with CAD with normal LV function (Control) and at cardiac catheterization in 14 CCMP pts. ErbB2 and ErbB4 receptor message levels were determined by the real time quantitative Taq Man PCR.
Results (*p<0.05 vs Control by ANOVA):

	Control (n=5)	CCMP (n=14)	AS (n=8)
LV EF (%)	69±3	19±2*	72±4
LV EDVI (ml/m^2)	73±13	150±21*	73±13
LV EDP (mmHg)	10±2	21±3*	17±2*
Erb2/GADPH (rel. units)	13.5±3.5	5.7±0.8*	5.3±0.7*
Erb4/GAPDH (rel. units)	2.9±0.5	1.8±0.4	1.2±0.2*

CCMP pts had lower LV ejection fraction (EF) and higher end-diastolic volume index (EDVI) vs control and AS pts. AS and CCMP pts had higher LV end-diastolic pressure vs controls. ErbB2 and ErbB4 message levels were lower in AS and CCMP pts vs controls. Note, in the whole study population, erbB2 and erbB4 levels inversely related with LV EDP (r = -0.75 and r = -0.50, both p<0.05) and with PCW (r = -0.68 and r = -0.62, both p<0.05). No significant relationship was observed with LV EF or LV systolic pressure.
Conclusion: Neuregulin receptors erbB2 and erbB4 are downregulated in pts with pressure overload hypertrophy or congestive cardiomyopathy. The inverse relationship between expression of both receptors and diastolic load suggests that disabled erbB receptor signaling may contribute to progression of heart failure in patients with pressure overload hypertrophy or congestive cardiomyopathy.

P1116 Non-excitatory cardiac contractility modulation electric signals normalize phosphorylation and expression of the sodium calcium exchanger in left ventricular myocardium of dogs with heart failure

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Background: The cardiac sarcolemmal sodium-calcium exchanger (NCX) is hyperphosphorylated in heart failure (HF) and its mRNA and tissue protein expression are up-regulated. These maladaptations can contribute to LV dysfunction in HF. We previously showed that in dogs with HF, short-term delivery of non-excitatory cardiac contractility modulation (CCM) electric signals to LV muscle during the absolute refractory period leads to improvement in LV function. This study explored whether short-term CCM therapy down-regulates the expression and normalizes the phosphorylation of NCX (P-NCX) in LV myocardium of dogs with HF.
Methods: Studies were performed in 6 dogs with coronary microembolizations-induced HF. CCM signals were delivered continuously for 4 hrs from epicardial leads placed on the LV anterior wall via a left throracotomy. At the end of therapy, LV anterior wall tissue was used to extract RNA. RNA was also extracted from LV tissue of 6 normal (NL) dogs and 6 dogs with untreated HF. mRNA expression for NCX was determined using reverse transcriptase polymerase chain reaction (RT-PCR). The RT-PCR product was confirmed as NCX by gene sequencing. Bands were quantified in densitometric units and normalized to GAPDH. Tissue homogenate was used to isolate phosphorylated proteins using a Phosphoprotein enrichment kit. SDS-extract was prepared from isolated phosphorylated proteins and from LV tissue homogenate. Total and P-NCX protein were quantified using Western blots. P-NCX was expressed in densitometric units normalized to total NCX protein.
Results: Compared to NL, mRNA expression for NCX increased in untreated HF dogs (table). CCM therapy restored NCX mRNA expression to near normal. Total and P-NCX protein increased in untreated HF dogs compared to NL. CCM therapy restored total and P-NCX to near normal levels.

	NL	HF-Untreated	HF + CCM
NCX mRNA/GAPDH	2.11 ± 0.13	3.83 ± 0.11*	2.93 ± 0.23**
Total NCX Protein	0.39 ± 0.02	0.62 ± 0.03*	0.43 ± 0.02**
P-NCX/Total NCX Protein	0.41 ± 0.03	0.83 ± 0.06*	0.48 ± 0.04**

*=p<0.05 vs. NL; **=p<0.05 vs. HF Untreated

Conclusions: In dogs with HF, short-term CCM therapy, normalizes P-NCX and downregulates total NCX protein and NCX mRNA expression. The observations may explain, in part, improvement of LV function seen in dogs with HF following short-term CCM therapy.

P1117 Increased expression and activity of the myocardial Na-K-2Cl cotransporter during ischaemic heart failure

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We have previously shown in isolated rat hearts that the loop-diuretic sensitive Na-K-2Cl cotransporter (NKCC) is activated by phenylephrine and angiotensin II by a mechanism involving the MAP kinase pathway. The NKCC mediates electroneutral ion transport and is a key regulator of cell volume in many cell types. A possible role of the NKCC in pathophysiological conditions like myocardial infarction and heart failure has not been studied before.
Aim: We assessed the hypothesis that the expression and activity of the myocardial NKCC are changed during ischemic heart failure in rats.
Methods: NKCC mRNA expression was analysed by real-time quantitative PCR in the cardiomyocyte (CM) fraction and non-CM fraction of myocardial tissue isolated from the left ventricle of rats 7 days after induction of myocardial infarction or sham operation. Furthermore, immunohistochemical analysis was performed to localise NKCC in the myocardium. In addition, NKCC activity measured as bumetanide-sensitive 86-rubidium (potassium analogue) influx was studied in isolated perfused failing rat hearts and sham-operated hearts in order to study whether the function of the NKCC was changed after induction of myocardial infarction (MI).
Results: The basal levels of NKCC mRNA expression were highest in the non-CM fraction, but an increased expression of the NKCC mRNA was found exclusively in the CM fraction (2.2-fold increase, p<0.001). Immunohistochemical analysis revealed the presence of NKCC immunoreactivity in the CMs and in vascular endothelial cells and smooth muscle cells, as well as in fibroblasts. The 86-rubidium influx in sham hearts were 3.1 ± 0.18 (n=7) and 2.8 ± 0.26 (n=8) ml/g heart tissue/10 min in the absence and presence of 50 μmol/l bumetanide, respectively. The 86-rubidium influx in post-MI hearts were 2.4 ± 0.18 (n=6) and 1.8 ± 0.16 (n=6) ml/g heart tissue/10 min in the absence and presence of bumetanide, respectively (27% reduction, p<0.01). This corresponds to a 100%increase in bumetanide-sensitive 86-rubidium influx(0.3 vs. 0.6 ml/g heart tissue/10 min in sham and post-MI hearts, respectively).
Conclusion: The NKCC is present and functional in the rat heart. Increased gene expression of NKCC in CMs and increased ion transport mediated by this cotransporter are found in ischemic heart failure. The results indicate a role of the NKCC during post-infarction remodelling and development of heart failure, possibly by changing intracellular ion content and cell volume of cardiomyocytes.

P1118 Activation of the calcineurin/NFAT signalling cascade in human hypertrophied myocardium

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Introduction: Cardiac hypertrophy is an independent risk factor for the development of heart failure. Altered Ca^{2+}-homeostasis and its functional effects in human hypertrophic heart have been successfully investigated. More and more molecular biological measurements have been focused on the gene regulation of the increased intracellular Ca^{2+} concentration. The calcium-sensitive phosphatase calcineurin (CN) is regarded as one potential regulator of the hypertrophic response. The aim of this study was to investigate the calcineurin dependent signal pathway in human hypertrophied myocardium.
Methods: We measured CN activity, CN protein expression, GATA-IV protein expression and expression of NFAT-3 (in nuclear and cytoplasmic extracts) in 6 biopsies from not hypertrophied (echocardiographic septal thickness <12 mm, left ventricular ejection fraction [EF] >60%) and 12 biopsies from hypertrophied (septal thickness >13 mm, 6 x EF >60, 6 x <60%) human hearts.
Results: In hypertrophied human myocardium (n=12) the calcineurin pathway was significantly activated compared to not hypertrophied myocardium (n=6). This could be shown by an increase in CN activity (0.09±0.1 vs. 0.14±0.02 nmol Pi/min/μl), an increased expression of CN subunit A and B (1046±33 DU vs. 1342±31 DU resp. 99±4 DU vs. 148±3 DU), an increased expression of GATA-IV (974±20 DU vs. 1079±16 DU) and a by shift of phosphorylated cytoplasmic NFAT-3 (4177±208 DU vs. 1809±123 DU cytoplasmic extracts) into the nucleus as dephosporylated nuclear NFAT-3 (475±3 DU vs. 556±2 DU nuclear extracts). The activation of the CN cascade was still significant when comparing biopsies from compensated (EF>60%, n=6) and decompensated (EF<60%, n=6) myocardium separately with not hypertrophied human hearts. Between the hypertrophied samples there was no significant difference but a tendency to an increased expression of CN A and B, GATA-IV and an increased shift of NFAT-III into the nucleus.
Conclusion: We found a significant activation of the Ca^{2+}-triggered calcineurin pathway in hypertrophied human myocardium. This was already present in compensated hypertrophy (EF>60%) and showed tendency to a further increase with progression of hypertrophy to heart failure (EF<60%). Our investigations in human myocardium give evidence for participation of the CN signalling cascade in development heart failure in human.

P1119 Microarray gene expression profiling in patients with congestive cardiomyopathy and pressure overload hypertrophy due to aortic stenosis

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We used the DNA microarray technique to study transcriptional profiles from LV biopsies in patients (pts) with LVH due to aortic stenosis (AS, n=9) and in congestive cardiomyopathy (CCMP,n=6). Pts with coronary artery disease and normal LV function served as normals (N, n=4). Expression levels of 12 565 transcripts were determined by Affymetrix HG-U95 Av.2 microarrays.
Results: LV mass index was higher in AS and CCMP pts vs N. CCMP pts had lower LV ejection fraction and higher systolic wall stress (WS) as compared to N (table). Statistical filtering identified significant (1.2 fold) changes in 109 genes (1%, delta = 0.24) in AS pts and 799 genes (21%, delta =0.24) in CCMP pts vs N. Among 27 commonly changes, AS and CCMP pts showed upregulation skeletal actin, troponin I and T, lamin A/C collagen I, proBNP and downregulation of myosin binding protein C and 3-OH MG Co-A synthase. Of note was a common upregulation of a transcription factor AE binding protein. While AS pts showed upregulation, CCMP pts showed downregulation of caldesmon, Janus kinase 1 and MAP kinase 4. In addition, among structural genes, CCMP was associated with downregulation of intermediate filaments proteins like catenin, plakophilin and cell adhesion molecules such as connexin 43 or [ALPHA]-integrin. Furthermore, AS pts were characterized by upregulation of several signaling molecules of Ras-MAPK family such as RAS, Janus kinase 2 or MAP kinase 4. In contrast, CCMP pts were characterized mostly by downregulation of several molecules of this signaling cascade. In addition, CCMP pts showed downregulation of transcription factors CREB, MEF 2C and HDAC.

Table 1

	Normal	AS	CCMP
LV mass (gm/m^2)	72±9	133±10*	139±14*
Systolic WS (kdyn/cm^2)	61±13	97±14	132±32+
LV ejection fraction (%)	74±2	64±5	31±5+

Conclusion: LV remodeling in pressure overload hypertrophy and congestive cardiomyopathy is related to divergent changes in genes governing critical pathways of the cell growth and survival. Identification of these genes could lead to novel description of molecular mechanisms governing LV remodeling and function in patients with failing myocardium

P1120 Targeted deletion of the nuclear factor kappa B subunit p50 reduces early mortality and prevents left ventricular dilatation after myocardial infarction

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Objective: Nuclear factor kappa B (NF-kB) is a ubiquitous transcription factor activated by various stimuli implicated in heart failure progression including reactive oxygen species, hypoxia, and inflammatory cytokines. NF-kB is involved in various cardiac pathophysiologic processes, such as ischemic preconditioning, unstable angina pectoris, and atherogenesis. However, the function of NF-kB in ischemic heart failure has not been determined yet. Therefore, we investigated left ventricular remodeling in mice with targeted deletion of the NF-kB subunit p50 after myocardial infarction.
Methods and Results: p50 knockout (KO) and wild-type (WT) animals underwent coronary artery ligation. Transthoracic echocardiography was performed at days 21 and 56 at mid-papillary levels. Early mortality was significantly lower in KO than in WT animals. p50 KOs exhibited significantly reduced ventricular dilatation over 8 weeks compared to WT controls (endsystolic diameters, WT vs. KO, 0.55±0.04 vs. 0.34±0.03cm) and preserved left ventricular contractility. Collagen content and the rate of apoptosis were similar in WT and KO. Unexpectedly, p50 KOs had a marked increase in the myocardial level of the cytokines TNF and IL-1β.
Conclusion: Deletion of the NF-kB subunit p50 improved early survival and reduced left ventricular dilatation after myocardial infarction. NF-kB might therefore be an attractive target to treat heart failure.

P1121 Targeted proteolysis activates calcineurin

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Background: Calcineurin (CnA) is important in the regulation of myocardial hypertrophy. We demonstrated that targeted proteolysis of the CnA autoinhibitory domain under pathological myocardial workload leads to increased calcineurin activity in human myocardium. Here we investigated the proteolytic mechanism leading to activation of calcineurin.
Methods and Results: In patients with diseased myocardium we found strong nuclear translocation of calcineurin. In normal human myocardium there was a cytosolic distribution of calcineurin. Stimulation of rat cardiomyocytes with Angiotensin II (210%±11; p<0.01, n=6) increased calpain activity significantly. Stimulation of cardiomyocytes with Angiotensin II (AngII) caused proteolysis of the autoinhibitory domain of calcineurin as demonstrated by Western Blotting. Inhibition of calpain by a membrane permeable calpaininhibitor (Calpaininhibitor III, Calbiochem) prevented proteolysis. Activity of calcineurin was assessed by transfection of cardiomyocytes with a specific reporter plasmid (pNFAT-LUCI, Stratagene) and subsequent measurement of luciferase activity. Calcineurin activity was increased after Angiotensin II stimulation (310%±29; p<0.01, n=6) and remained high after removal of Angiotensin. Addition of calpain inhibitors to the medium decreased calcineurin activity (110%±19; p=n.s., n=6) after removal of angiotensin. AngII stimulation of cardiomyocytes translocated calcineurin lacking the autoinhibitory domain into the nucleus as demonstrated by immunohistochemical stainings and transfection assays with GFP-tagged calcineurin. Calpaininhibition and therefore prevention of proteolysis of calcineurin enabled calcineurin exit from the nucleus.
Conclusion: 1) Angiotensin II stimulation of cardiomyocytes increased calpain activity, leading to 2) proteolysis of the autoinhibitory domain of calcineurin. 3) This causes an increase in calcineurin activity and results in nuclear translocation of calcineurin. 4) Loss of the autoinhibitory domain renders calcineurin constitutively nuclear and active, even after removal of the hypertrophic stimulus.

P1122 PI-3-kinase dependent inotropic effects of insulin in failing human myocardium

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Insulin exerts trophic effects in various organs including the heart. However, little and controversial data exist regarding direct functional effects on myocytes. We investigated inotropic actions and underlying subcellular mechanisms of insulin in isolated failing human myocardium.
Methods: Isolated ventricular trabeculae from failing human hearts (n=42), electric stimulation (1 Hz), isometric contractions, 37°C, 2.5mM Ca^{2+}. Simultaneous registration of intracellular Ca^{2+}-transients (aequorin method; n=5) or SR-Ca^{2+}-load (rapid cooling contractures, RCCs; n=7). Protocols: Single doses of insulin (0.3 and 3 I.U./L) 1) in glucose containing tyrode (n=9); 2) after pharmacological blockade of glycolysis (5mmol/l iodacetate; n=6) or substitution of glucose with pyruvate (n=10); 3) after blockade of PI-3-kinase (wortmannin 0.1μM; n=7), IGF-1-receptors (alpha-IR3-antibody), NCX-reverse mode (KB-R7943; 5μM), and DAG-kinase (DAG-inhibitor II; 1μM) in glucose-containing tyrode solution.
Results: Insulin concentration-dependently increased twitch force to 112±1% and 126±6% of baseline at 0.3 and 3 I.U./L, respectively (p<0.05 for both) in insulin-free solution. At 3 I.U./L, Ca^{2+}-transients increased to 116±4%, and SR-Ca^{2+}-load (RCC) to 115±5% (both p<0.05). Substitution of glucose with pyruvate (force increase to 110±3% and 107±2% at 0.3 and 3 I.U./L) or blockade of glycolysis (to 109±3% at 3 I.U./L; p<0.05 vs. unblocked) attenuated the inotropic response to the higher concentration of insulin. Blockade of PI-3-kinase (108±2% vs. 130±7%; p<0.05) largely reduced, and NCX reverse-mode inhibition (121±7% vs. 128±7%; p<0.05) attenuated inotropic effects of 3 I.U./L insulin, while IGF-receptor-blockade (126±7% vs. 130±16%) or DAG-kinase inhibition (134±10% vs. 131±7%) was ineffective.
Conclusions: Insulin exerts direct, Ca^{2+}-dependent positive inotropic effects in failing human myocardium. These effects involve PI-3-kinase-dependent signaling and reverse-mode NCX activation. At high concentrations of Insulin, the inotropic response is also glucose-dependent.

P1123 Gender-specific alterations of calcineurin activity in hypertrophic myocardium of galphaq-overexpressing mice

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Transgenic mice with five-fold overexpression of the Galphaq-protein develop cardiac hypertrophy. The phosphatase calcineurin has been shown to play a central role in the development of this disease and has been shown to influence protein expression as well as phosphorylation of the endothelial NO-synthetase (eNOS). The present study investigates whether gender-specific differences may exist in Galphaq-overexpressing mice regarding calcineurin activation and eNOS protein expression. We investigated heart to body weight ratio (a parameter characterizing the development of cardiac hypertrophy), calcineurin-activity and protein expression of the calcineurin subunits Aβ (catalytic subunit) and calcineurin B (Ca-calmodulin binding, regulatory subunit) as well as protein expression and phosphorylation of eNOS in female (Galphaq-F, n=8) and male (Galphaq-M, n=8) Galphaq-overexpressing mice as compared to female (WT-F, n=8) and male (WT-M, n=8) wild-type mice.
Heart-to-body weight-ratio, was significantly increased in female (Galphaq-F vs. WT-F: 0.48±0.02 vs. 0.42±0.03) and male (Galphaq-M vs. WT-M: 0.49±0.04 vs.

0.41±0.03) Galphaq-mice as compared to WT. The activity of calcineurin as well as the protein expression of its catalytic subunit Aβ were decreased in female (Galphaq-F vs. WT-F, calcineurin activity:14.9±2.0 vs. 1.0±0.2 pmol Pi/min/g; calcineurin Aβ protein: 279.1±23.9 vs. 190.5±25.0 DU/μg protein) but unchanged in male (Galphaq-M vs. WT-M, calcineurin activity: 10.1±2.0 vs. 9.8±1.7 pmol Pi/min/g; calcineurin Aβ-protein: 370.0±14.0 vs. 437.3±30.7 DU/μg protein) Galphaq-transgenic mice. The protein expression of calcineurin subunit B was upregulated in female, but down-regulated in male Galphaq-transgenic mice. eNOS-protein expression was significantly increased in WT-F compared to WT-M mice. Only in Galphaq-male eNOS-protein expression was increased. eNOS-Ser1177 phosphorylation was increased in WT-F as compared to WT-M and was unchanged in Galphaq-F, but decreased in Galphaq-M.
It is concluded that despite a similar cardiac pathological phenotype, gender-specific differences may exist regarding the underlying signal transduction pathways of cardiac hypertrophy in Galphaq-transgenic mice.

P1124 Intramyocardial injection of fibroblast growth factor-2 and heparin suppresses cardiac failure progression in rats with hypertensive heart disease

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Background: Reduction of coronary flow reserve due to the decrease of capillary beds and endothelial dysfunction of coronary arteries have been reported in patients with hypertensive heart disease (HHD). These findings suggest that underlying myocardial ischemia may contribute to the cardiac failure progression in HHD. Therefore, we evaluated whether fibroblast growth factor (FGF)-2 and/or heparin, which induce angiogenesis, may affect cardiac function of HHD.
Methods: We used Dahl salt sensitive (DS) rats, which have been loaded 8% salt since 6 weeks old, as HHD models. Left thoracotomy was performed to facilitate direct myocardial injection of 100μg of FGF-2 and 1.28μg of heparin (F+H group), 100μg of FGF-2 (F group), 1.28μg of heparin (H group) and saline (S group) in 9 weeks. In 13 weeks, echocardiography was performed. Blood pressure, plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels, heart-to-body weight were measured in 13 weeks. Capillary density was assessed by von Willebrand factor staining.
Results: The table shows that F+H group significantly decreased left ventricular diameter, plasma ANP and BNP levels, heart-to-body weight ratio, and significantly improved the reduction of FS and significantly increased capillary density compared with those in the S group. Thickness of left ventricular wall and blood pressure showed no differences among all groups.

	F+H group	F group	H group	S group
N	6	4	4	6
LV end-diastolic diameter (mm)	6.9±0.1**	7.5±0.01	7.6±0.1	7.6±0.1
LV end-systolic diameter (mm)	3.2±0.1*	3.7±0.1†	4.0±0.04	4.0±0.2
Fractional shortening (%)	53.8±0.4†	50.8±0.7	47.4±0.4	47.4±2.2
Plasma ANP level (pg/ml)	267.5±18.0*	405.0±45.6	400.0±38.7	395.0±55.5
Plasma BNP level (pg/ml)	98.8±18.4 †	125.0±11.9	180.0±20.8	220.0±71.4
Heart-to-body weight ratio (mg/g)	3.9±0.1*	4.4±0.1	4.8±0.2	4.8±0.2
Capillary density (/mm^2)	48.3±9.8*	31.2±2.9	15.0±0.6	16.7±1.4

LV=Left ventricular. *p<0.05 and **p<0.0001 versus F group, H group, S group. †p<0.05 versus S group. †p<0.005 versus H group, S group.

Conclusion: Intramyocardial injection of FGF-2 and heparin suppressed cardiac failure progression in DS rats. FGF-2 and heparin administration may be a new therapeutic strategy for HHD.

P1125 Blockade of angiotensin II type 1 receptor improves the ventricular arrhythmia morbidity in mice with left ventricular hypertrophy

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Angiotensin II type 1 receptor (AR) has been shown to be involved in generating arrhythmogenic substrate in ventricular hypertrophy.
Aim: We aimed to investigate if candesartan, an AR blocker, has antiarrhythmic effects, using mice left ventricular hypertrophy (LVH) model created by transverse aorta constriction (TAC) in male C57BL/6 mice.
Methods: Forty-eight mice were divided into 3 groups: TAC, candesartan (TAC and treatment with candesartan) and sham operation group. Candesartan at a dose of 0.1 mg/kg/d, which did not affect the systolic blood pressure. To observe the degrees of LVH, echocardiography was performed before, 2 and 4 weeks after the operation. Four weeks after the operation, electrophysiological studies (EPS) were performed by inserting a 2.0 F octapolar electrode catheter from the right external jugular vein into the right ventricle. After EPS, the mice were sacrificed, and the ratio of heart weight/body weight(HW/BW, mg/g) was measured.
Results: In the TAC group, both left ventricular wall thickness and the ratio of heart weight/body weight (HW/BW) was bigger than the sham operation group (left ventricular posterior wall in diastole (LVPWD) 1.07±0.27mm, and the ratio of HW/BW was 6.6±0.7(mg/g), p<0.01 compared with the sham operation group). Non-sustained ventricular tachycardia (NVT) was induced by programmed stimulation in 12 of 16 mice of TAC group (75%). In contrast, no VT could be induced in mice of sham operation group. In the cadesartan group, the drug significantly attenuated the development of LVH compared to the TAC group (LVPWD: 0.92±0.09mm, p<0.05; HW/BW 5.8±0.03(mg/g), p<0.01). However, these hypertrophic parameters were still significantly larger than those in the sham operation group. The ERP of AVN was restored to normal, and the incidence of the NVT was only 12.5% (p<0.01 vs TAC group).
Conclusion: Candesartan appeares to reduce fatal ventricular arrhythmia in TAC mice, presumably by preventing the ventricle electrical remodeling via inhibiting AT1 receptor.

P1126 JNK and ERK1/2 MAPK phosphorylation during chronic phases of left ventricular hypertrophy process in spontaneously hypertensive rats

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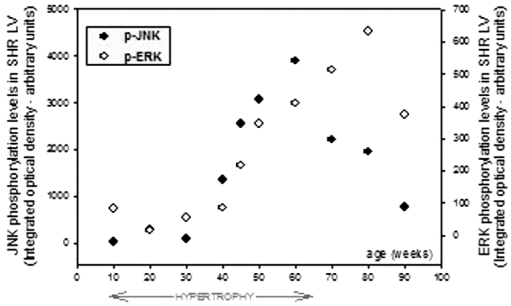
Age related alterations of cardioprotective and damaging agents in left ventricular hypertrophy can differ depending on its relative expression and activation. The role of extracellular signal-regulated kinase (ERK) and c-Jun NH2-terminal kinase (JNK) activation by phosphorylation in cardiac hypertrophic response remains confusing and contradictory. In this study we examined the phosphorylation of JNK (p-JNK) and ERK1/2 (p-ERK) during all stages of left ventricular hypertrophy in spontaneously hypertensive rats (SHR).
Methods: Left ventricles were removed, lysed and proteins were separated by SDS-PAGE and electroblotted onto nitrocellulose. Western blot analysis of phosphorylated ERK1/2 and JNK (54kDa isoform) mitogen activated protein kinase (MAPK) expression was performed using 160μg total protein of tissue lysate. Non crossreactive antibodies (Tyr204 and Thr183/Tyr185 phoshorylation sites for p-ERK and p-JNK respectively) were detected by chemiluminescent autoradiography.Image analysis of integrated optical density (IOD) was performed using Diversity Database Imaging Software (Biorad).
Results: are presented in the following graph as mean IOD arbitrary units:



p-JNK/p-ERK in left ventricle of SHR.

ERK1/2 phosphorylation is highly increased at end stage of hyper-trophy reaching a maximal response at 80 weeks of age. Expression of p-JNK increases by age reaching its peak activation at 60 weeks of age. Activation of both MAPKs is finally attenuated with aging.
Conclusions: p-ERK appears to be predominantly increased by decompensated left ventricular hypertrophy in contrast to p-JNK which appears to be activated during end stage hypertrophy.

P1127 p53 immunolocalization suggests a dual role in hypertrophied ageing left ventricles at the SHR model

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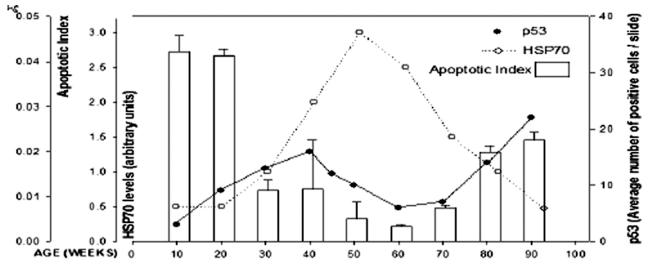
p53 tumor suppressor protein plays a major role in cellular response to DNA damage. Recently we have determined the course of apoptosis (A) and heat shock protein 70 [HSP70 (72kDa inducible)] immunohistochemical localization during all stages of hypertrophy in spontaneously hypertensive rats (SHR). In this study we evaluated the expression of p53 in correlation to the period of hypertrophy development [20-60 weeks of age (w)] and heart failure [>60 w].
Methods: Myocardial left ventricular tissue was removed, fixed and immunostained. The material was studied immunohistochemically with monoclonal anti-p53 and anti-HSP70 antibodies. Sections were scored for protein distribution of p53 and HSP70 protein-positive cells at 400X magnification. In situ detection of apoptotic cells in serial sections by terminal deoxynucleotidyl transferase-mediated nick end labeling of fragmented DNA, (TUNEL) was also performed.

Independent pathologist results were processed and archived using Image Pro Plus microscopy software.
Results: are presented in the following table. p53 activation is highly elevated during the period of established hypertrophy [30-50 w] where apoptosis is attenuated and HSP70 increases; as well as during decompensation stage [>80 w]; where HSP70 diminishes due to aging.



p53, HSP70 and A in SHR left ventricle.

(Apoptotic index (A) = estimated mean percent of TUNEL positive cells; HSP70 levels (mean) are estimated on an arbitrary 0-4 immunohistochemical staining scale; p53: average positive cells/slide).
Conclusions: Aging and stage of hypertrophy differ the level of HSP70 expression; which may regulate differential activation of p53; inducing multiple genes favouring growth arrest or apoptosis.

P1128 Angiotensin type I receptor blockers reduce tissue factor activity and plasminogen activator inhibitor type I antigen in hypertensive patients: a randomized, double-blind, placebo-controlled study

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Purpose: Angiotensin II stimulates the expression of tissue factor (TF) and plasminogen activator inhibitor type-1 (PAI-1) and AT1 receptor blockade (ARB) reduces PAI-1 and TF activities in experimental studies. We investigated the effects of ARBs on TF activity, tissue plasminogen activator (tPA), PAI-1 antigen levels, plasma renin activity (PRA) and aldosterone levels in hypertensive patients.
Methods: Placebo, losartan 100 mg, irbesartan 300 mg, and candesartan 16 mg daily were administered to 122 patients for 2 months.
Results: Compared with placebo, ARBs significantly reduced TF activity ($P<0.001$ by ANOVA), and candesartan was the most potent. Compared with placebo or losartan, irbesartan and candesartan significantly lowered plasma levels of PAI-1 antigen ($P<0.001$ by ANOVA) with no differences between the two. Compared with placebo, all ARBs lowered plasma levels of aldosterone (P=0.012 by ANOVA) and increased PRA (P=0.005 by ANOVA). There were significant correlations between the degree of change in TF activity and PAI-1 antigen levels (r=0.458, $p<0.0001$) and between the change in TF activity and PRA (r=-0.296, p=0.006), but not with the magnitude of reduction in blood pressure following ARB therapy.

ARB effects for FMD, TF activity, PAI-1

	Placebo (30)	Losartan (31)	Irbesartan(30)	Candesartan (31)
% FMD	10±4	31±8*	45±8*	37±7*
%TF activity	2±3	-6±2*	-18±4*	-40±6*
% PAI-1	24±10	50±14	-11±11*	-23±6*

Conclusions: ARBs significantly reduced TF activity, PAI-1 antigen levels, and aldosterone levels in hypertensive patients. The clinical significance of the varying potency of some ARBs needs to be further investigated.

P1129 AKT signaling in pacing-induced heart failure

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Background: Marked changes in energy substrate utilization occur during the progression of congestive heart failure (CHF) where free fatty acid utilization, as the primary souce of cardiac energy is severely diminished, oxidative phosphorylation is down-regulated and glucose uptake and utilization increase. While the molecular basis for the shift in substrate utilization has not yet been elucidated, we sought to examine in the canine model of paced-induced heart failure the potential role of the AKT pathway (previously implicated in the events of cardiac hypertrophy) in signaling the metabolic transition of CHF.
Methods: Left ventricular samples from early (1-2 weeks) and late (3-4 weeks) stages of pacing-induced CHF animals (n=6 and 6 respectively) were evaluated for the levels of both phosphorylated and non-phosphorylated AKT, as well as for AKT kinase activity and were compared to control unpaced animals (n=6). In addition, markers of cardiac hypertrophy(e.g. actin, ANP, BNP, beta-MHC and SERCA 2) were assessed by immunoblot analysis as were myocardial levels of free fatty acids and glucose.
Results: Significant increases in the phosphorylated AKT form (1.7 fold) and in AKT kinase activity (3 fold) were found in early paced animals; these levels declined in the late stages of pacing. Significant increases were also found in the myocardial free fatty acid content (mean 1.0 ± 0.27 vs. controls 0.41±0.13) and only a mild decrease in glucose level (10%) in late but not in early pacing. Markers of cardiac hypertrophy showed no differences in the paced animals compared to control.
Conclusion: Our data demonstrate that AKT signaling pathway is a contributory element in the early signaling events leading to the progression of pacing-induced heart failure, accompanying the shift in substrate utilization and, contrary to the transgenic mice model, is independent of cardiac hypertrophy. The decline in AKT phoshorylation and kinase activation in the later stages of the pacing-induced events is also consistent with the observed onset of myocardial apoptosis previously described in the pacing model, a process known to be reversed by AKT pathway activation.

P1130 Anti-apoptotic effects of growth hormone are associated with reverse cardiac remodelling in patients with heart failure secondary to idiopathic dilated cardiomyopathy

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Objective: Recent experimental and clinical data indicate that abnormal inflammatory and apoptotic processes contribute to the progression of chronic heart failure (CHF). We sought to study the effects of growth hormone (GH) administration on circulating soluble apoptosis mediators, and to investigate whether these GH-induced anti-apoptotic effects are associated with the reduction of left ventricular (LV) volumes in idiopathic dilated cardiomyopathy (IDC) patients.
Methods: Plasma tumor necrosis factor-a (TNF-a), its soluble receptors sTNFRI and sTNFRII, and plasma apoptosis mediators soluble Fas (sFas) and sFas Ligand (sFAsL) were measured (ELISA) in 12 IDC patients (NYHA 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 (VO2 max), as well as LV volume indices and end-systolic wall stress (ESWS) were also determined at the same period.
Results: Treatment with GH produced a significant reduction in plasma TNF-a (7.8±1.1 vs 5.5±0.9 pg/ml, $p<0.02$), sTNFRI (3.9±0.4 vs 3.2±0.3 ng/ml, $p<0.05$), sTNFRII (2.6±0.3 vs 2.2±0.2 ng/ml, $p<0.05$), sFas (4.4±0.8 vs 3.1±0.6 ng/ml, $p<0.05$) and sFasL (34.2±11.7 vs 18.8±7.3 pg/ml, $p<0.01$). A significant reduction in ESWS (841±62 vs 634±48 gr/cm^2, $p<0.005$), LV end-systolic volume index (LVESVI, 128±12 vs 102±12 ml/m^2, $p<0.01$) and LV end-diastolic volume index (LVEDVI, 227±16 vs 200±18 ml/m^2, $p<0.01$) as well as a significant increase in VO2max (15.3±0.7 vs 17.1±0.9 ml/kg/min, $p<0.005$) were also observed in the patient population after GH administration. Good correlations were found between GH-induced increase in VO2max and respective reduction of LVESVI (r=-0.55, p=0.05), as well as between GH-induced decrease of sFas (r=0.41, p=0.05) and sFasL (r=0.45, p=0.02) and reduction of LVESVI.
Conclusions: GH administration reduces circulating TNF system and soluble apoptosis mediators in patients with IDC. These GH-induced anti-apoptotic effects may be associated with the improvement in exercise capacity as well as with the reverse of LV remodeling (reduction of cardiac volumes) of patients with CHF and IDC.

P1131 Inhibition of the angiotensin type 1 receptor and differential regulation of inflammatory genes in human vascular endothelial cells

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Background: Angiotensin II may contribute to the pathogenesis of atherosclerosis through activation of the endothelial inflammatory response. These effects may be inhibited in part by blockade of the angiotensin type 1 (AT1) receptor. We wished to investigate the effect of angiotensin II receptor blockade on the regulation of inflammatory genes such as mitogen activated protein (MAP) kinases and adhesion molecules in human vascular endothelial cells.
Methods and Results: Human coronary artery endothelial cells (HCAEC) were pretreated with the AT1 receptor inhibitor losartan (LOS, 100 nM) for 24 hours and then exposed to the cytokine TNF-alpha (100 U/ml). Using Western blot analysis, TNF-alpha strongly activated the phosphorylation of JNK, p38, ERK1, and ERK MAP kinases in HCAEC. Treatment with LOS suppressed TNF-induced phosphorylation of JNK and p38 MAP kinase by 72 and 62 percent, respectively, but had no significant effect on ERK1 or ERK2. Using Northern blot analysis, LOS decreased TNF-alpha induced mRNA accumulation of vascular cell adhesion molecule-1 (VCAM-1) but did not affect mRNA accumulation of intracellular cell adhesion molecule-1 (ICAM-1) in HCAEC. Furthermore, pretreatment of

HCAEC with LOS and the AT2 receptor PD123319 (100 nM) returned TNF-alpha induction of VCAM-1 mRNA accumulation and the phosphorylation of JNK and p38 MAP kinases to control levels. No significant changes in TNF-alpha induced mRNA accumulation of VCAM-1 or phosphorylation of JNK, p38, ERK1, or ERK2 were observed in HCAEC pretreated with PD123319 only.
Conclusions: These findings suggest that there is differential regulation of MAP kinases and inflammatory genes by AT1 blockade in human vascular endothelial cells. Furthermore, these results suggest the presence of AT2 receptors in HCAEC and that inhibition of the AT1 receptor activates AT2 receptors in human vascular endothelial cells.

P1132 Selective beta1-blockade improves cardiac function and energy metabolism and increases expression of myocardial angiotensinogen in rats during early postinfarct remodeling

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Background: The concept of beta-blockade in congestive heart failure (CHF) has been confirmed by recent clinical trials. However, the mechanisms for the beneficial effects of beta-blockade in CHF are incompletely understood. The aim of this study was to evaluate the effects of beta1-blockade on myocardial energy metabolism, function, morphology and myocardial expression of angiotensinogen during early postinfarct remodeling.
Methods: Male rats 200-250 g were used. Myocardial infarction (MI) was induced by ligation of the left coronary artery. Only rats with large MI (> 35% of left ventricle) were selected The rats were randomised into two groups: MI rats treated with metoprolol (5mg/kg/h, n = 8) and MI rats treated with saline (n=6). Treatment with metoprolol started 3 days postinfarct during 4 weeks. All rats were investigated with in vivo 31P MRS for evaluation of myocardial energy metabolism. Ttransthoracic echocardiography was performed during resting and stress induced by transesophageal pacing. Plasma triglycerides were assesed by standard biochemical methods. Tissue expression of angiotensinogen mRNA was measured by reversed transcript polymerase-chain-reaction (RT-PCR).
Results: Treatment with metoprolol increased phosphocreatine/adenosine-triphosphate ratio indicating improved myocardial energy reserve ($p<0.01$). There was improvement in left ventricular (LV) systolic (ejection fraction, stroke volume, fractional shortening) and diastolic function (deceleration time of E-wave,(all $p < 0.05$) in resting condition but not during transesophageal pacing in the rats treated with metoprolol. LV dimensions and volumes were similar between the two MI groups but significantly higher compared to the normal values. There was no difference in plasma triglyceride content. Expression of angiotensinogen was increased in the beta-blockade group indicating activation of renin-angiotensin system (RAS) in myocardium.
Conclusions: High-dose beta-1 blockade during early postinfarct phase improves myocardial energy metabolism and LV function without antiremodeling effect and increases myocardial expression of angiotensinogen. Myocardial activation of RAS after beta-blockade treatment may have contributed to the absence of antiremodeling effects. Combination treatment with beta-blockade and ACE-inhibition may be important for attenuation/prevention of early postinfarct remodeling and for achievement of synergistic cardioprotection.

P1133 Endotoxin in vitro stimulates proliferation of peripheral blood mononuclear cells in patients with mild stable chronic heart failure, whereas in oedematous patients promotes apoptosis

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Background: Inflammatory immune activation is observed in patients (pts) with chronic heart failure (CHF). Lipopolysaccharide (LPS) translocated from the intestine into circulation during episodes of even subacute decompensation can modulate the activation of immunocompetent cells in CHF pts. The effect of LPS on the process of apoptosis of peripheral blood mononuclear cells (PBMC) participating directly in the body's immune response in CHF has not yet been established.
Methods: We examined 5 pts with stable CHF (3 men, age: 61±6 y, left ventricular ejection fraction [LVEF]: 32±6%, all in NYHA class II), 5 CHF pts with the presence of peripheral oedema (2 men, age: 66±3 y, LVEF: 32±3%, all in NYHA III) and 5 pts with CAD without CHF (all men, age: 64±5 y, LVEF: 54±7%). PBMC were cultured in standard conditions for 72 hours. In model A, PBMC were exposed to LPS from E. coli (O111:B4 - 5 ng/mL) for the last 24 hours, whereas in model B, PBMC were cultured without LPS. Percentages of PBMC in subsequent phases of cell cycle (apoptotic, G0-G1 and proliferative phases) were assessed using flow cytofluorometry with FACS.
Results: In CAD pts with preserved heart function, in vitro LPS exposition did not affect the parameters of cell cycle of PBMC (all $p>0.2$). In stable CHF pts (NYHA II) without peripheral oedema, LPS exposition resulted in an increased number of PBMC in proliferative phase (23.1±2.9% vs. 37.7±0.7%, p= 0.04), which was accompanied by trends towards an increase of PBMC in G0-G1 phase (23.0±2.5% vs. 35.4±2.9%, p=0.1) and a reduction of PBMC in apoptotic phase (10.6±2.9% vs. 4.8±1.6%, p=0.1). In severe CHF pts (NYHA III) with peripheral oedema, LPS exposition resulted in a significant increase in number of PBMC in apoptotic phase (4.1±1.6% vs. 14.1±3.7%, p=0.04) accompanied by a trend towards reduction of PBMC in G0-G1 phase (50.7±4.3% vs. 37.3±4.6%, p=0.09) without changes in PBMC in proliferative phase (21.7±1.9% vs. 21.3±3.5%, p=0.95).
Conclusions: Low concentrations of LPS in vitro tend to inhibit apoptosis and stimulate proliferation of PBMC in pts with stable mild CHF. In contrast, in those with clinical evidence of oedema LPS promotes apoptosis in PBMC. Whether this may explain a difference in inflammatory immune response to LPS exposition in vivo in CHF pts with and without cardiac decompensation needs to be further evaluated.

P1134 Peroxisome proliferator-activated receptor gamma activator ameliorates experimental autoimmune myocarditis by modulating Th1/Th2 balance

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Background: Rat experimental autoimmune myocarditis (EAM) model resembles the giant cell myocarditis in human. Recent studies have suggested that Th1 cytokines are involved in the initiation and progression of EAM, whereas Th2 cytokines are associated with the remission. Peroxisome proliferator-activated receptor gamma (PPARgamma), which is a member of a nuclear hormone receptor superfamily, has been known to affect not only glucose homeostasis but also immune response. In the present study, we examined whether pioglitazone, a PPARgamma ligand, has beneficial effects on EAM.
Methods: Lewis rats were immunized twice at day 1 and day 7 by foot pad injection of porcine cardiac myosin with adjuvant. Rats were divided into three groups: Group N, normal control rats (n=12); Group E, EAM rats (n=14); and Group P, EAM rats treated with pioglitazone (n=14). Rats were treated with pioglitazone (20mg/kg by gavage once a day) from day 7 to day 21. At day 21, all rats were sacrificed and examined by immunohistochemistry, RNA protection assay and RT-PCR.
Results: The affected inflammation area and %area of fibrosis were significantly smaller in group P than in group E (23.5±9.6% vs 36.6±8.4%, $p<0.05$ and 30.6±3.9% vs 38.6±7.1%, $p<0.05$). The heart weight (HW)/Body Weight(BW) ratio in rats of Group E was higher than rats of Group N, and the HW/BW ratio in Group P was less than that in Group E (Group N, 3.32±0.04; Group E, 5.31±0.65; Group P, 4.26±0.57). The number of infiltrated inflammatory cell was less in group P compared to group E. The mRNA level of macrophage inflammatory protein -1alpha (MIP-1alpha), which plays an important role in the recruitment of inflammatory cells in the early stage of EAM, was upregulated in the heart of Group E, but not in the heart of Group P. Furthermore, pioglitazone decreased serum concentration of Th1 cytokine IFNgamma and increased serum concentration of Th2 cytokine IL-4.
Conclusions: A PPARgamma ligand pioglitazone has cardioprotective effects through inhibition of MIP-1alpha expression and macrophage infiltration in myocarditis. Moreover, the alteration of the Th1/Th2 cytokine balance may contribute to the beneficial effect of pioglitazone.

P1135 Association of genomic CD14 polymorphism and the susceptibility for the development of chronic heart failure

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Background: Patients (pts) with chronic heart failure (CHF) show immunological activation, inflammatory changes and elevated plasma levels of TNFa and endotoxins. CD 14 is a receptor for endotoxin and binds components of bacteria. CD14 bearing monocytes respond to stimulation with increased synthesis of cytokines. We studied, if the C≥T promoter polymorphism (position –260) of the CD 14 gene is associated with a higher risk for the development of CHF.
Methods: We studied 100 pts with documented CHF (62 ± 13 y., LVEF 28 ± 8%) and 100 healthy subjects. CD14 genotyping was performed by means of a real-time PCR with fluorescence labeled hybridization probes.
Results: We included 100 consecutive pts with stable CHF without any signs of acute cardiac decompensation for the last 2 months and all of them on optimized medical therapy. 48 pts suffered from dilated cardiomyopathy and 52 from ischemic heart disease. In CHF pts the frequency of the T-allele was lower (38% vs. 48%, $p < 0.05$) and the frequency of the C-allele was higher (62% vs. 52%, $p < 0.05$) compared to controls. The distribution of CD14 genotypes in healthy controls was as follows: CC 32%, CT 41% and TT 27%. In CHF pts the TT genotype was significantly underrepresented compared to controls: CC 35%, CT 50% and TT 15%, $p < 0.05$.
Conclusions: The C-260T polymorphism of CD14 seems to influence the susceptibility for the development of CHF. The T-allele is less frequent in CHF pts compared to controls. The TT genotype could be a new genetic protective factor against the development of CHF.

P1136 Impact of pregnancy related heart failure on humoral immunity: clinical relevance of G3-subclass Igs in peripartum cardiomyopathy

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Peripartum cardiomyopathy (PPCM) represents a specific cause of heart failure (HF) in which the putative factors of disease remain obscure. HF is often characterised by immunoglobulins (Ig) that differ in subclass profiles with HF-aetiology. This discretion is likely to reflect differences in the underlying stimulants evoking these responses in disease. However given that progressive gestation is associated with immunological incompetence, the current study sought to determine whether the Ig-repertoire at class/subclass level differed in pts with pregnancy related HF as opposed to non-pregnancy related HF, i.e idiopathic dilated cardiomyopathy (DCM) and the clinical relevance of these Igs in PPCM.
ELISA levels of Ig class-G (total-Gt) and subclasses-G1, G2, G3 against cardiac myosin were evaluated in pts with PPCM (at baseline) from different geological locations; S.Africa (n=15), Mozambique (n=9) and Haiti (n=23). For comparative purposes, Ig-responses were also measured in healthy age and parity matched mothers (n=15) and pts with DCM (n=24) from SA. Comparison of Igs in DCM pts from the UK was also sought. Relation of the Igs with markers of inflammation: c-reactive protein (CRP), TNF-a and apoptosis: Fas-Apo-1, determined in PPCMs from SA, was also studied.
The Igs did not differ in any PPCM group sought in the present study. Igs, frequency and reactivity, were markedly and non-selectively raised in PPCM pts compared to DCM. Ig-frequency of G1, G2 and G3 in PPCMs from Haiti; 58, 66, 54%, Mozambique; 77, 66, 66% and SA; 47, 53, 53%, respectively, was higher compared to Igs in DCMs from SA; G1;8%, G2;8%, G3;21% or the UK (n=68) G1;10%, G2;8.8% G3;22% ($p<0.0001$). Hence, unlike the selective up-regulation of G3-Igs in DCM, all class/subclass-Igs were raised in PPCM pts. These Igs were independent of markers of inflammation; CRP and TNF-a or Fas-Apo-1. Of the serological variables, IgG3-reactivity (Igs with potential capacity to mediate tissue injury) discriminated NYHA-functional status at diagnosis. IgG3-positive pts were in a higher NYHA-class, (predominantly-IV) at initial presentation ($p<0.05$).
We conclude that PPCM is a clinically distinct entity. The very high levels of Igs at baseline warrants follow-up studies in these pts. Hence, the differential distribution of subclass-Igs in HF pts of different aetiologies may reflect differences possibly, in the impact, course and/or susceptibility of regulatory factors underlying these responses in disease. IgG3-positive status may identify PPCM patients with advance disease at diagnosis.

P1137 Inflammation and cardiotropic viral infection in dilated cardiomyopathy patients undergoing left ventricular assist device implantation

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Background: Left ventricular assist device (LVAD) implantation has been used as a "bridge to transplantation" and more recently as a "bridge to recovery" in end stage dilated cardiomyopathy (DCM). We determined inflammation and viral infection as etiological factors for inflammatory cardiomyopathy in DCM patients undergoing LVAD implantation.
Methods & Results: Immunocompetent infiltrates (CD3+, CD11a/LFA-1+, CD11b/Mac-1+ and Perforin+) and the expression of cell adhesion molecules (CAMs: HLA class I, HLA DR and ICAM-1) were quantified by digital image analysis in myocardial samples from DCM patients (n=24) undergoing LVAD implantation. The tissues were also examined for viral infection (enterovirus, adenovirus and Parvovirus B19) using nested polymerase chain reaction (nPCR). Increased CD3+ T-lymphocytes (>7.0 mm^2) were detected in n=13 (54%), Perforin+ cytotoxic T-lymphocytes (CTLs; >7.0 mm^2) were increased in n=6 (25%), and focally clustered infiltrates consistent with myocytolysis were observed in n=6 (25%) of the cases, respectively. CAMs abundance was confirmed in n=17 (71%) of the cases. Enteroviral genome was amplified in n=4 (17%), and Parvovirus B19 genome in n=6 (25%) of the samples, respectively. However, adenoviral DNA was not detectable in any case.
Conclusions: This analysis reveals that inflammatory cardiomyopathy is a frequent etiopathogenic condition in DCM patients undergoing LVAD implantation. The higher detection rate of focally clustered infiltrates suggestive of myocytolysis compared with previous reports on DCM patients with moderately impaired LV function may indicate an important mechanism of disease progression. Viral persistence does not seem to be substantially more frequent in these patients. The prognostic impact of our findings warrants further investigations.

P1138 Changes in myocardial cytokine expression during and after successful left-ventricular assist device explantation

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Left ventricular assist device (LVAD)s can be life-saving in patients with advanced heart failure. Reverse remodelling of the left ventricle can occur resulting in an improvement of left ventricular function sufficient to allow explantation of the device. The predictors, markers and mechanisms of myocardial recovery in these patients however remain unclear. We studied 12 patients undergoing LVAD implantation treated with a combination of heart failure therapy and LVAD unloading followed by stimulation of physiological hypertrophy using the beta2-agonist clenbuterol to promote myocardial recovery. Patients were studied by regular echocardiography, exercise testing and angiography for evidence of recovery. Nine of the patients underwent successful explantation and had further haemodynamic assessment along with myocardial biopsy 1 year following explantation. Three patients did not recover and required transplantation. Real time RT-PCR was used to quantitate the expression of TLR4 and the cytokines IL-6, IL-1 beta and TNF-alpha in the myocardium at implantation, explantation/transplant and 1 year post explantation. IL-6 expression showed a significant decrease in the myocardium of the recovered patients at explantation (0.25 ± 0.09) compared to the time of implantation (1 ± 0.17, $p<0.05$) and had decreased further (0.06 ± 0.03, $p<0.05$) at 1 year following successful explantation. IL-6 showed a reduction in the non-recovered patients that failed to reach significance. IL-6 correlated directly with pulmonary capillary wedge pressure ($p<0.001$) and inversely with ejection fraction ($p<0.005$). IL-1 beta showed a significant decrease at explantation (0.22+0.07) compared to implantation (1 ± 0.28, $p<0.05$), and this decrease was maintained at 1 year (0.28 ± 0.13 vs implant). IL-1 beta also showed a reduction in the non-recovered patients that failed to reach significance. IL-1 beta correlated inversely with ejection fraction ($p<0.05$) and thermodilution cardiac output. TNF-alpha showed a trend to decrease at the time of explantation and 1 year later but this was not statistically significant. TLR4 did not change in either the recovered or the non-recovered patients following implantation. In conclusion IL6 and IL1-beta correlate with clinical myocardial recovery as well as with specific haemodynamic parameters of recovery and might be useful predictors and markers of recovery. Their role in the underlying pathophysiology of recovery requires further investigation.

P1139 Elevated homocysteine level in chronic heart failure – marker of metabolic imbalance and independent predictor of poor outcome

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Background: Whether elevated homocysteine (HCY) level may play a role in the pathophysiology of chronic heart failure (CHF) syndrome has not been established.
Methods: We investigated a prevalence and clinical significance of hiperHCY (prospectively defined as HCY level ≥ 12 μmol/L) in an unselected population of 106 consecutive CHF pts (77 men, age: 65 ± 1 y, NYHA class II/III/IV: 52/41/13, left ventricular ejection fraction [LVEF]: 32 ± 1%, CHF aetiology -coronary artery disease [CAD] in 74%).
Results: HCY level was elevated in the whole CHF group (13.1 ± 0.7 μmol/L, $p<0.0001$ vs. reference value in our laboratory) and 55 (52%) pts had hiperHCY. Clinical data in those with hiperHCY vs. those with normal HCY level are shown in a Table 1.

Table 1

	NYHA class	CHF aetiology (%CAD)	LVEF (%)	Creatinine (mg/dL)	C-reactive protein (mg/dL)
HyperHCY (n=55)	2.9 ± 0.1*	80%	31 ± 1	1.4 ± 0.1*	8.1 ± 1.1*
NormalHCY (n=51)	2.4 ± 0.1	67%	33 ± 1	1.2 ± 0.1	5.5 ± 1.0

*$p<0.05$ - hyperHCY vs. normalHCY.

Additionally, there was a correlation between HCY and serum uric acid (a marker of metabolic imbalance) ($r=0.40$, $p<0.0001$). During the follow-up (median: 463 days, >12 months in all who survived) 19 (18%) patients died. HyperHCY was related to impaired survival in univariate (hazard ratio 3.9, 95%CI: 1.3-11.7, $p=0.01$) and multivariate analyses (adjusted for NYHA class and LVEF; $p<0.05$).
Conclusion: Elevated HCY level is common among unselected CHF pts, irrespectively of the underlying aetiology. HiperHCY is related to disease severity, proinflammatory status and metabolic imbalance, being also an independent marker of poor prognosis. Whether hiperHCY may become a therapeutic target in CHF warrants further studies.

P1140 Prognostic significance of an altered steroid profile in patients with chronic heart failure

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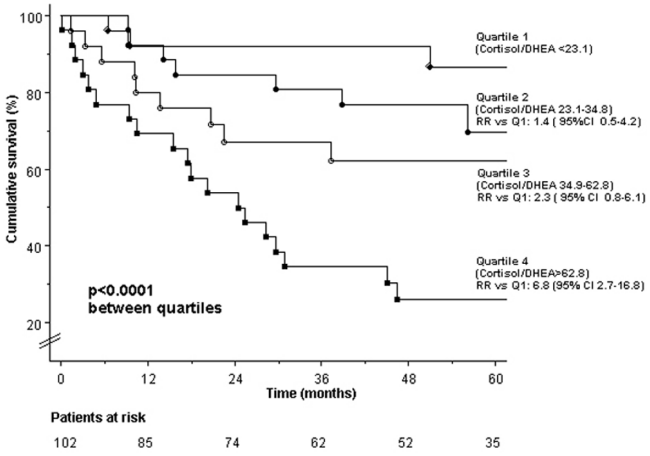
Background: Chronic heart failure (CHF)is characterised by a shift of adrenocortical biosynthesis from Dehydroepiandrosterone (DHEA; anabolic) to cortisol (catabolic) production. Therefore, the cortisol/DHEA ratio (CDR) is a marker of catabolic/anabolic steroid imbalance. Its prognostic utility in CHF is unknown.
Method & Results: Survival and CDR were analysed in 102 stable, male CHF patients (age 62±11y, NYHA class 2.6±0.7, CDR 50±5, urate 468±136 μmol/L, creatinine 124±43 μmol/L, BMI 26.1±4.4 kg/m^2, LVEF 26±11%, peak VO2 18.1±5.8 mL/kg/min, VE/VCO2-slope 38±13. During follow-up (55±40 months, all survivors: >16 months), 48 patients died (12-month mortality 15%, at 36 months: 38%). In univariant Cox analysis only CDR, urate, creatinine, NYHA, VE/VCO2, peak VO2, age (all $p<0.01$) and BMI (p=0.03) predicted survival. In bivariant models CDR was predictive of survival, independently of all other parameters. Urate, NYHA, VE/VCO2 and peak VO2 predicted survival, independently of CDR. In multivariant analysis, CDR ($p<0.0001$), urate (p=0.008), NYHA class (p=0.002), VE/VCO2 (p=0.04) but not peak VO2 ($p>0.2$) were independent prognosticators. We subdivided patients by CDR quartiles (Q, see Figure 1). Survival at 36 months for patients in Q1, Q2, Q3 and Q4 was 92, 81, 67 and 35%, respectively.



Conclusion: An altered steroid profile with an increase in catabolic/anabolic steroid imbalance(quantified by the cortisol/DHEA ratio) independently predicts impaired survival in CHF. Therapeutic strategies blunting catabolism and/or augmenting anabolism may confer prognostic benefits in CHF.

P1141 Effects of combined administration of vitamin E and atorvastatin on endothelial function and inflammatory process, in patients with ischaemic heart failure

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Previous studies have shown that ischemic heart failure is associated with endothelial dysfunction and increased levels of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a) and soluble form of vascular cell adhesion molecule (sVCAM-1). Statins as well as antioxidant vitamins, improve endothelial function in patients with coronary atherosclerosis, while their role in heart failure is unknown.
Aim: We assessed the effect of atorvastatin alone or in combined with vitamin E on endothelial function and inflammatory process in patients with ischemic heart failure.
Methods: Thirty-eight (38) patients with ischemic heart failure (NYHA II-IV) were enrolled. Seventeen (17) patients received atorvastatin 10mg/day (ATR), 7 patients received atorvastatin 10 mg/day plus vitamin E 400IU/day (ATR+E) and 14 received no treatment for 4 weeks (Controls). Forearm blood flow was measured using venous occlusion strain-gauge plethysmography. Endothelium dependent dilation (EDD) and endothelium independent dilation (EID) were expressed as the % change of flow from baseline to the maximum flow during reactive hyperemia or after sublingual nitroglycerin administration respectively.
Results: EDD was significantly improved in ATR group (from 40±5 to 88±13%, $p<0.01$) but not in ATR+E (from 45±6 to 65±15%, p=ns) or control group (from 50±5 to 46±6%, p=ns). Levels of IL-6, sVCAM-1 and TNF-a were decreased only in ATR group (from 7.9±0.8, 665±69 and 3.7±0.49 to 5.8±0.8 pg/ml $p<0.05$, 473±53 ng/ml $p<0.01$ and 2.62±0.17 pg/ml $p<0.05$, respectively) while remained unaffected in ATR+E (from 5.4±1.5, 868±91 and 3.99 ±0.80 to 3.2±0.8 pg/ml, 749±63 ng/ml and 3.01 ±0.77 pg/ml respectively, p=ns for all) and in controls (from 7.4±0.8, 610±65 and 4.54±0.91 to 6.2±0.9 pg/ml, 594±70 ng/ml and 4.32±0.58 pg/ml respectively, p=ns for all). EID remained unchanged in all groups (from 64±8, 66±12 and 71±6 to 66±9%, 72±13% and 68±9% respectively, p=ns for all)
Conclusions: Atorvastatin improves endothelial function and reduces inflammatory process in patients with heart failure while co-administration of vitamin E and atorvastatin may reduce these beneficial effects of atorvastatin.

P1142 Pravastatin reduces the inflammatory response to cardiopulmonary bypass after coronary revascularization

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Background: The effects of pravastatin have been documented in reducing LDL levels. In constrast, the effect of pravastatin in inflammatory function has not yet been demonstrated. This study was designed to evaluate action of pravastatin on inflammatory reaction after extracorporeal circulation.
Methods: In a prospective, randomized study, 20 patients undergoing eletive coronary artery bypass grafting were investigated. Ten patients received 80mg p.o. of pravastatin 36 and 12h before surgery, and a control group of 10 did not. Plasma levels of C-reactive protein, tumor necrosis factor-alfa, interleukin-6, interleukin-8 and postoperative blood loss were analysed before and after cardiopulmonary bypass.
Results: Interleukin-6 in both groups significantly increased after Cardiopulmonary bypass (CPB) when comparing to the measures pre bypass and there was no significant diferences between the two groups. Interleukin-8 increased (p=0.017) in group control at 6h after CPB compared with group P. C-reative protein was increased (p=0.015) in group pravastatin before CPB compared with control. Median levels are 9.9 (7.0-15.6) and 5.0 (5.0-9.3) mg/dL. Despite this previous elevation, at 24h after CPB group P showed significantly lower levels than group control (p=0.004). Median levels are 62 (38.7-73.6) and 109.0 (104.0-112.0) mg/dL in groups P and C, respectively. Postoperative blood loss was significantly lower in group pravastatin than in group control (p=0.019).
Conclusions: Our data suggest that pravastatin pre-treatment preceding CPB reduced systemic inflammatory response. The effects of administration are immediate and antinflammatory action is not mediated by lipid lowering. Pravastatin also reduced mediastinal postoperative bleeding.

P1143 The Relationship of High Sensitivity C Reactive Peptide (hsCRP) measurements to known prognostic indicators in patients assessed for heart failure in an outpatient setting

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Background: A raised high sensitivity CRP (hsCRP) has been shown in several recent epidemiological trials to be an independent risk factor in the development of congestive heart failure. HsCRP levels have also been noted to correlate with the severity of heart failure, as well as readmission rate to hospital.
Methods: We analysed 1091 patients who attended our outpatient clinic for assessment of symptoms suggesting a possible diagnosis of heart failure. All patients had a standard clinical history and medications recorded. All patients had a hsCRP measurement taken together with a full biochemical and haematological profile. They also completed a 6 min walk test, quality of life questionnaire and underwent echocardiographic assessment of left ventricular (LV) function at their clinic visit. Heart failure was diagnosed according to ESC criteria.
Results: 622 (57%) were men, the mean age of the population was 71±10 yrs. The median and inter-quartile range of hsCRP in those diagnosed with heart failure (n=577) was 4.1 (range 2.4 to 9), which was not significantly different from patients without heart failure (n=514); 4 (range 2.2 to 6.8). Amongst patients with heart failure, hsCRP was significantly higher in patients with more severe symptoms, and shorter corridor walk distance but was poorly related to LVEF. Median (IQR) hsCRP in patients with NYHA class I (n=104) was 3.4 (range 1.6-5.1) but 6.5 (range 4.2 to 11) in NYHA class IV (n=13) In patients with a 6min walk test distance >500m (n=17), hsCRP was 2.8 (range 1.0 to 5), and in those with distance <250m (n=184), 5.6 (range 3.3 to 12). However, comparing patients with mild (LVEF 40-49%) to patients with severe LV systolic dysfunction (LVEF <30%), hsCRP was similar 4 (range 2.5 to 8.6), n=83, versus 4.1 (range 1.8 to 11),n= 97, respectively.
Conclusion: High sensitivity CRP does not appear to be a useful diagnostic tool in patients with suspected heart failure. It is increased in patients with more severe symptoms and greater functional limitation but is poorly related to the underlying severity of LV systolic dysfunction.

P1144 Time dependency of neuro-hormonal variations after cardiac resynchronisation therapy in heart failure patients

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The aim of this study was to analyse the changes in neuro-hormonal profile occurring after cardiac resynchronisation therapy (CRT) in heart failure patients (pts). Thyrty-two pts (mean age 66±9 yrs, ischemic heart disease in 17) with drug-refractory heart failure (NYHA class = 3.0±2.5) and wide QRS (≥130 ms) were implanted with a device for CRT.

The neuro-hormonal profile was assessed at rest before CRT, at 3-month follow up (all patients) and at 12-month follow-up (20 patients) by measuring adrenaline (A), nor-adrenaline (NA), BNP, ANP, aldosterone (Ald), plasma renin activity (PRA), endothelin (E), interleukin 6 (IL-6), TNF and soluble receptors (sTNFR1 and sTNFR2), chromogranin A (CgA).

Results: At 3-month follow up both an improvement in NYHA class (from 3.0±2.5 to 2.3±0.6, $p<0.001$) and a reverse structural remodelling at echo were observed, with a significant decrease in ventricular end-diastolic (ED) and end-systolic (ES) volumes (ED = from 241±78 to 208±71 ml, $p<0.001$; ES = from 175±62 to 140±62 ml, $p<0.001$), a significant decrease in mitral regurgitation score (from 2.6±1.1 to 2.0±0.9, $p<0.001$) and an improvement in left ventricular ejection fraction (from 27.0±7.8 to 34.2±10.2%, p=0.001). These changes were associated with a significant reduction of ANP (from 139.8±104.3 to 95.5±58.8 pg/ml, p=0.007) and BNP (from 277.6±229.7 to 216.3±179.5 pg/ml, p=0.041) without significant changes in the other neuro-hormones (A, NA, Ald, PRA, E, IL-6, TNF, sTNFR1, sTNFR2, CgA).

The analysis of short-term variations in the neuro-hormonal profile, available in 23 cases, revealed that for ANP and BNP no significant changes occurred at 1 week after CRT, while the decrease became significant at 1-month for ANP (94.67±72.14 pg/ml, p=0.028 vs. baseline) and at 3-month for BNP (178.674±131.7 pg/ml, p=0.043 vs. baseline). No significant changes in ANP and BNP were found comparing 3-month and 12-month levels.

In conclusion, the reverse structural remodelling associated with CRT and detectable at 3-month follow up is associated with a time-dependent neuro-hormonal remodelling, with significant changes involving both ANP and BNP. The reduction in ANP and BNP levels seems to be stable, since no significant changes occur at 12-month versus 3-month follow up.

P1145 The role of cytokines and CRP in the secretion of vascular endothelial growth factor after acute myocardial infarction

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Background: Vascular Endothelial Growth Factor (VEGF) is an angiogenic factor, the release of which can cause the development of collateral circulation in patients with acute myocardial infarction (AMI). There are several factors that can probably stimulate the secretion of VEGF. Since AMI is an inflammatory process, the aim of this study was to determine whether the serum levels of inflammatory cytokines [interleukin-6 (IL6), interleukin-8 (IL8) and tumor necrosis factor (TNF-a)] and CRP are related with VEGF release after AMI.

Methods: The study included 60 consecutive patients (44 men, mean age 66.3±16.7 years) who presented with Q-wave AMI and were thrombolysed with 20 IU reteplase within the first 6 hours after the onset of the chest pain. Serum IL6, IL8, TNF-a and VEGF levels were measured at admission (prior to the beginning of thrombolysis) and at the 7th day after the AMI.

Results: IL6 on the 1st day was correlated positively with VEGF on the 7th day (r=0.461, p=0.004).

IL8 on the 1st and 7th day were correlated positively with VEGF on the 7th day (r=0.332, p=0.041 and r=0.349, p=0.032).

TNF-a on the 1st day was correlated positively with VEGF on the 7th day (r=0.461, p=0.004).

CRP on the 1st day was correlated positively with VEGF on the 7th day (r=0.428, p=0.001).

Conclusions: The initial serum inflammatory cytokines and CRP levels were significantly positively correlated with VEGF levels at the 7th day (which are near to the max values of VEGF) after the AMI. This suggests that the release of VEGF is probably stimulated either by the initial inflammatory process that starts immediately after the onset of AMI or/and by the inflammatory cytokines and CRP themselves.

P1146 Urotensin II and TNFalpha induce neutral endopeptidase in human cardiac fibroblasts

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Background: Neutral Endopeptidase (NEP) is involved in regulation of the myocardial renin-angiotensin system, bradykinin and ANF and therefore important in pathological cardiovascular growth. NEP is expressed in the human heart and is activated in patients with heart failure and left ventricular hypertrophy (LVH). We now ask if the novel vasoactive peptide urotensin II (UII) and the growth factor TNFalpha contribute to NEP activation in human cardiac fibroblasts (hCF) and if these effects were disease specific.

Methods: HCF were isolated from 10 explanted hearts of patients with dilated cardiomyopathy (DCM) undergoing heart transplantation and 8 unused donor hearts (Con). HCF where stimulated with UII (10^{-7} mol/L) and TNFalpha (10ng/ml) for 6 to 24 hrs in duplicates. NEP mRNA was determined by quantitative real time PCR (Light Cycler) and NEP protein by semiquantitative Western Blot. GAPDH served as external control for mRNA and protein expression.

Results: NEP showed a time dependent increase on mRNA- and protein level. The highest induction of NEP mRNA by UII was seen after 12 hrs (355% of non stimulated hCF, p=0.01), whereas stimulation with TNFalpha reached its maximum up to 24hrs. NEP protein increased after 12 hrs UII and TNFalpha to 213 and 195% of non stimulated controls (both $p<0.05$), respectively. Thus increase in NEP mRNA following stimulation with UII and TNFalpha was not significantly different in Con and DCM. A tendency torwards a faster increase of NEP protein in Con did not reach significance.

Conclusion: We confirmed NEP mRNA- and protein expression in hCF and showed that NEP mRNA and protein is differentially regulated by UII and TNFalpha. Activation of myocardial NEP by UII and TNFalpha could diminish benefitial effects of ACE-inhibitor therapy in DCM and point to a further mechanism on how TNFalpha acts cardiodepressive.

P1147 p38-MAPK mediates the early negative inotropic effect of TNF-alpha in murine hearts. Evidence of synergy between a direct negative inotropic effect and coronary constriction

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Background and goal: Tumor necrosis factor-alpha (TNF) exerts a negative inotropic effect on the myocardium from various species. TNF activates p38-MAPK and this kinase is thought to depress contractility in a calcium-independent manner. We therefore examined TNF effects on contractility in mice lacking the p38-MAPK activator, MKK3.

Methods: The left ventricular developed pressure (LVDP; isovolumic contraction), coronary flow, p38-MAPK and HSP27 phosphorylation, as well as the end-diastolic v LVDP (or Frank-Starling) relationship were analyzed in outbred, mkk3 wild-type (WT), and mkk3 knock-out (KO) isolated mouse hearts exposed to 10 ng/ml TNF i.c. for 15 min after 40 min of stabilization. Some hearts received SB203580 (p38-MAPK catalytic site inihibitor; 1 μM) for 20 min starting 5 min before TNF infusion. All protocols were run under constant pressure and constant flow conditions since TNF also has vasoconstrictive properties.

Results: TNF (10 ng/ml) for 15 min significantly reduced LVDP and coronary flow in outbred and mkk3-WT mice. This early negative inotropic effect of TNF was associated with a significant phosphorylation of both p38-MAPK and HSP27. However, TNF did not reduce the LVDP and did not phosphorylate p38-MAPK and HSP27 in mkk3-KO mice despite some reduction in coronary flow. Similarly, TNF caused a significant depression of the Frank-Starling relationship in both outbred and mkk3-WT, but not mkk3-KO mice. Furthermore, SB203580 attenuated TNF-induced negative inotropy, as well as p38-MAPK and HSP27 phosphorylations. Comparing constant pressure vs constant flow models of heart perfusion, we found that TNF-induced coronary constriction can act in synergy with a direct effect of TNF on cardiomyocytes to cause p38-MAPK activation, and consequently a negative inotropy.

Conclusion: Our results implicate p38-MAPK in the early and dual negative inotropic effect of TNF, and may be of relevance to the pathogenic actions of this cytokine in heart failure.

P1148 Distinct pattern of myocardial gene expression of interleukin-6 in acute pressure and volume overload

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Introduction: Growing evidence suggests that myocardial expression of cytokines contribute to cardiac remodeling during heart failure progression. In the present study we evaluated, in vivo, in an experimental model of acute pressure and volume overload, the profile of interleukin-6 (IL-6) myocardial gene expression.

Methods: Male Wistar rats (n=39) were instrumented with the introduction of a micromanometer in the right ventricle (RV) and assigned to one of the following protocols: (i) RV pressure overload (Pr-Ov) of 120' (n=7) or 360' (n=6), with pulmonary trunk banding; (ii) RV volume overload (V-Ov) of 120' (n=7) or 360' (n=6), with dextran40 infusion; (iii) sham of 120' (n=7) or 360' (n=6). At the end of the experimental protocols RV free-wall samples were collected for mRNA relative quantification (two-step RT real-time PCR) of IL-6, normalized for GAPDH. Results are expressed in arbitrary units (AU) using sham as reference; sham 120' and 360'=1AU.
Results: In Pr-Ov, there was an early and sustained increase of peak systolic (basal=24.3±1.0; 120'=55.1±4.1; 360'=50.0±5.2mmHg) and end-diastolic (basal=0.6±0.35; 120'=3.7±0.83; 360'=4.9±1.4 mmHg) RV pressures. In V-Ov, end-diastolic (basal=3.1±1.2; 120'=7.0±1.5; 360'=8.9±2.5mmHg) and peak systolic (basal=25.9±1.0; 180'=32.1±2.1; 360'=42.4±3.3mmHg) RV pressures progressively increased. In Pr-Ov, IL-6 expression increased at 120' (3.8±1.2 AU) but not at 360' (1.6±0.4 AU). In V-Ov IL-6 mRNA levels increased significantly only at 360' (120'=2.4±1.1 AU; 360'=7.7±2.6 AU).
Conclusions: The present study demonstrates that acute pressure and volume overload induces a distinct profile of IL-6 myocardial gene expression. Pressure overload induces an early rise in myocardial expression of IL-6, whilst volume overload progressively increases ventricular IL-6 mRNA levels. Given the prohypertrophic and anti-apoptotic effects of the cytokines from the IL-6 family, our results suggest that this pathway might contribute to the different patterns of ventricular remodeling in pressure and volume overload.

ISCHAEMIA BASIC ASPECTS

P1149 Regional myocardial work index measured by strain rate echocardiography reflects myocardial energetic levels during different stages of experimentally induced acute ischaemia

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Background: ATP is a primary source of energy for actin-myosin cross-bridge cycling. Ischemia decreases levels of ATP and other high-energy nucleotides, thus leading to impairment of cross-bridge cycling. Consequently, contraction regional myocardial work (RMW) is reduced. Combined with left ventricular pressure (LVP), strain rate echocardiography (SRE) allows measurement of contraction. We hypothesized that RMW index (RMWI), expressed as the area within a pressure-strain loop, will reflect local myocardial nucleotide levels and allow prediction of the energetic status of myocardium during ischemia.
Method: In 13 open-chest pigs, we occluded the middle left anterior descending coronary artery for 3 different time periods (5, 4, and 4 animals for 30-60, 90-120 and 180-240 min of ischemia). Another 3 animals were sacrificed without any intervention and used as baseline. Longitudinal strains were measured in control (mid posterior) and ischemic (apical anteroseptal) regions simultaneously with LVP. At baseline and following the periods of occlusion, biopsies were obtained from the control and ischemic regions, and levels of high-energy phosphates (ATP, GTP, and ADP) were measured. RMWI was measured selectively for the isovolumic and ejection phases of contraction at the same time periods as biopsies were obtained.
Results: ATP levels (mean± SD nmol/mg of protein at baseline, 30-60, 90-120 and 180-240 min of ischemia) decreased significantly ($p<0.05$) in the ischemic region (22.7±7.1 to 6.8±3.8, 2.3±1.7 1.6±0.6; respectively), without significant changes in control regions (21.8±8.6 to 26.1±7.0, 26.6±7.3, 25.5±7.2; respectively). Similarly RMWI (mean± SD at the same time periods) decreased significantly ($p<0.05$) during ischemia in the ischemic regions (+0.64±0.23 to -0.01±0.13, -0.05±0.01, -0.06±0.06; respectively) and remained unchanged in control regions (+0.72±0.16 to +0.54±0.10, +0.48±0.27, 0.50±0.07; respectively). ATP levels correlated closely with RMWI (r=0.91, $p<0.0001$).
Conclusion: SRE allows not only quantitation of local contraction function, but, in association with ventricular pressure, could become a novel tool for monitoring of myocardial energy metabolism in the acutely ischemic region. Such application may contribute to better understanding and optimal treatment of ischemic metabolic debt.

P1150 Effect of acetylsalicylic acid on the delayed protection against infarction and on the activation of Nuclear Factor-kB in the preconditioned myocardium

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Background: NF-kB is known to play an essential role in the intracellular signal transduction of the Second Window of Protection (SWOP). It has been reported, that ASA can inhibit NF-kB dependent gene activation in leukocytes and endothelial cells through preventing phosphorylation and subsequent degradation of the inhibitor-KK. ASA is the most widely used nonsteroidal anti-inflammatory drug (NSAID), and it is often applied in antythrombotic therapy for patients with ischaemic heart disease.
Aims: The aim of this study was to investigate the effect of three different doses of acetylsalicylic acid (ASA) on the activation and nuclear translocation of NF-kB in the preconditioned myocardium.
Materials and methods: Conscious rabbits were subjected to 4 cycles of 5min coronary occlusion/5 min reperfusion together with three different doses of ASA (5mg/kg; 25 mg/kg; 130 mg/kg). After 30 min reperfusion we determined the activation with electromobility shift assay (EMSA) of NF-kB.
Results: Neither 5 mg/kg nor 25 mg/kg of ASA interfered with the NFkB activation. In contrast, NFkB activation and late PC effect were completely abrogated by 130 mg/kg of ASA.
Conclusion: The administration of ASA either at antithrombotic doses (5 mg/kg), which are widely used to prevent cardiovascular events in patients, or at analgesic/antipyretic doses (25 mg/kg) does not interfere with the induction of transcription factor NFkB. In contrast, high doses of ASA (130 mg/kg), in case of acetylsalicylic acid accumulation abrogate NFkB induction, suggesting that nonselective doses of NSAIDs should be used with caution in patient with atherosclerotic cardiovascular disease, because they may deprive the heart of its innate defensive response.
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P1151 3′, 4′-Dihydroxyflavonol prevents the loss of eNOS expression and attenuates lethal reperfusion injury during experimental myocardial infarction

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Purpose: recent evidence indicates that flavonoids can reverse endothelial dysfunction, a phenomenon frequently present during myocardial ischemia and reperfusion (I/R) injury. This study investigated the effects of a synthetic flavonol, 3', 4'- dihydroxyflavonol (DiOHF) on myocardial I/R injury, neutrophil accumulation and the expression of inducible and endothelial nitric oxide synthase (eNOS) in postischemic myocardium.
Methods: in anesthetized sheep, the left anterior descending coronary artery was occluded distal to its second diagonal branch for 1 hour to achieve regional ischemia followed by 2 hours of reperfusion. Animals were randomly received either DiOHF (5 mg/kg, i.v.) or vehicle treatment (n=6) during ischemia but shortly before reperfusion. Systemic and regional cardiac performance, creatine kinase and infarct size were determined, and myocardial tissues were collected for immunoblot and histological analysis.
Results: DiOHF treatment significantly reduced infarct size (51±5.6% versus 73±6.4% in vehicle, $P<0.05$) and creatine kinase release (2031±273 versus 3390±381 U/ml in vehicle, $P<0.05$), improved regional myocardial contractility, accompanied by well-preserved eNOS protein expression and decreased neutrophil infiltration (36±7.4 versus 127±11.9 neutrophils/field in vehicle; $P<0.05$) in postischemic myocardium. Correlation analysis discovered that the levels of eNOS protein were inversely associated with infarct size ($r = -0.96$, $P<0.05$) and the number of neutrophils accumulated in the myocardium ($r = -0.88$, $P<0.05$).
Conclusions: DiOHF treated shortly before reperfusion effectively prevented the loss of myocardial eNOS expression after I/R in ovine hearts, which is closely associated with reduced neutrophil infiltration and attenuated myocardial infarct size.

P1152 Intra-aortic balloon counterpulsation increased coronary blood flow during reperfusion in an ischaemia/reperfusion experimental model but not in the intact heart

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Background: Studies of the effects of the intra-aortic balloon pump (IABP) have reported an increase or no change in coronary blood flow (CBF).
Purpose: To determine the changes in CBF produced by the IABP in intact coronary arteries and during reperfusion in an ischemia/reperfusion experimental model.
Methods: A 30-ml IABP was placed in the descending aorta of 7 open-chest pigs. Each pig underwent occlusion of the mid left anterior descending (LAD) coronary artery for 1 h, followed by reperfusion for 1.5 h. The effect of IABP support on systolic aortic pressure (SAP) and peak diastolic aortic pressure (pDAP) was recorded. The mean CBF, distal to the LAD occlusion site, was measured with a transit-time ultrasound flowmeter, at baseline and during reperfusion, with and without the IABP.
Results: The results of IABP support on aortic pressures and CBF, both in the intact heart (baseline) and during reperfusion, are shown in the table.
Conclusions: In the intact heart, IABP caused a decrease in CBF, probably because of a lesser myocardial O2 demand from a decrease in afterload produced by counterpulsation. During reperfusion, when the O2 demand of ischemic tissue is increased, IABP produced an increase in pDAP and CBF and, therefore, in O2

		Reperfusion (min)				
		Baseline	5	30	60	90
CBF (ml/min)	IABP off	27.8±14.0	58.0±16.0	50.6±12.0	36.7±13.0	30.6±10.0
	IABP on	25.5±13.0	63.0±17.0	55.3±14.0	40.9±13.0	34.6±13
	p	0.001	0.023	0.002	0.005	0.011
SAP (mmHg)	IABP off	116±19	110±17	112±23	116±9	114±9
	IABP on	107±18	104±18	105±23	109±11	108±10
	p	0.003	0.003	0.000	0.000	0.002
DAP/pDAP (mmHg)	IABP off	81±18	79±16	81±21	86±10	83±11
	IABP on	107±18	99±23	122±24	115±15	111±15
	p	0.000	0.002	0.000	0.000	0.000

supply, suggesting that implementation of the IABP during reperfusion may be an effective intervention to reduce infarct size.

P1153 Effects of dual gene transfer of VEGF and PDGF-BB on angiogenesis and cardiac function in chronic myocardial infarction model

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Objective: Therapeutic angiogenesis is one of the promising therapies for myocardial infarction. However, establishment of the functional vessels is still an open problem. Dual delivery of recombinant VEGF165 and PDGF-BB with a polymeric system can result in the formation of a mature vascular network in the legs. Dual gene transfer is an alternative way but has rarely been done. In this study we investigated effects of dual gene transfer of VEGF-165 and PDGF-BB on angiogenesis and the cardiac function in a chronic myocardial infarction model.
Methods: One week after myocardial infarction, rats were randomly separated into two cohorts. One cohort was kept for another week and the other for four weeks. Rats in both cohorts were got intramyocardial injection of plasmids. Treatments compared in each cohort are: VEGF165, PDGF-BB, VEGF165+PDGF-BB and placebo plasmid. Cardiac function was measured by echocardiography during the experiment. Hearts were harvested for analysis of cardiac morphology, capillary and arteriolar densities. Comparison between the groups was made by 1-way ANOVA, followed by Fisher PLSD test.
Results: Gene transfer of VEGF165 and VEGF165+PDGF-BB, but not PDGF-BB, increased capillary density (19% and 17%, respectively, $P<0.001$). VEGF165, PDGF-BB and VEGF165+PDGF-BB all increased the arteriolar density (65%, 116% and 95%, respectively, $P<0.01$). The combination VEGF165+PDGF-BB did not increase capillaries and arterioles further than single factor treatments. After 1 week of treatment, cardiac function was improved with VEGF and VEGF+PDGF-BB comparing to the placebo ($P<0.01$). No effect was found with PDGF-BB. VEGF165+PDGF-BB treatment did not improve cardiac function further than VEGF. However, there was no functional difference between all groups after 1 month of treatment. No cardiac histological morphology difference between the groups was observed.
Conclusions: (1) VEGF165 and VEGF165+PDGF-BB stimulated both capillary and arteriolar growth while PDGF-BB preferentially stimulated arteriolar growth. (2) VEGF165 and VEGF165+PDGF-BB, but not PDGF-BB, induced transient cardiac function improvement in the chromic myocardial infarction model. (3) The combination VEGF165+PDGF-BB did not further increase the cardiac function and angiogenesis with plasmid transferring comparing to the single growth factor treatments.

P1154 Mitochondrial permeability transition mediates the cardioprotective effect of trimetazidine

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Mitochondrial permeability transition (MPT) is a crucial event in both necrosis and apoptosis resulting from sustained myocardial ischemia-reperfusion, and recent reports suggest that it may play a role in ischemic preconditioning. The aim of the present study was to determine whether trimetazidine (TMZ), a well-known anti-ischemic agent, may protect the heart through modulation of MPT pore.
In protocol 1 (n=10/group), anesthetized NZW rabbits underwent 30 min of coronary artery occlusion followed by 4 hours of reperfusion. Prior to this, they underwent either no intervention (control, C), preconditioning by 5 min ischemia/5 min reperfusion (PC), or an IV bolus of 5mg/kg TMZ, 10 min before ischemia (TMZ). Infarct size was assessed by TTC. In protocol 2 (n=9/group), myocardium was excised from the area at risk of C, PC, TMZ and sham hearts, and mitochondria were isolated for further assessment of Ca^{2+}-induced MPT, using a calibrated Ca^{2+} sensitive microelectrode. Ca^{2+} overload was expressed as μM Ca^{2+}/mg of mitochondrial proteins and used here as an index to assess MPT.
In protocol 1, preconditioning significantly reduced infarct size that averaged 21±4% of the risk region versus 63±6% in controls. TMZ dramatically limited infarct size to 34±4% ($p<0.005$ vs C). In protocol 2, Ca^{2+} overload required for MPT pore opening was significantly reduced in the C group ($p<0.001$), averaging 12±5 μM/mg of mitochondrial proteins, versus 109±9 μM/mg in sham animals. Pretreatment by TMZ and preconditioning prevented this phenomenon, with Ca^{2+} overload averaging 35±10 μM/mg and 37±8 μM/mg, respectively ($p<0.05$ vs C).
These data suggest that trimetazidine protects the heart following a prolonged ischemic insult possibly via a modulation of the mitochondrial permeability transition.

P1155 Cardioprotective effect of an endothelin receptor antagonist during ischaemia/reperfusion in the severely atherosclerotic mouse heart

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Objective: Endothelin (ET) receptor antagonists have been shown to be cardioprotective during myocardial ischemia and reperfusion via a nitric oxide-dependent mechanism. The aim of the study was to investigate whether the dual ETA/ETB receptor antagonist bosentan is cardioprotective during ischemia and reperfusion in severely atherosclerotic mice which have impaired nitric oxide bioavailability.
Method: Buffer-perfused hearts from apolipoprotein E/LDL receptor double knock out (KO) mice and wild type (WT; C57bl) mice were subjected to 35 min ischemia followed by 30 min reperfusion. The hearts received vehicle, the ETA/ETB receptor antagonist bosentan (10 μmol/l) or ET-1 (1 nmol/l) (n=7-8).
Results: The rate-pressure product (RPP; left ventricular developed pressure x heart rate) at the end of reperfusion was equally impaired in WT and KO mice given vehicle (34±8% and 29±9% recovery of the pre-ischemic value, respectively). Bosentan significantly improved the recovery of RPP to 57±10% in WT and to 68±10% in KO mice ($P<0.01$ vs. vehicle). ET-1 further depressed the recovery of RPP in the WT group to 15±4% ($P<0.05$ vs. vehicle), whereas there was only a minor negative influence of ET-1 on RPP in the KO group (22±4% recovery). Similar effects were obtained on the recovery of left ventricular end-diastolic pressure, left ventricular developed pressure and dP/dt during reperfusion. Bosentan improved the recovery of coronary flow in both KO and WT mice, but the recovery of coronary flow was significantly better in the KO mice given bosentan (135±15%) than in the WT group given bosentan (111±12%; $P<0.01$). In addition, the detrimental effect of ET-1 on coronary flow was more pronounced in the KO group than in the WT group (39±8% vs. 59±10% recovery, respectively; $P<0.01$). Coronary outflow of nitric oxide during reperfusion was enhanced in both groups following bosentan administration.
Conclusions: The ETA/ETB receptor antagonist protects from ischemia/reperfusion injury in the atherosclerotic mouse heart. The more pronounced effects of ET receptor blockade and stimulation on coronary flow in atherosclerotic animals indicate an increased activation of the ET system in atherosclerotic coronary arteries.

P1156 Neither levosimendan nor dobutamine infusion during myocardial reperfusion affected the extent of the no-reflow phenomenon in a porcine ischaemia-reperfusion experimental model

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Background: Inotropic support is often necessary in the setting of acute myocardial infarction, especially when complicated with cardiogenic shock.
Purpose: To examine the effect of levosimendan and dobutamine, agents with positive inotropic properties widely used in clinical practice, on the extent of the no-reflow phenomenon (NRP) and coronary blood flow (CBF) in a porcine experimental model of ischemia-reperfusion.
Methods: In 18 animals after mid-thoracotomy, the left anterior descending coronary artery was ligated for 60 min, followed by 120 min of reperfusion. At 50 min of the ischemia period, the animals were randomly assigned to three groups. Group A (n=6) animals received no medication, whereas in group B (n=6), levosimendan (24μg/kg as a bolus dose, followed by 0.2μg/kg/min infusion) and in group C (n=6), dobutamine (10μg/kg/min) were administered during reperfusion, starting 10 min before the end of the ischemia period. The NR area was assessed by thioflavine staining and was expressed as a percentage of the area of the left ventricle at risk (AAR). Coronary flow was recorded by a probe of an ultrasound transit time flowmeter, placed at the site of the ligation and CBF during reperfusion was expressed as a percentage of baseline CBF.
Results: Neither levosimendan nor dobutamine infusion affected NRP compared to controls (55.4±5.2% versus 45.7±10.7 versus 49.7±15.9%, respectively, p=ns between groups). There was a tendency for higher CBF in group A, in comparison to both groups B and C, but this difference was not statistically significant.
Conclusions: Levosimendan and dobutamine infusions had an insignificant effect on NRP and CBF when administered during the reperfusion period in a porcine experimental model of acute myocardial infarction. According to these results, levosimendan and dobutamine can be used safely in the setting of acute myocardial infarction.

P1157 Inhibition of protein kinase C activates Akt/PKB and blocks apoptosis in the remote myocardium after regional myocardial infarction

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Background: In the remote, surviving myocardium after a regional myocardial infarction, activation of apoptotic markers can be found as early as 3 hours after the onset of ischemia. This activation could be shown to be mediated by angiotensin AT-1 receptors. The signal transduction mechanisms mediating this activation of apoptosis downstream to the AT-1 receptors are not fully elucidated. Protein kinase C (PKC) is coupled to AT-1 receptors. Goal of this study was to test if PKC is involved in the AT-1 receptor dependent activation of apoptosis early after myocardial infarction.
Methods: Rats were pre-treated with chelerythrine (5 mg/kg/d, 24 h) or saline and then subjected to myocardial infarction by ligation of the left anterior descending coronary artery in situ (LIG) or sham operation (SHAM). After 6 hours, rats were sacrificed, and transmural biopsies were taken from the non-ischemic posterior wall of the left ventricle. In these biopsies, activation of caspase-3, phosphorylation of Akt/PKB, the bcl-2/bax ratio (all by Westernblot analysis) and DNA fragmentation (LM-PCR) were determined.
Results: In the saline-treated animals subjected to LIG, a significant activation of caspase-3 (167% of SHAM), a shift of the bcl-2/bax ratio towards the pro-apoptotic bax (81% of SHAM) and increased DNA fragmentation could be observed. Phosphorylation of Akt/PKB was at the level of SHAM. Pre-treatment with chelerythrine normalized the bcl-2/bax ratio in the animals subjected to LIG. Activation of caspase-3 occurred in a comparable amount as in the saline animals (152% of SHAM). In those animals, however, LIG lead to a significant increase of Akt Phosphorylation (250% of SHAM), together with a reduction of DNA fragmentation to the level of SHAM.
Conclusion: Inhibition of protein kinase C blocks the execution of apoptosis in the remote area after regional myocardial infarction, as shown by reduced DNA fragmentation. It is postulated that this is not due to inhibition of pro-apoptotic mechanisms, since activation of caspase-3 persisted. Instead, it is postulated that this inhibition is due to an activation of anti-apoptotic signalling pathways including Akt/PKB.

P1158 Thrombospondin-1 suppresses inflammation and limits expansion of fibrosis in healing myocardial infarcts

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Purpose: Healing of a myocardial infarct depends on suppression of the inflammatory response after scar formation and prevention of its expansion to normal areas. We observed that expression of Thrombospondin (TSP)-1, a potent inhibitor of angiogenesis and activator of TGF-beta, is localized in the border zone of healing canine infarcts and hypothesized that it may suppress the inflammatory response, inhibiting local angiogenesis and limiting expansion of fibrotic tissue to the non-infarcted area.
Methods: A canine and a murine model of reperfused myocardial infarction were used. Morphometric variables and gene expression were studied in wild type and TSP-1 -/- mice using immunohistochemistry and RNAse protection assays. In vitro experiments examined the effects of TSP-1 stimulation on canine endothelial cells.
Results: TSP-1 mRNA was induced in canine infarcts after 1 h of ischemia and 3-7 days of reperfusion. TSP-1 protein was localized in the extracellular matrix and microvascular endothelium of the ischemic border zone after 5-28 days of reperfusion. Isolated canine venular endothelial cells showed constitutive expression of TSP-1 mRNA, which was downregulated by TNF-alpha and IL-1beta but was markedly induced by TGF-beta and bFGF. TSP-1- stimulated canine endothelial cells demonstrated a significant downregulation of MT1-MMP, but not TIMP-1 or TIMP-2 mRNA expression. Murine infarcts also exhibited marked TSP-1 deposition in the border zone. Control and sham-operated TSP-1 deficient hearts showed no evidence of inflammation. However, infarcted TSP-1 -/- mice had significantly higher collagen alpha1(I) mRNA synthesis and increased macrophage and myofibroblast accumulation in the infarct ($p<0.05$), with extensive infiltration of the neighboring non-infarcted area, when compared with their wildtype littermates ($p<0.01$). Furthermore, expression of the pro-inflammatory cytokines IL-1beta, IL-6 and TNF-alpha and of the chemokines MCP-1 and MIP-1alpha was much higher in infarcted TSP-1 knockout animals, possibly because of impaired TGF-beta activation. Infarcted TSP-1 knockouts showed significantly higher left ventricular end-diastolic volume ($p<0.05$) than wildtype mice, suggesting more extensive remodeling.
Conclusions: Our findings suggest that TSP-1 expression in the border zone of healing myocardial infarcts may act as a barrier, limiting expansion of the inflammatory process to the non-infarcted myocardium. These effects may regulate post-infarction remodeling.

P1159 Plasminogen activator inhibitor-1 is regulated by glycoprotein 130 ligands in human adipose tissue

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Background: Adipose tissue is a prominent source of plasminogen activator inhibitor-1 (PAI-1), the primary physiological inhibitor of plasminogen activation. Elevated levels of PAI-1 are found in obese subjects and are associated with an increased risk of thromboembolic events. On the other hand a correlation between levels of the glycoprotein 130 (gp130) ligand interleukin-6 (IL-6) and obesity has been described. We could show recently that gp130 ligands upregulate PAI-1 in cardiac myocytes (Macfelda and Weiss et al., J Mol Cell Cardiol. 2002 Dec;34(12):1681-91). Here we investigate whether the gp130 ligands oncostatin M (OSM), IL-6, leukemia inhibitory factor (LIF) and cardiotrophin-1 (CT-1) regulate PAI-1 expression in human adipose tissue.
Methods: Primary human preadipocytes were prepared by collagenase digestion of adipose tissue. To induce adipose differentiation preadipocytes were cultured under hormone-supplemented conditions. Differentiation was verified by staining with Sudan III. Preadipocytes and adipocytes were treated with OSM (100ng/ml), IL-6 (100ng/ml), LIF (104U/ml) and CT-1 (100ng/ml), respectively, for 48h.
PAI-1 antigen in supernatants was quantified by a specific ELISA, mRNA levels for PAI-1 were determined by Real Time PCR (RT-PCR).
Results: OSM and CT-1 significantly up-regulated PAI-1 production in both preadipocytes and adipocytes dose dependently up to 7-fold and 13-fold (OSM) and up to 4-fold and 3.5-fold (CT-1). IL-6 also significantly increased PAI-1 production in preadipocytes up to 4.5-fold and in adipocytes up to 6.5-fold whereas LIF induced only a minor increase of PAI-1 (1.5-fold) in both cell types. These results were confirmed by RT-PCR on the level of specific mRNA expression.
Conclusion: We could show that selected gp130 ligands significantly upregulate PAI-1 expression in cultured human preadipocytes and adipocytes. We postulate that gp130 ligands participate in the modulation of PAI-1 synthesis in adipose tissue and we hypothesize, that high levels of circulating gp130 ligands such as IL-6 found in obese patients could contribute to the well-documented upregulation of PAI-1 in these subjects.

P1160 Gene expression analysis of the atherosclerotic plaque in apoe−/− mice: effect of inhibition of platelet adhesion by glycoprotein IB blockade

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Background: Adhesion of platelets to the vascular endothelium plays a central role in the development of atherosclerotic lesions. Inhibition of platelet adhesion profoundly reduces leukocyte accumulation in the arterial intima and attenuates atherosclerotic lesion formation in APO E-/- mice suggesting platelets as a major player in atherogenetic processes. Yet, only limited data are available regarding the effect of platelet inhibition on the molecular mechanisms governing atherosclerosis.
Methods and Results: This study sought to investigate the effect of platelet adhesion on gene expression during the development of atherosclerosis in Apo E-/- mice. Therefore, we performed a gene expression analysis of plaque material from Apo E-/- mice and analyzed the effect of inhibition of platelet adhesion after 14 weeks of treatment with an GPIb-antibody. We identified 92 out of 2400 genes that were differentially expressed during the development of atherosclerosis, whereas the expression of known housekeeping genes was unchanged. Profound changes took place in genes associated with transcription, proliferation, cell interaction and inflammation. Interestingly, inhibition of platelet adhesion affected the mRNA expression of some genes with known pro-atherosclerotic effect such as AXL tyrosin kinase, PDGF-A, and P-selectin. Additionally, inhibition of platelet adhesion resulted in a significant reduction in macrophage migration inhibitory factor (MIF) expression after 14 weeks. It has been shown lately that MIF is involved in recruitment of monocytes to the atherosclerotic plaque. Inhibition of MIF resulted in a reduced macrophage content in atherosclerotic plaques in mice. Likewise, expression of the monocyte marker CD14 was also significantly reduced by blockade of platelet adhesion in our model indicating that reduced MIF expression was followed by a reduction in monocyte adhesion. This data were further validated by gene-specific PCR.
Conclusions: The gene expression analysis of plaque material from ApoE-/- mice offers a promising method to gain a better understanding of the molecular mechanisms leading to atherosclerosis and to systematically analyze the effect of relevant drugs. Additionally, our data suggest that early adhesion of platelets to the atherosclerotic endothelium may lead to the recruitment of inflammatory cells such as monocytes by the induction of the cytokine MIF. This may represent an important mechanism in the development of the atherosclerotic lesion.

P1161 Hepatocyte growth factor and cardiovascular thrombosis in patients admitted to the intensive care unit

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Objectives: The aim of this study was to investigate the relationship between Hepatocyte growth factor (HGF) and thrombosis in patients with chest pain.
Background: HGF has been reported to be a marker of atherosclerosis and of thrombi synthesis, but the relationship between HGF and proven coronary thrombi has not described.
Methods: One hundred seven patients with chest pain (61 acute myocardial infarction, 18 unstable angina, 15 stable angina, 9 acute aortic dissection, and 4 pulmonary thromboembolism; 65 male and 42 female; 66 ± 11 years old) were enrolled. The presence of thrombi was evaluated by angiography, intravascular ultrasonography, angioscopy, and computed tomography. Serum HGF concentrations were measured using a new enzyme-linked immunosorbent assay.
Results: Serum HGF was significantly higher in the patients with acute myocardial infarction (335.0 ± 197.5 ng/mL), unstable angina (269.1 ± 152.7 ng/mL), acute aortic dissection (320.3 ± 116.5 ng/mL), and pulmonary thromboembolism (292.5 ± 101.9 ng/mL), than in those with stable angina (171.2 ± 56.1 ng/mL). Serum HGF concentration was also higher in those patients with proven thrombi than in those patients without (326.7 ± 189.7 ng/mL vs. 226.9 ± 110.8 ng/mL).
Conclusion: Increased serum HGF concentrations correlate with the presence of thrombi in patients with acute coronary syndrome, acute aortic dissection, and pulmonary thromboembolism. This is the first report describing the relationship between increased HGF concentrations and the presence of coronary thrombi, and is also the first report investigating HGF concentrations in patients with acute aortic dissection and pulmonary thromboembolism.

P1162 Intra-aortic balloon counterpulsation decreased the extent of the no-reflow phenomenon and infarct size in an ischaemia/reperfusion experimental model

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Background: The beneficial effects of the IABP on the outcome of patients undergoing primary angioplasty in the setting of acute myocardial infarction have been controversial. We sought to investigate the effects of the IABP on the extent of infarct size, the no-reflow phenomenon and coronary blood flow (CBF) during reperfusion in an ischemia-reperfusion experimental model.
Methods: A 30-ml IABP was placed in the descending aorta of 11 open-chest pigs. Each pig underwent occlusion of the mid left anterior descending (LAD) coronary artery for 1 h, followed by reperfusion for 2 h. The mean CBF, distal to the LAD occlusion site was measured with a transit-time ultrasound flowmeter. In 6 experiments, IABP support was used during reperfusion. At the end of each experiment the infarcted (IA) and the no-reflow (NRA) area were also measured with the use of coloring matters (tetrazolium and thioflavine).
Results: The results are shown in the table. CBF at reperfusion was normalized with respect to baseline values (% of baseline CBF).

Table

		Reperfusion (min)						
	IABP	1	15	30	45	60	90	120
CBF	yes	241±88%	240±63%	189±57%	155±43%	90±71%	87±43%	55±61%
(ml/min)	no	121±112%	73±105%	50±83%	51±75%	17±63%	-0.07±45%	-18±45%
	p	0.06	0.01	0.01	0.03	0.05	0.05	0.01
NRA	yes							36.4%
	no							69.4%
	p							0.01
IA	yes							36.7%
	no							72.0%
	p							0.02

Conclusions: The IABP succeeded in reducing the infarct size and the no-reflow phenomenon, probably due to increased CBF during the reperfusion period.

P1163 Tumor necrosis factor-alfa blockade to modulate the T cell- driven immune response in patients with unstable angina

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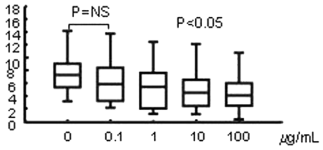
Background: Tumor necrosis factor-alfa (TNF-alfa) is a pro-inflammatory cytokine that activates NF-kB and favours the expansion of CD4+CD28null T-cells, a subset of T-cells that drives the immune response. The CD4+CD28null T lymphocytes are unusual (< 1%) in healthy subjects but are expressed in high frequencies in unstable angina (UA) and are related to worse prognosis.
Aim: We used Infliximab, a monoclonal antibody against TNF-alfa, to modulate the immune and inflammatory response in patients with UA.
Methods: Peripheral blood was collected from 17 patients admitted to our coronary care unit with UA(Braunwald 's IIIB). The in vitro production of TNF-alfa was assessed after lipopolysaccharide-challenge (LPS 1ng/mL) with and without increasing doses of Infliximab (0.1, 1, 10 and 100 μg/mL). Before and after in vitro challenge, TNF-alfa levels were measured by an ELISA kit. The frequency of CD4+CD28null T- cells was assessed by flow cytometry after 24 hours incubation of whole blood with and without Infliximab (0.1, 1, 10 and 100 μg/mL).
Results: TNF-alfa production significantly increased after LPS-challenge (median) (from 0 to 266.3 pg/ml, P = 0.03). TNF-alfa production was significantly reduced by 0.1 μg/mL of Infliximab (to 0.43 pg/ml, P=0.001) and totally inhibited by higher doses of Infliximab. A high percentage of CD4+CD28null T-cells was present at baseline (6.2%). After incubation with 1, 10, and 100 μg/mL of Infliximab, the CD4+CD28null T-cells percentage decreased to 4.9%, 4.5% and 4.1%, respectively (P<0.05 by ANOVA, figure).



Frequency (%) of $CD4^{+}CD^{null}$ T-cells after incubation with increasing doses of iInfliximab.

Conclusion: The production of TNF-alfa induced by LPS and the frequency of CD4+CD28null T-cells are reduced by Infliximab. These results may introduce alternative therapeutic strategies for the treatment of patients with UA.

P1164 The homing of peripherally injected marrow mononuclear cells is related to the extent of myocardial injury after experimental cryodamage in rats

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Background: homing of peripherally injected marrow mononuclear cells (MMNCs) has recently been demonstrated in an experimental animal model of cryodamaged heart (1). Being the mechanism underling this phenomenon still unknown, we aimed this study to verify the hypothesis that the number of homed MMNCs is related to the extension of the infarcted area (cryodamage) in an experimental model.
Study design and methods: twelve donors and 12 recipient inbred isogenic adult (4 weeks old) Fisher rats were used to mimic autologous transplantation. In recipient rats myocardial damage was obtained by cryoinjury. MMNCs were purified, labeled with PKH26 (red fluorescent cell dye), and infused 7 days after the injury through the femoral vein of recipient rats. One week after peripheral administration, the number of homed MMNCs was assessed and correlated to the infarct size measured by planimetry and expressed as percentage of LV area that was hypo- or hyperechogenic with respect to non-infarcted regions.
Results: labeled cells were found only in the injured myocardium of the treated animals (n = 6); a mean of 12 ± 3 PKH26 + cells per section examined were found; the interobserver variability of the cell count was less then 3 percent. A significant correlation ($p < 0.01$) was found between infarct size and the estimated number of cells.
Conclusion: our results indicate that the homing of MMNCs depends on the extension of the myocardial injury; we therefore hypothesize that chemoattraction to this area takes place possible through the network of cytokines released by the damaged tissue.
(1) Haematologica 2003; 88:614-621.

P1165 Can radiofrequency ablation affect hematopoietic progenitors cells recruitment?

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Background: Endothelial progenitors cells (EPC), which have been isolated from CD34+ cells are mobilized after heart injury and undergo differentiation to both mature endothelial cells and myocytes. In addition high proportions of stem cells have been recently demonstrated in atrial tissue. It is not known however if other types of myocardial damage, as those induced by radiofrequency (RF) delivery during ablation procedures, can also represent a trigger for CD34+/EPC recruitment. This would mean that atrial necrosis is sufficient to induce EPC recruitment despite the absence of myocardial ischemia. We aimed to assess whether myocardial necrosis itself, as that induced by RF ablation, determines CD34+/EPC recruitment.

Methods: 15 patients with acute coronary syndromes (ACS) without ST elevation (mean age 67 ± 12 years), 9 with and 5 without TpI increase, and 7 (mean age 54 ± 9 years) who underwent a RF ablation procedure presenting evidence of myocardial necrosis (mean Tp elevation: 1,39 ± 0,84 pg/ml) were selected. The circulating CD34+ mononuclear cells count were quantified on days 1, 3, 5, 7, 10 and 14 after the ischemic/necrotic event. At day 10, EPC were quantified as CD34+ cells coexpressing AC133 and VEGFR2 by flow cytometry.
Results: CD34+ cells count are presented in the table.

Results: CD34+ cells count are presented

Day	1	3	5	7	10	14
ACS TpI -	3.6 ± 1.6	2.7 ± 1.7	3.6 ± 2	3.3 ± 1.9	3.2 ± 1.7	2.7 ± 1.5
ACS TpI +	3.6 ± 1.2	2.9 ± 1.4	4.5 ± 1.6	4.7 ± 1.6	6.4 ± 2.8 *	4.3 ± 2.6
Post-Abl	3.1 ± 1.4	3 ± 1.4	3.3 ± 1.9	3.6 ± 2.2	5 ± 2.6 *	3 ± 2

* p < 0.05 on post-hoc analysis vs CD34+ on days 1, 7 and 14.

In patients with necrosis no correlation was observed between TpI elevation and CD34+ cells degree. CD34+ cells showed a positive correlation to EPC (r = 0.79; p < 0.001).
Conclusions: Myocardial injury induced by RF ablation represent a novel trigger for pheripheral CD34+ recruitment. No differences were observed between RF and ACS Tp+ patients, underscoring the role of necrotic injury in this setting. Interestingly this elevation was not related to the amount of TpI elevation. Further studies are warranted to investigate the potential effects of progenitor cell-derived myocites on atrial remodeling and/or their relation with cardiac arrhythmias.

P1166 Effects of a single episode of lower limb ischaemia on endothelial progenitor cells in patients with peripheral arterial occlusive disease and healthy subjects

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Background: Walking training above the ischemic threshold significantly improves symptoms of claudication and maximum walking distance in patients with PAOD Fontaine II b. However, the mechanisms mediating this clinical effect remain largely unclear. Recent experimental investigations have shown that circulating endothelial progenitor cells (cEPCs) play a considerable role in ischemic neoangiogenesis. Aim of the present study was to assess the effects of limb ischemia induced by a maximum walking test in patients with stable PAOD on cEPC release. Healthy subjects with acute limb ischemia induced by suprasystolic inflation of a RR-cuff served as healthy controls.
Methods: Patients with PAOD of Fontaine type II b (n=14) underwent a treadmill walking test (3.5 kmph; slope of 12%) until reaching the maximal tolerable walking distance (avg. duration of ischemia 8.3±2.1 min). Ischemia in healthy subjects (n=10) was induced by a 15 min suprasystolic occlusion of one thigh. Complete arterial occlusion was verified by doppler.
CEPCs were quantified by FACS analysis (CD34/KDR double positve) and by cell culture (DiLDL/Lectin double positve after 4 days in culture).
Plasma VEGF concentration was measured by ELISA. Samples were evaluated before as well as 2; 4; 6; 8; 24 and 48 hours after ischemia.
Results: PAOD patients had a significant increase in cEPCs vs. begin (FACS: 3.2±0.8, p<0.05; Cell culture: 2.9±0.5 p<0.05; ELISA: 4.4±1.2 p<0.05). A similar effect was observed after acute ischemia induced in healthy subjects (FACS: 3.2±0.7 p<0.05; Cell culture: 3.2±0.8 p<0.05; ELISA: 3.8±1.3 p<0.05). In both groups the maximal increase was reached at 48 h after ischemia.
Conclusion: These results indicate that ischemia seems to be a potent stimulus for a significant release of cEPCs in PAOD patients and healthy subjects. Circulating EPCs may contribute to neoangiogenesis and improved peripheral perfusion in patients with stable PAOD on walking training.

P1167 Infarct size limitation by lipoxygenase inhibition in patients with ST-elevation acute coronary syndromes: acute effects and long-term outcomes

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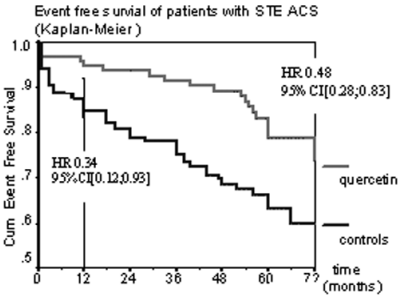
Aim: Main determinants of outcomes of patients (pts) with acute myocardial infarction (MI) are mass of infracted myocardium and speed of formation of necrotic zone. There is a relationship between extent of myocardial damage and subsequent left ventricular (LV) dilatation, dysfunction. We have hypothesized that prognosis of pts with STE ACS can be improved by administration of cardioprotective drug with nitric oxide (NO) modulating and lipoxygenaze blocking properties.
Methods: In a prospective randomized study enrolled 198 pts (age 53.2±0.7 yrs) with STE ACS within 12 hrs from symptoms onset (3.7±0.2 hrs). 93 pts received study drug quercetin (Q) intravenously during 5 days in addition to standard therapy. All pts underwent echocardiography within 10 days. Serum levels of NO products (NO3/NO2) and leukotrien (LT) C4 were assessed within 3 days from admission. Infarct size index (ISI) was calculated using serial MB-CPK measurements.
Results: Pts in the Q group were less likely to develop LV failure and PVC by 7th day after admission (OR 0.49;[0.26;0.95] and OR 0.39[0.22;0.71]respectively). Declines of NO3/NO2 and LT C4 were greater in Q groupISI than in controls (by 85% vs 26%,p<0.01 and by 27% vs 7%,p<0.05 respectively). was greater in controls (p<0.01) than in Q group. Increase in LV ejection fraction was registered in Q treated pts (10%, p<0.05) rather than in control group (6%,p>0.1). Composite endpoint of death, recurrent MI or unstable angina was registered in control group more frequently (p<0.05) [figure].



Conclusions: Our findings suggest that metabolic modulatory and cardioprotective effect of iv form of lipoxygenase inhibitor Q can reduce myocardial damage, improve LV function and further prognosis of patients with STE ACS.

P1168 Complement C3 serum levels and genotype and their relationship to coronary artery disease

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Several pieces of evidence indicate that the complement system is activated in patients with atherosclerotic disease. Previous studies have shown that serum C3 levels are elevated in patients with a history of myocardial infarction (MI) and a polymorphic variant of C3 (C3F) may predispose to MI.
We measured C3 levels in 278 patients undergoing coronary angiography for typical symptoms of coronary artery disease (CAD) and 269 healthy age and sex matched controls. Levels were correlated to elements of the metabolic syndrome, coronary artery score and C3 common allelic variants C3F and C3S.
Serum levels of C3 were significantly higher in patients compared with controls (1.15g/l and 0.92 g/l respectively; p<0.001). In the patient group, there was a positive correlation between C3 levels and BMI, fasting glucose, HbA1c, fibrinogen and a negative correlation with HDL. There was no correlation between C3 levels and age, sex, cholesterol, LDL, TG, WHR, history of smoking, hypertension or coronary artery score. Patients with previous MI (n=88) had higher C3 levels but this fell short of statistical significance (p=0.07). However, analysing a subgroup who were not on statin treatment (n=134), individuals with previous MI (n=19) had significantly higher C3 levels compared with the rest (1.20 g/l and 1.10 g/l respectively, p=0.023). Also, patients with diabetes (n=21) had significantly higher C3 levels compared with non-diabetics (1.24 g/l and 1.14 g/l respectively; p=0.02). In the control group, a positive correlation was detected between C3 serum levels and BMI, fibrinogen, cholesterol, LDL and TG. No correlation was found with age, sex, fasting glucose, HDL or WHR.
At the gene level, C3S allele frequency was 381 (79%) and 315 (78%) in patients and controls respectively. There was no difference in allele distribution comparing patients with controls. Taking both groups together, C3 levels in individuals with C3SS genotype (n=271) were 1.05 g/l (1.03-1.08), C3SF (n=154) 1.01 g/l (0.98-1.04) and C3FF (n=18) 0.98 g/l (0.88-1.09) but the difference just failed to reach statistical significance (p=0.06). However, the combined group of C3SF and C3FF individuals had significantly lower C3 levels compared with C3SS individuals (1.01 g/l and 1.05 g/l respectively; p=0.02).
In summary, this work has shown that patients with CAD have high serum complement levels, which correlate with markers of the metabolic syndrome. Also, we have found that C3SS genotype is associated with higher serum C3 levels, suggesting that C3SS individuals have an increased risk of developing CAD.

P1169 Metabolic protection in acute myocardial infarction with glucose–insulin–potassium solution. The Macedonian Acute Myocardial Infarction (MAMI) study

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Objectives: Several studies in the past, especially in the prethrombolytic era, showed favorable results concerning survival in the acute setting of myocardial infarction (MI). Nevertheless several elements regarding the efficacy of GIK infusion remain undetermined in thrombolysed MI.

Aim: The aim of our study was to assess the clinical efficacy of GIK infusion as an adjunctive therapy to thrombolysis in acute MI.
Methods: We studied 549 consecutive patients with STEMI (463 male, 81 female, mean age 60.3+11.56 years) who received thrombolysis with rt-PA. Two hundred thirty seven patients (Group A: 199 male,38 female, mean age 61.52+10.5 years) were randomized within 8 hours from the onset of symptoms to receive GIK solution (20% glucose, 40IU soluble insulin, 54 mEq K+ per litre) at an infusion rate of 2ml/kg/hr over 12 hours. The control group (Group B, n= 312, 267 male, 45 female, mean age 60.37 years received 1000ml 0.45% sodium chloride, by intravenous 12-hr infusion at a rate of 2ml/kg/hr. We studied the epidemiological, clinical and biochemical characteristics of patients, as well as, the extent of infarction and left ventricular systolic function (ejection fraction EF). Moreover mortality and complications (congestive heart failure, reinfarction, postinfarction angina, arrhythmias) during the inhospital period and at 30 days follow-up were studied.
Results: Left ventricular ejection fraction remained higher in Group A patients (48.01+7.4 vs 42.13+6.4/p<0.001), even though the extent of myocardial damage (as determined by peak CPK/CK-MB values) did not differ significantly between two groups. Group A patients had 2.8% lower mortality than Group B patients (p= 0.048) during inhospital period while at 30 days follow up mortality was 5.4% lower (p=0.04). Moreover the incidence of complications was reduced by 8.4% in Group A patients during the inhospital period as well as the 30 days follow up.
Conclusions: Glucose, insulin, potassium infusion as adjunctive therapy to thrombolysis in acute MI resulted in a significant mortality reduction. The favorable effects of GIK infusion in survival and complications following an acute MI seem to last at least for 30 days after discharge.

P1170 Benefit of glucose-insulin-potassium infusion in-patients treated with thrombolytic therapy – one-year follow-up

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Background: The use of glucose-insulin-potassium (GIK) infusion in patients with acute myocardial infarction (AMI) is still a controversial issue.
Objectives: In this prospective, randomized, open label study we evaluated benefit of GIK infusion in patients with STEMI treated with thrombolytic therapy on mortality and major coronary events (reinfarction, angina pectoris, arrhythmias, heart failure and revascularisation) within one year.
Methods: One hundred and twenty patients with STEMI, mean age 56.6 ± 10.2 years, m/f ratio 81/37, were randomized within 12 hours from the onset (mean 3.1±1.8 h) to GIK infusion (25% glucose, 50IU soluble Insulin per liter and 80mmol KCl per liter at an infusion rate of 1ml/kg/h and thrombolytic therapy (Streptokinase 1.5 MU/30-60min) (GIK group) vs. thrombolytic therapy only (Control group). All other therapy was standard for AIM and same in both groups. GIK infusion was not completed in two patients. The groups did not differ in age (GIK 56.6 ± 10.6 vs. Control 56.7 ± 9.7 years); in m/f ratio (GIK 52/26 vs. Control 29/11) and max values of CK (GIK 1559.8 ± 1246.7 vs. Control 1605.5 ± 1089.7 U/l). Patents with unstable diabetes before admission were excluded.
The results were as follows (Table 1): there were significant reductions of reinfarction, angina pectoris, arrhythmias and heart failure within one year of AMI in GIK group vs. Control group. Control group had significantly high relative risk for composite of events: mortality, severe heart failure (Killip class>2), reinfarction and VT, VF within one year (RR=5.56, 95% CI 2.24-13.83, p=0.0002).

Table 1

	GIK group (N=78)	Control group (N=40)	Log Rank	p
Reinfarction	5 (6.4%)	11 (27.5%)	12.65	0.0004
Angina pectoris	36 (46.2%)	31 (77.5%)	28.81	0.0000
Arrhythmias	29 (37.2%)	33 (82.5%)	27.28	0.0000
Heart failure	11 (14.1%)	29 (72.5%)	51.90	0.0000
Revascularisation (PCI, CABG)	11 (14.1%)	6 (15.0%)	0.74	0.3892
Mortality	3 (3.8%)	5 (12.5%)	3.31	0.0691

Conclusions: Glucose-insulin-potassium infusion used as an adjunct to thrombolytic therapy in first 12h of STEMI significantly decreased major coronary events (reinfarction, angina pectoris, arrhythmias and heart failure) within one year.

P1171 Troponin t elevation at baseline and failure of reperfusion after acute myocardial infarction. An on-time substudy

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Purpose: An elevated cardiac Troponin T (cTnT) at baseline is a well known risk factor in patients (pts) with non ST elevation acute coronary syndromes (ACS). Only few data exist on the value of cTnT elevation in ST elevation ACS and there are no data whether cTnT elevation is still a risk factor when all pts are treated with a glycoprotein 2b/3a blocker.
Methods: The On-TIME (Ongoing Tirofiban in Myocardial Evaluation) trial evaluated the effect of early, pre-hospital initiation vs. Cath-lab initiation of Tirofiban in 507 pts with acute STEMI, who were referred to undergo primary angioplasty. Measurement of cTnT was done upon arrival in the PCI centre, shortly before angiography in 444 pts (88%). All angiographic parameters were analysed by an independent core-lab. Successful PCI was defined as TIMI 3 flow and Myocardial Blush Grade (MBG) 3. Clinical outcome was assessed at 1-year follow-up.
Results: CTnT was positive (>0.05 μg/l) in 208 pts (47%). A positive cTnT was more often seen in elderly pts, in female pts, in pts with diabetes, in pts with an anterior MI, in pts with signs of heart failure (Killip > 1) and in pts who presented > 90 min after symptom onset (p<0.05 for all comparisons). Pts with a positive cTnT less often had PCI success with MBG 3 (42% vs. 63%, p<0.001) and a significantly higher one year mortality (4.9% vs. 1.3%, p=0.031). A positive troponin T was an independent predictor of PCI failure after multivariate analysis (OR: 1.9, 95% CI: 1.8-2.9).
Conclusion: In pts who undergo primary angioplasty for STEMI, who all are pretreated with a glycoprotein 2b/3a blocker, a positive cTnT at baseline determines a high risk population and is an independent predictor of unsuccessful reperfusion after angioplasty for acute myocardial infarction.

P1172 A randomized open-label study of transfer for primary percutaneous coronary intervention with glycoprotein IIb/IIIa inhibitor versus on-site thrombolysis in patients with acute myocardial infarction

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Background: The benefit of primary angioplasty over thrombolysis in ST elevation myocardial infarction (STEMI) has been demonstrated. The best reperfusion therapy in STEMI in patient presenting to hospital without catheterization facilities is not clearly defined and has been under investigation in several trials. The delay of onset of primary angioplasty caused by transportation may question the benefits of this strategy over thrombolysis. Treatment with GP IIb/IIIa inhibitors for transportation for primary PCI may be the option to hold this advantage in AMI treatment.
Methods: Patients with STEMI (duration of AMI < 12 hours, typical clinical and ECG signs of AMI) were randomized in 13 community hospitals located 20-150 km from the cath lab. Patients were randomized to on-site thrombolytic therapy (streptokinase) or to transportation for primary PCI with adjunctive therapy with tirofiban (10 μg/kg bolus i.v. in the emergency room of hospital of admittance and i.v. infusion 0.1 μg/kg/min during transportation and primary PCI). All patients with cardiogenic shock were obligatory treated with primary PCI but were excluded from analysis.
Results: 341 patients were randomized into the study (169 to thrombolysis and 172 to transfer for PCI). Groups were well balanced according to basic characteristics. Mean time from onset of MI to randomization was: 139±133 min in transported group vs 143±117 min in thrombolytic group (p=0,94). Mean time of tirofiban administration to PCI in transported group: 121±36 min. Anterior AMI: 42,6% vs 41,5% (p=0,85). Mean delay to primary PCI was 158±60 min and to thrombolytic therapy 44±43 min.(p<0,0001). No patient died or required resuscitation during transport. Hospital outcomes for primary PCI group vs thrombolytic group: mortality 2,9% vs 8,28% (p=0,03); re-AMI 1,16% vs 3,55% (p=0,15): stroke 0% vs 1,18% (p=0,15). Patients randomized to transport had a reduced hospital stay: 9 ± 3 days vs 14 ± 7 days (p<0,0001); and less recurrence of ischemia 2,9% vs 15,38% (p=0,0001). 17 (10,05%) thrombolytic patients had to be transported for PCI (rescue PCI or due to postinfarct angina). Combined analysis (using combined rate of death/re-AMI/stroke) for transported group vs thrombolytic group revealed rate of 4,07% vs 13,02% (p=0,003) respectively.
Conclusions: Early outcomes of two treatment strategies showed that transportation for primary PCI with adjunctive therapy with GP IIb/IIIa inhibitor- tirofiban is superior to on-site thrombolysis for patient with STEMI presenting to hospital without catheterization facilities.

P1173 Is primary angioplasty superior to fibrinolysis in saving myocardial function? The DANAMI-2 echocardiographic substudy

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Introduction: The DANAMI 2 study showed that a strategy of primary percutanous intervention (PCI) is superior to fibrinolysis in the treatment of acute ST-elevation myocardial infarction. It is unknown whether PCI compared to fibrinolysis saves myocardial function.
Methods: Of the 1572 patients randomized in the DANAMI 2 study 1262 (80.2%) underwent transthoracic 2-dimensional echocardiograms at hospital discharge and after 30 days. Wall motion index (WMI) was estimated semi-quantitatively using a 16 segment-score in 626 fibrinolysis-treated and 636 PCI-treated patients.
Results: Patients had similar WMI whether randomized to fibrinolysis or PCI at baseline (1.52±0.38 vs. 1.54±0.38). Similarly at 30-days there was no difference

in WMI between fibrinolysis and PCI (1.55±0.39 vs. 1.58±0.38, both p=NS). Patients treated with fibrinolysis increased significantly over 30 days (mean delta-WMI 0.044±0.33, p=0.01 for paired analysis). Similarly PCI treated patients increased by a mean of 0.069±0.34, p<0.001. However the increase in WMI was not different between treatment groups. Further analyses showed that there was no difference in WMI between PCI and fibrinolysis treated patients in different subgroups (i.e. sex, age over or below 63, systolic blood pressure over or below 120 mmHg and WMI over or below 1.2).
Conclusion: PCI was not superior to fibrinolysis in saving myocardial function estimated by WMI at 30 days follow up.

P1174 Immediate and 1-year outcome of primary PTCA of bifurcation lesions for acute myocardial infarction

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Primary PTCA is now a well established treatment of AMI but angioplasty of bifurcation lesions remains more challenging and have never been evaluated in this specific context.
Aim of the study: To assess the immediate and 1-year outcome of primary PTCA of bifurcation lesions for AMI compare to non-bifurcation lesions.
Methods: We retrospectively analyzed data from a single center data base of 646 patients admitted for AMI < 12 hours. Clinical follow-up was obtained for 96% of the cohort.
Results: A bifurcation lesion was involved in 150/646 (23%) AMI, (68% type 1; 16.7% type 2; 8% type 3 and 7.3% type 4). The infarct-related artery was the left main in 2.6%, LAD in 65.4%, circumflex/marginal in 16% and RCA in 16%. The therapeutic strategy was a provisional T stenting in 89.3% of the pts with a double guide wire in 48%. A stenting was performed in 89.3% of the pts (92.4 in the main branch, 7.6% in both branchs) and a final kissing balloon was performed in 22% of the cases.

Table

	Bifurcation lesion	Non-bifurcation lesion	p
Male	84%	82%	NS
Age	59 ± 14	59 ± 13	NS
History of prior MI	13%	12%	NS
Cardiogenic shock	7%	7%	NS
IIbIIIa inhibitor	30%	26%	NS
Procedural success	Main branch: 89.3%	90%	NS
Sub-acute stent thrombosis	3%	2%	NS
In-hospital MACE	7%	7%	NS
In-hospital death	3%	2%	NS
1-year follow-up			
Re-AMI	5.7%	7.4%	NS
TLR	10.6%	9.2%	NS
Death	12.1%	12.1%	NS
Total MACE	22.7%	20.7%	NS

Conclusion: A bifurcation lesion was involved in nearly 1/4 of the patients referred for AMI in the catheterization laboratory. Immediate and long term outcome of angioplasty in this situation appeared identical to PTCA involving non-bifurcation lesion.

P1175 Randomized comparison between stent and balloon in patients with anterior myocardial infarction undergoing primary angioplasty. A substudy of the Zwolle-6 randomized trial

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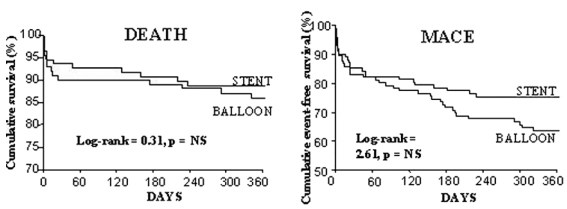
Purpose: In the Zwolle 6 randomized trial 1683 patients were randomized before angiography to stent (S) or balloon (B), without any exclusion criteria. In this study we present data form the subanalysis in patients with proximal left anterior descending coronary artery (LAD) occlusion.
Methods: A total of 218 patients with STEMI underwent primary angioplasty of proximal LAD (107 randomized to S and 111 to B). All angiographic, clinical and 1-year follow-up data were prospectively collected. The primary endpoint was major adverse cardiac events (MACE) (death, reinfarction, and/or reintervention at 1-year).
Results: The cross-over rates from B to S and S to B were 35.1% and 13.1%, respectively. No difference was observed in 1-year mortality and MACE (figure).



Conclusions: Our study is the first randomized trial comparing stenting and balloon angioplasty in a large cohort of unselected, consecutive patients. This subanalysis showed that routine stenting does not improve clinical outcome in patients undergoing primary angioplasty for proximal LAD occlusion.

P1176 Unsuccessful reperfusion in patients with ST-segment elevation myocardial infarction treated by primary angioplasty. Insights from the Zwolle myocadial infarction study

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Abstract. Introduction. Several studies have shown that patency of the epicardial vessel does not guarantee optimal myocardial perfusion. The aim of the current study was to identify clinical and angiographic correlations of unsuccessful reperfusion by the use of myocardial blush grade.
Methods: A total of 1548 patients with STEMI underwent primary angioplasty. All data were prospectively collected. Successful reperfusion was defined as post-procedural TIMI 3 flow with myocardial blush grade 2-3.
Results: Poor myocardial reperfusion was observed in 358 patients (23.1%), and was associated with a larger infarct size (2328±1802 vs 1617±1405, p < 0.0001) and impaired ejection fraction (40±11 vs 44±11, p < 0.0001). At multivariate analysis preprocedural TIMI flow 0-1, anterior infarction, ischemic time, postprocedural residual stenosis, advanced Killip class at presentation and age were identified as independent predictors of poor myocardial reperfusion (Table). At 1-year follow-up a total of 92 patients (5.9%) had died. At multivariate analysis, including clinical and angiographic variables, unsuccessful reperfusion was an independent predictor of 1-year mortality (RR [95% CI] = 3.17 [2.02-4.98], p<0.0001).

Predictors of unsuccessful reperfusion

Variable	Odds Ratio [95%CI]	p value
Preprocedural TIMI flow 0-1	2.63 [1.88-3.69]	< 0.0001
Anterior infarction	2.12[1.62-2.77]	< 0.0001
Postprocedural stenosis (%)	1.03 [1.02-1.04]	<0.0001
Ischemic time (minute)	1.001 [1.001-1.002]	<0.0001
Killip class > 1	1.72 [1.11-2.66]	0.014
Age (years)	1.012 [1.00-1.024]	0.045
Preprocedural stenosis (%)	0.98 [0.97-1.01]	NS

Conclusions: The prevalence of poor myocardial reperfusion is relatively high patients undergoing primary angioplasty for STEMI, with a significant impact on 1-year mortality. Preprocedural TIMI flow, anterior infarction, ischemic time, Killip class at presentation, and age were independently associated with unsuccessful reperfusion. Therefore, future research should be focused on these high-risk patients and treatment strategies should be developed either by mechanical or pharmacological approach, to improve myocardial perfusion and clinical outcome.

P1177 Primary percutaneous coronary intervention improved hospital and long-term outcome in octogenarians with acute ST-elevation myocardial infarction results of the MITRAplus registry

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Background: In clinical practice many patients (pts) with acute ST-elevation myocardial infarction (STEMI) are older than 80 years (y). Little is known about acute reperfusion therapy (aRT) for STEMI-pts in this age. The risks of aRT for STEMI might exceed the benefits with advancing age and so aRT may be harmful to the very old pts.
Methods: We compared aRT for STEMI in unselected pts ≥80y in clinical practice in the prospective, multicenter MITRAplus registry of consecutive STEMI in Germany.
Results: Of a total of 36336 consecutive pts with STEMI 5165 pts (14%) were ≥ 80y. From these older pts 29% did receive aRT: 1039 (19.5%) thrombolysis, 460 (8.5%) primary PCI. The main determinants of withholding aRT were (OR; CI): advancing age (0.90; 0.89-0.92), heart failure at admission (0.65; 0.54-0.78), diabetes mellitus (0.75; 0.65-0.86), renal failure (0.52; 0.39-0.69), prehospital delay > 4 hours (0.28; 0.24-0.33), and female gender (0.73; 0.65-0.83). Hospital and long-term mortality were 31.8%/41.4% without aRT, 30.4%/25.8% with thrombolysis, and 15.2%/15.0% with primary PCI (Multivariate analysis, see table).

STEMI pts ≥ 80y	Hospital Mortality	15-month-Mortality
Thrombolysis	OR 0.95; CI 0.81-1.12	OR 0.58; CI 0.39-0.88
Primary PCI	OR 0.39; CI 0.27-0.57	OR 0.43; CI 0.20-0.93

Summary and Conclusion: In clinical practice 14% of pts with STEMI were ≥ 80 y. These pts did receive aRT in only 29%. Thrombolysis did not influence hospital mortality, but was associated with a 42% reduction of 15-month mortality. Primary PCI for STEMI in pts ≥ 80 y was associated with a 61% reduction of hospital and an additional 57% reduction of 15-month mortality.

P1178 Subacute patency rate of the infarct-related artery with prophylactic vs therapeutic doses of subcutaneous enoxaparin following recanalization with tenecteplase and intravenous unfractionated heparin

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Purpose: In ST-elevation myocardial infarction (STEMI) undergoing thrombolysis with fibrin-specific agents, an early course of intravenous unfractionated heparin (UFH) followed by low-dose subcutaneous UFH, is warranted. While low-molecular-weight heparin Enoxaparin is currently not recommended as an adjunct to thrombolysis, it may be given subcutaneously following intravenous UFH cessation. Since optimal dosing of Enoxaparin is not standardized, we aimed at comparing the efficacy and safety of prophylactic (4000 U once daily) vs therapeutic (100 U/kg twice daily) regimens of subcutaneous Enoxaparin in STEMI undergoing successful thrombolysis.
Methods: All patients with STEMI and electrocardiographic signs of achieved recanalization following tenecteplase and intravenous UFH, consecutively referred to our Catheterization Laboratory between June 2002-November 2003 for predischarge coronary angiography, were prospectively evaluated. The primary endpoint was the infarct-related artery (IRA) TIMI flow grade at pre-discharge coronary angiography, while secondary end-points were the occurrence of venous thromboembolism and either major or minor hemorrhages.
Results: One-hundred twenty-three patients were evaluated: 57 (men/women 45/12, mean age 65.8 ± 8.1 years) receiving prophylactic doses, and 66 (men/women 45/21, mean age 62.6 ± 11.8 years) treated with therapeutic doses of subcutaneous Enoxaparin. The IRA patency rate was comparable in the two groups: 84% vs 86% TIMI 3 (p=NS) and 11% vs 9% TIMI 2 (p=NS) flow grades, respectively. No episodes of venous thromboembolism nor major hemorrhages occurred in neither group, while minor bleedings (14% vs 18%; p=NS) were comparable.
Conclusions: Once-a-day prophylactic regimen of subcutaneous Enoxaparin appears preferable to twice daily therapeutic regimen in patients with STEMI undergoing successful recanalization with tenecteplase and intravenous UFH. While having comparable efficacy and safety in fact, the adoption of prophylactic regimen is less cumbersome and expensive.

P1179 Echocardiographic evaluation of the effect of autologous bone marrow stem cells mobilization with granulocyte colony stimulating factor on the left ventricular remodelling in post-infarction rats

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Objectives: To evaluate the effect of autologous bone marrow stem cells mobilization with granulocyte-colony stimulating factor (G-CSF) on left ventricular remodeling and function after myocardial infarction (MI) in rats with echocardiography.
Materials and methods: Forty male SD rats were randomized into CSF-treated group (n=16), control group (n=16) and sham-operated group (n=8). G-CSF(150μg/kg/d) or saline were injected subcutaneously for 5 days since 6h after the coronary artery ligation or sham-operation. Echocardiography was performed before, 1 day, 2 weeks and 6 weeks after myocardial infarction to evaluate the change in left ventricular shape and function. Rats were then sacrificed and hearts were sectioned for histological study to calculate the scar index.
Results: In the CSF-treated group, left ventricular dimension (LVDd and LVDs) was much smaller(LVDd 0.72cm±0.03cm vs.0.83cm±0.02cm,P=0.006,LVDs 0.34±0.03cm vs.0.55cm±0.03cm,P<0.001) left ventricular ejection fraction (LVEF) and fractional shortening (FS) were improved significantly (LVEF 87.6%±2.9% vs.62.5%±2.5%,FS 52.7%±2.4% vs 30.6%±2.0%,p<0.001)while the value of Tei index was lower (0.23±0.06 vs 0.44 ±0.05,P=0.009)when compared with those of the control group. Rats in the CSF-treated group had smaller scar size(37.3±11.0% vs 51.9±11.5%,P<0.05)than the control group.
Conclustions: Mobilization of autologous bone marrow stem cells with G-CSF improves ventricular remodeling and heart function after myocardial infarction in rats. Echocardiography is an essential tool to evaluate the effect.

P1180 Failure of short-term functional improvement after unselected bone marrow stem cell administration in a porcine model of myocardial infarction

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Purpose: Regeneration of infarcted myocardium by transplanting stem cells into the infarct region has been proposed to prevent heart failure by angiogenesis and myogenesis. Thusfar most experimental studies have been performed in small rodent models. Consequently, we studied the effect of bone marrow (BM) injection in a porcine model of myocardial infarction (MI) induced left ventricular (LV) remodeling.
Methods: In 9 domestic swine (2-3 months old swine), the proximal left circumflex coronary artery was balloon-occluded for two hours followed by reperfusion, while 6 swine underwent a sham procedure. One week after induction of MI or sham procedure, all swine underwent magnetic resonance imaging (MRI) to asses global and regional LV function. Then, 3 of the 9 MI swine received autologous crude BM (a total of ~10*9) cells and 6 MI-swine received medium. Four weeks later all swine underwent a follow-up MRI.
Results: One week after MI, end-diastolic volume (EDV) and LV weight (LVW) were greater, while regional wall thickening (SWT MI zone) and ejection fraction (EF) were lower then in sham swine (table). Significant further LV dilation was observed between 1 and 5 weeks post-MI compared to sham. Crude BM had no effect on these MI-induced changes.

		sham (n=6)	MI+medium (n=6)	MI+BM (n=3)
BW (kg)	baseline	24 ± 3	27±2	26 ± 1
	follow-up	43 ± 4	43 ± 3	43 ± 3
LVW (g)	baseline	52 ± 4	65 ± 6 *	67 ± 5 *
	follow-up	81 ± 5	100 ± 7 *	100 ± 7 *
EDV (mL)	baseline	65 ± 4	88 ± 1 *	101 ± 14 *
	follow-up	81 ± 5	117 ± 13 *	136 ± 7 *
EF (%)	baseline	60 ± 3	49 ± 3 *	44 ± 2 *
	follow-up	65 ± 3	57 ± 5	56 ± 1*
SWT MI zone (%)	baseline	-	-17 ± 4	-23 ± 3
	follow-up	-	-25 ± 6	-38 ± 9

BW= body weight; baseline = 1 wk post-MI; follow-up = 5 wk post-MI. Data are ± SEM, *P<0.05 vs Sham, +P<0.05 MI+BM vs MI+medium

Conclusions: In swine crude BM does not improve global and regional indices of LV function.

P1181 Safety of bone-marrow stem cell mobilization induced by granulocyte-colony stimulating factor in patients undergoing delayed revascularization for ST-segment elevation myocardial infarction

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Adult human stem cells are considered to improve regional and global contractility after myocardial infarction. The present investigator driven phase I, open-label study investigates safety and feasibility of peripheral blood stem cell (PBSC) mobilization induced by G-CSF in patients undergoing delayed percutaneous coronary intervention (PCI) for ST elevation myocardial infarction (STEMI).
Methods and Results: G-CSF (10μg/kg/d over 5 days) was administered subcutaneously after successful PCI in patients (n=6, mean age 58.3±4.3 years) suffering from STEMI (time to PCI >6h). Objectives were occurrence of major adverse cardiac events, such as death, (re) myocardial infarction, coronary bypass grafting, or acute coronary syndrome. Laboratory analyses assessed white blood cell count, number of CD34+ cells, liver function tests, inflammatory markers, such as C-reactive protein, interleukin-6, tumor necrosis factor-(TNF)-a, TNF-receptors p55 and p75. Laboratory analyses were compared to patients suffering from STEMI without stem cell mobilization (n=4). Global and regional cardiac functions were assessed using magnetic resonance imaging. CD34+ cells increased from 2.7±0.5/μL before treatment to 61.8±21.1/μL at day 5 (p<0.001). No major adverse events occurred. No significant increase of inflammatory parameters were observed when compared to control. Ventricular volumes and global ventricular function remained unchanged from baseline to 12 week follow-up, whereas regional systolic ventricular thickening of the main infarct segment improved from 0.26±0.4 mm to 2.28±0.7 mm (p=0.08).
Conclusions: Treatment with G-CSF in STEMI patients undergoing PCI is feasible and safe resulting in significant mobilization of PBSCs. Regional left ventricular function was non-significantly improved in the long term. G-CSF may have potential of supporting myocardial regeneration of infarcted tissue after late revascularization. This pilot trial provides the basis for future randomized, controlled studies.

P1182 Efficacy of granulocyte colony stimulating factor on improvement of ischaemic heart failure in patients undergoing delayed revascularization for ST-segment elevation myocardial infarction

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This Phase I study compares the effects of peripheral blood stem cells induced by G-CSF on the improvement of ischemic heart failure in patients undergoing delayed percutaneous coronary intervention (PCI) for ST segment elevation myocardial infarction (STEMI).

Methods: Patients were treated either with G-CSF (10 μg/kg/d s.c.) over 5 days, first administered 24 hours after successful PCI (>6h after onset of STEMI), or with Placebo. Changes from baseline over 3 months of follow-up of global and regional myocardial function were assessed using magnetic resonance imaging (MRI). Mobilized stem cell populations were characterized using flow cytometry.
Results: In total, 14 patients (G-CSF n=8, Placebo n=6, mean age 58±3 years, angina to PCI interval 42±16 hours, mean peak CK 3260±450 U/L) were included into the present interim analysis. CD34+ cells increased from 2.7±0.6/μL to 61±16/μL at day 5 ($p<0.001$). Besides a significant increase in CD 34+ cells, other stem cell populations, such as endothelial progenitor cells (EPC), were shown to be increased in the peripheral blood. Assessed by MRI, left ventricular ejection fraction was reduced in similar extent at baseline (G-CSF: 40±4%, Placebo: 42±2%) and remained unchanged after 12 weeks (G-CSF: 39±5%, Placebo: 45±1%, p=0.522). Systolic wall thickening of the main infarct segment increased from baseline (G-CSF: 1.1±0.6 mm, Placebo: 0.6±0.4 mm, p=0.749) to 4 week MRI in G-CSF treated patients whereas in placebo treated patients no change in regional wall motion of the infarct segment was observed (G-CSF: 3.2±0.8 mm, Placebo: 0.1±0.9 mm, p=0.05. Recovery of regional myocardial function of infarct area at 3 month follow-up was significantly improved when compared to baseline (p=0.028). After 3 months a non-significant functional recovery was also present in control patients.
Conclusions: G-CSF treatment in STEMI patients undergoing PCI resulted in significant mobilization of stem cell populations such as EPC. Regional myocardial function improved more rapidly from baseline to 12 weeks of follow-up in comparison to Placebo treatment. Stem cell mobilization using G-CSF may have potential of supporting myocardial regeneration after late revascularization.

P1183 Effects of intracoronary bone marrow cell transfer on regional wall motion recovery in patients after myocardial infarction

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Background: We have recently shown in the prospective and controlled BOOST-trial that intracoronary transfer of autologous bone marrow cells (BMC) 4.8±1.3 days after successful percutaneous coronary intervention (PCI) significantly enhances global left ventricular ejection fraction (LV-EF) recovery in patients acute ST-elevation myocardial infarction. Here, we assessed the effects of BMC transfer on regional wall motion and regional LV-EF by magnetic resonance imaging (MRI).
Methods: MRI was performed 3.5±1.5 days after PCI and after 6 months in n=30 patients randomized to BMC-transfer and n=30 control patients. Image analysis was performed by two investigators blinded to treatment assignment. The endocardial and epicardial borders were traced in all end-diastolic and end-systolic short-axis slices. Myocardial segments showing late contrast enhancement at baseline were defined as the infarct region. An automated contour finding algorithm was used (software MASS 4.0). Regional LV function was assessed by determining systolic wall motion in the infarct region and border zone. Systolic wall motion was defined as the systolic radial displacement of the endocardial contour. In addition, regional LV-EF was determined by calculating EF only in slices showing late contrast enhancement.
Results: At baseline, there were no significant differences between the control and BMC transfer groups in regional LV-EF and systolic wall motion in the infarct region or border zone. After 6 months, BMC transfer significantly increased regional LV-EF (P=0.04) and systolic wall motion in the infarct border zone (P=0.03) as compared to the control group. The treatment effect in the BMC transfer group was 5.7% (95% CI, 0.2 to 11.3) for regional LV-EF and 1.1mm (0.1 to 2.1) for systolic wall motion in the infarct border zone. By contrast, systolic wall motion in the infarct region was not significantly enhanced by BMC transfer (p=0.32).
Conclusion: These data from the randomized-controlled BOOST-trial indicate that autologous BMC transfer enhances regional left ventricular function recovery. Positive effects on regional contractility appear to be restricted to the border zone of the myocardial infarct.

P1184 The amount of circulating endothelial progenitor cells CD133 is related to the efficacy of microvascular reperfusion after primary coronary angioplasty for acute ST elevation myocardial infarction

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Purpose: the bone-marrow derived endothelial progenitor cells are found in the peripheral blood of patients (pts) with ST-elevation acute myocardial infarction (STEMI), but their relation to clinical, angiographic and other laboratory findings is unknown.
Methods: thirty-two pts with STEMI (24 men, mean age 64, range 50-83 years) treated with primary coronary angioplasty with stent implantation (PTCA) within 6 hours of symptoms onset were studied. In all pts the efficacy of microvascular reperfusion was assessed by grading contrast medium in the myocardium at the end of PTCA (blush grade 0-1 = absent-poor reperfusion; blush 2-3 = good-optimal reperfusion). Blood samples were drawn from a peripheral vein 2 to 12 hours after PTCA (T-0) and 5 to 7 days thereafter (T-1). The membrane expression of the cells antigen CD34 and CD133 was evaluated by cytofluorimetric analysis.
Results: a significant increase between T-0 and T-1 was found for both CD34+ (T-0= 1.18+0.23; T-1= 1.98+0.23 cells/uL, $p<.001$) and CD133+ cells (T-0= 0.43+0.38; T-1= 0.76+0.44 cells/uL, $p<.001$). The number of CD34+ and CD133+ cells was unrelated to age, sex, time of ischemia, Killip class, type of infarction (anterior vs inferior), peak CK, LV wall motion score index, peak of leukocytes and peak of granulocytes. However, number of CD133+ cells was directly related to blush grade 2-3 at both T-0 (p=.05) and T-1 ($p<.05$). Moreover there was an inverse correlation between number of CD133+ cells and peak of monocytes at both T-0 (p=.04) and T-1 (p=.03).
Conclusions: these data show that endothelial progenitor cells can be found few hours after primary PTCA in the peripheral blood of pts with STEMI and that their number increases 5 to 7 days thereafter. The relation between number of CD133+ cells and a good-optimal myocardial blush suggests that the trigger for their increase is represented by reperfusion following prolonged myocardial ischemia.

P1185 Releasing of CD34+ bone marrow stem cells in acute myocardial infarction

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The bone marrow stem cells are pluripotential primary cells with ability to self-renewal, differentiation and plasticity. They can move from the marrow to the blood, among other things, in response to ischemia (for instance in acute coronary syndrome).
Purpose: We investigated the quantitative changes of CD34+ stem cells in the blood of patients with acute myocardial infarction (AMI).
Methods: Flow cytometry (FACS Calibur, Becton-Dickinson) analysis of CD34+ stem cells was performed in 20 patients with AMI. The blood was drawn four-times on days: 1-2, 3-4, 7-8 and 10-11. 17 patients were treated with primary PCI on the first day of AMI. 2 patients were treated with fibrinolytic agents. In one case the vessels were unobstructed. 18 patients were typically treated with statins.
Results: The lowest number of CD34+ cells (mean 2110/μl) was observed on 1-2 day of AMI, the highest (mean 3231/μl) on day 3-4. The statistical analysis (Anova) showed significant differences between consecutive measurements in percentage of CD34+ cells (p=0.006) and leukocytosis ($p<0.001$). The differences in absolute number of CD34+ cells were very close to statistical significance (p=0.07). Statistical analysis (U Mann-Whitney Test) showed that an absolute number of CD34+ cells was significantly higher (U=18.5; p=0.03) on day 3-4 in the group with troponine T level >2 ng/ml comparing with the group with troponine T level "T2 ng/ml and in the group with anterior MI (U=14.5; p=0.007) comparing with the group of inferior MI. We did not detect statistically significant differences in the groups of patients with diabetes, hypertension, hyperlipidemia and smokers. The highest releasing of CD34+ cells was observed ealier than in Shintani study which confirmed it on 7 day of AMI.
Conclusion: We found that releasing of CD34+ stem cells from bone marrow to the blood is highest on day 3-4 of AMI. In our opinion it is probably an important phenomenon restoring circulation in ischemic heart tissue.

P1186 Immediate effects of fluvastatin on circulating sEPCR and TFPI in acute coronary syndromes

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Statins reduce cardiovascular events when used in patients with unstable coronary artery disease. Such effects may be mediated by changes in non-lipid cardiovascular risk factors including hemostatic factors. Tissue factor pathway inhibitor (TFPI) inhibits the initial reaction of tissue factor mediated coagulation pathway. Soluble endothelial protein C (sEPCR) inhibits protein C activation and activated protein C anticoagulant activity.The aim of our study is to evaluate the immediate effects of fluvastatin treatment on plasma free TFPI and sEPCR levels in patients with unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI).
Methods: We studied 57 consecutive patients from patients admitted to our emergency department with a diagnosis of UA or NSTEMI. Subjects were randomized to placebo (n=29) or 80 mg fluvastatin (n=28). All patients were treated orally with aspirin, metoprolol, intravenous nitroglycerin infusion, and subcutaneous enoxaparin. Venous blood samples were taken as soon as possible after patients had been admitted to our emergency department and 6 hours after therapy.

Results: sEPCR levels decreased significantly in the group receiving fluvastatin but were unchanged in the placebo group. Both statin and plasebo treatment significantly increased free TFPI from baseline. However, free TFPI increased 450% in the fluvastatin group and increased 155% in the placebo patients producing a significant difference in a percent change between the groups.

Table 1. Plasma sEPCR and free TFPI levels

		Fluvastatin	Placebo	p
sEPCR (ng/ml)	Baseline	153.7±134.3	143,7±126.5	0.3
	After therapy	141.0±120.9	140.6±134.7	0.9
	p	0.001	0,6	
Free TFPI (ng/ml)	Baseline	14.56±13.3	11,73±8.3	0.7
	After therapy	50.38±24.6	23.63±9.8	0.0001
	p	0.0001	0.0001	

Conclusions: These results suggest that fluvastatin administration significantly improved critical hemostatic molecules in power of an antithrombotic effect just within six hours in patients with UA and NSTEMI. These immediate effects of fluvastatin may, in part, explain the benefical effects on mortality and morbidity observed in clinical trials of statins.

P1187 Acute changes of gene expression in the non-ischaemic region two hours after myocardial infarction

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The present study analysed, in a model of acute severe ischemia, biventricular function and acute alterations of myocardial gene expression profile in the non-ischemic myocardium.

Open-chest male Wistar rats were instrumented with left (LV) and right ventricular (RV) tip micromonometers for intracavitary pressure measurements and randomly assigned to 2 groups: (i) ischemia, subjected to LAD ligation (n=7); (ii) sham (n=7). Hemodynamic recordings were made before and 30 and 120min after LAD ligation. In the end (120 min) free-wall samples from the remote, non-ischemic LV and RV were collected for mRNA quantification by two step RT and real-time PCR of: SERCA2a, phospholamban (PLB), Na^+/Ca^{2+} exchanger (NCX), ppET-1, IGF-1, ACE, IL-6, iNOS, HIF-1a, Na^+/H^+ exchanger (NHE) and BNP. Results presented as mean±SEM, $p<0.05$.

At 30 min of ischemia, there was a significant decrease of LV peak systolic isovolumetric pressure and dP/dtmax (12.8±5.7% and 21.9±6.3%, respectively), which recovered at 120 min. No significant changes of these parameters were observed in the RV. On the other side, relaxation rate was slowed in both ventricles at 30 and 120 min of ischemia: dP/dtmin decreased 23.4±9.8% (LV) and 10.7±4.3% (RV), while the time constant tau increased 22.6±8.3% (LV) and 72.5±11.4% (RV). Compared to sham, expression of the following genes, in the non-ischemic myocardium, was significantly altered 120 min after LAD ligation: LV-SERCA2a (-52.7±7.1%), LV-PLB (+30.6±4.4%), LV-NCX (-30.8±6.3%), LV-IGF-1 (+120.1±24.5%), LV-BNP (+146.6±65.5%), LV-IL-6 (+497.2±104.6%), LV-HIF-1a (+37.5±11.8%), RV-NHE (+155.3±70.0%), RV-ppET-1 (+88.8±26.4%), RV-IL-6 (+197.5±42.4%) and RV-HIF-1a (+91.8±48.9%).

In our model, acute severe ischemia induced transient LV systolic dysfunction and sustained biventricular diastolic dysfunction. This was accompanied by a change in myocardial gene expression profile: modulation of myocardial expression of genes involved in cardiomyocyte's calcium kinetics and IGF-1 in the LV; increase in ppET-1 and NHE in the RV. These different patterns of myocardial remodelling might depend on distinct load conditions and inflammatory pathway activation, given the selective increase of BNP and the disproportional elevation of IL-6 in the LV.

P1188 Improvement of left ventricular remodeling and function in rats with heart failure after myocardial infarction by the eNOS transcription modulator S2431

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Nitric oxide (NO) production by the endothelial NO synthase (eNOS) is diminished in congestive heart failure (CHF). We investigated the effects of the eNOS gene transcription modulator S2431 (Aventis) on cardiac remodeling in CHF rats after extensive myocardial infarction (MI). Starting seven days post-MI, rats were treated for 9 weeks with placebo, or with S2431 (25ppm) incorporated into the diet. In vivo left ventricular (LV) pressure-volume relationship was analyzed using conductance catheter (Millar Instruments). Atrial natriuretic factor (ANF), brain natriuretic peptide (BNP) and GAPDH gene expression was determined by real time PCR. eNOS and AKT protein levels were determined by Western blots analysis (see table).

	Sham	Placebo CHF	S2431 CHF
MI size%		49.4±1.2	49.4±2.2
LVSP (mmHg)	146±3	112±3*	118±5*
LVEDP (mmHg)	4.7±0.9	18.5±1.9*	11.6 ±3.0*¶
dP/dtmax (mmHg/s)	12310±632	7544±499*	9002 ±710*¶
dP/dtmin (mmHg/s)	9150±474	4844±302*	6257 ±569*¶
LVESV (μl)	227±12	810±45*	534±75*#
LVEDV (μl)	518±43	1087±34*	812±57*#
LV collagen density (%)	3.0±0.3	4.8±0.3*	3.6±0.25¶
ANF/GAPDH	0.23±0.05	3.02±0.4*	2.00±0.4*¶
BNP/GAPDH	0.37±0.06	1.073±0.16*	0.69±0.09*¶
p-eNOS/eNOS	0.374±0.04	0.260±0.05*	0.379±0.03¶
p-AKT/AKT	1.51±0.3	0.98±0.18	1.58±0.20¶

*$p<0.05$ vs Sham; ¶$p<0.05$, #$p<0.01$ vs Placebo CHF

The eNOS transcription modulator S2431 improved LV function, reduced LV filling pressure, end-systolic volume (LVESV) and end-diastolic volume (LVEDV). Increased LV fibrosis and ANF and BNP gene expression, markers of hypertrophy and/or failure, were attenuated by S2431. In addition, S2431 increased phosphorylated eNOS and AKT protein levels in the surviving LV myocardium. These data demonstrate the improvement of cardiac failure by S2431 after MI. Endothelial NO synthase modulation is a promising therapeutic option in heart failure.

P1189 The pro- and antiinflammatory markers (vascular endothelial growth factor, interleukin-10) in patients with acute myocardial infarction and chronic stable angina

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Purpose: Interleukin-10 (IL-10) is a pleiotropic cytokine produced by activated monocytes, lymphocytes and mast cells with potent immunospuressive and anti-inflammatory activity. Decreased plasma levels of IL-10 were shown in patients with unstable angina. Vascular endothelial growth factor (VEGF) is a multifunctional cytokine for endothelial cells with potent angiogenic, mitogenic and vascular permeability-increasing activity. The expression of VEGF is markedly upregulated by tissue hypoxia. The aim of the study was to assess plasma levels of VEGF and IL-10 in patients with acute myocardial infarction (AMI) and stable chronic angina (SA) and correlate the values with CHD risk factors, left ventricular ejection fraction (LVEF), extent of coronary atherosclerosis on angiography and an established inflammatory risk factor hsCRP.

Patients and methods: 50 patients with AMI and 30 with SA were enrolled. Levels of IL-10 and VEGF were measured using ELISA kits.

Results: IL-10 levels in AMI pts were lower than in SA pts (9.81±5.0 vs. 22.63±8.38 pg/mL; $p<0.00001$). IL-10 levels were lower in AMI and SA pts with multiple CHD risk factors than in pts with 2 or less risk factors (SA: 19.48±2.94 vs. 23.77±2.94 pg/mL; $p<0.005$; AMI 8.64±4.43 vs. 11.85±4.09 pg/mL; $p<0.05$) and pts with AMI and multi-vessel than with single-vessel disease (8.45±3.86 vs. 10.72±3.95 pg/mL; $p<0.05$). VEGF levels in AMI pts were higher than in SA pts (312.0±67.0 vs. 221.0±50 pg/mL; $p<0.005$). VEGF levels were higher with in AMI pts with multivessel disease than in pts with single-vessel disease (348.74±45.23 vs. 252.05±21.12 pg/mL; $p<0.005$), with LVEF $<$ 40% and Killip class III-IV than in pts with LVEF $>$ 40% and Killip class I-II (338.8±51.59 versus 271.8±50.51 pg/mL; $p<0.005$ and 340.71±52.94 versus 275.45±49.48 pg/mL; $p<0.05$, respectively). HsCRP concentrations in AMI pts were higher than in SA 0.24±0.47 vs. 0.42±0.14; $p<0.0001$). HsCRP was correlated with IL-10 ($r=-0.413$; $p<0.05$) and VEGF ($r = 0.319$; $p<0.05$).

Conclusion: AMI is associated with elevated VEGF levels and decreased concentration of IL-10. These findings are particularly evident in AMI patients with multiple CHD risk factors, multi-vessel coronary artery disease, low LVEF and higher Killip class.

P1190 Increased thermal heterogeneity of the culprit lesion is prolonged in patients with recent myocardial infarction: the role of inflammation

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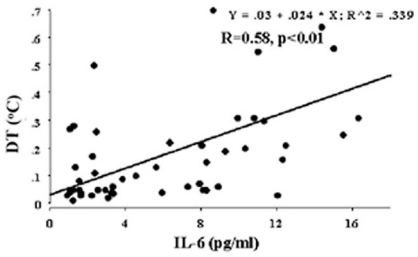
Increased thermal heterogeneity has been demonstrated in atherosclerotic plaques, with the higher temperature recorded in acute myocardial infarction (MI). The purpose of the present study was to investigate whether increased plaque temperature is maintained for a prolonged period after MI and to explore the role of inflammation.

Methods: We enrolled 55 patients (pts), 29 with recent MI (2-4 months) and 26 with chronic stable angina (CSA). Total cholesterol, C-reactive protein (CRP), interleukin-6 (IL-6) and soluble adhesion molecules were measured in the whole study population. All pts underwent coronary plaque temperature measurements. Temperature difference (DT) was designated as the temperature of the culprit atherosclerotic plaque minus the temperature of the proximal healthy vessel wall.

Results: In pts with recent MI DT was 0.19±0.18°C, while in those with CSA was 0.10±0.08°C ($p=0.03$). DT was positively correlated with CRP ($R=0.50$, $p<0.01$), IL-6 ($R=0.58$, $p<0.01$) (figure), and intercellular adhesion molecule-1 (ICAM-1) ($R=0.40$, $p=0.03$) levels.



Conclusion: Increased plaque temperature is observed for an extended period after myocardial infarction. The persistence of increased plaque temperature and increased levels of CRP, IL-6 and ICAM-1 in pts with recent MI is suggestive that there is sustained inflammatory response within the culprit atherosclerotic plaque.

P1191 Seasonal variation of C-reactive protein in apparently healthy Koreans

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Purpose: CRP, has been known emerging recognized marker of the potential risk of myocardial infarction and stroke. Several studies have reported an increased incidence of cardiovascular events during the winter months. So we investigated seasonal variation of CRP measured by means of a high-sensitivity immunoradiometric assay in apparently healthy Koreans.
Methods: The study included 14171 apparently healthy Koreans. (8398 men and 5773 women, 46.0±11.2 years of age). Anthropometric indices of adiposity, metabolic variables, BP and several cardiovascular risk factors were measured. The high sensitivity CRP was measured by Immunonephelometry.
Results: The mean(SD) CRP level in this population was 1.06(1.54)mg/L. Mean(SD) CRP level in spring, summer, fall and winter were 1.03(1.45) mg/L, 0.97(1.39) mg/L, 1.13(1.64) mg/L and 1.10(1.62) mg/L, respectively.
After adjustment for age, sex, fasting blood sugar, low density lipoprotein-cholesterol, body mass index, waist-hip ratio, high density lipoprotein-cholesterol, the odds ratios of elevated CRP of the spring, fall and winter season were 0.986(95% CI, 0.906-1.347 p=0.326), 1.292(95% CI, 1.067-1.563 p=0.009) and 1.306(95% CI, 1.081-1.578 p=0.006), respectively, as compared to the summer seasons.
Conclusions: The results indicate a highly significant seasonal variation in CRP, with higher values during the winter and fall as compared to the summer. The elevated plasma CRP level appear to be related to their increased risk in cardiovascular events, which are more prominent during the winter months.

P1192 No coronary atherosclerotic disease in high risk patients for atherosclerosis with low levels of hs-CRP: a protective role?

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Background: Despite the presence of multiple traditional risk factors some patients do not develop significant coronary atherosclerosis (CAD). We studied the prevalence of this phenomenon in order to search for possible protective factors against the deleterious effects of multiple risk factors.
Methods: Out of 1890 consecutive patients (pts) with stable angina admitted for elective coronary angiography, between January 1998 to December 1999, we identified 84 pts with 3 or more conventionally defined risk factors (hypercholesterolemia, diabetes, hypertension, obesity, smoking, family history of CAD) and a normal coronary angiography. All angiographies were then reviewed quantitatively (Medis QCA). 44 pts (group A) had completely normal arteries (23 male, range 38-76 years old; risk factors: 75% family history, 23% diabetes, 68% hypercholesterolemia, 70% smoking, 75% hypertension, 23% obesity).
As a control group we selected in our clinical database 44 pts (group B), matched for sex, age and risk factors, with multivessel (>70% stenosis) CAD, clinically stable for more than 6 months. Blood levels of hs-PCR and HDL and LDL cholesterol were measured in all pts.
Results: As aspected from the inclusion criteria, no difference was observed between group A and B in classical risk factors prevalence and blood cholesterol levels (HDL 41,7±9.8 mg/dl vs 43,5±13.2 mg/dl and LDL 136.1±35.0 mg/dl vs 141.0±43.7 mg/dl respectively). Conversely there was a statistically significant difference between the hs-PCR values between group A and B (median and 25°-75° percentile respectively 1.97 mg/l; 0.93-4.73 mg/l vs 2.97 mg/l, 1.61-5.06 mg/l; p<0.05).
Conclusions: Despite the presence of multiple coronary risk factors, pts with low hs-CRP values may have angiographically normal coronary arteries, suggesting that a chronic subclinical inflammation may be a necessary condition for the development of angiographically detectable coronary atherosclerosis.

P1193 Interleukin-6 but not C-reactive protein increase after coronary angioplasty is related to an impaired mid-term outcome

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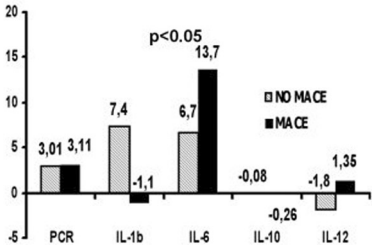
Purpose: High C-reactive protein (CRP) and interleukin-6 (IL-6) serum concentrations are related to an increased coronary event risk. GP IIb-IIIa inhibitors reduce CRP and IL-6 after coronary angioplasty (CA). We studied if CRP and IL-6 drug induced reduction could improve mid-term outcome.
Methods: Fifty patients who underwent a CA were included. We excluded patients with inflammatory, metabolic or neoplastic diseases. Inflammation markers studied were: CRP, IL-6, IL-1beta, IL-10, IL-12 and TNF-alfa. In 25 patients a GP IIb-IIIa infusion was initiated immediately after the procedure, and continued for 24 hours. The other 25 patients received standard antithrombotic therapy. End-point was the occurrence of a major adverse coronary event(MACE): death, infarction, angina or revascularization. Mean follow-up was 24 months.
Results: Only CRP and IL-6 increased after CA. Although both CRP and IL-6 increases were reduced by GP IIb-IIIa treatment, there was a trend towards an increased two-year event-free survival in treated patients(84% vs 62.5%; p=0.15). Interestingly, IL-6 mean increase, but not CRP mean increase after CA in all patients (treated and non treated), was higher in the patients who had a MACE. There were no post angioplasty CK/MB elevations. Troponin I mean levels were similar in patients with and without MACE (2.9±1.6 vs 4.9±8.05 μg/L;p=ns). Actual results are shown in the figure.



Inflammation markers increase.

Conclusions: A short 24 hour GP IIb-IIIa treatment blocks CRP and to a less extent IL-6 increase after CA, but it did not significatively modify the mid-term outcome. Patients with a MACE, independently they were treated or not, had a higher IL-6 mean post-angioplasty increase. A treatment directed to reduce IL-6 after CA could improve midterm patient outcome.

P1194 Higher white cell count but not hs CRP is associated with adverse outcome in medically managed patients following cardiac catheterisation

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Aims: Highly sensitive C Reactive Protein (hs CRP) has been suggested as a clinically useful risk marker in vascular disease. We sought to compare the prognostic value of hs CRP, white cell cout (WCC) and clinical risk markers in patients undergoing diagnostic cardiac catheterisation (CC)who were subsequently medically managed.
Methods: 2337 consecutive consenting patients undergoing CC were enrolled at the CTC Liverpool. Patient data, current drug therapy, symptom scores, and catheter reports were prospectively recorded and validated in an electronic archive. Blood was drawn at the start of the CC and WCC determined by Coulter counter, hs CRP by ELISA in serum. Study endpoints were death from all cause, or non fatal myocardial infarction (MI) prior to percutaneous coronary or surgical intervention, and within a year of enrolment.
Outcomes were determined by national death registry, telephone enquiry at one year and fom hospital records.

Independant risk predictors of death or myocardial infarction

	Hazard ratio (per unit increase)	95% CI Lower	95% CI Upper	Significance
Age (mean61.9)	1.042	1.015	1.071	p=0.002
lvef(mean58.6%)	0.968	0.952	0.983	p<0.000
Aortic stenosis (7.7%)	4.062	2.117	7.793	p<0.000
PVD (5%)	2.423	1.208	4.862	p=0.013
Unstable within 2 months (25.5%)	1.866	1.098	3.171	p=0.021
Number ofvessels >50% stenosed	1.371	1.093	1.719	p=0.006
hs CRP (mean 5.6)	1.043	0.973	1.118	p=0.223
WCC (mean 7.8x1000)	1.246	1.115	1.393	p<0.000

Results: 2071 patients did not have immediate revascularisation and had complete descriptive data. 84 (4.1%) died or experienced non fatal MI without revascularisation. hs CRP was offered to the Cox model as a continuous variable, first including, then excluding the 125 (6%) with hs CRP >16 mg/L (HR 1.004 (95% CI .997-.011) p=.289, HR 1.074 (95%CI 1.007-1.146)p=0.029 respectively). The weak hs CRP association was lost when WCC was added to the model see table.
Conclusion: WCC but not hs CRP is an independant and clinically meaningful prognostic marker in patients receiving medical therapy after cardiac catheterisation. Higher WCC and clinical risk markers should be used to identify high risk patients waiting for percutaneous coronary or surgical intervention.

P1195 Selected acute phase proteins in patients treated with coronary stenting

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Purpose: Despite many studies concerning risk factors for complications and restenosis including research projects on acute phase proteins, an exact risk stratification is still under investigation. The aim of the study was to assess the relationship between levels of biochemical inflammatory markers and rate of restenosis and MACE (deaths, myocardial infarctions and renewed revascularisations analysed together) in patients with CAD treated with coronary stenting.
Methods: The study was designed as a prospective, cohort trial with 1-year follow-up. Levels of C-reactive protein (CRP) and serum amyloid A (SAA) were measured by a nephelometric method in 154 patients with CAD (39 females, 115 males, aged 31-81 years) undergoing single vessel coronary stenting. Blood samples were collected before the procedure and after 6, 24 hours and 1, 3, 6, 12 months. Clninical follow-up visits were performed 7 days*, 1*, 3, 6*, 12 months (* with exercise test) after procedure. Any symptoms of restenosis were verified angiographically.
Results: CRP concentrations evaluated at 24 hours and 6 months after procedure have demonstrated to be predictive factors of MACE (24 hours after stenting: $p<0.03$, OR between the highest and the lowest tertile 2.1; 6 months after stenting: $p<0.03$, OR 1.89) and restenosis (24 hours after procedure: $p<0.04$, OR 2.2; 6 months after PTCA: $p<0.03$, OR 1.88) in logistic regression model. SAA values analysed before the procedure, 6, 24 hours and a month after stenting and CRP levels evaluated before stenting and after 6 hours, 1, 3, 12 months have not affected any incidence of mentioned end points. Peak concentrations of CRP and SAA were detected 24 hours after the intervention. Between CRP values measured 24 hours and 6 months after stenting a high, significant, linear correlation was present (r=0.58, $p<0.00001$). The extent of atherosclerosis evaluated as a number of arteries affected with the process has not correlated with CRP concentration.
Conclusions: Our results confirm a crucial role of inflammation in destabilization of atherosclerotic lesions and in the restenosis process and suggest a presence of an inflammatory reaction caused by coronary stenting. Patients, who underwent coronary stenting with an elevated CRP level a day after the procedure (> 6.3 mg/l), are at higher risk of major cardiac events and restenosis and require careful cardiac follow-up over several months after the procedure in comparison to the patients with a low level of this marker (CRP < 2.5 mg/l) who are in the low risk group.

P1196 Multiple complex stenoses, high neutrophil count and C-reactive protein levels in patients with chronic stable angina

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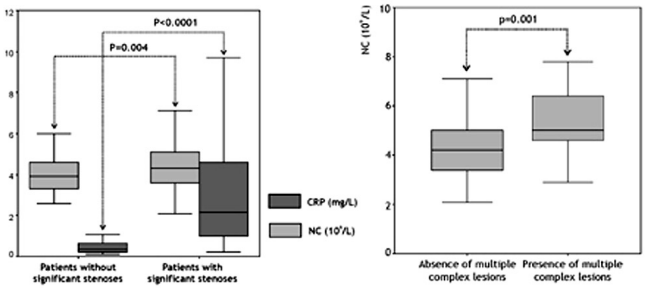
Purpose: Inflammation plays an important role in atherosclerosis and has been implicated in the genesis of acute coronary syndromes. Neutrophil count (NC) and C-reactive protein (CRP) are markers of ongoing inflammation and predictors of cardiovascular risk. We sought to assess whether inflammatory markers are associated with stenosis morphology in patients with chronic stable angina.
Methods: We studied 150 patients with chronic stable exertional angina, 121 with significant coronary artery stenosis (>50% diameter reduction) and 29 without. Blood samples were obtained at study entry for the measurement of CRP and NC. Stenoses were classified as "complex" (irregular or scalloped borders, ulceration or filling defects) or "smooth" (absence of complex features). Multiple complex plaques were defined as >3. Extent of coronary artery disease was assessed by a validated vessel score.
Results: Baseline NC and CRPlevels were higher in patients with significant stenoses compared to patients without (figure, left). No association was found between disease extent and CRP or NC. A significant correlation was observed however, between NC(r=0.28, p=0.002), but not CRP, and stenosis complexity. NC was higher in patients with multiple complex lesions than in patients without multiple complex stenoses (figure, right). Multiple regression analysis showed median NC (OR: 4.05; CI 95% 1.9 to 10.4; p=0.038) and vessel score (OR: 5.03; CI 95% 2.2 to 11.7; $p<0.001$) to be independent predictors of the presence of multiple complex lesions.



Conclusions: CRP levels and NC are higher in angina patients with significant coronary stenoses compared to those without. In patients with significant coronary stenoses, NC, but not CRP, correlates with angiographic plaque complexity.

NON-CORONARY INTERVENTIONS

P1197 Trans-catheter catheter closure of post-infarct ventricular septal defects using the amplatzer device; new strategy, new hope

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Introduction: Post-infarct ventricular septal defect (PIVSD) carries an abysmal prognosis which is not greatly improved by surgery. Many surgeons also prefer to operate a few weeks after septal rupture by which time many would have perished. New technology allows for transcatheter closure of acquired ventricular septal defects; we report our initial experience involving 10 centres led by a congenital heart interventionist as most adult cardiologists lack exposure to this technique.
Methods: Between September 2001 and November 2003, 19 patients were considered for catheter closure of a PIVSD using a proactive medical approach and implantation of an Amplatzer VSO device. Five (3 female) were not carried out because of old age (1), moribund state (1), bowel perforation (1), hospital decision (1) and inability to cross the VSD (1). Fifteen patients (8 male and 7 female) received 18 devices, 10 during the acute phase and 5 late after infarction. The age range was 57 to 78 years (Mean 65.4). The earliest implant was 3 days after the PIVSD and the longest 2.4 years. The 10 acute cases had 11 devices, all were on a balloon pump and 3 had coronary stenting. The intra-aortic balloon was weaned in all within 7 days. One patient had bypass graft (BG) and PIVSD closure prior to device closure. The 5 in the chronic group were in controlled failure and all had previous BG; 3 also had previous surgical VSD repair and 1 had an aneurysmectomy. Two had 2 devices inserted during different sessions.
Results: All patients survived the procedure but there were 4 late deaths due to septicaemia (1), leg gangrene from balloon pump (1), failure to close VSD (1) and tricuspid valve damage from the procedure (1). One developed a pericardial effusion and another a small aortic dissection. Three have small residual shunts, 2 in the acute and 1 in the chronic group. One of the transcatheter patients required subsequent surgery for tricuspid valve repair.
Conclusion: Transcatheter closure of PIVSD is feasible, the initial results are encouraging and provide hope for a condition with an otherwise dire outlook. A proactive approach with intensive care, balloon pump, early revascularisation and defect closure appear to be the key factors for success. The Amplatzer VSO device appears to result in closure in the majority but some PIVSDs may progress. Through experience in closure of congenital VSDs, paediatric cardiologists are in a strategic position to take this development forward.

P1198 Efficacy and safety of intracardiac ultrasound-guided percutaneous closure of interatrial septal defects

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Purpose: Percutaneous closure of interatrial septal defects of the ostium secundum type has become the treatment of choice in most cases. The correct positioning and deployment of the device is routinely guided by transesophageal echocardiography (TEE).
Aim: The aim of the present study was to assess the safety and efficacy of an alternative guidance technique for device deployment using intracardiac ultrasound (IU) without the need of TEE.
Methods: Percutaneous closure of interatrial septal defects of the ostium secundum type was performed in 83 consecutive adult patients (age > 18 years) diagnosed from 2000 to 2004. In all patients both right and left femoral vein puncture

was performed. A 9 Fr sheath was advanced to the right atrium (RA) through the left femoral vein, through which an Ultra ICE IVUS catheter hooked to an Ultraview console was advanced and positioned in the right atrium. A basal intracardiac ultrasound image was obtained in order to measure the size of the defect and of the septal borders, and to visualize surrounding structures to be avoided. The Amplatzer device was used in all cases. Deployment was done through the right femoral vein, and was guided solely by IU and fluoroscopy. The device was released after confirmation of correct device positioning and safety manoeouvres. A transthoracic echocardiogram was performed posteriorly to confirm correct positioning and the presence of residual shunt.

Table 1. Procedural characteristics.

Age (yr)	38±14
Female gender (%)	79,5
Most frecuently used device (mm)	27±4
Left to right shunt after 48 hours (%)	9
Procedural time (min)	68±28
Fluoro time (min)	14±12
Procedural success (%)	96,2
Complications (%)	0

Conclusions: Percutaneous closure of interatrial septal defects with the Amplatzer device under IU guidance appears to be a safe alternative to conventional TEE guidance. IU does not require patient anesthesia or orotracheal intubation, possibly reducing total cost and facilitating logistics.

P1199 Assessment of atrial septal defects for percutaneous closure: a comparative study in adult patients with cardiac magnetic resonance and trans-oesophageal echocardiography

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Many adult patients with secundum-type atrial septal defects (ASDs) are able to have these defects fixed percutaneously. Traditionally this has involved an assessment of ASD size, geometry and atrial septal margins by transoesophageal echocardiography (TOE) prior to percutaneous closure. This is a semi-invasive technique and all of the information required could potentially be obtained by noninvasive cardiac magnetic resonance imaging (MRI). We compared the assessment of ASDs in consecutive patients being considered for percutaneous ASD closure using cardiac MRI and TOE.
Consecutive patients with ASDs diagnosed on transthoracic echocardiography (TTE) were invited to undergo both TOE and cardiac MRI. The TOE imaging was performed with a Sonos 5500 (Philips) TOE system with a multiplanar 7.0mHz phased-array transducer. Cardiac MRI was performed with a 1.5 T Siemens Sonata system. Steady state free precession cine MR imaging was performed in both short and long axis views through the ASD using contiguous slices (i.e. no slice gap). Assessment of atrial septal margins, maximal and minimal defect dimensions was performed with both techniques. Analyses between TOE and MRI were made using simple linear regression analysis.
Total cardiac MRI examination time was approximately 20 minutes and comparable to the TOE examination time. A total of 9 patients (M:F = 3:6, mean age 39.6 years ± 19.5) were included in the analyses. There was an excellent agreement between cardiac MRI and TOE for estimation of maximum defect size (r=0.99, $p < 0.001$). There was good agreement between cardiac MRI and TOE for prediction of the Amplatzer septal occluder (ASO) size (cardiac MRI r=0.70, TOE r=0.68). The ASO was the only device used in this study for percutaneous ASD closure. Furthermore, in 2 patients in whom TOE was unable to be performed cardiac MRI was used to successfully direct percutaneous ASD closure.
Cardiac MRI agrees closely with TOE assessment of ASD parameters in the work-up for percutaneous closure. Potentially cardiac MRI could be used instead of TOE for this purpose.

P1200 Randomized equivalence study of percutaneous transvenous mitral commissurotomy between Inoue balloon technique and metallic dilator technique

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Background: Percutaneous transvenous mitral commissurotomy (PTMC) is a treatment of choice for symptomatic mitral stenosis (MS). The Inoue balloon technique is the most popular one due to its safety and ease to perform but the cost is high. For this reason, the reusable metallic dilator was invented to reduce the intervention cost. However, there was no randomized control study to show that the metallic dilator is as effective as the Inoue balloon technique.
Patients & Method: From 7 February 2001 to 25 August 2003 we have randomized 280 cases (male: female = 65:215, age range from 15-69 yr.) of MS patient suitable for PTMC to the comparative study between the Inoue balloon and the metallic dilator. There were 143 cases in the Inoue group(group 1) and 137 cases in the metallic group(group 2). Patients' characteristics were comparable between 2 group except for the higher incidence of AF in the first group. Good immediate results were defined as echocardiographic measurement of both mitral valve area (MVA) greater than 1.5 cm^2 and mitral regurgitation was < 3+.
Results: There were 85.3% good immediate results in the Inoue group compared to 80.3% in the metallic group. PTMC had resulted in increase MVA from 0.86 + 0.19 cm^2 to 1.70 + 0.26 cm^2 (95%CI = - 0.84, - 0.88 to - 0.79) in the Inoue group and from 0.86 + 0.21 cm^2 to 1.71 + 0.30 cm^2 (95% CI = - 0.85, - 0.90 to - 0.79) in the metallic group.
Conclusion: PTMC using the metallic dilator technique is as effective as the Inoue balloon technique.

P1201 Balloon angioplasty for coarctation of the aorta – acute, midterm and long-term results

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Purpose The aim of this study was to detect the middle- and longterm outcome after balloon angioplasty of coarctation of the aorta with or without stentimplantation. The main focus was the alteration of systolic blood pressure and the occurrence of complications such as aneurysm formation or late restenosis.
Methods: Since 1985 56 patients (16 female) underwent angioplasty for coarctation. The age ranged between 5 to 55 years (median 27±12 years). One patient was treated for stenosis of the descending aorta at the age of 15 years.
11 patients had undergone surgery before, thus were dilated for recoarctation. In 12 patients a stent was implanted primarily. One stepwise dilatation with stentimplantation was performed for a total occlusion of the isthmus. Two patients underwent repeat dilatation with stent implantation in a second session.
Long-term follow-up included repeat angiography or CT or MRI scan and 24-h-bloodpressure or questionnaire.
Results: In 54/60 procedures the residual gradient was 20 mmHg or less. The stenosis of the descending aorta could only be widened in a second session as the first dilatation was not successful. Residual gradient was 25 mmHg.
The mean systolic gradient decreased from 55±22 mmHg to 12±14 mmHg. The mean systolic blood pressure was reduced from 163±26 mmHg to 134±15 mmHg. The following acute complications occurred:
One patient experienced a transitory ischemic attack that resolved within 24 hours. One pleural effusion occurred in another patient lasting for 2 days. Dissection was found in 9 patients. 18 patients experienced severe pain during dilatation. Bleeding occurred in one case. Neither of the acute complications required further treatment.
Follow-up was performed after up to 18 years (median 2±6 years).
The mean systolic blood pressure amounted to 132±12 mmHg after 3-12 months, 128±9 mmHg after 1-5 years and 130±16 mmHg after more than 5 years.
Long-term complications included aneurysm formation in 3 patients that were dilated for coarctation of the isthmus. One patient underwent surgery. One aneurysm was excluded by implantation of an endoprosthesis. The third aneurysm is being watched closely. Another aneurysm was detected in the patient that had been treated for stenosis of the descending aorta. In this patient an endoprosthesis was implanted as well.
One patient needed surgery for restenosis 16 years after angioplasty.
One patient died 1 year after dilatation.
Conclusion: Balloon angioplasty for coarctation permanently reduces systolic blood pressure. However long-term complications occur and should be considered.

P1202 Transcatheter closure of patent foramen ovale in patients with orthodeoxia-platypnea

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Dyspnea and arterial saturation decrease on upright position in elderly subjects is described as platypnea-orthodeoxia syndrome (POS). POS is secondary to the occurrence of an atrial right to left shunt through a patent foramen ovale. This French multicentric study reports on 78 patients (medium age: 67 ± 11,3 years) with POS who had transcatheter closure of the PFO; more frequent associated diseases were pneumonectomy in 36 patients, an ascending aorta aneurysm in 11. In all patients, the diagnosis was confirmed by transthoracic or/and transoesophageal echocardiography. Five different devices were used: Amplatz (45), Cardioseal (13), Sideris (11), Das Angel Wings (8) and Starflex (1). The closure was successful in 76 patients (97.4%); Oxygen saturation increased immediately after occlusion (84,6 ± 10,7% to 95,1 ± 6,4; $p<0,001$). Dyspnea grade involved since grade 2,7±0,7 to grade 1±1 ($p<0,001$). A small residual shunt was immediately observed in 5 patients (3 with the Cardioseal device, 1 with the Sideris and 1 with the Amplatz). A second device was successfully implanted in one case (Cardioseal). Two early deaths occurred without relationship with the procedure (1 due to a sepsis probably related to the pneumonectomy, another due to the respiratory insufficiency). Other complications was a small shunt between the aorta and

the left atrium, two atrial fibrillation and a left sided thrombus which disappeared with anticoagulant therapy. At a mean follow-up of 15 ± 12 months, there were 7 late deaths related to the underlying disease. Percutaneous occlusion of the foramen ovale is safe and give excellent results thanks to a steady amelioration of devices. This technic enables some patients in precarious conditions, to avoid a surgical closure.

P1203 Percutaneousleft atrial appendage occlusion using an amplatzer device for prevention of thromboembolic complications in patients with atrial fibrillation

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Background: In patients (pts) with non-rheumatic atrial fibrillation (AF), the vast majority of thrombi originate from the left atrial appendage (LAA). Mechanical occlusion of the LAA might represent an alternative treatment to anticoagulation for prevention of embolism. The aim of our study was to determine the feasibility of percutaneous LAA occlusion with an Amplatzer device, using a transseptal approach under local anesthesia without echocardiographic guidance.
Methods: Between June 2002 and October 2003, 17 consecutive pts with paroxysmal (n=6) or permanent (n=11) AF underwent percutaneous LAA occlusion. Their mean age was 62±7 years (range 51-80), 82% were male. Coronary artery disease was present in 2 (12%), LV EF was 60±8% (range 45-70%), and LA size was 51±13mm. All were poor candidates for oral anticoagulation. Device position and sealing of the LAA were assessed using transesophageal echocardiography (TEE) at 6 months (11 pts) or transthoracic echocardiography at 1 day (3 pts).
Results: An Amplatzer device (ASD Occluder in 15, PFO and VSD Occluder in 1 each) was implanted under fluoroscopic guidance. Three pts underwent simultaneous percutaneous closure of an associated atrial septal defect or patent foramen ovale, 1 patient had simultaneous mitral balloon valvuloplasty, 2 pts ablation for AF and 1 coronary angioplasty. Periprocedural complications consisted of 2 cases (12%) of device embolization into the LA, both requiring surgical removal with surgical closure of the LAA, and of 2 (12%) vascular access site problems (AV-fistulae), requiring later elective correction. Follow-up TEE at 6 months revealed 1 case (6%) of late asymptomatic device embolization into the infrarenal aorta. The device was percutaneously retrieved into the femoral artery, from where it was surgically extracted. In 14 pts with a device in place, follow-up echocardiography revealed complete LAA occlusion in 12 (86%), and partial LAA occlusion in 2 (14%). No systemic embolic events were observed during short-term follow-up (mean 0.8±0. 4 years; median 0.8 years; total 11 patient-years), under acetylsalicylic acid and clopidogrel.
Conclusion: Percutaneous LAA occlusion using Amplatzer devices appears feasible. However, the embolization rate of 3/17 underscores the need for more specifically designed devices for this procedure. Larger patient numbers and longer follow-up will determine the efficacy of percutaneous LAA occlusion for prevention of thromboembolic events.

P1204 A decision making strategy to avoid unnecessary closure of patent foramen ovale: data from a multicentre trial on 424 cases

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Purpose: The probability of PFO being the mediator of paradoxical embolism prompted the quest for a therapeutic and preventive strategy in PFO symptomatic patients. The present study prospectively assessed mid-term results of catheter closure in PFO patients with/out atrial septal aneurysm (ASA) according to strict inclusion criteria.
Methods: Between June 1999 and December 2003, 424 consecutive patients aged 48±15 years (range 14-75) underwent attempted transcatheter closure of PFO using different occluder devices. Their diagnoses were objectively documented by CT/MRI ischemic stroke (n=156) and/or transient ischemic attack (TIA) (n=235), peripheral and coronary arterial embolism (n=19), multiple events occurred in 37 patients; 57 patients suffered from migraine with aura. ASA was observed in 124 (30%) patients. According to our decision making algorithm, indications for PFO catheter closure were: 1) paradoxical embolism with PFO and right-to-left shunt (RLS) on constrast transthoracic (TTE) or transesophageal (TEE) echocardiography and contrast Transcranial Doppler (c-TCD) in basal conditions and under Valsalva maneuver; 2) platypnea-orthodeoxia syndrome; 3) refractory hypoxemia; and 4) migraine with/out aura and RLS by c-TCD suffering from previous stroke/TIA.
329 patients underwent the percutaneous procedure under intracardiac echocardiography (ICE) guidance alone with local anesthesia; the remaining 95 procedures were performed under TEE guidance and general anaesthesia. Patients were discharged home the day after on 100 mg aspirin per day for 6 months; prophylactic antibiotic therapy was recommended for 12 months.
Results: The devices (399 Amplatzer PFO Occluder; 14 Amplatzer Multifenestrated Septal Occluder; 7 Gore Helex Septal Occluder; 4 PFO Star X) were placed correctly in all patients. Mean fluoroscopy and procedural time were 9.5 ± 5 minutes and 56 ± 21 minutes, respectively. No major recurrent thromboembolic events were observed.
Conclusion: We suggest to stratify symptomatic PFO patients in different risk classes to different therapeutic options with a rigorous decision making strategy that must include c-TCD which likely represent the most valid alternative to the so called gold-standard color Doppler TEE and may even be superior to assess the functional consequences of RLS at the brain level.
Catheter closure of PFO with or without ASA is safe and effective ensuring high closure rate and could be advocated as first line treatment in patients with large shunts who relapse despite adequate antithrombotic treatment.

P1205 Initial single-centre experience with the intrasept articulating device for percutaneous closure of the patent foramen ovale

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Background: Devices to close a patent foramen ovale (PFO) are continuously improving. The ideal device is characterized by a minimum of foreign material, a low profile as well as where both sides of the device adjust naturally to the interatrial septum. We wanted to evaluate the feasibility, safety, and efficacy of the Intrasept articulating device (CARDIA, Burnsville, MN), having a low profile and two umbrellas articulating to each other for self-adjusting to the septum.
Patients and methods: All patients referred for PFO closure from May 2003 (dependent on availability of the device) until January 2004 were eligible for inclusion in the study. Their medical files were reviewed with focus on indication for PFO closure, (peri)procedural characteristics, and short-term outcome. Continuous and nominal variables are reported by mean±standard deviation and proportions, respectively.
Results: Twenty-five patients (11/14 male/female, mean age 55±11 years) were selected. The indication for closure was prevention of recurrent cryptogenic stroke. A significant right-to-left shunt was documented by a transesophageal echocardiogram and in four patients the PFO was characterized by an aneurysm (16%).
An Intrasept articulating device was implanted successfully in all 25 patients (100% success rate). Two device sizes were used: 25 mm (n=23) and 30 mm (n=2). The procedures were performed under general anesthesia, mean fluoroscopy time was 6±2 minutes. Immediately after positioning of the device residual shunting was absent in 20/25 patients by contrast echocardiography and/or angiography in the right atrium. Two procedures were complicated by a groin hematome. The latter was related to the procedure, not to the device. Mean follow-up time was 4.2±2.2 months. In this period no short-term complications were reported. In patients with follow-up of more than 6 months (n=5), no residual shunting was detected on contrast transoesophageal echocardiogram.
Conclusions: The Intrasept (CARDIA, Burnsville, MN) articulating device could be positioned in all patients, indicating high feasibility. Safety was determined by the absence of complications related to the device. In most patients no residual shunting could be detected immediately after closure, suggesting high efficacy.

P1206 The chronic efficacy of percutaneous mitral annular reduction

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Aim: To investigate the chronic efficacy of a percutaneous mitral annular reduction(PMAR)device in an ovine model of progressive dilated cardiomyopathy and mitral regurgitation (MR).
Background: Mitral valve is a common component of heart failure and dilated cardiomyopathy. Previously we have shown in the above model that it is possible to utilise PMAR to eliminate or minimalise MR in an acute setting.
Methods: Dilated cardiomyopathy and MR were created in 9 adult sheep by rapid ventricular pacing (190 bpm) for 5 weeks. Pacing was stopped and left ventricular (LV) and left atrial (LA) dimensions were assessed using transthoracic echocardiography (TTE). The degree of MR was assessed using colour doppler. A PMAR device (Cardiac Dimensions Inc,Kirkland WA) was inserted under fluroscopic guidance into the coronary sinus via a jugular vein access sheath. The device was tensioned so as to achieve a 20-25% reduction in the mitral annulus long axis dimension and then locked in place. Another TTE was performed. Rapid pacing was reinstated for an additional 28 days and then a final TTE was performed.
Results: MR, expressed as jet area/LA area, was 29±2.4% at implant, significantly reduced, 1.8 ±1.6%, after implant and was unchanged after 4 weeks of additional high rate pacing, 2.4±1% as was the post implant mitral annulus dimension. LA area did not change from implant, 21±1.6, to the final study,19±1 cm^2 however LV area significantly increased 33.5±2.3, 36.3±2.2cm^2 during this period.
Conclusions: In this model of progressive dilated cardiomyopathy and MR PMAR with this device largely eliminated MR at implant and was able to sustain this position (and mitral annulus dimension) despite ongoing pacing. LA area also

was unchanged, illustrating the contribution of MR to LA dilatation in this model. The rapid pacing resulted in the LV continuing to dilate.
Percutaneous mitral annular reduction with the CardiacDimensions device may offer an exciting and relatively non-invasive option for the treatment of MR in dilated cardiomyopathy and heart failure.

P1207 Sildenafil improves forearm blood flow in patients with Raynauds phenomenon

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Raynaud's phenomenon (RP) is a condition in which spasm of small peripheral blood vessels diminishes blood supply. Many vasodilators and antioxidant agents including alfa-tocopherol have been used to treat RP, but none has proved to be consistently effective. Sildenafil, a specific inhibitor of phosphodiesterase-5, enhances nitric oxide-mediated vasodilation by inhibiting cGMP breakdown. We hypothesized that this effect should also take place in peripheral vascular beds and sildenafil could provide a novel therapeutic option for improving vascular functions in patients with RP. We therefore conducted a randomized double-blind cross-over study to compare the effects of sildenafil and alpha-tocopherol in 15 RP patients (14 female and 1 male). Forearm blood flow (FBF) was assessed using a near-infrared time-resolved spectroscopy procedure during which upper arm venous flow was occluded by applying 40 mmHg for 10 seconds in each 20-second cycle. FBF, blood pressure (BP) and plasma cGMP concentrations were measured before and 1 hour after the patients received a single oral dose of either sildenafil (50 mg) or alfa-tocopherol (100 mg). Sildenafil significantly increased basal FBF by 75%, from 0.59 $\pm$ 0.10 to 1.03 $\pm$ 0.20 μM/sec (mean $\pm$ SEM, $p < 0.01$) and plasma cGMP concentrations by 32%, from 3.7 $\pm$ 0.5 to 4.9 $\pm$ 0.6 pmol/mL (mean $\pm$ SEM, $p < 0.001$). On the contrary, alpha-tocopherol had no effect on these parameters (FBF, 0.70 $\pm$ 0.07 and 0.76 $\pm$ 0.08 μM/sec; plasma cGMP concentration, 4.1 $\pm$ 0.7 and 4.1 $\pm$ 0.8 pmol/mL, before and after the treatment, respectively, mean $\pm$ SEM, $p > 0.05$). Treatment with sildenafil decreased systolic and diastolic BP from 127 $\pm$ 3 to 119 $\pm$ 3 mmHg and from 73 $\pm$ 2 to 68 $\pm$ 2 mmHg, respectively (mean $\pm$ SEM, $p < 0.01$). Treatment with alpha-tocopherol again had no effect on BP. No adverse events were observed throughout the study. We conclude that sildenafil increases forearm blood flow, most likely through the accumulation of cGMP, and can be used as a valuable vasodilator for RP patients.

P1208 When smoking is combined with caffeine they exert an unfavourable synergistic effect on arterial stiffness

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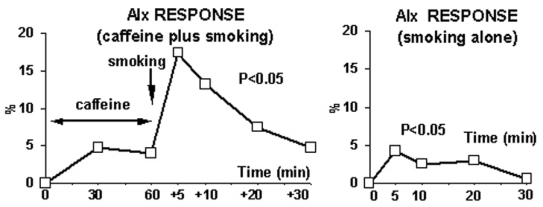
Background: Wave reflection along the arterial tree is an index of arterial stiffness and has been identified as an independent predictor of cardiovascular risk. In contemporary lifestyle, the habitual consumption of caffeine is often associated with smoking; however, their combined effect on arterial stiffness and wave reflection has not been defined.
Methods: We studied 10 healthy subjects (34$\pm$10yrs) in a randomized, placebo- and sham procedure-controlled, cross-over design (200mg of caffeine -equivalent to 1-2 cups of coffee- and 60 min later smoking one standard cigarette - 1.1 mg nicotine - or placebo and sham smoking). Furthermore, the subjects were studied on two separate occasions with smoking and sham-smoking alone. We used a validated system (Sphygmocor©) that employs applanation tonometry and appropriate acquisition and analysis software for pulse wave analysis. Augmentation index (AIx) was measured as an index of wave reflection. Higher values of AIx indicate increased arterial stiffness and wave reflection from the periphery and vice versa.
Results: Caffeine led to a substantial increase in AIx (by 4.7%) and smoking increased further AIx (by 13.4%, left figure), an increase larger than that produced by smoking alone (4.2%, right figure). Pressures increased (aortic systolic by 8.9 with caffeine and by an additional 7.5 mmHg with smoking; diastolic: by 7.3 with caffeine and by an additional 4.4 mmHg with smoking).
Conclusions: When smoking is combined with caffeine intake they interact and exert a synergistic unfavorable effect on arterial stiffness. This finding provides new insights into the combined effects of smoking and caffeine on the cardiovascular system.



AIx response.

P1209 Physical exercise reduces vascular free radical production

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Background: The molecular mechanisms of vasoprotection by physical exercise are only partially known. Reactive oxygen species (ROS) contribute to endothelial dysfunction and atherogenesis. An important source of vascular ROS is the NADPH oxidase, which is regulated by the small GTP-binding protein rac1.
Methods and Results: C57/Bl6 mice were randomized to voluntary training on running wheels (4 wk, n=8-12 per group, mean running distance 5100 $\pm$ 800 m/24h) or no running wheel condition. Exercise reduced vascular superoxide release determined by [8-amino-5-chloro-7-phenylpyridol[3,4-d]pyridazine-1,4(2H,3H)dione] (L-012) chemiluminescence to 56.7 $\pm$ 4.4% ($p<0.01$). Lipid peroxidation of the aortic wall was lowered to 67.3 $\pm$ 9% ($p<0.05$). The activity of superoxide producing NADPH oxidase was measured by a lucigenin-enhanced chemiluminescence assay and was reduced to 52.5 $\pm$ 17.9% ($p<0.05$) in the exercise groups. To further characterize the underlying mechanisms, rac1 GST-PAK pull down assay were performed. Running inhibited rac1 activity to 62 $\pm$ 14% ($p<0.05$). To address the significance of the anti-oxidative effects of voluntary running, experiments were repeated with Apo E -/- mice fed high-cholesterol diet (n=8-12 per group). Running decreased vascular superoxide production to 55 $\pm$ 14% and significantly improved endothelium-dependent vasorelaxation in isolated aortic segments, but did not alter endothelium-independent vasodilation. Exercise reduced atherosclerotic lesion formation in the ascending and descending thoracic aorta as compared with sedentary mice (oil red staining).
Conclusions: Voluntary running exercise inhibits vascular rac1 GTPase and NADPH oxidase activity and reduces vascular free radical release. Physical training is a powerful intervention to improve endothelial function and to prevent the development of atherosclerosis.

P1210 Carotid fibrous collagen rich plaques, and not atheromatous inflammatory plaques, are associated with increased risk of embolism during carotid endarterectomy

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Background: Using transcranial doppler (TCD), embolisms are frequently observed during carotid endarterectomy (CEA). The origin of these carotid emboli as well as their clinical relevance is unknown. Objective of the present study was to investigate the relation between the occurrence of carotid emboli and plaque phenotype.
Methods: For the present study, 163 patients were monitored using TCD. All embolisations were counted during release of the surgical clamp. If during one heartbeat a large number of embolisations occurred that could not be counted separately the arbitrary number of 20 emboli was given.
In each carotid plaque the following stainings were performed to characterize the plaque: picro Sirius red (collagen and fat), CD68 (macrophages), alfa actin (smooth muscle cells), haematoxilin (thrombus and calcifications) and elastin. All cross-sections were categorized as revealing no/minor or moderate/heavy staining. All plaques were also categorized into three groups (fibrous, fibro-atheromatous or atheromatous) according to overall plaque presentation.
Results: Plaques that strongly stained for collagen and smooth muscle cells were associated with the presence of significantly more emboli compared with plaques that revealed minor collagen (see table). In contrast, atheromatous lesions were associated with less embolisms(5,9$\pm$1,5)compared with fibrous (10,4$\pm$1,9) and fibroatheromatous plaques(15,4$\pm$3,5) (p=0.03). Surprisingly, the presence of thrombus in the plaque was not associated with the occurrence of embolisms during operation.

Embolisation during endarteriectomy

Staining	No - minor	Moderate - heavy	p-value
Collagen	5,4$\pm$1,5	12,6$\pm$2,0	0,05
Smooth muscle cells	7,5$\pm$1,6	12,9$\pm$2,2	0,08
Macrophage	10,1$\pm$1,7	11,8$\pm$2,6	0,50
Thrombus	12,3$\pm$3,1	10,2$\pm$1,8	0,22

Conclusion: The presence of a fibrous, collagen and smooth muscle cell rich, plaque is associated with increased incidence of embolisms as observed with TCD. Thus, embolisations are not triggered by the endarteriectomy of unstable atheromatous, inflammatory and thrombotic plaques but by endarteriectomy of stable fibrous plaques.

P1211 Determination of ultrasound criteria for the diagnosis of internal carotid artery stenosis 70–99%

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Purpose: Contrast injection cerberal angiography has been considered for the "gold standard" for the diagnosis and surgery of the carotid artery stenosis. In the last years many centers recommend carotid endarterectomy on the basis of duplex sonography results alone. Before this practice is adopted it is vital that each centre establishes the correlation between duplex ultrasound and angiography in their laboratory.
Regarding to the variability of the velocity measurements it is necessary for each sonographic laboratory to establish there own criteria for grading the internal carotid artery stenosis. These criteria enables noninvasive, safe and inexpensive selection of patients for carotid surgery (or angiography).
Methods: for this purpose 142 patients had undergone both duplex scanning and carotid angiography. Duplex ultrasound studies were performed on a Hewlett-Packard Sonos color duplex system. Carotid angiography was perfomed with use of digital subtraction imaging. Maximal peak systolic (PSV) and end diastolic velocities (EDV) in the internal (ICA) and common carotid arteries (CCA) had been measured. Receiver operator curves were generated to predict a $\geq$ 70% angiograhic stenosis. These curves describes sensitivity, specificity, positive and negative predictive value and accuracy of each criterion: PSV ICA, EDV ICA, PSV ICA/PSC CCA and EDV ICA/EDV CCA.
Results: see table.

Diagnostic criteria for $\geq$70% stenosis

Criterion	SEN %	SPEC %	PPV %	NPV %	Accuracy %
V MAX ICA $\geq$ 215cm/s	98,4	98,9	98,4	98,9	98,7
EDV ICA $\geq$ 65cm/s	88,9	98,9	98,2	98,2	94,8
V MAX ICA/V MAX CCA $\geq$ 2,7	92,1	93,3	90,6	94,4	92,8
EDV ICA/EDV CCA $\geq$ 3,7	85,7	97,8	96,4	90,7	92,8

VMAX=peak velocity, VMIN=enddiastolic velocity, ICA=internal carotid artery, CCA=common carotid artery, SEN=sensitivity, SPEC=specificity, PPV=positive predictive value, NPV=negative predictive value.

Conclusion: these diagnostic criteria enables noninvasively determine the degree of the internal carotid artery stenosis and select the appropriate therapeutic option for the patient.

P1212 Assessment of renal artery flow reserve following varying hyperaemic stimuli in humans

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Stenotic reno-vascular atherosclerosis, leading to renal dysfunction and hypertension, is increasingly treated by percutaneous transluminal angioplasty (PTA) and stenting, but with variable post-procedural outcome. This unpredictable response may be due to the presence of irreversible damage to the glomerular circulation. We propose that the reno-vascular hyperaemic response may differentiate patients who will benefit from PTA.
Aims: (1)To identify the ideal hyperaemic pharmacological agent in patients with normal renal arteries and function (Group 1). (2)To determine the effect of 'renal' and varying doses of intravenous dopamine on renal flow (Group 2).
Methods: In both groups of normotensive(140/79$\pm$4/2mmHg) patients, the effects of varying pharmacological stimuli were investigated by continuous renal artery flow velocitometry (FlowWire, Volcano) and by quantitative angiographic assessment of the dimensions of the renal artery. Group 1 (n=11): Intra-renal (IR) bolus isosorbide dinitrate (600mg), IR bolus papaverine (30mg), IR infusion fenoldopam (0.1, 0.3 and 1.0mg/kg/min), IR bolus fenoldopam (0.05, 0.1, 0.2, 0.4 and 0.8μg/kg) and IR bolus dopamine (10, 15, 20, 25 and 50mg/kg). Group 2 (n=10): Intravenous dopamine (3, 5, 10, 20, 30 and 40mg/kg/min). The flow velocity values were corrected for changes in baseline mean arterial blood pressure. Data are presented as mean$\pm$SEM.
Results: An increase in renal flow was observed for all agents tested, however, the percentage increase in flow when compared to isosorbide dinitrate (least increase; 51$\pm$7%) was more pronounced for fenoldopam IR infusion (132$\pm$17% at 1.0 mg/kg/min, p=0.0007), fenoldopam IR bolus (117$\pm$10% at 0.8 μg/kg, p=0.0002) and dopamine IR bolus (130$\pm$19% at 50 mg/kg, p=0.004). Although a gradual increase in flow was observed with increasing doses of intravenous dopamine, a percentage change of more than 50% was only observed at a dose of 20 μg/kg/min or more (3 μg/kg/min = 12$\pm$10%, 5 μg/kg/min = 30$\pm$19%, 10 μg/kg/min = 38$\pm$14%, 20 μg/kg/min = 55$\pm$17%, 30 μg/kg/min = 61$\pm$14%, 40 μg/kg/min = 67$\pm$12%). No significant change in vessel diameter was observed (Group 1: Pre = 5.34$\pm$0.35mm, Post = 5.32$\pm$0.35 mm; Group 2: Pre = 5.67$\pm$0.22 mm, Post = 5.51$\pm$0.28 mm) suggesting that increases in flow velocity correlated with absolute renal blood flow.
Conclusions: In patients with normal renal arteries, (1)Dopamine (50μg as an IR bolus) is the easiest and cheapest means to reach maximal hyperaemia. (2)Contrary to previous observations, the increase in renal blood flow with 3 or 5 μg/kg/min of dopamine is minimal when compared to higher doses.

P1213 Traditional and emergent cardiovascular risk factors among patients with acute coronary syndrome in presence or absence of peripheral arterial disease

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Background: Peripheral arterial disease (PAD) frequently coexist with coronary artery disease. A few studies suggest that some cardiovascular risk factors (CRF) have different value for the development of atherosclerosis in the two vascular regions.
Objective: To evaluate the prevalence of traditional and emergent CRF among patients with acute coronary syndrome (ACS) with or without PAD.
Methods: A prospective study of 141 consecutive patients (<70 years old) admitted to our hospital with ACS was performed. A diagnosis of PAD was based on an ankle brachial index $\leq$ 0.9. Traditional CRF, C-reactive protein (CRP), homocysteine (Hcy), serum amyloid A (SAA), lipoprotein(a), fibrinogen, apolipoprotein (apo) A1 y B100, and microalbuminuria (microAlb) levels were measured. Apo E, angiotensin converting enzyme (ACE), glycoprotein IIb-IIIA (PIA), plasminogen activator inhibitor-1 (PAI-1)genotypes were also detemined.
Results: Patients were stratified into 2 groups, according to presence (37 P, 26% of total, ACS-PAD group) or absence (104 P, ACS group) of PAD. Gender was not different but patients in ACS-PAD group (g) were older(62$\pm$6 vs 58$\pm$9 years, p=0.02). There were no differences between the two groups in prevalence of dyslipemia and history of smoking, but ACS-PAD g had a longer smoking exposure. There were significantly higher prevalence of diabetes (35% vs 19%, p=0.05) and hypertension (81% vs 53%, p=0.003)in ACS-PAD g. Significative values are shown in the table 1. Logistical regression analysis showed that poorly controlled diabetes (OR 6.3, 95% CI 1.1-36.7), time-dependent exposure to tobacco (OR 1.5 per decade, 95% CI 1.2-2.0), and higher pulse pressure (OR 1.9 per 10 mmHg, CI 1.3-2.7) were independent predictors of the presence of PAD. We did not find a higher prevalence of any genetic polymorphism in ACS-PAD g.

Table 1

	Smoking exposure (years)	Pulse blood pressure (mmHg)	CRP† (mg/L)	Hcy† (μmol/L)	SAA† (μg/mL)	MicroAlb† (mg/L)
ACS-PAD g	35	57	3.1	11.45	5.2	4.89
ACS g	24**	45**	2.18*	9.4**	3.7*	3.1*

Median (†) is expressed for non-normal distribution. *p<0.05 **p<0.01

Conclusions: 1) Unknown PAD is relatively common in patients with ACS. 2) Several traditional and emergent CRF are more prevalent in patients with ACS and PAD and some of them are independent predictors of PAD. 3) Elevation of inflammatory markers in some patients with ACS may be due to affected peripheral vascular region.

P1214 PIA1/A2 gene polimorphism of platelet gyicoprotein IIIA and peripheral arterial disease. The PACE study

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Background: Mutations in the genes that encode glycoprotein IIIA (GPIIIA) result in disorders of platelet binding. Because platelets play a pivotal role in atherosclerosis and arterial thrombosis, we tested the possible link between GPIIIA polymorphism PIA1/A2 and peripheral arterial disease (PAD).
Methods: Fortyeight patients with symptomatic PAD (mean age 67$\pm$8 years,41 males) and 50 age- and sex matched controls, with no cardiovascular history, participating in the PACE study gave their informed consent to genotyping. A replication study was conducted in 100 patients with coronary artery disease (CAD) (mean age 60.21$\pm$10.49, 75 males) and 100 blood donors. PIA1/A2 genotype was determined by polimerase chain reaction on restriction lenght fragment polymorphism on genomic DNA derived from peripheral blood sample. At follow up, cardiovascular events including death, acute myocardial infarction, or stroke were evaluated.
Results: The PIA2 allele was more frequent in PAD patients than in matched controls (35.4% vs 16%, p=0.037). Furthemore, the incidence of PIA2 allele in PAD was also higher than CAD patients (18%) and blood donors (12%) (p for trend =0.03). After a mean follow up of 15$\pm$8 months, the relative risk of any cardiovascular event was 0.82 (95% CI 0.67-1.01) among PAD patients. Among CAD patients, it was 1.06 (95%CI 0.542-1.866) after a mean follow up of 16$\pm$4 months. In both groups, we found no evidence of association between the PIA2 allele and myocardial infarction or stroke.
Conclusion: Our data indicates that PIA2 allele has an high prevalence in pa-

tients with symptomatic atherosclerosis, particularly in those with PAD, but it is not associated with any increase in subsequent risk of myocardial infarction or stroke.

P1215 Prognostic implications of carotid plaque characteristics in acute coronary syndrome

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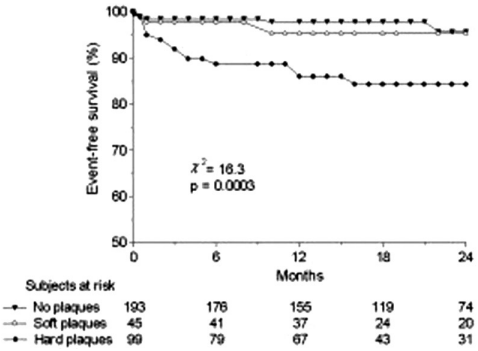
Purpose: To evaluate the relationship between ultrasonographic features of carotid plaques and outcomes of pts presenting with acute coronary syndromes (ACS).
Methods: 337 consecutive pts with ACS (mean age 64±10, 77% - males) were evaluated by coronary angiography and Doppler ultrasound of the carotid arteries within 15 days from the acute coronary event. A carotid plaque was defined as as a focal intima-media thickening of >50% relative to adjacent sites on visual assessment. Soft plaques were defined as low echoic structures without any region indicating calcification, whereas hard plaques contained a high echoic area of calcification. The pts were followed up prospectively for a mean period of 19 months.
Results: Carotid plaques were revealed in 144 (43%) pts. Of them, 45 (31%) pts had soft plaques, and 99 (69%) pts had hard plaques. The groups did not differ with regard to the prevalence of 1-,2-,or 3-vessel coronary artery disease. The prevalence of clinically relevant carotid disease was 13% (19 pts) for stenosis >50% and 6% (9 pts) for stenosis >70%.
13 cardiac deaths, 17 non-fatal myocardial infarctions (MI) and 29 cases of unstable angina requiring hospitalization were registered during follow-up. The presence of carotid plaques was independently associated with hard events (cardiac death and MI): RR 4.0 (95% CI, 1.4-11.1). Pts with hard plaques had a higher incidence of hard events during follow-up compared with pts with soft plaques or without carotid plaques (figure).



Cardiac death/MI at follow up.

Conclusions: Hard carotid plaques, even if non-stenotic and asymptomatic, predict cardiovascular mortality and future MI's in pts with ACS. For the purpose of risk stratification, an ultrasound examination of carotid arteries should be considered in all pts with ACS.

P1216 Impairment of cerebral autoregulation in patients with severe carotid artery stenosis

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Aim: To compare hemodynamic changes in cerebral flow in asymptomatic and symptomatic patients with internal carotid artery (ICA) stenosis.
Material and methods. Seventy-nine patients with ICA-stenosis >70% were divided in two groups: Group I consisted of 28 asymptomatic patients, mean age 65.9±7.6 years (20M,8F). Group II included 51 symptomatic patients, mean age 63.1±7.5 years (43M,8F), subdivided in Group IIA - 30 patients with unilateral ICA-stenosis, and Group IIB - 21 patients with bilateral ICA-stenosis. Control Group consisted of 35 aged-mached subjects without significant lesions within extra- and intracranial arteries. On transcranial color-coded Doppler ultrasound, flow velocities in both middle (MCA), anterior (ACA), posterior (PCA) cerebral arteries and presence of anterior (ACoA) and posterior (PCoA) communicating arteries were assessed.
Results: Absent or hypofunctional ACoA was more frequent in Group II than in Group I (39.2% vs 7.1% of patients; p=0.002). Patients in Group I had higher flow velocities in contralateral to ICA stenosis: MCA by 13% and ACA by 34% (p=0.032 and p=0.001), as compared to Control Group, while no differences were observed in ipsilateral to ICA stenosis: MCA and ACA (p=0.192 and p=0.151). Patients in Group II had increased flow velocities in contralateral ACA by 17% (p=0.044), but not in MCA (0.756), and decreased flow velocities within ipsilateral MCA by 47% and ACA by 13% (p<0.001and p=0.045), as compared to Control Group. In Group II, patients with bilateral ICA stenosis had decreased flow velocities in both MCAs (0.022 and p=0.006), as compared to patients with unilateral ICA stenosis. Functional PCoA was more often found in patients with ICA stenosis >90% (p=0.005), or bilateral ICA stenosis (p<0.001).
Conclusions: 1) Patients with functional ACoA remain more often asymptomatic due to preserved flow velocities in ipsilateral MCA and ACA, whereas decreased velocities in ipsilateral MCA and ACA are observed in symptomatic patients often due to hypofunctional ACoA. 2) Patients with bilateral ICA-stenosis have impaired flow in both MCAs as compared to patients with unilateral ICA-stenosis. 3) Frequency of functional PCoA in asymptomatic and symptomatic patients is the same, but presence of functional PCoA depends on grade of the ICA stenosis and more often occurs in bilateral ICA-stenosis.

P1217 Embolic protection devices for carotid artery stenting: is there a difference between filter and distal occlusive devices?

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Background: Embolic protection devices (PD) may lower the incidence of cerebral ischemic events during carotid artery stenting (CAS). However it is unknown if there is a difference between filter (F-PD) and distal occlusive (O-PD) PD to achieve this goal.
Methods: We analysed the data of the prospective CAS registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK).
Results: Between 11/2001 and 7/2003 709 patients (pt) were treated with a PD assisted CAS: 533 pts (75%) were treated with a F-PD and 176 pts (25%) with an O-PD. Besides the overall increase in the use of PDs during CAS (2003: 77%), there was a steady increase in the use of F-PD (2003: 92%) compared to O-PDs. Pts-characteristics and clinical events during hospitalisation are shown in the table.

Table

	O-PD n=176 (100%)	F-PD n=553 (100%)	p-value
Age (years)	68	69	0.734
Male gender	69.3%	72.0%	0.498
Symptomatic carotid stenosis	64.5%	53.4%	0.011
Presence of a thrombus	11.4%	18.1%	0.059
Pre-dilatation without PD	53.0%	26.5%	<0.001
Stent implantation	100%	98.9%	0.165
Clinical events			
Death	0.0%	0.4%	0.424
TIA ipsilateral	4.0%	2.0%	0.141
Stroke ipsilateral	2.3%	1.5%	0.457
All death or stroke	2.3%	1.8%	0.700

Logistic regression analysis showed that the type of the PD used during CAS was no independent predictor of the combined endpoint of death or stroke (p=0.958).
Conclusions: In clinical practice of CAS in Germany F-PD is currently the preferred method of cerebral protection. There was no difference in the occurrence of cerebral ischemic events between F-PD and O-PD during the hospital stay after CAS.

P1218 Endovascular stenting for the treatment of chronic mesenteric ischaemia

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Background: Surgical revascularization, the traditional treatment for chronic mesenteric ischemia (CMI) carries significant morbity and mortality. Recent small series with limited follow-up have suggested that percutaneous revascularization for CMI may be a feasible alternative to surgery.
Methods and Results: Fifty-seven consecutive patients (63 ± 12 years, 61% females) with chronic mesenteric ischemia, received endovascular stents in 74 mesenteric arteries (celiac: n=44, 59%; superior mesenteric: n=20, 27%; inferior mesenteric, and bypass grafts:n=10, 14%) The indications for the procedure were: chronic abdominal pain (14 ± 16 months) in 91% (n=52); post-prandial abdominal pain in 88% (n=50); weight loss in 56% (n=32; 23 ± 12 pounds); nausea/vomiting/fullness in 21% (n=12), diarrhea/constipation in 21% (n=12); hematochezia in 12% (n=7); and asymptomatic (as prophylaxis prior to aneurysm repair and CABG) in 5% (n=3). Angiographic success (residual diameter stenosis < 30%) was obtained in 98.6% (73 vessels), procedural success (angiographic success and absence of major complications) was attained in 95% (70 vessels) and symptoms relief in 91% (52 patients). There was one in-hospital death, two vascular access thrombosis, and one stent migration. At 26 ± 23 months of follow-up (range: 2 to 94 months), 9 patients died (16%). Of the survivors with more than

6 months of follow-up (43 patients and 52 vessels), 37 patients (80%) and 42 vessels (81%) had an imaging diagnostic study (angiographic CT or duplex ultrasound) to assess stent patency, showing stent restenosis in 15 patients (40%) and 16 vessels (38%), with 10 patients developing recurrence of symptoms. All patients were successfully re-treated with balloon angioplasty (n=7) or restenting (n=3) and 2 patients with additional brachytherapy.
Conclusion: Endovascular stenting is an attractive alternative treatment for CMI, which can be performed with a high procedural success and low complication rate. There is a moderate restenosis rate after 6-months post-procedure.

P1219 Thrombin injection for treatment of iatrogenic pseudeaneurysms:experience in 413 patiens

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Background: After percutaneous catheter introduction a pseudoaneurysm occasionally develops at the site of puncture. This can be treated surgically by means of operation or ultrasound controlled compression.
A new method is to inject Thrombin into the aneurysm. We evaluated safety and efficacy in a multicenter registry.
Patients and Methods: In 413 consecutive patients (age 69 $\pm$ 10) a pseudoaneurysm (412 femoral artery, 1 brachial artery) was diagnosed 0 to 64 days (median 2 days) after a catheter intervention. The mean diameter of the aneurysm was 2,7 $\pm$1,2 cm. Prior ultrasound controlled compression failed in 82 patients. 14/412 pseudoaneurysms were complicated.
0,04 to 4,0 ml (mean 0,6 $\pm$ 0,6) of thrombin solution according to, i.e. 20U/ml to 2000U/ml (median 485 U/ml) were slowly injected into the aneurysm under ultrasound guidance.
Results: The procedure was technically successful in all patients: In 369/413 patients the aneurysms thrombosed within seconds after injection. A second thrombin injection was necessary in 29 patients and 6 patients needed a third injection. In 4 patients the injection initially resulted in a partial occlusion of the aneurysm followed by a spontaneous complete seal. 9 patients needed surgery for removal of the resulting hematoma. Complications: temporary thrombus formation (n=2) without further consequences, transient paresthesia in the leg during injection (n=1 patient). In one patient the thrombin was injected accidentally into the femoral vein resulting in a deep vein thrombosis.
Conclusion: Iatrogenic pseudoaneurysms after the catheter interventions can by treated safely and effectively by direct thrombin injection. In this multicenter registry the complication rate was very low. This therapy has become the method of choice in our institutions.

P1220 The effect of intravascular brachytherapy of renal arteries after percutaneous transluminal renal angioplasty on left-ventricular function and mass regression assessed by echocardiography

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Purpose: The aim of our study was to evaluate the influence of intravascular brachytherapy (IVBT) procedure performed after percutaneous transluminal renal angioplasty (PTRA) on long term echocardiographic, hemodynamic function, left ventricular mass regression and type of LV hypertrophy (LVH).
Methods: 59 patients (pts.) aged 51,6$\pm$8 years with severe hypertension complicating renal artery atherosclerotic stenosis, were treated with PTRA and randomised to Group I (PTRA alone) and group II (PTRA followed by IVBT). Subsequent IVBT with PARIS® catheter and Microselectron HDR (Nucletron) system for peripheral areries was performed. PTRA was optimised by IVUS control and follow-up effect was assessed with QCA. LV mass and functional parameters before PTRA and in 311$\pm$152 days follow up were analyzed in echocardiographic examination with reference to reason type of procedure.
Results: IVUS and QCA data provided that IVBT of renal arteries is safe an effective method in prevention of restenosis in long term observation after PTRA. Control stenosis was significantly different 33,9$\pm$11,7% in group I and 25,5$\pm$12,3% in group II (p=0,0096). Follow up analysis of blood pressure shown better control of diastolic arterial pressure in IVBT group. In both analyzed groups elevated left ventricular mass index (LVMI) was observed (p=0,94). No significant differences in intraventricular septum (IVS) to posterior wall (LVPW) ratio, relative LV wall thickness, volume parameters and LV ejection fraction among both groups were found. In follow up study the values of LVMI and IVS to LVPW ratio were significantly lower (p=0,021) and (p=0,004) in PTRA+IVBT group in comparison to PTRA group. Analysis of left ventricular geometry and type of hypertrophy revealed marked reduction of concentric LVH in follow up in IVBT group (before: 19 (61,3%) in follow up: 13 (41,9%)).
Conclusion: Echocardiographic analysis comparing several LV parameters in PTRA alone and PTRA + IVBT groups revealed that PTRA and brachytherapy was associated with better control of blood pressure, significant LV mass regression and reduction of concentric hypertrophy in long term observation.

P1221 Clinical significance of stent fractures after angioplasty and stent implantation in the femoral artery

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Purpose: The objective of this study was to investigate the frequency and clinical relevance of stent fractures after angioplasty and stent implantation in the femoral artery.
Methods: A total number of 108 patients (75 male, mean age 70 years) with femoral artery obstructions treated by implantation of self-expanding nitinol stents were enrolled in a systematic follow-up protocol including colour-coded duplex sonography and x-ray examinations of the stents. Only stents implanted into the superficial femoral artery were included.
Results: In total 211 stents with a mean stent length of 15.7 cm (1 stent in 49 patients, 2 stents in 29 patients, 3 or more stents in 30 patients) were implanted. After a mean time of 10.4 months, stent fractures were detected in 51 patients (47,2%). In 33 cases the stent fracture was associated with a relevant restenosis or reocclusion (64.7%). In contrast, only 26 of 57 patients (45.6%) without stent fracture developed in-stent reobstructions. According to Kaplan Meyer estimates, the primary patency rate at 12 months was significantly lower for patients with stent fractures (49.5% vs. 71.5%, p=0.007). The frequency of stent fractures at 12 months was clearly depending on the length of the stented segment ($<$ 8 cm: 25.0%, 8-16 cm: 30.0%, $>$ 16 cm: 45.0%) and on the number of stents (1 stent: 26.6%, 2 stents 29.6%, 3 and more stents 53.6%).
Conclusions: According to these data, there is a considerable frequency of stent fractures after long segment femoral artery stenting, which is associated with a higher in-stent restenosis and reocclusion rate.

P1222 Evaluating the optimal activated clotting time during percutaneous carotid artery stenting

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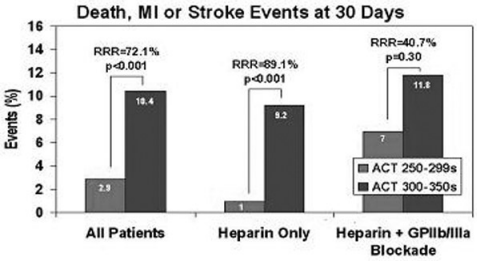
Background: Although unfractionated heparin (UFH) is routinely used during carotid artery stenting (CAS), there is no published data evaluating the optimal activated clotting time (ACT) during CAS.
Methods: Patients who underwent CAS at the Cleveland Clinic from February 1998 to October 2003 were followed in a prospective Carotid Intervention Registry. We excluded patients who did not have peak procedural ACT recorded. All patients received UFH with ACT measured with the Hemochron device (International Technidyne Inc, Edison, NJ). We compared the outcomes of those with ACT 250-299s vs. 300-350s. A separate analysis was performed based on glycoprotein (GP) IIb/IIIa inhibitor use. The incidence of death, stroke, and myocardial infarctions (MI) at 7 and 30 days were assessed.
Results: Of 641 patients who underwent percutaneous carotid interventions, 601 had peak procedural ACT recorded. In this cohort, procedural success was 98.7%, carotid stents were deployed in 97.5%, and the combined incidence of death, stroke, and/or MI was 4.0% at 7 days, and 6.1% at 30 days. Those with ACT 250-299s had significantly lower combined event-rate compared to those with ACT 300-350s at both 7 and 30 days (figure). Similar results were seen among patients who received UFH alone (n=395). In contrast, patients who received GP IIb/IIIa inhibitors (n=207) had a non-significant trend towards lower event-rate with ACT 250-299s. Patients who received GP IIb/IIIa inhibitors also had higher in-hospital bleeding (9.2% vs. 3.3%, p=0.004) and hemorrhagic strokes (2.4% vs. 0.3%, p=0.02) compared to UFH alone.



Conclusions: In our single-center experience, the optimal peak procedural ACT associated with the lowest combined death, stroke, and/or MI rate was between 250-299s with UFH during CAS.

P1223 Treatment strategies in femoral pseudoaneurysms. Single-centre experience in 206 consecutive patients

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Purpose: Femoral pseudoaneurysms are a well known complication after catheter interventions. Ultrasound-guided compresion and operation are accepted treatments. Aneurysm closure with thrombin injection has become an attractive alternative treatment option.
Methods: Between January 1996 to January 2004 in 206 consecutively patients (age 66 ±12.3 Jahre) was diagnosed a pseudoaneurysm of femoralartery in 1 to 30 days (mean: 2 d) after catheter intervention. Treatment was performed due to an individualized decision primary with ultrasound-guided compression in 65 patients (aneurysm diameter 1,5 ±1cm), primary operation in 3 patients (diameter 4 ± 2 cm) or primary using thrombin solution injection (0,03 - 2,1 ml, middle 0.6 ± 0.6 ml) in 138 patients (diameter 4 ± 3 cm). Secondary was operated in 22 patients after compressionstrial unsuccessfully and 1 after unsuccessful thrombin injection; secondary was treated in 13 patients with thrombininjection after unsuccessful compression. In no case of patient was compression necessary who were secondary treated with operation or thrombin injection.
Results: Ultrasound-guided Compression was successfull in 30/65 patients. In 6/65 patients compression was very painful. Skin nekrosis occurred in 1 pt and 2 had to be operated to remove hematoma. In the remaining 35 patients with ineffective compression, successful thrombin injection was performed in 13 pts. Operation was performed in 22 pts. In 10 of these woundhealing was delayed and 3 pts. had to undergo operation by after bleeding; 1 pt. twice.
Complete Pseudoaneurysm closure could be achieved in 125/138 pts (91%)after one thrombin injection. A second thrombin injection was needed in 7 pts and in 5 pts 3 to chieve complete closure of pseudoaneurysm. The only complication that occurred was mild fever in 1 pt. In the thrombin group finally 4 patients (3%) had to undergo operation for hematoma removal in 3 and for persisting bleeding in 1 pt. No other complications occurred.
Hospital stay for the compression group was 2 ± 1 day, for operation group 7 ± 2 days and for the thrombin injection group 1 ± 1 days.
Conclusion: Direct thrombin injection appears to be the treatment of choice for femoral pseudoaneurysms. It provides high success rates with short hospital stays and avoids operative treatment in the majority of patients.

P1224 Changes in tubular function after renal artery stenting

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Objective: To evaluate the urine microglobulin changes after interventional therapy in patients with renal artery stenosis (RAS).
Methods: According to the results of renal artery angiography, 69 consecutive patients with RAS were divided into 2 groups: 44 patients with severe RAS (luminal narrowing >70%) (Group I) and 25 with mild-to-moderate RAS (luminal narrowing >50% but <70%) (Group II). The urine a1 and b2-microglobulin(a1, b2-MG) levels were measured respectively. Procedural success rate, complication, serum creatitine and the urine a1, b2-MG concentrations 3 months after the procedure were also recorded. The long-term follow-up outcomes were compared between the 2 groups.
Results: Before renal intervention, urine a1 ([5.2±2.5] ng/ml vs [3.0±2.7] ng/ml, P <0.001)and b2-MG ([377±173] ng/ml vs [202±184] ng/ml,P<0.001) levels were significantly higher in Group I than in Group II. However, the urine a1-MG of the 2 groups did not exceed the normal range(<6 ng/ml). Three months after stenting procedure, the urine b2-MG ([237±187] ng/ml vs [377±173] ng/ml, P<0.01) level in Group I was significantly decreased, but urine a1-MG in Group I and microglobulin in Group II were unchanged. There were significant difference in improvement of blood pressure between the 2 groups (62.5% vs 9.1%, P <0.01). Compared with Group II, Group I patients had more re-admission(22.5% vs 9.1%)and renal failure(5% vs 0)and higher mortality(5% vs 0). Multivariate analysis revealed that persistent elevation of urine b2-MG was an independent predictor for re-hospitalization and occurrence of renal failure after renal artery stenting (OR=3.01, 95%CI 1.01-8.95, P =0.036).
Conclusions: Severe RAS may cause damage of tubular reabsorption. Renal artery stenting improves tubular function, but in patents with persistent elevation of urine b2-MG, the rates of re-admission and renal failure remain high.

P1225 The diverter – a novel endovascular device for stroke prevention by emboli rerouting to the external carotid artery: evaluation in a swine model

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Purpose: A novel endovascular "stent-like" device (the Diverter) has been designed to prevent embolic stroke by rerouting emboli away from the internal carotid artery (the "guarded" artery) into branches of the external carotid artery. The aim of this study was to test the feasibility and safety of this novel approach in a swine model.
Methods and Results: Diverters (n=77) were percutaneously implanted and evaluated up to 6 months in swine ilio-femoral bifurcations. Doppler ultrasound demonstrated no alteration in blood flow volume ratios between the parent and "guarded" arteries with flow ratios of 0.56±0.03, 0.56±0.03, and 0.55±0.04 at pre-implantation, after 1-5 weeks and after 7-14 weeks, respectively. Quantitative morphometry analysis of the tissue coverage over the "mesh-guarded" ostium demonstrated that neo-intimal growth ceases within about 8-12 weeks [percentage of tissue coverage after 2, 4, 8, 12 and 24 weeks- 3±3%, 3±5%, 9±7%, 12±12% and 12±14%, respectively]. The cellular proliferation rate at the Diverter "guarding-mesh" portion assessed by BrdU immunohisto-labeling, decreased from 19±7% and 13±5% after 1 and 3 weeks to 3±3% and 0.7±0.5% at 12 and 24 weeks respectively. Autologous distal embolization from the Diverter was not observed in the swine kidneys after 1-month post aortic implantation crossing both renal arteries. In vitro emboli rerouting efficacy demonstrated that rerouting started at particles >300μm and increased up to 100% for particles exceeding 500μm.
Conclusions: This study demonstrates the safety and efficacy of a novel endovascular device designed to prevent embolic stroke in an animal model. Based on these results, a clinical trial in high-risk AF patients ineligible to anticoagulation treatment has been initiated.

HYPERTENSION

P1226 Role of autonomic restoration on the reduction of left ventricular hypertrophy in patients with essential hypertension treated with the angiotensin II antagonist valsartan

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Purpose: The autonomic imbalance accelerates the progression of left ventricular hypertrophy (LVH) as a powerful predictor for cardiovascular events. The angiotensin II antagonist valsartan (ARB) is used in terms of regression for LVH, however, the role of ARB on the autonomic imbalance is unknown in patients (pts) with essential hypertension (HT).
Methods: Thirteen HT pts (9 males 63±7 y.o.;4 females 71±2) without previous medication were selected and treated with ARB (160mg/day) for 11 months. They underwent 24-hour ECG, echocardiogram (UCG) and (123) I-metaiodobenzylguanidine scintigram (MIBG) before and after medication. LV mass index (LVMI), early (E) and late (A) diastolic velocities and E/A ratio were obtained and delayed heart-to-mediastinum count ratio (H/M) and washout rate (WR) were determined. Heart rate variability (HRV) was assessed by power spectral analysis to evaluate the low frequency (LF) power, high frequency (HF) power and L/H ratios.
Results: see table.

Effect of valsartan on cardiac function

		Baseline	Valsartan	p-value
Blood pressure	Systolic (mmHg)	172 ± 22	130 ± 17	0.0001
	Diastolic (mmHg)	99 ± 9	82 ± 11	0.0001
UCG	LVMI (g/m^2)	175 ± 61	150 ± 45	0.002
	E (m/s)	0.38 ± 0.16	0.45 ± 0.11	0.048
	A (m/s)	0.63 ± 0.08	0.70 ± 0.12	NS
	E/A	0.61 ± 0.22	0.67 ± 0.20	0.044
MIBG	H/M	2.99 ± 0.47	3.14 ± 0.56	NS
	WR (%)	23.5 ± 10.4	19.7 ± 10.9	0.015
Heart rate variability	log LF (msec2)	2.23 ± 0.33	2.38 ± 0.31	0.025
	log HF (msec2)	2.06 ± 0.37	2.10 ± 0.40	NS
	log (L/H)	0.18 ± 0.28	0.27 ± 0.34	NS

UCG; ultrasound echocardiogram, LVMI; left ventricular mass index, MIBG; (123)I-metaiodobenzylguanidine, H/M; heart to mediastinum ratio, WR; washout rate, NS; not significant

Conclusion: This is the first evidence that the reduction of LVMI and the recovery of diastolic function were related to the amelioration of both HRV and sympathetic overactivity. Therefore, ARB may suppress the progression of LVH and improve the diastolic function through restoration of autonomic imbalance.

P1227 Role of sympathetic and baroreflex mechanisms in the pathophysiology of the hypertensive disease in women

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Objective: Autonomic factors have been suggested as potential gender-specific pathogenetic mechanisms involved in the development of the hypertensive state in premenopausal women. No study, however, has so far systematically investigated this hypothesis.
Design and Methods: In 14 untreated mild-to-moderate male essential hypertensives (MHT age 41.9±2.6 yrs) and in 12 age-matched female essential hy-

pertensives (FHT) we measured beat-to-beat mean arterial pressure (MAP, Finapres), heart rate (HR, EKG), and efferent postganglionic muscle sympathetic nerve traffic (MSNA, microneurography, peroneal nerve) at rest and during arterial baroreceptor manipulation induced by stepwise i.v. infusion of vasoactive drugs. Data were also collected in two groups of age-matched male and female normotensive controls (MC: n=10, FC: n=10). FHT and FC were all studied in the midlutheal phase.
Results: For similar body mass index (BMI: FHT 24.1±0.5, MHT: 23.9±0.4 kg/m^2) and MAP (113.3±2.1 vs 113.3±2.3 mmHg), FHT displayed values of HR and MSNA (i.e. the markers of adrenergic tone at cardiac and peripheral level, respectively) almost superimposable to those found in MHT (HR: 69.8±2.3 vs 71.4±1.9 b/min, MSNA: 61.3±2.9 vs 64.2 bursts/100 hb, p=NS). MSNA, but not HR, was significantly greater ($p<0.01$) in FHT and MHT as compared to MC and FC (MSNA: 38.3±2.4 and 34.7±2.0 bs/min). Baroreflex control of HR was markedly and similarly reduced in MHT and FHT (-32±8 and -34±5%, $p<0.01$) as compared to MC and FC, while baroreflex MSNA modulation was superimposable in all the 4 groups and thus unaffected by the hypertensive state in both gender.
Conclusions: These findings provide the first evidence that the sympathetic and reflex abnormalities characterizing the hypertensive state are not affected by gender. This suggests that at least in the premenopausal period neuroadrenergic mechanisms do not represent the specific pathophysiological features differentiating the development of the hypertensive state in the female gender.

P1228 Ventricular arrhythmias and left ventricular hypertrophy: non-invasive parameters in estimating arrhythmogenic potential

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Objective: The aim of the study was to examine the correlation between nonivasive parameters and venticular arrhythmias (VA) in patients (pts) with essential hypertension and different types of left ventricular hypertyrophy (LVH).
Method: We examined 110 pts (average age 56.6 ± 8.5 years; 70 male and 40 female) with essential hypertension and LVH (35 pts with concentric LVH, 38 with eccentric LVH and 37 pts with LVH and positive exercise testing). There were 31 healthy people (18 male, 13 female) in the control group. All pts were examined by means of echocardiography (two indipendent examiners - Acuson-Sequoia), exercise testing, 24-h Holter monitoring, 24-h ambulatory blood pressure monitoring, heart rate variablity, ventricular late potentils, spectral turbulence analysis and QTc interval dispersion.
Results: Left ventricular mass index was 162.9 ± 29.1 g/m^2 in the group with LVH and 112.6 ± 23.4 g/m^2 in the control group. According to Lown and Wolf's classification of VA, 22 patients (20.0%) were found to have grade I arrhythmia, 12 (10.9%) presented grade II, 15 (13.6%) grade III, 13 (11.8%) grade IVa, 21 (19.1%) grade IVb, 11 (10.0%) grade V and 16 patients (14.5%) were free from premature ventricular complexes, namely grade 0 arrhythmia. It was statistically significantly greater than in the control goup ($p < 0.001$). Patients with LVH and myocardial ischemia had grater frequency of complex VA than other subgroups ($p < 0.05$). We found out a weak but statistically significant correlation between VA and: left ventricular mass index ($r = 0.248$; $p < 0.05$), night sistolic blood pressure ($r = 0.216$; $p < 0.05$), night diastolic blood pressure ($r = 0.223$; $p < 0.05$), percentage of night falls in sistolic and diastolic blood presure ($r = 0.223$; $p < 0.05$) and diastolic left ventricular function (E/A: $r = -0.229$; $p < 0.01$) in the group with LVH. The QTc interval dispersion was greater in the group with LVH than in the control group (58.3 ± 21.0: 49.8 ± 10.3 ms; $p < 0.05$). Late potentials were more frequent in the group with LVH (23.6% - 26/110 pts) than in the control group (3.2% - 1/31 pts). There were no differences between groups in heart rate variability and spectral turbulence analysis.
Conclusion: Patients with ventricular arrhythmias and left ventricular hypertrophy have greater left ventricular mass index, high night sistolic and diastolic blood pressure, diastolic dysfunction and they belong to the nondipper group. Left ventricular hypertrophy and myocardial ischemia contribute originating more complex ventricular arrhythmias.

P1229 Skin sensivity to electrical stimuli at different blood pressure levels in man

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Objectives: Diminished pain perception in humans with high blood pressure (BP) was shown in early investigations. However this association is not so well known. The assessment of dermal both pain and tactile sensitivity to electrical stimuli was the aim of this study. We introduced the original modification of electrical skin stimulation test (ESST) to evaluate the tactile (TT) and pain threshold (PT) in subjects with different systolic (SBP) and diastolic blood pressure (DBP).
Desing and Methods: 74 consecutive patients (males, aged between 38-61 years, no pharmacological medication) with coronary artery disease (CAD) were examined. Serious concomitant diseases, diabetes not included. The constant current electrical stimulator and the concentric shock electrode placed on the volar forearm were used. TT was considered as the minimum current intensity that evoked a touch sensation under the electrode, PT - a weak painful sensation like a pinprick. BP was measured by conventional sphigmomanometer before the ESST.
Results: The individual TT and PT data, received due to the ESST were highly reproducible, variation coefficient about 5-7%. The average TT was 0.21±0.01 mA and PT 1.52±0.09 mA. SBP range was 105-172 mmHg, DBP 70-103 mmHg. According to quintiles (Q) of SBP distribution the TT level was: QI (<120 mmHg) 0.18±0.01 mA; QII (120-133 mmHg) 0.21±0.03 mA; QIII (134-141 mmHg) 0.21±0.01 mA; QIV (142-148 mmHg) 0.22±0.01 mA; QV (>148 mmHg) 0.24±0.01 mA. The highest TT was found in patients with SBP>148 mmHg (QV), the lowest TT at SBP<120 mmHg (QI, $p<0.01$). There was the direct correlation between SBP and TT ($r=0.25$, $p<0.05$) and between SBP and PT ($r=0.25$, $p<0.05$). No correlation between DBP and PT was noted. TT was significantly higher in patients with DBP equal or above 90 mmHg compared to TT at DBP below 90 mmHg (0.23±0.01; 0.19±0.01 mA correspondingly, $p<0.01$).
Conclusion: We established that in CAD patients the high BP was assoniated with disturbed skin sensitivity to both pain and tactile stimuli. These findings provide further evidence of a relation between hypertension and decreased sensitivity to noxious stimuli in human. A simple well-reproducible ESST method may be used for investigating tactile and pain perception at different clinical conditions.

P1230 Non-dippers have high blood brain natriuretic peptide levels in the elderly with hypertension

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Blood brain natriuretic peptide (BNP) levels are good predictors of left ventricular end-diastolic pressure. However, the stimuli for BNP production and secretion remains to be investigated in the elderly with left ventricular hypertrophy (LVH). We reported that LVH in the elderly was associated with a diminished nocturnal decline in blood pressure (BP) (non-dipper).
Purpose: To examine the relations among BNP levels, LVH, and nocturnal BP.
Methods: We measured the blood BNP levels, performed echocardiography and the ambulatory blood pressure monitoring (ABPM) in 137 elderly individuals aged over 60 years old (mean age, 70.1±8.3 yrs, male 37%) with hypertension. Left ventricular mass index (LVMI) was calculated with Devereux formula. Patients with severe valvular diseases, decompensated heart failure, and other systemic diseases were excluded.
Results: Systolic BP was 139.7±19.6 mmHg and diastolic BP was 82.3±10.9 mmHg. LVMI was 131.6±26.5 g in male, and 128.5±43.2 g in female, respectively. Mean BNP levels were 33.4±33.3 pg/ml. BNP correlated with the mean 24-hour ambulatory systolic BP ($r=0.27$, $p=0.002$), the nighttime systolic BP ($r=0.30$, $p=0.0007$), daytime systolic BP ($r=0.25$, $p=0.004$), and nighttime pulse pressure ($r=0.38$, $p=0.0001$). Non-Dipper showed higher BNP levels than dipper ($p=0.002$). BNP showed no correlation with BP measured by conventional BP monitoring. BNP did not correlate with the diastolic BP. LVMI showed a very weak tendency of correlation with the BNP levels ($r=0.18$, $p=0.06$). This was compatible with a recent report, in which BNP was shown not to be a good marker for screening of LVH among hypertensive patients. Although blood BNP levels increased with the age ($r=0.39$, $p=0.0001$), nighttime systolic BP were independent determinants of BNP levels by multivariate analysis. The cut-off value of BNP≥50pg/ml predicted a higher nighttime systolic BP and a larger left atrial dimension.
Conclusions: High blood BNP levels without decompensation may predict high nocturnal BP, but not LVH in the elderly with hypertension. High blood BNP levels might be indicative of neurohumoral activation, and therefore, be one of surrogate endpoints of hypertensive end-organ damage.

P1231 Lack of relation between the quality of sleep and degree of blood pressure fall at night

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Objective: Subjects undergoing ambulatory blood pressure monitoring (ABPM) commonly complain of a poor quality of sleep (QOS), which might partly explain the poor reproducibility of night-time (N)BP fall in several studies. Aim of our study was to investigate the relationship between QOS and N fall of BP and heart rate (HR).
Methods: 101 untreated (or with treatment withdrawn since at least 10 days) mild essential hypertensive patients (mean age±SD 51±10 years, 42 male, 59 female) undergoing 24 h ABPM were administered a questionnaire on QOS, including information on difficulty of falling asleep, duration of N sleep and number of times subjects got up at N. Dippers (D) and Non Dippers (ND) were those with NBP fall respectively >10% or < 10% of daytime BP. The comparison between subjects reporting different QOS and with different N P fall was made by ANOVA.
Results: 69 patients were D both for systolic (S) and diastolic (D) BP, while 32 were ND for either SBP or DBP. In all subjects HR was significantly reduced at N with no differences between D and ND (Table 1).

Table 1

	Day SBP/DBP	Night SBP/DBP	Day HR	Night HR	dSBP/DBP at N	dHR at N	% Males
D	139.0±13.6/ 85.4±9.3	115.0±14/ 67.3±9.1	79.2±8.1	66.1±9.8	-24.9±7.8/ -19.0±5.3	-13.0±6.0	28
ND	145.5±13.8 92.6±9.6°	137.8±13.1*/ 83.6±7.1*			-7.7±3.7*/ -9.0±4.5*	-11.8±4.2	35

BP (mmHg) and HR (bpm) in D and ND. *p<0.001, °p<0.05. d=delta.

Among all 101 patients, 38% complained of difficulties in falling asleep, 22% got up once and 40% more than once at night, and 27% did not wake up, with no significant difference between D and ND. The different measures of the BP effects of N sleep were not related with QOS parameters. ND, but not D, woke up mainly to void their bladder.

Conclusions: Besides perceived QOS other factors involved in neural cardiovascular control at N may be responsible for differences in NBP changes. Dipping status doesn't seem to be affected by perceived QOS nor by the frequency of getting up at N, but it is affected by the cause of waking up (mainly voiding in males). Whether men labelled as ND because they got up to void have or have not the same degree of cardiovascular risk as subjects labelled as ND for other reasons, this remains to be investigated by longitudinal studies.

P1232 Comparison of two cardiovascular risk stratifications in predicting presence of silent myocardial ischaemia in hypertensive patients

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Objectives: To compare the value of cardiovascular risks estimated by the Framingham and SCORE charts in predicting the prevalence of silent myocardial ischemia (SMI) in asymptomatic hypertensive patients.

Patients and Methods: The study group consisted of 217 patients (96 male, 121 female, mean age 57±10 years) with uncomplicated essential hypertension. Mean duration of hypertension was 7±6 years. After physical and laboratory examination, the ten years absolute risk was estimated using Framingham model and SCORE risk chart developed for high-risk countries. SMI was detected with exercise thallium-201 myocardial perfusion scintigraphy.

Results: According to Framingham risk stratification, 32 of the cases (15%) were in high, 51 (24%) in moderate and 134 (61%) in low risk groups. Cardiovascular disease risk derived from SCORE chart was equal or higher than 5% in 89 of the cases (41%). Correlation between the two scoring systems was very good (r=0.79; p<0.001).

SMI was detected in 61 patients (28%), of whom 41 (67%) had angiographically confirmed coronary artery disease, whereas the remaining 20 patients had normal coronary arteries. Both Framingham risk score and SCORE points were significantly higher in SMI (+) patients compared to SMI (-) patients (Framingham score: 15±10 vs. 7±7, p<0.001; SCORE: 11±10 vs. 4±5, p<0.001). Sensitivity, specificity, positive and negative predictivity of a high-risk Framingham score for predicting SMI was 36%, 94%, 69% and 79% respectively. A cardiovascular disease risk equal or greater than 5% in SCORE model had 66% sensitivity, 69% specificity, 45% positive and 84% negative predictivity for SMI.

Conclusion: Compared to Framingham equation, a risk stratification based on SCORE chart is a more sensitive method to select hypertensive individuals who need further investigation for SMI. It also has a higher negative predictivity to exclude SMI (-) patients.

P1233 Reflected pressure waves affect left ventricular mass and geometry in hypertension

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Purpose: Stiffening of large arteries has been shown to be associated with left ventricular (LV) concentric remodeling in hypertension. Since the increase in arterial stiffness is known to enhance the phenomenon of pressure wave reflection, in this study we investigated the relationships of both amplitude and timing of reflected pressure waves (RPWs) with LV geometry in hypertension.

Methods: We studied 99 untreated uncomplicated hypertensive patients and 71 healthy subjects. We measured LV mass index and relative wall thickness by echocardiography. Augmentation index (AI) and pressure (AP), transit time of RPWs expressed as percent of ventricular ejection (TT/ET) were measured on carotid pressure waveforms obtained by applanation tonometry. Aortic stiffness was assessed by aortic pulse wave velocity (PWV).

Results: In the overall population LV mass was significantly related with age (r =.36), systolic blood pressure (r =.49), PWV(r =.39), AP (r =.40) and AI, (r =.34), (all p<.0001), while relative wall thickness was significantly related with age (r=.34) systolic blood pressure r =.35), PWV (r =.43), TT/ET (r = -.36) (all p<.0001). In multivariate analyse, gender, systolic BP and AP were independent predictors of LV mass index (multiple R= .56, p<.0001), while both PWV and TT/ET were independent predictors of LV relative wall thickness (multiple R= .46, p<.0001).

Conclusions: Our data suggest that aortic stiffening and enhancement of pressure wave reflection are independent determinants of LV mass and geometry. Stronger reflected pressure waves are a stimulus for LV hypertrophy, while higher PWV and earlier reflected pressure waves induce concentric remodeling.

P1234 Low-dose Perindopril, indapamide and eccentric, concentric left ventricular hypertrophy in the PICXEL study

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Objective: To compare the effect of a low-dose combination strategy based on Perindopril/Indapamide (Per/Ind from 2/0.625 to 8/2.5mg) to enalapril (Ena from 10 to 40mg) on Left Ventricular Hypertrophy (LVH), according to eccentric or concentric LV geometry.

Methods: 556 hypertensive patients with LVH (LVMI: females >100, males >120 g/m^2), were randomly treated for 1 year in the PICXEL study (Preterax In a double blind Controlled study Vs Enalapril in LVH). LVH was assessed by a Central Echocardiography Committee in a reading blinded to visit sequence, patient and treatment. Eccentric LVH is defined by a relative wall thickness < 0.43.

Results: After one year, in the 556 patients, LVMI, LVIDd and PWTd are significantly reduced with Per/Ind compared to Ena (Per/Ind -13.6 g/m^2, -1.26 mm, -0.45 mm; Ena -3.9 g/m^2, +0.02 mm, -0.15 mm, P<0.01). Blood pressure decreases significantly more with Per/Ind than Ena (SBP/DBP changes -22.0/-10.3 vs -17.5/-8.3 mmHg, P<0.01). Per/Ind superiority in reducing LVMI remains after adjustment on BP change.

For both LVH geometries, LVMI decreases significantly more with Per/Ind than Ena. In concentric LVH (30% of the population), LVMI regression is greater than in eccentric LVH, due to significant reduction of wall thicknesses.

Tolerability is good with Per/Ind vs Ena: cough 4.1% vs 4.4%, hypokaliemia (<3.4 mmol/l) 3.5% vs 1.2% and hyperkaliemia (> 5.8 mmol/l) 0.3% vs 1.8%.

Echo and BP results

ITT End-Base	Eccentric LVH			Concentric LVH		
mean±SD	Per/Ind (n=200)	Ena (n=188)	P value	Per/Ind (n=84)	Ena (n=84)	P value
LVMI, g/m^2	-12.2±23.0**	-1.2±23.4	P<0.0001	-17.1±25.7**	-9.9±23.9*	P<0.05
LVIDd, mm	-2.10±3.93**	-0.52±4.00	P<0.001	0.74±3.63	1.23±3.92	P=0.23
IVSTd, mm	-0.18±1.85	-0.10±1.85	P=0.55	-0.98±1.89**	-0.72±1.82*	P=0.20
PWTd, mm	-0.08±1.31	0.22±1.32	P<0.05	-1.33±1.65**	-0.97±1.59**	P=0.10
SBP, mmHg	-20.4±15.0**	-17.2±15.9**	P<0.01	-25.8±15.3**	-18.1±14.5**	P=0.001
DBP, mmHg	-10.0±8.6**	-8.2±9.5**	P=0.03	-11.2±8.8**	-8.7±10.1**	P<0.025

Between group difference: echo. alpha 5%, BP alpha 2.5%. Within group difference (alpha 2.5%): **P<0.0001, *P<0.001

Conclusion: PICXEL demonstrates that a low-dose Perindopril 2mg/Indapamide 0.625mg combination reduces both concentric and eccentric LVH significantly more than Ena, and more than expected from blood pressure reduction alone. In high risk concentric LVH, LVH reduction is more pronounced.

P1235 PPR1, a novel cardiac and secreted protein found in HDL 3: a link between metabolic X syndrome and heart disease

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Introduction: We have shown that obesity, hyperinsulinism and arterial hypertension induced in dogs by 9 weeks of hyperlipidic and hypercaloric diet (HFD) have a strong impact on heart rate variability that could be explained at least in part by impaired on M2 muscarinic receptor level. Since other early molecular events were predictable we further analysed the cardiac transcriptome by DNA microarrays hybridization and found 40 differentially regulated genes comprising a group of gene coding for putative new proteins. Elucidation of new protein function could lead to a better understanding of heart physiopathology.

Results: Computer analysis of new cDNA coding sequences proposed that one could encode for a secreted protein (PPR1) that contains a putative Apolipoprotein domain. Analysis of PPR1 gene expression in human tissues showed high expression in heart, adipocytes and adrenal cortex. Rabbits were immunized against peptides representative of specific immunogenic domains for this protein. These rabbits antisera were used to reveal PPR1 protein in human heart, adipose tissue and blood. Moreover, secretion of PPR1 was shown in a cell culture model of adipocytes. Human sera ultracentrifugation allowed us to separate VLDL, LDL, HDL2 and HDL3 lipoproteins fractions. Western blotting analysis

showed that PPR1 was part of the HDL3 fraction that is known to be protective against atherosclerotic cardiovascular disease.
Conclusion: PPR1 could be involved in a protective mechanism against lipids accumulation in heart that occurs in obesity. Current production of tagged recombinant PPR1 protein will allow to study the putative role of PPR1 in HDL3. Moreover, as a step towards elucidation of PPR1 function, specific impact of obesity or arterial hypertension on PPR1 synthesis regulation are under study.

P1236 Chronic abrogation of sympathetic nerve overactivity exerts beneficial effects during pressure-overload hypertrophy, expecially when transition to heart failure is taking place

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In the course of experimental pressure-overload hypertrophy (POH), chronic abrogation of sympathetic nerve overactivity by chemical sympathectomy (Sx) has markedly beneficial functional and survival effects. However, it is not clear whether these effects are more pronounced during the earlier stages of the myocardial response to pressure-overload as opposed to the later stages of the disease, i.e. when the transition to decompensated heart failure (associated with a marked increase in sympathetic activity) is taking place.
To evaluate the time course of the beneficial effects of chronic abrogation of sympathetic nerve overactivity during POH, Sprague-Dawley rats were subjected to abdominal aortic banding (B) or sham operation (S), to subsequently undergo either Sx (6-hydroxydopamine, 150 mg/kg i.p. twice a week) or vehicle (Vh) treatment. Echocardiography was performed after 4 (4wk) and 10 weeks (10wk), to obtain M-mode derived left ventricular (LV) end-diastolic (EDD, mm) and end-systolic (ESD, mm) diameters, as well as endocardial (FSendo, %) and midwall (FSmw, %) fractional shortening. Carotid systolic blood pressure (SBP, mmHg) was measured at sacrifice, and LV and lung weights were indexed to body weight (g/100 g).

Results

	n	EDD	ESD	FSendo	FSmw	LVi	LUNGi
SVh-4wk	10	5.6±0.1	1.9±0.1	66±6	17±3	2.2±0.1	3.6±0.1
SVh-10wk	9	7.1±0.3#*	1.9±0.1	65±10	17±2	1.9±0.1	2.9±0.5
BVh-4wk	8	5.6±0.1	2.3±0.1*	60±8	14±2*	3.2±0.1*	4.0±0.3
BVh-10wk	10	9.5±0.3#*	2.6±0.1#*	56±10*	14±2*	3.0±0.5*	4.3±1.2*
SSx-4wk	10	5.9±0.1	2.6±0.1&	57±11&	17±2	2.2±0.1	4.0±0.1
SSx-10wk	10	7.1±0.3#*	2.9±0.1&	56±10&	20±2	2.0±0.2	3.6±0.4
BSx-4wk	8	5.4±0.3	2.1±0.1	62±11	15±2	3.0±0.1*	4.6±0.2
BSx-10wk	15	9.5±0.3#*	3.2±0.1&	58±8	17±2&	2.5±0.3&	3.7±0.6&

*p<0.05 B vs. corresp. S; #p<0.05 10wk vs. corresp. 4wk; &p<0.05 Sx vs. corresp. Vh

During the first 4 weeks, sympathectomy did not interfere with the extent of LV hypertrophy, end-diastolic dilation or lung congestion induced by POH, although myocardial systolic function (at the midwall) was preserved. During the further progression of experimental POH, sympathectomy reduced the degree of LV hypertrophy, systolic dilation and dysfunction, and prevented pulmonary congestion.

P1237 Hypertension and the risk of adverse cardiovascular outcomes following MI: The VALIANT experience

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Purpose: Hypertension (HTN) is a known risk factor for development of ischemic heart disease and myocardial infarction (MI). We assessed the relationship between prior HTN and adverse events post-MI in patients enrolled in the VALIANT trial.
Methods: VALIANT enrolled 14,703 patients with heart failure, left ventricular systolic dysfunction, or both following MI. Patients were randomized to receive valsartan, captopril, or both. History of HTN was assessed at the time of enrollment. The risk of HTN was assessed in a multivariable model accounting for known covariates.
Results: A total of 8575 patients enrolled in VALIANT had a history of HTN prerandomization. Mean pre-randomization BP in hypertensive patients was 127/74 compared with 117/70 in patients without a history of HTN. Hypertensive patients tended to be older (66.2 ± 11.2 vs 62.9 ± 12.4, p<0.0001), were more likely to be women (71% vs 53%, p<0.0001), and were more likely to be on an antihypertensive medication (p<0.0001). History of HTN was associated with an increased risk of total mortality (HR 1.47 [1.36,1.59]), cardiovascular mortality (HR 1.52 [1.40,1.66]), death or heart failure (HR 1.64 [1.54,1.76]), stroke (HR 1.70 [1.39,2.07]), or any cardiovascular event (cardiovascular death, MI, heart failure, cardiac arrest, stroke) (HR 1.53 [1.44,1.63]). After adjusting for baseline covariates, HTN remained an independent predictor of experiencing a cardiovascular event (HR 1.14 [1.07,1.22]).
Conclusions: Patients with pre-existing HTN are at increased risk for cardiovascular events post-MI, including heart failure, recurrent MI, stroke, cardiovascular death, and overall mortality. Even after adjusting for known covariates, HTN remains an independent predictor of experiencing a cardiovascular event post-MI.

P1238 Prevalence of primary aldosteronism among unselected 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: One thousand and sixty unselected hypertensive patients (563 female and 501 male, 472 untreated and 592 treated, age 23-70 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: One hundred and twenty-two of the 1064 hypertensive patients had an aldosterone/renin ratio greater than 25; in 1154 of them confirmatory studies were carried out. Using an aldosterone concentration above 7.5 ng/dl after saline infusion as the diagnostic cut-off, 59 patients had biochemically confirmed primary aldosteronism. Among these individuals, only eight were hypokaliemic; an adrenal mass was detected in 19 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 5.7% of the adult hypertensive patients.

P1239 Prediction of stroke by self-measured blood pressure at home in relation to the number of measurement: the Ohasama study

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Purpose: To determine the optimum number of blood pressure self-measurements taken at home (home blood pressure) in relation to their predictive value for stroke risk, and to compare the predictive value of conventional (screening) blood pressure (two measurements) and home blood pressure values for the same or less number of measurements (one or two measurements).
Methods: We obtained more than 14 measurements of home blood pressure from 1491 people aged 40 years or over without a history of stroke (mean age = 61 years, men 37%) in the general population in Japan, and followed them up after a mean period of 10.6 years. The prognostic significance of blood pressure for stroke risk was examined using the Cox proportional hazards regression model, which was adjusted for possible confounding factors.
Results: Of the 1491 subjects, 136 had a first onset of stroke or transient ischaemic attack (TIA). This was due to cerebral infarction in 95 (69.9%); intracerebral hemorrhage in 25 (18.4%); subarachnoid hemorrhage in 10 (7.4%); TIA in three (2.2%); and unknown causes in three (2.2%). The predictive value of home blood pressure increased progressively with the number of measurements, showing the highest predictive value with the average of whole measurements (mean = 25 measurements, 35% increase in the risk of stroke per 10 mmHg elevation in blood pressure). The initial-first home blood pressure values (1 measurement) showed a significantly greater relation with stroke risk than conventional blood pressure values (mean of 2 measurements) (19/8% increase in the risk of stroke per 10 mmHg elevation in initial home/conventional systolic blood pressure values, respectively). Goodness of fit of the model including home and conventional blood pressures significantly decreased when home blood pressure was removed, but not conventional blood pressure.
Conclusions: There was no threshold for the number of home blood pressure measurements within the range 1-14 measurements for increasing the predictive power of stroke risk. It should be emphasized that home blood pressure has a

stronger predictive power than does conventional blood pressure, even for less number of measurements, suggesting that, in addition to the number of measurements, other factors such as the lack of the white-coat effect may be associated with superior predictive power of home blood pressure measurements.

P1240 The relationship among plasma adiponectin concentration, essential hypertension, left ventricular mass index, and left ventricular diastolic function

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Purpose: Adiponectin, an adipocyte-specific plasma protein, is decreased in patients with coronary artery disease, and adiponectin has been known for its anti-inflammatory and anti-atherogenic effects. The purpose of this study is to characterize the relationship among plasma adiponectin concentration, essential hypertension, left ventricular mass index (LVMI), and left ventricular diastolic function.
Methods and Results: In 275 patients (137 male and 138 women), body mass index (BMI) and plasma adiponectin concentration, which was assessed by ELISA were measured. We calculated left ventricular mass index (LVMI), E/A ratio, deceleration time (DT), isovolumetric relaxation time (IVRT) by using echocardiograms. The plasma adiponectin concentration of hypertensive group was significantly lower than that of non-hypertensive group (9.9 $\pm$ 9.8ug/mL vs. 12.9 $\pm$ 9.5ug/mL, $p<0.05$). Plasma adiponectin showed a negative correlation with LVMI ($r= -0.329$, $p<0.001$), BMI ($r= -0.290$, $p<0.001$), IVRT ($r= -0.485$, $p<0.05$), and showed a positive correlation with E/A ratio ($r= +0.359$, $p<0.001$).
Conclusion: Our results suggest that a decrease in plasma adiponectin concentration is associated with an increase in blood pressure and BMI, the progress of left ventricular hypertrophy (LVH), a decrease in LV diastolic function.

P1241 Antiendothelial cell antibody levels in healthy offspring of hypertensive patients

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Background: According to international literature, elevated levels of antibodies to endothelial cells (antiendothelial cell antibodies AECA) and to b2-glucoprotein 1 (b2GP1) play an important role at the early stages of atherosclerosis process and of borderline hypertension. Aim of this study was to compare the AECA levels of healthy offspring of hypertensives (HOH) to those of healthy offspring of normotensives (HON), matched for age, sex and BMI.
Methods: One hundred HOH (56M, 44F) mean age 18$\pm$2,6 yrs and BMI 22,6$\pm$1,5 kg/m^2 (Group A) and 90 HON (48M, 42F) mean age 18$\pm$2,9 yrs and BMI 23$\pm$1,9 kg/m^2 (Group B) were studied. Both group subjects were matched for sex, age and BMI. IgG and IgM AECA levels were determined in each subject using an enzyme linked immunosorbent assay (ELISA). AECA levels were expressed as mean value$\pm$SD.
Results: In 25/100 subjects of group A were detected elevated IgG AECA levels (25%) vs. 1/90 of group B (1,1%, $p<0,001$). IgM AECA levels were elevated in 17 out of 100 in group A (17%) vs. none of group B ($p<0,001$). Mean values of both IgG and IgM AECA plasma levels in each group are shown below:

	Group A (n=100)	Group B (n=90)	P
IgG AECA	0,082$\pm$0,04	0,054$\pm$0,02	<0,001
IgM AECA	0,1030$\pm$0,09	0,098$\pm$0,06	<0,001

Conclusions: Our findings show that healthy offspring of hypertensives have significantly higher AECA levels compared to healthy offspring of normotensives. This may have prognostic significance for the future development of essential hypertension in this group of healthy subjects.

P1242 Adequacy of control of hypertension in patients with high risk of cardiovascular disease

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Purpose: to know if hypertension is adequately controlled in subjects with high risk of cardiovascular disease, when attended in outpatient clinics of Medicine departments of Spanish hospitals.
Methods: CIFARC is a cross-sectional survey of adequacy of control of cardiovascular risk factors, among patients with high risk of cardiovascular disease. The study is carried out by members of the Spanish Society of Internal Medicine who belong to hospitals all over the country. Data are collected electronically via Internet. Patients are adults with high or very high cardiovascular risk, as defined by a 20% absolute risk at 10 years, in the Framingham study. The following details are recovered from every participant: epidemiologic data, cardiovascular risk factors, adequacy of control of those risk factors, and information about use of medical resources. In this sub-study an analysis is made of adequacy of control of hypertension.
Results: of the total of 2264 patients of the CIFARC study, 1689 (74.6%) have received the diagnosis of hypertension. Among hypertensive patients, median of age is 68 years (interquartile range 59 to 74 years), 903 (53.5%) are male and 786 (46.5%) are female; 1072 (63.5%) have a systolic blood pressure equal or superior to 140 mm Hg, 602 (35.6%) have a diastolic blood pressure equal or superior to 90 mm Hg, and 1106 (65.5%) have inadequate control of systolic, diastolic or both modalities of blood pressure; 1571 (93,0%) are taking antihypertensive medications. Hypertensive patients have used medical resources, because of cardiovascular disease, a median of 3 times throughout the previous 12 months (interquartile range 2 to 6 times), and take a median of 5 pills per day (interquartile range 3 to 7 pills). Comparing patients with adequate control of hypertension with those with inadequate control, there is no difference in age, or number of times they have used medical resources; although patients with adequate control of hypertension are more frequently male (P = 0,004) and take more pills per day (P = 0,002).
Conclusions: among patients high or very high cardiovascular risk, control of hypertension, and particularly systolic hypertension, is inadequate.

P1243 Comparative effects of ACE inhibitor perindopril and angiotensin II receptor antagonist valsartan on the left ventricular hypertrophy and diastolic function in hypertensive type 2 diabetic patients

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Objective: It has been reported that antihypertensive drugs differ with regard to left ventricular (LV) mass reduction and LV diastolic function improvement. The aim of present study was to compare the effect of ACE inhibitor perindopril (P) or angiotensin II receptor antagonist valsartan (V) alone or in combination on LV mass index (LVMI) and diastolic function in hypertensive type 2 diabetic patients (pts).
Design and Methods: Seventy five hypertensive type 2 diabetic pts with LV hypertrophy (LVMI $>$ 116 g/m^2 for men and $>$ 106 g/m^2 for women) were randomly assigned to P 8 mg daily (14 males and 11 females, aged 51-64 years), or V 160 mg daily (15 males and 10 females, aged 50-63 years), or P 4 mg and V 80 mg daily in combination (13 males and 12 females, aged 49-64 years). Echocardiography and Doppler-echocardiography were performed at baseline and after 9 month of therapy. The parameters of LV hypertrophy, ratio of the early filling velocity (E) to late filling velocity (A) – E/A ratio, isovolumic relaxation time (IVRT) and deceleration time (DT) were evaluated.
Results: BP was lowered in all groups to less than 130/85 mm Hg. LVMI reduced from 159,3$\pm$7,0 to 137,4$\pm$3,3 g/m^2 with P ($p<0,01$), from 160,3$\pm$7,2 to 144,2$\pm$3,0 g/m^2 with V ($p<0,01$), from 161,6$\pm$7,3 to 130,1$\pm$3,4 g/m^2 with P and V in combination ($p<0,001$). The decrease in LVMI was essentially caused by a reduction of LV wall thickness and diameter. At the end of the study E/A ratio increased with P (1,34$\pm$0,07 vs 0,97$\pm$0,04, $p<0,01$), with V (1,18$\pm$0,05 vs 0,96$\pm$0,04, $p<0,01$), with P and V in combination (1,43$\pm$0,06 vs 0,98$\pm$0,05, $p<0,001$); IVRT decreased with P (72,1$\pm$5,3 vs 98,9$\pm$6,1 msec, $p<0,01$), with V (79,9$\pm$5,4 vs 97,6$\pm$6,4 msec, $p<0,01$), with P and V in combination (67,1$\pm$4,8 vs 98,8$\pm$5,8 msec, $p<0,001$). DT passed with P (142,3$\pm$9,2 vs 187,3$\pm$10,2 msec, $p<0,01$), with V (156,9$\pm$8,9 vs 188,0$\pm$9,9 msec, $p<0,01$), with V and P in combination (133,8$\pm$9,3 vs 187,7$\pm$10,2 msec, $p<0,01$).
Conclusions: Our results showed that in hypertensive type 2 diabetic pts combined therapy with P and V induced greater effects on LV structure and diastolic function compared to monotherapy independent of similar reduction in BP. But P alone induced greater regression of LV hypertrophy and improvement in diastolic function than V. So, ACE inhibitors alone or in combination with other drugs seem to be the best choice for hypertensive type 2 diabetic pts.

P1244 Blood pressure variability, collagen metabolism and large artery stiffness in diabetic hypertensives

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Background: arterial hypertension among diabetic patients is one of the most important factors determining CV-prognosis, mainly due to arterial damage.Carotid -femoral pulse wave velocity (AoPWV) is considered as an independent risk factor for CV-mortality in various hypertensive populations and depends on collagen turn-over in arterial wall.
Aim: to compare blood pressure profiles,AoPWV, and plasma collagen markers between healthy controls, hypertensives and diabetic hypertensives.
Methods: We compared three groups: G1- 24 healthy controls (mean age 53.3$\pm$9.5 yrs, G2- 43 mild or moderate hypertensives (mean age 55.3$\pm$8.6 yrs, mean duration of hypertension 12.3$\pm$3.8 yrs), G3- 20 diabetic hypertensives (mean duration of hypertension 11.6$\pm$2.0 yrs, duration of DM t.2 - 12.3$\pm$3.8 yrs). 24-h BP monitoring using SpaceLabs 90207, AoPWV using Complior® device

and plasma levels of collagen metabolites:PICP- carboxyterminal propeptide of procollagen type I, PINP- aminoterminal propeptide of procollagen type I, and PIIINP-aminoterminal propeptide of procollagen type III were determined. ANOVA was used for statistical analysis.
Results: Mean systolic (SBP) and diastolic blood pressure(DBP) from 24h-ABPM were higher in G2 and G3 groups than in control group but in post-hoc Scheffe test SBP and DBP between G2 and G3 were not different. SBP (G1-118.0±6.9mmHg, G2-132.4±7.2 mmHg, G3-135±8.2 mmHg, ANOVA main effect $p<0.01$, Scheffe test for G2 vs G3 $p>0.05$.). DBP (G1-75.7±5.1mmHg, G281.1±6.4mmHg, G3-84.4±9.9mmHg, ANOVA main effect $p<0.01$, Scheffe test for G2 vs G3 $p>0.05$). Statisticaly significant differences between groups G2 and G3 in post-hoc Scheffe test were found for BP variability indices: standard deviation of SBP (G1-13.0±2.6 mmHg, G2-12.3±2.7mmHg, G3- 17.3±6.4 mmHg,$p<0.05$) and standard deviation of DBP (G1-10.6±2.7mmHg, G2-10.2±3.0mmHg, G3-15.4±3.1mmHg, $p<0.05$) as well as for AoPWV (G1-8.8±1.2m/s, G2-9.7±1.5m/s, G3-12.3±1.2m/s $p<0.05$),PICP (G1-132.5±23.2μg/l, G2-138.4±28.4μg/l, G3-149.5±28.4μg/l, $p<0.05$)and PINP (G1-43.7±12.3μg/l, G2-51.5±13.4μg/l, G3-64.7±14.7μg/l,$p<0.05$).
Conclusion: Blood pressure variability and collagen type I metabolism determine arterial stiffness in diabetic hypertensives.

P1245 Association of risk factors with increased pulse wave velocity detected by a novel method from two-channel photoplethysmography

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Objectives: Coronary risk factors are associated with increased pulse wave velocity (PWV). We developed a new method for measurements of aortic PWV from simultaneously recording of digital volume pulse on finger and toe detected by 2-channel photoplethysmography (PPG). We tested the correlation between PWV measured from this new method (PWV-DVP) with PWV measured by applanation tonometry (PWV-AT) and evaluated the association between risk factors and PWV detected by this new method.
Methods: We enrolled 100 asymptomatic subjects (46 women, age 19-64 years) in this study. All subjects rested in supine position for 20 minutes before measurements. PWV was measured both by 2-channel PPG and by applanation tonometry at the same time. The 2-channel PPG system we developed could record digital volume pulse simultaneously from finger and toe. Time of pulse transition could be measured by the time difference between 2 digital volume pulses. The system could measure transition time averaged from consecutive digital volume pulses in 5 seconds in every measurement automatically. PWV was calculated from distance between finger and toe divided by transition time. Carotid-femoral PWV was also measured by applanation tonometry (SphygmoCor, AtCor, Sydney, Australia). Average of 3 measurements from both methods were recorded.
Results: PWV-DVP was significantly correlated with PWV-AT ($r = 0.787$, $p < 0.001$). Both PWV-DVP ($r = 0.401$, $p < 0.001$) and PWV-AT ($r = 0.458$, $p < 0.001$) were significantly correlated with age. After multivariate analysis controlled by age, heart rate, systolic blood pressure, and diastolic blood pressure, PWV-DVP was still significantly correlated with PWV-AT ($r = 0.669$, $p < 0.001$). Subjects with hypertension (N = 10) had significant higher PWV-DVP than subjects without hypertension (8.04 ± 1.83 vs. 6.49 ± 0.92 m/s, $p < 0.001$). Subjects with dyslipidemia (N = 16) also had higher PWV-DVP than those without dyslipidemia (7.27 ± 1.55 vs. 6.39 ± 0.93 m/s, $p = 0.044$).
Conclusion: PWV measured by 2-channel PPG system was correlated with traditional method very well. Hypertension and dyslipidemia were associated with higher PWV-DVP. Our method is a reliable, simple, and technique-independent method for measurement of aortic PWV.

P1246 Effect of coronary artery stenosis on the plasma atrial natriuretic peptide, N-Terminal proatrial natriuretic peptide, and brain natriuretic peptide in patients with coronary artery disease

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Objective: Plasma atrial natriuretic peptide (ANP), N-terminal proatrial natriuretic peptide (N-ANP), and brain natriuretic peptide (BNP) are useful noninvasive biochemical markers for monitoring the left ventricular function, remodeling, and hypertrophy in cardiovascular disease. However, the effects of coronary artery stenosis on the natriuretic peptides remain unknown. This study was conducted to examine whether coronary artery stenosis affects the natriuretic peptides in patients with coronary artery disease (CAD).
Methods and Results: *Study 1:* The hundred four consecutive patients with normal left ventricular function (EF>60%) who were suspected of having CAD were studied. Plasma ANP, N-ANP, and BNP levels were measured by specific immunoradiometric assays. CAD was defined as coronary artery stenosis >75% and was further divided into two groups: proximal lesion (CAD-p) and distal lesion (CAD-d) groups. N-ANP, BNP, and ANP levels were all higher in patients with CAD than in those without it, whereas there were no differences in hemodynamic variables between these two groups. Furthermore, there were significant differences in these peptides between the control and CAD-d groups (N-ANP: 242±117 vs. 446±279 fmol/ml, $p<0.001$; BNP: 18±22 vs. 52±16 pg/ml, $p<0.01$; ANP: 22±18 vs. 55±67 pg/ml, $p<0.01$). N-ANP was further increased in CAD-p (518±288, $p<0.05$) compared to CAD-d, whereas there were no differences in BNP or ANP between CAD-d and CAD-p (BNP: 54±54 pg/ml, $p=0.68$; ANP: 60±70 pg/ml, $p = 0.33$). If the cut-off values of these peptides were taken as ANP>20, N-ANP>300 and BNP>18, the sensitivity, specificity, and positive predictive value of each peptide were as follows: (ANP: 72%, 62%, 76%; N-ANP: 54%, 74%, 77%; BNP: 64%, 69%, 77%).
Study 2: Plasma natriuretic peptides levels were measured before and 3-6 months after percutaneous coronary intervention (n=58) in patients with recent onset myocardial infarction. Plasma level of natriuretic peptides significantly decreased in patients without restenosis (n=46) (ANP: 91±15 to 39±7; BNP: 134±28.9 to 41±9; N-ANP: 688±81 to 407±52: all $P<0.05$). However, these levels did not change after coronary intervention in patients with restenosis (n=12) (ANP: 57±19 to 50 ± 20; BNP: 102±35 to 57±13; N-ANP: 567±178 to 508±126: all NS).
Conclusions: These results suggest that coronary artery stenosis affects the natriuretic peptides levels in patients with CAD and that natriuretic peptides may be useful noninvasive biochemical markers for the detection restenosis in patients who received percutaneous coronary intervention.

P1247 Inverse relationship of plasma homocysteinemia and left ventricular ejection fraction in hypertensive patients with and without coronary artery disease

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Background and aim: High plasma homocysteine (tHcy) has been associated with excess risk of cardiovascular events but its association with coronary artery disease (CAD) is controversial and there is no information on its impact on left ventricle ejection fraction (LVEF). Thus, we aimed to determine the relationship of tHcy with LVEF and CAD in hypertensive (HT) and normotensive (NT) high risk patients (pts) referred for coronary angiography.
Design and Methods: In 936 consecutive pts (age 62±10 yrs) undergoing quantitative coronary angiography for suspected CAD we measured LVEF, total plasma homocysteine (tHcy), folate levels, and MTHFR T677C polymorphism. CAD was graded according to the modified Duke Index score; hypertension was defined according to the ESH/ESC guidelines; hyperhomocysteinemia (HHcy) was defined as tHcy levels exceeding the 90th percentile of values observed in healthy volunteers, eg ≥15.46 mmol/L.
Results: A CAD score index >0 was found in 704, e.g. 75%, (CAD group) and HT was present in 60% of all patients, more commonly in CAD than non-CAD. Neither HHcy nor tHcy showed any relationship with the extent of CAD or with HT (even when pts were divided according to the extent of CAD and also when tHcy values were adjusted for its determinants). A significant and inverse relationship of tHcy with LVEF was found in HT with ($p=0.015$) and without ($p=0.0005$) previous myocardial infarction, but not in NT. Multivariate logistic regression analysis also identified tHcy ($p<0.0001$) as the single strongest predictor of a low (<40%) LVEF.
Conclusions: HHcy was common in pts referred for coronary angiography but did not differ between HT and NT pts and between CAD and non-CAD pts. In HT, but not in NT, pts tHcy predicted a low LVEF both in those without and in those with previous myocardial infarction.

P1248 The effect of phytoestrogens on oxidative stress and ischaemic myocardium

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Purpose: We have previously shown that conjugated equine estrogens administered in ovariectomized female rabbits significantly reduce myocardial infarct size compared to placebo. The cardioprotective effects of estrogen are in part attributed to their antioxidant activity. We now investigated whether genistein, a phytoestrogen derived from soybeans, similarly protects ischemic myocardium and if so whether this is associated with reduction of oxidative stress.
Methods: We studied 3 groups of sexually mature New Zealand white female rabbits. Group A (n=4) were normal controls, group B (n=8) were ovariectomized 4 weeks prior to the experiment and group C (n= 5) were ovariectomized and treated with genistein (0.2 mg-kg-day subcutaneously) for 4 weeks. Subsequently all animals underwent 30 minutes of ischemia and 120 minutes of reperfusion. Blood samples were drawn at the beginning of the experiment. Infarct and risk areas were delineated by Zn-Cd fluorescent particles and tetrazolium chloride staining. The infarct size was expressed as a percentage of the risk zone (I/R%). Malondialdehyde concentration (MDA), a measurement of lipid peroxidation, was determined spectrophotometrically at 586 nm and expressed as micromoles.
Results: We analyzed our results with one way analysis of variance (ANOVA).

There were no significant differences between the groups. Genistein failed to reduce infarct size (B vs C NS) and estrogen deprivation for 4 weeks was not associated with larger myocardial infarctions (A vs B NS). Likewise we found no significant differences in MDA plasma levels implying that both ovariectomy and ovariectomy plus genistein therapy do not modify lipid peroxidation.

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	I/R%	MDA (μM)
A (n=4)	43.79 ±2.96	2.1±.0.29
B (n=8)	43.05±28.37	1.7±0.14
C (n=5)	44.5±25.47	1.99±0.39

Mean ± SE

Conclusion: Estrogen deprivation, at least during short term, does not increase oxidative stress and is not associated with larger myocardial infarctions. Genistein fails to decrease lipid peroxidation and does not protect ischemic myocardium.

P1249 Reduction of microvascular flow reserve impairs endothelial function in conduit arteries of patients with essential hypertension

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Background: A diminished flow reserve in resistance vessels is a hallmark of hypertensive microvascular disease. Hypertension is associated with structural alterations in the microcirculation and a reduced endothelium dependent dilation in conduit arteries. Both have been demonstrated to predict future cardiovascular events. We hypothesized that a reduced microvascular flow reserve impairs endothelial function in upstream conduit arteries in patients with arterial hypertension.
Methods: In 43 hypertensive patients (HT) and 38 normotensive controls (NT) endothelial function of the brachial artery was assessed by measurement of flow-mediated dilatation (FMD) using high resolution ultrasound. Microvascular flow reserve (FR) in forearm vasculature was determined via measurements of forearm blood flow at rest and during increments of reactive hyperemia using venous occlusion plethysmography.
Results: Brachial artery FMD was markedly impaired in HT (3.6±0.3%) as compared with NT (10.2±0.3%), whereas maximum brachial artery diameter following endothelium-independent dilatation was similar in both groups. In the forearm vasculature of hypertensive patients the microvascular flow reserve was significantly reduced (3.2 in HT versus 6.0 in NT during reactive hyperemia after 5 min of ischemia. Impaired FR was associated with reduced brachial artery FMD only in HT ($r=0.60$, $p<0.01$). Multiple stepwise regression analysis identified FR as a strong independent variable determining the extent of brachial artery FMD ($r^2=0.46$, $p<0.01$). In HT the dose response curve of FMD upon stepwise increases of FR was significantly shifted to the right. Normalization of FR improved brachial artery FMD in HT by more than 60%.
Conclusions: In essential hypertension a reduced forearm microvascular flow reserve contributes to the endothelial dysfunction of upstream conduit arteries. These findings may have therapeutic and prognostic implications in patients with arterial hypertension.

P1250 Association between urinary albumin excretion rate and left ventricular geometric adaptations, in essential hypertensive patients without left ventricular hypertrophy: a way to better risk assessment?

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Purpose: Alterations of left ventricular (LV) geometry and augmented urinary albumin excretion rate (UAER) are both associated with increased cardiovascular risk. In this study, we sought to investigate the possible association between LV concentric remodeling and UAER, in essential hypertensive subjects.
Methods: From a population of 95 consecutive newly diagnosed, untreated non-diabetic patients with stage I to II essential hypertension, we selected 57 hypertensives [42 men, mean age=48 years, office blood pressure (BP)=147/95 mmHg] with normal LV mass. All participants were divided into two groups, according to relative wall thickness (RWT) values: group A-normal LV geometry (RWT<0.45) and group B-LV concentric remodeling (RWT>0.45). Additionally, UAER was determined in three non-consecutive 24h urine samples by nephelometric methods and all subjects underwent 24-h BP monitoring.
Results: For the pooled population, body mass index (BMI) was 26.93±2.5 kg/m^2, total cholesterol was 241±31 mg/dl, triglycerides were 134±63 mg/dl, low density lipoprotein-cholesterol was 153±14 mg/dl and UAER was 20.3±9 mg/24h. Regarding the echocardiographic data, left ventricular mass index (LVMI) was 104.5±22 g/m^2, RWT was 0.42±0.07 and left atrial diameter was 3.5±0.31 cm. UAER was correlated with office systolic BP ($r=0.27$, $p<0.05$), 24-h systolic BP ($r=0.39$, $p<0.001$), ambulatory pulse pressure ($r=0.38$, $p<0.01$) and LVMI ($r=0.32$, $p<0.05$). Furthermore, the group with LV concentric remodeling (n=27), compared to the group with normal geometry (n=30) had significantly increased age (50±7 years vs 45±5 years, $p<0.03$), BMI (28.2±4 kg/m^2 vs 27.5±2 kg/m^2, $p<0.05$), office systolic BP (154±9 mmHg vs 145±4 mmHg, $p<0.05$) and higher UAER (21.5±6 mg/24h vs 19.7±8 mg/24h, $p<0.05$).
Conclusions: Augmented UAER is accompanied by adverse LV geometric pattern, even in newly diagnosed essential hypertension. Echocardiographic evaluation of LV geometry, in conjunction with UAER determination may contribute to better cardiovascular risk stratification, in this setting.

P1251 Doppler tissue imaging in the assessment of diastolic function in hypertensive patients

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Left ventricular hypertrophy is a major risk factor of cardiac dysfunction in hypertensive patients. It has been shown that in patients with hypertension tissue Doppler imaging (TDI) is able to detect impairment of diastolic function more accurately than transmitral Doppler. The aim of this study was to asses by TDI the diastolic function in different geometric patterns of left ventricular hypertrophy in hypertensive patients. We studied 224 p with hypertension. Left ventricular hypertrophy was diagnosed by cardiac mass index and relative wall thickness. We measured E, A, E/A and DTE from transmitral Doppler and e, a e/a from tissue Doppler at the level of the septal and lateral mitral annulus. We found four geometric patterns: Normal LV, concentric remodeling, concentric hypertrophy and eccentric hypertrophy.
Results:

	Normal LV	Concentric Remodeling	Concentric Hypertophy	Excentric hypertrophy
	66 (29%)	38 (17%)	86(38%)	34(15%)
E/A	1.1 + 0.2	1,06 + 0.2.	0.79 + 0.2	0.85 + 0.2
DTE	225 + 21	235 + 22	276 + 30	245 + 24
e/a	0.95 + 0.2	0.68 + 0.2	0.64 + 0.2	0.80 + 0.2

Conclusion: In our series, 53% of hypertensive patients had left ventricular hypertrophy diagnosed by cardiac mass index. Transmitral pulsed Doppler showed abnormalities only in patients with left ventricular hypertrophy. TDI was able to detect impairment of diastolic function in all geometric patterns, including normal LV. The abnormal pattern was more severe in concentric forms with and without hypertrophy. Our findings suggest that many hypertensive patients with an echocardiogram reported as normal, because they had not hypertrophy and had normal transmitral Doppler, could have concentric remodeling and impaired diastolic function if studied by TDI.

P1252 Mild renal impairment is associated with increased cardiovascular risk in hypertensive patients

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Purpose: Cardiovascular and renal disease share the same major risk factors. Normal renal function is validated by a creatinine clearance value >60 ml/min, or a serum creatinine <1.4 mg/dl in men and <1.2 mg/dl in women. Aim of the present study was to evaluate the cardiovascular risk profile in hypertensive patients (pts) with mild renal impairment.
Methods: We retrospectively studied 4511 consecutive pts with uncomplicated essential hypertension. Pts with renal insufficiency (serum creatinine >2mg/dl) were excluded. All had been subjected to full clinical, echocardiographic and biochemical evaluation after the diagnosis of essential hypertension was established, and before the initiation of any antihypertensive treatment. Regarding the abovementioned cutoff values, mild renal impairment was certified in 941 pts (20.9%).
Results: Pts with mild renal impairment had a significantly higher incidence of diabetes mellitus (24.3 vs 11.3%, $p<0.00001$), impaired glucose tolerance (20.8 vs 16%, $p=0.0005$), eccentric and concentric left ventricular hypertrophy (31.5 vs 17.8% and 47.3 vs 28.2% respectively, $p<0.00001$ for both) and microalbuminuria (70 vs 34.3%, $p<0.00001$). Moreover, they were characterized by significantly higher values for left ventricular mass (154 vs 136 g/m^2, $p<0.00001$), urine microalbumin (49 vs 29 mg/L, $p<0.00001$) and microglobulin excretion (10.8 vs 7.4 mg/L, $p<0.00001$), total cholesterol (232 vs 222 mg/dl, $p<0.00001$), fibrinogen (338 vs 302 mg/dl, $p<0.00001$) and PAI-1 (3.24 vs 2.73 IU/L, $p<0.00001$). Plasma renin activity was comparable between pts with and without mild renal impairment (1.20 vs 1.23 ng/ml/h, p=NS). The significance of these differences persisted even after adjustment for the pts' age.
Conclusion: Mild renal impairment is associated with an unfavorable cardiovascular risk factor profile and greater target organ damage in an essential hypertensive population.

P1253 Is carotid artery intimal-medial thickness, a predictor of cardiovascular changes in hypertensive children with end stage renal failure?

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Hypertension is an important risk factor that causes irreversible changes in various systems. This study was designed to display carotid artery intimal medial thickness (cIMT) and associated left ventricular echocardiographic parameters in children with end stage renal disease and receiving antihypertensive treatment.
Methods: The study group was consisted of 28 children who were on chronic dialysis treatment (18 children on peritoneal dialysis, 10 children on hemodialysis) and seperated into two groups according to their antihypertensive treatment. Twenty eight healthy aged-matched children were taken as the control group. The carotid intimal-medial thickness was measured echocardiographically. Left ventricular mass(LVM), posterior wall thickness (PWT), interventricular septum thickness (IVS), left ventricular end diastolic dimension (LVED) were calculated during diastole.
Results: The cIMT, LVED, IVST, LVM measurements of hypertensive group were statistically different than the control group ($p<0.05$) and there was a positive correlation in between cIMT and LVM (r=0.555 for the right side, r=0.464 for the left side) in the hypertensive group. There were no statistically significant difference of cIMT, LVED, IVST, LVM, PWT measurements in between normotensive group and control group. The prevalence of increased cIMT was 25%. Subjects with increased cIMT had higher LVM (224 g $\pm$ 96.34 vs 129.19 g $\pm$ 60.82) than those with normal cIMT.
Conclusions: The increase in cIMT is correlated with the increase in LVM and may be accepted as a valuable indicator of cardiovascular chances in hypertensive children.

P1254 Cardiac and renal expression of natriuretic peptides system during chronic renal failure progression

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Although systemic hypertension (HT) is an early and almost universal finding during chronic renal failure (CRF) progression, its pathophysiology remains largely unknown. In this disease, HT is accompanied by systemic activation of natriuretic peptides (NP) system with increased cardiac production and secretion of NP. In the present study, we evaluated cardiac and renal expression of NP system in a model of renal mass loss, before development of HT. Male Wistar-Han rats were submitted to right kidney nephrectomy (Unx; n=7) or to Unx+excision of both left kidney poles (3/4nx; n=7), and compared with Sham (n=7). Animals were housed in metabolic cages for fractional excretion of Na^+ ($FENa^+$) and creatinine clearance (Ccreat) evaluation. Two weeks later, a left ventricular (LV) tip micromanometer was used to measure peak systolic and end-diastolic pressures, dP/dtmax, dP/dtmin, and time constant of isovolumetric relaxation Tau. At the end, samples from LV free-wall, renal cortex and medulla were collected for mRNA relative quantification by two-step RT and real-time PCR of atrial natriuretic peptide (ANP), natriuretic peptide type-B (BNP), NP receptor types A (NPR-A) and C (NPR-C), normalized for GAPDH (results presented as mean$\pm$SEM; $P<0.05$). Two weeks after surgery, the remnant renal mass in Unx and 1/4nx increased 40$\pm$7% and 69$\pm$4%, respectively. Ccreat decreased 33$\pm$2% in Unx and 63$\pm$3% in 14nx. $FENa^+$ in Unx and 1/4nx increased 66$\pm$4% and 131$\pm$7%, respectively. There were no significant differences in LV haemodinamics between the 3 groups. In LV and renal cortex no differences were detected in ANP, BNP, NPR-A and NPR-C mRNA levels. In renal medulla NPR-A expression decreased both in Unx and 1/4nx (-34$\pm$13% and -68$\pm$10%, respectively). Our results indicate a distinct modulation of local cardiac and renal NP system early in CRF progression. In the heart, the absence of alterations in both LV haemodinamics and myocardial NP system gene expression suggests that cardiac overload is essential for NP systemic activation. In the kidney medulla, decreased NPR-A mRNA suggests a precocious activation of this local system independently of systemic haemodinamics.

VALVE SURGERY

P1255 Videothoracoscopic-enhanced biventricular resynchronization: an alternative to failed attempts in endovenous cardiac resynchronization therapy for chronic heart failure

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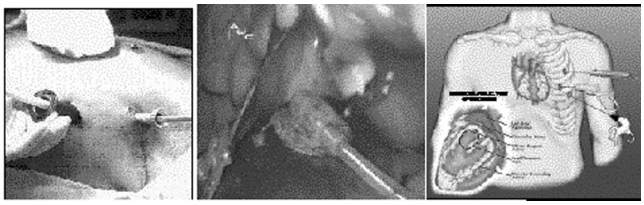
Purpose: Ventricular resynchronization might be achieved in a minimally invasive fashion using a video-thoracoscopic assisted (VAT), direct left ventricular (LV) epicardial approach.The purpose of this clinical,prospective, multicentric study was to evaluate the feasibility of a new operation technique (Malleable Tool 10626 and epimyocardial lead 5071,Medtronic)for critical heart failure patients (CE certification).
Methods: 15 patients with congestive heart failure (NYHA class 3.5$\pm$0.4) and a widened QRS complex (186$\pm$33 ms), 1 pt with pacemaker decubitus and sepsis, underwent transvenous right cardiac electrode positioning and surgical VAT assisted LV lead placement after failed coronary sinus cannulation. Mean patient age was 60$\pm$5 years,LV ejection fraction (EF) was 24$\pm$3%,8 patients had previous cardiac or thoracic surgery, surgical technique see picture.
Results: 16 epicardial leads were successfully placed on the posterobasal surface of the LV. Intraoperative lead threshold was 1.21$\pm$0.57 V at 0.5 ms, R-wave was 12.6$\pm$5.4mV, and impedance was 609$\pm$153 Ohms at 0.5 V, time of final electrode position (incl. measurements) was only 5.7$\pm$1.4 minutes, time of skin-skin procedure was 68$\pm$23 minutes. There were no surgical complica-tions. Improvements in exercise tolerance (14 of 16 patients), EF(34$\pm$8%) and QRS duration (150$\pm$18 ms) were significant at three to six months follow-up $p<0.001$). Lead thresholds have remained unchanged (1.4$\pm$0.28 V at 0.5 ms) and a significant drop in impedance (410$\pm$67 Ohms, $p<0.001$) has been measured.



Surgical approach.

Conclusions: Surgical VAT assisted LV lead placement with Malleable Tool 10626 and epimyocardial Lead 5071 is an effective and novel technique for biventri-cular pacing in critical heart failure patients.

P1256 Intraoperative bypass- and coronary angiography: a novel approach to quality control and a platform for simultaneous catheter-based intervention in innovative coronary surgery?

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Background: The implementation of innovative coronary artery revascularization procedures requires intense quality control of performed anastomosis. Totally endoscopic coronary artery bypass grafting (TECAB) is a robotic- dependent procedure, performance of which involves learning curves.
We assessed the safety and efficacy of C-arm based bypass- and coronary angiography in quality control of endoscopically sutured LIMA-LAD anastomosis and explored a potential platform for simultaneous surgical and catheter-based intervention in OR setting.
Methods: Between October 2001 and February 2004 thirty patients underwent a TECAB procedure; 29 operations were performed on the arrested heart and 1 on the beating heart. In 27 patients intraoperative angiography was performed by a cardiologist, additionally 20 patients underwent follow-up CAG up to 3 months postoperatively. An OEC 9800 mobile C-arm and femoral access with a 7F LIMA catheter were used for intraoperative fluoroscopic imaging.
Results: In 2 patients intraoperative angiography showed an extravasation of contrast agent, source of bleeding was identified and repaired by clip placement on the harvested LIMA pedicle and additional anastomotic sutures. One intramural haematoma of distal LIMA and one proximal occlusion of target vessel led to manual redo of the target anastomosis through sternotomy. Additionally in one patient with acute intraoperative occlusive RCA thrombosis subsequent PTCA with stenting were performed.
The imaging quality of intraoperative angiography was judged as adequate by an experienced interventional cardiologist. All patients left the operating room with

patent grafts, there were no perioperative myocardial infarctions and no hospital mortality. There were no femoral access and catheter related complications. Grafts patent intraoperatively were also patent on follow-up angiography, however in one patient, who had undergone revision of the anastomosis, an occlusion of the proximal target vessel was shown, which was not present on intraoperative aniography.
Conclusions: Our experience suggests that bypass- and coronary angiography performed in OR setting in robotic totally endoscopic coronary bypass operations allows adequate and immediate quality control of graft patency and may allow prevention of serious early post-operative complications such as cardiac tamponade and peri-operative AMI. Intraoperative angiography creates a possible platform for simultaneous surgical and catheter-based coronary interventions.

P1257 The prevalence of renal artery stenosis and carotid stenosis in hypertensive patients with coronary artery disease

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Background: It has been shown that coronary artery disease coexists with peripheral vascular disease. The aim of this study was to evaluate the incidence of renal artery stenosis in hypertensive patients with coronary artery disease.
Methods: 169 patients with coronary artery disease and arterial hypertension underwent coronary, renal and carotid angiography on the same occasion (Group A). 169 age- and sex matched patients with coronary artery disease without arterial hypertension served as the controll group (Group B).
Results: In the investigated patients (n=338) 16,5% had increased creatinine level, 27% had diabetes mellitus (group A n=48 versus group B n=53; p=n.s.), 68% had hyperlipidemia (group A n=106 versus group B n=123; p=n.s.), 63% were smokers (group A n=101 versus group B n=111; p=n.s.), 45% had family history for coronary artery disease (group A n=70 versus group B n=82; p=n.s.). Coronary angiography revealed one vessel disease in 29% of patients (group A n=51 versus group B n=47; p=n.s.), two vessel disease in 31% (group A n=49 versus group B n=56; p=n.s.) and three vessel disease in 40% (group A n=69 versus group B n=66; p=n.s.). Significant renal artery stenosis (> 70%) was found in 19% of patients (group A n=51 versus group B n=13; p <0.01), non-significant atherosclerotic lesions were present in 21% of patients (group A n=31 versus group B n=40; p=n.s.). Carotid angiography revealed atheromatic plaques in 73% of patients (group A n=96 versus group B n=151; p <0.001). Carotid stenosis with a narrowing greater than 70% were present in 15% of patients (group A n=42 versus group B n=10; p <0.001).
Conclusion: In patients with coronary artery disease and arterial hypertension renal and carotid artery stenosis were observed significantly more often than in patients with coronary artery disease without arterial hypertension. The high prevalence of renal and caritid artery stenosis in these patients indicate, that patients with coronary artery disease and arterial hypertension should be screened for atherosclerotic lesions in large arteries and renal artery stenosis. Both are potentially correctable diseases.

P1258 Results of a screening program for abdominal aortic aneurysm during transthoracic echocardiography in hypertensive patients

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Purpose: This study was designed to assess the utility of transthoracic echocardiography (TTE) as a screening test for occult abdominal aortic aneurysm (AAA) in hypertensive patients older than 50 years of age.
Methods: In hypertensive patients underwent to TTE, longitudinal and transverse images of the abdominal aorta were obtained during the diaphragmatic position of the TTE. AAA was defined as an abdominal aortic dimension (antero-posterior or lateral) ≥3 cm. Exclusion criteria included prior AAA repair, known abdominal aortic aneurysm and inadeguate images of the abdominal aorta.
Results: One thousand and eigth hundred ten patients met the study inclusion criteria (980 males; 830 females; mean age 73 years, range 50 to 92 years). An occult AAA was identified in 202 patients (11.2%), 141 patients were men (69.8%), with a mean age of 74 years and a mean duration of hypertension of 16 years. Three hundred and eighteen (17.5%) patients had a smoke habits and 91 patients (5%) had a positive family history of AAA. All aneurysms were infrarenal except 100 (5.5%); the mean diameter was 3.8 cm (range 3-5.1). Laminated thrombus was present 70 patients (3.9%). Imaging of the abdominal aorta during TTE required an average of 7.1 minutes (range 5-14 minutes).
Conclusions: AAA is frequently asymptomatic and often occult on physical examination. Ultrasonography is highly accurate in the diagnosis of AAA and screening for AAA can be readily incorporated into the TTE examination. Abdominal aorta can be accurately imaged in the majority of patients (94%) undergoing TTE. The present study shows that the incidence of occult AAA detected by TTE in hypertensive patients older 50 years of age is significant. Screening for occult AAA in this patient population should be a routine extension of TTE.

P1259 Long-term statin use is associated with a reduced mortality after successful abdominal aortic aneurysm surgery

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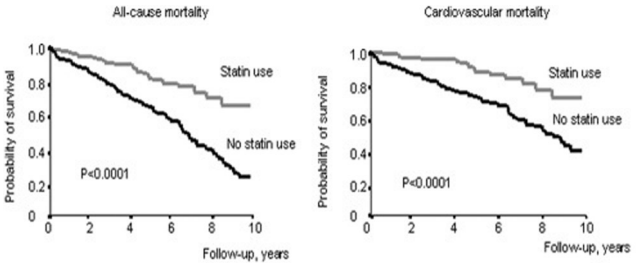
Purpose: To explore the potential long-term beneficial effect of statin use after successful abdominal aortic surgery.
Methods: Between 1991-2001, 570 patients underwent abdominal aortic aneurysm repair at the Erasmus Medical Center. Of that 519 (91%) patients survived surgery beyond 30 days and of these 510 patients (98%) were followed until February 2003 (median of 4.7 years [25th-75th percentile, 2.7-7.3 years]). Patients were evaluated for statin use and β-blocker therapy, and clinical risk factors (advanced age, prior myocardial infarction, history of angina, diabetes mellitus, history of stroke, renal dysfunction, history of heart failure and chronic pulmonary disease). All-cause and cardiovascular mortality were evaluated during long-term follow-up.
Results: Death occurred in 205 (40%) patients, 140 of whom died from cardiovascular causes. The incidence of all-cause (18% vs. 50%; p<0.001) and cardiovascular mortality (11% vs. 34%; p<0.001) were significantly lower in statin users compared to non-statin users. After adjusting for clinical risk factors and β-blocker use, the association between statin use and reduced incidence of all-cause (adjusted hazard ratio, (HR), 0.4, 95% CI, 0.3-0.6; p<0.001) and cardiovascular mortality (HR, 0.3, 95% CI, 0.2-0.6; p<0.001) persisted. β-blocker use was also associated with a significant reduction in all-cause (HR, 0.7, 95% CI, 0.5-0.9; p=0.01) and cardiovascular mortality (HR, 0.7, 95% CI, 0.4-0.9; p=0.01). There was no evidence of an interaction between statin use and all-cause and cardiovascular mortality in subgroup of patients according to β-blocker use or clinical risk factors.



Conclusion: Long-term statin use is associated with a reduced incidence of all-cause and cardiovascular mortality.

P1260 Transluminal stent-graft placements for the treatment of acute aortic dissection: mid-long-term follow-up

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Background: Transluminal stent-graft treatment for aortic dissection is a relatively new procedure and it represents a safer alternative to conventional surgical approach.
Methods: Fourteen consecutive patients (9 male, mean age 62±16 yrs) with complicated acute aortic dissection because of an intimal tear in the descending aorta underwent transluminal stent-graft placement. Clinically, the patients (pts) presented: severe anemia (N=3), hematic pleural effusion (N=2), acute renal failure (N=4), persistent back pain with lower limb ischemia (N=3) and progressive enlargment of the false lumen (N=2). Angiography was performed by right radial artery approach; graft placements was performed after surgical exposure by right femoral artery. All pts were managed by general but than 3 by spinal anesthesia. After treatment all pts underwent serial spiral-CT scan at 7 days, 3 and 12 months.
Results: Stent-graft deployment in the true lumen of the aorta was technically successful in all cases. Nineteen stent-graft were used in 14 pts (two Excluder,GORE™ and seventeen Talent LPS,Medtronic™). Six pts (46%) suffered left subclavian artery occlusion without urgent need of carotid-vertebral by-pass. No major neurological events were reported. Two pts required transitory hemodialysis for severe acute renal failure, one pts had wound infection and three pts received blood transfusion for severe anemia. At 7 days CT-scan showed residual endoleak type 1 in one pts (7%) who was managed medically and retrograde perfusion of the false lumen from infra-diagframmatic aorta in 4 pts (28%). Hospitalization mean time was 11 ± 7 days. All pts were teated with Ticlopidine (250 mg/day) for one year. Two pts died: one (female, 57 yrs old), with ascending aortic aneurysm, died during thoracotomy for Bentall intervention; the other one (male, 62 yrs old) with multivessel coronary disease died for acute pulmonary edema on

day 8. At the 11 ± 3 months follow-up 12 pts were alive without new hospitalization. The CT-scan showed residual endoleak type 1 in one (8%) and persistent false lumen retroperfusion in 3 pts (25%) without any prosthesis migration or rupture.
Conclusion: Our results indicate that the endovascular treatment of acute thoracic aortic dissection is technically feasibile with a relatevely low moratlity and morbidity rates. In these patients a careful clinical-instrumental follow-up is necessary to recognize and treat potentially delayed complication.

P1261 Advantages of endovascular AAA repair in elderly patients at very high surgical risk

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Background: The mortality rates of surgical treatment of Abdominal Aortic Aneurysms (AAA) in elderly patients (pts)with significant comorbidities still range between 6% and 14%. Aim of this study was to investigate whether endovascular treatment(EVT) of AAA is a safer procedure in such pts.
Methods: Fifty-nine patients with AAA were divided in two groups, a group of 29 pts (28 males; mean age = 70.46±5.36 yrs) underwent endovascular treatment (EVT Group) and the other (30 males; mean age=67.73±6.05 yrs) underwent open surgery (OS Group). The EVT Group had more comorbidities and a very high surgical risk score (See Table 1). They were considered fit to endovascular treatment if they showed a suitable anatomic morphology at CT-scan and angiography. All pts were followed during hospitalization(H) and up to 12 months. They underwent a CT-scan 2 weeks, 6 months and 12 months after discharge.
Results: The one month mortality was 0% in EVT Group vs 13.33% in OS Group ($p<0.05$). Four pts of OS Group died because of treatment-related organ dysfunctions. The mean hospitalization length was 7.5±2.4 vs 12.9±3.6 days ($p<0.05$). At 6 month follow-up(F-UP) two pts of EVT Group affected by trivessel CAD had a sudden death. One patient of EVT Group had a type II endoleak at 12-month CT-scan. At 12 month F-UP reintervention rate was 0% in EVT group vs 15.4% in OS group(p= 0.02). The total 12 month mortality was 6.9% in EVT group vs 23.3% in OS group(p=0.07). The 12 month AAA-related mortality was 0% in EVT vs 16.7% in OS group($p< 0.02$)

	EVT group	OS group	p
Hypertension	19 (65%)	11 (37%)	<0.05
Dyslipidemia	18 (62%)	10 (33%)	<0.05
Diabetes	10 (34%)	4 (13%)	<0.05
COPD	15 (51%)	15 (50%)	NS
Renal failure	9 (11%)	2 (7%)	0.01
CAD	22 (76%)	17 (56%)	NS
Heart failure	15 (52%)	6 (20%)	<0.01
Max diameter	68.48±10.54	65.80±15.74	NS
ASA Class IV	21 (73%)	6 (20%)	<0.01

Conclusions: EVT of AAA in elderly pts at very high surgical risk is safer and less invasive. It is associated with a significant lower rate of early mortality and reintervention, a shorter H length and an increased 12 month survival.Table 1

P1262 Chronic aortic dissection: surgical experience during a 20 year period

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The purpose of this study is to report our experience in the surgical management of patients with chronic aortic dissection over the last 20 years.
Methods: From January 1981 to December 2001, 156 patients (108 men, 48 women, mean age 51,1 years) underwent surgery for chronic aortic dissection; 28 had a Marfan syndrome. Dissections involving the ascending aorta were considered to be type A (N= 121) and these without ascending aorta involvement were considered to be type B (N = 35). In group A, ascending aorta only was involved in 50 patients, ascending aorta and arch in 39 patients, the whole aorta in 32 patients. Forty patients had a previous ascending aorta aneurysm; 54 had a previous cardiac surgery; 21 had a pseudoneurysm of the ascending aorta; the mean interval between the two operations was 7,4 years.
Coronary artery diseased occurred in 12 patients. Statistical analysis was performed using SAS software. In group A, separate valve replacement, composite valve graft with reimplantation of coronary arteries by an 8 mm Dacron graft, or directly into the graft were used. When aortic arch reconstruction was needed, partial circulatory arrest and antegrade selective cerebral perfusion were used. Eight patients underwent a total replacement of the aorta. In group B, either derivation with occlusion of the isthmus, or resection and graft replacement were used.
Results: The operative mortality rates were 17,3% for all the patients, 15% in group A, 25,7% in group B. Uni and multivariate analyses showed pseudoaneurysm, extension of the dissection, operation for type B dissection were independent predictors of operative mortality. These factors were also predictors of late mortality. Actuarial survival rates including early mortality were at 8 years 50 ± 10% for group A and 30 ± 5% for group B. But it was 60% at 8 years for the patients with involvement of the ascending aorta only.
Summary: In summary extension of the dissection, pseudoaneurysms and operative management of type B dissection are predictors of operative and late mortality which remains high, and unchanged these last years.

P1263 Increased incidence of coronary artery ectasias in patients operated for ascending aortic aneurysms

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Objectives: Coronary artery ectasia (CAE) is associated with ectasia elsewhere, specifically of the abdominal aorta, up to 20.8% and of the peripheral arteries, veins and pulmonary artery. The aim of the present study was to evaluate the incidence of CAE in patients with aneurysms of the ascending aorta.
Methods: We retrospectively studied the coronary arteriograms of 82 patients (57 males, 63±15 years old and 25 females, 67±12 years old) who underwent planned surgical repair of an ascending aorta aneurysm and an age-matched control group of 92 consecutive patients (69 males, 63±13 years old and 23 females, 66±16 years old) who underwent coronary arteriography during the same period. CAE was defined, according to the established criteria, as a local or diffused coronary dilatation that exceeds the diameter of the angiographically apparently normal adjacent segments by a factor greater than 1.5.
Results: The baseline demographic characteristics (smoking habits, blood pressure, heart rate, etc) were similarly distributed in both groups, by the exception of the history of aortic valvular disease (pts: 90% vs. controls 16%, $p<0.001$). The incidence of CAE was 21 (26%) among patients and 5 (5.4%) among the controls (p=0.001). Multivariate logistic regression analysis revealed that presence of CAE 5-fold (odds ratio =5.2, $p<0.001$) the likelihood of having ascending aorta aneurysm, after controlling for several confounders. Obstructive coronary lesions were documented in 21 (26%) subjects in the group with ascending aorta aneurysms, and in 67 (73%) in the control group (p=0.003).
Conclusions: To the best of our knowledge we revealed for the first time that CAE commonly exists with aneurysms of the ascending aorta. It presents with the same frequency seen in abdominal aortic aneurysms. It could be suggested that both processes share common physiopathologic mechanisms, such as increased proteolytic activity of the arterial wall. This may explain the lower incidence of obstructive lesions in this category of patients, as compared to controls.

P1264 The comparison of separate stent-graft and conventional stent-graft for the endovascular treatment of chronic type B aortic dissection

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Purpose: The separated stent-graft is a newly designed device that reduces the profile of the stent, allowing the introduction through a 12F sheath while the special design minimizes stent migration during deployment. In this study, we wanted to compare the immediate and midterm outcomes of separated stent graft with those of the single piece conventional stent-graft.
Methods: Retrospective analysis was done on 35 patients diagnosed with chronic type B aortic dissection, specifically thoracic aortic dissection, who underwent endovascular stent-graft deployment at our institute from September of 1997 to April of 2003. The indications were dynamic obstruction, aortic diameter of 6cm or more, continous false lumen leakage and progression of dissection despite adequate medical treatment. Seventeen patients underwent separated stent-graft deployment(Group I) while eighteen patients underwent conventional stent-graft deployment.(GroupII) Results: Twelve males and five females at an average age of 58.8±11.6 underwent separated stent-graft deployment while ten males and eight females at an average age of 56.1±12.8 underwent conventional stent-graft deployment. Angiographic success, defined as deployment resulting in complete coverage of the entry tear without any significant endoleak, was achieved in 13/17(76.5%) for group I and 12/18(66.7%) for group II.(p = 0.521) Clinical success, defined as the complete obliteration or complete thrombosis formation of the false lumen at followup, was achieved in 12/17(70.6%) for group I and 11/18(61.1%) for group II.(p=0.555) Clinically significant type I endoleaks were evident at followup in 3 patients for group I and 3 patients for group II. There were 2 cases of distal stent graft migration and 2 vascular access site complications for group II where as group I had no such findings. Except for 2 patients in group II who were lost to followup, all the other patients are currently alive and being followed up at our outpatient clinic.(19.5±11.6months for group I and 34.2±21.5months for group II.) Conclusions: The use of the separated stent-graft minimized vascular access site complications and was absent of stent migration without the need for vigorous blood pressure reduction during the deployment. Also, the immediate and midterm results were comparable to the conventional stent-graft suggesting the possible usefulness of this device for the treatment of thoracic aortic dissection.

P1265 Therapy and clinical outcome of postsurgical aneurysm formation after surgical correction of aortic coarctation

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Objectives: To investigate the postoperative outcome of aneurysm formation after surgical correction of aortic aneurysm. Background: Aneurysm develop in 9% late after corrective surgery of coarctation of the aorta with a 36% mortality if left untreated. Treatment and postprocedural long-term results, however, are unknown.
Methods: Of 25 cases of aortic aneurysm requiring corrective surgery 152±78 months after initial coarctation repair 8 were located in the ascending aorta (type A) and 17 at the site of previous repair (local type). Average diameter was 88 ± 31mm for type A aneurysm and 56±18 mm for local type (p = 0,003). All aneurysm were resected and synthetic graft was interponed.
Results: Emergency surgery was indicated in 37% for type A aneurysm and 23% for local type (p = 0,64). There was one early postoperative death for local type compared with no death for type A aneurysm (p=0,48). Cardiovascular events including aortic valve insufficiency, reformation of aortic aneurysm, subdural hemorrhage and acute coronary syndrome, occurred in seven patients (28%). Event free interval was 104 month (confindence interval 70-135 month). Kaplan-Meyer analysis revealed a trend for higher incidence of postoperative cardiovascular events for type A aneurysm (p=0,08).
Conclusions: Patients after resection of aneurysm after surgical correction of aortic coarctation were at high risk for cardiovascular events.

P1266 Aortic valve calcifications and coronary atherosclerosis

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Aim of study: Assessment between aortic valve calcifications and severity of coronary atherosclerosis in patients before aortic valve replacement.
Methods: Study group consists of 74 patients - 52 men and 12 women, 60,5 (+10,7) years old with aortic valvular stenosis (transvalvular maximal gradient above 50 mmHg). In all patients scrupulous anamnesis was performed including atherosclerosis risk factors as a: hypertension, dyslipidemia, diabetes, smoking, cardiovascular diseases in near family. In study group the following biochemical parameters were measured: total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, white blood cells and serum creatine. All patients were undergone transthoracical echocardiography and selected parameters were recorded as: LVEDd, IVSDd, LVPWDd, LA, EF, FS, SV, EDV, maxAo gradient, aortic valve calcifications. Consequently coronary angiography in multiple views was performed with standard Judkins and Sones technique.
Results: Occurrence of significant stenoses in coronary arteries was significantly greater in patients with severe aortic valve calcification compared to persons with small or without calcifications (45% vs. 23%; p<0,05). Total cholesterol level was higher in patients with coronary atherosclerosis than in those without changes in coronary vessels - 241,7 (+46,0)mg% vs. 205,5 (+41,6)mg%; p<0,05. Similarly LDL-cholesterol concentration was greater in patients with than without significant atherosclerotic changes in coronary arteries - 159,3 (+27,9)mg% vs. 130,9 (+35,9)mg%; p<0,05. Patients with severe aortic calcification characterized higher level of LDL-cholesterol compared to those with only small calcium deposits of the aortic valve - 148,3 (+38,0)mg% vs. 128,0 (+21,4)mg%; p<0,05.
Conclusions: Aortic valve calcifications correlate with coronary atherosclerosis. Severity of aortic valve sclerosis similarly to more often occurrence of significant coronary artery disease is associated with higher cholesterol concentrations. This observations may suggest statin treatment as possible retardation of progression both coronary atherosclerosis and aortic valve sclerosis.

P1267 Impairment of ventilatory parameters in patients with severe aortic valve stenosis and pulmonary hypertension

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Background: Severe aortic valve stenosis (AS) often coincides with secondary pulmonary hypertension (PH). In this study, the influence of PH on ventilatory parameters in pts with severe AS was examined.
Methods: 169 pts (70 ± 9 y., 102 m) with isolated severe AS (invasive mean aortic pressure gradient > 45 mmHg) were studied by left and right heart catheterization and bodyplethysmography. PH was defined as mean pulmonary artery pressure > 25 mmHg.
Results: 30 pts (18%) had a history of chronic obstructive pulmonary disease and 64 pts (38%) were smokers or ex-smokers. In 52 pts (31%) FEV1 was < 75% of normal values. PH was found in 71 pts (42%) with a mean pulmonary artery pressure of 33 ± 7 mmHg. In pts with and without PH the mean aortic pressure gradient (52 ± 20 mmHg each, n.s.) and the aortic valve opening area (0.9 ± 0.3 cm^2 each, n.s.) were comparable. AS pts with PH showed a reduced vital capacity (83 ± 17% vs. 90 ± 16% of normal values, p < 0.05) and a reduced FEV1 (81 ± 20% vs. 90 ± 19%, p < 0.05) compared to pts without PH. The functional residual capacity and residual volume were not different in both groups. Mean exspiratory flow at 25% (53 ± 34% vs. 61 ± 38%, p < 0.05) and 75% (73 ± 30% vs. 82 ± 27%, p < 0.05) of the exspiration time was lower in PH pts. In pts with PH, the flow-volume-diagram characteristically showed signs of "small airway disease".
Conclusions: Pts with severe AS often show impaired ventilatory parameters. PH in severe AS leads to an additional impairment of ventilatory parameters and a "small airway disease". This should be taken into account in the preoperative evaluation of pts with severe AS with regard to the pulmonary risk and potential perioperative pulmonary complications.

P1268 The prevalence of left ventricular systolic dysfunction in patients with chronic non-ischaemic mitral regurgitation

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Background: Chronic severe mitral regurgitation (MR) leads to left ventricular systolic dysfunction and irreversible myocardial damage. Doppler echocardiography provides an accurate non-invasive method for quantitative assessment of the severity and complications of MR. Early left ventricular contractile dysfunction, reversible after surgical intervention, develops when the ejection fraction remains normal and patients are asymptomatic, so an additional index of systolic performance should also be used. Dp/dt is a parameter determining the isovolumic phase of cardiac function.
The present study aimed to evaluate the efficacy of Doppler-derived dp/dt in predicting outcome in patients with chronic severe MR.
Material and methods: 81 patients (58 M, 23 W) with chronic non-ischemic MR (from 3+ to 4+ grade; aged 30 - 76; mean 56±10.8 years), were enrolled into the present study. The echocardiographic measurements were taken in compliance with the guidelines of the American Society of Echocardiography. The ejection fraction (EF) was calculated using the modified biplane Simpson's method. The quantification of mitral regurgitation was performed using the PISA method and vena contracta width (VCW) measured by colour flow Doppler. The index dp/dt was obtained from the continuous-wave Doppler spectrum of mitral regurgitant jet.
Results: Fifty-seven patients among 81 were asymptomatic, the remaining symptomatic 24 patients underwent surgical intervention. The follow-up spanned 6 - 32 months, mean 22±5.7. The mean effective regurgitant orifice area - 0.46 ± 0.19 cm^2, regurgitant volume - 54.10 ± 27.78 ml, vena contracta width - 9.35 ± 2.83 mm, dp/dt 1006 ± 385 mmHg/s, were reported. All symptomatic patients had depressed contractility - EF < 60% and dp/dt <1200 mmHg/s. In the group of asymptomatic patients, 30 (52.6%) had normal systolic function - EF >60% and dp/dt > 1200 mmHg/s, 27 patients (47.4%) also had EF >60%, but a decreased dp/dt index < 1200 mmHg/s.
Conclusions: In patients with chronic MR and preserved ejection fraction the decreased values of dp/dt revealed the early contractile dysfunction. Among the asymptomatic patients the values of dp/dt < 1200 mmHg/s identified the subgroup of patients who should best be referred to a prompt surgical intervention.

P1269 Multiple episodes of infective endocarditis

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Introduction: Infective endocarditis is not necessarily an isolated episode. Further episodes may involve the same or different valves. They are defined as relapse or reinfection according to microbiological and chronological parameters.
Objective: To study the unique features of patients with a second or further episodes of infective endocarditis (IE).
Methods: We analysed 310 consecutive episodes of lef-sided infective endocarditis. All of them were definite episodes according to Duke criteria. For each episode, epidemiological, clinical, microbiological, echocardiographic, therapeutic and prognostic data were assessed.
Results: There were 24 patients (pt) (7.7%) with multiple episodes of IE (group-gr- I) and 286 pt (92.3%) with only one episode (gr II). Among pt with multiple episodes, 4 were relapses and 20 were reinfections (median time, 2 years, range 1 to 70). One pt had four ep and other pt had three ep. Two pt (8.3%) were intravenous drug abusers. The incidence of prosthetic endocarditis was higher in gr I (75% vs 32.9%, p<0.001). Pt were ≥ 65 years in 20.8% of gr I and 43.4% of gr II, p=0.03. Clinical data (including symptom duration until admission, and clinical presentation form) were similar for both groups. There were no differences regarding the microbiological pattern. But in 25% of pt of gr I, vs 10.5% of gr II, the causative microorganism could not be isolated, p= 0.03. Detection of vegetations by transthoracic (TTE) or transesophageal (TEE) echocardiography was equal for both groups. Vegetations were ≥ 10 mm in 56.3% vs 77.4%, respectively, p=0.05. Aortic prosthetic infection prevailed in gr I (45.8% vs 16.8%, p=0.002), and mitral native involvement was more frequent in gr II (20.8% vs 44.6%, p= 0.02). Periannular complications were more common in gr I (50% vs 29%, p= 0.03). Embolisms were more rare in gr I (12.5% vs 30.8%, p=0.05). The frequence

of heart failure was similar, p=0.42. Cardiac surgery was equally common in both groups, p=0.89. Mortality rates were similar: 33.3%, gr I, and 33.9%, gr II, p =0.95.
Conclusions: Patients with multiple episodes of infective endocarditis, compared to those suffering only one episode, 1) The prevalence of prosthetic endocarditis is higher. 2) The causative microorganism more frequently remains unidentified. 3) Vegetation size is smaller and embolisms are less frequent. 4) Periannular complications are more frequent. 5) Surgical approach remains as frequent as in isolated episodes. 6) Mortality rates are similar.

P1270 Restrictive annuloplasty and coronary revascularization in ischaemic mitral regurgitation results in reverse left ventricular remodelling

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Background: Data on combined CABG and restrictive annuloplasty in patients with ischemic cardiomyopathy are scarce, and the effect on reverse left ventricular (LV) remodeling is unknown.
Methods and Results: 51 patients with ischemic LV dysfunction (LV ejection fraction 31±8%) and severe mitral regurgitation (grade 3-4+) underwent CABG and restrictive annuloplasty with stringent down-sizing of the mitral annulus (by 2 sizes, Physioring, mean size 28±2). Serial transthoracic echocardiographic studies were performed (before surgery, within 3 months and 1.5 years after surgery), to assess mitral regurgitation, transmitral gradient, leaflet coaptation and left atrial and LV reverse remodeling. Clinical follow-up (NYHA class, survival, events) was assessed at 2-year follow-up.
Early operative mortality was 5.6%; at 2-year follow-up all patients were free of endocarditis and thrombo-embolism, and 1 needed re-operation for recurrent mitral regurgitation; 2-year survival was 84%. NYHA class improved from 3.4±0.8 to 1.3±0.4 (P<0.01) with all patients in class I/II. Intra-operative transesophageal echo showed minimal (grade 1+) mitral regurgitation in 8 patients and none in 43, without stenosis. Leaflet coaptation was 0.8±0.2 cm. These values remained unchanged; all patients had no or minimal (grade 1+) mitral regurgitation at 2-year follow-up. LV end-systolic and end-diastolic dimensions decreased from 51±10 to 43±12 mm (P<0.001) and from 64±8 to 58 ±11 mm (P<0.001). LA dimension decreased from 53±8 to 47±7 mm (P<0.001).
Conclusion: Excellent results of combined restrictive annuloplasty and CABG were obtained; residual mitral regurgitation was absent/minimal at 2-year follow-up, associated with a significant reduction in left atrial dimension and LV reverse remodeling.

P1271 Why angina in aortic valvular stenosis?

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The aim of the study was to analyze the factors contributing to the development of anginal pain common in patients with aortic valvular stenosis.
Methods: The study included 74 consecutive patients, aged 60,5 (+10,7), with severe acquired valvular aortic stenosis (maximum systolic pressure gradient above 50 mmHg). The history of angina and its severity according to CCS classification and of common atherosclerosis risk factors was taken. The laboratory tests included: lipidogram, white blood count, creatine. The transthoracal echocardiography (TTE) data were collected: LVEDd, IVSDd, LVPWDd, LAd, EF, SF, SV, EDV, ESV, maximum systolic transvalvular pressure gradient and degree of aortic insufficiency. Coronary angiography was than performed with standard technique. Haemodynamic protocol involved LVEDP, PCWP, CO, PASP, aortic pressure gradient,aortic insufficiency evaluation.
Results: Patients with severe anginal symptoms (CCS III/IV) were older (66,5 (+6,2)years vs. 58,8 (+11,1)years; p<0,05), had higher LDL cholesterol (161,0 (+39,5)mg% vs. 137,8 (+31,7)mg%; p<0,05) and triglycerides (153,1 (+66,5)mg% vs. 102,0 (+34,7)mg%; p<0,05) level, more often had obesity (31,2% vs. 12,1%; p<0,05) and positive family history of ischemic heart disease (IHD) – (25,0% vs. 5,2%) than patients with mild (CCS I/II) or without symptoms. They had also higher number vessels with significant stenoses (1,0 (+1,03) vs. 0,5 (+0,86); p<0,05), which most frequently presented in left anterior descending artery. The maximum systolic pressure gradient according to TTE (85,1 (+29,0)mmHg vs. 77,2 (+29,4)mmHg; p<0,05) and according to invasive measurements (75,7 (+24,9)mmHg vs. 57,7 (+31,8)mmHg; p<0,05) were also higher in symptomatic patients. The interventricular septum measured using TTE was thicker in patients with severe anginal symptoms than in patients with mild or without symptoms (1,63 (+0,22)cm vs. 1,51 (+0,27)cm; p<0,05).
Conclusion: The frequency of anginal symptoms in patients with severe aortic valvular stenosis is higher than actual frequency of significant coronary stenosis on angiography. Angina if more common in a subgroup with coronary stenoses than in patients without coronary heart disease and the severity of anginal symptoms correlates with the number of coronary arteries involved. The severity of angina also correlates with the maximum pressure gradient across the aortic valve and the thickness of interventricular septum. In the study group hypercholesterolaemia, obesity and positive family history of IHD were more often found in patients with severe (CCS III/IV) symptoms.

P1272 Plasma levels of brain natriuretic peptide and symptoms in elderly patients with aortic stenosis

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Background: The correct assessment of symptoms is very important in elderly patients (pts) with aortic stenosis (AS), but frequently this is difficult due to reduced physical activity underestimating physical impairment. Aim of the present study is to evaluate the relationship between plasma brain natriuretic peptide (BNP) levels and symptoms in elderly pts with AS.
Methods: We studied 64 consecutive pts (35 males; mean age 76±9 years) with AS (aortic valve area: 0.9±0.3 cm^2). All pts underwent independent evaluation of symptoms, transthoracic echocardiography, and measurement of plasma levels of BNP (ADVIA centaur, Bayer). Symptoms were classified according to the NYHA class (NYHA: I=19, II=21, III=13, IV=11 pts).
Results: Mean values of BNP were significantly increased in more symptomatic pts: NYHA I: 105±110, NYHA II: 220±352, NYHA III 290±327, NYHA IV: 1254±849 pg/mL (p<0.001). BNP values were able to identify with good diagnostic accuracy pts in III-IV class (area under the ROC curve =0.78 (95% IC 0.66-0.87; best cut-off =254 pg/mL). BNP levels were also correlated with the severity of mitral regurgitation (MR): MR 0-1/3 (n=43): BNP=184±285; MR 2/3 (n=15): BNP=634±794; MR 3/3 (n=6): BNP=1126±830 pg/mL (p<0.001). In univariate analysis BNP levels were correlated significantly with left ventricular ejection fraction (r=-0.63, p=0.000), end-systolic diameter (r=0.54; p=0.000), end-diastolic diameter (r=0.48; p=0.000), left ventricular mass index (r=0.47, p=0.000), relative wall thickness (r=0.38, p=0.002), age (r=0.33, p=0.007). In multivariate analysis BNP levels were indipendently correlated with 1) ejection fraction, 2) left ventricular mass index, 3) age.
Conclusions: Plasma BNP levels are significantly correlated with symptoms in elderly pts with AS. BNP is also correlated with age, MR and several indices of left ventricular function, in particular ejection fraction and hypertrophy. The measurement of BNP could be useful in these patients for the clinical decision making and the choice of the optimal timing for surgery.

P1273 Does vasodilator therapy delay the need for aortic-valve replacement in chronic aortic regurgitation?

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Vasodilator agents are considered useful in the management of asymptomatic chronic aortic regurgitation (AR). The aim of this study was to assess whether treatment with nifedipine or enalapril really improved the natural history of AR by delaying the need for valve replacement (VR).
Methods and results: Ninety-five consecutive, asymptomatic pts with isolated, chronic, severe AR and normal ejection fraction (EF)were randomized to receive nifedipine 40 mg/day (group 1; n= 32), enalapril 20 mg/day (group 2; n=32) or no treatment (group 3; n=31). The characteristics at baseline of the 95 patients are listed in Table 1. Predetermined criteria for VR were the appearence of clinical symptoms, and/or EF< 50%, EDD≥70 and EDS≥50 mm. Pts were followed-up by a single clinician and a single echocardiographist who was blinded to the therapy administered. Mean follow-up was 7±2 years. No patient was lost. Sixteen patients left the treatment (n=11 group 1; n=5 group 2) because of adverse effects. Thirty-nine patients (41%) needed VR (7 pts due to symptoms, 16 asymptomatic pts fulfilling echo requirements and 16 fulfilling both clinical and echo). Other three patients died, two of them of cardiac cause (1 group 1, 1 group 3; one suddenly and the other of heart failure, both fulfilled surgical criteria but they had refused it. There were not significant differences by actuarial analysis of Kaplan-Meier in the need for VR between groups of treatment (n=12 group 1; n=16 group 2; n=11 group 3). The time to VR was not different in the 3 groups.

Table 1

	Nifedipine n=32	Enalapril n=32	No treatment n=31	p
Age (yr)	44±15	44±10	44±14	NS
Sex (female, male)	7/25	4/28	10/21	NS
EDD (mm)	64±7	68±6	64±5	NS
EDS (mm)	44±5	46±5	44±5	NS
EF (%)	60±7	59±6	59±6	NS

Conclusions: In our 7 years follow-up study, enalapril and nifedipine failed to show a beneficial effect in severe, asymptomatic AR. The role of vasodilators in this condition is questioned by our results.

P1274 Aortic stiffness is associated with the degree of functional mitral regurgitation

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Mitral regurgitation (MR) is strictly related to ventricular afterload. However, the relation between aortic stiffness, which is a main determinant of ventricular afterload, and the quantitatively assessed mitral regurgitation is unknown.

Methods: 105 patients (age 60±15; 75% male) with dilated cardiomyopathy and functional MR was consecutively studied. Left ventricular (LV) volumes and ejection fraction (EF), LV outflow tract stroke volume (SV) were measured. Aortic pulse wave velocity (PWV), a known marker of aortic stiffness, was determined as the time (t) taken by the pulse wave to travel from the descending aorta to the abdominal aorta by Doppler flow recordings and the distance (d) travelled by the pulse wave was measured over the body surface as the distance between the two recording sites. Mitral effective regurgitant orifice (ERO), regurgitant volume (RV) and fraction (RF) were measured by means of proximal isovelocity surface area method.

Results: The mean PWV was 6.3±3.7 m/sec (range: 2.6-25.4). PWV was significantly associated with ERO (r=0.33 p=0.005), RV (r=0.33 p=0.0007) RF (p=0.43 p<0.0001). The degree of volume overload expressed as RF was strongly affected by ERO (r=0.88 p<0.0001), but RF was associated with PWV independently of ERO and EF (p<0.0001 for ERO; p=0.015 for PWV and p=0.02 for EF).

Conclusion: Aortic stiffness is an important determinant of functional mitral regurgitation severity. Aortic stiffness should be considered and important therapeutic target in patients with dilated cardiomyopathy in order to ameliorate both LV function and mitral regurgitation.

P1275 Adverse remodeling in severe aortic stenosis is due to increased myocardial apoptosis

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Background: Aortic stenosis (AS) entails pressure overload of the left ventricle and hypertrophy as adaptive responses. Several structural modifications occur in the pressure-overloaded heart leading ultimately to heart failure (HF). Myocardiocyte loss through apoptosis may be responsible for the progression to HF in severe AS. To this aim we sought to ascertain the in vivo relevance of apoptosis in patients with severe AS and left ventricular hypertrophy (LVH) undergoing valve replacement.

Methods and Results: We prospectively selected 5 patients with LV hypertrophy secondary to isolated aortic stenosis, with preserved systolic function and free from coronary artery disease. After baseline echocardiographic evaluation, myocardial biopsies were obtained from the LV anterolateral free wall during aortic valve replacement surgery and analysed with TUNEL and activated caspase-3 assays for apoptosis. Apoptotic rate (AR) was increased in pressure-overloaded hearts more than 100-fold vs controls (1.2% [0.8-1.4] vs. 0.01%[0.01-0.03], P=0.007). Immunostaining revealed increased bax protein expression in cases in comparison to controls. The AR correlated directly with parameters of adverse remodeling (end-systolic volume) and diastolic dysfunction (increased central venous pressure values, E/A values at transmitral flow pattern).

Conclusions: High apoptotic rate and intense expression of proapoptotic bax protein suggest that apoptosis may play a pivotal role in ventricular remodeling secondary to isolated pressure overload in the human heart and later in the transition from compensated hypertrophy to failure. These findings may provide innovative therapeutic tools in the management of pressure overload-induced HF.

P1276 Coronary atherosclerosis in patients with valvular heart disease

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Clinical data show coexistence of acquired heart disease and coronary atherosclerosis (CA). We analyze the correlation between CA risk factors and the presence of coronary heart disease in patients with different valvular heart disease (VHD).

Methods: 155 consecutive patients aged 58,2±9,7, 101 men and 54 women, hospitalized in years 2000-2002 and referred for invasive studies prior to elective valvular surgery were analyzed. The patients were divided into 4 groups according to the dominant VHD: aortic stenosis (AS) - 47,7%, aortic insufficiency (AI) - 16,8%, mitral stenosis (MS) - 21,3%, mitral insufficiency (MI) - 9,0%. Other 8 patients (5,2%) with combined aorto-mitral VHD were excluded from the study. The history of common atherosclerosis risk factors was taken: smoking, hypertension, diabetes mellitus, family history. The laboratory tests included: lipidogram, white blood count and serum creatine. The transthoracal echocardiography data were collected: LVEDd, IVSDd, LVPWDd, LAd, EF, SF, SV, EDV, ESV, maximum systolic aortic gradient, degree of AI, MVA, degree of MI and presence of valvular calcifications. Coronary angiography was performed with standard technique.

Results: In patients with AS, the atherosclerotic changes in coronary arteries had the same occurrence as in those with AI (36,5% vs. 34,5%; NS). Similarly was, when MS and MI where compared (9,1% vs. 21,4%; NS). In patients with aortic VHD (sum of SA and AI), the atherosclerotic changes in coronary arteries were more frequently detected than in patients with mitral VHD (sum of MS and MI); 36,0% vs 12,8%; p<0,05).

Patients with aortic VHD were older (59,3 + 10,5years vs. 55,9 + 7,8years; p<0,05), usually male (74% vs. 46%; p<0,05), had higher total cholesterol level (219,9 +47,8mg% vs. 199,7 +39,4mg%; p<0,05) and more frequently suffered from anginal symptoms (1,47 +1,08CCS class vs. 0,51 +0,83 CCS class; p<0,05) than patients with mitral VHD. In the latter group there were a higher percentage of women and the symptoms of congestive heart failure were more common (2,34 +0,7NYHA degree vs. 2,03 +0,69NYHA degree; p<0,05).

Conclusion: The frequency of CA is more often among patients with aortic VHD than in patients with mitral VHD. Aortic VHD is often associated with older age, male sex and higher serum total cholesterol level. The higher distribution of atherosclerosis risk factors among patients with aortic VHD may suggest common etiological pathways of both diseases. The elevated serum cholesterol and the presence of significant coronary stenoses may imply routine statin treatment in this group.

AORTIC INTERVENTIONS

1277 Do we need to stent discrete coarctation of the aorta? Coarctation angioplasty in 49 patients with discrete coarctation, 16 years follow-up results

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The immediate and intermediate term results of balloon angioplasty (BA) for patients with aortic coarctation (AC) have been encouraging. The long-term results have not been well characterized.

Methods: Follow-up data of 49 pts (mean age 22 7 years) undergoing BA for discrete AC at median interval of 10.2 years (range 1-16 years) including cardiac catheterization, MRI, and Doppler echocardiography form the basis of this study.

Results: No early or late deaths occurred. BA produced a reduction in peak AC gradient from 66 23 mm Hg to 10.8 7 mm Hg (P< 0.0001). Follow-up catheterization 12 months later revealed a residual gradient of 6.2 6 mm Hg (P<0.001). Four patients (7.5%) with suboptimal initial outcome with peak gradient > 20 mm Hg had successful repeat angioplasty in 3 pts, one pt underwent surgery. Aneurysm developed at the site of dilation in 4 pts (7.5%). MRI follow-up results revealed no new aneurysm or appreciable changes in the size of preexisting 3 aneurysms and one pt underwent surgical repair. No recoarctation was observed, no appreciable changes in the Doppler gradient across the AC site were noted. The Doppler gradient across coarctation decreased from 57.6 17 to 16 8.4 mmHg at one year and 13.0 6.9 mmHg at last follow-up. The blood pressure had normalized without medication in 31 (63%) of the 49 patients.

Conclusion: (1) Long-term results of BA for discrete AC are excellent and should be considered as first option for treatment of this disease; (2) Remodeling of the aorta was observed over the years in young pts; and (3) Stenting is not indicated in discrete coarctation.

1278 Immediate changes in global and regional left ventricular systolic function after percutaneous heart valve implantation for symptomatic aortic stenosis

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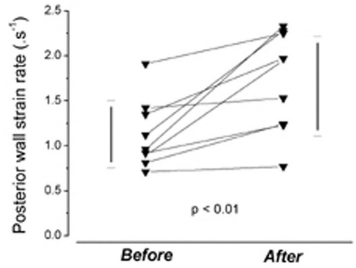
Background: The newly developed percutaneous heart valve (PHV) implantation technique decreases transaortic pressure gradient in patients with aortic stenosis. PHV replacement effects on left ventricular (LV) global and regional systolic function are currently unknown.

Methods: 8 patients with severe aortic stenosis had 2D echocardiography at baseline and 24 hours after PHV implantation to evaluate changes in LV volume, and LV ejection fraction. Regional function, i.e. systolic posterior wall velocity (Sv) as well as systolic posterior wall strain (Ss) and strain rate imaging (Ssri) was assessed by tissue Doppler imaging from a short axis view.

Results: At 24 hours, a significant reduction in transaortic mean pressure gradient (from 46 ± 15 to 8 ± 3 mm Hg; P<0.0001) was accompanied by an increased in aortic surface area (from 0.59 ± 0.11 to 1.69 ± 0.11 cm^2; P<0.0001). LV end-diastolic volume remained unchanged (102 ± 36 to 101 ± 11 mL; P = ns) whereas LV ejection fraction was improved (48 ± 18 to 56 ± 12%; P < 0.01). Obvious enhancement in regional LV displacement (Sv increased from 2.2 ± 0.5 to 4.6 ± 0.9 cm.s-1; P < 0.001) and deformation (Ssri increased from 1.0 ± 0.25 to 1.72 ± 0.57 s-1, P < 0.01, figure and Ss increased from 11 ± 5 to 18 ± 9%; P < 0.05) were evidenced.



LV deformation and PHV implantation.

Conclusions: Immediately after PHV replacement, improvement of LV global and regional systolic function was observed.

1279 Stentgraft implantation in thoracic aorta – actual results and euroscore risk stratification scale

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Objective: Aim of the study was to compare the actual complications and mortality rate with risk predicted by EUROSCORE risk stratification scale.
Materials and methods: Since January 2002 23 patients were proposed an endovascular treatment of descending thoracic aorta. In the group there were 5 women and 18 men, mean age was 51,14±13 years. Eight patients were treated due to chronic posttraumatic aneurysm, four were with atheromatous aneurysm, nine with dissection (Type B Stanford), one with intramural hematoma, one with aneurysm that developed 28 years after treatment of coarctation of aorta. Patients' risk of complication was calculated using an EUROSCORE risk scale.
Results: All patients were successfully discharged from hospital after 9±2 days (procedure time 2,5±0,4 h). One patient had stentgraft displacement, that was treated with additional stentgraft implantation. There were no neurologic complications. All the patients were in high or medium risk according to EUROSCORE.
Conclusion: EVAR is mini invasive procedure that offer low mortality and risk of serious complications, allows for shortening of hospital stay.

1280 Transluminal endovascular graft placement with INOUE stent graft for thoracic aortic aneurysms and dissections

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Background: Transluminal Endovascular Graft Placement (TEGP) has limitation in managing severe bend or side branches of the thoracic aortic lesions. The feasibility and efficacy of TEGP with Inoue stent graft(SG) for treatment of thoracic aortic aneurysms and dissections was investigated.
Methods: From Aug.1997 to Feb. 2004, we performed TEGP with Inoue SG in 48 patients(pts.) and 48 cases(mean age, 70years). Thirty five pts.(74%) were very high risk for open repair or good candidates for TEGP. The cases consist of 1 ascending, 3 arch, 19 distal arch, 8 descending, 17 dissecting. Thirteen of the cases had straight, 20 had single branched, 8 had dual branched, 7 had triple branched grafts.
Results: In all cases but one, SGs were implanted successfully to the intended sites. There was only one early death because of cerebral infarction in thrombus-rich distal arch aneurysm case. The other major complications were 2 major stroke, 3 minor stroke, 1 supra-mesentric artery embolism and 2 paraparesis. After Oct. 2001, there were no death and major stroke by using detachable filters and reduction of sheath size. The mean follow-up was 27 months (range, 1-63 months). Two dissecting cases had persistent endoleaks needed re-TEGP after 6 months and 3 years. One distal arch aneurysm patient had late type I endoleak after 3 years and underwent surgical repair.
Conclusions: Inoue SG can be used in many types of thoracic aortic aneurysms and dissections involving major branches of aortic arch or having severe bend and is especially useful for high risk pts.