Day 2

Sunday 31 August 2003

THE CUTTING EDGE IN POSITRON EMISSION TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

103 Insulin-stimulated ^{18}F-fluorodeoxyglucose uptake is delayed in GLUT4-deficient mice hearts

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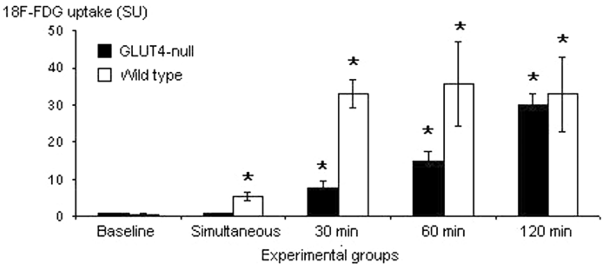
Purpose: This study investigated the time course of insulin-stimulated myocardial glucose uptake (MGU) in transgenic mice with ablation of GLUT4, the predominant insulin-responsive glucose transporter, using ^{18}F-2-Deoxy-2-fluoro-D-glucose (FDG).
Methods: MGU was studied in GLUT4-null (G4N, n=50) and wild-type (WT, n=51) mice using FDG in-vivo by positron emission tomography (PET) imaging and in-vitro using tissue biodistribution (BIO). Time course of MGU was assessed by time-variable injections of glucose (1g/kg)+insulin (8U/kg) and FDG (40μCi): simultaneous injection, 30-, 60-, and 120-minute delay. MGU was also evaluated in isolated perfused hearts under short-term (30 minutes) and long-term (60 minutes) insulin administration.
Results: At baseline, PET showed comparable MGU, in G4N (0.66$\pm$0.12) and WT (0.67 $\pm$0.11), p=0.7. After simultaneous injection WT showed a 3.5-fold increase in MGU (2.45$\pm$0.45, p=0.03) while G4N presented no significant increase (1.11$\pm$0.24). After 60 minutes MGU was comparable in G4N (3.19$\pm$0.60) and WT (2.66$\pm$0.47). BIO results (illustration, * = p$<$0.05 in comparison to baseline), confirmed the lack of an increase in MGU early after insulin in G4N (0.81$\pm$0.23) in contrast with a 10-fold increase in WT (5.29$\pm$1.04, p=0.03). G4N exhibited a delayed response to insulin achieving values comparable to WT after 120 minutes (29.9$\pm$3.0 and 32.9$\pm$10.1, respectively). A comparable late response in MGU in G4N was obtained in isolated heart preparations.



Time course of myocardial ^{18}F-FDG uptake

Conclusions: Despite the absence of GLUT4, G4N increase myocardial glucose uptake in response to insulin with a delayed time course. Increased GLUT1 translocation or expression of one or more of the new GLUTs mediate this compensatory mechanism.

104 Decreased left-ventricular function in experimental diabetes associated with beta-adrenergic receptor down regulation assessed by positron emission tomography

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Objectives: The presence of cardiac autonomic neuropathy (CAN) in diabetes is associated with a striking increase in cardio-vascular morbidity. Although in diabetes the association of CAN and myocardial sympathetic denervation has been clearly demonstrated, the potential alteration of cardiac beta-adrenergic receptor (BAR) density and its potential consequences on cardiac function remain unclear. The purpose of this study was to evaluate in a minipig model the effects of diabetes on left ventricular (LV) BAR density by Positron emission tomography (PET) and on cardiac contractile function by echography.
Methods: In 10 male minipigs (Yucatan, 8-9 months old), diabetes was induced by 2 intravenous injections of Streptozotocin 50 and 55 mg/kg); 6 other pigs served as control group (CG). BAR concentration was determined in all pigs 6 months after diabetes induction in the LV myocardium using PET according to a previously validated technique. We used C-11 labeled CGP 12177 as a ligand and a modeling approach based on a modified graphical method applied on myocardial PET time-activity-concentration-curves obtained using a 2-injection protocol.
Results: The protocol injection of STZ used in this protocol induced a stable and long lasting hyperglycemia in 7 pigs (diabetic group=DG) while 3 other pigs (diabetes-escaped pigs:DEG) showed a progressive recovery after 1 month of hyperglycemia, their glycemia being similar to that of controls at 6 months. Diabetes decreased myocardial BAR density (15.6 $\pm$ 4.0 vs. 20.8 $\pm$ 4.6 pmol/ml, DG vs. CG, respectively, p$<$0.05). This effect did not appear imputable to STZ since DEG did not show any alterations of BAR density (19.2 $\pm$ 4.4, p=NS). The alteration of BAR density in myocardium was heterogeneous, the most important decrease in BAR being found in antero-apical area (p$<$0.05). Cardiac function analysis by echography showed a 15% decrease in LVEF (p$<$0.001), and a 10% increase (p$<$0.01) in LV-end-diastolic volume while LV mass remained unaltered.
Conclusions: In minipigs, chronic hyperglycemia decreases the density of BAR, especially in the anterior wall, and leads to impaired LV contractile function. These alterations may contribute to the observed increase in mortality diabetes associated with CAN.

105 The effect of biventricular pacing on myocardial function and oxidative metabolism in severe dilated cardiomyopathy

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Purpose: Biventricular pacing is a recently discovered technique to treat patients affected by heart failure and with a desynchronised ventricular activation and it has beneficial effects on left ventricular function. The aim of the study was to investigate the effects of biventricular pacing on global and regional left ventricular function and oxidative metabolism in patients with severe dilated cardio-myopathy.
Methods: Ten subjects with end-stage heart failure and dilated cardiomyopathy (NYHA III, LVEF $<$35%, LBBB + QRS $>$140-150 ms) and previously installed biventricular pacemaker were investigated. The patients were studied pacemaker ON and OFF (at least 1 day before the studies) on separate days. All medication was withdrawn 2 days beforehand. Left ventricular function was measured using doppler echocardiography. LV oxidative metabolism was measured using positron emission tomography and monoexponential clearance rate of [11C]acetate (kmono). On the study day when pacemaker was OFF [11C]acetate study was performed also during low dose dobutamine infusion (5-10μg/kg per min).
Results: Biventricular pacing enhanced global LV stroke volume significantly (from 621$\pm$5 to 72$\pm$18 mL, p$<$0.05). Similar effect was seen by dobutamine infusion (to 74$\pm$24 mL, not statistically significant, p=0.24). Global LV oxidative metabolism (Kmono) was unchanged by pacing (0.047$\pm$0.01 to 0.49$\pm$0.01, ns.). In contrast, dobutamine infusion induced significant increase in Kmono values (to 0.063$\pm$0.01).
Regional results: The anteroseptal Kmomo was significantly higher as compared to other myocardial regions when pacing was OFF. Pacing normalised anteroseptal Kmono and due to simultaneous enhancement of LV function myocardial efficiency was enhanced by 22% in the anteroseptal regions of LV.
Conclusions: Biventricular pacing improves LV function in the patients with severe dilated cardiomyopathy. This improvement is not accompanied with increased oxidative demand in contrast to the effects of dobutamine. The work efficiency is improved and increased anteroseptal oxidative metabolism is normalised by biventricular pacing. Biventricular pacing appear to have energetically favorably effects on myocardial oxidative metabolism in patients with heart failure and desynchronised ventricular activation.

106 In vivo quantification of absolute perfusion in mice with myocardial infarction by spin labelling magnetic resonance imaging

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Background: To date, quantification of perfusion in mice has been performed by invasive techniques only. Aim of this work was to establish the quantification of the absolute perfusion in the murine myocardium in vivo by MRI and apply it to mice with myocardial infarction (MI).
Methods: All experiments were performed at 7 T with a home built optimized coil combination. Using spin labelling, assessment of perfusion is based on the quantification of T1 after slice-selective and global spin inversion in separate acquisitions. T1 mapping was performed by ECG-triggered inversion recovery snapshot FLASH with adiabatic hyperbolic secant inversion pulse. Imaging parameters: FOV 30 mm x 30 mm, matrix size 64 x 64 with zerofilling to 128 x 128, slice thickness 2 mm. Cine MRI was performed for determination of LV mass, volumes and MI size: slice thickness 1 mm, echo-time 1.2 ms, resolution 230 μm. Sham operated (N=11) and infarcted (N=7) NMRI mice were anesthetized with isoflurane. MI was induced by ligation of the left coronary artery four weeks prior MRI.
Results: Average perfusion was 701 $\pm$ 53ml/100g*min in sham at a heart rate of 442 $\pm$ 25 beats per minute. Mice with MI showed significantant reduction of perfusion in the infarcted areas to values below 15% of healthy myocardium. Perfusion in the remote areas was decreased as well (476 $\pm$ 81ml/100g*min, $p<0.05$ vs. sham). LV mass was increased after MI (sham 92.8 $\pm$ 2.3mg, MI 151.1 $\pm$ 14.1mg, $p<0.05$). MI size was 40 $\pm$ 7%, EF was reduced after MI (MI 31 $\pm$ 6%, sham 61 $\pm$ 3%, $p<0.05$).
Conclusion: Perfusion results are in the range of previous microsphere studies. MI scar thickness was determined by cine MRI to be 530 $\pm$ 4μm. At a resolution of 469μmx469μm, partial volume errors may lead to an overestimation of perfusion in this area. Isoflurane is known to have vasodilatory properties, the given data may not represent true baseline values. Decrease of perfusion in the remote myocardium after MI is caused by left ventricular remodelling consisting of hypertrophy and consecutive reduction of relative capillary density or higher left ventricular filling pressures in mice with heart failure. The presented method allows for absolute in vivo quantification of murine myocardial perfusion for the first time. It provides perfusion maps at a single pixel resolution of 469μm x 469μm and is sensitive enough to detect local reductions after MI. It is a promising tool for the characterisation of transgenic mouse models and can be used for investigation of post MI remodeling.

107 Detection of pulmonary vein stenoses after radiofrequency catheter ablation in patients with atrial fibrillation using magnetic resonance imaging: a long-term follow-up

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Radiofrequency catheter ablation (RFCA) of atrial myofibrils at the orifice of pulmonary veins (PV) for curing atrial fibrillation (AF) causes frequently diameter reduction (DR) which can even lead to severe stenosis or vessel occlusion. However, the time course of PV stenoses is not yet sufficiently investigated. To determine the appropriate follow-up period, we examined the PV of patients (pts) with RFCA using magnetic resonance imaging (MRI) over a period of one year.
Method: 307 PV of 108 pts (53$\pm$10y) with AF were examined before, one day after and three months (112$\pm$34d) after RFCA with MRI (1.5T, Sonata®, Siemens, Erlangen). A subset of 138 PV (43 pts, 54$\pm$10y) had an additional one year follow-up (331$\pm$100d). For MRI, a non-gated contrast enhanced FISP-3D sequence followed by a 3D reconstruction (MPR) was used. The ostium and the proximal 20 mm of all PV were evaluated and measured.
Results: see table below.

Time course of diameter changes

138 PV	Preinterv.	1 d after	3 mo.s after	1 year after	p
Diameter [mm]	15.6$\pm$2.5	14.1$\pm$3.0	13.8$\pm$3.2	13.6$\pm$3.8	$<$0.001
DR in %	_	9$\pm$17	11$\pm$21	12$\pm$24	0.04
Rel. Freq. of DR	_	14.20%	11.90%	13%	n.s.
Rel. Freq. of ST	_	3.70%	7.90%	10.10%	0.013

DR = diameter reduction $>$/=25 and $<$50%, ST = stenosis (diameter reduction $>$/=50%)

Conclusion: One year after radiofrequency ablation there are significantly more stenoses detectable than one day after (10% vs 4%). An additional 13% show moderate diameter reduction. Progressive diameter reduction was found in 16%. A long term follow-up over at least one year seems to be necessary. MRI as a non-invasive technique is proved to be suitable for this purpose. Different ablative strategies should be compared using this method.

108 Cardiac catheterization with magnetic resonance fluoroscopic guidance

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Purpose: Radiation exposure during cardiac catheterization, limited image planes and poor soft tissue definition are disadvantages of x-ray fluoroscopy that could be overcome with the use of magnetic resonance (MR) imaging. This study evaluates the feasibility of real-time MR imaging (MR fluoroscopy) to guide left and right heart catheterization.
Methods and Results: Anesthetized pigs (n=7) with defects of the atrial septum (ASD) were catheterized using venous and arterial access. A prototype active tracking catheter was used to obtain blood pressures and samples from cardiac chambers and great vessels using antegrade, transseptal and retrograde approaches. MR fluoroscopy was used for catheter steering. Velocity-encoded cine MR imaging was used to measure pulmonary and aortic blood flow to calculate vascular resistances. Image planes used during catheter manipulation employed rapid sequencing to planes directed by the catheterizer to include the tip of the catheter and the chamber to be entered. All areas of interest were effectively entered and samples obtained. In the presence of an acute ASD, a Qp/Qs ratio of 1.3$\pm$0.2 was measured and no significant differences in pressure between inferior vena cava, right and left atrium were found. Pulmonary and aortic flow were 4.9$\pm$0.6 and 3.7$\pm$0.4 l/min, and pulmonary and systemic vascular resistance were 312$\pm$134 and 2006$\pm$336 dynes sec cm-5.
Conclusions: Left and right heart catheterization using MR guidance is feasible and safe. The combination of hemodynamic catheterization data with anatomical and functional MR imaging may significantly improve the evaluation of patients with congenital heart disease while avoiding radiation exposure.

INFLAMMATION AND ATHEROSCLEROTIC PLAQUE RUPTURE

113 Chlamydia pneumoniae constituents in human atheroma colocalize with ceroid deposits

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Background: Immunohistological detection of several Chlamydia pneumoniae (CP) antigens within polymerase chain reaction (PCR)-negative atheroma has suggested a controversial link between the bacterium and atherosclerosis. Our study aimed to evaluate whether positive immunohistology is really explained by the presence of chlamydial antigens, or due to cross-reactivity with non-chlamydial plaque constituents.
Methods: Two hundred and five different, surgically removed human arterial segments were examined for CP DNA in triplicate by conventional PCR using three different primer pairs and by real-time PCR in two different laboratories. Fragments of one hundred lesions were studied by immunohistochemistry using 1 CP-specific and 2 Chlamydia genus-specific monoclonal antibodies. Eight mammary vessels obtained during coronary bypass surgery, and 6 fetal aorta's obtained at autopsy, were also included. Serial sections of 8 atheroma were examined by Western blotting and histological staining. To rule out background staining derived from autofluorescent ceroid deposits, adjacent sections were viewed with a fluorescence microscope under UV light excitation.
Results: Immunohistological positivity for CP was frequently seen in human atherosclerosis: CP membrane protein RR402 was detected in 79% of the cases, chlamydial heat shock protein 60 in 17% and chlamydial lipopolysaccharide in 11% of the specimens. Mammary arteries also scored positive. Antigenic positivity was not related to the extent of atherosclerosis (Stary classification). Fetal aortic tissue was negative for chlamydial immunoblotting and antigenic staining. PCR analysis did not detect CP specific DNA in any of the lesions. Histological staining for CP colocalised with UV light-induced ceroid autofluorescence. In addition, chlamydial proteins were not detected by Western blotting in adjacent tissue sections, although pure CP proteins, as a positive control, showed reactivity.
Conclusion: The absence of CP DNA in human atherosclerosis, together with negative western blot analysis for CP proteins, and significant colocalization of positive CP immunohistology with autofluorescent ceroid, suggest cross-reactivity with non-chlamydial plaque constituents.

114 Neointimal smooth muscle cells display a proinflammatory phenotype resulting in increased leukocyte recruitment mediated by chemokines and adhesion molecules

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Purpose: Leukocyte recruitment is crucial for the response to vascular injury in spontaneous and accelerated atherosclerosis. Whereas the mechanisms of leukocyte adhesion to endothelium or matrix-bound platelets have been characterized, less is known about the proadhesive role of smooth muscle cells (SMCs) exposed after endothelial denudation.
Methods and Results" In laminar flow assays, neointimal rat SMCs (niSMCs) supported a 2-3-fold higher arrest of monocytes and 'memory' T lymphocytes than medial SMCs, which was dependent on both P-selectin and VLA-4, as demonstrated by blocking antibodies. The increase in monocyte arrest on niSMCs was triggered by the CXC chemokine KC, whereas that of 'memory' T cells was triggered by stromal cell-derived factor (SDF)-1alpha. In contrast, monocyte chemotactic protein (MCP)-1 secreted by niSMC was not involved in monocyte arrest. This functional phenotype was paralleled by a constitutively increased mRNA and protein expression of P-selectin and all relevant chemokines in niSMC, as assessed by quantitative real-time RT-PCR, flow cytometry and ELISA, which may be related to the constitutive up regulation of IkappaB-alpha kinase (IKK) activity. Double immunofluorescence confirmed a colocalization of P-selectin and SMC-specific alpha-actin in a subset of niSMC in vitro, as well as in luminal cells of injured mouse arteries.
Conclusions: Our data reveal that niSMC support increased VLA-4-dependent leukocyte arrest under flow conditions, which is mediated by an increased expression of P-selectin and chemokines, thereby defining a proinflammatory phenotype of niSMCs. In addition, P-selectin expression in a subset of niSMC may identify an endothelial cell like-SMC with the propensity to form luminal cell lining in denuded vessels.

115 Stabilization of atherosclerotic plaque by blockade of macrophage migration inhibitory factor after arterial injury in apolipoprotein E-deficient mice

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Macrophage migration inhibitory factor (MIF), a cytokine that controls cell-mediated inflammatory responses, is upregulated in early atherogenesis and during the progression of atherosclerosis, however its functional contribution to lesion development has not been evaluated.
We studied the effect of a blocking anti-MIF monoclonal antibody (MIF mAb) on neointima lesion formation following wire-induced carotid injury in apolipoprotein E-deficient (ApoE-/-) mice on high cholesterol diet. Either MIF mAb or a control mAb was injected twice weekly (100 μg per injection) up to 3 weeks after carotid injury. Neointimal plaque volume was determined in serial sections of the common carotid artery in a standardized distance from the bifurcation stained with Movats pentachrome. Neointimal macrophage and smooth muscle cell (SMC) content was evaluated by quantitative immunohistochemistry using Mac-2- and SMC-specific alpha-actin Ab. Cellular MIF expression in murine neointimal lesions was studied by immunostaining. Serum samples were analyzed for lipids, MIF and cytokine levels.
Treatment with MIF mAb did not affect serum levels of total cholesterol and triglycerides in ApoE-/- mice. Immunohistochemistry revealed endothelial MIF staining in ApoE-/- mice on a high cholesterol diet. As early as 24 h after endothelial denudation MIF immunoreactivity (IR) was detectable in SMC. Double immunofluorescence staining confirmed MIF expression in neointimal SMC and macrophages. Serum levels of MIF in this setting were increased at 6 h after injury and plateaued at 24-48 h. Notably, the blockade of MIF resulted in a 50% reduction of macrophage content in neointimal lesions (26$\pm$6.3% vs. 52$\pm$6.4% Mac-2 IR-positive area, n=5, p$<$0.02). Concomitantly, the neointimal content of SMC was increased in ApoE-/- mice treated with MIF mAb (44$\pm$4% vs. 24$\pm$1.5% SMC-specific alpha-actin IR-positive area, n=5; p$<$0.001). Differences in total plaque volume between MIF and control mAb-treated ApoE-/- mice were not significant (0.0093$\pm$0.0013 mm^3 vs. 0.0117$\pm$0.0021 mm^3, n=5). Serum levels of proinflammatory cytokines, such as IL-2, IL-4, IL-6 and TNF-alpha, were increased in MIF mAb-treated mice, excluding anti-inflammatory effects of MIF mAb via regulating these mediators.
Inhibition of MIF resulted in a shift of the cellular composition of atherosclerotic plaques towards a more stabilized phenotype with reduced macrophage/foam cell content and increased SMC content. Total plaque volume was not significantly altered by MIF blockade, which may be explained by a compensatory increase in proinflammatory cytokines.

116 Frequency and distribution of dendritic cells in fibro-calcific versus lipid-rich atherosclerotic carotid plaques – contribution of dendritic cells to plaque destabilization

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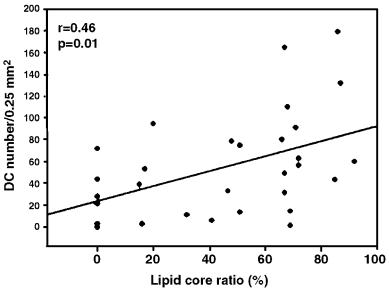
Background: Atherosclerotic (AS) plaques can be classified as stable (fibro-calcific) or vulnerable (lipid-rich). The importance of T-cells (TC) and macrophages (MO) for plaque destabilization is well known. Dendritic cells (DC) probably sustain inflammation in AS through activation of TC. Currently, little is known about the role of DC in plaque destabilization. Thus, we analyzed the frequency and distribution of DC in lipid-rich versus fibro-calcific plaques.
Methods: Carotid plaques of 30 patients were histologically and immunohistochemically analyzed with monoclonal antibodies to DC (Fascin), MO (CD68), TC (CD3) and DC activation markers. The areas of the lipid core and the entire plaque were digitally analyzed (Nikon DXM 1200). The lipid core ratio (LCR) was calculated (lipid core/entire plaque). AS plaques were classified by their LCR as fibro-calcific ($<$50%) or lipid-rich ($>$50%). Inflammatory cells were digitally counted.



Frequency of DC compared to LCR.

Results: Stroke or transient ischemic attack were more frequent in patients with lipid-rich (55%) than with fibro-calcific plaques (33%). The mean DC number was significantly higher (T = -2.4, p = 0.02) in lipid-rich (73/0.25 mm^2) than fibro-calcific (35/0.25 mm^2) plaques. The frequency of DC significantly correlated to the LCR (r = 0.46, p = 0.01). The DC distribution in fibro-calcific/lipid-rich plaques was: plaque shoulder 1 (39%/37%), plaque shoulder 2 (11%/11%), fibrous cap (21%/12%), lipid core (18%/28%), media (8%/7%) and contralateral intima (3%/5%). The expression of DC activation markers were higher in lipid-rich plaques.
Conclusions: The higher number of activated DC in lipid-rich plaques compared to fibro-calcific plaques and their abundance in rupture-prone plaque shoulders suggest a critical role of DC in plaque destabilization.

117 C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle in-vitro and in-vivo

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Purpose: Accumulating evidence suggests that C-reactive protein (CRP), in addition to predicting vascular disease, may actively facilitate lesion formation via inciting endothelial cell activation. Given the central importance of angiotensin type 1 receptor (AT1-R) in the pathogenesis of atherosclerosis, we examined the effects of CRP on AT1-R expression and kinetics in vascular smooth muscle (VSM) cells. In addition, the effects of CRP on VSM migration, proliferation, and reactive oxygen species production were evaluated in the presence and absence of the angiotensin receptor blocker, losartan. Lastly, the effects of CRP (and losartan) on neointimal formation were examined in-vivo in a rat carotid angioplasty model.
Methods and Results: The effects of human recombinant CRP (0-100μg/mL) on AT1-R transcript, mRNA stability and protein expression were studied in cultured human VSM cells. AT1-R binding was assessed by 125I-labled angiotensin II (Ang-II). VSM migration was assessed by wound cell migration assays, whereas VSM proliferation was determined via using [3H]-incorporation and cell number. The effects of CRP (and losartan) on Ang-II induced reactive oxygen species (ROS) production were evaluated by 2',7'-dichlorofluorescein (DCF) fluorescence. Lastly, the effects of CRP (and losartan) on neointimal formation, VSM cell migration, proliferation and matrix formation were studied in-vivo in a rat carotid artery balloon injury model. CRP markedly upregulated AT1-R mRNA and protein expression, and increased AT1-R number on VSM cells. CRP promoted VSM migration and proliferation in-vitro, and increased ROS production. Furthermore, CRP potentiated the effects of Ang-II on these processes. In the rat carotid artery angioplasty model, exposure to CRP resulted in an increase in cell migration and proliferation, collagen and elastin content, AT1-R expression and an increase in neointimal formation; these effects were attenuated by losartan.
Conclusions: CRP, at concentrations known to predict cardiovascular events, upregulates AT1-R mediated atherosclerotic events in vascular smooth muscle in-vitro and in-vivo. These data lend credence to the notion that CRP functions as a proatherosclerotic factor, in addition to a powerful risk marker.

118 Tissue factor is released by human vascular smooth muscle cells upon uptake of aggregated low-density lipoprotein by low-density lipoprotein receptor-mediated internalization

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Low density lipoprotein receptor (LRP) mediates internalization of aggregated low density lipoprotein (agLDL) which in turn upregulates its expression in human vascular smooth muscle cells (VSMC). The lipid-rich microenvironment of the atherosclerotic plaque may influence the thrombogenicity of the vascular wall. Tissue factor (TF) is the main initiator of the blood coagulation system The aim of this work has been to investigate the effect of aggregated LDL of the intima on TF expression and release by human VSMC.

Methods: Cultured human VSMC were obtained from human coronaries of explanted hearts at transplant operations. LRP-expressing VSMC in parallel with non-LRP expressing VSMC (LRP-/VSMC) were incubated with native LDL (nLDL) and agLDL (100 μg/mL) for increasing times. TF mRNA and protein expression levels were analyzed by Real time PCR and Western blot analysis, respectively.TF microparticle content of the supernatants was measured by flow cytometry.

Results: Both nLDL and agLDL transiently increase TF mRNA expression to the same level after 2 hours of incubation. Western blot analysis of the cells revealed that agLDL, but not nLDL, induced a significant decrease in cellular TF antigen (49 kDa) content in a time-dependent (by 70±8 at 24 hours and by 80±12 at 48 hours) and dose-dependent manner (from 36±2.4% at 50 μg/mL to 90±12% at 300 μg/mL). The decrease of cellular TF content induced by agLDL uptake was dependent of LRP-agLDL binding because it was not observed in LRP-/VSMC. Western blot analysis of the VSMC supernatants revealed that secreted TF antigen (54-55 Kda) increased in VSMC incubated with agLDL. In agreement, flow cytometry indicated that content of TF-rich microparticles was higher in VSMC incubated with agLDL. LRP-/VSMC did not show an increase in TF secretion in presence of agLDL. Incubation with agLDL did not alter any tested apoptosis-related gen in these cells.

Conclusions: AgLDL internalization, which leads to lipid-loading of VSMC, induces TF microparticle release but only in LRP expressing cells. The increased release of TF microvesicles by LRP-mediated lipid-loading of VSMC could have important consequences for the prothrombotic transformation of the vessel wall with the advancement of atherosclerosis.

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RATIONALE FOR TREATING INFLAMMATION IN HEART DISEASE

119 Transforming growth factor B-1 and activation leukocyte in patients with essential hypertension

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Objective: The aim of the present study was to investigate the possible involvement of peripheral blood leukocyte and circulating transforming growth factor B-1 (TGF-B1) in the pathogenesis of essential hypertension.

Design and Methods: We examined 38 untreated hypertensive men (age 49,1 ± 1,0 yrs, LV mass index was 142,7 ± 6,6 g/m^2) and 10 normotensive healthy volunteers (age 47,2 ± 1,5 yrs). Endothelial function was assessed by measuring flow-mediated dilatation (FMD) of radial artery using high resolution ultrasound. In all subjects 24-hour ABP monitoring, echocardiograms, carotid intima-media thickness were performed. Flow cytometric analysis was carried out to measure expression CD3, HLA-DR, CD25, CD11b, CD69, Fas and Bcl-2 in lymphocytes in whole blood samples. Neutrophils' (PMN) adherence to ECV304 cell line was quantificated. The white blood cell (WBC) was measured by a Sysmex, KX-21. The serum concentration of TGF-B1 was measured by ELISA method.

Results: Serum TGF-B1 level was increased in hypertensive group compared with normotensive (79,2±5,1and 41,9±6,8 pg/ml, $p<0,01$). We revealed increased WBC count, PMN adherence and the number of circulating CD69+, Fas+, Bcl-2+, CD11b+, but not HLA-DR+, CD25+ lymphocytes in hypertensive patients. Univariate analysis showed positive relation between TGF-B1 level and the number of CD11b+(r=0,392, p=0,03), Bcl-2+(r=0,371, p=0,02), Fas+(r=0,439, p=0,007), adhesion PMN (r=0,393, p=0,02). TGF-B1 level and leukocyte activation markers were related with LV mass index, carotid intima-media thickness and decrease of FMD in hypertensive patients.

Conclusion: Our results showed the potential role of TGF-B1 and activation leukocyte in development of left ventricular hypertrophy and pathogenesis of atherosclerosis in patients with essential hypertension.

121 Sub-suppressor dose of candesartan prevents perivascular inflammation and myocardial fibrosis, but not myocyte hypertrophy, in hypertensive hearts

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Angiotensin II (Ang II) is implicated in the mechanism of cardiac remodeling. Also, the pro-inflammatory effects of Ang II are suggested in various diseased situations. Recently, we have shown that pressure overload transiently induces TGF-beta-mediated myocardial fibrosis that expands from perivascular to intermuscular spaces, leading to diastolic dysfunction. However, the upper stream event of TGF-beta induction remained unknown. Thus, we sought to determine whether the Ang II-mediated inflammatory process is involved in myocardial remodeling in hypertensive hearts. Male Wistar rats were treated everyday with the low dose (0.1mg/kg/day) of candesartan, an angiotensin AT1 receptor-specific blocker, or saline from day -7, and underwent a suprarenal aortic constriction (AC) at day 0. This dose of candesartan was the maximum dose for the agent not to induce the suppressor effect in AC rats. In AC+saline (control) rats, myocardial ACE activity was transiently increased after day 1 with a peak at day 3, declining to the baseline level by day 14, whereas plasma renin activity was not changed. And, in control rats, myocardial MCP-1 expression and perivascular accumulations of ED1-labeled macrophages and BrdU-labeled proliferating fibroblasts were induced after day 1 with a peak at day 3. Thereafter, left ventricular hypertrophy associated with cardiomyocyte hypertrophy and perivascular fibrosis progressively developed after day 7 in control rats. In AC+candesartan rats, myocardial MCP-1 expression was significantly suppressed at day 3. And, not only macrophage accumulation but also fibroblast proliferation were remarkably reduced at day 3. Moreover, perivascular fibrosis, but not myocyte hypertrophy, was significantly ameliorated at day 14 in AC+candesartan rats. In conclusion, sub-suppressor dose of candesartan prevented MCP-1-mediated inflammatory process and subsequently TGF-beta-mediated myocardial fibrosis, but not myocyte hypertrophy, in hypertensive hearts, through the mechanism independent of the change in blood pressure. These results suggest that the Ang II-mediated inflammatory process plays a key role in myocardial fibrosis in hypertensive hearts.

120 ICAM-1- and MCP-1-mediated macrophage infiltration plays a key role in cardiac remodelling in hypertensive rats

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Myocyte hypertrophy and myocardial fibrosis progress during cardiac remodeling in hypertensive (HT) hearts. Inflammatory process is implicated in myocardial remodeling. MCP-1 and adhesion molecules regulate transmigration of inflammatory cells. Thus, we studied the causal relation of macrophage infiltration to myocardial remodeling and the roles of ICAM-1 and MCP-1 in macrophage infiltration, in HT hearts. HT was induced by constricting the suprarenal aorta of Wistar rats. ED1-labeled macrophages were first observed in the perivascular space at day 1. macrophage accumulation was peaked at day 3, declining to lower level by day 28. A robust increase in BrdU-labeled proliferating fibroblasts was found in the perivascular area at day 3, returning to lower level by day 28. After day 7, myocardial fibrosis and myocyte hypertrophy developed. Myocardial TGF-beta mRNA was upregulated after day 3, and peaked at day 7, lasting until day 28. Immunoreactive ICAM-1, but not VCAM-1, was transiently expressed on the coronary endothelial cells, at days 1-3. And, macrophage accumulation was observed in the interstitium adjacent to the ICAM-1-labeled arteries. Furthermore, MCP-1 mRNA was transiently expressed in HT hearts after day 1 with a peak at day 3, declining to the baseline by day 7. And, immunoreactive MCP-1 was expressed mainly in the intramyocardial vessel wall. For blocking ICAM-1 or MCP-1 function, a neutralizing monoclonal antibody (NAb) against ICAM-1 or MCP-1 was administered from day -1 to day 28. ICAM-1 or MCP-1 NAb had no effects on arterial pressure and myocyte hypertrophy. In the ICAM-1 NAb-treated rats, macrophage infiltration at day 3, fibroblast proliferation at day 3, TGF-beta expression at day 7, and cardiac fibrosis at day 28 were reduced in HT hearts by 81%, 75%, 63%, and 70%, respectively, versus the control IgG-treated rats. MCP-1 functional blocking reduced macrophage infiltration, fibroblast proliferation, TGF-beta expression, and myocardial fibrosis in HT hearts by 67%, 70%, 70%, and 59%, respectively, versus control IgG treatment. In conclusion, the ICAM-1- and MCP-1-mediated macrophage infiltration may play an initial role in myocardial fibrosis in HT hearts by activating fibroblasts.

122 Increased production of tumour necrosis factor-alpha in peripheral lymphocytes in patients with heart failure

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Purpose: Increases in circulating proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha), have been proposed to play an important role in pathogenesis of heart failure. TNF-alpha has been shown to be produced in myocardium itself in patients with heart failure. However, contribution of other sources of TNF-alpha production, such as in peripheral lymphocytes, to heart failure remains unknown. We studied changes in lymphocyte subsets and productivity of TNF-alpha in peripheral lymphocytes in patients with heart failure, and analyzed the relationship between lymphocyte function and severity of heart failure.
Methods: Symptomatic patients with ischemic heart disease, idiopathic dilated cardiomyopathy, hypertensive heart disease, and valvular heart disease (NYHA II-IV, n=34, age 75 $\pm$ 9 years, ejection fraction [EF] 51 $\pm$ 17%; mean $\pm$ SD) were compared with asymptomatic patients (NYHA I) and normal subjects (n=18, age 61 $\pm$ 15 years, EF 68 $\pm$ 6%). The number of peripheral CD3, CD4 and CD8 lymphocytes (then calculating CD4/CD8 ratios), and intracellular production of TNF-alpha in CD4 lymphocyte (fraction of TNF-alpha-positive CD4 (TNF-alpha/CD4) [%]), 4 hours after activation with phorbol 12-myristate 13-acetate and ionomycin in the presence of brefeldin A, were quantified by immunofluorescent flow cytometry.
Results: Plasma brain natriuretic peptide (BNP) levels negatively correlated with EF (r = -0.51, $p<0.01$), and positively correlated with plasma TNF-alpha levels (r = 0.62, $p<0.01$) in NYHA I-IV patients. Whereas the absolute numbers of CD3 cells were not significantly altered, CD4/CD8 ratio was higher in NYHA II-IV group than in NYHA I and normal group (1.91 $\pm$ 1.0 vs. 1.37 $\pm$ 0.35, $p<0.05$). After activation, TNF-alpha/CD4 fraction increased more in NYHA II-IV group than in NYHA I and normal group (19.6 $\pm$ 11.2% vs. 10.7 $\pm$ 9.4%, $p<0.01$), negatively correlated with EF (r = -0.33, $p<0.05$), and positively correlated with the plasma TNF-alpha levels (r = 0.34, $p<0.05$).
Conclusions: These results suggest that in heart failure, helper T cell (CD4) is dominant relatively to suppressor/cytotoxic T cell (CD8), and that TNF-alpha production in helper T cell is upregulated, thus leading to an increase in circulating TNF-alpha levels. These abnormalities in immune system may contribute to pathogenesis of heart failure. CD4/CD8 ratio and TNF-alpha/CD4 in peripheral lymphocytes could be a feasible and good marker to assess the severity of heart failure.

123 Unfractionated heparin causes pro-inflammatory interactions between platelets and leukocytes

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Background: Unfractionated heparin (UFH) is a widely used anticoagulant and forms part of the routine treatment during coronary intervention. Unfractionated heparin may be associated with adverse platelet activation. Previous studies have also suggested that UFH may have anti-inflammatory properties mediated by blockade of P-selectin-initiated cell adhesion. Platelet-monocyte binding (PMB) is a sensitive marker of platelet activation and is largely P-selectin dependent. The effect of UFH and other anticoagulants on PMB has not been investigated
Methods and Results: Peripheral venous blood was collected from 18 healthy volunteers into sodium citrate alone (control) or sodium citrate with UFH (1 U/ml), enoxaparin (0.8 U/ml) or lepirudin (5.6 mg/ml). PMB was determined by 2-colour immunofluorescent labeling using specific platelet and monocyte markers, followed by immediate flow-cytometric analysis. Compared to controls (16.2 $\pm$ 1.6%), PMB was increased following the addition of UFH (20.1 $\pm$ 1.9%, $p<0.001$) but not following the addition of enoxaparin (16.9 $\pm$ 2.0%, p=ns) or lepirudin (17.0 $\pm$ 2.2% p=ns). To investigate the mechanism of this increase, further experiments were performed in blood from 8 healthy controls anticoagulated with PPACK. Platelet surface expression of P-selectin was quantified using 2-colour flow-cytometric analysis following the in vitro addition of UFH (1U/ml). P-selectin expression was significantly increased in UFH treated whole blood (6.9 $\pm$ 1.2% vs. 3.2 $\pm$ 0.5%, $p<0.01$). PMB was also assessed following specific blockade of P-selectin using an anti-P-selectin monoclonal antibody (CLB-thromb/6, 10 μg/ml). P-selectin blockade reduced PMB by 65% in whole blood (26.2 $\pm$ % vs. 9.1 $\pm$ 1.4% $p<0.001$). P-selectin blockade in whole blood with UFH (1U/ml) reduced PMB to a similar level (7.4 $\pm$ 0.9% vs. 9.1 $\pm$ 1.4% p=ns).
Conclusion: PMB is augmented in whole blood exposed to UFH, via a P-selectin dependent mechanism. This was not evident in whole blood treated with enoxaparin or lepirudin. Thus UFH not only activates platelets, but also increases platelet binding to peripheral blood monocytes, with potential pro-inflammatory consequences. This has implications for the routine use of UFH in current clinical practice.

LATE FINDINGS AFTER TREATMENT FOR CONGENITAL HEART DISEASE

125 Nature of progression of discrete subvalvular aortic stenosis in adults: a comparison in patients surgically treated in childhood and unoperated adults with mild obstruction

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Purpose: Early surgical intervention for mild discrete subvalvular aortic stenosis has been advocated to prevent rapidly progressive obstruction and secondary aortic valve injury. We sought to compare the progression of subaortic obstruction and aortic regurgitation in adults who have been operated on in childhood or have reached adult life without surgery. **Methods:** Left ventricular outflow tract peak systolic pressure gradient and aortic regurgitation degree, estimated by Doppler echocardiography, were analyzed in 152 patients $>$ 15 years old (mean 33 $\pm$ 16) with discrete subaortic stenosis. Surgical repair before the age of 15 years had been performed in 51 patients (Surgical group) and 101 patients had not undergone previous surgical repair (Non surgical Group). Sequential changes in pressure gradient and aortic regurgitation were determined for 69 patients with two or more echocardiograms performed with at least a two-year interval. Actuarial freedom from new surgical intervention over 15 years of age was compared in both groups. **Results:** Peak systolic pressure gradient was 42 $\pm$ 32 mm Hg in surgical group and 50 $\pm$ 41 mm Hg in non surgical group (p = NS). Aortic regurgitation degree was 2.0 $\pm$ 0.8 in surgical group and 1.5 $\pm$ 1.1 in non surgical group (p = 0.003). After 5.9 $\pm$ 2.3 years of follow up (range 2 to 10.6), pressure gradient increased from 38 $\pm$ 29 mm Hg to 46 $\pm$ 35 mm Hg ($p < 0.001$) but aortic regurgitation degree did not vary significantly over time. The slope of change in pressure gradient was 1.9 $\pm$ 4 mm Hg per year of follow-up in surgical group and 1.5 $\pm$ 3 mm Hg in non surgical group (p = NS). The actuarial freedom from new surgical intervention in surgical group was 98% at the age of 20 years, 92% at the age of 25 years and 71% at the age of 30 years compared with 100%, 96% and 93% in non surgical group (log rank = 7.98; p = 0.0047). **Conclusions:** Progression of subaortic obstruction in adults with discrete subvalvular aortic stenosis is slow either in unoperated or postsurgical patients. Aortic regurgitation is common but rarely progressive in both groups. Patients who have been operated on in childhood are more likely to have significant aortic regurgitation and need for new surgical intervention during adulthood. These data do not support early surgical intervention in patients with mild discrete subvalvar aortic stenosis.

126 Aortic complications of coarctation of aorta in adults: aneurysm, pseudoaneurysm, infective endarteritis, dissection, fistulae and aortic rupture

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Purpose: Severe aortic complications might occur in adults with aortic coarctation (AoCo) despite successful surgical repair in childhood. The aim of this study was to report the prevalence and predisposing conditions for aortic complications in adults with operated or unoperated AoCo. **Methods:** A total of 235 adults diagnosed with AoCo (mean age 27 $\pm$ 13 years) were retrospectively reviewed. Treatment had been performed by surgery in 181 patients (Group I) and by balloon angioplasty or primary stenting in 28 patients (Group II). 26 patients with mild pressure gradient at diagnosis had not undergone previous intervention (Group III). Aneurysm, pseudoaneurysm, dissection, mycotic aneurysm, fistulae and aortic rupture, which result in death or need for operation, were considered to be aortic complications. Prevalence and predictors of aortic complications were analysed. **Results:** Aortic complications were found in 39 patients (17%): Ascending aortic aneurysm (22); descending aortic aneurysm (10), aortic rupture (2), pseudoaneurysm (2), aortic dissection (2), mycotic aneurysm (2), aortobronchial fistula (1) and fistula ruptured into right ventricle (1). Three patients had more than one type of complication. There was no differences among the three groups of treatment with respect to complications: Group I, 28 (15%), Group II, 5 (18%) and Group III, 4 (15%). The prevalence of ascending aortic aneurysm was 9% in Group I, 11% in Group II and 12% in Group III (p=NS) and descending aortic aneurysm accounted for 4% in the three groups (p=NS). A significant relation between residual pressure gradient, systemic hypertension or age at repair and the occurrence of aortic complications was not found. Only current age (33 $\pm$ 15 vs 26 $\pm$ 12 years, $p<0,01$) and bicuspid aortic valve (76% vs 53%, $p<0,01$) were found to be predisposing conditions for aortic complications. **Conclusions:** Aortic complications are common in adults with AoCo. Ascending and descending aortic aneurysm are the most frequent ones, but aortic rupture, dissection, pseudoanuerysm, mycotic aneurysm and fistulae may also occur during long-term follow-up. Previous repair by surgery or percutaneous intervention does not prevent their occurrence. The only predisposing conditions for aortic complications appear to be age and bicuspid aortic valve.

127 Myocardial fibrosis and surgical scarring in operated adult congenital heart disease

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Purpose: The aetiology of ventricular dysfunction late in adult congenital heart disease (ACHD) is not entirely clear and contributes significantly to morbidity and mortality. Cardiovascular magnetic resonance (CMR) imaging with late gadolinium detects myocardial fibrosis after infarction. CMR can image the right as well as left ventricle well. We hypothesised that myocardial hyperenhancement would be demonstrable in these patients implicating a role for infarction/fibrosis in right ventricular pathogenesis. **Methods:** Adults with repaired tetralogy of Fallot (TOF, n=11, 3 female, 8 male, mean age 35y) or transposition of the great arteries palliated with the Mustard operation (TGA, n=3, 1 female, 2 male, mean age 30y) underwent cine and late gadolinium CMR. Mean time from surgery was 26 years for Mustard and 29 years for TOF patients.
Results: Myocardial hyperenhancement was seen in 13 (93%) patients. In 11(85%), hyperenhancement appeared to reflect the previous surgical intervention with focal hyperenhancement within the right ventricular outflow tract (RVOT) free wall after incision or resection (n=10), at the site of VSD patch suture (n=7) and in the left ventricle after previous apical vent (n=5). In 3 other patients (15%), there was unexplained right ventricular (RV) hyperenhancement, which was extensive in 2.

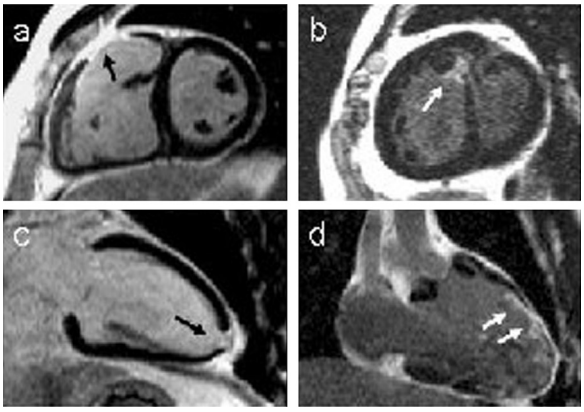

Figure. (a) RVOT in repaired TOF (b) VSD site (c) apical vent (d) RV hyperenhancement.

Conclusion: Myocardial hyperenhancement after late gadolinium CMR imaging is common in adult congenital heart disease patients post surgery. Surgical scarring can be detected decades post operatively in both the right and left ventricle. There is a subgroup with additional hyperenhancement unexplained by surgery directly which merits further investigation.

128 Significance of exercise-induced hypertension in adults after successful repair of aortic coarctation: relation to end organ damage

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Objectives: Hypertension is a frequent finding in patients after successful repair of aortic coarctation. Additionally, a considerable amount of these patients (20-35%) is normotensive at rest, but shows a hypertensive reaction on exercise. The significance of exercise blood pressure profiles in these patients and their relation to outcome and organ damage is not known. If an increased prevalence of organ damage could be demonstrated in post-coarctectomy patients with exercise-induced hypertension, treatment would be justified.
Methods: One hundred and thirty seven patients (89 male; mean age 31.2, SD 11.1 years; time after operation 7.8, SD 7.1 years) underwent a maximal, symptom limited treadmill exercise test (Bruce protocol). Exercise-induced hypertension was defined by a maximal systolic blood pressure $>$ 200 mmHg. A mean day systolic blood pressure $>$ 140 mmHg at 24 hour ambulatory blood pressure monitoring (ABPM) was considered hypertensive. Patients were studied by echocardiography to assess left ventricular mass. Ultrasound investigations of the carotid arteries were performed to determine carotid Intima-Media-Thickness (IMT). Overnight urine specimens were examined for the presence of microalbumin.
Results: Of the 137 patients 28 (20%) were known to have sustained hypertension and received medication. The remaining 109 patients had normal office readings and were divided into two groups: 72 patients (53%) without exercise-induced hypertension (group 1); 37 patients with exercise-induced hypertension (group 2). IMT of the common carotid artery was signicantly increased in group 2 compared to group 1 (0.64(0.139) vs. 0.57(0.098), p=0.008). There was a significant difference in left ventricular mass in males between these groups (127(29)g/m^2 vs. 149(44)g/m^2, p=0.029). Urinary microalbumin was within normal range in all patients. Of the 37 patients with exercise-induced hypertension 20 patients (54%) had hypertension at ABPM. These 20 patients had higher IMT of the common carotid artery than the remaining 17 patients, normotensive at ABPM (0.68(0.14)mm vs. 0.59(0.13)mm, p=0.044). Left ventricular mass was not different between the latter patient groups (151(39)g/m^2 vs. 146(49) g/m^2, p=0.744).
Conclusions: Patients with exercise-induced hypertension after successful repair of aortic coarctation have increased carotid Intima-Media-Thickness and increased left ventricular mass compared to normotensive patients. This increased end organ damage may justify antihypertensive treatment.

129 Severity of congenital heart disease shows a weak association with patients quality of life

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Congenital heart disease constitutes a wide spectrum of heart defects with varying levels of disease severity, affecting the progress of the disease, the prognosis, and the functional status. In addition to the medical problems, these patients are also faced with specific social and psychological concerns, influencing their quality of life (QoL). We explored whether the severity of the heart disease is associated with patients' QoL.
Methods: Using a correlational, cross-sectional design, this study included 629 patients (60.1% males) with a median age of 24 (Q1=20; Q3=29) years. Inclusion criteria were 18 years or older, Dutch-speaking and literate, followed-up at the University Hospitals of Leuven, and oral informed consent. In the absence of a gold standard for classification of disease severity of congenital heart defects, severity was operationalised in terms of [1] initial diagnosis (classification of 'Task Force 1' of the 32nd Bethesda conference), [2] illness course (Disease Severity Index), and [3] current functional status (NYHA, Ability Index, classification of Gewillig). QoL was measured using a Linear Analogue Scale (LAS), the Satisfaction with Life Scale (SWLS), and the Schedule for Evaluation of Individual Quality of Life - Direct Weighting (SEIQoL-DW).
Results: Scores derived from the disease severity classification systems were weakly, negatively associated with QoL parameters (see table). Functional status parameters showed the highest correlations with QoL.

Disease severity and quality of life

	LAS	SWLS	SEIQoL-DW
Task Force	-0.06	-0.07	-0.02
Disease Severity Index	-0.10*	-0.12	-0.01
NYHA	-0.17**	-0.24**	-0.17**
Ability Index	-0.15**	-0.24**	-0.11*
Classification of Gewillig	-0.14**	-0.16	-0.13*

Spearman's Rho correlation coefficient: *p$\leq$0.05; **p$\leq$0.01

Conclusion: This study revealed that severity of congenital heart disease is marginally associated with patients' QoL. Functional status is more related to patients' appraisal of QoL in contrast to initial diagnosis or illness course. This information is critical to develop key interventions to enhance QoL in this patient population, and to provide appropriate counselling.

130 Natural history of the atrial septal defect in the age of echocardiography

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Background: The natural history of atrial septal defect (ASD) is changing due to the early diagnosis and closure in childhood. However, many asymptomatic patients survive into adulthood and many surgeons did not operate the asymptomatic patients with ASD in the middle age, over 40.
Aim: To assess the natural history of ASD in unoperated adults in various age groups. Patients and methods: In 1995-2002 we examined clinically and echocardiographically 134 consecutive adults with unoperated ASD type II, who were referred to our Centre for adults with congenital heart disese. Patients were divided into 3 groups according to their age: group A: 18-40 years: 52 pts, mean age 27±5,4 years; group B: 41-60 years: 52 pts, mean age 51±6,8 years; group C: age over 61: 30 pts, age 72±7,9 years.
Results: functional class NYHA increased significantly with age: A: 1,7±0,9; B: 2,3±0,7; C: 3,1±0,8; p(AB)<0,01; p(BC)<0,05; p(AC)<0,001. There were no significant differences in the size of the ASD and shunt. Size of ASD in group A: 17±7 mm; B: 21±8 mm; C: 19±9 mm; p: NS. Left-to-right shunt Qp/Qs: A: 2,2±0,72; B: 2,4±0,82; C: 2,8±0,89; p:NS. Pulmonary artery pressure (PAP) increased with age: PAPs: A: 26±6; B: 38±9, C: 58±12 mmHg; p(AB)<0,01; p(BC)<0,05; p(AC)<0,001. In the oldest group there was significant increase in the frequency of atrial fibrillation (AF) and mitral regurgitation (MR). AF in group A: 6%; B: 8%; C: 67%. MR in group A: 0%; B: 10%; C: 73%.
Conclusion: There is a significant deterioration of the clinical and hemodynamical variables in patients with unoperated ASD after the age of 60, even if they had been asymptomatic or only mildly symptomatic in their middle age. The reason may be the progression of the pulmonary hypertension, progression of the mitral regurgitation due to altered geometry of the mitral annulus and frequent atrial fibrillation. Patients with AF in their middle age were more likely to be operated than patients in sinus rhythm. Our results support the strategy of early closure of all significant ASDs which are diagnosed in adults, regardless of symptoms.

THE BURDEN OF CARDIOVASCULAR DISEASE IN THE ELDERLY

131 Atrial fibrillation as a risk factor for impaired cognitive function in older patients

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Atrial fibrillation (AF) is an independent risk factor for transient ischemic attack and cerebrovascular stroke. One of symptoms of central nervous system (CNS) injury is impaired cognitive function. The study aim was to evaluate the relation of the presence of AF with cognitive function in older patients hospitalized of any reason. The study group consisted of 2267 consecutive patients (65 - 99 years old; 1473 female). Physical examination, resting ECG and Mini-Mental State Examination (MMSE) used for cognitive function evaluation were taken in all individuals. AF was found in 642 patients and symptoms of focal CNS injury (detailed neurological physical examination and/or head CT) 291 patients. AF was associated with significantly decreased MMSE score in patients without (21.4 ± 6.4 vs. 22.7 ± 6.3 points; p<0.001) and with symptoms of CNS injury (16.3 ± 6.8 vs. 18.6 ± 8.0 points; p=0.027). AF was more common in patients from lower MMSE quartiles (Q), i.e. it was in 193 (34.0%) patients from the 1st Q, in 165 (29.1%) subjects from the 2nd Q, in 157 (27.7%) individuals from the 3rd Q and in 127 (22.4%) patients from the 4th Q (p<0.001 for trend between quartiles). Univariate logistic regression (adjusted for patient age and gender) revealed that the risk of impaired cognitive function was increased for AF (OR: 1.6; 95% CI: 1.3-1.9; p<0.001), symptoms of CNS dysfunction (OR: 2.2; 95% CI: 1.7-2.9; p<0.001) and particularly for the co-existence of both factors (OR: 2.8; 95% CI: 1.7-4.3; p<0.001). Patients with neither AF nor symptoms of CNS dysfunction had a decreased risk for impaired cognitive function (OR: 0.5; 95% CI: 0.4-0.6; p<0.001). AF in older patients is associated with cognitive dysfunction both in those who have or do not have symptoms of CNS injury.

132 Age and atrial fibrillation inducibility

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The purpose of the study was to evaluate the effects of age on the atrial fibrillation (AF) induction. AF induction is used as a diagnostic test of atrial vulnerability in adults. AF prevalence is known to increase in elderly people and electrophysiologic changes were reported during the life; however, the effects of age on AF induction are unknown.
Methods: population of study consisted of 741 patients without spontaneous AF, aged from 16 to 85 years (y)(mean 61±15), admitted for an electrophysiologic study, which was indicated for dizziness or ventricular tachyarrhythmia. Programmed atrial stimulation was systematically performed: 1 and 2 extramuli were delivered in sinus rhythm and 2 atrial driven rhythms (600, 400 ms). Univariate and multivariate analysis of patients clinical and electrophysiological data was performed.
Results: AF inducibility defined as the induction of AF lasting more than 1 minute, was paradoxically decreased in the elderly patients (>70 y) compared to patients younger than 70 y (p <0.01): AF was induced in 40% of 63 patients younger than 40 y, 39% of 101 patients aged 40 to 50 y, 37% of 131 patients aged 50 to 60 y, 38% of 223 patients aged 60 to 70 y and only 28% of 223 patients older than 70 y. There was no significant correlation with the sex, the presence of dizziness, the presence of an underlying heart disease, the left ventricular ejection fraction, the presence of salvos of atrial premature beats on Holter monitoring and the intra-atrial conduction time. There was a significant correlation with a longer effective atrial refractory period in the elderly (226±41 ms) than in younger patients (208±31 msec) (p<0.001). Increased atrial refractory period and age > 70 years were independent factors of decreased AF inducibility.
Conclusion: AF induction is facilitated by the presence of a short atrial refractory period in patients younger than 70 years and programmed atrial stimulation should be interpreted cautiously in these patients. In the opposite, the increase of atrial refractory period could protect the patients older than 70 years against AF inducibility.

133 Is the smokers paradox present in older patients with acute myocardial infarction? Results of the PPRIMM75 Registry

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Background: Although smokers (S) are at an increased risk of myocardial infarction (MI), the outcome of MI is better in S than in non-S. The reason for this paradox is uncertain but it has been attributed, at least in part, to the younger age of S.
Methods: To assess if the smoker's paradox is present in a population of advanced age, we studied baseline characteristics and outcomes in 677 consecutive patients enrolled in the PPRIMM75 Registry from 1988 to 1997 (aged >75 years and admitted to our CCU with a first MI).
Results: S were younger (79 vs 80.7 years)*, and less frequently female (5.4 vs 63%)*, diabetic (26 vs 34%, p=.06) and hypertensive (32 vs 57%)*, but had more often peripheral artery disease (24 vs 11%)*. S arrived earlier (delay <6 hours: 30 vs 38%, p=.08) and were more frequently in Killip class I (77 vs 63%)*. They had similar rates of ST-segment elevation MI (84 vs 85%) and anterior MI (34% in both groups). No differences between S and non-S were found in the use of reperfusion therapy (35 vs 30%, p=.30), echocardiography and coronary angiography, but stress tests were more frequently used in S (34 vs 13%)*. LVEF was similar in both groups. During hospitalisation, S showed a lower incidence of cardiac complications: pulmonary congestion (32 vs 44%, p<.02), cardiogenic shock (14 vs 19%, p=.13), mechanical complications (6 vs 10%, p=.16). In-hospital death was 22% in S and 33% in non-S (p=.01). After adjusting the difference in age by logistic regression analysis smoking remained as an independent predictor of death (OR: 0.62; 95%CI: 0.39-0.99). However, when the other baseline clinical differences differences were taken into account, smoking lost its "protective" effect (OR: 0.75; 95%CI: 0.45-1.26).
Conclusion: The smoker's paradox can also be observed in elderly patients with acute MI. The better prognosis of MI associated with smoking at advanced ages is mainly due to the more favorable clinical profile of smokers at the time the infarct occurs.
* p<0.01.

134 Detection of potentially life-threatening arrhythmias by systematic Holter monitoring in asymptomatic elderly population

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Previous Holter ECG-monitoring studies have suggested that bradyarrhythmias contribute significantly to sudden cardiac death particularly in the elderly. The present study was designed to analyse the prevalence and evolution of bradyarrhythmias in an unselected elderly population.
Methods: We have prospectively analyzed with 24-hour Holter monitoring all 109 residents of a geriatric institution (age 84±6 years, range 68-99, 76% women). A previous diagnosis of coronary artery disease was present in 11%, valvular disease 8%, hypertrophic cardiomyopathy 7%, dilated cardiomyopathy 1% (total structural heart disease 27%). Cardiovascular symptoms were recorded in 17.7% of the Pts (palpitations 7%, dizziness 5.3%, chest pain 2.7%, syncope 2.7%). A history of high blood pressure was present in 56% of the Pts. Bradyarrhythmias were defined accordingly to ACC/AHA Guidelines for pacemaker implantation. Results: Sinus rhythm was present in 97 patients (Pts) (89%) and permanent atrial fibrillation (AF) in 12 Pts (10.6%). A class IIa ACC/AHA indication of permanent pacemaker implantation due to bradyarrhythmias was established in 6 asymptomatic Pts (5.5%). High degree A-V block in 3 Pts in sinus rhythm and 3 Pts in AF with pauses > 3 sec or requirement of antiarrhythmic drugs. The presence of AF was associated with an increase of bradyarrhythmias incidence ($p<0.0001$). During a follow-up of 9±4 months (range 3-14), 6 asymptomatic Pts died (5.5%), 3 Pts in sinus rhythm and 3 in AF ($p<0.01$). Two Pts refused permanent pacemaker implantation and one of them died suddenly during the follow-up.
Conclusions: 1) The systematic use of 24-Hour Holter monitoring detects potentially life-threatening bradyarrhythmias in asymptomatic elderly population. 2) Atrial fibrillation was the most prevalent arrhythmia and was associated with severe conduction disturbances and death.

135 Inadequacy of cardiovascular preventative therapy among high-risk elderly patients in the United Kingdom

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Background: Cardiovascular risk reduction benefits are well-known for high-risk middle-aged patients. However, high-risk elderly patients may have greater safety and efficacy concerns. We evaluated cardiovascular preventative care in elderly vs middle-age patients using data from a large health care database.
Methods: The study population was derived from the General Practice Research Database containing medical data from 400 general practices and 3.5 million patients, enrolled from January, 1998 to December, 2001. High risk patients were defined as those >45 years of age with an incident diagnosis or treatment of coronary heart disease (CHD), transient ischemic attack (TIA) or stroke, peripheral arterial disease, diabetes or hypertension. Cardiovascular and resource use outcomes are defined below.
A total of 273,262 high risk patients (54% male) were identified. High risk status, CVD recurrence rate, resource use, and polypharmacy rates were all significantly greater for elderly patients versus those < 65 years of age ($p<0.0001$). Statin usage was low, particularly in patients >70 years of age ($p<0.0001$).

Study Outcomes Among High Risk Patients

Age-Range:	45-64	65-69	70-74	75-89	80+
Total N	466,883	84,139	77,615	70,560	87,842
Prevalence of High Risk	23%	48%	53%	54%	53%
Rate of recurrent CVD	9.5%	12.2%	14.3%	15.3%	18.3%
Office visits/yr	8.9	9.3	9.8	10.2	10.8
Hospitalizations/yr	1.2	1.3	1.3	1.4	1.6
Statin use	21%	23%	17%	9%	2%
Polypharmacy (≥5 agents)	37.7%	43.2%	44.7%	44.5%	44.8%
% of statin users taking 3A4 inhibitors	13.0%	13.7%	13.1%	12.7%	11.5%
% of statin users taking 2C9 inhibitors	11.6%	11.7%	12.6%	12.2%	13.1%

Conclusions: Elderly patients in the UK constitute a greater management challenge compared to middle-aged patients due to their elevated CVD risk, polypharmacy, and resource use. This elevated risk may warrant more intensive statin therapy according to UK guidelines. However, statins metabolized by 3A4 and 2C9 pathways may place elderly patients at risk for drug-related interactions due to greater polypharmacy.

136 Impact of age on quality of care of patients presenting to an emergency department with chest pain

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Age is often a major consideration at Emergency Department (ED) in the evaluation of chest pain, with regards to triage and treatment.
Purpose: We sought to determine if, in the era of critical pathways, age may cause a selection bias in choosing management strategies at ED, thus affecting negatively the quality of care in the elderly.
Methods: In 2001, 1,551 patients> 65 years old (age: 71±15 years) and 2,833 younger patients (age: 52±18 years) arrived to ED because of chest pain and a possible myocardial infarction (MI). At entry, all patients were risk-stratified on the basis of AHCPR's classification and were then managed according to recently developed ED critical pathways. Pathways include a protocol for ruling out MI (i.e. q3 hour ECGs and serum markers of myocardial necrosis for 9 hours) as well as pre-specified indications for Doppler echocardiography, continuous 12-lead ST-segment monitoring, and exercise stress testing.
Results: During a mean stay of 12±10 hours at ED, no significant differences between older and younger patients were seen in the use of continuous 12-lead ST-segment monitoring (27% vs 17%, NS) and Doppler echocardiography (38% vs 25%, NS). Diagnostic accuracy for MI at ED was similar between older and younger patients (60% vs 65%, NS). More elderly patients were hospitalised (15% 3%, $p<0.05$), while more younger patients were discharged home directly from ED (66% vs 27%, $p<0.05$). For the two different age groups, there were no differences at ED in the length of stay (6±3 vs 7±5 hours, NS) and in all-cause in-hospital mortality rate (0.5% vs 0.1%, NS). The quality of care indicators were similar in older and younger patients, as no difference was seen in door-to-thrombolysis interval (25±15 vs 21±17 min, NS), door-to-balloon time (71±25 vs 68±21 min, NS), or time to transfer to CCU or cardiac wards (95±35 vs 109±44 min, NS).
Conclusions: In chest pain patients presenting to ED, hospital admission rates and in-hospital cardiac events increase with age, but the use of diagnostic tools and quality of care are similar to all ages. Thus, in the era of critical pathways, age "per se" does not seem to cause a selection bias in choosing patients' management strategies in chest pain.

EVOLUTION OF CARDIOLOGY PRACTICE AND OUTCOMES

137 Comparison of 5-year mortality following acute myocardial infarction in 1984–1988 and 1989–1993

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Purpose: To determine on a population basis the long-term survival of patients discharged after myocardial infarction (MI) and to compare events occurring during 1984-1988 with the ones during 1989-1993.
Methods: The study population comprised all persons aged 25-74 in the Halifax County MONICA MI database who, between 1984 and 1993, were discharged after a definite or possible myocardial infarction (MONICA criteria). Patient names, sex, birth date and last know residence were submitted to Statistics Canada for a possible match with deaths between 1984 and 1998 recorded in the Canadian Mortality Database (CMDB). A probabilistic algorithm was used to find the most likely match. Multiple matches were resolved by inspection. Patient characteristics were extracted from the MONICA database. Their association with 5-year survival was assessed by chi-square statistics and multivariate logistic regression.
Results: During the study period we obtained data for 3666 patients, 71.3% were men; 22.9% of the patients died during the 5-year follow-up period. The average 5-year mortality was 25.2% during 1984-88 and 20.8% during 1989-93 ($p=0.001$). Within each period there was no significant time trend in 5-year mortality. The patients during the two time periods differed significantly ($p<0.01$) with respect to male sex (73.7% vs. 69%), mean heart failure index (1.04 vs. 1.22), history (Hx) of PCI (0.51% vs. 5.6%); treatment during event with PCI (4.8% vs. 17.3), CABG (10.5% vs. 15.8%), thrombolysis (7.1% vs. 29.9%); and discharge medications ACE-I (4.4% vs. 17.3%), ASA (35.3% vs. 70.6%), and beta-blocker (45.7% vs. 55%). Association between 5-year mortality and patient characteristics/treatment did not differ between the two time periods with odds ratios > 1.0 for heart failure index, male sex, Hx of PCI and diabetes, and ACE-I treatment; OR < 1.0 for treatment with acute PCI or thrombolysis, and discharge medication ASA or beta-blocker.
Conclusion: In comparison with 1984-89, patients discharged between 1989-93 had more severe disease. Nevertheless, 5-year mortality declined by 17%, which we attribute to the introduction of thrombolysis and PCI in our centre in late 1988 and the more aggressive treatment with CABG, ASA and beta-blocker discharge medication.

138 Heart failure after myocardial infarction: a 20-year community study

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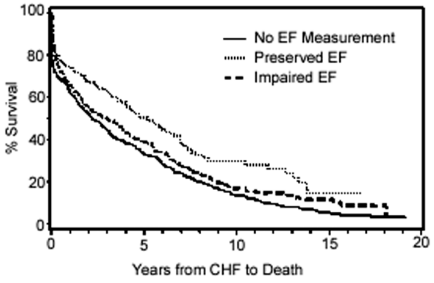
Objectives: To characterize the presentation and outcome of patients with heart failure (HF) after acute myocardial infarction (MI) according to their left ventricular function (LV) assessment and examine survival among those patients.
Background: Little is known about the presentation, evaluation and outcome of HF post-MI and how it may have changed over time.
Methods: Using the Rochester Epidemiology Project, all incident MIs in Olmsted County, Minnesota between 1979 and 1998 were identified and validated using standardized criteria. Left ventricular ejection fraction (LVEF) was assessed by echocardiography, catheterization or nuclear angiography.
Results: Between 1979 and 1998, among 2171 patients with incident MI, 810 (37%) experienced HF during 6.9 (5.4) years (SD) of follow-up. Persons who experienced CHF were more likely to be women (57%) and had a mean (SD) age of 74 (12); 59% had LVEF measured within 60 days after the HF event. Median survival was 3 years and older age, male sex, comorbidity, and impaired LV function were all associated with increased risk of death. Patients with no LV function assessment had the worst outcome. Survival did not improve over the two decades of the study (P=0.27) even after adjustment for other prognostic characteristics.



Conclusion: In this geographically defined cohort of patients with HF after MI, LVEF was frequently under-ascertained after the HF event. Survival was poor and remained unchanged over the two decades of the study period.

139 Pulse pressure: an independent predictor of cardiovascular mortality in 12,763 middle-aged men: 25 year follow-up of the Seven Countries study

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Background: Hypertension is a dominant characteristic in the prediction of cardiovascular disease (CVD). However, much attention has been given over the years to which blood pressure is the best measure for CVD events. The aim of this study was to evaluate the effect of pulse pressure on CVD mortality.
Methods: Sixteen cohorts of in total 12,763 men aged 40-59 in seven countries (one cohort in the USA, two in Finland, one in the Netherlands, three in Italy, two in Croatia (former Yugoslavia), three in Serbia (former Yugoslavia), two in Greece, two in Japan) were surveyed from 1958 to 1964. Risk factors and personal characteristics were measured and follow-up for vital status and causes of death were carried out over 25 years (1985). Analyses were based on comparisons of mean levels of risk factors and death rates within the 16 cohorts.
Results: The relation of pulse pressure and 25-year CVD mortality was strongly positive and significant in all cohorts (age adjusted hazard ratio (HR) varied among cohorts from 1.06 to 1.17 per 5 mm Hg, $p < 0.05$). Moreover, statistical analysis (based on Akaikes' Information Criterion) revealed that pulse pressure levels were the best predictor for CVD deaths among all blood pressure measurements. This trend was recognizable in normotensive, borderline and sustained hypertensive men, where CVD mortality increased with the level of pulse pressure. Pulse pressure levels were also a significant predictor for coronary heart disease deaths (pooled HR per 5 mm Hg = 1.10, 95% CI 1.08 to 1.11) as well as stroke (pooled HR per 5 mm Hg = 1.13, 95% CI 1.12 to 1.17).
Conclusion: Based on a large, multicultural, population sample of middle-aged men, we revealed that pulse pressure was the best predictor for CVD mortality, among all arterial blood pressures. A potential explanation is that the increase in pulse pressure levels represents the decreased distensibility of the systemic arterial system.

140 Thirty-year trends in cardiovascular disease risk factors in Finland

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The aim of the study was to assess thirty-year trends in major cardiovascular disease risk factors in Finland. The cardiovascular disease risk factor levels of the population have been assessed in Finland since 1972 in population surveys conducted in five-year interval. In the beginning, surveys were done to evaluate the North Karelia project. Later, the surveys have been conducted in connection of WHO MONICA project (1982-1992) and as the National FINRISK Study (1997-2002). Stratified random sample of population aged 25 to 64 years is drawn from population register. Depending on the survey year and the number of survey areas the sample size has varied from 8000 to 12000. Survey includes a self-administered questionnaire assessing health related factors, physical examination and blood sampling for assessment of serum lipids. The serum cholesterol levels have decreased significantly in Finland from 1972 to 1997 both among men and women. During the last five years from 1997 to 2002 the decrease has levelled off and the serum cholesterol changed among men from 5.54 mmol/l to 5.51 mmol/l and among women from 5.45 mmol/l to 5.34 mmol/l. Blood pressure levels have decreased significantly both among men and women from 1972 to 2002. Among men both the systolic and diastolic blood pressure decreased statistically significantly between years 1997 and 2002: SBP from 138 mmHg to 137 mmHg (p=0.005) and DBP from 85 mmHg to 82 mmHg ($p<0.001$). Among women only distolic blood pressure decreased statistically significantly from 80 mmHg to 77 mmHg ($p<0.001$). Systolic blood pressure level remained unchanged being 132 mmHg. Smoking rates have decreased significantly among Finnish men from 1972 to 1997. Between 1997 and 2002 smoking rate increased among men from 31% to 35% (p=0.01). Among women the smoking rates have increased slightly until 1992. Between 1992 and 1997 the increase in smoking among women levelled off, but between 1997 and 2002 smoking rate has increased again from 20% to 24% (p=0.005). The average cardiovascular risk factor level has decreased markedly in Finland until 1997. According to the latest risk factor survey in 2002 the trend in risk factor levels is not as favourable any more. Smoking rates are increasing both among men and women and the remarkable decline seen in serum cholesterol levels among Finnish population has levelled off. However, blood pressure levels are continuously decreasing both among men and women.

141 The rule of halves for hypertension no longer exists in Glasgow

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Purpose: The rule of halves for hypertension (HBP) is that 50% of those with HBP are known, 50% of these are treated and only 50% of these, adequately so. Our Health Authority strategy for prevention of CHD and stroke included an incremental, funded approach in primary care to improving the recording and treatment of HBP. **Methods:** In 1997, as part of a health promotion initiative, 211 of 217 practices (1M, principally deprived urban population, 600+ GPs) audited blood pressure (BP) recording (all patients 40-84yrs. N=379,359). The recording target increased annually. Treatment targets are now included and recording of smoking habit to promote global risk assessment and ensure behavioural risk factors are addressed in hypertensive patients. Locally agreed HBP guidelines (including advice about behavioural change support services) apply across primary/secondary care and support the initiative. Customised software supports a paperless audit.
Results: This collaboration between GPs, the Primary Care Trust and the Health Authority, has proved successful. The table shows recording and target BP achievement. Recording is more, and target achievement less, with age. There is variation between practices.

	1997 (%)	1998 (%)	1999 (%)	2000 (%)	2001 (%)	2002 (%)
BP ever recorded	66.5	78.4	82.7			
BP recorded <5 yrs			68.3	79.0	79.1	81.4
HBP				15.5	18.5	18.4
HBP treated						88.6
HBP treated and controlled					65.6	67.4
HBP + smoking recorded					21	21

% of patients with BP recorded within different time periods; % with HBP treated and controlled (<160 systolic and <95 diastolic); % HBP with smoking recorded.No value means audit data not requested for that year for that variable.

Conclusion: The control of hypertension is an important part of CHD and stroke prevention. In this population with high CHD mortality, high deprivation levels, a network approach and a common purpose to address prevention, hypertension identification and management can improve greatly, completely breaking the rule of halves. There remain substantial gains to be made in prevention as agreed target BP levels fall.

TARGETTING SIGNALLING PATHWAYS IN LEFT-VENTRICULAR HYPERTROPHY

143 Beneficial effects of combined blockade of angiotensin type 1 receptor and HMG-CoA reductase on left-ventricular remodelling and ventricular vulnerability in infarcted rats

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Background Reactive cardiomyocyte hypertrophy after myocardial infarction is an important risk factor for arrhythmias. Both angiotensin receptor antagonists and 3-hydroxy-3-methylgultaryl coenzyme A (HMG-CoA) reductase inhibitors have been shown to decrease cardiovascular morbidity and mortality. Whether combination treatment may be superior to either drug alone on cardiomyocyte hypertrophy remains unclear. **Methods and Results** After ligation of the left anterior descending artery, rats were randomized to both, 1, or neither of the angiotensin receptor antagonist olmesartan (0.01, 0.1, 1, and 2 mg/kg per day) and HMG-CoA reductase inhibitor pravastatin (5 mg/kg/day) for four weeks. Each drug, when given alone, decreased cardiomyocyte sizes isolated by enzymatic dissociation at the border zone compared with vehicles. However, compared with either drug alone, combined olmesartan and pravastatin prevent cardiomyocyte hypertrophy to a larger extent. The myocardial endothelin-1 levels at the border zone were 6.5-fold higher ($P < 0.0001$) in the vehicle group compared with the sham group, which can be inhibited after pravastatin administration. Further evaluation of combination therapy with a low dose of olmesartan (0.01 mg/kg/day) significantly prevented cardiomyocyte hypertrophy compared with pravastatin alone (3020 368 vs. 3202 406 m in the pravastatin-treated group, $P = 0.04$). With the highest dose of olmesartan (2 mg/kg/day) in combined therapy, we observed a further reduction of cardiomyocyte hypertrophy although tissue endothelin-1 levels remained stable in combination groups. Measurements of arrhythmic score mirrored those of cardiomyocyte hypertrophy. **Conclusions** Dual-therapy with pravastatin and olmesartan, which produced an additive reduction in cardiomyocyte hypertrophy in a dose-dependent manner after myocardial infarction through different mechanisms, decreases the propensity of the heart to arrhythmogenesis. Because cotreatment with statins and olmesartan acts in an additive manner, these observations provide important therapeutic implications in pharmacotherapy of clinical practice.

144 Blocking p193 and p53 pro-apoptotic pathways has positive effects on cardiac morphology and function after myocardial infarction

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Purpose: Blocking the p193 and p53 pro-apoptotic pathways has shown to alleviate cardiomyocyte death after myocardial infarction. We investigated whether antagonization of these pathways in mice would be reflected by better cardiac morphology and performance.
Methods: The p193 and p53 pro-apoptotic pathways in mice were antagonized by the expression of cardiac-restricted transgenes that express dominant-negative interfering p193 and p53 genes. Double transgenic mice (p193 and p53), mice expressing p193 or p53 only and non-transgenic littermates (control mice) were generated. Under anaesthesia the left coronary artery was ligated via thoracotomy, the chest was closed, and the mice were allowed to recover. After 4 weeks we measured pressure-volume loops in 7 double transgenic, 7 p193, 7 p53 and 6 control mice. After physiological measurements the hearts were excised and histologically analysed.
Results: The systolic function of the double transgenic mice in terms of dP/dtmax (mmHg/s) was significantly better compared with the control mice (5477.4 ± 278.9 vs 4430.0 ± 465.2; $p<0.05$). Also there was a better diastolic function, as measured by dP/dtmin (mmHg/s), in the double transgenics (-4190.6 ± 227.1 vs -3207.8 ± 282.9; $p<0.05$). Another diastolic parameter, tau (ms), showed a better outcome as well, (13.1 ± 0.7 vs 16.2 ± 0.9, $p<0.05$). Further differences between both groups were higher end-systolic pressures, significant lower end-diastolic pressures and higher myocardial oxygen consumption in the double transgenic group. The p193 only transgenic mice also scored better systolic and diastolic function compared with the control mice, although this was a bit less pronounced than in the double transgenic mice. The cardiac function of the p53 only transgenic mice was comparable with the control mice. Histological analysis revealed smaller infarct size in double transgenic and p193 only transgenic mice compared with non-transgenic and p53 only transgenic mice (42% vs 52% of the left ventricle, $p<0.05$). In latter two groups apoptosis rates of cardiomyocytes in the peri-infarct area were up to a 100-fold higher compared with double and p193 only transgenics. Also muscle fiber diameters in the surviving myocardium in the non-transgenic and p53 only transgenic mice were significantly bigger compared with the other two groups, suggesting higher rates of reactive hypertrophy.
Conclusions: These findings indicate that antagonization of both the p193 and the p53 or only the p193 pro-apoptotic pathways has positive effects on cardiac morphology and function after myocardial infarction.

145 Gene transfer of the mechanically induced gene IEX-I inhibits cardiac hypertrophy in vivo

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Mechanotransduction participates in both physiological and pathological processes of the cardiovascular system and plays an important role in the transition from cardiac hypertrophy to heart failure. We recently identified the immediate early response gene iex-1 as a strongly strain-induced gene in cardiomyocytes. Aim of this study was to investigate functional effects of selective cardiac gene transfer of iex-1.
Replication defective adenoviral vectors for overexpression of iex-1 (AdIEX) and of the reporter gene gfp (AdGFP) were constructed using the padEASY system. Cardiac hypertrophy was induced after thoracotomy by transverse aortic banding (TAC, n=12) in male FVB mice (8-10 weeks). Control animals underwent exactly the same procedure except that the banding was removed after surgery (sham, n=12). During surgery, AdIEX (n=6) and AdGFP (controls, n=6) were injected into the left free wall (2x10e9 pfu in 25 μl) of animals of both groups. After 7 days, the animals were sacrified, the hearts removed, fixed in paraformaldehyde (4%) and paraffin-embedded. Infected cardiomyocytes were detected by positive cellular flourescence of GFP. Cross-sectional area (CSA) of infected and non-infected cells was assessed by quantitative microscopy.
TAC induced robust hypertrophy after 7 days as compared to sham surgery (CSA: 257.9 ± 54.9 vs. 152.4 ± 27.6 sqμm; $p<0.0001$). Overexpression of iex-1 significantly inhibited cardiac hypertrophy in response to TAC as compared to AdGFP-infected controls (CSA: 136.3 ± 31.5 vs. 262.5 ± 34.4 sqμm; $p<0.001$). In the sham group, no significant differences in cell size were found between animals infected with AdIEX compared to AdGFP-infected animals (CSA: 132.0 ± 38.2 vs. 152.8 ± 30.2 sqμm; p=NS).
In conclusion, our findings demonstrate that adenoviral gene transfer of the mechanically inducible gene iex-1 has distinct anti-hypertrophic effects in vivo.

146 Targeted disruption of ryanodine receptor type 2 in the heart suppresses pressure overload-induced cardiac hypertrophy but impairs cardiac functions

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Purpose: Ryanodine receptor type 2 (RyR2) is a main calcium-induced calcium release-receptor of intracellular calcium stores in cardiac myocytes. Although calcium has been reported to play an important role in the development of cardiac hypertrophy as well as in excitation-contraction coupling, there has been no information concerning the role of RyR2 in pressure overload-induced cardiac hypertrophy. We therefore examined the role of RyR2 in the development of cardiac hypertrophy induced by pressure overload using adult heterozygous RyR2 knockout mice (RyR2 KO mice).
Methods and Results: There were no significant differences in body weight, heart rate, blood pressure and cardiac functions between RyR2 KO mice and littermate wild type mice at basal condition. Constriction of transverse aorta (TAC) caused similar degree of systolic blood pressure elevation in wild type mice and RyR2 KO mice. After two weeks of TAC, marked hypertrophic responses were induced in the heart. Wall thickness of the left ventricle (LV), size of cardiomyocytes and extent of LV fibrosis were increased, and the reprogramming of specific gene expression was observed in wild type mice. In contrast, all of the hypertrophic responses induced by TAC were significantly weak in RyR2 KO mice. Moreover, at three weeks after TAC, end diastolic pressure of LV was higher in RyR2 KO mice than in wild type mice, and the both maximum and minimum dP/dt were smaller in RyR2 KO mice than in wild type mice. These results reveal that in response to pressure overload, RyR2 KO mice do not develop to cardiac hypertrophy but show impaired cardiac functions.
Conclusion: Our results suggest that RyR2 plays important roles in development of cardiac hypertrophy and in maintaining of cardiac functions.

147 Chronic overexpression of cardiac angiotensinogen suppresses basal ex vivo heart function and cardiomyocyte contractility in hypertrophic transgenic mice

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Angiotensin II (AngII) is known to induce cardiac growth and modulate myocardial contractility. Elevated levels of endogenous AngII are thought to contribute to the development of cardiac hypertrophy in hypertensives, but little is known about the long term functional effects of cardiac exposure to AngII in normotensives.
Aim: To investigate the effects of chronic cardiac overproduction of AngII on ex vivo heart function and isolated cardiomyocyte contractility.
Methods: Normotensive heterozygous transgenic mice (TG) harbouring multiple copies of a cardiac specific rat angiotensinogen gene (Hypertension, 31:1324-1330, 1998) were studied at age 30-40 weeks and compared with wild-type (WT) littermates. Left ventricular function was measured ex vivo in crystalloid perfused Langendorff mounted hearts (36°C) using a fluid filled PVC balloon interfaced to a pressure transducer (MLT844, ADInstruments). Isolated left ventricular cardiomyocytes were prepared by enzymatic dissociation and paced to contract by field stimulation at 5 Hz (36°C). Cell contraction kinetics were measured using a high resolution (1 ms) digital imaging system.
Results: There was no difference in the mean (±sem) intrinsic heart rate of TG and WT (352±12 vs 368±21 bpm, n = 10 & 7). Under standardised end-diastolic pressure conditions, TG hearts exhibited a significant reduction in peak developed pressure (138.5±8.2 vs 161.5±3.1 mmHg) and maximum rate of pressure development (4.48±0.11 vs 3.69±0.24 mmHg/ms). Time to relaxation was also significantly prolonged in the TG hearts (77.2±1.7 vs 71.1±2.1 ms). In isolated cardiomyocytes, although no difference in maximum shortening was observed between TG and WT (4.19±0.50 vs 4.99±0.45% diastolic length, n=15 & 16) there was a significant reduction in normalised maximum rate of shortening in the TG myocytes (2.57±0.20 vs 3.79±0.34 cell length/s). In TG cardiomyocytes the contractile cycle time was prolonged, with time to relaxation increased by almost 50% (52.9±3.0 vs 36.2±2.2 ms).
Conclusion: These data demonstrate that chronic in vivo exposure to elevated levels of intracardiac AngII is associated with significant contractile abnormalities evident in individual cardiomyocytes and in the intact heart. Our findings suggest that endogenous overproduction of cardiac Ang II, independent of changes in blood pressure, is sufficient to induce ventricular remodelling that culminates in impaired cardiac function which may precede failure.

148 Activation of E2F transcription factors in cardiac hypertrophy

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Abstract Objective: Cardiac hypertrophy is a complex phenotype induced by a number of stimuli and may lead to cardiomyopathy and heart failure. Present knowledge suggests that cell cycle regulatory proteins take part in the development of hypertrophy. We have investigated the activation and regulation of the E2F transcription factor during the hypertrophic response.
Methods: The expression and activity of E2F, the retinoblastoma protein and the G1 cyclin-cdk complexes in cardiomyocytes were studied during seruminduced hypertrophy in isolated, neonatal cardiomyocytes. The E2F transcription factor activity was inhibited directly by expression of a DN-Rb protein and indirectly through pharmacological manipulation of the G1 cyclin-cdk complexes.
Results: The activity of E2F and the cyclin D-cdk4/6 kinase complex were upregulated during serum induced hypertrophy in cardiomyocytes. The E2F activity was downregulated when inhibiting cdk4/6 or cdk2 kinase activity, but hypertrophic growth was only impaired when inhibiting the cyclin D-cdk4/6 complex. Inhibiting the E2F transcription factor directly by expression of a DN-Rb protein also impaired hypertrophic growth. The induced E2F activity during the hypertrophic response induced the expression of cyclin D and cyclin E. However, PCNA expression was not induced.
Conclusion: These data suggest that E2F transcription factor activity is involved in the hypertrophic response, activating genes necessary for hypertrophic growth but not for DNA synthesis. This activity seems to be controlled by the cyclin D-cdk4/6 complex. Hence, these data supports the notion that cell cycle regulatory proteins regulate hypertrophic growth in cardiomyocytes.

REGULATORY EFFECTS OF ENDOTHELIAL CELLS: FROM ANGIOGENESIS TO ISCHAEMIA

149 Cytochrome P450 2C9 induces cycloxygenase-2 expression in endothelial cells

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The endothelial cytochrome P450 epoxygenase 2C9 (CYP 2C9) plays an important role for vascular homeostasis via metabolising arachidonic acid into epoxyeicosatrienoic acids (EETs). EETs do not only activate Ca^{2+}-dependent K^+-channels and protein kinases, they also induce angiogenesis. The different signalling pathways leading to EET-induced angiogenesis are not yet completely understood. COX-2 is known to be involved in angiogenic processes and its expression correlates with the formation of new blood vessels. Therefore we investigated whether CYP 2C9 overexpression modulates the expression of COX-2.
To investigate the effect of CYP 2C9 on COX-2 expression, human umbilical vein endothelial cells (HUVEC) were infected with CYP 2C9 sense or antisense adenoviral constructs. Overexpression of CYP 2C9 induced a two-fold increase in COX-2 protein expression, an effect which was accompanied by a two- to three-fold increase in COX-2 promoter activity. The CYP 2C9-induced expression of COX-2 was sensitive to the specific CYP 2C9 inhibitor sulfaphenazole. Furthermore, the protein kinase A inhibitor KT5720 attenuated the CYP 2C9-induced increase in COX-2 promoter activity and protein expression. Moreover, exogenous application of 11,12-EET led to an increase in COX-2 expression in endothelial cells. Stimulation with 11,12-EET markedly increased intracellular cyclic AMP levels and activated and therefore induced DNA-binding of the cyclic AMP-response element-binding protein (CREB). Taken together, these data show, that CYP 2C9 induces COX-2 expression in endothelial cells via a cyclic AMP-dependent pathway, a mechanism which probably contributes to the CYP 2C9-induced angiogenic response.

150 Transplantation of spleen-derived progenitor cells influences neointima formation after vascular injury

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Introduction: Transplantation of endothelial progenitor cells (EPCs) has been shown to contribute to neoangiogenesis and regeneration of infarcted tissue. Endothelial cell damage followed by a rapid neointima formation is one important pathophysiological step of atherosclerosis and restenosis after angioplasty. Accelerated reendothelialization impairs neointima formation by inhibition of smooth muscle cell proliferation. In this study we evaluated the possible role of transplanted spleen-derived progenitor cells on reendothelialization and neointima formation in a mouse model of arterial injury.
Methods and Results: EPCs are a scarce population of cells in the peripheral blood. Therefore isolated spleen derived mouse mononuclear cells (MNCs) were expanded ex-vivo in endothelial basal medium. After 4 days in culture about 85% of cells showed uptake of Dil-acetylated LDL and lectin binding. FACS analysis and immunocytochemistry revealed that these cells express Sca-1 and various endothelial cell lineage markers including VEGFR-2. To evaluate the effect of stem cell transplantation on reendothelialization after vascular injury, mice received either 1x106 PKH-26 or dil-LDL labeled spleen derived MNCs or ex-vivo expanded EPCs i.v. on the day of surgery and 24 h later. En-face microscopy showed transplanted cells at the site of injury on day 4 and on day 14 after surgery. A single dose of FITC-labeled lectin 30 minutes before tissue harvesting demonstrated the endothelial phenotype of attached, transplanted cells. To evaluate the biological effect of transplanted cells, neointima formation was measured in transplanted and placebo treated mice. Morphometric analysis revealed a significant reduction of neointima formation after cell transplantation.
Conclusion: Transplanted EPCs contribute to repair mechanisms after vascular injury. Acceleration of reendothelialization leads to decreased neointima formation. These results provide novel insights in stem cell biology and provide further information for stem-cell based therapeutic strategies for the treatment of vascular dysfunction and restenosis after angioplasty.

151 Charaterization of endothelial progenitor cells derived from umbilical cord blood

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Background: Bone marrow-derived endothelial progenitor cells (EPCs) circulate in peripheral blood and can incorporate at sites of neovascularization. These cells are thought to share a common origin with haematopoietic stem cells. Human umbilical cord blood is known to contain large number of haematopoietic stem/progenitor cells, and therefore could constitute a novel source for isolating and expand EPCs. In the present study we have characterized cultured EPCs derived from umbilical cord blood with regards to their cellular phenotype, replicative capacity and functional characteristics, and also compared these parameters with those displayed by human umbilical vein endothelial cells (HUVEC).
Results: Mononuclear cells cultured with VEGF for 21 days gave rise to colonies of proliferating adherent cells, the majority of which incorporated acetylated LDL and stained with Ulex Europaeus lectin 1, confirming their endothelial lineage. A fraction of EPC (~8%) still expressed the haematopoietic stem/progenitor cell antigen CD133, whereas this marker was not expressed by HUVECs. In contrast, while all HUVEC expressed the endothelial cell antigen CD146, only 60% of EPCs-derived cells were CD146+. bFGF or VEGF-A stimulated both EPC and HUVEC proliferation, whereas placental growth factor was mitogenic only in EPCs. Telomerase activity was 2.5 times higher in EPCs than in HUVECs; furthermore, this activity was sustained in later passage EPCs, but not in HUVECs. In a Matrigel assay, EPCs on their own formed less developed tubule networks than those formed by HUVECs.
Conclusions: EPCs derived from umbilical cord blood maintain and inmature endothelial phenotype following in-vitro culture. These findings suggest that expansion of EPCs prior to transplantation may be a suitable approach to increase the success of cardiovascular stem cell therapies.

152 Shear stress regulates smooth muscle cell-endothelial cell interaction

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Vascular endothelial cells (ECs), which exist in close proximity to vascular smooth muscle cells (SMCs), are constantly subjected to blood flow-induced shear stress. Although the effect of shear stress on endothelial biology has been extensively studied, the influence of SMCs on endothelial response to shear stress remains largely unexplored. In the present study, the potential role of SMCs in regulating the shear stress-induced gene expression in ECs has been examined using our parallel-plate co-culture flow system, in which these two types of cells were separated by a porous membrane. In this co-culture system, SMCs tended to orient perpendicularly to the flow direction, whereas the ECs were elongated and aligned with the flow direction. Under static condition, co-culture with SMCs induced EC gene expressions of intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and E-selectin, while attenuated that of endothelial nitric oxide synthase (eNOS). Shear stress significantly inhibited the SMC-induced adhesion molecule gene expressions. These EC responses under static and shear conditions were not observed in the absence of close communication between ECs and SMCs, and they were also not observed when ECs were co-cultured with fibroblasts instead of SMCs. Our findings indicate that under static condition co-culture with SMCs induces ICAM-1, VCAM-1, and E-selectin gene expressions in ECs. These co-culture effects are inhibited by shear stress and require specific interaction between ECs and SMCs in close contact.

153 Tetrahydrobiopterin depletion leads to endothelial nitric oxide synthase dysfunction in ischaemic hearts

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Endothelial nitric oxide synthase (eNOS) function is impaired in ischemic hearts. However, the mechanisms of ischemia-induced eNOS impairment remain poorly understood. eNOS activity requires availability of key cofactors, such as tetrahydrobiopterin (BH4). Previous studies have shown that lack of BH4 is a major determinant of eNOS dysfunction in hypercholesterolemia and hypertension. Yet, whether decreased BH4 is involved in ischemia-induced eNOS dysfunction is unclear. Accordingly, we evaluated the time course of changes in BH4 content and eNOS activity in isolated rat hearts subjected to 30, 45 and 60 min global ischemia at 37°C. BH4 content was measured on cardiac homogenates by HPLC using electrochemical detection; eNOS activity was determined by L-[14C] arginine to L-[14C] citrulline conversion. Ischemia led to a dramatic decrease in BH4 content within 30 min; this loss was paralleled by a substantial and progressive reduction in eNOS activity (Table). To investigate whether decreased eNOS activity was causally related to ischemia-induced depletion in BH4 level,parallel experiments were performed in which eNOS activity was measured after addition of an excess (10 μM) of exogenous BH4. BH4 addition substantially restored eNOS activity when ischemia was limited to 30 min (Table), whereas no increase in eNOS activity was observed when the assay was performed in presence of BH4 after more prolonged time of ischemia (45 and 60 min).

BH4 and eNOS

	Baseline	30 min ischemia	45 min ischemia	60 min ischemia
BH4 (pmol/mg)	2.51±0.51	0.45±0.09*	0.38±0.05*	0.31±0.14*
eNOS (pmol/min/mg)	0.16±0.02	0.08±0.01*	0.04±0.01*	0.03±0.01*
eNOS + BH4 (pmol/min/mg)	0.27±0.02	0.24±0.01	0.11±0.01*	0.04±0.01*

Time course of BH4 content and eNOS activity at baseline and during ischemia; eNOS activity measured both under basal conditions and after addition of exogenous BH4 (values are mean±SEM of 5 experiments; *=p<0.01 vs baseline)

Taken together, our data for the first time demonstrate that ischemia induces a major loss in cardiac BH4 content and that eNOS activity is critically anchored to BH4 bioavailability in this setting. Supplementation with exogenous BH4 may partially restore eNOS function (at least within certain time frame), thereby representing a potentially relevant tool to treat altered eNOS activity in ischemic heart disease.

154 Effects of raloxifene, tamoxifene and β-oestradiol on angiotensin type 1 receptor expression in human umbilical artery endothelial cells incubated with high concentrations of glucose

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Diabetes and high-glucose concentrations are important risk factors of coronary heart disease (CHD) and accelerated progression of atherosclerosis. AT1R is thought to mediate the major cardiovascular effects of angiotensin II: cell migration and proliferation, vasoconstriction and free radicals generation. Thus, modulation of expression of AT1R gene may play an important protective role in atherosclerosis. Estrogens decrease expression of AT1R in endothelial cells in normoglyceamic conditions in vitro, but there is no evidence if this effect could be observed in hyperglycemic conditions (e.g. in patients with diabetes). The purpose of the study was to compare the effects of beta-estradiol, raloxifene and tamoxifene on AT1R expression in endothelial cells (EC) incubated with normal (5 mM) and elevated (15 mM) levels of glucose.
Methods: ECs obtained from human umbilical artery (HUAEC) were incubated in selective growth medium with supplement containing ECs growth factors. Just before experiment, cells were cultured in serum-free medium containing normal or high glucose concentration. In parallel, medium was supplemented with beta-estradiol, raloxifene and tamoxifene in two concentrations 1 and 10 microM/l. After 48h cells were harvested, and total cellular RNA were isolated. AT1R mRNA levels were calculated using real time RT-PCR technique. Expression of AT1R mRNA was normalized using mRNA levels of glucose-6-phosphate dehydrogenase as reference gene.
As a control, cells cultured in medium containing normal (5 mM - CN) or high glucose level (15 mM - CH) were used. Statistical analyses were performed using ANOVA test.
Results: High glucose concentration evokes significant overexpression of AT1 receptor (324% higher than in CN group). Observed effect of glucose was diminished by co-incubation with beta-estradiol, raloxifene and tamoxifene. AT1 expression in cells incubated with tested drugs and high glucose concentration was statistically significantly lower than in CH cells (170% vs. 324%), but significantly higher than in CN cells. There were no statistical differences between tested substances.
Conclusions: Observed positive effect of raloxifene, tamoxifene and estradiol on AT1R downregulation may have important protective role in atherosclerosis development. However, future clinical studies are necessary to confirm the importance of this observation.

STRESS AND HYPERTENSION

155 Role of nerve firing, norepinephrine reuptake and angiotensin neuromodulation for sympathetic nervous augmentation in essential hypertension

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Background: The mechanisms responsible for sympathetic activation occurring in essential hypertension are still poorly understood. Potential contributors include central mechanisms, alterations in norepinephrine disposition and interaction with other neurohumoral factors, such as angiotensin II.
Methods and Results: To address this issue, regional sympathetic activation was studied comprehensively using microneurography and radiotracer dilution methodology in 24 untreated hypertensive patients and 11 age-matched normotensive subjects both before and after intravenous administration of the neuronal norepinephrine (NE) reuptake inhibitor desipramine (0.3mg/kg). Regional angiotensin II concentrations were measured in parallel. Compared to their normotensive counterparts, hypertensive subjects displayed increased muscle sympathetic nerve activity ($p<0.01$) and total systemic and regional (cardiac and renal) NE spillover at baseline ($p<0.05$). Whole body NE reuptake and the fractional extraction of 3[H]NE across the heart, an indicator of cardiac neuronal NE reuptake, were lower in hypertensive subjects (58±15 vs 70±12%; $p<0.05$). Desipramine lowered total body NE spillover by ~25-30% in both groups but elicited a more pronounced reduction of fractional 3[H]NE extraction in normotensive subjects than in hypertensive subjects (-51±12 vs -37±10%; $p<0.05$). Cardiac NE spillover increased only in normotensive subjects and was similar to that of hypertensive subjects after desipramine infusion (23.5±12.9 vs 24.2 ±12.8 ng/min; p=ns). DNA sequencing analysis of the NE transporter gene did not reveal any mutations which could account for reduced transporter activity. Arterial and coronary sinus angiotensin II concentrations did not differ between the two groups and were not related to indices of sympathetic activation.
Conclusions: Increased rates of sympathetic nerve firing and reduced neuronal reuptake of norepinephrine both contribute to sympathetic activation in essential hypertension, whereas a peripheral neuromodulating influence of angiotensin II seems to be excluded.

156 Rilmenidine sympatholytic activity preserves mental and orthostatic sympathetic response and epinephrine secretion

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Purpose: To study the sympathetic properties of rilmenidine (RIL) and its blood pressure (BP) lowering activity.
Methods: Randomised, double-blind, 6-week cross-over study with 1-week placebo (PLA) run-in period, two 2-week active treatment terms (RIL 1 mg od or PLA) at 1-week PLA wash-out interval. In 15 hypertensive patients, norepinephrine (NE) and epinephrine (E) kinetics and intra-arterial BP measurements were performed at rest, after mental stress (MS) and head-up tilt (HuT) tests, at the end of each active treatment period.
Results: RIL significantly decreased NE spillover rate at rest but preserved the increase after both MS and HuT tests. Intra-arterial BP rose after MS and remained stable after HuT in the two treatment groups. E secretion was 162.3±106.6 ng/min while supine on placebo, was unchanged with HuT, and increasedby 76.8±162.6 ng/min with MS (p=0.019). RIL was without effect on E secretion under all conditions.

NE spillover rate and intra-arterial SBP

n=15	PLA	RIL	PLA-RIL	
	mean±SD	mean±SD	adjusted mean±SE	between group p
NE spillover rate (ng/min)				
Rest	582.0±260.8	358.7±155.3	205.8±61.2	p=0.005
MS-rest	168.9±218.4*	136.5±116.3**	54.2±32.5	ns
HuT-rest	134.5±261.2	147.5±120.1***	-51.0±76.1	ns
Intra-arterial SBP (mmHg)				
Rest	175.2±18.3	159.5±19.5	15.0±4.1	p=0.003
MS-rest	23.7±16.6*	28.1±16.6*	-1.6±4.2	ns
HuT-rest	-1.5±16.7	-4.2±13.5	2.8±4.4	ns

Within group p: *p<0.001; **p=0.004; ***p=0.008

Conclusion: This study confirms the sympatholytic activity of RIL at supine rest and shows that RIL preserves sympathetic reactivity to mental stress and head-up tilt, with no deleterious postural effect on BP. The sympatholytic action of RIL contrasted with its failure to suppress E secretion, affirming that here, as elsewhere, sympathetic nervous and adrenal medullary function can be disconnected.

157 Chronic sympathectomy improves survival and attenuates cardiac dysfunction during the progression of pressure-overload hypertrophy to heart failure

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Chronic overactivity of the sympathetic nervous system is known to contribute to left ventricular (LV) functional deterioration and to mortality in the congestive heart failure (CHF) syndrome, and beta-blocker treatment has been unquestionably shown to exert clinical benefit in this setting. However, it is still unknown whether more extensive interference with sympathetic activity has even stronger protective effects than beta-blockade (Bb).
Methods: The course of pressure overload-induced LV hypertrophy, dysfunction and failure obtained by surgically banding the abdominal aorta (B) was evaluated in Sprague-Dawley rats subjected to chronic treatment with vehicle (Vh), Bb (oral propranolol, 60 mg/kg) or chemical sympathectomy (Sx, 6-hydroxydopamine, 150 mg/kg i.p. twice a week). Concurrent groups of sham-operated (S) rats were studied. Ten weeks after surgery, carotid systolic blood pressure (SBP) and LV echo-derived endocardial fractional shortening (FS), end-diastolic (EDD) and end-systolic (ESD) internal dimensions were measured. Excised lung (LUNGi), right ventricular (RVi) and LV (LVi) weight indices (g/100 g body weight) were measured.
Results: In the banded groups, 10-week survival was 60% in Vh, marginally improved by Bb (69%) but strongly improved by Sx (94%, $p<0.01$ vs Vh); survival was 100% in all S groups. Further results are shown in the Table.

Results

	n	EDD(mm)	ESD(mm)	FS(%)	SBP(mmHg)	LVi(g/100g)	RVi(g/100g)	LUNGi(g/100g)
S-Vh	9	7.1±0.3	4.3±0.2	42±2	102±12	1.9±0.1	0.5±0.1	2.9±0.6
S-Sx	11	7.2±0.3	4.4±0.2	39±2	96±15	2.0±0.2	0.6±0.1	3.6±0.4
S-bB	10	6.9±0.2	4.1±0.2	38±3	100±15	2.0±0.5	0.6±0.1	3.5±0.9
B-Vh	10	9.5±0.3*	6.3±0.3*	28±4*	154±19*	3.0±0.5*	0.8±0.3*	4.3±1.2*
B-Sx	15	8.6±0.3*#	5.8±0.3*	35±2#	159±18*	2.5±0.6*#	0.6±0.1#	3.7±0.6
B-bB	11	8.3±0.3*#	5.9±0.3*	33±4	150±12*	2.5±0.7*#	0.7±0.3	3.8±1.2

Means±SD; *p<0.05 vs corresponding S; #p<0.05 vs B-Vh.

Conclusions: In the course of experimental pressure overload, chronic sympathectomy favourably affects the degree of hypertrophy, chamber dilation, systolic dysfunction, lung congestion and right ventricular involvement; even more importantly, it improves survival. Therefore, extensive interference with sympathetic activity in an experimental syndrome leading to LV hypertrophy, dysfunction and failure has strong beneficial functional and survival effects over and above beta-blockade.

158 Importance of arterio-venous fistulas on sympathetic nerve activity and on arterial baroreflex sensitivity in renal transplanted patients

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Objective: The acute bradycardia induced by the occlusion of an arteriovenous fistula (AVF), known as the Nicoladoni-Branham sign, is considerably larger than that which occurs during a carotid sinus massage. This suggests increased arterial baroreflex sensitivity during acute AVF occlusion. Moreover, the influence of acute AVF occlusion on muscle sympathetic nerve traffic (MSNA, by microneurography) is unknown. We therefore assessed the effects of acute AVF occlusion on baroreflex sensitivity and on MSNA in patients with stable functional kidney grafts and patent AVF.
Design and methods: We measured blood pressure (BP), MSNA, heart rate (HR), cardiac output (CO) and arterial baroreflex sensitivity at baseline and during acute, 30-second pneumatic AVF occlusions for in 19 renal transplant recipients.
Results: During the first 5 seconds of the AVF occlusion, mean BP increased from 97 ± 4 to 114 ± 5 mmHg ($p<0.0001$) while MSNA decreased to 42 ± 17% of baseline values (n=11; $p<0.01$) and HR decreased from 71 ± 2 to 61 ± 2 bpm ($p<0.0001$). The largest increases in BP were accompanied by the most marked decreases in both MSNA (r=-0.76, $p<0.0001$) and HR (r=-0.69, $p<0.0001$) during the first 5 seconds of the AVF occlusion. During AVF occlusion baseline CO of 7.1 ± 0.3 decreased to 5.7 ± 0.3 l/min ($p<0.0001$) while baroreflex sensitivity increased from 9 ± 1 to 16 ± 2 ms/mmHg ($p<0.01$).
Conclusions: Arterial baroreceptor activation and increased arterial baroreflex sensitivity decrease heart rate during AVF occlusion. In addition our study is the first to demonstrate that sympathetic nerve traffic decreases during the Nicoladoni-Branham sign.

159 Abnormal neurovascular control during exercise and mental stress in hypertensive patients

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Hypertension has been, at least in part, associated to increased sympathetic nerve activity and vascular resistance. We hypothesized that muscle sympathetic nerve activity during exercise and mental stress would be exaggerated in hypertensive patients, whereas muscle blood flow would be reduced when compared to normotensive controls. We studied 12 hypertensive patients (HP, 42±2 years, body mass index= 27.6±1 kg/m^2) and 14 body mass index- and age-matched normotensive controls (NC, 38±2 years, P=0.13; body mass index= 25.5±1 kg/m^2, P=0.10) during isometric handgrip exercise (3 minutes) at 10 and 30% of maximal voluntary contraction, when central command, mechanoreceptors and metaboreceptors were selectively activated, and during Stroop Color World Test (3 minutes). We measured muscle sympathetic nerve activity (MSNA) directly from peroneal nerve by microneurography, forearm blood flow by venous occlusion plethysmography, and blood pressure by oscillometric automated method. Baseline MSNA burst frequency (36±1 vs. 22±1 bursts/min, P=0.00001) and mean blood pressure (114±3 vs. 94±2 mmHg, P=0.0001) were higher in HP than in NC. Forearm vascular conductance was lower (1.84±0.2 vs. 2.99±0.3 units, P=0.0001) in HP when compared to NC. During 10% exercise, MSNA burst frequency (39±1 vs. 25±2 bursts/min, P=0.0008) and mean blood pressure (116±4 vs. 99±2 mmHg, P=0.00001) were higher in HP than in NC. In contrast, forearm vascular conductance (2.1±0.2 vs. 3.4±0.4 units, P=0.0001) was lower in HP than in NC. Similarly, during 30% exercise, MSNA burst frequency (44±2 vs. 33±2 bursts/min, P=0.0001) and mean blood pressure (133±3 vs. 113±3 mmHg, P=0.0001) were higher in HP than in NC. However, forearm vascular conductance (2.2±0.3 vs. 4.3±0.6 units, P=0.0001) was lower in HP than in NC. Mental stress elicited greater MSNA burst frequency (40±1 vs. 28±2 bursts/min, P=0.0001) and mean blood pressure (121±5 vs. 99±2 mmHg, P=0.0001) responses in HP than in NC. In contrast, forearm vascular conductance (3.0±0.3 vs. 4.7±0.6 units, P=0.01) was lower in HP than NC. Exercise or mental stress provokes exaggerated increase in MSNA in HP. In addition, this neural response seems to have hemodynamic implications, since forearm vascular conductance is attenuated and blood pressure is enhanced during those two physiological maneuvers in HP.

160 Adrenergic activation characterizes human obesity independently by obstructive sleep apnea

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Objective: Conflicting evidence is available on whether the sympathetic overactivity characterizing human obesity is a hallmark of the overweight state or it rather occurs only when obesity is coupled with the presence of obstructive sleep apnea (OSA).

Design and Methods: We studied 27 male normotensive subjects classified, according to body mass index (BMI) and presence or absence of OSA (overnight respiratory polysomnography), as leans without OSA (L-, n=7, BMI:23.7±0.7kg/m^2, age:52.6±2.2 yrs, mean±SEM), leans with OSA (L+, n=6, BMI:23.9±0.6 kg/m^2, age:52.5±1.9 yrs), obese without OSA (O-, n=6, BMI:31.0±0.9 kg/m^2, age:55.0±2.5 yrs) and obese with OSA (O+, n=8, BMI:31.1± 0.7 kg/m^2, age:54.7± 2.2 yrs). In each subject measurements were performed in the resting awake state for 30 min and included mean arterial pressure (MAP, Finapres), heart rate (HR, EKG), plasma norepinephrine (NE, HPLC), muscle sympathetic nerve traffic (MSNA, microneurography), plasma leptin (RIA) and insulin sensitivity (Homa).

Results: Subjects with OSA were characterized by similar increases in the apnea/hypopnea index at the polysomnographic study. For similar MAP (93.2± 2.9 vs 92.3± 3.1mmHg) O+ showed MSNA values significantly greater than O_ (78.4±2.8 vs 63.2±4.4 bs/100hb, p<0.05). This was the case also for L+, which displayed MAP similar to L- (94.3±2.3 vs 93.8±1.9 mmHg) but significantly greater MSNA values (71.1±2.6 vs 43.4±3.8 bs/100hb, p< 0.02). MSNA was significantly increased in O- vs L- (63.2± 4.4 vs 43.4±3.8 bs/100hb, p< 0.02) but not in O+ vs L+ (78.4±2.8 vs 71.1±2.6 bs/100hb, p=NS). NE, although significantly greater in obese than in lean subjects, failed to show significant differences between subgroups with or without OSA. This was the case also for leptin and insulin resistance.

Conclusions: These data provide the first evidence that, when proper comparisons are made, obese subjects display a sympathetic overactivity independently on OSA. They also show that 1) the presence of OSA markedly increases sympathetic drive in lean individuals, 2) in subjects with OSA the presence of obesity does not potentiate the degree of sympathetic activation and 3) obese subjects with and without OSA display a similar profile of metabolic alterations.

MECHANISMS OF MYOCARDIAL DYSFUNCTION

161 Ser16-, but not Thr17-phosphorylation of phospholamban influences frequency-dependent force generation in human myocardium

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Dependent Force Generation in Human Myocardium

Objectives: β-adrenoceptor/cAMP-dependent Ser16- as well as Ca^{2+}-dependent Thr17-phosphorylation of phospholamban (PLB) influences SERCA 2a-activity and thus myocardial contractility. Methods. To determine the cross-signaling between Ca^{2+} and cAMP pathways, the phosphorylation of Ser16- and Thr17-PLB was studied at increasing stimulation frequencies as well as in the presence of β-adrenergic stimulation in isolated ventricular trabeculae from failing (dilative cardiomyopathy, DCM, heart transplants, n=10) and non-failing human myocardium (donor hearts, NF, n=13). In addition, we measured the intracellular Ca^{2+}-transient (fura-2) at increasing stimulation frequencies (0.5 to 3.0 Hz). As the Na^+/Ca^{2+}-exchanger (NCX) may compensate reduced SERCA 2a-activity in DCM, NCX- and SERCA 2a activity were studied as well. Only DCM with unchanged proetein expression of the Na^+/Ca^{2+}-exchanger were used. Results. In DCM, diastolic $[Ca^{2+}]_i$ was increased and systolic $[Ca^{2+}]_i$ as well as Ser16 PLB-phosphorylation were decreased as compared to NF (0.5 Hz, diastolic $[Ca^{2+}]_i$: 134±27 vs. 73±33 nmol/L; systolic $[Ca^{2+}]_i$: 186±29 vs. 289±63 nmol/L, PLB Ser16 P: 5594±1011 vs. 9213±1137 densitometric units). The positive Ca^{2+}/force relationship in human non-failing myocardium was accompanied by a frequency-dependent increase in Ser16-PLB, but not Thr17-PLB phosphorylation. After application of isoprenaline (1 μM), a profound increase in Ser16-PLB phosphorylation was accompanied by a small increase in Thr17-PLB phosphorylation, only in NF. Conclusions. The frequency-dependent phosphorylation of Ser16-PLB may favour an increase in Ca^{2+}-transient and force generation in man. Cross talk signaling of Ser16/Thr17-PLB phosphorylation after β-adrenergic stimuation exists in non-failing, but not in failing human myocardium. The Ca^{2+}-dependent CaM-kinase activity may be altered in human heart failure.

162 Human cardiac performance is genetically modulated by ile-164 polymorphism of beta-2 adrenergic receptor

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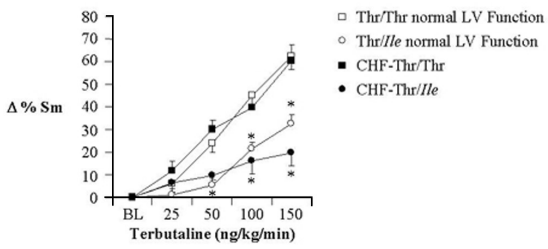
Background: Genetic heterogeneity of BETA2-adrenergic receptor with Thr164Ile polymorphism is associated with a poor prognosis in patients with congestive heart failure. The mechanisms underlying the poor prognosis are not entirely clear. We tested the hypothesis that Thr164Ile polymorphism directly modulates myocardial contractile performance.

Methods: We screened 916 subjects for the Ile-164 polymorphism. Thirty-three subjects were found positive for the Ile-164 variant (allele frequency ~3%). Cardiac contractile response to a BETA2-adrenergic receptor agonist terbutaline, as assessed from the peak myocardial velocity of systolic shortening (Sm) by tissue Doppler imaging, was studied in 16 subjects with Ile-164 variant and in 15 matched controls.

Results: Terbutaline induced a blunted increase (DELTA) in heart rate in subjects with the Ile-164 polymorphism vs controls (DELTA10±2 bpm vs DELTA20±3 bpm, p<0.05). In subjects with normal LV function, peak terbutaline-induced increase in Sm was lower in subjects with Ile-164 variant as compared to controls (figure 1). In patients with dilated cardiomyopathy (CHF), controls showed a preserved BETA2 adrenergic-mediated increase in Sm (figure). In contrast, subjects with Ile-164 had minimal BETA2 adrenergic-mediated increase in Sm (DELTA20±6% NS vs baseline).



Conclusion: The presence of the BETA2-adrenergic Thr164Ile polymorphism negatively modulates adrenergic-mediated cardiac responses. The severely impaired myocardial inotropic response in carriers of the Ile-164 variant may account for the poor outcome in patients with chronic congestive heart failure.

163 Potential role of cardiodepressant autoantibodies in cardiac dysfunction of patients suffering from dilated cardiomyopathy

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Background: Immunoadsorption (IA) which removes cardiac autoantibodies from plasma represents an additional therapeutic approach in dilated cardiomyopathy (DCM).
Methods: Before IA antibodies were purified from plasma of 45 DCM patients (LVEF<30%). We analyzed the functional effects of antibodies (300mg/L) on calcium transient and on systolic cell shortening in adult rat cardiomyocytes. After in-vitro analysis, in all patients IA was performed in 4 courses, at one-month intervals until month three.
Results: Antibodies from 29 patients (cardiodepressant group) induced a reduction (>10%) of calcium transient (-16.5±1.9%) and a simultaneous reduction (>10%) of cell shortening (-21.2±1.8%) on cardiomyocytes ($p<0.001$). Antibodies from 16 patients (non-cardiodepressant) did not influence significantly calcium transient or cell shortening. During the first IA course the cardiodepressant group showed an acute increase in cardiac index (CI) from 2.2±0.1 to 2.9±0.1 L/min/m^2 ($p<0.001$). In the non-cardiodepressant group hemodynamics did not significantly change throughout the three months. After three months before the last IA course (prolonged effects) the CI was 2.1±0.2L/min/m^2 in the non-cardiodepressant group and 2.9±0.1 L/min/m^2 in the cardiodepressant group ($p<0.001$). In contrast to non-cardiodepressant group, after three months in the cardiodepressant group LVEF increased from 20.8±1.1 to 30.5±1.1% ($p<0.01$).
Conclusions: In a subgroup of DCM patients cardiac antibodies may play a functional role in cardiac dysfunction. Evidence for cardiodepressant antibodies predicts hemodynamic benefit during IA.

164 The stretch-dependent slow force response depends on activation of Na^+/H^+-exchange but not to changes in pHi in mammalian myocardium

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Introduction: Mammalian myocardium is characterized by a biphasic response to stretch with an initial rapid, followed by a delayed increase in force. The initial phase is attributed to increased myofilament Ca^{2+} sensitivity, but the mechanism of the delayed phase remains unknown. We tested whether stretch-dependent Na^+/H^+-exchange (NHE) activation and consecutive changes in pHi underly the slow force response (SFR).
Methods: Rabbit left ventricular trabeculae (n=40) were electrically stimulated (0.2 Hz, 300C, isometric contractions). The muscles were loaded with the fluorescent pH-indicator BCECF-AM (15μM for 45 min). Protocol: stretch to optimum muscle length (lmax), unstretch to 88% lmax for 30 min (=base). Stretch to 98% lmax with simultaneous registration of force and pHi changes, and repetition of the same protocol with the same muscle after blocking NHE (HOE 642 3μM) or the "reverse mode" Na^+/Ca^{2+} exchanger (KB-R 7943 5μM) in either bicarbonate-containing (Tyrode (T)) or bicarbonate-free (HEPES (H)) buffer. pH-signals after each experiment were calibrated with the "high-K^+-Nigericin"-method.
Results: Stretch from 88% to 98% resulted in an increase in developed force to 210.1±24.6% (in T; $p<0.05$) and to 200.8±30.7% (in H; $p<0.05$) of basal values. 66.3±1.9% and 70.4±9.4% of force increases occur with the rapid phase, and 33.7±1.9% and 29.6±9.4% during the delayed phase (SFR). During SFR pH increased from 6.72±0.13 to 6.82±0.13 in T (p=n.s.), and from 6.98±0.04 to 7.12±0.02 in H ($p<0.05$). HOE 642 reduces SFR slightly by 16.1±7.2% in T (p=n.s.), and by 26.1±13.3% in H ($p<0.05$). There was no difference in pH increase in T but in H pH increased only from 7.00±0.06 to 7.02±0.06 (p=n.s.). Thus pH increase was reduced compared with controls. KB-R 7943 reduced SFR by 21.8±7.2% in T ($p<0.05$) and by 27.9±17.9% in H ($p<0.05$). There was no difference in pHi in T and H either with or without KB-R 7943. No blocker affected the initial stretch-dependent force increase.
Conclusion: NHE and reverse-mode NCX activation contribute to the slow force response to stretch. Under bicarbonate-containing physiological conditions, pHi is maintained despite increased NHE activity, while the SFR in bicarbonate-free buffer is accompanied by NHE dependent intracellular alkalinization.

165 Biphasic contractile and progressive structural remodelling during chronic volume overload in dogs

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Introduction: Although left ventricular (LV) hypertrophy is thought to be compensatory, this response can eventually progress into heart failure. In failing hearts a negative and depressed force-frequency relation (FFR) together with a decreased sarcoplasmic reticular Ca^{2+}-ATPase:Na^+/Ca^{2+} exchanger (SERCA:NCX) protein ratio has been observed. Their evolution and relation with contractile function, however, is poorly understood. Thus we investigated the temporal behavior of contractile and structural remodeling in relation to LV protein contents of SERCA and NCX during 16 wks of bradycardia induced volume overload.
Methods: Volume overload was induced by atrio-ventricular block (AVB) in 13 dogs. The FFR was assessed under anesthesia by determining LV dP/dtmax during idioventricular rhythm (IVR) and temporary ventricular pacing at 40-130 beats/min at 0, 6 and 16 wks of AVB. LV dimensions and mass were derived from serial 2D-echocardiograms. SERCA and NCX protein contents at 6 and 16 wks of AVB were compared to those of control dogs (n=7). Data are presented as mean ± SD; * and # = $p < 0.05$ compared to before AVB and to wk 6, respectively.
Results: Acute AVB decreased heart rate (41±12 bpm*) and cardiac output (-18±16%*). In time, two phases of adaptation to volume overload were recognized. After 6 wks of AVB (phase 1), cardiac output had normalized due to an increase in LV systolic function (LV dP/dtmax at IVR: +57±21%*). By that time the slope of the FFR became negative (-1029±491* mmHg) and LV wall mass and cavity volume increased by 25±15%* and 37±19%*. Between 6 and 16 wks of AVB (phase 2), cardiac output was maintained, but LV systolic function decreased by 27±19%#, while the slope of the FFR remained negative (-557±471* mmHg). LV wall mass and cavity volume further increased by 12±7%# and 25±11%#. Although absolute SERCA and NCX protein contents were not changed in time, the SERCA:NCX protein ratio was 32±14%* lower at wk 16 than in control hearts.
Conclusions: The evolution of structural and contractile remodeling after AVB is different. A negative FFR and a reduced SERCA:NCX ratio can be present in compensated hypertrophy.

166 Transforming growth factor-beta1 mediated cardiac fibrosis in chronic heart failure: potential contribution of activated lipopolysaccharide

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Introduction - We have previously demonstrated that transforming growth factor-beta1 (TGFb1) mRNA is increased in peripheral blood mononuclear cells (PBMCs) of chronic heart failure (CHF) patients (pts). However, factors leading to this activation have not been determined. To examine this, we explored a range of stimuli for TGFb1 in PBMCs including neurohumoral factors and LPS. Given that infiltrating mononuclear cells may release factors that act on resident cardiac fibroblasts to stimulate collagen, we also determined the effect of TGFb1 and other growth factors on markers of fibrosis within the heart.
Methods - (1) PBMCs from normal subjects & CHF pts were cultured in DMEM with 1% FCS and stimulated with PHA 5μg/ml & LPS 20μg/ml, ET-1 or AngII (both 10-7M) for up to 48 hours. TGFb1 mRNA was measured by real time PCR. (2) Left ventricular fibroblasts (VFs) were isolated from explanted human heart and used at passage 4-5. VFs were seeded at 50,000 (proline studies) or 150,000 (RNA studies) cells/well, serum starved for 48 hours then stimulated with various growth factors: TGFb1,15ng/ml; ET-1, AngII, UII, all 10-7M; TNFalpha, 100ng/ml. Cells were harvested at 6-48 hours, alpha1(I)-procollagen and CTGF mRNA were measured and collagen production estimated by [3H]-proline incorporation.
Results - We observed a time-dependent increase in TGFb1 mRNA with PHA/LPS stimulation in PBMCs, maximal at 48 hours, greater in CHF pts (393±98%, n=4) than normal subjects (235±54%, n=4; both $p<0.05$). In contrast, neither ET-1 or AngII increased TGFb1 mRNA in either group. TGFb stimulation of VFs increased alpha1(I)-procollagen mRNA in a time dependent manner, maximal at 48 hours (264±13%, $p<0.01$). ET-1, AngII, UII and TNFalpha had no effect on alpha1(I)-procollagen mRNA. TGFb1, AngII and ET increased CTGF mRNA in a time dependent manner, maximal at 24 hours (TGFb1 298±9%; ET-1 192±11%; AngII 159±5%; all $p<0.02$). TNFalpha and UII had no effect CTGF gene expression. All growth factors increased [3H]-proline incorporation at 48 hours: TGFb1, 206±25%; ET-1, 160±24%; TNFalpha, 73±11%; AngII, 57±7%; UII, 24±7% (all $p<0.02$ vs unstimulated cells).
Conclusions - PHA/LPS but not ET-1 or AngII increased TGFb1 mRNA in PBMCs, with cells from CHF pts more responsive to this stimulus. TGFb1 was the most potent stimulus for collagen production in human VFs. These data suggest that factors activated in the setting of CHF, such as LPS, may increase collagen production via downstream induction of TGFb1, which we have shown to be potently pro-fibrogenic within the heart.

CORONARY ARTERY BYPASS SURGERY

179 Isoflurane during reperfusion does not exert a protective effect on cardiomyocytes

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Background: Isoflurane as a pretreatment decreases infarct size, enhances recovery from myocardial stunning and preserves intracellular ATP (1,2). However, when this anesthetic was given during reoxygenation in isolated rat hearts its benefit was only modest (3). We therefore investigated the effect of isoflurane on ischemia/reoxygenation injury in single cardiomyocytes when applied during reoxygenation only.
Methods: After institutional approval, ventricular myocytes were obtained by enzymatically dissociating rat hearts. They were stained with the fluorescent dyes Fura-2 and BCECF to monitor intracellular calcium ($[Ca^{2+}]_i$) and pH (pHi), respectively. Myocytes were exposed to an acidic medium (pH: 6.3) that also contained deoxyglucose while pO2 of the buffer was reduced to $<$ 15 mmHg. After 30 minutes of simulated ischemia, cardiomyocytes were reperfused for 50 minutes with a glucose containing Tyrode's solution (pH: 7.4) in the presence (n = 35) or absence (n = 40) of 2 MAC of isoflurane (rat minimum alveolar concentration: 0.31 mM). Cardiomyocytes were continuously stimulated electrically. Apart from $[Ca^{2+}]_i$ and pHi, diastolic cell length, systolic cell shortening and arrhythmic events were determined. ANOVA was employed for statistical analysis. A $P < 0.05$ was considered to be statistically significant.
Results: During ischemia, $[Ca^{2+}]_i$ and arrhythmic events increased while pHi and the degree of cell shortening decreased. During reoxygenation, $[Ca^{2+}]_i$ further increased in both groups whereas pHi remained depressed. $[Ca^{2+}]_i$ was almost twice as high in the isoflurane group throughout reoxygenation ($P < 0.05$). Contracture (23 vs. 10%) and decreased cell shortening was observed more frequently in isoflurane treated cells ($P < 0.05$). Diastolic cell length was 75% of initial length in the isoflurane group vs. 97% at the end of reoxygenation ($P < 0.05$). Additionally, arrhythmic events appeared to be more prominent in the isoflurane group.
Conclusion: Isoflurane given after ischemia at 2 MAC increases $[Ca^{2+}]_i$ and enhances cell contracture. Furthermore, it decreases systolic cell shortening and impairs diastolic relengthening. These findings are in contrast to those obtained with halothane, another volatile anesthetic, which empties sarcoplasmic Ca^{2+} stores (4). Thus, the combination of higher intracellular Ca^{2+} and ATP levels during reoxygenation in the isoflurane group could account for the observed differences (5).
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180 Troponin elevation following coronary artery bypass surgery, is it relevant?

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Background Troponin elevation following percutaneous intervention although uncommon is associated with a worse clinical outcome. A rise after cardiac surgery is frequent but its association with clinical outcome is unclear.
Objective To assess the association between post-operative peak troponin levels and clinical outcomes.
Methods The study group consisted of 98 patients undergoing on pump non emergent coronary artery bypass grafting at a University teaching hospital, mean age 62.8 (range 35-80), 85% male, mean number of grafts 3.05 (range 1-5). Exclusion criteria included Renal failure, Ejection fraction $<$ 35%, Malignancy, Chronic inflammatory conditions and concurrent infection. Blood samples were taken at baseline, 12 and 24 hours following the onset of cardiopulmonary bypass. Troponin T levels were assayed immediately using a Cardiac T Quantitative Reader (Roche Diagnostics). The clinical endpoints analysed were inotrope use, time to extubation, time to ICU discharge and length of hospital stay. Troponin values were divided into tertiles and the association between them and the clinical variables were tested by a Kruskall Wallis Rank Sum test.
Results Baseline troponin was zero in all but one case and only one patient did not have a rise post operatively (range 0.09 – 2.1).

Troponin Tertiles vs clinical variables

Troponin	0-0.32 (N=33)	0.32-0.53 (N=32)	$>$ 0.53 (N=33)	P Value
Intubation Hrs	5 (4-6.5)	6 (5-7)	6 (5-8)	0.176
ICU Discharge Hrs	21 (19.5-24)	22 (19.25-24)	22 (21-26.5	0.041
Hospital Stay Days	6 (5-7)	6 (6-8)	7 (5.5-7	0.14

There was no difference between the groups in inotrope use.
Conclusion While many patients undergoing on pump non-emergent coronary artery bypass surgery have a large post-operative troponin rise this did not correlate with clinical outcomes apart from longer ICU stay.

181 Which patients should undergo duplex carotid screening prior to coronary artery surgery?

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Purpose: Despite surgical techniques and medical care improvements, the rate of stroke after coronary bypass artery grafting (CABG) remains stable, mainly due to the ageing of the candidates and a growing prevalence of multifocal atherosclerotic patients. Around half of these events are due to the high prevalence of cerebrovascular disease in these patients. We aimed to study the risk factors of the presence of significant carotid lesions in these patients in order to optimize the screening.
Methods: We prospectively studied 1043 consecutive candidates for CABG. A first subgroup of 825 patients was studied to establish the predictive model. In addition to their clinical and coronary angiography data, the results of physical examination and ankle-brachial index (ABI) measurements were noted. Next they benefited from a systematic Duplex study. Those with an artery stenosis $>$50% were considered as having significant lesions. A multivariate analysis by logistic multiple regression was then performed to determine significant risk factors. The following 218 patients benefited from the same assessment protocol, and the ability of the model to predict $>$50% stenosis of the neck arteries has been assessed, comparing to Duplex data.
Results: Among the first 825 patients, 108 (13.1%) had at least one significant lesion on their neck arteries. The independent risk factors were: past history of stroke or transient ischemic attack, neck bruit, patent peripheral arterial disease (PAD), subclinical PAD (ABI$<$0.85), and age $>$70 years. Among the subsequent 218 patients, the presence of at least one of these factors was able to detect 24 out of 26 (92.3%) patients with a significant stenosis, and could rule out 41% of them from a systematic Duplex screening. The overall sensitivity of this approach is at 90%, with a negative predictive value of 96%, permitting to reduce dramatically the number of Duplex assessments by excluding low-risk patients.
Conclusions: The excellent sensitivity of this risk assessment approach, enhanced by the use of a bedside ankle-brachial index measurement, is able to perform a cost-effective screening of cerebrovascular disease in CABG patients.

182 Predictive value of EUROSCORE on long-term outcome in cardiac surgery patients

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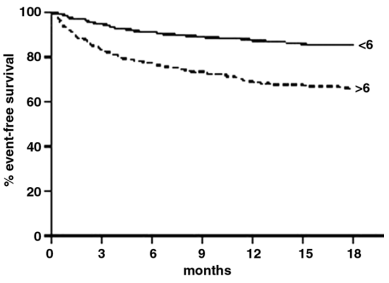
Background: The European System for Cardiac Operative Risk Evaluation EUROSCORE has shown good performance in the prediction of in-hospital and 30-day mortality in patients undergoing cardiac surgery. Aim of this work was to assess whether EUROSCORE may predict long-term outcome when compared to standard risk factors.
Methods: We assessed by a multivariate Cox proportional hazards model the impact of age, gender, left ventricular ejection fraction (LVEF), type of surgery and EUROSCORE on long-term all-cause mortality and a combined end point of mortality and cardiovascular events in a 2000-2002 cohort of cardiac surgery patients.



EUROSCORE and event-free survival.

Results: We assessed 1230 patients (mean age 65 $\pm$ 11 years, 32% female) who underwent cardiac surgery at our institution. Surgical procedure was coronary artery bypass grafting in 64%, valvular surgery in 18%, combined coronary and valvular in 15%, and miscellaneous in 3%.The RR of 30-day mortality (n=34, 2.8%) was 1.28 (95% C.I. 1.20-1.37, $p < 0.0001$) for each EUROSCORE point. During 20$\pm$9 months follow-up, 44 additional patients died and 217 were admitted for a cardiovascular event (57%) or procedure (43%). By multivariate analysis, independent predictors of all-cause mortality were EUROSCORE (RR 1.17, 95% C.I. 1.10-1.26, p$<$0.0001), age (RR of 1.05, 95% C.I. 1.02-1.09, p=0.004) and LVEF (RR 0.97, 95% C.I. 0.95-0.99, p=0.01). Event-free survival was independently associated to EUROSCORE (RR 1.17, 95% C.I. 1.13-1.21, p$<$0.0001) and LVEF (RR 0.99, 95% C.I. 0.97-0.99, p=0.001); a EUROSCORE $\geq$6 had a 2.7 RR (95% C.I. 2.7-3.9, p$<$0.0001) of events.
Conclusions: In a cohort of cardiac surgery patients, EUROSCORE was the strongest predictor of long-term event free survival; a $\geq$6 score mandates closer monitoring during follow-up.

183 The prognostic significance of early cardiac enzyme release following isolated coronary artery bypass grafting

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Release of cardiac enzyme (CE) following otherwise successful percutaneous coronary intervention has been associated with increased medium term mortality. We sought to determine the relationship between post operative cardiac enzyme release and one year survival following isolated coronary artery bypass surgery (CABG).

Method: Between 1/1/1999 and 31/12/2001 3,024 consecutive patients underwent isolated CABG. Patient characteristics were prospectively recorded in a cardiac surgical database. Cardiac enzyme release, taken as the highest single measurement recorded within the first 24 hours post-op, was abstracted from an electronic archive. All cause mortality for the cohort was taken from a national registry of deaths. The relationship between cardiac enzyme release and one-year mortality was assessed by multivariate Cox proportional hazards analysis.

Results: Data were complete for 2922 (97%) patients. The mean age of the cohort was 64 years, 20% were female, 17.5% diabetic, 14% had peripheral vascular disease, 3% had renal dysfunction, 81% had three vessel disease, 9% had ejection fraction below 30%, 2.5% had had prior cardiac surgery. CK MB isoenzyme (Roche immuno inhibition assay, reference range 5-24 U/l) was recorded in 2570 (85%),total CK in 352 (12%). Four hundred and ninety eight patients (16.5%) had CE release three or more times the upper limit of the reference range (ULR), two hundred and twenty nine (7.6%) had CE five times ULR, 59 (1.9%) had CE ten or more times ULR. There were 122 (4%) deaths. Co variables offered to the model included age, sex, renal dysfunction, diabetes, cigarette smoking, emergency surgery, peripheral vascular disease, poor left ventricular function, re-do surgery and the number of grafts done. Cox proportional hazard analysis revealed that cardiac enzyme release 3-5x ULR (adjusted RR 1.8, 95% CI 1.6 to 2.9, p=0.008) and cardiac enzyme release six or more times ULR (adjusted RR 3.8, 95% CI 2.4 to 6.0, $p<0.0001$) were independently associated with increased one-year mortality.

Conclusions: Increased cardiac enzyme release within the first 24 hours following CABG is independently associated with higher one-year mortality. The threshold values of cardiac enzyme release and orders of magnitude of association with all cause mortality are similar to those observed elsewhere following percutaneous coronary intervention. The definition of peri-operative myocardial infarction following coronary artery bypass surgery should include elevation of cardiac enzyme three or more times the upper limit of normal.

184 Troponin I as a marker of perioperative cardiac damage after coronary artery bypass grafting

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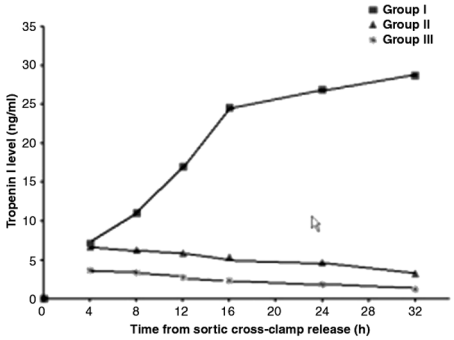
Purpose: To evaluate the usefulness of Troponin I (cTn I) in diagnosis of minimal myocardial damage (MMD) and perioperative myocardial infarction (PMI) after CABG.

Material and methods: We studied 115 patients (95 men; 83%) aged 36-79 (mean 61) who underwent CABG in Dept. of Cardiovascular Surgery and Transplantology in Cracow. Serial ECG recordings and measurements of cTnI and CK/CKMB act. (before and 4,8,12,16,24 and 32 hours after surgery) were done. PMI was diagnosed acc.to our own algorithm (ECG: ST segment changes, new Q wave, new BBB; cTnI, CK/CKMB level, hemodynamic status; regional contractility disturbances in ECHO).

Results: 3 groups of patients were identified: Gr.I: signs of myocardial infarction in ECG (n= 26)



Gr.II: non-specific ECG changes and/or slight TnI level increase (max 5-6 ng/ml) (n =42)

Gr.III: patients with uncomplicated perioperative course (n = 47).

Diagram presents dynamic changes of cTnI in all groups. In patients with hemodynamic complications (low cardiac output, cardiac arrest) significantly higher levels of cTn I were observed (53,2±17,3 and 96,6±37,3 ng/ml respectively, $p<0,001$) than in patients with uncomplicated postoperative course (3,7±1,4 ng/ml).

Conclusions: 1) Measurements of cTnI after CABG are of great value in diagnosis and monitoring of PMI and MMD. 2) cTnI measurements helps to verify non-specific ECG changes and false positive or negative CK/CK MB levels. 3) Patients with uncomplicated perioperative course had small cTn I increase, so that the cut off value for these patients was 3,7 ng/ml.Changes of cTnI in all groups.

NEW CLINICAL THERAPEUTIC APPROACHES IN MYOCARDIAL ISCHAEMIA

185 Beneficial effect of pre-ischaemic administration of enteral nitrates on infarct size

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Background: The administration of nitrates and NO donors in the setting of an acute myocardial infarction has been investigated in multicentric trials with deceiving results. However, maneuvers aimed to increase NO levels or cGMP content in reperfused myocardium in experimental models, have consistently proved to reduce reperfusion injury. The purpose of this study was to investigate the effect of prior oral administration of 5-isosorbide mononitrate (5-IMN) on the extent of necrosis induced by a transient coronary occlusion.

Methods: Farm pigs (35.2±1.1 kg) were anesthetized with thiopental (30 mg/kg i.v.), intubated and mechanically ventilated. Three animals that received increasing enteral doses of 5-IMN were used to select the dose necessary to ensure adequate plasma concentrations of the drug. Thirty-four animals randomly received either 0.3mg/kg of enteral 5-IMN or placebo. Fourty-five min later, endothelial injury was induced in the mid left anterior descending coronary artery (LAD) with an intracoronary catheter, and then the artery was occluded for 48 min. Heart rate (HR), aortic (AP) and left ventricle pressure (LVP), regional myocardial contractility (intramyocardial ultrasonic crystals), and coronary blood flow (CBF) were continously recorded. Bleeding time and in vitro platelet aggregation were studied with serial determinations. After 2 hours of reperfusion, the area at risk (AR) and infarct size (IS) were measured (fluorescein injection and trifeniltetrazolium reaction, respectively).

Results: Plasma levels of 5-IMN achieved a plateau phase 45 min after oral administration. There were no differences between groups in HR, AP, LVP, CBF or regional myocardial contractility throughout the experiment. Neither bleeding time nor ex vivo platelet aggregation before occlusion or at the end of reperfusion were affected by treatment, and 70% of the animals that received 5-IMN presented cyclic flow reductions during reperfusion, compared to 71.4% in the control group. The AR involved 12.2±0.8% and 11.8±0.6% of the ventricular mass in treatment and control groups, (p=n.s.), but IS was significantly reduced in the 5-IMN group: 29.9±5.2% vs 50.4±6.4% of the area at risk, p=0.03.

Conclusion: Enteral administration of 5-IMN before coronary occlusion reduces ischemia-reperfusion injury in the situ pig heart by mechanisms independent of coronary blood flow, platelet activation or hemodynamic variables.

186 Anti-anginal and anti-ischaemic effects of the If current inhibitor ivabradine versus atenolol in stable angina. A 4-month randomised, double-blind, multicenter trial

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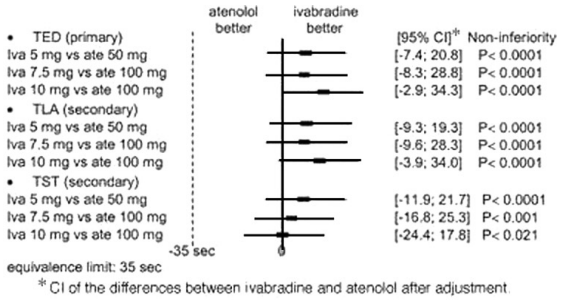
Ivabradine, a novel selective heart rate reducing agent acting on the SA node, has shown anti-ischemic and anti-anginal activity in a placebo-controlled trial. The objective of this study was to demonstrate the non-inferiority of the anti-anginal and anti-ischemic effects of ivabradine compared to atenolol in a larger trial with a longer follow-up.

Methods: In a double-blind, parallel-group trial, 939 patients with a ≥3-month history of stable angina and documented CAD were randomised to either 2 groups with ivabradine 5 mg bid or to a third group with atenolol 50 mg od for 1 month. Patients were then force-titrated to either ivabradine 7.5 mg bid or 10 mg bid in the first 2 groups and to atenolol 100 mg od in the third group for 3 additional months. Patients underwent exercise treadmill tests (ETT) at randomisation (M0), and after 1 (M1) and 4 (M4) months of therapy.

Results: Total exercise duration (TED) at trough (primary endpoint) was increased from M0 to M4 by 86.8±129.0 sec and 91.7±118.8 sec with ivabradine 7.5 and 10 mg bid respectively and by 78.8±133.4 sec with atenolol 100 mg. TED improved at M1 by 64.2±104.0 sec with ivabradine 5 mg and by 60.0±114.4 sec with atenolol 50 mg. Time to limiting angina (TLA) and time to 1 mm ST segment depression (TST) were also consistently increased. Non-inferiority of ivabradine vs atenolol was shown for all doses and ETT criteria. Side effects of beta-blockers such as AV block, sexual dysfunction and bronchospasm were not observed with ivabradine. A higher incidence of mild visual symptoms was noted with ivabradine, causing only 5 patients to withdraw from treatment.



Conclusion: Monotherapy with ivabradine is at least as effective and safe as atenolol in patients with stable angina.

187 Testosterone replacement therapy improves ischaemic threshold and mood in hypogonadal men with angina

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Background: Men with coronary artery disease have lower serum testosterone than men with normal coronary angiograms and we have found that 23% have testosterone levels below normal range. Since testosterone is an efficacious vasodilator, we hypothesised that physiological replacement therapy could improve ischaemic threshold.

Methods: Patients were recruited following angiography confirming coronary disease. 8 men completed the study; at baseline all had low serum testosterone and were diagnosed androgen deficient by an endocrinologist. Patients were randomised to a single blind crossover study. Testosterone (Sustanon 100) or placebo was given for 1 month, following a month washout period the patient crossed over to the alternate treatment. Patients were assessed at baseline and 1 month of each treatment arm. The primary outcome was time in seconds to 1mm ST depression during exercise electrocardiography (Bruce protocol). Patients were also assessed with questionnaire (Beck Depression Inventory and ADAM hypogonadal questionnaire). Results are recorded as mean ± sem and were analysed by comparing the difference (delta value) of exercise time and questionnaire score from baseline to 1 month of each treatment phase (paired t-test).

Results: The change in time to ST depression with testosterone therapy was significantly greater than with placebo (77±16secs v 7.2±11secs, p=0.002). There were also significant improvements in questionnaire scores during testosterone phase when compared to placebo; BDI (-3.3±1.7 v -0.4±1.8, p=0.02) and ADAM (-2.3±0.5 v 0.3±0.7, p=0.05).

Conclusions: Nearly a quarter of men with coronary disease have low serum testosterone. Hormone replacement in these men improves ischaemic threshold and mood.

188 Rebound worsening in exercise performance was not observed after abrupt ranolazine withdrawal in patients with chronic angina in CARISA

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Purpose: Ranolazine (RAN), a member of a new class that partially inhibits fatty acid oxidation, increases exercise capacity in chronic angina pts when added to background antianginal drug therapy (CARISA: Circ 2001;104:25:1Be-4Be). The effect on exercise capacity of abruptly stopping RAN in chronic angina pts has not been studied.

Methods: In CARISA 823 pts with chronic angina on stable doses of atenolol, diltiazem, or amlodipine were randomized to double-blind treatment with RAN 750 mg bid, 1000 mg bid or placebo. After completing 12 wks of RAN double-blind treatment, pts entered a 48-hour, double-blind, rebound assessment period during which they either continued their RAN regimen or were switched to placebo. A modified Bruce exercise test (ETT) was performed at 48 hrs and results were compared to those obtained at baseline.

Results: Of the 823 pts, 727 pts had an assessment for possible rebound. Pts withdrawn from RAN (table; columns B and C) had exercise durations on repeat assessment that were not significantly different from pts who continued placebo during the entire period (A) (p>0.05; table). Exercise capacity was maintained in pts continuing RAN (D,E) whereas exercise capacity was diminished when pts were switched to placebo (B,C).

Treatment (12 wk period/rebound period)

Change from Baseline during Rebound Phase in Seconds (mean ± SE)				
Placebo/ Placebo (A) n=243	RAN 750 mg bid/ Placebo (B) n=128	RAN 1000 mg bid/ Placebo (C) n=118	RAN 750 mg bid/ RAN 750 mg bid (D) n=120	RAN 1000 mg bid/ RAN 1000 mg bid (E) n=118
Total ETT				
93 ± 8	98 ± 11	90 ± 12	119 ± 15	123 ± 13
Time to Angina Onset				
121 ± 9	134 ± 13	119 ± 13	148 ± 16	158 ± 15
Time to Onset of 1 mm ST Depression				
120 ± 10	135 ± 13	129 ± 14	151 ± 16	155 ± 14

Conclusion: The anti-anginal effect of ranolazine on exercise capacity is lost when drug therapy is withdrawn in pts on background beta-blockers or calcium channel antagonists after 12 wks of therapy but no evidence for rebound worsening of exercise performance was observed after RAN withdrawal.

189 Ranolazine decreases haemoglobin A1C (HbA1c) in angina patients with diabetes: carbohydrate and lipid parameters in MARISA and CARISA

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Introduction: Ranolazine (RAN), a member of a new class of drugs that partially inhibits fatty acid oxidation (pFOX), increased treadmill exercise capacity in pts with chronic angina both alone (MARISA, N=191) and when added to background anti-anginal therapy with atenolol, diltiazem, or amlodipine (CARISA, N=823). Angina frequency and nitroglycerin consumption were reduced by RAN. The most frequently reported adverse events (dizziness constipation and nausea) were generally mild and occurred in fewer than 10% of patients. The potential use of RAN in diabetics is of interest because approximately one in four angina pts has diabetes.
Methods: HbA1c was measured at baseline and endpoint in diabetic patients in CARISA, a 3-group, parallel, double-blind, 12-week study. Triglycerides, and total, HDL, and LDL cholesterol were measured in both MARISA and CARISA at baseline and endpoint. Laboratory evaluations continued in 550 patients who completed MARISA or CARISA and received open-label RAN for a mean treatment duration of 448 days.
Results: Efficacy and tolerability of RAN were similar in both diabetic and non-diabetic patients in both MARISA and CARISA (previously reported). In diabetic patients in CARISA (N=131), RAN 750 and 1000 mg bid were associated with a mean absolute reduction in HbA1c of 0.48%age points and 0.70%age points, respectively, compared to placebo at 12 weeks (each $p<0.01$). The reductions versus placebo were greater in those pts on insulin (N=31; 0.84 and 1.05%age points), on 750 and 1000 mg bid ($p<0.02$ and $p<0.01$), respectively. Fasting glucose was not affected by RAN in diabetic patients in CARISA, regardless of insulin treatment; one hypoglycemic episode was reported on placebo and one on RAN. After 12-24 months of open-label treatment, HbA1c decreased from baseline in the diabetic patients by 1.1%age points. During the first 12 weeks of RAN treatment of diabetic patients in CARISA, mean total and LDL cholesterol increased by up to 16 and 11 mg/dL, respectively; however, because of mean increases in HDL cholesterol up to 5 mg/dL, the HDL/LDL ratio changed little. Over 3 years of open-label treatment in the combined MARISA/CARISA diabetic population, total and LDL cholesterol decreased from baseline, while HDL cholesterol continued to increase.
Conclusion: RAN caused no apparent adverse effects on diabetic glycemic control and was associated with significant decreases in HbA1c. After moderate initial increases, total and LDL cholesterol decreased to below baseline with continued treatment, while HDL continued to increase.

190 Efficacy of trimetazidine in stable angina patients resistant to a beta-blocker treatment: TRIMPOL II, a double-blind, randomized, placebo-controlled, multicenter trial

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The study aimed to assess the antianginal efficacy of trimetazidine, a metabolic anti-ischemic agent which optimizes cardiac metabolism, in patients with persistent angina pectoris despite a beta-blocker treatment.
Methods: Patients with stable angina despite a full dose of beta-blocker treatment (metoprolol, MTP, 50mg bid) were included in this double-blind, randomized, placebo-controlled, multicenter study in 2 parallel groups. Before inclusion all patients had two positive treadmill exercise tests separated by one week. At inclusion (W0) patients were randomized to trimetazidine (TMZ, 20mg tid) or placebo (Pbo, tid) on top of metoprolol for a 12-week treatment period. A treadmill test was again performed after 12 weeks (W12). Efficacy evaluation was done with ergometric criteria: exercise test duration, time to 1-mm ST-segment depression, total workload, time to onset of angina, rate-pressure product at peak exercise and clinical symptom measurements: mean number of angina attacks per week and mean nitroglycerin consumption per week. The analysis was performed in the intention-to-treat population including all randomized patients (n=426). All statistical tests were conducted at the 5% significance level.
Results: Both treatment groups (TMZ n=211, Pbo n=215) were comparable in terms of demographic and ergometric criteria at baseline. The results are shown in the table.
Conclusion: In all randomized patients from the TRIMPOL II study who had still stable angina despite a full dose of beta-blocker, treatment with trimetazidine significantly improved all exercise test criteria and significantly reduced clinical symptoms compared with placebo, without any hemodynamic changes. The antianginal efficacy of trimetazidine was teamed with an excellent tolerability.

Change (W12-W0) in:	Trimetazidine	Placebo	P value*
Exercise test duration (s)	56 ± 90	34 ± 94	<0,010
Time to 1mm ST segment depression (s)	75 ± 108	38 ± 127	<0,010
Total workload (METs)	1,05 ± 1,73	0,47 ± 1,72	<0,010
Time to onset of angina (s)	70 ± 96	34 ± 105	<0,010
Rate-pressure product (HR x SBP)	653 ± 3397	395 ± 3680	NS
Mean number of anginal attacks per week	-1,54 ± 2,56	-0,99 ± 4,51	<0,010
Mean nitroglycerin consumption per week	-1,10 ± 2,31	-0,58 ± 3,81	<0,010

* Mann-Whitney test

ADJUNCTIVE PHARMACOLOGY DURING AND AFTER PERCUTANEOUS CORONARY INTERVENTION

203 Safety of very low dose of heparin during percutaneous coronary intervention: ACT, anti-Xa and creatine kinase monitoring

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Background: Recent reports have advocated the use of very low dose unfractionated heparin (UFH) (2500 to 5000 IU) among patients undergoing percutaneous coronary intervention (PCI). The optimal activated clotting time (ACT) arbitrary recommended for PCI is between 300 and 350 s, rarely attained with low doses of UFH. The purpose of this study was to evaluate anticoagulation ranges for low-dose UFH regimens during PCI, monitoring APTT, anti-Xa activity and ACT.
Methods: We prospectively included 300 patients who underwent an ad hoc PCI receiving 3000 (n=222) or 4000 (n=78) UFH units. Patients pre-treated by UFH or low weight molecular heparin were excluded from the study. At the end of the procedure, ACT (Hemochron 401, ITC), APTT and anti-Xa activity (Behring Coagulation Timer) were assayed for each patient arterial blood sample. A good anticoagulation level was defined by an anti-Xa activity > 0.4 IU/ml and APTT ratio >2.5. Creatine kinase (CK) was systematically assayed 8 to 12 hours after PCI (N<150 U/l), periprocedural MI was defined by CK>450. A clinical evaluation was performed at 7 and 30 days.
Results: Age was 64±13 years. Weight:77±11.7 kg. Current smokers: 31%, diabetes: 20%, hypertension: 49.7%, dyslipidemia: 63%. Prior PCI: 48%, prior CABG: 11.5%, prior MI: 34%. Acute coronary syndrome: 70%. Mean heparin dose: 3274 ± 459 IU. ACC/AHA classification: A:19.5%, B1:35.9%, B2:32.3%, C: 12.3%. Stenting: 84%, primary stenting: 76%. Biological results: ACT: 187±36 s, anti-Xa 0.77±0.3 IU/ml, APTT>120s: 94%. CK:61±59U/l. Rate of complications: false aneurysm:1%, minor groin hematoma:3%, urgent revascularisation:1 patient, MI 0%, death 0%. No MACE at 7 and 30 days.
Conclusion: PCI with very low dose UFH (3000 to 4000 IU) appeared to be safe. Anti-Xa activity was within therapeutical ranges and APTT ratio was >4 in 94% of the cases despite low mean ACT of 187. These findings may explain the safety of PCI with low dose heparin.

204 Atorvastatin does not inhibit clopidogrel in patients undergoing coronary stenting in randomized data from the interactions of atorvastatin and clopidogrel (INTERACTION) trial

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Background: Atorvastatin and clopidogrel are of proven benefit and are commonly used following stent implantation. Some but not other retrospective data have raised the possibility that the antiplatelet effects of clopidogrel are inhibited by atorvastatin. The randomized INTERACTION trial was designed to address this issue by serial measurements of various platelet characteristics by conventional, as well as whole blood aggregometry, point of care tests with two rapid analyzers, and assessment of 14 major receptors on the platelet surface, and formation of platelet-leukocyte microparticles by whole blood flow cytometry.
Methods: A total of 75 patients undergoing coronary stenting were given 325 mg aspirin daily for at least one week, and 300 mg clopidogrel before stenting. Other antithrombotic agents were prohibited. Patients were assigned at random to atorvastatin (10-80mg), another statin (simvastatin (20-40mg); pravastatin (10-40mg); lovastatin (20mg); and fluvastatin (20-80mg) at the discretion of the treating physician, or no statin beginning 30 days before stenting. Platelet studies were performed at baseline as well as 4 and 24 hours after stent implantation.
Results: At baseline, platelets were significantly less activated in both statin groups as compared with the patients on no statin as reflected by adenosine diphosphate induced conventional aggregometry, Ultegra Analyzer, and SPAN12 receptor expression. Despite phasic changes in platelet characteristics after administration of clopidogrel, there were no significant differences in the platelet measurers between groups at 4 and 24 hours after loading with clopidogrel with the exception of the constantly diminished expression of the anti protease-activated G-protein-coupled (PAR-1) thrombin receptor measured by SPAN12 antibody in both groups of patients assigned at random to statins.
Conclusion: Statins in general, and atorvastatin in particular did not affect the ability of clopidogrel to inhibit platelet function in patients undergoing coronary stenting. The pattern of platelet inhibition by clopidogrel was almost identical in patients assigned at random to atorvastatin, other statins, or no statins. These randomized data raise the possibility that statins may inhibit platelets directly via as yet unknown mechanism(s) presumably related to the cleavage of an alfa- thrombin by PAR-1 receptors. These unexpected findings require a priori hypothesis testing in randomized trials of larger sample size.

205 A randomised study with simvastatin for preventing in-stent restenosis and neointimal growth as assessed by intravascular ultrasound: a preliminary report

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Purpose: HMGcoA reductase inhibitors (Statins) have already proven to reduce major events after coronary stenting. Conflicting data, possibly attributable to their huge intraclass variability, have been reported on the efficacy of statins in reducing in-stent restenosis. The aim of this study was to investigate the safety and efficacy of simvastatin in preventing in-stent restenosis.
Methods: Normocholesterolemic (Total cholesterol <210 mg/dl and/or LDL cholesterol <130 mg/dl) consecutive patients with stable angina pectoris and a single native de-novo coronary lesion requiring revascularization were randomized to placebo or simvastatin (20 mg/daily) at least 2 weeks before, and continuing for 12 months after successful coronary stenting. Exclusion criteria were: acute coronary syndromes, diabetes, ongoing statin treatment. Primary endpoint were binary in-stent restenosis (stenosis >70% of reference vessel diameter) as measured by quantitative coronary angiography (QCA), and neointimal growth, as measured by intravascular ultrasound (IVUS), at 12-month follow-up catheterization; secondary endpoints were safety of simvastatin treatment and major cardiovascular events (MACE).
Results: A total of 71 patients (37 simvastatin, 34 placebo) entered the study. To date, 49 patients (69% of total; 26 simvastatin, 23 placebo) completed a 6-months clinical follow up. MACE were 1 (4%) and 4 (17%), respectively in the simvastatin and placebo-treated patients (P<0.05). No drug-related serious event (myositis, increased hepatic transaminase, allergic reaction) or discontinuation of therapy was reported among the simvastatin-treated patients. To date, 13 patients (18% of total; 7 simvastatin, 6 placebo) had repeat catheterization (mean follow up period: 11±2 months). Binary restenosis was 1/7 (14%) and 1/6 (17%), respectively for simvastatin and placebo-treated patients. No significant difference was noted between simvastatin and placebo-treated patients regarding: minimal lumen area (5.4±1.5 mm^2 vs 6.3±2.4 mm^2;P=NS), neointimal volume index (=[stent volume-lumen volume]/stent length) (3.7±1.7 mm^3/mm vs 3.8±2.4 mm^3/mm;P=NS), % obstruction volume (=[stent volume-lumen volume]/stent volume%) (36±13% vs 35±25%;P=NS).
Conclusion: Prolonged treatment with oral simvastatin (20 mg/daily) is safe and reduces major adverse events after coronary stenting. Preliminary IVUS data are inconclusive about the role of simvastatin in preventing in-stent restenosis and neointimal growth.

206 Is platelet inhibition by clopidogrel durable over 30 days of treatment?

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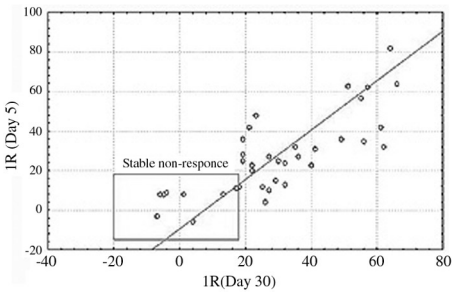
Background: Long term stable platelet inhibition likely affects the occurrence of stent thrombosis. Whether clopidogrel exerts stable inhibition in patients undergoing stenting is unknown.
Methods: We studied platelet inhibition by clopidogrel (300mg load/75 mg qd) + aspirin (325mg) in 37 patients undergoing elective coronary stenting. Platelet aggregation (5 and 20 μmol/L ADP) and stimulated p-selectin by flow cytometry were determined at baseline and after 5 and 30 days of treatment. The inhibitory response (IR) was defined as the baseline % aggregation (5 and 20 μmol/L ADP) or % positive cells (p-selectin) minus the respective value at day 5 and day 30.
Results: IR at day 30 strongly correlated with the IR at day 5 (5μmol/L ADP, r = 0.8; 20 μmol/L ADP, r = 0.8; p-selectin, r = 0.7). (Figure). Non-response (<18% change from baseline (5μmol/l ADP) was observed in 14/37 patients at day 5 and did not change in 9/37 of these patients over 30 days (figure).



5 and 30 day/5 μmolar ADP.

Conclusion: The inhibitory response to clopidogrel is durable and patient-specific over 30 days. In most patients, 30 day platelet reactivity is well predicted by 5 day reactivity. The majority of non-responders after 5 days of therapy will remain non-responders at 30 days. The early detection of non-response may limit the occurrence of stent thrombosis.

207 Pretreatment platelet reactivity strongly affects the inhibitory response from clopidogrel

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Background: The effect of pretreatment platelet reactivity on the response to clopidogrel is unknown. Patients with the most reactive platelets at baseline may remain the most reactive after clopidogrel treatment and thus be at greatest risk for thrombosis.
Methods: Aggregation (Agg) (%) by 5 μmol/L ADP and stimulated p-selectin expression (% positivity) by flow cytometry (P-s) were determined at baseline and at 1 and 5 days after elective coronary stenting (n = 96). All patients received aspirin (325 mg) and a standard clopidogrel regimen (300mg load in lab then 75mg qd). Per protocol, GP IIb/IIIa inhibitors were witheld. Baseline reactivity was divided into high (Agg > 70%, P-s > 50%), moderate (Agg 60-70%, P-s 40-50%), and low (Agg < 60%, P-s < 40%) and the response to clopidogrel was determined in each group.
Results: Age was 68 ± 7 yrs. At day 1 Agg remained greatest in patients with high pretreatment reactivity (67 ± 11) vs. moderate (56 ± 15), p=.004; and vs. low (48 ± 9), p<.0001). At day 5 these differences between groups were no longer significant (high (40 ± 16), moderate (36 ± 18), low (35 ± 17). At day 1, P-s was also greatest in high patients (35±17) as compared to patients with low pretreatment reactivity (16 ± 7, p.0009) and at 5 days remained persistently elevated in the high group (31 ± 12%) as compared to the moderate (19 ± 13%, p=.06) and low groups (20 ± 7%, p=.04).
Conclusion: The early response to standard clopidogrel therapy for coronary stenting is strongly affected by the pretreatment reactivity of the platelet. Patients with the highest pretreatment reactivity remain the most reactive after treatment and may be at greatest risk for thrombosis. Alternative pharmacologic strategies should be investigated in these patients.

208 Procedural success and clinical outcome of percutaneous coronary interventions in patients presenting with stent thrombosis

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Background: Stent thrombosis (ST) is encountered in 1-2% of patients (pts) following percutaneous coronary intervention (PCI), and is associated with major morbidity and mortality. Immediate reperfusion therapy by repeat PCI is the treatment of choice. However safety, efficacy and long-term outcome following repeat PCI for ST is not established.
Methods: Between November 1995 and May 2002, a total of 4927 consecutive pts underwent PCI with stent implantation at our institution. Following initial PCI, all pts were treated with a dual antiplatelet regimen (acetylsalicylicacid 100mg/d with either ticlopidine 250 mg BID for at least 2 weeks, or clopidogrel 300 mg loading dose followed by 75 mg qd for at least 4 weeks). Angiographic and clinical (MACE) outcome of all pts presenting with ST undergoing repeat PCI was retrospectively assessed. Recanalisation was considered successful if a residual stenosis <50% and TIMI flow 3 were achieved. Myocardial infarction (MI) was defined as a creatin kinase (CK) elevation >2x the upper limit of normal. 30 day and long-term clinical outcome were obtained by a questionnaire.
Results: 85 ST (1.7%) were encountered in a total of 80 (1.6%) pts. Nine (0.2%) were categorized as acute (<24 hours after stent implantation), 58 (1.2%) subacute (>24 hours <30 days) and 18 (0.3%) late (>30 days) ST. Repeat PCI for ST was successful in 75 (94%) pts. Percent diameter stenosis significantly decreased from 94±15 to 14±23 ($p< 0.001$), whereas minimal lumen diameter (MLD) increased from 0.2±0.4mm to 2.3± 0.7mm ($p<0.001$). MI was diagnosed in 71 (89%) patients (non-Q-wave MI in 68 (96%) pts, Q-wave MI in 3 (4%) pts). Peak CK and troponin-I levels were 1045±1144 U/l and 225 ± 271 μg/l, respectively. Left ventricular ejection fraction was not significantly different between the initial and repeat PCI (57%±14 to 53%±13, p=ns). In-hospital and 30 day death following repeat PCI were encountered in 3 pts (4%) and 7 pts (9%), respectively. MI and TVR rate after 6 month were 3% and 4%, respectively. During a mean follow-up time of 1.5±1.3 years, 10 pts (12%) died. Late ST was associated with higher mortality than subacute ST (17% vs 9%,p=0.6), but not significantly.
Conclusions: Repeat PCI for pts presenting with ST appears safe and effective with procedural success and mortality rates comparable with that of patients undergoing primary PCI in the setting of ST-elevation infarction. Late ST may be associated with a higher mortality risk.

ESC LECTURE ON CLINICAL CARDIOLOGY – THE GRÜNTZIG LECTURE

239 Efficacy of high-dose bolus tirofiban compared to regular dose glycoprotein IIb/IIIa inhibitors on platelet aggregation inhibition in myocardial infarction patients treated with primary angioplasty

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Background: Glycoprotein IIb/IIIa inhibitors reduce thrombotic complications in patients undergoing percutaneous coronary intervention. Little is known about the extent of platelet aggregation inhibition (IPA) in patients (pts) with acute myocardial infarction (MI).
Methods: IPA was measured at 5 time points in pts with acute MI who underwent primary coronary angioplasty (PCA) and were treated with Clopidogrel (C) alone, Clopidogrel in combination with Abciximab (A), Tirofiban (T) or high-dose bolus Tirofiban (HT). Clopidogrel was administered before acute angiography (300 mg orally). Glycoprotein IIb/IIIa inhibitor bolus was given after acute angiography (CAG) and before PCA, immediately followed by maintenance infusion. Abciximab was administered as bolus of 0.25 mg/kg followed by infusion of 0.125 μg/kg/min (max. 10 μg/min). Tirofiban was administered as bolus of 10 μg/kg followed by infusion of 0.15 μg/kg/min. High-dose Tirofiban was administered as bolus of 25 μg/kg followed by infusion of 0.15 μg/kg/min. IPA was assessed on a routine blood cell counter (Sysmex K4500; demonstrated correlation coefficient of 0.90 with ICHOR CBC analyzer [Array Medical]) with EDTA/PPACK as anticoagulant using 20 μM ADP as agonist (%).

Table I. Mean IPA (%) ± SD

	on admission	before CAG	after PCA	1 hr after PCA	6 hrs after PCA
C (n=24)	13.1 ± 21.1	18.5 ± 22.0	16.8 ± 21.3	42.7 ± 33.3	42.0 ± 29.1
C + A (n=24)	21.2 ± 24.2	19.4 ± 22.2	55.5 ± 24.7	53.3 ± 24.3	57.6 ± 24.5
C + T (n=28)	11.5 ± 17.2	18.1 ± 24.7	57.4 ± 28.5	58.0 ± 27.3	73.3 ± 15.8
C + HT (n=16)	6.7 ± 5.4	7.8 ± 8.3	83.8 ± 13.4	69.9 ± 15.9	58.0 ± 20.7

Results: IPA was highly variable among pts. Mean IPA ± SD for the different agents at 5 time points are shown in Table I.
Conclusion: This is the first study in which IPA is measured in acute MI pts treated with primary PCA and Clopidogrel in combination with different GPIIb/IIIa inhibitors. IPA was highly variable among pts. Only with high-dose bolus Tirofiban sufficient peri-procedural platelet aggregation inhibition was found. Further research is needed to assess the effect of bolus and maintenance infusion dose adjustment of GPIIb/IIIa inhibitors on clinical outcome.μ±

240 Fate of patients admitted with ST-elevation myocardial infarction not receiving reperfusion therapy. Results from the European Heart Survey of acute coronary syndromes

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Background: Early reperfusion therapy has been shown to improve outcome in patients with ST elevation myocardial infarction (STEMI)and is therefore recommended in the current guidelines of the ESC.The purpose of this analysis was to evaluluate the fate of patients with STEMI not receiving reperfusion therapy.
Methods: A total of 4431 patients with the initial diagnosis STEMI were enrolled in the Euro Heart Survey Acute Coronary Syndromes. While 2472 received early reperfusion therapy with thrombolysis (n=1556, 35.2%) or primary percutaneous coronary intervention (PCI, n=916, 20.6%) 1959 (44.2%) were treated initially conservatively.
Results: Patients not receiving reperfusion were older (68.0 vs. 61.0 years) and had a longer pre-hospital delay (270 vs. 136 min), received less often aspirin (93.3% vs. 98.5%), ACE inhibitors (62.3% vs. 69.0%), beta blockers (76.5% vs. 85.6%)and statins (49.7% vs. 63.6%). The clinical events occurring until day 30 are listed in the table.

Clinical events until day 30

	No reperfusion	Reperfusion	p-value
Death	10.3%	6.3%	0.001
Reinfarction	2.3%	3.0%	n.s.
Major bleeding	1.1%	2.0%	0.01
Stroke	1.1%	0.6%	0.01

Conclusions: Patients admitted with STEMI not receiving early reperfusion therapy are older and treated less often with medical therapies recommended in the current guidelines. This results in an significant increase in 30-day mortality. Therefore all efforts should be made to increase the rate of patients treated with early reperfusion therapy and adjunctive therapies adherent to recent guidelines.

241 Valsartan versus angiotensin-converting enzyme-inhibition in acute coronary syndrome after successful stent implantation of the culprit lesion – results from the VALVACE trial

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The ValPREST trial could demonstrate a significant reduction of in-stent-restenosis (ISR) in type B2/C lesions when 80mg Valsartan (Val) for six months after stent implantation was given. This was mainly true for cases with acute coronary syndrome (ACS). Valid recommendations for the treatment of ACS include only ACE inhibitors (ACEi). This was the reason why 700 patients were randomised to Val (LVEF > 50%) or ACEi captopril, benalapril or ramipril (LVEF < 50%) after stent implantation in complex type B2/C lesions.
Results: Control coronary angiography was done in 89% after six months. ISR rate in all patients on Val was 19.5% versus 34% on ACEi ($p<0.005$), in ACS 14% versus 43% ($p<0.0001$) and in stable angina 28% versus 27.5%. In cases with diabetes ISR rate under Val was 24% and under ACEi 43% ($p<0.01$). These results were not significantly influenced by additional CSE inhibition in a total of 83% of patients. However MACE were not significantly different in both groups.
In conclusion, in terms of additive pharmacological treatment of ACS after successful stent implantation of the culprit lesion angiotensin receptor antagonists seem to be more effective than ACE inhibitors due to more favourable vascular effects thus reducing ISR rate and reintervention rate.

ACUTE HEART FAILURE: NEWS FROM THE EMERGENCY ROOM AND ICU

250 Elevated troponin T is not associated with mortallity in the medical intesive care unit

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Introduction: The significance of measuring troponin in patients admitted in a medical intensive care unit (MICU) for non-cardiac reasons is uncertain. In this retrospective study, we tested the hypothesis that abnormal troponin level is an independent risk factor for mortality in MICU. Methods: We examined the APACHE III database and serum troponin T levels of 1947 patients consecutively admitted to the MICU at the Mayo Clinic, between August 2000 and December 2001. Troponin T levels greater than 0.1 ng/mL were considered elevated. Chi Square, Mann-Whitney U and logistic regression tests were used for statistical comparisons. The logistic regression model included hospital mortality as dependent and troponin levels and predicted mortality rates as independent variables. Risk ratios (RR) and their 95% confidence intervals (95% CI) were calculated by logistic regression analysis. P-value $<$ 0.05 was considered significant. Results: One patient with incomplete data was excluded. Troponin was measured in 1214 (62%) of the 1946 patients at admission or during MICU stay. The APACHE III predicted mortality rate of patients whose troponin was measured was 24% compared to14% of those whose troponin was not measured ($p<0.0001$). The observed mortality rate of patients whose troponin was measured was 24% compared to 12% of those whose troponin was not measured ($p<0.0001$). Among the patients whose troponin was measured, survivors' and non-survivors' median admission troponin levels were 0.02 ng/mL and 0.03 ng/mL (p=0.0119), respectively, and the highest troponin levels 0.04 ng/mL and 0.07 ng/mL (p=0.0002), respectively. Among the 1214 patients whose troponin was measured, 122 of the 291 non-survivors (42%) had elevated troponin compared to 296 of 923 survivors (32%) (P=0.0022). Logistic regression analysis showed that neither the admission (p= 0.4648; RR = 1.114, 95% CI = 0.80-1.62) nor the highest troponin level (p = 0.3610; RR = 1.16, 95% CI = 0.84-1.61) was independently associated with mortality The APACHE predicted mortality rate was independently associated with mortality ($p < 0.0001$). Conclusions: Among patients admitted to MICU, serum troponin level is likely to be measured in sicker patients with higher mortality. Elevated serum troponin level is not an independent risk factor for mortality.

251 Clinical prognostic score for short-term events in patients with cardiogenic pulmonary edema

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Background: Cardiogenic pulmonary oedema (CPO) is a common reason of hospitalisation connected with high mortality, however there are only few data concerning the factors predicting long- and short-term prognosis. No prognostic scales are used in this condition to date.
Aim: This study was performed to establish a simple score predicting the in-hospital prognosis in patients with CPO.
Methods and Results: We studied 276 Pts (128 males, 148 females; median age 70 years) hospitalised due to CPO (mean duration of hospital stay 12$\pm$7 days). During the index hospitalisation 58 Pts (21%) died and 218 Pts (79%) were discharged. 44 clinical variables were included in the analysis. Univariate and multivariate statistical analysis revealed that the most significant predictors for in-hospital mortality were: acute myocardial infarction (RR=2,12; 95%CI 1,36-3,31), heart rate $>$ 115/min. (RR=2,13; 95%CI 1,33-3,4), systolic blood pressure $=<$ 130mmHg (RR=3,61; 95%CI 2,21-5,89) and white blood cells $>$ 11500/mm^3 (RR=2,26; 95%CI 1,39-3,65) on presentation. The presence of each factor was rated 1 and the absence - 0 points. The pulmonary oedema prognostic score - POPS - was defined as a sum of all points. According to the final score the study group was divided into 5 subgroups with POPS from 0 to 4: POPS 0 - 53 Pts (19%), POPS 1 - 95 Pts (34%), POPS 2 - 85 Pts (31%), POPS 3 - 32 Pts (12%) and PRPO 4 - 11 Pts (4%). Pts with POPS 0 had very good short-term prognosis with 2% in-hospital mortality rate (RR=0,07; 95%CI 0,01-0,52) whereas mortality in Pts with POPS 4 was 64% (RR=3,31; 95%CI 1,98-5,51). To determine the optimum cut-off value for POPS, a receiver operating characteristic curve analysis was applied proving good discriminative ability of POPS (area under curve = 0,78; 95%CI 0,72-0,83). Scores 0-1 had sensitivity of 79%, specificity of 62%, 36% positive and 92% negative predictive value for in-hospital mortality (RR=4,43; 95%CI 2,46-7,99).
Conclusions: Pulmonary oedema prognostic score is a simple bedside tool allowing a precise prediction of in-hospital prognosis after acute cardiogenic pulmonary oedema. This index can be easily used in each patient on presentation after ECG, blood pressure and white cell count are obtained.

252 Development of a comprehensive new endpoint for the evaluation of new treatments for acute decompensated heart failure: results with levosimendan in the REVIVE-1 study

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Traditionally, intravenous (IV) drugs in decompensated heart failure (HF) have been evaluated based on their hemodynamic effects. Thus, no endpoint to measure symptomatic improvement in decompensated HF has yet been validated. To do so, we adapted the clinical composite (which has been validated in trials of chronic HF) to the evaluation of IV levosimendan in a pilot trial of acute decompensated HF (REVIVE-1).
A total of 100 patients who were hospitalized for worsening HF and had dyspnea at rest despite IV diuretics were randomized (double-blind) to receive placebo (PBO, n=49) or IV levosimendan (LS, n=51), given as a loading dose of 12 μg/kg over 10 min and followed by a continuous infusion (0.1 μg/kg/hr for 50 min and 0.2 μg/kg/hr for 23 hr); patients were then followed closely for 4 additional days. Patients were classified as improved if they reported their HF to be moderately or markedly improved at specific timepoints. Patients were classified as worse if they died or received an IV medication for worsening HF during the 5-day study period. Patients were considered unchanged if they were neither improved nor worse. Different models using different definitions for improvement and worsening were prospectively and retrospectively examined. The initial model defined improvement based on the responses at 24 hr and at 5 days and restricted the definition of worsening to the use of IV vasodilators or inotropic agents. Using this model, improvement was observed more frequently with LS than PBO (49% vs 33%) with no between-group difference in the proportion of patients who were worse (overall P=0.229). When the definition of worsening was expanded to include the use of IV diuretics for worsening HF and confined to the occurrence of clinical events, LS-treated patients not only were more likely to show improvement (51% vs 33%) but were less likely to exhibit worsening (20% vs 35%), overall P=0.043. When the definition of improvement was expanded to include the responses at 6 hr (in addition to 24 hr and 5 days), the separation between the treatment groups increased even further (improvement in 33% vs 14% and worsening in 24% vs 37%), overall P=0.029 (LS vs PBO).
These findings indicate that a clinical composite approach can be used to develop an endpoint that distinguishes the effects of IV LS in the setting of acute decompensated HF. The new endpoint is now being used prospectively to evaluate the effects of LS in a definitive second study (REVIVE-2).

253 Randomized comparison of intraaortic balloon support versus a percutaneous left-ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock

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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 cardiac output before the stunned 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.
Patients in cardiogenic shock after an AMI, with intended revascularization of the infarct related artery, were randomized to either IABP or percutaneous VAD support. Exclusion criteria were mechanical complications after AMI or severe neurologic dysfunction. Since 08/2000 15 patients were randomized to VAD and 17 to IABP support. Predicted mortality probability was similar in both groups (72% vs. 75%, p=n.s.). By VAD support hemodynamic and metabolic parameters could be reversed more effectively in comparison to IABP treatment (table).

	IABP pre	IABP post	VAD pre	VAD post
Cardiac Index (l/min/m^2)	1.5 ± 0.4	1.7 ± 0.4	1.7 ± 0.3	2.1 ± 0.4*
Mean blood pressure (mmHg)	68 ± 11	72 ± 12	63 ± 13	76 ± 11*
Heart rate (beats/min)	108 ± 26	105 ± 25	112 ± 12	105 ± 12
PCWP (mmHg)	26 ± 6	21 ± 6	20 ± 4	14 ± 4*
CVP (mmHg)	14 ± 5	13 ± 6	12 ± 4	9 ± 3
Mean PAP (mmHg)	10 ± 3	28 ± 6	29 ± 11	22 ± 4*
Lactate (mmol/l)	6.5 ± 5.0	5.3 ± 3.7	4.5 ± 2.2	3.0 ± 1.2*

* denotes p<0.05 pre vs. post

However, complications as bleeding requiring transfusion of blood components (n=14 vs. n=4, p<0.001), limb ischemia (n=5 vs. n=0, p=0.02), or elevated temperature >38.5°C (n=15 vs. n=9, p=0.04) were encountered more frequently after VAD support. 30-day-mortality was similar (IABP 45% vs. VAD 40%, log-rank, p=0.63).
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.

254 Significantly lower doses of tezosentan are effective in the treatment of acute heart failure: an interaction with endothelin-1 levels?

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In patients with acute heart failure, tezosentan, an IV dual endothelin (ET-A/B) antagonist, in doses of 50 and 100 mg/hr, was shown to improved cardiac index (CI) and wedge pressure but without substantial clinical effects. In the present study the effects of lower doses of tezosentan were investigated.
Methods: 130 patients, hospitalized due to acute heart failure, with dyspnea at rest, CI < 2.5 L/min/m^2 and PCWP ≥ 20 mmHg, were randomized in a double-blind fashion to receive either placebo or tezosentan 0.2, 1, 5 or 25 mg/h for 24 hours.
Results: Tezosentan induced a dose dependent increase in CI peaking in the 5 and 25 mg/h groups. The vasodilatatory effect was 50% lower in the 1 mg/h group and similar to placebo in the 0.2 mg/h group. Maximal wedge pressure decrease was observed in the 5 and 25 mg/h groups, but also in the 1 mg/h group, although the maximal effect in this group was observed at 24 hours. The hemodynamic effects, mainly on wedge pressure, were maintained, and in the 1 mg/h even enhanced, after drug discontinuation, throughout 24 hours of follow-up. The rate of recurrent worsening heart failure (WHF) at 48 hours was different in the 5 groups, mainly due to a major decrease in the WHF rate in the 1 mg/h and to a lesser extent the 5 and 25 mg/h groups (p=0.005), which was maintained at 30 days. Dyspnea score improved gradually in the 1 mg/h arm throughout treatment and 24 hours of follow up, while improving transiently in the 5 and 25 mg/h and not changing in the placebo and 0.2 mg/h groups.
Endothelin-1 (ET-1) levels were correlated with recurrent WHF. In the placebo and 0.2 mg/h groups recurrent WHF was related to higher baseline ET-1 levels, while in the high dose tezosentan groups (≥ 5 mg/h) recurrent WHF was correlated with a more pronounced ET-1 increase during treatment. Similarly to wedge pressure, BNP was significantly reduced (-30%) in all tezosentan treatment groups but not by placebo.
Conclusions: Lower doses of tezosentan are effective in improving the hemodynamics and possibly outcome of patients with acute heart failure since these doses induce a maximal effect on wedge pressure and BNP while avoiding the significant tezosentan induced vasodilatation and ET-1 increase observed with the higher (≥ 5 mg/h) doses.

255 Abciximab treatment for acute myocardial infarction: mortality in patients with cardiogenic shock

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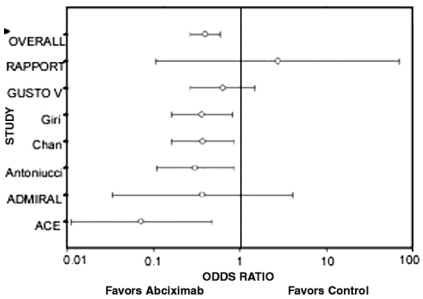
Objective: CS associated with acute myocardial infarction (AMI) represents one of the highest risk conditions in cardiovascular disease. In the percutaneous coronary intervention (PCI) setting, we compared the mortality risk of AMI patients with CS in abciximab (ABX)- and control (C)-treatment groups.
Methods: Meta analysis was performed and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the primary endpoint of all-cause mortality at 30 days using a random effects model.
Results: A total of 18,056 patients were enrolled in the studies, out of which 466 (2.6%, range 0.5% to 100%) had CS (n= 240 and n= 226 for the ABX and C group, respectively). Other treatments varied among the studies, but included: stents (24.5%), aspirin (99.7%), heparin (99.7%), thienopyridines (9.3%) or thrombolytics (99.3%). Available demographic data for the ABX and C groups, respectively were: mean age = 66, 66 yr; female = 36, 40%; median weight =77, 75kg; hypertension = 51, 49%; prior congestive heart failure = 11, 5%; diabetes = 28, 29%; and any bleeding =35, 19%. Death occurred in 29% and 46% of the ABX and C groups, respectively. We found a significant treatment effect in favor of ABX overall: OR = 0.385 (CI = 0.256, 0.580), p <0.0001; % relative and absolute risk reductions of all-cause mortality =43 and 19, respectively. This is equivalent to a number needed to treat (NNT) of 5.3. ORs and CIs for all-cause mortality are shown below.



Conclusions: In patients undergoing PCI, an exceptionally high 30-day mortality risk is predicted for this small group of AMI patients with CS. ABX, combined with PCI, produces a 57% relative risk reduction and a very low NNT (5.3).

VENTRICULAR REMODELLING POST MYOCARDIAL INFARCTION – BENCH TO BEDSIDE

265 p38 mitogen-activated protein kinase inhibition prevents early adverse ventricular remodelling in the immediate post-myocardial infarction setting

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Background: We have previously demonstrated that treatment with a p38 MAPK inhibitor (p38i) for 3 weeks commencing 1 week following myocardial infarction (MI) in rats attenuated pathological cardiac remodeling and improved LV function. However it is uncertain whether these benefits are observed following early commencement of p38i-treatment in the immediate post-MI setting.
Methods: To investigate the effects of p38i on acute LV remodeling and dysfunction post-MI, RWJ-67657 (50mg/day, po) was given to rats (MI+p38i, n=7) for 1 week, from 24h post-MI. MI controls (MI+V, n=7) and sham-operated rats (n=6) received vehicle.
Results: MI+V demonstrated haemodynamic impairment at 1 week post-MI. p38i-treatment of MI rats from 24h post-MI resulted in significantly lower LVEDP cf. MI+V (MI+V: 25.4±4.8mmHg, MI+p38i: 16.1±1.5mmHg, $p<0.05$). Both lung/body weight (LWBW) and heart/body weight (HWBW) ratios in MI+p38i were significantly reduced cf. MI+V (LWBW: MI+V: 14.4±1.3, MI+p38i: 9.6±0.1, $p<0.05$ vs MI+V; HWBW: MI+V: 5.1±0.3, MI+p38i: 4.2±0.3, $p<0.005$ vs MI+V). LV dilation within the first week post-MI was inhibited in MI+p38i cf. MI+V (deltaLVIDd: MI+V: 0.22±0.03cm, MI+p38i: 0.12±0.03cm, $p<0.05$). There were also trends towards improvements in fractional shortening and relative wall thickness with early p38i intervention. Functional impairment post-MI was associated with increased myocardial collagen content. Compared to MI+V, hydroxyproline content (μg hydroxyproline/mg tissue) in MI+p38i was reduced in the non-infarct zones (NIZ) (sham: 3.4±0.8μg/mg, MI+V:3.4±0.4μg/mg, MI+p38i: 2.4±0.4μg/mg, $p<0.05$ vs MI+V) and infarct zone (IZ) (MI+V: 8.48±0.6μg/mg; MI+p38i:7.0±0.8μg/mg, $p<0.05$ vs MI+V). Increases in alpha1(I) procollagen gene expression post-MI were inhibited in MI+p38i (IZ: -43%, NIZ: -40%, $p<0.05$ vs MI+V). Consistent with reductions in collagen expression following p38i-treatment, there was also suppression of gene expression of the profibrogenic factors TGFβ1 (NIZ: -62.7%, $p<0.05$; IZ: -5%, p=NS vs MI+V) and CTGF (IZ: -43%, $p<0.05$; NIZ: -5%, p=NS vs MI+V) in MI+p38i cf. MI+V. Additionally, MMP-2 gene expression was elevated in MI+p38i cf. MI+V (IZ: 10-fold, NIZ: 11.7-fold, $p<0.05$). While p38i reduced early myocardial collagen accumulation post-MI, it did not exacerbate infarct expansion (absolute delta infarct size: MI+V:15.5%, MI+p38i: 12.2%, p=NS vs MI+V).
Conclusions: These results demonstrate that early intervention with the p38i post-MI attenuates cardiac haemodynamic impairment and pathological collagen deposition in rat heart without exacerbating infarct expansion.

266 Angiotensin type 1 receptor-dependent inhibition of early apoptosis in the remote, non-ischaemic myocardium after infarction

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Background: Remodeling of the non-ischemic myocardium after myocardial infarction can be effectively prevented by ACE inhibition (ACEI) and possibly by angiotensin AT-1 receptor blockade (AT1B). The exact molecular mechanisms of this treatment have not been clarified. It could be shown earlier that as early as 1 day after infarction, biochemical markers of apoptosis such as activation of caspase-3 occur in the surviving myocardium after infarction. Hypothesis of this study was that, after infarction, ACEI and AT1B both are operative by preventing the early activation of apoptosis in the remote, surviving myocardium.
Methods: Male wistar rats (150g) were pretreated with ramiprilat (RA, 10 μg/kg daily i.p.), irbesartan (IRB, 50 mg/kg daily i.p.), or saline (SA) for 1 week. Regional myocardial infarction was induced by ligation of the left anterior descending coronary artery. Sham-operated animals served as controls in all groups. Afer 1 day, transmural biopsies from the non-ischemic area of the left ventricle were taken. Expression of caspase-3, of procaspase-3, of bcl-2, bcl-x and bax were determined by Westernblot analysis. In parallel, DNA-laddering was quantified by a polymerase chain reaction.
Results: The activation of caspase-3 seen early after infarction was completely prevented both by RA and IRB (SA, 183±35% of sham, RA, 88±8%, IRB, 87±17%, $p<0.05$ for both comparisons). In the same manner, the significant shift of the bcl/bax quotient to the pro-apoptotic bax (Sa, 71±7% of sham, $p<0.05$) was abandonned by RA (109%) and IRB (103%). DNA-laddering, however, could only partially reversed by RA and IRB.
Conclusion: In the surviving myocardium after infarction, the early activation of biochemical parameters of apoptosis can by inhibited by ACEI and AT1B via an angiotensin AT-1 receptor-dependent pathway. Inhibition of early apoptosis could be one important mechanism of the beneficial effects of ACEI and AT1B in the remodeling after infarction.

267 Left-ventricular function after primary angioplasty for acute myocardial infarction is determined by evolution of tissue reperfusion

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Objective: This study sought to analyze the evolution of myocardial perfusion during follow-up after primary angioplasty and relate it to final left ventricular function.
Background: Analysis of myocardial blush has been used to assess tissue reperfusion immediately after angioplasty for acute myocardial infarction (AMI). There is little knowledge on the subsequent development of myocardial perfusion.
Method: In 101 patients with first AMI angiographic myocardial blush grade (MBG) and TIMI frame count (CTFC) were analyzed immediately after intervention and at follow-up 7.5±5.6 months later. Cineventriculography was performed at follow-up angiography to define left ventricular function.
Results: 5 patients had occluded stents or flow limiting restenosis. In the remaining 96 patients myocardial perfusion defined by MBG was improved at follow-up in 38 patients, unchanged in 50 patients and worse in 8 patients. Patients with improvement of abnormal blush determined immediately after intervention to normal blush at follow-up (N=30 patients) had compared to patients with persistently abnormal blush (N=19) a lower peak creatine kinase (850±1311 vs. 1802±2091 U/l, p=0.038) and a better left ventricular ejection fraction at follow-up (37.4±9.7 vs. 53.7±11.1%, $p<0.001$). Multivariate analysis proved evolution of MBG from acutely to follow-up to be an independent predictor of LV-function (R2=0.177, $p<0.001$) in addition to initial infarct size defined by the sum of ST-segment elevation (R2=0.138, p=0.001) and infarct location (R2=0.044, p=0.033). Evolution of MBG had a better predictive value for left ventricular ejection fraction >55% at follow-up than MBG assessment after intervention only (area under the receiver operator characteristics curve 0.796, 95% CI 0.698-0.873 vs 0.699, 95% CI 0.594-0.791, respectively, p=0.002).
Conclusion: Tissue reperfusion after angioplasty for AMI is characterized by frequent improvement over time as indicated by repeated MBG analysis. Evolution of perfusion after acute myocardial infarction is an independent predictor of final left ventricular function.

268 Clinical and echocardiographic predictors of left-ventricular remodelling after ST-elevation myocardial infarction

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Background: After ST elevation myocardial infarction (STEMI), left ventricular(LV) remodelling portends an unfavourable impact on prognosis. The early identification of patients (pts) at increased risk for remodelling may have implications on the management strategy. The aim of this study was to determine the clinical and echocardiographic predictors of LV remodelling in pts with STEMI.
Methods: We studied 105 consecutive pts (88 men), mean age 55.5 ± 9.2 years, with a first non-fatal STEMI. The MI was anterior in 50 pts and inferior in 55. Reperfusion therapy was performed in 94 pts (fibrinolysis in 77 and primary PTCA in 17). An echocardiogram (echo) was performed in all pts between day 3 post-MI and discharge and a second echo was done between months 3 and 6. Discharge medication included an angiotensin converting enzyme inhibitor in 96% of pts and a beta-blocker in 87%. LV remodelling was defined as an increase in end-diastolic volume greater than 20% between the 2 echos. We evaluated the impact of baseline demographic parameters, clinical characteristics (risk factors for CAD, MI location, heart failure manifestations on admission), peak CK-MB, baseline white blood cell count and in-hospital echocardiographic findings(LV volumes, ejection fraction, wall motion score, mitral Doppler flow pattern and presence of pericardial effusion).
Results: LV remodelling occurred in 16 pts (15%), 13 with anterior MI and 3 with an inferior MI (p=0.008). Independent predictors of LV remodelling were wall motion score>23 (odds ratio=26.5; 95%CI: 3.2-220.2; p=0.002), the presence of heart failure manifestations on admission (odds ratio=9.5; 95%CI: 1.1-79.8; p=0.038) and the presence of a restrictive pattern on mitral Doppler flow on the first echo(odds ratio=9.7; 95%CI: 1.0-95.1; p=0.05).These predictors were identified on multivariate analisys after adjustment for the effect of demographic parameters, white blood cell count, presence of pericardial effusion an LV volumes on the first echocardiogram.
Conclusion: Findigs from the baseline clinical evaluation and predischarge echocardiogram provide complementary information regarding the risk for development of LV remodelling after STEMI in patients on optimized therapy. Risk stratification of these patients may be improved by the combined use of these predictors.

269 Perfusion-metabolic mismatch in Tl-201 and BMIPP scintigraphic imaging in patients with successful reperfusion after myocardial infarction related to subsequent left-ventricular dilatation

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Background: Left ventricular (LV) remodeling has been known to result in the clinical worse outcome after myocardial infarction (MI), however even the early successful reperfusion could not prevent LV remodeling in clinical setting.
Methods: Forty three patients with first anterior MI who received early successful reperfusion underwent both Iodine-123 15-(p-iodophenyl)3R, S-methylpentadecanoic acid (BMIPP) and Thallium-201 (Tl) SPECT 1 month after the onset. The left ventricle was divided into 18 segments, and regional myocardial uptakes of the tracers in each segment were scored from 0 (normal) to 3 (no activity). More reduced BMIPP uptake than Tl uptake in each segment was determined as Tl/BMIPP mismatch. LV end-diastolic volume index (EDVI) were measured by LV graphy performed at 1 (1M) and 6 months (6M) after onset. Significant dilatation of end-diastolic volume index (EDVI) defined as more than 20% increase during the study period was observed in 12 patients (group D) and not in 31 patients (group N). Myocardial respiratory quotient (RQ) at infracted region, a reflection of myocardial substrate utilization, was determined by aorta and the anterior interventricular vein blood gas determinations.
Results: There were no significant differences between two groups in age, gender, time from the onset to reperfusion, angiographic characteristics, infarct size, hemodynamics, and medications during the study period. Tl/BMIPP mismatch, defined as was observed in 12 patients (100%) in group D, whereas mismatch was seen in 20 patients (64.5%) in group D. ($p < 0.01$).The ratio of total defect score for Tl to that for BMIPP was smaller in group D than those in group N (5.6±0.3 vs.3.2±0.3, $p<0.01$). RQ in group D (0.98±0.7) was close to 1.0 and significantly higher than that of group N (0.82±0.3).
Conclusion: Persistent metabolic damaged myocardium is identified as reduced BMIPP uptake at rest despite normal or normalized perfusion after successful reperfusion and glucose utilization, leading to subsequent LV dilatation. Adjunctive metabolic intervention in addition to the reperfusion will be necessary to prevent LV remodeling.

270 Effects of late recanalization of infarct related artery on left-ventricular remodelling, regional contractility and myocardial ischaemia and viability: a prospective randomized study

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Purpose: to investigate the effects of late recanalization of IRA on left ventricular (LV) remodeling, regional contractility and myocardial ischemia (E) and viability (RJ)6 mo later. Methods: we randomized 36 pts 12h after anterior myocardial infarction with occluded IRA to angioplasty (Open-18 pts) or no intervention (Occ-18 pts). Pts underwent Tl-201 scintigraphy plus gated SPECT (GPS)and delayed enhanced and tagging magnetic resonance imaging (MRI) at enrollment and 6 mo later. The anterior wall of the LV was divided into 7 segments and scored according to the degree of Tl-201 uptake:0-no uptake, 1-severe hypoperfusion, 2-moderate, 3-mild, 4-normal. LV end diastolic (EDV), end systolic (ESV) volumes, ejection fraction (EF), Infarct size (IS) and transmurality (IT)were measured by MRI and GPS. The influence of IT on strains circumferential shortening (Ecc)was analized on infarcted LV segments. Results: There wasn't difference of the EDV and ESV between groups. EF increased in the open group by MRI. GPS didn't show difference between E and RJ in the open group. Both groups, IS and IT were similar. Ecc improved on infarcted segment independent of the IT, however there wasn't difference between groups.

	Open (enrollment x 6 mo follow-up)	Occluded (enrollment x 6 mo follow-up)
EDV (MRI) *	(98.28 ± 32.29) x (102.52 ± 30.62)	(93.68 ± 24.50 x 106.08 ± 34.59)
ESV (MRI) *	(57.32 ± 30.75) x (54.99 ± 28.89)	(52.46 ± 21.23 x 60.69 ± 32.30)
EF (MRI) #	(43.59 ± 11.79) x (48.59 ± 12.88)	(45.51 ± 9.82 x 44.75 ± 10.86)
IS (MRI) *	(18.00 ± 8.97) x (16.66 ± 9.76)	(18.11 ± 8.08) x (18.00 ± 6.29)
IT(MRI) <50% *	(-0.09 ± 0.06) x (-0.13 ± 0.04)**	(-0.07 ± 0.03) x (-0.09 ± 0.02)**
IT (MRI) >50% *	(-0.04 ± 0.03) x (-0.07 ± 0.05)**	(-0.05 ± 0.04) x (-0.09 ± 0.07)**
EDV (GPS) *	(142.83 ± 60.45) x (144.89 ± 66.26)	(171.38 ± 64.23) x (175.00 ± 69.51)
ESV (GPS) *	(97.50 ± 61.83) x (91.83 ± 61.92)	(128.13 ± 70.30) x (120.19 ± 70.34)
EF (GPS) *	(36.06 ± 12.67) x (41.50 ± 13.74)	(28.81 ± 13.14) x (35.06 ± 12.48)
E (GPS)*	(0.56 ± 0.55) x (0.59 ± 0.45)	(0.48 ± 0.43) x (0.70 ± 0.42)
RJ (GPS)*	(0.65 ± 0.59) x (0.60 ± 0.45)	(0.57 ± 0.40) x (0.69 ± 0.40)

*p = NS between open and occluded groups.**$p < 0.05$ (Ecc) between enrollment and 6 mo follow-up. #$p < 0.05$ between open and occluded group

Conclusions: late recanalization of IRA didn't improve LV remodeling, EDV and ESV, and there wasn't difference between groups for contractility, E and RJ in the infarcted segment at 6 mo later.

ARRHYTHMIA DEVICE THERAPY: WHAT ARE THE LIMITS?

276 Mortality and cause of death in single-lead VDD versus 2-lead DDD pacing

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Purpose: Single-lead VDD pacing has been proven to be reliable and safe and has become a therapeutic alternative to two-lead DDD pacing in patients (pts.) with AV-block. The prospective, randomized VDD-vs.-DDD-Study compared both therapies in the six year long-term follow-up. The results for the mortality and the causes of death will be presented here.
Methods: One hundred eighty pts. were randomized into two groups: 90 pts. with single-lead VDD-pacing (VDD), and 90 pts. with dual-lead DDD-pacing (DDD). Both groups were comparable with respect to all observed critera (e.g., age, sex, atrial diameter, ejection fraction). The pts. condition was recorded during the last routine follow-up and analyzed using the Kaplan-Meier survival analysis (log-rank test). The causes of death were classified into cardiac, cerebro-vascular, non-cardiac and unknown.
Results: The mean follow-up time was 4.9 ± 1.8 yrs. (VDD) and 4.2 ± 1.9 yrs. (DDD), respectively ($p > 0.01$; t-test). There were 15 (VDD) and 27 (DDD) documented deaths. Six years after implantation the cumulative survival rate was 82% (VDD) and 64% (DDD), respectively. A significant difference ($p < 0.05$) between both groups was observed after 4 yrs. The number of pts. in each class of cause of death for both groups was:

cerebro-vascular:	7 DDD vs 0 VDD
cardiac:	8 DDD vs 8 VDD
noncardiac:	9 DDD vs 6 VDD
unknown:	3 DDD vs 1 VDD

Five of seven pts. with a cerebro-vascular cause of death (all DDD) developed permanent atrial fibrillation (AF) at a mean time of 3.8 ± 1.1 yrs. before they died
Conclusions: There is a significant lower mortality in VDD compared to DDD during longterm follow-up. This difference is due to cerebro-vascular events exclusively in DDD occurring predominantely after development of permanent AF. VDD pacing should be the preferred pacing mode in pts. with AV-block.

277 Is there quality of life improvement after upgrading to dual-chamber pacing in patients with VVI pacemakers?

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Background: Significant differences in quality of life (QoL) between single-ventricular and dual-chamber pacing are not well demonstrated in all patients, and only some subgroups of patients may benefit from dual-camber pacing. Furthermore, in randomised trials of different pacing modes, many patients with single-ventricular pacing devices develop clinical pacemaker syndrome. The aim of our study was to assess QoL changes in VVI patients upgraded to dual-camber pacing.
Method: We prospectively studied consecutive VVI patients who needed pacemaker replacement because of battery depletion and pacing mode was upgraded to dual-chamber pacing. Twenty-seven patients (17 men and 10 women, aged 74±15 years old) were upgraded from VVI to DDD pacing during a 5 years period. In 12 (A group) upgrading was because of clinical pacemaker syndrome, and in 15 (B group) because of doctor's choice without pacemaker syndrome. A QoL test (SF-36) was performed before upgrading and after 3-6 months of dual-chamber pacing
Results: There were no significant modifications in QoL after upgrading (SF-36: 69.3 vs 72.3, p=NS). Only those patients with pacemaker syndrome (A group) showed a significant improvement in QoL (SF-36: 63.2 vs 71.3, $p<0.005$).
Conclusions: Upgrading from single-ventricular pacing to dual-chamber pacing does not show improvement in QoL. In this way, upgrading stimulation mode only seems to be justified in those patients with clinical pacemaker syndrome.

278 Exercise-induced changes of atrial sensing in patients with dual-chamber implantable cardioverter defibrillators

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Aims: Despite the use of improved algorithms and technology by the manufacturers of dual chamber transvenous implantable cardioverter defibrillators (dcICDs), the incidence of device-related adverse events, especially during exercise, is relatively high. We investigated the effects of treadmill exercise on atrial sensing in patients who have been implanted with a dcICD.
Methods: We studied 15 consecutive patients (mean age 51±19 years, 73% males) with a dcICD, implanted 12±11 months before examination, who were regularly followed in the outpatients department of our hospital and were willing to undergo treadmill exercise by the modified Bruce protocol. The patients were exercised for 9±3 minutes achieving 6±2 METS of workload. Tip to tip, sensed P wave amplitude was monitored continuously, and the intracardiac electrograms from 8 consecutive cardiac cycles in each phase of the exercise testing were recorded on paper, scanned through a flatbed scanner, scale adjusted, magnified and measured onscreen using a previously described computer-based method in order to improve accuracy and reproducibility of the measurements.
Results: Sensed P wave amplitude was significantly lower at peak exercise compared to baseline values at rest (3.6±1.2 vs 4.4±1.4mV, P=0.003) and compared to the third minute of the recovery period (3.6±1.2 vs 4.3±1.3mV, P=0.001). P wave at peak exercise was reduced by an average of 16±17% (range -2 to 66%), and values at implantation were not significantly correlated to the observed changes at peak exercise (R=0.091, P=0.747). P wave oversensing, P wave undersensing and exaggeration of far field sensing were documented in three of the studied patients. Two of them had experienced episodes of inappropriate therapy delivered by the device.
Conclusions: Atrial sensing of dcICDs is significantly reduced during treadmill exercise. The average reduction or P wave amplitude was found to be 16% but can reach 60% in selected cases. P wave values at implantation do not seem to predict the magnitude of exercise-induced changes of atrial sensing. Given the increasing role of dcICDs in prevention of sudden cardiac death, and the relatively high incidence of device-related adverse events, our results, if verified by larger studies, should be taken into consideration by physicians involved in implantation and programming of dcICDs.

279 Left-ventricular mechanics during right-ventricular apical or left-ventricular-based pacing in patients with chronic atrial fibrillation after atrioventricular junction ablation

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Purpose: His ablation and permanent right ventricular (RV) apical pacing is an acceptable therapy for drug refractory atrial fibrillation (AF), despite the fact that long-term pacing from RV apex results in diminished left ventricular (LV) function. In this study, for the first time in humans, we evaluated LV systolic and diastolic function during RV apical and LV-based (LV free wall or biventricular) pacing in such patients.
Methods: The study included 8 patients (3 men, mean age 61.6 ± 3.2 years), 5 with normal and 3 with impaired LV systolic function due to non-ischemic dilated cardiomyopathy. All of them were implanted with a biventricular pacemaker system and underwent atrioventricular junction (AVJ) ablation for chronic AF with high ventricular response despite optimal treatment.
One day after ablation, during a routine coronary angiography, we analyzed LV pressure-volume loops using the conductance catheter to evaluate acute changes in LV systolic and diastolic performance during RV apical, LV free wall and biventricular pacing in random order.
Results: Angiography revealed that all patients had mitral valve regurgitation, which improved dramatically during LV-based pacing compared to RV apical pacing. As regards LV systolic function, LV free wall or biventricular pacing significantly improved end-systolic pressure (+11.5%) and volume (-12.9%) compared to RV pacing ($p<0.05$). Similarly, cardiac index (+9.5%), stroke work (+9%), preload recruitable stroke work (+12.1%), maximal rate of rise of LV pressure (dP/dtmax) (+8.9%), LVEF (+29.4%), and end-systolic elastance (+23.5%) were also significantly improved ($p<0.05$).
On the other hand, LV diastolic filling parameters, as end-diastolic pressure (-18.3%) and volume (+14.3%) were better during LV-based pacing ($p<0.05$) while LV relaxation parameters like -dP/dtmax (+2.2%) and passive diastolic chamber stiffness (+2.8%) showed no clear change (p=NS).
There were no significant differences in any of the measured parameters between LV free wall and biventricular pacing.
Conclusions: Acutely, LV-based pacing is superior to RV apical pacing, in terms of LV systolic function, in patients with AVJ ablation for drug refractory AF, independently of normal or impaired LV systolic function. Our results also suggest that LV filling is better during LV-based pacing in these patients.

280 Device longevity has not improved over the last 16 years: single centre implantable cardioverter-defribrillator experience

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Background We present data on 415 subjects (522 implants) prospectively followed for a total of 14,315 months (mean 55 months). This amounts to ~8% of all UK ICDs; a representative picture of practice between 08/1986 and 10/2002.
Results 23% of subjects died; median survival 98-months. Implant rate has increased ten-fold since 1990. Age at implant has increased from 55 (SD 26) in 1988 to 70 (9) years in 2002 (P=0.001). Implants for primary prevention have increased, but still only accounts for 8% of devices. The frequency of EPS assessment prior to implant has reduced (85% in 1990 v 35% in 2002; $P<0.001$). Amiodarone usage has decreased (65% in 1986-1991 to 34% in 2001-2; $P<0.001$) and B-blockers have increased (16% v 55%; $P<0.001$). Box changes (BC) accounted for 20%. Device longevity (median 51 months) has not improved (RR (95% CI) for >1996 vs <1996 1.16 (0.7-1.9); p=0.56). BC subjects were younger (60(SED 1) v 64 (6) years) and had better ejection fractions (39(20) v 35(1)%. Both $p<0.05$). Subjects with appropriate therapies (50%) were no more likely to have BC (RR 0.98 (95% CI 0.64-1.49); p=0.91). Conversely, inappropriate therapies (RR 1.93 (1.13-3.3); p=0.02) and electrical storm (RR 1.88 (1.11-3.18); p=0.02) were markers for BC. The groups did not differ in use of drugs likely to affect defibrillation or pacing thresholds. Dual chamber devices have increased from 0% in 1997 to 69% in 2002. BC were actually less likely to have been fitted with a dual chamber system (10% vs 45%; P=0.001); and >95% of dual systems were programmed to DDI-40 suggesting that bradycardia therapy was unlikely to contribute to unaltered ICD longevity.
Conclusion Changing indications for ICDs implant have resulted in a rise in implant rate, recipient age and a decrease in EP studies. ICD longevity has not improved. Subjects requiring a BC were more likely to be young, with better ventricles and have had multiple therapies. Manufacturers product data states that static current drain has reduced by 30-50% during this time implying that unchanged longevity is not related to the proliferation in elaborate diagnostics. More likely the drive for smaller generator size has negated the improvements in battery and capacitor technology.

281 Prospective evaluation of Pacemaker lead endocarditis: 6 months preliminary results

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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 6 months follow-up PM related infections were reported in 32 patients (0.5%). Infection was significantly correlated with fever [RR=9.8(3.5-27.1)] and temporary pacing wire before implantation[RR=3.14(1.1-8.8)], heparin infusion[RR=2.4(1.1-5)], more than 3 persons in the operating room[RR=2.3(1.1-4.7)], early re-intervention [RR=9.4(4.3-20)] and the absence of antibiotic prophylaxis[RR=2.9(1.4-6.3)]. 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 infection was 0.5% at 6 months. Risks factors of PM related infection at 6 months were: fever, temporary pacing wire, heparin infusion, more than 3 persons in the operating room, early re-intervention and the absence of antibiotic prophylaxis.

DO WE UNDERSTAND WHY RESYNCHRONIZATION WORKS IN HEART FAILURE

291 Biventricular pacing in severe congestive heart failure: effects on neurohormonal assessment

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Biventricular pacing in patients with severe congestive heart failure (CHF) and complete left bundle branch block (LBBB) reduces the NYHA class improving quality of life. The aim of the study was to assess the effect of biventricular pacing on neurohormones [brain natriuretic peptide (BNP), aldosterone (ALDO), endothelin1 (E1), big-endothelin (BigE) and TNF-alfa.
Methods: 25 CHF patients (18 males) underwent implantation of biventricular pacemaker and plasma determination of neurohormones at baseline and at 9-month follow-up. Patients included had complete LBBB (QRS>140 ms), left ventricular ejection fraction (LVEF)<30% and NYHA III-IV. The causes of CHF were: dilatative cardiomyopathy in 56%, CAD in 32%, valvular heart disease in 8% and hypertensive in 4%. The neurohormonal plasma determination was obtained with immunoradiometric assay. The dosage of carvedilol, digoxin and enalapril remained unchanged during the study period; only the dosage of furosemide was reduced (baseline 47.7 mg/die vs FU 30.5 mg/die, p=0.006).
Results: the PM implantation was successful in 24/25 subjects, mean age 69±7. The functional class improved at 9-month follow-up (NYHA class from 3,15±0,49 to 1,15±0,49 p=0.001). The results of neurohormones are depicted in table 1.

Table 1

	BNP pg/ml	END. fmol/ml	Big-End fmol/ml	TNF-alfa pg/ml
Baseline	180,83 ± 192,31	2,O7 ± 4,56	1,82 ± 1,55	26,33 ± 48,44
Follow-up	102,48 ± 130,12	2,66 ± 5,38	0,87 ± 0,74	27,51 ± 34,53
P	0,037	0,076	0,007	0,930

Conclusions: biventricular pacing improves the NYHA class in severe CHF patients (p=0.0001). The resynchronisation therapy reduces BNP and BigE (p=0.037 and p=0.007, respectively) without modifying TNF-alfa, ALDO and E1.

292 Heart rate variability footprint to monitor patients with end-stage heart failure treated by cardiac resynchronisation therapy

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Introduction: Heart rate variability (HRV) is a non-invasive measure of sympathic activity and reflects the status of patients with end stage HF. HRV changes can be used to monitor heart failure patients treated with a biventricular device. We studied HRV changes obtained via a novell patient centric diagnostic tool available in the dedicated biventricular defibrillator (Renewal, Guidant, MN, USA) after implantation and 6 weeks later in 64 patients with class III-IV heart failure.
Methods: Between July 2001 and May 2002, 78 Renewal ICD's (incl. patient centric diagnostics) were implanted in our hospital. 10 patients were excluded from the HRV-study because of atrial pacing. During follow-up 4 patients died because of progressive heart failure (both at implant date in end-stage class IV). Of the remaining 64 patients "footprints" of HRV were measured as percentage of square plot surface (X-axis heart rate, Y-axis RR-variability) on the third day after impantation and 6 weeks later. Correlations were made with the Minnesota quality of life (QOL) score and 6 min walking test (MWT).
Results: Comparison between the baseline plot and the 6 weeks plot showed improvement in HRV in 71% of the patients, footprint percentage increased with 31 ± 12% (min 10%, max 52% improvement). In 29% of the patients no improvement was seen. The improvement and deterioration obtained with the patient centric diagnostic tool correlated significantly with the improvement or deterioration in QOL score and 6-MWT.
Conclusion: A significant correlation was found between HRV changes and changes in QOL and 6-MWT. The novell patient centric diagnostic tool allowing to obtain HRV footprints should be used to monitor heart failure patients treated with resynchronization therapy.

293 Biventricular pacing improves heart rate variability in patients with chronic heart failure

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Purpose: Cardiac resynchronisation therapy (CRT) using bi-ventricular pacing is an emerging treatment for patients with chronic heart failure and ventricular dyssynchrony. The effect of CRT on heart rate variability (HRV) recorded by the device has not been elucidated so far.
Methods: In 45 patients (age 66±11 years, NYHA class 2.9±0.6, EF 24±7% at implant) with implanted CRT device (InSync III®, Model 8042, Medtronic Inc.) the time domain measures of 5 minutes medians of the HRV (SDANN) recorded by the device were exported and analysed. "Seven days mean values" of the daily SDANN values obtained by the device were compared after implant (IMP), at 1 month (1m) and at 3 months (3m) after implant. Atrial intervals during atrial high rate episodes were excluded. The non-parametric Wilcoxon test for paired variables was used to compare the trend in HRV.
Results: Representing an early response to CRT therapy, the 7-day mean SDANN parameter revealed a low variability in heart rate (65±21 bpm). One month after implant (IMP) HRV significantly increased up to 74±24 bpm ($p<0.005$) with further improvement after three months to 78±24 bpm, $p<0.001$ compared to IMP.
Conclusions: In patients with severe heart failure, increased HRV due to cardiac resynchronisation therapy could reflect a reduction in sympathetic nerve activity in these patients. Therefore, the time domain HRV parameter SDANN could be used as a measure of clinical response in patients with bi-ventricular pacing.

294 Is the release of brain natriuretic peptide a predictor of improved left-ventricular function in patients with heart failure and cardiac resynchronization therapy?

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The release of Brain Natriuretic Peptide (BNP) is increased in patients with reduced left ventricular (LV) function. Cardiac resynchronization therapy (CRT) is known to improve cardiac hemodynamics and reduce LV volumes in patients with heart failure and ventricular conduction disturbance. Therefore, we investigated the effects of CRT on BNP levels and LV volumes in these patients.
Methods: 16 patients (12m, 65±12y, mean EF 23±5%) with left bundle branch block (QRS 171±30ms) receiving CRT were investigated. BNP levels were measured using the Triage BNP test (Biosite Diagnostics, USA). As BNP levels depend on renal function, serum creatinine and BUN levels were measured simultaneously. LV endsystolic (ESV) and enddiastolic volumes (EDV) and EF were determined by echocardiography. Blood samples and echo data were collected before pacemaker implantation (baseline) and after 18±8 weeks of CRT.
Results: Patients were divided into two groups: Group A showed baseline BNP levels below the median (460 pg/ml), group B above the median. The effects of CRT on BNP levels and LV volumes are shown in the table. During CRT, there was no significant change in creatinine (1.5±0.4 vs 1.4±0.4 mg/dl) and BUN (62±31 vs 61±35 mg/dl).

Effects of CRT on BNP and LV parameters

Group		BNP (pg/ml)	EDV (ml)	ESV (ml)	EF (%)
A	Baseline	275±136	218±43	165±37	24±9
	CRT	187±143*	212±50	129±43*	39±13*
B	Baseline	726±263	256±103	210±100	19±6
	CRT	564±415	248±109	185±104	25±10

mean ± SD, * $p<0.05$ vs. baseline

Conclusion: Patients with lower baseline BNP levels showed a significant decrease in BNP release and LV endsystolic volumes and an increase in EF during CRT. Thus, baseline BNP levels might be used as a predictor of improved LV function during CRT in patients with advanced heart failure and left ventricular conduction disturbance.

295 Effects of cardiac resynchronization therapy on ventricular-arterial coupling in patients with congestive heart failure

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Patients with congestive heart failure (CHF) and wide QRS, show long-term clinical benefits from cardiac resynchronization therapy (CRT). The clinical efficacy of CRT has been ascribed to the left ventricular remodeling, but the underlying mechanisms are not completely investigated. It is well known that in normal hearts the ventricular-arterial coupling (VAC) is direct to obtain the better mechanical efficiency, while in CHF pts tends to optimize the external work with disadvantage for the ventricular functioning. Aim of our study was evaluate the effects of CRT on the VAC in CHF pts. Study population: 59 pts (47 males, mean age 72 $\pm$ 9 y.o.) with CHF in NYHA class III/IV, cardiomyopathy of any origin and prolonged QRS duration, underwent to CRT. A complete echocardiographic examination was performed before and one week after the implantation procedure in order to evaluate Effective arterial elastance (Ea) and Ventricular elastance (Ees). Ea was considered as the relationship between systolic aortic pressure and stroke volume while Ees the relationship between systolic aortic pressure and end systolic volume index. The VAC was calculated as the ratio between Ea and Ees (Ea/Ees). Ejection fraction (EF) and end systolic/diastolic volume (ESVi/EDVi) were also measured. Results: CRT significantly reduced ESVi (135,91 $\pm$ 43,72 ml/m^2 vs 110,91 $\pm$ 45 ml/m^2, p<0,0001), EDVi (178,46 $\pm$ 50,44 ml/m^2 vs 167,91 $\pm$ 57,54 ml/m^2, p<0,002), leading to an increase of EF (24,37 $\pm$ 5,77% vs 35,06 $\pm$ 7,69%, p<0,001). It also reduced Ea (2,41 $\pm$ 0,88 mmHg/ml vs 1,88 $\pm$ 0,65 mmHg/ml, p< 0,0001; and the relatives indexed values: 1,34 $\pm$ 0,55 mmHg/ml/m^2 vs 1,05 $\pm$ 0,39 mmHg/ml/m^2) and Ea/Ees relation (2,65 $\pm$ 1,57 vs 1,61 $\pm$ 1,04, p<0,0001; normal value 0,8). A significant correlation (p<0.05) was found between Ea/Ees vs ESVi (r = 0,65); Ea/Ees vs EDVi (r = 0,75); EF vs Ea/Ees (r = 0,67); Ea/Ees vs the variation of ESVi induced by CRT (r = 0,52; p<0,01). Conclusions: CRT determined a significant reduction of ventricular volumes and an increase in EF. It also reduced Ea (index of aortic impedance) and ameliorates VAC expressed as a reduction of Ea/Ees. The ESVi reduction was in part due to variation of Ea/Ees. The changes in VAC improve the ventricular efficiency and have to be considered as an important feature for the final result of CRT.

296 Monitoring of patients activity in chronic heart failure by pacemaker devices: a novel marker for individual improvement after CR?

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Purpose: Cardiac resynchronisation therapy (CRT) using bi-ventricular pacing is an emerging treatment for patients with severe heart failure and ventricular dysynchrony. Recently, sensors have been incorporated into CRT devices to enable continuous physical monitoring of the patient. The aim of the study was to assess the effect of CRT on the individual physical activity recorded by the device in addition to NYHA class as an estimate of clinical improvement.
Methods: In 56 patients (age 66 $\pm$ 11 years, NYHA class 2.9 $\pm$ 0.6, EF 24 $\pm$ 7% at implant) with implanted CRT device (InSync III®, Model 8042, Medtronic Inc.), the minutes of daily physical activity (MDPA) recorded by an activity sensor were exported and analysed. "Seven-day means" of the MDPA values were compared from the first week after implant (IMP), at 2 weeks (2w), at 1 month (1m) and at 3 months (3m) after implant. The non-parametric Wilcoxon test for paired variables was used to compare the trend in MDPA.

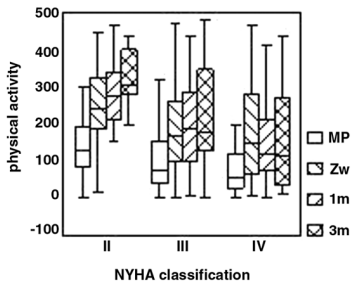

Fig. 1. Trend on physical activity by NYHA.

Results: Overall analysis revealed low physical activity, mean MDPA 108 $\pm$ 89 min/day in the first week of CRT therapy. Thereafter it significantly increased to 170 $\pm$ 112 min/day in the second week, 211 $\pm$ 120 min/d at 1m; and 235 $\pm$ 134 min/d at 3 m, p < 0.001 compared to baseline and second week, p (3m vs. 1m) = 0.012. Grouped analysis of the MDPA measures in relation to patient NYHA classification at baseline is given in Fig. 1.
Conclusions: CRT improves physical activity measured by an activity sensor in patients with severe heart failure with the greatest improvement seen already within the first month. Since less physical activity was observed in patients with high baseline NYHA classes minutes of daily physical activity measured by the device can be assumed to reflect individual physical activity.

BLOOD BORNE PROGENITOR CELLS FOR MYOCARDIAL REGENERATION

319 Endothelial regeneration of vein grafts by circulating progenitor cells

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Background: Previously we showed that a large number of endothelial cells in vein grafts undergo apoptosis or necrosis during the first few days followed by endothelial regeneration.
Methods and Results: In the present study we investigated the kinetics of endothelial cell death and regeneration in vein grafts using transgenic mice carrying LacZ genes driven by the endothelial TIE2 promoter. We demonstrated that the endothelium of donor vessels denuded completely by 72 h, and neoendothelium appeared 24 h after grafting. When vein isografts were performed between TIE2-LacZ and wild-type mice, beta-gal+ cells were observed on the surface of vein segments at 48 h. These beta-gal+ cells were only seen on the endothelial surface of vein segments grafted into TIE2-LacZ mice 1, 2 and 4 weeks after surgery, suggesting recipient origin. Interestingly, beta-gal+ cells were evenly distributed on the surface of the whole vein segment grafted into TIE2-LacZ mice, indicating a contribution of circulating progenitor cells. When wild-type veins were grafted into a chimeric mouse carrying TIE2-LacZ genes in bone marrow cells, about 30% of total endothelial cells displayed beta-gal+ staining.
Conclusion: We provide the first evidence that endothelial cells of vein grafts are derived from circulating progenitor cells, of which 30% are derived from bone marrow progenitor cells.

320 "Homing effect directs mesenchymal stem cells to develop a myogenic phenotype

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Background: The transplantation of stem cells seems to become a promising new strategy for the treatment of patients with end stage heart failure. In this study we investigated the capacity of mesenchymal stem cells transplanted into rat myocardium to develop a myogenic phenotype.
Methods: Rat MSCs were isolated according to Caplan's method. After the separation of the non-mesenchymal subpopulation the adherent rMSCs were further cultivated. For a later detection within the target area the eGFP gene was introduced into the rMSCs using an adenovirus-mediated transfection. The chest of the rats was opened via mini-thoracothomy, a cryolesion generated and 1 Mill. cells (5 injections; 50μl each) were injected into the border zone the lesion (6x4mm). 3 weeks later rats were sacrificed, hearts excised and analysed via fluorescence microscopy and immunohistochemistry. The following mAbs were used: Smooth muscle actin (SMA), muscle actin (MA), troponin T-C, myosin heavy chain (MHC), desmin and the endothelial cell specific marker CD31.
Results: Rat MSCs within the target tissue showed a high rate of viability (70-80%). Furthermore single rMSCs were detected that could be stained positive for myocyte specific markers. However, the cells did not develop myofibers in this early state of development. In addition we could find a high incidence of small blood vessels in the transplantation area.
Conclusion: 1. The "homing effect" of injured rat myocardium might direct transplanted rMSCs into a myogenic differentiation pathway. 2. The finding of a high incidence of blood vessels within the transplantation area might point to an angiogenic potential of rMSCs as well. 3. These findings have to be verified in additional experiments with a longer follow up of at least 6 weeks.

321 Via induction of differentiation from human bone marrow derived mesenchymal stem cells to adult cardiomyocytes?

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Background: The transplantation of human bone marrow-derived mesenchymal stem cells (hMSC) into the myocardium is a promising new technique for a hemodynamic improvement of heart function. However, it is not yet clear which cells are suited best for the task of restoring structure and function and/or the formation of new vessels within the infarct area. In this study we investigated various growth factors (GF) and GF-combinations concerning their ability to induce the formation of cardiomyocytes from hMSC in-vitro.
Methods: hMSCs were isolated and cultivated according to Caplan's method. After the separation of the non-mesenchymal subpopulation the adherent hMSCs were treated with 5-Azacytidine (10μM), VEGF (1ng/ml), bFGF (10ng/ml), G-CSF (20ng/ml), Epo (2,5 mU/ml) and 5-Azacytidine (10μM/ml)+bFGF (10ng/ml). Immunohistochemical analysis was done periodically during a 12 week follow up using the following myogenic antibodies: Smooth muscle actin (SMA), muscle actin (MA), troponin T+T-C, actinin, alpha-SR-1 and desmin.
Results: Compared to unstimulated controls stimulated hMSCs changed morphology and up to 85% of MSC became positive for the myogenic marker SMA. RT-PCR analysis showed the expression of early cardiomyocyte transcription factors Oct-4, Nkx2.5 and GATA4 as well as markers specific for adult cardiomyocytes like atrial myosin light chain (MLC2a) and ventricular myosin light chain (MLC2v). A de-differentiation could not be detected during the 12 week follow up. But – as described in other publications – we could not show any spontaneously contracting myocytes even after adding Acetylcholin (1mM).
Conclusion: 1. Using GFs we were able to induce a myogenic phenotype in up to 85% of hMSCs. 2. Spontaneously contracting myocytes could not be generated from GF-treated hMSCs.

322 Endothelial cell protection with dextran sulfate: a novel strategy to prevent acute vascular rejection in hamster-to-rat cardiac xenotransplantation

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Purpose: Acute vascular rejection (AVR), as occurring in hamster-to-rat cardiac xenotransplantation, can be prevented by complement depletion using cobra venom factor (CVF) combined with sustained T-cell immunosuppression by cyclosporin A (CyA). In this setting, long-term survival of hamster hearts, defined as "accommodation", is achieved in the presence of graft-specific antibodies and complement. Endothelial cells (EC) protect themselves by upregulation of genes like Bcl-2, A20 or heme oxygenase 1 (HO-1). We have shown recently that low molecular weight dextran sulfate (DXS) acts as an EC protectant and prevents complement– and NK cell-mediated cytotoxicity in vitro. In this study we evaluated whether daily administration of CyA combined with repeated injections of DXS could prevent AVR of hamster-to-rat heart xenografts.
Methods: Hamster heart xenotransplantations were performed into Lewis 1A rats. Recipients were treated by daily administration of CyA (10 mg/kg) from the day of transplantation and received intravenous injections of DXS (up to 50 mg/kg) starting one day after surgery. Immunofluorescence for anti-donor IgM and IgG antibodies, complement products and HO-1 was done on hamster hearts. Anti-hamster xeno-antibodies were measured by CELISA. In addition, complement activity in serum was assessed by standard hemolytic assays.
Results: Untreated and CyA-only treated recipients rejected their grafts in 4.0 ± 0.6 days (n=10). Among treated, grafted recipients (n=19), 40% became long-term graft survivors (>30 days) and the remaining 60% rejected their graft in 14.3 ± 7.2 days. In both long-term surviving and rejecting grafts, deposition of rat IgM and C3 were observed. Combined with the expression of HO-1 on long-term survivors' EC, these results indicate that "accommodation" had occurred. In addition, complement activity was intact in rat serum after DXS injections, and unlike CVF the DXS-treatment did not induce systemic complement depletion.
Conclusions: Our preliminary data indicate that intravenously administered DXS is able to prevent antibody- and complement mediated acute vascular rejection in vivo supporting the hypothesis that DXS can act as a "repair coat" that functionnaly restores activation induced loss of heparan sulfate proteoglycans and protects EC from damage.

323 Intramyocardial transplantation of human embryonic stem cells in rats with acute myocardial infarction

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Background Stem cells have emerged as an attractive and promising new therapeutic approach for treatment of heart diseases. While human adult stem cells have been successfully used for cardio-reparation both in animals and humans, this was not the case with pluripotent human embryonic stem cells (hES). The aim of this study was to evaluate feasibility and safety of myocardial hES cell transplantation into rats with acute myocardial infarction (MI).
Methods Male Sprague-Dawley rats ~200 g were used. MI was induced by direct cryo-injury using 3 mm probe. This procedure resulted in anterior MI engaging ~15-20% of left ventricle (LV). The rats were randomized to two groups: rats with MI treated with vehicle (control, n = 8), rats with MI treated with 1 million hES cells (hES, n = 8). Four MI rats treated with hES cells received cyclosporine (5 mg/kg/d). The hES cells were suspended in 0,05 ml buffer and transplanted by intramyocardial injection into the viable myocardium close to the infracted area directly after cryo-injury. All animals were investigated with transthoracal echocardiography, continuous ECG and LV catheterization 1 week after transplantation. Post-mortem, the hearts were evaluated histologically for detection and characterization of hES cells.
Results There were no deaths in the rats treated with hES cells. Variables of LV function and morphology are given in the table. No arrhythmias were detected in the rats treated with hES cells. dP/dT was similar in both groups. There were no signs of abnormal tissue growth at the site of hES cell engraftment. Preliminary data have confirmed the presence of human cells in the infarcted area.

Echocardiography

	E/A	EF %	LVVd ml	LVDd mm	HR bpm
hES	1.3 ± 0.1#	41 ± 2	0.41 ± 0.02	8.7 ± 0.1	295 ±14
control	3.1 ± 0.6	41 ± 0.5	0.43 ± 0.04	8.9 ± 0.1	272 ± 8

p=0.05 v. control, E/A = mitral E-wave/A-wave ratio, EF=ejection fraction, LVVd=left ventricular volume in diastole, LVDd=left ventricular diameter in diastole, HR=heart rate

Conclusion Transplantation of hES cells is feasible and safe in the rat model of acute myocardial infarction. The use of hES may be an important approach for cardio-reparation and reconstitution of normal cardiac structure and function in the future.

324 Coagulation factor VIIa stimulates migration by activation of the mitogen-activated protein kinase p38 and the GTP-ase Rac

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Aim: Tissue Factor (TF), the surface receptor for the serine protease factor VIIa (FVIIa) and the initiator of the extrinsic coagulation cascade, supports angiogenesis, tumor metastasis and proinflammatory responses by activation of extracellular, protease-dependent signaling pathways. The molecular mechanisms that are independent of the proteolytic activity of FVIIa are not yet known.
Methods: The human bladder carcinoma cell line J82 (HTB-1) that expresses high levels of TF was obtained from American Tissue Culture Collection and grown in Dulbecco's modified Eagle medium (DMEM, Gibco) supplemented with 10% fetal calf serum, glutamin, penicillin and streptomycin. Migration towards FVIIa or proteolytically inactive FFR-FVIIa (Novo Nordisk) was analyzed in a Boyden chamber assay. Analysis of the mitogen-activated protein kinase (MAPK) p38 was performed using in vitro kinase assays and activation of the GTPase Rac was measured after precipitation of RacGTP with its immediate downstream effector p21-activated kinase. For transfection experiments cells were transiently transfected using Effectene (Qiagen, Crawley; UK).
Results: Migration of J82 cells was dose-dependently enhanced by a chemotactic gradient of FFR-FVIIa in a Boyden chamber assay. Because a comparable increase in the number of migrated cells was observed after stimulation with proteolytic active FVIIa the protease activity is not reqiured for stimulation of migration. This effect was specific for TF since in the presence of inhibitory anti-TF-antibodies abolished the increase in migration by FVIIa and FFR-FVIIa was abolished. Acitve site-inhibited FFR-FVIIa was sufficient to activate the MAPK p38 and the GTPase Rac to a similar extent than FVIIa. This was required for the stimulation of migration because inhibition of the MAPK p38 by SB203580 or overexpression of dominant negative p38 or the GTPase Rac abolished TF-induced migration. Thus, FFR-FVIIa binding to TF enhanced migration by activation of p38 and the GTPase Rac.
Conclusion: Stimulation of migration by TF-mediated activation of the MAPK p38 and the GTPase Rac provides a rationale to the understanding of the proangiogenic, proinflammatory and prometastatic functions of TF.

COMPUTER DEMONSTRATIONS

325 Guideline assessment supporting tools and ontologies in clinical cardiology

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Within the ESC guideline task forces, policy conferences, working groups and study groups are generating guidelines and protocols to standardize diagnosis and treatment in cardiovascular disorders at a European level.
Currently these extensive guidelines are only available in written form, and therefore hard to access, e.g. ESC guideline on Sudden Cardiac Death: 76 pages, executive summery 16 pages. Modern knowledge technology techniques might be useful in making this information approachable. However, on a more modest scale decision support systems are currently under development, based on local protocols and in cooperation with existing patient information systems, to support treatment and to generate warnings in conflicting situations. GASTON, (Guideline Assessment Supporting Tools and ONtologies) the decision support system described in this study is currently evaluated in clinical practice. Using this interactive system in defining guidelines, three layers are distinguished: the flow diagram, the underlying rules and the communication with external data sources and care providers about the actual patient status. In the first layer, the flow charts derived from the guidelines and protocols are drawn, and annotated using natural language. Secondly, the underlying criteria are defined, using a domain specific vocabulary and a dedicated toolbox. Finally the communication of the patient data: manually, directly by an electronic patient record form or by a link to an existing data source should be defined. As stated above in Europe and also in the Netherlands, the impact of protocols in clinical cardiology is growing rapidly, making excellent supporting knowledge engineering tools essential. Being so successful in small-scale guideline representation, a project was initiated to assess the feasibility of using GASTON as a knowledge representation environment for a large number of national guidelines. In this project, launched by the ICIN, the Interuniversity Cardiology Institute of the Netherlands, all participating centers are implementing various (parts of) currently accepted national guidelines in a uniform way including the guidelines for diagnosis and treatment of Atrial Fibrillation, Heart Failure and Acute Coronary Syndromes. The separate definition of flow diagrams and underlying rules enables the design of a language-independent knowledge representation. Based on the official ESC guidelines set, national adaptations and translations become feasible and documentable. Ultimately all ESC guidelines might be represented in this unambiguous digital format.

326 Mobile access to always up-to-date clinical information improves quality of care

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Introduction: Until recently, cardiologists at the Leiden University Medical Center (LUMC) had to use their their desktop PC's to retrieve medical information such as clinical guidelines, medication information, risk prediction calculators, calculation of physiological determinants (valve area, vessel resistance, etcetera). Or even worse, they had to revert to clinical guidelines in printed format. Today, much of this clinical information is available on-line via a web-browser on a PC, but this still is not the perfect solution for the mobile cardiologist.
Solution: We have chosen to provide all staff members and residents at the Department of Cardiology at the LUMC with a Palm Tungsten-T Personal Digital Assistant (PDA). Relevant cardiology guidelines, such as the European (ESC) and national guidelines are available on the PDA in a format using flowcharts with hyperlinks. The GASTON decision support system is used to convert existing guidelines into flowcharts in PDA-format. Primary risk-prediction software, developed earlier in our department, is also available on the PDA. Furthermore, medical calculators and medication subscription software are available on the PDA. To ascertain that each cardiologist always has the most up-to-date information on his PDA, Bluetooth Access Points (PICO Connect) are placed at various places through the department, allowing the Palm Tungsten-T to connect wirelessly to the network. Extended Systems Inc.'s XTNDConnect Server software is used for central synchronization and administration purposes. Finally, by synchronizing the PDA with the information that is available on the Exchange server of the LUMC, the cardiologist has always up-to-date information about schedules, notes, and access to their corporate e-mail.
Conclusion: The ability to have up-to-date clinical information on an easy to use PDA directly at the point-of-care allows consistent diagnosis and treatment of all cardiology patients according to the latest guidelines, thereby vastly improving the quality of care. Detailed information about the system setup will be presented; the PDA applications will be demonstrated.

327 Pocket PC based tele-echocardiography

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The evolution of portable handheld technologies gave clinicians access to medical images on ultraportable computers. We explore the reliability and clinical utility of interpreting echocardiograms send by internet over standard telephone lines to a pocket PC.
A series of echocardiographic studies including 20 M-mode still frames, and 61 cardiac cycles (31 2-D echos, 30 colour-flow echos) were measured and interpreted in our Hospital, and then they were compressed (JPG and MPEG-1) using commercial software and send to a pocket PC. Two experienced echocardiographers received the images, measured off-line the M-mode recordings and interpreted the cine-loops. Results were compared with the measurements and diagnosis made in the echocardiography laboratory.
Every study was judged sufficient for interpretation. A good agreement ($r = 0.91$) was found for the 52 M-mode linear measurements between the off-line echocardiographers and the echo laboratory. No clinically significant error was observed in the diagnostic interpretation of the 61 cine-loops by the pocket PC echocardiographers.
Conclusion: Our results indicate that transmission of echocardiograpic images over standard telephone line to a pocket PC is feasible, and provides the basis for an accurate, low cost system of tele-echocardiography.

328 Heart failure patient simulator

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Purpose: The general availability of computers has made educational software an interesting tool for furthering training in medicine. Recently, interest in multimedia applications has stimulated the search for efficient software, directed towards interactive education in cardiology.
"Cardioactive" is based on case studies where you are presented with a patient and can continuously enter suggestions for investigations and treatment from your keyboard. The simulated patient immediately reacts according to the treatment suggested. The first patient you are confronted with suffers from dyspnea 1 month after an acute myocardial infarction.
The program starts with an interview of a patient by her physician regarding her present and past medical history. The interview is presented as a short movie on the computer screen. At first a suggestion of diagnosis is presented, followed by an opportunity to suggest different investigations. The software includes all current prices for every investigation. The investigator has the opportunity to treat the patient with any cardiovascular drug. At follow-up visits, the patient's symptoms, clinical and laboratory values change depending on the treatment suggested. In addition, the patient's risk-score changes and is presented on-line. If an investigation is ordered, the results of this investigation are presented either as an on screen video or as graphics showing x-ray or ECG. In addition to the end result of all treatments an assessment of the total cost for all investigations as well as medical treatment is presented.
Hard- and software requirements: An IBM compatible computer with soundblaster running WindowsTM3.1 or higher or Windows-95 with a CD-ROM x8 or faster.

POSTER DISPLAY I

HEART FAILURE

P329 The effects of atrial natriuretic peptide-NPRA interaction on human vascular function in vivo

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Background: Atrial natriuretic peptide (ANP) plays an important role in cardiovascular control but its effects on veins remain controversial. Importantly, no studies to date have conclusively shown that basal ANP levels contribute to resting vascular function in humans, a prerequisite for accepting that ANP is a physiologically important vasoactive peptide in health.
Methods and Results: Combining equilibrium blood-pool-scintigraphy (EBPS) with a conventional occlusion technique (radionuclide plethysmography) we examined the effects of ANP and the NPRA selective ANP-receptor antagonist A71915 on forearm vascular volume in healthy subjects. Creating pressure/volume relations (PVR) we determined changes in vascular volume, compliance and tone. EBPS was then used to assess the effects of systemic administration of A71915 on regional intestinal vascular volume. Infusion of ANP increased forearm vascular volume in a dose dependent manner (max. 20%; $p<0.001$), exerting a maximum venodilating effect at plasma levels equivalent to those seen in heart failure. A71915 increased venous tone thereby decreasing vascular volume by $9.6 \pm 1.1\%$; $p<0.001$ (forearm) and $2.6 \pm 0.5\%$; $p=0.01$ (intestinal beds). Performing dose-ranging studies we further assessed the potency and specificity of A71915 in the forearm resistance vasculature. At an infusion ratio of 50:1 A71915 almost completely abolished the effect of ANP on forearm blood flow.
Conclusion: ANP regulates regional vascular volume and tone without affecting compliance. This effect was seen over a wide range of physiological and pathophysiological plasma levels. In health, the effects of ANP on FBF are almost exclusively mediated via the NPRA receptor.

P330 Differential activation of left-ventricular interleukin-6 and brain natriuretic peptide gene expression in experimental heart failure

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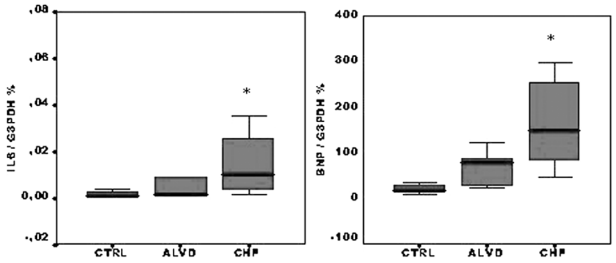
Circulating interleukin-6 (IL-6) as well as brain natriuretic peptide (BNP) concentrations are increased in congestive heart failure (CHF). However, their relative activation in left ventricular (LV) myocardium has not been well characterized in CHF. We therefore analyzed cardiac gene expression of IL-6 and BNP in rabbits with pacing-induced heart failure. Rabbits developed asymptomatic left ventricular dysfunction (ALVD) (n=5) by rapid right ventricular pacing with 330bpm for 10 days. Further progressive pacing with 360bpm and 380bpm for 10 days each led to CHF (n=18). Left ventricular mRNA expression of IL-6 and BNP referring to glyceraldehde-3-phosphate-dehydrogenase (GAPDH) was analyzed quantitatively by real time PCR (light cycler®, Roche). LV fractional shortening (FS) and systolic wall stress (LVSWS) were assesed by echocardiography (12 MHz probe). Both, IL-6 and BNP gene expression increased step-wise during the progression of CHF. As compared to control (n=12), IL-6 and BNP mRNA expression were both significantly elevated in CHF (figure, IL-6: $p< 0.05$; BNP: $p< 0.005$). However, the relative increase of BNP in CHF was greater than that of IL-6 (659% vs. 314%) and BNP expression even exceeded expression of the houskeeping gene GAPDH by 64%. In addition, BNP mRNA expression correlated positively with LVSWS (r=0.47; p=0.05) and inversely with FS (r= - 0.76; p= 0.01), whereas no correlation was present with IL-6.
In summary, IL-6 and BNP gene expression both increase step-wise during the progression of CHF, but with a greater relative increase of BNP. Because of the steeper and greater activation, BNP may be a superior marker of LV dysfunction and CHF than IL-6.



IL-6 and BNP cardiac gene expression.

P331 N terminal pro-brain natriuretic peptide is the most powerful predictor of mortality in patients with advanced heart failure

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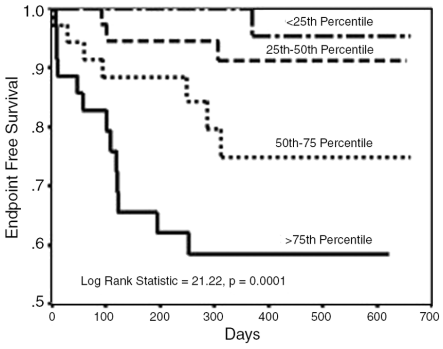
Purpose: The selection of patients for cardiac transplantation (CTx) is notoriously difficult and traditionally involves clinical assessment and an assimilation of markers of the severity of CHF such as the left ventricular ejection fraction (LVEF), maximum oxygen uptake (peak VO2) and more recently, composite scoring systems e.g. the heart failure survival score (HFSS). The prognostic ability of NT-proBNP in advanced heart failure is unknown and no studies have compared NT-proBNP to standard clinical markers used in the selection of patients for transplantation. The purpose of this study was to examine the prognostic ability of NT-proBNP in advanced heart failure and compare it to that of the LVEF, peak VO2 and the HFSS.
Methods: We prospectively studied 142 consecutive patients with advanced CHF referred for consideration of CTx. Plasma for NT-proBNP analysis was sampled and patients followed up for a median of 374 days.
Results: The primary endpoint of all-cause mortality was reached in 20 (14.1%) patients and the combined secondary endpoint of all-cause mortality or urgent CTx was reached in 24 (16.9%) patients. An NT-proBNP concentration above the median was the only independent predictor of both all cause mortality ($chi^2=6.03$, p=0.01) and the combined endpoint of all cause mortality or urgent CTx ($chi^2=12.68$, p=0.0004). NT-proBNP split into quartiles is shown in the figure against endpoint free survival. LVEF, VO2 and HFSS were not independently predictive of mortality or need for urgent cardiac transplantation in this study.



Quartiles of NT-proBNP and prognosis.

Conclusion: A single measurement of NT-proBNP in patients with advanced CHF, can help to identify patients at highest risk of death, and is a better prognostic marker than the LVEF, VO2 or HFSS.

P332 Brain natriuretic peptide, but not norepinephrine, predicts improvements in left-ventricular structure and function in patients with chronic heart failure enrolled to Val-HeFT

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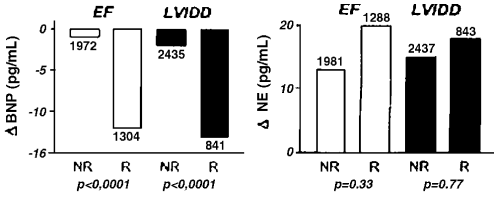
Background: Although both BNP and NE are elevated in heart failure (HF), their relationships to LV remodeling, ejection fraction (EF) and diameter (LVIDd) are not clear.
Methods: Val-HeFT (Valsartan Heart Failure Trial) randomized 5,010 pts in NYHA class II-IV receiving precribed HF therapy. Plasma BNP was measured by IRMA, NE by HPLC/electrochemical detection in 2 core labs at baseline and during follow-up. Serial echocardiographic (Echo) exams were recorded and read at each site with monitored quality control. Valsartan (V) and placebo (P) patients were defined for exploratory analysis as responders (R) if EF increased $\geq$ 5% or LVIDD decreased $\geq$ 0.5 cm one year after randomisation. Non-responders (NR) did not meet these criteria.
Results: At baseline, BNP correlated with Echo variables (inversely with EF and directly with LVIDd) better than NE. Overall, there was greater reduction in BNP, smaller increase in NE and improvement in echo in V compared to P. In the pooled population (Figure), the median decrease in BNP was significantly greater in R than in NR. A similar trend was seen in both P and V patients even if the difference between R and NR was less marked in P. Median NE changes did not differentiate between R and NR.



Median change from baseline to month 12

Conclusion: BNP is an indicator of the severity of LV dysfunction in HF at baseline. Changes in BNP, but not in NE, reflect those of EF and LVIDd. Thus, a decrease in BNP, but not NE, appears to be an index for improvement in LV structure and function.

P333 Detection of differences in diastolic function between viable and non-viable myocardial segments by strain rate analysis

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Background: Diastolic function analysis has been suggested for detection of myocardial ischemia. Analysis of diastolic function for assessment of myocardial viability has not been evaluated. Strain rate (SR) analysis allows quantitative segmental analysis of myocardial function and has been used during dobutamine stimulation for assessment of myocardial viabilty.
Methods: In 37 patients with ischemic left ventricular dysfunction myocardial viability was assessed using low dose (10 μg/kg/min) 2D DSE, strain rate imaging and F18-fluorodeoxyglucose positron emission tomography (PET). Peak early diastolic (E-wave) and late diastolic (A-wave) myocardial SR was determined at baseline and during low-dose dobutamine stress from apical views.
Results: 192 segments with dyssynergy at rest were classified by ^{18}FDG PET as viable in 94 cases and non-viable in 98 cases. There were no significant differences in peak E-wave and A-wave SR at rest between viable and non-viable segments. With dobutamine stimulation peak E-wave SR increased significantly for viable segments while it was unchanged for non-viable segments. Peak A-wave SR increased for viable and non-viable segments. However, during dobutamine stimulation peak A-wave SR for viable segments was significantly larger than for non-viable segments.
Conclusions: Viable myocardial segments demonstrate an increase in early as well as late diastolic SR with dobutamine stimulation while non-viable segments are non-responsive to dobutamine. Diastolic SR analysis during dobutamine stimulation may add to systolic function analysis in the assessment of myocardial viability.

Diastolic strain rate parameters

	Viable by PET (N=94)	Non-viable by PET (N=98)	P
Peak E-wave SR at rest (1/s)	0.89 $\pm$ 0.51	0.77 $\pm$ 0.49	0.103
Peak E-wave SR with dobutamine (1/s)	1.06 $\pm$ 0.51*	0.78 $\pm$ 0.48#	<0.001
Peak A-wave SR at rest (1/s)	0.71 $\pm$ 0.55	0.57 $\pm$ 0.47	0.055
Peak A-wave SR with dobutamine (1/s)	1.00 $\pm$ 0.56*	0.71 $\pm$ 0.58¶	<0.001

*P<0.01 vs rest, #P=0.835 vs rest, ¶P=0.023 vs rest

P334 Intraventricular dyssynchrony in ischaemic cardiomyopathy improves after surgical ventricular restoration

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Objective: Myocardial activation-contraction sequence abnormality is common in dilated cardiomyopathy with interventricular conduction delay, and leads to contraction dyssynchrony that impairs left ventricular (LV) ejection. Ischemic cardiomyopathy results in non-uniform contraction, relaxation and filling (intraventricular dyssynchrony) which may be independent of electrical conduction delay. Surgical ventricular restoration (SVR) is an emerging technique that restores LV geometry and shape. This study evaluated sequential regional contraction/relaxation and mechanical performance in patients with previous anterior MI undergoing SVR.
Methods: Thirty patients (mean age 58$\pm$8 years) with depressed LV function. LV pressures and angiography (heart paced at 100 beats/min) were performed before surgery, during heart catheterization, and before discharge. Endocardial time motion of 15 regional segments, global pressure/volume (P/V) loop, segmental pressure/length loop (P/L), index of synchrony (SI; segments reaching maximal motion (end systole)/15), and index of uniformity (UI; effective area/theoretical area x 100) were calculated.
Results: QRS duration (ms) from 100 $\pm$ 17 to 114 $\pm$ 28 (p 0.09). The mean SI and UI significantly improved after SVR from 0.23$\pm$0.12 to 0.60$\pm$0.13 ($p< 0.0001$) and from 28$\pm$17 to 47$\pm$17 ($p<0.0001$), respectively. The number of normal P/L loops increased and P/L loop abnormalities decreased with a consistent decrease in right- and left-oriented CCW loops and left CW loops ($p<0.006$). Functional parameters significantly improved: ejection fraction (%) 30$\pm$13 to 45$\pm$12 ($p<0.001$), end-diastolic volume index (ml/m^2) 202$\pm$76 to122$\pm$48 ($p<0.001$), end-systolic volume index (ml/m^2) 144$\pm$69 to 69$\pm$40 $p<0.001$), end-systolic pressure 122$\pm$15 to 104$\pm$22 ($p<0.016$), end-systolic pressure/volume ratio (mmHg/ml) 1.06$\pm$0.7 to1.60$\pm$0.8 ($p<0.001$), peak filling rate (EDV/sec) 1.75$\pm$0.7 to 2.32$\pm$0.7 ($p<0.0001$), minimum pressure (mmHg) 12$\pm$9 to5$\pm$4 ($p<0.003$), capillary wedge pressure (mmHg) 14$\pm$7 to 10$\pm$4 ($p<0.0001$), mean pulmonary artery pressure (mmHg) 21$\pm$8 to 13$\pm$6 ($p<0.001$), and diastolic stroke work (g/m/min) 19$\pm$12 to 13$\pm$8 ($p<0.016$).
Conclusion: This is the first study to describe that mechanical intraventricular dyssynchrony is central to LV dysfunction in ischemic cardiomyopathy, independent of conduction delay. SVR improves LV performance through a "mechanical re-synchronization" of contraction with improved synergic distribution of parietal stresses. This may explain why bi-ventricular pacing therapy is less effective in ischemic than in non-ischemic cardiomyopathy with conduction delay.

P335 Systolic or diastolic, interventricular or intraventricular dyssynchrony in dilated cardiomyopathy: which is most important?

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Background: Cardiac resynchronization is now an accepted therapy for dilated cardiomyopathy (DCM). Its benefit is related to the correction of the systolic dyssynchrony (DYS) either between left and right ventricles [Inter DYS] or between left ventricular walls [Intra DYS]. However, little is known about the presence of a diastolic DYS in these pts, neither about the respective incidence of Intra and Inter DYS.
Objectives: to compare the respective occurrence of Inter and Intra, and diastolic (D) and systolic (S) DYS in a population of pts with DCM with or without LBBB.
Methods: 116 pts with DCM (84 primary, 32 ischemic) were studied by echo and Tissue Doppler Imaging (TDI). S and D parameters were measured using the delays between the onset of QRS and the onset of the TDI velocity curves. The septal and lateral walls of the left ventricles were used to assess Intra DYS. Similar measurements between lateral free walls of right and left ventricles were used to assess Inter DYS. Dyssynchrony (diastolic or systolic) was defined as a delay $>$ 40 ms.
Results: Systolic and diastolic DYS were observed in 58 (56%) and 77 (75%) pts, respectively. S and D, Intra and Inter delays increased with increasing QRS width but they were weakly related to QRS duration (table).

	n	S Inter (ms)	S intra (ms)	D Inter (ms)	D Intra (ms)
QRS $<$ 120 ms	40	24 $\pm$ 21	23 +/27	34 $\pm$ 37	18 $\pm$ 26
QRS 120-150 ms	34	34 $\pm$ 31	21 $\pm$ 27	49 $\pm$ 49	40 $\pm$ 55
QRS $>$ 150 ms	42	56 $\pm$ 45	41 $\pm$ 35	80 $\pm$ 57	43 $\pm$ 42
r		0.4	0.3	0.36	0.24

Among 40 pts with QRS $<$ 120 ms, 43% and 31% presented with S Inter and S Intra DYS, respectively, and 43% and 29% presented with D Inter and D Intra DYS, respectively by TDI.
Conversely, among 42 pts with QRS $>$ 150 ms, 30% and 42% had no significant S Inter and S Intra DYS, respectively, and 15% and 32% had no significant D Inter and D Intra DYS, respectively.
Conclusion: The diagnosis of asynchrony can not be made on ECG data only. Among pts with DCM, Inter and Intra delays by TDI are frequently observed but are weakly related to QRS duration. Both Inter and Intra Dyssynchrony may be observed in pts with or without LBBB. Diastolic DYS is more frequent than systolic and may be observed alone in some pts.

P336 Long-term effects of Nebivolol on left-ventricular function and exercise capacity in patients with idiopathic dilated cardiomyopathy

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Purpose: The beneficial effect of beta-blockers on the treatment of patients (pts) with chronic congestive heart failure has been demonstrated, but there is evidence of differential effects among them. Nebivolol, a new third generation, beta 1- blocking agent, has not been adequately studied in these patients. We assess the effects of Nebivolol on left ventricular (LV) function and exercise tolerance in patients with idiopathic dilated cardiomyopathy (IDC).
Methods: Sixty patients, aged 55 $\pm$ 9.5 y, with angiographically proven IDC, ejection fraction (EF)$<$45%, in stable New York Heart Association (NYHA) class II-III, entered a double-blind, 1:1 randomized Nebivolol or placebo (up to three months)trial. A complete echocardiographic study and exercise test with Naughton protocol was performed at baseline, three months and one year later on all patients.
Results: There were no significant baseline differences regarding NYHA class, heart rate (HR), LVEF, systolic blood pressure (BP) or echocardiographic variables between the 2 groups. During the first 3 months follow–up, 4 pts in the Nebivolol (13,3%) and 5 (16,6%) in the placebo group discontinued treatment.
A significant decrease was found in NYHA class (2,22 $\pm$ 0,31vs2.53 $\pm$ 0.44,p=0,02), resting HR (69,2 $\pm$ 8,4 vs 74,2 $\pm$ 8 b/min, p=0,05) and systolic BP(119 $\pm$ 9,7 vs 144 $\pm$ 12,3 mmHg, p$<$0,001) and an increase in LVEF (38,8 $\pm$ 7,3 vs 33,1 $\pm$ 10%, p=0,04) in the Nebivolol group compared to placebo, after 3 months treatment.
Indices of diastolic LV function were also improved. The velocity time integral of late LV filling (7,3 $\pm$ 2,1 vs 5,5 $\pm$ 1,3cm, p=0,01) increased and the atrial wave of the pulmonary vein flow (0,29 $\pm$ 0,04 vs 0,39 $\pm$ 0,06 cm/sec, p=0,01) decreased significantly. There was a decrease in maximum exercise duration (ExD) (737 $\pm$ 319 vs 861 $\pm$ 427 sec, p=0,01) mainly due to reduced HR at peak exercise (122 $\pm$ 11,3 vs 138 $\pm$ 12,8 beats/min, p$<$0,001). There was no significant difference in the placebo group in all aforementioned parameters at follow-up. At 12 month follow-up, 2 additional pts stopped Nebivolol while 2 other pts were lost. We found no further significant changes in HR, BP or echo indices compared to 3 months findings. However, the ExD increased significantly (1176 $\pm$ 626 vs 930 $\pm$ 364 sec,p= 0.03)after one year treatment.
Conclusion: In patients with idiopathic dilated cardiomyopathy Nebivolol improves LV systolic and diastolic function and functional NYHA class after 3 month treatment, while after an initial decrease in ExD a significant improvement at 12 months was achieved.

P337 ExTraMATCH: exercise training meta analysis of trials in chronic heart failure patients. Reduction in mortality and hospitalization

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Background: There is a growing acceptance among specialists treating heart failure (HF) that exercise training is safe and may offer an exciting new non-pharmacological approach by beneficially influencing symptoms and prognosis.
Objectives: To determine the effects of exercise training programme among HF patients.
Review methods: Randomised trials of an exercise training programme versus control in patients with HF and left ventricular dysfunction, from which results were available before December 2000, were identified from Medline, search of abstracts of presentations at international congresses, examination of reference lists. Only the original individual patient data-sets of trials constituted the data source for the metaanalysis. Trials had to use a method of randomisation that precluded prior knowledge of the next treatment to be allocated and comparisons had to be unconfounded – that is, to have randomisation only to exercise training or control. The main outcome measures included death, hospitalisation for cardiac and non-cardiac cause and the combined endpoint of death or hospitalisation.
Results: Nine data-sets satisfying the entry criteria were identified, including 801 patients. Allocation to exercise training programme significantly reduced hospitalisation (odds ratio=0.53, 95%CI= 0.35-0.79, P$<$0.001) and the combined endpoint of death and hospitalisation (odds ratio=0.60, 95%CI= 0.43-0.83, P=0.02). There was no significant reduction in the number of deaths (odds ratio=0.82, 95% CI 0.58-1.18, p=NS) but Kaplan-Meier analysis of the individual patient survival time data indicated a significantly lower mortality and lower combined mortality and hospitalisation in the exercise-trained patients (p=0.007 by logrank test).
Conclusions: This meta-analysis suggests that exercise training significantly reduces hospitalisations in HF patients by approximately a half, and may favourably influence survival. The number needed to treat to prevent one hospitalisation at two years was 13, and to prevent one death or hospitalisation was 12.

P338 Is the dobutamine stress echocardiography a predictor of cardiac events or death in the late-follow-up of heart transplantation? Four-years prospective evaluation

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Background: Cardiac allograft vasculopathy (CAV) remains the major cause of death in long-term cardiac transplantation follow-up. Nevertheless, annual angiographic evaluation is difficult to be routinely performed. We determined the predictive values of clinical risk factors and noninvasive tests of cardiac allograft vasculopathy for the development of cardiac events or death in asymptomatic patients with normal ventricular function in the long-term follow-up after heart transplantation. **Methods:** We studied 39 patients with mean ages 48 $\pm$ 13 years, submitted to heart transplantation and followed during a period of 48 months. They underwent thallium scintigraphy, treadmill stress test, dobutamine stress echocardiography and also were submitted to angiographic evaluation to determine the presence of CAV. The occurrence of acute myocardial infarction, congestive heart failure or death was prospectively observed during a period of 4-years of follow-up for all the patients. **Results:** CAV was documented by angiography in 15 patients(38%). Three patients presented acute myocardial infarction and other seven developed congestive heart failure, representing an incidence of 25% of cardiac events during the studied period. Nine deaths were documented during the same observation time (23%). Univariate analysis showed that elevated body mass index, positive thallium scintigraphy and positive dobutamine stress echocardiography were significantly associated with the occurrence of cardiac events or death during the follow-up time. In the absence of coronary angiography, stepwise logistic regression identified positive dobutamine echocardiography as the unique independent predictor for the occurrence of both cardiac events (p=0.005) or death (p=0.02).
Conclusion: The occurrence of cardiac events or death, long-term after heart transplantation is elevated in the follow-up of this studied population. On the other hand, these facts may be strongly predicted by the performance of dobutamine stress echocardiography, a well tolerated method, in the absence of routine angiographic evaluation.

CARDIAC ARRHYTHMIAS: CLINICAL ISSUES

P339 Determinants of changes in left-ventricular function and atrial size in patients with persistent atrial fibrillation in the RACE study

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Background: Restoration of sinus rhythm (SR) in persistent atrial fibrillation (AF) may improve left ventricular function and reduce atrial dimensions.
Objective: To assess determinants of improvement of left ventricular function and reduction atrial diameters in patients included in RACE (rate control versus electrical cardioversion in persistent atrial fibrillation).
Methods: Patients were randomized to rate control (n=256, negative chronotropic drugs aimed at a heart rate < 100 bpm and oral anticoagulation) or rhythm control (n=266, serial electrical cardioversions, antiarrhythmic drugs and oral anticoagulation as needed). Improvement of left ventricular function (echocardiographic fractional shortening) and decrease of left atrial diameter (four chamber apical view) were calculated as the difference between baseline and 2 years of follow-up.
Results: A total of 283 patients were analyzed. Rhythm control was associated with a significant reduction of left atrial size (p=0.037) especially if SR was maintained (p=0.000). Patients with hypertension showed progressive increase of atrial size (p=0.043), independent of the strategy.
Rhythm control was associated with a significant improvement of fractional shortening only if SR was maintained (p=0.02). A long duration of AF before study entry was associated with worsening of fractional shortening irrespective of treatment strategy (p=0.020). No other clinical characteristics were related to changes in left atrial size and fractional shortening.
Conclusion: Rhythm control has beneficial effects on left ventricular function and left atrial size mainly if it leads to persistent sinus rhythm.

P340 The impedance cardiogram recorded through two defibrillator pads is a potential haemodynamic sensor of ventricular fibrillation

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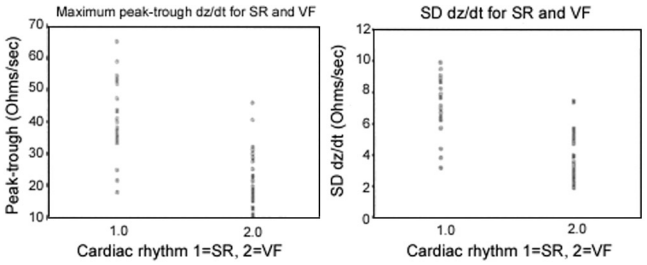
Purpose: A haemodynamic sensor has the potential to enhance the efficacy of therapy delivered by automated external defibrillators. Accurate detection of cardiac output could reduce the delivery of inappropriate shocks and increase the specificity of computer based treatment algorithms for cardiac arrest. We sought to determine if the impedance cardiogram facilitated detection of cardiac output.
Methods: Episodes of ventricular fibrillation(VF) were induced in 4 anaesthetised and ventilated pigs. The impedance cardiogram (ICG) was determined by passing a low amplitude sinusoidal current between two defibrillator pads, one placed on the right upper sternal chest and the second placed over the apex. The ICG was recorded simultaneously through the defibrillation pads along with the electrocardiogram (ventilation was suspended during recordings). The ICG was converted into the first order derivative (dz/dt) using the BioBench Physiological Data Acquisition and Analysis software. Twenty four five second episodes of sinus rhythm (SR) were recorded, as were 30 five second episodes of ventricular fibrillation. The maximum peak-trough (dz/dt) was noted for each five second recording. Dz/dt was sampled at 500 per second and the standard deviation (SD) for each five second recording calculated.
Results: Shown are the maximum peak-trough dz/dt and standard deviation dz/dt for SR and VF (see picture). The mean for maximum peak-trough dz/dt (40.52 Ohms/sec) and standard deviation dz/dt (7.25) ICG were significantly higher for SR compared to VF (dz/dt 22.31: SD 3.83; p<0.001).



Conclusion: The first order derivative of the ICG recorded through two defibrillation/electrocardiogram pads has the potential to be a haemodynamic sensor for ventricular fibrillation.

P341 An under-recognized subepicardial macroreentrant ventricular tachycardia due to left-ventricular aneurysm in patients with normal coronary arteries

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Background: In patients with apparently normal hearts, monomorphic ventricular tachycardia (VT) may only involve the subepicardial myocardium.
Methods and Results: Four patients (pts) with exercised-induced syncope due to VT with right bundle branch block (RBBB) morphology were investigated. Surface ECG showed a small q wave in leads II, III and aVF during sinus rhythm (SR) in all 4 pts. Left ventricular (LV) angiography showed one aneurysm in 3 pts or two aneurysms in one patient. All aneurysms were in the LV infero-lateral wall. Coronary arteries were normal in all 4 pts. During electrophysiological study, 6 unstable VTs (CL 200-305 ms) and one stable (CL 370 ms) were reproducibly induced. During SR, endocardial mapping was normal in all 4 patients. Maps via the coronary sinus demonstrated fragmented and late potentials in one pt without transthoracic epicardial mapping. In the remaining 3 pts, the epicardial mapping showed that an area with fragmented and late potentials in the left infero-lateral wall near the mitral annulus, which was anatomically consistent with the LV aneurysm. Pacing the site with late potentials resulted in progressive prolongation with similar morphology and final induction of clinical VT with a distinct diastolic potential in those 3 patients. During tachycardia, epicardial mapping showed a macroreentrant VT with focal endocardial activation in the pt with stable VT; a diastolic potential was only recorded on the epicardium and coincided with the late potential in the same area in the other 2 pts with unstable VT. Irrigated epicardial ablation was only performed in 3 patients and successfully abolished those VTs with 12-28 applications. No VT recurred in 2 patients during follow-up of 2 and 8 months. Clinical VT recurred after 6 months of ablation and was successfully ablated in a repeated epicardial ablation in one patient. In the remaining patient without transthoracic epicardial ablation, ICD was implanted with multiple shocks during a follow-up of 31 month.
Conclusion: In patients with normal coronary arteries and LV aneurysm, exercise-induced VT with RBBB morphology may have a subepicardial arrhytmogenic substrate, which may be amenable to epicardial ablation.

P342 Fifteen minutes latent period for bolus intravenous amiodarone to exert its antiarrhythmic effect – experimental study

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Background: The aim of the study was to examine the early time course of changes in ventricular fibrillation (VFT) and defibrillation (DFT) thresholds after an i.v. bolus of amiodarone (A) in an experimental pig model of transient myocardial ischemia.
Methods: VFT and relative effective ventricular refractory period (ERP) were measured in 15 anesthetized open-chest pigs after 3min of regional coronary ischemia before (time 0) and 2, 15, 30, 60 and 90 min after 5 mg/kg i.v. bolus of A injected in 15 sec (Group I, n=10) or normal saline (Group II, n=5). DFT was also measured by systematically increasing the stored voltage until defibrillation was accomplished. Hemodynamics, acid-base balance and temperature were kept stable throughout the experiments.
Results: The time course of VFT, ERP and DFT in the 2 study groups were as follows: (table).

Time course of VFT, ERP and DFT

Time (min)	0	2	15	30	60	90
Group I						
VFT(mA)	9,2 ± 4,6	11,4 ± 8,4	13,7 ± 6,5*#	34,2 ± 28,7*#	50,3 ± 37,8*#	53,2 ± 38,8*#
ERP(ms)	197 ± 26	204+/25	211 ± 38	212 ± 40*	220 ± 34*#	227 ± 32*#
DFT(J)	14,5 ± 15,2	14,2 ± 14,8	9,3 ± 9,4	12,2 ± 7,9	8,2 ± 6,8	7,2 ± 3,2
Group II						
VFT(mA)	9,5 ± 6,7	11,4 ± 9,8	9,6 ± 6,1	9,4 ± 5,3	8,2 ± 6,8	9,4 ± 4,2
ERP(ms)	205 ± 32	206 ± 30	212 ± 33	205 ± 31	186 ± 31	178 ± 28*
DFT(J)	11 ± 5,7	13 ± 6,7	10,6 ± 6,1	12 ± 9,2	7,2 ± 7,2	11,8 ± 7,6

* p<0,05 vs time 0, # p<0,05 vs control.

Conclusion: In this experimental study, amiodarone increased VFT and ERP steadily over time, starting 15 minutes after bolus iv administration and reaching a plateau by 60 minutes, without any effect on DFT.

P343 Epilepsy patients who suffer sudden unexpected death show signs of increased myocardial fibrosis, a potential substrate for malignant arrhythmias

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Purpose: Sudden unexpected death in epilepsy (SUDEP) is a phenomenon nearly 24 times more frequent among epilepsy patients as compared to a normal population. Based on autopsy and clinical studies it has been hypothesized that repetitive ischemia during epileptic seizures may lead to patchy myocardial fibrosis, which is a marker of ischemic damage and a potential substrate for malignant arrhythmias causing sudden cardiac death. The aim was to examine if pathological fibrosis could be found in the myocardium of epilepsy patients dying of SUDEP. **Methods:** All consecutive autopsy cases of SUDEP were prospectively collected from January 1998 to September 2000. Epilepsy as a direct cause of death was accepted when no other explanation was found by autopsy, microscopy, or chemical analysis. An age and gender matched control group was selected from consecutive non-epileptic cases from the same period consisting of persons who died from accidents, suicides, or homicides. From each heart, 13 tissue blocks were cut from predefined locations in the myocardium as well as multiple blocks covering the conductive system. The blocks were processed for microscopy and sections were stained with a battery of connective tissue stains. The sections were evaluated in a blinded manner by an experienced cardiovascular pathologist. The myocardial sections were also quantitatively evaluated in random locations of the myocardium and the subendocardial myocardium by using a point-counting system (magnification 160x). **Results:** Twenty-three SUDEP cases and 21 controls were collected. Eight of the epilepsy patients and 6 controls could not be evaluated by histology due to pronounced autolysis. The final analysis included 15 SUDEP cases (6M/9F, mean age 40.9 years (14-58)) and 15 controls (9M/6F, mean age 38.4 years (27-58)). The epilepsy patients were all on anti-epileptic drugs. In 3 cases serum levels of antiepileptic drugs were undetectable. The blinded evaluation by the pathologist revealed significant myocardial fibrosis in 6 SUDEP cases, and in 2 control cases (p=0.21). There was no difference in the degree of fibrosis in the conductive system of the groups. The blinded quantification (mean % fibrosis $\pm$ SD) demonstrated a trend towards more fibrosis in the myocardium (8.0$\pm$3.1 vs. 6.5$\pm$2.4, p=0.17) and subendocardial myocardium (8.5$\pm$4.1 vs. 6.5$\pm$3.1, p=0.14) of the SUDEP cases.
Conclusions: Our findings of a trend towards more myocardial fibrosis support the hypothesis that this fibrosis may serve as a substrate for malignant arrhythmias causing sudden unexpected death in epilepsy patients.

P344 Does out-of-hospital cardiac arrests in Switzerland increase during FIFA World Cup?

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Background: In Switzerland the estimated number of Sudden Cardiac Deaths (SCD) averages 8,000 per year. Anger and mental stress were shown to increase the risk of SCD.The FIFA World Cup 2002 was one of the most successful sporting events. According to the FIFA data the total TV audience of the FIFA World Cup in Switzerland was estimated near 11 million. Knowing that psychological stress and sometimes anger are usual for most viewers of the soccer play we postulate that during this competition the increase of out-of-hospital cardiac arrests (OHCA) would be registred. **Methods:** In Switzerland the MICU's (Mobile Intensive Care Unit) qualified to carry out the emergency cardiac care for out of hospital cardiac arrests are also often called in to examine the people found dead. We retrospectively analysed MICU registers in some major cities of Switzerland (Geneva, Lausanne, Fribourg, Neuchâtel, Délemont, Porrentruy and Lugano) during the FIFA 2002 World Cup (period A) and during the same period in 2001 (period B). Only non-traumatic cardiac arrests of presumed cardiac origin in adults were selected for our study. Statistics were calculated following Poisson model. **Results** are presented in the table.

Period A (01.06-30.06.02)	Period B (01.06-30.06.01)	P
59 Pts	37 Pts	0.005
Males 43 Pts (73%)	Males 25 Pts (68%)	NS
Females 16 Pts (27%)	Females 12 Pts (32%)	NS
Mean age/SD (years) 70/25	Mean age/SD (years) 68/26	NS
SCD at home 44 Pts (75%)	SCD at home 24 Pts (65%)	NS
Mean time of ACLS 8.6 min	Mean time of ACLS 8.2 min	NS
First recorded rhythm:	First recorded rhythm:	-
Asystole/PEA 50 Pts (85%)	Asystole/PEA 31 Pts (84%)	NS
Ventricular Fib. 9 Pts (15%)	Ventricular Fib. 6 Pts (16%)	NS

Conclusions: The significant nearly 60% increase of the OHCA during FIFA 2002 World Cup (P=0.005) was noted. More than two-thirds of all events occurred at patient's home. (The increase of SCD at home, however statistically non significant, was registred during the FIFA 2002 World Cup.) Despite short ACLS intervals the small number of patients reached in ventricular fibrillation must also be mentioned.

P345 Ventricular fibrillation induction at cardioverter-defibrillator implantation: a controlled comparison between direct current and shock on T

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The most critical phase during implantable-cardioverter-defibrillator (ICD) implants is ventricular fibrillation (VF) induction that may be obtained by two methods: by delivering of shock on the T wave or by applying a direct current. Aim of this study was to evaluate the effectiveness of DC Fibber (DC) induction protocol in comparison with Shock on T (SoT) induction protocol in inducing VF. SoT tries to induce VF with a low energy (0,6J) shock wave delivered during the vulnerability period of the ventricle but, many times, a slower, organised arrhythmia - as a VT - more than a real VF is induced; DC Fibber algorithm, available in St.Jude Medical ICDs, allows to induce VF by desynchronising the ventricular activity with a 9V direct current (DC) pulse along the defibrillation pattern. **Methods:** For the first VF induction, all the patients were randomly allocated to DC Fibber or Shock on T induction protocol. Cross-over to the alternative method was scheduled once, after four consecutive attempts (at predefined values) performed with the same method followed by a last additional attempt, according to the investigator. End point of induction was to induce VF leading to arrhythmia detection. **Results:** 100 patients undergoing ICD implantation were enrolled and allocated to DC (first induction in 50 cases) or to SoT. Overall, VF was induced in all the 100 patients. 47 out 50 (94%) DC and 31 out of 50 (62%) SoT inductions were successfully performed at the first attempt; further attempts were requested to induce VF in 19 out of 50 (38%) patients with SoT and 3 out of 50 (6%) with DC. Cross-over was necessary only for 5 patients (10%) randomly allocated to SoT. The use of antiarrhythmic drugs was homogeneous in the patient population.
Conclusions: DC Fibber algorithm guarantees a very high percentage of successful inductions of a real VF at first attempt, also reducing the incidence of spontaneous arrhythmia terminations following device detection and before therapy delivery. Moreover, DC Fibber is faster than SoT and can be useful for reducing the time of anaesthesia and VF testing in hemodynamically unstable patients who cannot tolerate long induction procedures during ICD implant.

P346 Prognostic value of electrophysiological testing in patients with chronic chagas disease and ventricular arrhythmias detected by Holter monitoring

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Background: Chagas' Disease (CD) is an infectious condition characterized by chronic affection of multiple organs, including the heart. Impairment of cardiac function, conduction disturbances and ventricular arrhythmias occur as the disease progress. Sudden cardiac death is a major concern. **Objective:** Our aim was to evaluate the role of Electrophysiological Testing (EPT) to identify chagasic patients presenting with ventricular arrhthmias on Holter monitoring who are at risk of serious arrhythmic events. **Methods:** We selected 41 consecutive patients with CD with complex ventricular arrhythmias on Holter monitoring (Lown III,IVa and IVb), with any degree of ventricular disfunction. Holter monitoring was indicated regardless of symptoms. Patients were submitted to EPT. If sustained monomorphic VT was observed, the patient was started on amiodarone. Sudden death and other clinical arrhythmic events were assessed. **Results:** The mean ejection fraction observed was 52$\pm$16%. Sustained Monomorphic VT was observed on the EPT of 5 patients (12,2%); Group I (n=5). Mean survival in non-inducible patients (Group II) was 115 months versus 27 months in GI (p<0,0001). All deaths from GI were sudden. All patients from GI presented with non- sustained VT(lown IVb) on Holter monitoring. The mean ejection fraction in GI was 32$\pm$11% versus 55,2$\pm$14,9% observed in GII (p=0,002). Sensibility and Especificity of EPT for sudden death prediction was 71% and 100%, respectively.
Conclusions: 1) Inducibility of sustained monomorphic VT at EPT is an important prognostic factor for prediction of serious arrhythmic events in CD patients presenting non sustained VT on Holter monitoring 2) This finding seems to be independent of the degree of cardiac dysfunction. 3) Amiodarone was not effective in preventing sudden death in this subset of patients.

P347 Plasma C-reactive protein level is a predictor of successful direct current cardioversion of atrial fibrillation

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Background: Atrial fibrillation (AF) is associated with raised circulating levels of C-reactive protein (CRP), with levels related to the 'burden' of AF. We hypothesised that plasma CRP might prospectively predict successful DC cardioversion of AF.
Methods: We measured plasma CRP among 54 AF cases (mean age±sd 67±9 years, 74% male) scheduled for DC cardioversion, and related CRP levels to procedural success. Factors associated with successful DC cardioversion ($p<0.05$) on univariate analysis were entered into a multivariate model.
Results: 35 of 54 (65%) cases successfully cardioverted to sinus rhythm (see table). These cases were younger, more likely to be receiving class I or class III drugs and had lower plasma levels of CRP than those who remained in AF (see table). A plasma CRP level above the median value for the cohort was associated with a reduced chance of successful cardioversion (OR 0.21 (95% CI 0.06-0.72), p=0.013), and remained an independent predictor of cardioversion successs after adjusting for age and use of class I or class III drugs in a multivariate model (OR 0.25 (95% CI 0.07-0.91), p=0.029).

Table 1: Successful vs. Unsuccessful DCC

	Successful DCC (n=35)	Failed DCC (n=19)	p
Age (sd), years	65 (10)	70 (6)	0.035
Male, %	71	79	0.547
Hypertension, %	51	68	0.228
Heart Failure, %	26	21	0.702
Diabetes Mellitus, %	17	16	0.899
Ischaemic Heart Disease, %	31	37	0.687
Class I or III antiarrhythmic, %	29	5	0.042
Duration of AF (IQR), weeks	26 (12-39)	28 (16-44)	0.656
C-reactive protein (IQR), mg/ml	0.20 (0.10-0.38)	0.32 (0.25-0.48)	0.040

Normally-distributed data expressed as mean (sd) and compared by Students t-test. Non-parametric data expressed as median (IQR) and compared by Mann-Whitney U-test. Categorical data expressed as percentages and compared using Chi-squared test.

Conclusion: Measurement of plasma CRP may help to identify AF patients likely to benefit from DC cardioversion. Inflammation may be linked to 'permanence' of AF. Larger studies are required to confirm these findings and to establish the predictive value of other inflammatory markers in AF.

P348 Arrhythmiogenesis and obesity

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Background: The heart rate variability (HRV) as a marker of the heart autonomic tone, the QT dispersion (QTd) as a marker of heart repolarization and the late potentials (LPs) as a marker of reentrant ventricular tachycardia have been introduced as methods that can improve the diagnosis and prognosis of severe arrhythmias especially in coronary artery disease (CAD) patients. Obesity has been referred as independent risk factor for CAD and arrhythmiogenesis as well.
Methods: 26 obese patients (10 male, 16 female, mean age 56±6,2 years, body mass index-BMI>30 kg/m^2) were studied. The pts had an obesity history of more than 5 years. A diet of 1200 kcal/day and regular physical exercise (120min/day walking) was prescribed for four weeks. At baseline and at the end of 4th week, all pts estimated for body weight and BMI and underwent: 1) A Holter ECG to assess the HRV by the high frequency component (HF)of the HRV power spectrum (parasympathetic activity) and the ratio of low frequency (LF) to HF (L/H ratio: sympathetic activity). 2) A continuous resting ECG to assess the dispersion of QT (normal values<70ms. 3) A signal-averaging ECG (SAECG) to assess the LPs based on: (1) the filtered QRS duration (QRS<110ms) (2) the time that the QRS remains <38μV (low-amplitude signals, LAS) and (3) root-mean-square voltage of the terminal 40ms of QRS (RMS>20μV). At the end of 4th week all pts underwent an exercise treadmill testing (ex-T). None of them had a history of arterial hypertension (AH), diabetes mellitus (DM) and CAD. Statistical analysis performed using the SPSS.10 ($p<0.05$).
Results: A significant weight loss was observed in all pts (BMI from 32.7 kg/m^2 to 29.5 kg/m^2, $p<0.01$). The mean values of the two components of HRV assessment improved significantly ($p<0.01$): HF from 104.1 ms^2 to 126.1 ms^2 and L/H from 3.0 to 2.5. The mean QTd values improved significantly (from 72.2 ms to 60.3 ms, $p<0.05$). The mean values of the three components of LPs improved significantly: QRS from 116 ms to 105 ms ($p<0.05$), LAS from 42 ms to 33 ms ($p<0.05$) and RAS from 18 μV to 24 μV ($p<0.05$). At baseline, 12 (46.1%) obese pts had abnormalities: 7 (26.9%) pts in one of the ECG tests, 2 (7.7%) in two and 3 (11.5%) in all three. At the end of 4th week, 5 (19.2%) obese pts had abnormalities in one of the ECG tests, none in two and 1 (3.9%) in all three. 7 (27%) pts had a positive ex-T for CAD that confirmed angiographically in 6 of them (only one pt had QTd and LPs abnormalities).
Conclusion: It seems that obesity is connected strongly with arrhythmiogenesis irrespectively of coronary artery disease.

MISCELLANEOUS ASPECTS OF ARRHYTHMIAS

P349 Left atrial diastolic dysfunction as a factor predisposing to lone atrial fibrillation

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Lone atrial fibrillation (LAF) comprises 1-30% of all cases of this arrhythmia. Mechanisms underlying the occurrence of LAF are poorly defined.
The aim of the study was to investigate factors predisposing to lone atrial fibrillation.
Material and methods: Studied group consisted of 19 pts (11 males, 8 females) mean age 49.6 ± 8.7 with recurrent lone atrial fibrillation. 16 healthy persons mean age 48.2 ± 9.3 served as control group. Each subject at least 30 days after last episode of atrial fibrillation underwent echocardiographic study, which included evaluation of left ventricular ejection fraction (LVEF), left atrial dimension (LA), peak velocity of early (E) and late (A) transmitral flow, deceleration time of E wave (DT), isovolumic relaxation time (IVRT), total ejection isovolume index (TEI), flow propagation velocity of E wave (Ep), peak velocity of systolic (S), diastolic (D) and atrial reversal (AR) pulmonary venous flow, acceleration (SAT) and deceleration time (SDT) of S wave.
Results: Pts with LAF showed significantly lower values of SAT (174.2 ± 67.2 vs 230.7 ± 82.3, $p< 0.05$) and higher values of SDT (259.8 ± 83.4 vs 163.6 ± 54.2, $p< 0.01$) compared to control group. No significant differences between studied and control group were found with respect to other estimated parameters.
In conclusion: This study suggests, that pts with lone atrial fibrillation have abnormalities of left atrial diastolic function, such as reduction of SAT and prolongation of SDT, which might be a predisposing factor for occurrence of this atrial arrhythmia.

P350 Biventricular systolic wall motion velocities are decreased in patients with chronic atrial fibrillation

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Background: Atrial fibrillation (AF) leads to cardiomyopathy in the long term. In this study we evaluated biventricular systolic long-axis wall motion velocities with pulsed tissue Doppler imaging (TDI) in patients with chronic AF and paroxysmal AF (PAF).
Methods: Thirty-seven patients with PAF (mean age: 67±9, m/f:12/25), 23 patients with chronic AF (mean age 58 ± 14, m/f: 11/12) and 24 control subjects (55 ±8, m/f: 12/12) were studied. Patients with PAF were in sinus rhythm during the examination. Left ventricular end-diastolic diameter (LVEDD) and fractional shortening (FS) were measured by M-mode echocardiography. Pulsed TDI was used to measure systolic biventricular long axis myocardial velocities
Results: LVEDD of the patients with chronic AF was not different compared to controls (5.3±0.5 vs 5.12± 0.4 cm, p= 0.7). FS of the patients with chronic AF was similar to controls (35±6.9% vs 39±7%, p=0.9).Mean heart rate was similar between the groups. Biventricular systolic long axis velocities were significantly lower in patients with chronic AF compared to controls. In patients with PAF long axis systolic velocities didnot differ compared to controls (table).

Systolic long axis velocities (cm/s)

Group	Lateral S	Septal S	Anterior S	Inferior S	RV-S
Control	9,9 ± 2.3*	7.8 ± 1.4**	10.3±2.8 ***	9.7 ± 2.1 #	13.9 ± 2.3 ¶
PAF	9.8 ± 2.1	7.6 ± 1.8	9.0 ± 2.7	8.1 ± 1.8	15.4 ± 4.5
Chronic AF	7.0 ± 1.1	5.3 ± 1.1	6.9 ± 1.5	5.5 ± 1.1	10.9 ± 2.9

*p<0.001 vs chronic AF, **p<0.001 vs chronic AF, *** p=0.03 vs chronic AF,# p=0.03 vs chronic AF, ¶ p=0.002 vs chronic AFS: peak systolic pulsed tissue-Doppler velocity, RV: right ventricle

Conclusion: Long axis myocardial velocities are decreased in patients with chronic AF despite preserved global systolic functions.

P351 Determination of abnormal left-ventricular myocardium by unipolar non-contact electrograms

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Determination of the arrhythmogenic substrate during sinus rhythm is used among entrainment and activation mapping for the diagnosis of complex ventricular tachyarrhythmias and to guide ablation therapy. For bipolar electrograms, a good correlation between abnormal myocardium determined by voltage mapping during sinus rhythm and histological changes has been shown. Noncontact mapping (ENSITE) allows the reconstruction of unipolar peak-to-peak voltage maps (UVMs) based upon the maximum deflection of 2048 virtual unipolar electrograms. Unipolar voltage maps of normal left ventricles in 10 female sheep and 10 patients without structural heart disease were used to define normal left ventricular myocardium based upon UVMs. Abnormal myocardium was defined during sinus rhythm by a unipolar peak-to-peak voltage of </= 5.3 mV. In 16 sheep with chronic experimental MI, infarct size determined by UVMs was compared with pathology(group 1, n=7), and NMR (group 2, n=9). In 6 patients with remote MI and a history of ventricular tachycardia, simultaneous mapping with ENSITE and the electroanatomical mapping system (CARTO) was performed. Abnormal myocardium defined by CARTO had a bipolar voltage of </= 1.5 mV. The area of abnormal myocardium determined by UVMs (ENSITE) and bipolar voltage maps (CARTO) was compared using linear regression analysis (group 3). UVMs always correctly detected the region of MI. There was a positive correlation between the extent of abnormal myocardium determined by UVMs and the infarcted area determined by the reference method (group1: r=0.76, $P<0.05$; group 2: r=0.75, $P<0.05$; group 3: r=0.83, $P<0.05$) in all groups. The area of abnormal myocardium determined by UVMs was usually larger than the area of infarction assessed by histology, NMR and CARTO (group 1: 15 ± 4 vs. 7.1 ± 3 cm, $P<0.05$; group 2: 17 ± 11 vs. 9.1 ± 3 cm, P=NS; group 3: 64.9 ± 33 vs. 47.4 ± 22 cm, P=NS). UVMs based upon virtual unipolar electrograms allow the determination of abnormal left ventricular myocardium. The addition of substrate mapping using multiple virtual unipolar electrograms may further improve the capability of noncontact mapping in order to guide ablation therapy of complex ventricular tachyarrhythmias.

P352 Voltage and activation mapping: how the recording technique affects the outcome of catheter ablation procedures in patients with congenital heart disease

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Introduction: Endocardial mapping is mandatory prior to radiofrequency catheter ablation (RFCA). Mapping can be performed using either unipolar or bipolar recordings. Impact of the recording technique used was studied in patients with and without structural heart disease using the 3-D electroanatomical CARTO mapping system.
Methods: Patients (n=44, 16 M, 43±16 yrs) referred for RFCA of atrial flutter (AFL, n=18), focal atrial tachycardia (FAT, n=4), atrio-ventricular nodal reentrant tachycardia (AVNRT, n=5) or scar related atrial reentrant tachycardia (IART, n=17) were studied. Voltage- and activation maps were constructed during tachycardia. The unipolar and bipolar voltage distribution in the different groups was studied to establish a cut-off voltage value to facilitate delineation of scar tissue.
Results: Electrograms were recorded during tachycardia (FAT: n=246, CL = 449 ±35 ms, AVNRT: n = 182, CL = 359 ±47ms, AFL: n = 1164, CL = 255 ±56 ms, IART: n = 2431, CL =280 ±74 ms). Unipolar voltages were > bipolar voltages ($p<0.001$). Unipolar voltages smaller than 1.0 mV were equally distributed in both AFL and IART patients. Bipolar voltages smaller than 0.1mV were only found in patients with IART, and subsequently 0.1mV was used as a cut-off value to delineate scar tissue. No unipolar cut-off value could be established. Timing of unipolar and bipolar local activation was correlated in patients with FAT ($p<0.001$), AVNRT ($p<0.001$), AFL ($p<0.01$) and (due to fragmentation) weakly in IART patients ($p<0.01$).
Conclusion: The recording technique used has a considerable impact on reconstruction of reentrant pathways and on the outcome of RFCA. In patients with congenital heart disease, bipolar recordings are preferable, as they allow voltage based scar tissue delineation and are less susceptible to noise or far-field potentials.

P353 Contactless localization and imaging of ventricular preexcitation in an unshielded EP laboratory with a novel 36-channel magnetocardiographic instrumentation

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Multichannel Magnetocardiography (MMCG) is a contactless method, which provides non-invasive three-dimensional (3D) imaging of cardiac electrogenetic phenomena. However a multichannel system reliable in an unshielded hospital environment was needed for clinical application. We have recently installed the first 36-channel instrumentation for MMCG operating in an unshielded EP catheterization laboratory, and validated its accuracy for cardiac source localization. In this study MMCG was used for 3D imaging of ventricular preexcitation (VPX).
Method: the 36-channels DC-SQUID system sensitivity is 20 fT/Hz1/2. MMCG from 36 points of the anterior chest wall (measuring grid 20 x 20 cm) lasts 90 seconds. Equivalent current dipole (ECD), Effective Magnetic Dipole (EMD) and distributed currents model (DCM) models are used in the inverse calculations for 3D localization and imaging of VPX. Localization results are transferred into 3D realistic heart/torso models and onto MRI images. 38 WPW pts were investigated, at least twice, to test for reproducibility. 27 pts were also studied during pacing-induced maximal VPX. The study was designed and ethically approved as a non-invasive study only. MMCG localization of VPX was compared with that achiavable with most recent ECG algorithms.
Results: ECG classification of VPX was certain in 26/38 pts (68.4%), uncertain in 10/38 pts (26.3%), unreliable in 2/38 pts (5.2%). MMCG classification of VPX was certain in 35/38 pts (92.1%), uncertain in 3/38 pts, with complex activation patters during the delta wave, suggesting multiple activation pathways, unpredictable with ECG. MMCG was in agreement with ECG in 26/38 pts (68.4%). In the 12 pts unclassifiable with ECG, MMCG provided a clear-cut localization of VPX.
Conclusion: This study demonstrates that 36-channel MMCG provides fast and reliable non-invasive localization of VPX also in an unshielded EP laboratory. As compared to ECG, MMCG is more accurate to classify, non-invasively, complex paraseptal VPX and DCM is effective to identify multiple accessory pathways. Furthermore MMCG provides quasi real-time 3D electroanatomical imaging and integration with MRI.

P354 Sequence of atrio-ventricular electrical excitation during nodal reentry tachycardia influences the development of atriomyopathy

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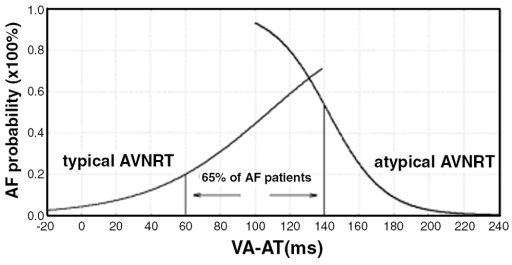
Background: Higher occurrence of atrial fibrillation (AF) in patients (PTS) with nodal reentry tachycardia (AVNRT) was reported, but the impact of the electrophysiological properties of tachycardia on AF-occurrence has not yet been resolved.
Material and method: study population consisted of 107 consecutive PTS,in which during electrophysiologic study AVNRT was stimulated.Two groups were selected:AF Gr(n=22)with sustained AF during EPS,controls(n=85)without AF. We performed comparative analysis of: tachycardia rate (VV), atrio (A)-ventricular(V) activation time (AV-AT), VA-AT and indexes AV-AT/VV, VA-AT/VV during typical (typ) and atypical (atyp)AVNRT. Logistic regression models were used to identify AF-risk factors for both AVNRT forms.
Results:

Comparative analysis

	AF typ	Control typ	AF atyp	Control atyp
VV ms	344,2	352,5	328,3	341,7
AV-AT ms	287,5	299,7	194,7	151,2
VA-AT ms	72,2	51,5*	132,7	189,7***
AV-AT/VV%	82,5	84,7	58,5	43,4
VA-AT/VV%	20,5	15,1**	41,1	56,3

*p=0,002 vs AFtyp **p=0,008 vs AFtyp ***p=0,02 vs AFatyp

Logistic regression revealed VA-AT as AF-risk factor for both typical (OR 32.7,p=0.005) and atypical AVNRT (OR 0.004, p=0.04), VA-AT/VV% only for typical(OR 20.2,p=0.01).



Logistic regression.

Conclusions: critical range of atrio-ventricular excitation during tachycardia facilitates the development of atriomyopathy and AF in AVNRT-PTS.

P355 Prevalence of inflammatory gene polymorphisms in atrial fibrillation patients

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Atrial fibrillation (AF) is the most frequent rhythm's disorder with high prevalence in general population. A number of risk factors possibly associated with AF have been studied, but the pathogenesis of the disease remains to be elucidated. Recently, the involvement of inflammatory processes in AF has been demonstrated, but no data are available on genetic polymorphisms of the inflammatory proteins in AF. In the present study, we investigated the prevalence of 1059G/C C-Reactive Protein (CRP), -174G/C Interleukin 6 (IL-6) promoter gene, and -511 C/T Interleukin 1Beta (IL-1Beta) promoter gene polymorphisms in 150 patients with AF (mean age 73 $\pm$ 8; 84 males and 66 females) and in 150 apparently healthy subjects, recruited from blood donors and staff of our hospital, age and sex-matched. 1059G/C CRP, -174G/C IL-6 and -511 C/T IL-1Beta polymorphisms were analyzed by PCR and by a microarray technology using electronic chip (Nanogen technology). Both in patients with AF and in control subjects the genotype distributions were in Hardy-Weinberg equilibrium. The rare allele frequencies of 1059 G/C CRP, -175 G/C IL-6 and -511 C/T IL-1Beta polymorphisms in AF patients (0.061 $\pm$ 0.001, 0.32 $\pm$ 0.027 and 0.38 $\pm$ 0.028 respectively) were not significantly different than those found in control subjects (0.067 $\pm$ 0.015, 0.32 $\pm$ 0.027 and 0.31 $\pm$ 0.026 respectively). Genotype distribution of CRP and IL-6 polymorphism was similar in AF patients and control subjects. The prevalence of IL-1Beta -511 CT and CC genotypes in AF patients (62.7%) was higher, but not significantly (p=0.079) different, than that found in control subjects (52.0%). In conclusion, our data show a trend towards a significant difference in genotype distribution of the IL-1Beta polymorphism. Further studies are required to confirm these preliminary data on a larger number of AF patients.

P356 Spatial variations in the atrial fibrillation frequency in the multi-channel magnetocardiogram

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Introduction: The mechanism of multiple re-entrant pathways is thought to be responsible for sustaining atrial fibrilllation (AF). Aim: To investigate the frequency characteristics of the atrial waveform using a multi-channel magnetocardiogram (MCG).
Methods: The 49 MCG channels covering a circular area of 21 cm diameter over the chest surface were recorded. Atrial activity was isolated from ventricular activity by the selection of QRST free sections of AF. Fourier analysis identified the frequency characteristics of the atrial waveform recorded at the 49 sensor locations. Principal component analysis (PCA) was applied to each atrial waveform section. 10 sections with mean (sd) duration of 0.9 s (0.1 s) were obtained from one patient, providing 490 AF waveforms.
Results: Across the 49 channels for any one QRST free section there were one to three discrete peak frequencies observed, listed in table. The frequencies were spatially grouped indicating spatial organisation with a single frequency, mean (sd) 7.2 (0.6) Hz, dominating the centre of the measurement area. The lower, 4.7 (0.9) Hz, and higher, 8.6 (0.3) Hz, frequencies dominated the upper periphery. There were statistical differences between the three frequency groups (ANOVA, $p < 0.05$). PCA separated these frequencies into different components.

AF Section	Frequency 1	Frequency 2	Frequency 3
1	5.6	7.8	8.9
2	4.0	7.0	-
3	4.2	7.4	-
4	3.5	7.8	-
5	-	6.5	-
6	4.7	5.9	8.3
7	5.5	7.2	8.2
8	5.5	7.8	8.9
9	5.9	7.1	-
10	3.8	7.6	-

AF characteristic frequencies (Hz)

Conclusions: The number of characteristic frequencies observed may indicate the number of re-entrant pathways. The frequencies may relate to the length of pathway. Spatial grouping may relate to the locations of the pathways.

P357 Mechanisms of longstanding permanent atrial fibrillation using non-contact and electroanatomical mapping in the left atrium

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The human left atrium (LA) is a complex structure and little is known of the mechanisms that sustain atrial fibrillation (AF). Epicardial electrode arrays applied during surgery and non contact (ESI) mapping balloon deployed in the right atrium (RA) have both been used to map AF. We describe percutaneous LA mapping of permanent AF patients (pts) for the first time. METHODS: LA mapping was performed with ESI and electroanatomical (Carto) systems in 6 pts (5 male) during permanent AF and on restoration of sinus rhythm (SR) prior to undergoing a 'catheter maze' procedure. Duration of AF was 6$\pm$5 yrs (mean$\pm$SD) and pts last had SR 11$\pm$5 months before their procedure. LA diameter was 4.9$\pm$1.1cm. Carto was used to construct a unipolar voltage map from 104$\pm$47 contact points during AF. Detailed analysis of ESI data was performed off-line in 30 sec segments of continuous recording. RESULTS: 0, 1 and 2 wavefronts (WFs) were seen in 2%, 63% and 34% of the total sampled time. >2 WFs was recorded <1% of the total time. Sites of earliest activation of the LA confirmed during SR were the superior, posterior and anterior septum (43$\pm$27ms after p wave). Unipolar voltages were significantly greater in the LAA (1.8$\pm$0.8mV) compared to anterior (0.8$\pm$0.4mV) and posterior (0.5$\pm$0.3mV) LA ($p<0.01$). LAA AF cycle length was 138$\pm$16ms, with beat to beat variation of 8.4$\pm$3.3ms compared with 22.9$\pm$4.9 in other areas ($p<0.01$). Consistent patterns of activation seen were right to left traversing of the LA roof, and a WF circuiting in a cephalo-caudal direction bounded by the left PVs posteriorly and the vertical midline of the anterior wall in front. CONCLUSION: We observed that permanent AF in a dilated LA appears to be driven predominantly by single WFs and that endocardial activation is frequently reinitiated focally from PV, epicardial and RA breakthrough sites. Re-entry circuits occur in the anterior wall, roof and around the LAA. The role of the LAA in permanent AF appears to be more important than first thought and needs further investigation.

P358 Angiotensin-converting enzyme-inhibitor and beta-blocker therapy: possible effective prophylaxis of post-discharge new-onset atrial fibrillation following cardiac surgery

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Atrial fibrillation (AF) is a common complication after coronary artery bypass surgery (CABG) occurring in up to 40% of patients. It was proved, that higher risk of AF occurrence is influenced by advanced age, low ejection fraction or atrial ischemia. We analysed the other possible predictors and methods of prophylaxis of late, post-discharge AF after CABG.
Methods: medical histories of 185 patients who had undergone coronary surgery (135 men and 50 women) were analysed (between January 2000 and December 2002). Mean age of pts: 62,3 years; BMI: 27,1, mean history of coronary artery disease: 4,9 years. They were admitted to Ischemic Heart Disease Department after 4th postoperative day. Mean duration of hospital stay: 10 days.
Results: AF occurred in 28,6% (53/185) patients. Age of patients with AF was higher: 65,3$\pm$8 (SEM 1,1) vs 61,1$\pm$9 (0,8), p=0,005. They had longer history of CAD: 6,4$\pm$6 (0,8) vs 4,4$\pm$5 (0,4), p=0,0163. AF occurred in 25% patients with <3 grafts in comparison with 73% pts with more than 3 grafts (p=0,0019). No significant differences in AF occurrence between patients with cardiopulmonary bypass or without and with left main artery surgery were observed. Patients treated with beta-blockers before and after CABG had lower incidence of AF: before CABG -35% vs 73% not treated (p=0,005) and after CABG- 26% vs 100% not treated ($p<0,0001$). Patients treated with ACE inhibitors before and after CABG had lower incidence of AF as well: before CABG-11% vs 58% ($p<0,0001$) and after CABG- 18% vs 61%, $p<0,0001$). 100% patients without either ACE-I or beta-blocker, before or after surgery had AF in comparison with 32% with any treatment, before or after (p=0,012).
Conclusions: advenced age, duration of CAD, number of grafts are possible predictors for post-discharge AF following cardiac surgery. Beta-blockers and ACE-inhibitors seem to be effective in prophylaxis of post-discharge new-onset AF.

P359 Intracoronary endothelin-1 infusion combined with systemic isoproterenol treatment: antagonistic arrhythmogenic effect

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Endothelin-1 (ET-1) secretion and sympathetic activation may play important role in clinical arrhythmia formation. In vivo interactions between these systems are not defined. We studied the effects of low dose intracoronary ET-1 infusion and intravenous isoproterenol (ISO) infusion in 18 anaesthetised open chest mongrel dogs (weight: 24±2 kg, heart weight: 179±13 g) after AV-ablation. Mean arterial blood pressure, coronary blood flow (CBF), left ventricular contractility (dP/dt), ECG, right and left ventricular epi- and endocardial monophasic action potential (MAP) were recorded. 30 pmol/min intracoronary ET-1 was given to Group A (n=6), 0,2 μg/kg/min intravenous ISO to Group B (n=6), both ET-1 and ISO to Group C (n=6) for 30 min. Group A: Prolongation of 90% MAP duration (MAPd90) occurred in all studied regions (left ventricular epicardial – LVepi- MAPd90 0 vs 30 min: 296±22 vs 369±20 ms, $p<0.05$), early afterdepolarisations (EAD) appeared in 3 dogs. Dominantly polymorphic non-sustained ventricular tachycardias (nsVT) appeared in 6, ventricular fibrillation (VF) in 3 cases. Oly slight CBF decrease was observed before the appearance of severe arrhythmias (0 vs 15 min: 18.8±2.7 vs 14.6±2.7 ml/min). Group B: ISO caused MAPd90 shortening in all studied regions (LVepi 0 vs 15 min: 298±18 vs 237±24 ms, $p<0.005$). Monomorphic nsVT-s occurred in 6, atrial fibrillation (AF) in 3 dogs. Group C: Similar CBF increase and MAPd90 shortening in all studied regions (LVepi 0 vs 15 min: 302±18 vs 243±13 ms, $p<0.05$) as observed in Group B was found. Additive effect of ET and ISO on dP/dt (0 vs 15 min: 1860±201 vs 3300±538 Hgmm/s, $p<0.05$) was observed. Monomorphic and polymorphic nsVT-s appeared in all cases. However, neither VF nor AF developed. Concluding our results, ISO prevented ET-1 induced MAP duration prolongation, EAD formation and VF. Furthermore, ET-1 showed protective effect against the development of ISO induced AF.

ATRIAL FIBRILLATION: PATHOPHYSIOLOGICAL ASPECTS

P360 Does alcoholic intoxication really promote atrial fibrillation? Experimental evidence against the proarrhythmic effects of ethanol

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Background: Alcohol has long been implicated in the development of atrial fibrillation (holiday heart syndrome), but its electrophysiologic actions have not been studied in detail and remain unclear.
Aim & Methods: We evaluated the electrophysiological, hemodynamic histological and ultrastructural effects of alcohol in 21 chloralose-anesthetized dogs (10-27 kg) at baseline and after 2 cumulative intravenous doses of ethanol: first dose 1.5 ml/kg (plasma level 191 mg/dL); second dose 1.0 ml/kg (plasma level 267 mg/dL). In 13 closed-chest dogs (5 with intact autonomic nervous system, 5 under complete autonomic blockade and 3 sham controls), electrophysiologic parameters, programmed stimulation and monophasic action potential (MAP) recordings were undertaken in the right atrium and right ventricle. 2D echo was performed in 3 additional dogs. In the remaining 5 dogs, open-chest biatrial epicardial mapping with 8 bipoles on the bundle of Bachmann was undertaken.
Results: In closed-chest dogs with intact autonomic nervous system, ethanol did not change mean arterial pressure. Also, no effects were noted on surface ECG variables: sinus cycle length; P wave duration; PR interval; QRS duration; and QTc. No changes were observed on PA, AH and HV intervals, corrected sinus node recovery time and Wenckebach point. At a cycle length of 300 ms, no significant effects were noted on atrial (98 vs 98 vs 98 ms) and ventricular (150 vs 160 vs 150 ms) ERP and on right atrial MAP90 (97 vs 92 vs 96 ms). These results were not altered by autonomic blockade. No changes occurred in sham controls. In open-chest dogs, at rapid rates (200 ms), ethanol did not affect inter-atrial conduction time (62 vs 63 vs 63 ms), conduction velocity (125 vs 125 vs 124 cm/s) and wavelength (12.4 vs 12.2 vs 12.6 cm). Further, ethanol did not alter left atrial ERP (100 vs 98 vs 102 ms). Atrial arrhythmias were not induced in any dog, either at baseline or after ethanol. 2D echo, histological and ultrastructural findings did not differ between controls and ethanol-treated dogs.
Conclusion: Ethanol at medium and high doses has no effects on atrial electrophysiological parameters. These findings suggest that acute alcoholic intoxication does not promote atrial arrhythmias.

P361 Interleukin-6 levels and autonomic modulation in patients with paroxysmal atrial fibrillation

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Background: C-reactive protein (CRP), a marker of systemic inflammation, has been found to be elevated in patients with atrial fibrillation (AF). Autonomic nervous system plays a potentially important role in the occurrence and maintenance of AF. CRP and proinflammatory cytokines, like interleukin-6 (IL-6), have been implicated in autonomic nervous control in various clinical settings.
Aim: To investigate possible relations between heart rate variability (HRV), a marker of autonomic tone, and the level of CRP and IL-6, in patients with paroxysmal atrial fibrillation, after sinus rhythm restoration.
Methods: Forty patients with paroxysmal AF, no recent infection and no acute myocardial ischemia, who underwent sinus rhythm restoration by drugs, were studied prospectively. Blood sampling for measurement of CRP and IL-6, and 24-hour electrocardiographic recording for HRV analysis were obtained immediately after conversion to sinus rhythm.
Results: A positive relation existed between IL-6 levels and the time domain indices of heart rate variability: pNN50, rMSSD, and a negative relation for the frequency domain index: LF/HF ratio. No statistically significant relations existed between CRP and HRV indices.

Relations of CRP, IL-6 and HRV

	IL-6=4.43 (3.3-12.4) pg/ml median (25th-75th percentile)		CRP=4.68 (2.08-30.3) mg/dl median (25th-75th percentile)	
	r	p	r	p
SDNN	-0.27	0.27	-0.3	0.1
pNN50	0.48	0.05	0.14	0.46
rMSSSD	0.5	0.04	0.12	0.52
LF/HF	-0.75	0.001	-0.3	0.13

Conclusion: In patients with paroxysmal atrial fibrillation a positive relation between IL-6 levels and parasympathetic indices of HRV, suggests a possible role of inflammation in autonomic modulation that may facilitate arrhythmia occurrence.

P362 Beneficial effect on atrial remodelling of spironolactone in a rat model of post-ischaemic heart failure

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Background: The arrhythmogenic substrate of atrial fibrillation (AF) is composed of marked functional and structural abnormalities of the atrial myocardium including fibrosis (F) and dystrophic myocytes (DM). This atrial remodeling is also seen in hemodynamic overloaded atria (A) and during heart failure (HF).
Methods: We used the rat model of HF post-myocardial infarction (MI) to study the reversibility of the atrial remodeling. Echocardiography, invasive hemodynamic measurements were performed to characterize the cardiomyopathy. Histological analysis of the LA was performed with Masson's trichrome and picrosirius red assays. Our study comprised 8 groups of 11 rats: Sham, MI, MI+spironolactone, MI+lisinopril, MI+atenolol, MI+lisinopril+spironolactone, MI+lisinopril+atenolol, MI+lisinopril+spironolactone+atenolol. Treatments begun 3 months after MI if HF was achieved and lasted one month.
Results: 3 months after MI, all rats were in HF with hemodynamic (left ventricle end disatolic pressure, LVEDP>20 mmHg), and echocardiographic signs of LV dysfunction with dilated A. After one month of therapy, all rats were sacrified. There was a marked F at the periphery of trabeculae and surrounding hypertophied atrial myocytes with extensive myolysis in the MI control group. In addition, enlarged A with an increase of its weight/body weight ratio was observed. There was a correlation between atrial F and LVEDP (r2=0.60; $P<0.001$). While LVEDP was reduced in all treated groups without difference between treatments, only spironolactone (alone or combined with other treatments) had a significant effect on atrial remodeling reversibility.
Conclusion: Changes in the hemodynamic loading conditions of A is a major factor for the constitution of the atrial myocardium remodeling. Such remodeling is sensitive to both HT treatment and especially to spironolactone therapy.

P363 Mechanisms of temporal variation in cycle length of human atrial fibrillation

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Background: The exact mechanism of the variations in atrial fibrillation cycle length (AFCL) is unknown. In this study, we investigated to what extent beat-to-beat alterations in conduction of fibrillation waves can explain irregularities in AFCL.
Methods: In 15 pts with normal atria undergoing a thoracotomy AF was induced by rapid atrial pacing. Epicardial mapping of the free wall of the right atrium was performed with a 244 unipolar electrode array (4 cm diameter). In each patient, isochronal maps were constructed of 12 seconds of AF (60±19 'beats'). At the center of the mapping area, AFCL was determined by measuring the time intervals between consecutive fibrillation waves. Temporal variations in AFCL (d-CL) were related to beat-to-beat changes in conduction pattern.
Results: The median AFCL was 161±26 ms with a d-CL was of 14±7 ms. The majority of the fibrillation waves (66±22%) were 'linked' to each other (<45° change in direction).
Differences in conduction velocity of these linked beats caused a variation in AFCL of 10±4 ms. In addition, beat-to-beat changes in direction of activation (>45°) and epicardial breakthrough of fibrillation waves occurred in respectively 27± 18% and 7±11%. This resulted in a d-CL of 13±5 and 7±8 ms. The overall variation in AFCL caused by beat-to-beat changes in conduction under the mapping electrode (diameter 4 cm) was 10±2 ms.
Conclusion: To a large part, the temporal variation in AFCL can be attributed to beat-to-beat changes in conduction of the fibrillation waves. These changes include both alterations in conduction velocity and changes in pathway.

P364 Altered connexin40 expression is related to atrial dilation in patients with chronic atrial fibrillation

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Purpose: Atrial fibrillation (AF) is frequently associated with atrial dilation. Such dilation increases the risk of initiation and perpetuation of AF, and also reduces the chances of maintaining sinus rhythm after successful electrical cardioversion. However, in patients with AF, many of the underlying cellular changes associated with atrial dilation remain elusive. The present study investigates the hypothesis that in patients with chronic AF, gap junction remodelling is related to atrial dilation.
Methods: Ten patients with chronic (>six months) AF, undergoing cardiac surgery, were included in this study. According to the pre-operative echocardiograms, the patients were divided into two groups: those with a normal sized right atrium (right atrial minor axis $\leq$ 4.9 cm; n=4) and those with a dilated right atrium (right atrial minor axis $>$ 4.9 cm; n=6). During cardiac surgery, right atrial appendage samples were obtained from each patient. The samples were immediately frozen in liquid nitrogen for assessment by quantitative western blotting (for connexins 43 and 40) and immunoconfocal microscopy (for connexins 43, 40 and 45). All connexin analyses were performed blind.
Results: By western blotting, normalised connexin40 protein was significantly lower in the group of patients with dilated right atria compared to that with normal sized atria (0.60±0.22 vs. 1.01±0.32, p=0.02). By contrast, normalised connexin43 protein was not significantly different between the two groups of patients (1.80±0.75 vs. 1.41±1.34, respectively, p=0.48). Using immunohistochemistry and confocal microscopy, the labelling patterns of connexins 43, 40 and 45 appeared similar in both groups of patients.
Conclusions: In patients with chronic AF, reduced connexin40 expression is related to atrial dilation; connexin43 expression is unaltered. This diminution of connexin40 gap junctions may impair the conduction velocity in the AF reentrant circuits and, hence, perpetuate AF. As atrial dilation is a negative predictor of maintaining sinus rhythm after electrical cardioversion of AF, gap junction remodelling may contribute to this failure.

P365 C677T and A1298C methylene-tetrahydrofolate reductase gene polymorphisms in atrial fibrillation

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its incidence increases with advancing age, with a prevalence of 4% in subjects >60 years old and >10% in those >80 years old. AF is associated with a 5-fold increased risk of developing stroke, probably as a result of embolization of left atrial thrombus. Elevated plasma total homocysteine (tHcy) concentrations have been identified as a risk factor for cerebrovascular disease. Hyperhomocysteinemia may be associated with the presence of polymorphisms in genes codifying for enzymes involved in the Hcy metabolism, in particular C677T and A1298C in 5,10-methylenetetrahydrofolate reductase (MTHFR) gene. Aim of this study was to evaluate homocysteinemia and the prevalence of the C677T and A1298C MTHFR gene mutations in patients affected by AF. We studied 150 patients with AF [mean age 73 8.84, 84 males and 66 females] and 189 healthy control subjects comparable for sex and age. tHcy plasma levels were determined by FPIA. For C677T and A1298C MTHFR mutation detection, DNA was amplified by PCR and genotype was determined with a microarray technology using electronic chip (Nanogen technology). For the microarray technology we designed and validated two specific oligonucleotide sets (biotinilated PCR primers, Cy5 and Cy3 labeled reporter and stabilizer oligonucleotides). tHcy plasma levels were significantly higher in AF patients than in controls (14.0, 9.0-41.1 micromol/L versus 8.7, 1.6-24.0 micromol/L, p=0.0001). The distribution of C677T and A1298C MTHFR genotype frequencies among AF patients and control subjects is in Hardy-Weinberg equilibrium. No differences between AF patients and control subjects in 677T and 1298C allele frequencies were observed (0.46 0.029 versus 0.42 0.025 and 0.29 0.026 versus 0.30 0.024, respectively). The prevalence of homozygotes for the C677T polymorphism in AF patients was higher (22.7%) than in controls (14.3%), but there was no significant difference (Chi square=3.43, p=0.064). Neither difference in the prevalence of homozygotes for the A1298C polymorphism in AF patients and controls was observed. In AF patients and controls a significant genotype-phenotype relationship between tHcy levels and C677T polymorphism was observed ($p<0.0001$ and $p<0.05$, respectively). In conclusion our results stress the interest to extend the study to a larger number of subjects and polymorphisms of gene involved in homocysteine metabolism in order to better understand their possible role in atrial fibrillation.

P366 Atrial depolarization assessed with wavelet analysis in patients with paroxysmal atrial fibrillation

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The aim of this study was to identify the possible atrial activation patterns using the P wave wavelet analysis in patients with paroxysmal atrial fibrillation (PAF).
Methods: The P wave was analyzed using the Morlet wavelet in 40 patients with a history of PAF (Group A, 17 males, mean age 63.8 $\pm$ 10.2 years) and in 29 normal individuals (Group B, 11 males, mean age 61.7 $\pm$ 8.54 years). Recordings using a 3-channel digital recorder (Galix Biomedical Instrumentation, Inc. USA) were obtained from all patients in sinus rhythm at resting conditions for 10 minutes. All ECGs were digitized with a sampling frequency of 1000Hz. Using a custom-made software, wavelet parameters expressing the mean and peak energy of the P wave were calculated for each ECG orthogonal lead (X,Y,Z) and the vector magnitude (VM) at three frequency bands (200-160Hz, 150-100Hz and 90-50Hz). The P wave duration was also measured in these axes. T-test, chi-square and ANOVA were used were appropriate for statistical analysis.
Results: The P wave duration was significantly longer in all axes in Group A patients. The peak energies at 150-100Hz and 90-50Hz frequency bands at the X axis were lower in Group A. The mean and peak energies in all frequency bands were significantly higher in Group A. These findings suggest a different activation wavefront in patients with PAF, mainly along the Z axis, i.e. the postero-anterior direction. Anisotropic conduction and the possible presence of dispersion of refractoriness at the anterior and posterior-lower right atrium may explain this activation pattern in PAF patients.
Conclusions: The P wave Morlet wavelet analysis in patients with PAF is indicative of a different activation along the postero-anterior direction. The latter may be explained by different conduction characteristics at the anterior and posterior-lower right atrium.

P367 Left atrial remodelling after short-duration atrial fibrillation in hypertrophic hearts

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Background: The aim of the study was to evaluate the left atrial (LA) contribution to left ventricular (LV) filling after short duration of atrial fibrillation (AF) in hypertrophic hearts.
Methods: We selected 100 patients (pts) with a first diagnosis of hypertension who had a moderate LV hypertrophy. Pts were hospitalized because of an acute episode of AF cardioverted within 48 hours from the onset. Pts population included 71 men and 29 women with a mean age of 58 $\pm$ 9 years. Pts were compared with a control population of 100 pts cardioverted because of lone AF without cardiac hypertrophy (mean age of 59 $\pm$ 10 yrs). Atrial function and size were assessed by Doppler-echocardiography and the following parameters were measured: transmitral peak A velocity (A), atrial filling fraction, atrial ejection force, peak E velocity (E), deceleration time, and isovolumic relaxation time (IVRT), LA maximal (LA max vol) and minimal volume (LA min vol), LV cardiac mass index (LVMI).
Results: All pts had an increased LVMI (289 $\pm$ 43 vs control 110 $\pm$ 40 g/m^2; $p<0.001$). Diastolic function was impaired in the study group: peak E vel was 0,56 $\pm$ 0,09 m/sec vs control 0,77 $\pm$ 0,10 m/sec, peak A vel was 0,81 $\pm$ 0,15 m/sec vs control 0,57 $\pm$ 0,12 m/sec, dec t was 285 $\pm$ 40 ms vs control 202 $\pm$ 31 ms, IVRT was 118 $\pm$ 24 ms vs control 89 $\pm$ 13 ms. LA max vol was increase in the study group during AF (36 $\pm$ 9 vs 34 $\pm$ 8 in control pts, p=n.s.) and decreased after conversion to sinus rhythm from 36 $\pm$ 9 to 30 $\pm$ 6 cm^3 ($p<0.001$) in hypertensive pts and from 34 $\pm$ 6 to 28 $\pm$ 5 cm^3 ($p<0.001$) in control pts. The reduction of LA max vol was lower in pts with hypertrophy (-16.7% vs control -20.6%; $p<0.01$). Atrial mechanical function was reduced in the study group (AEF was 10 $\pm$ 2 dynes vs control 16 $\pm$ 4; $p<0.001$). Univariate analysis showed that the best predictors of the delay in the recovery of atrial contraction was an increased LVMI (>250 g/m^2) and a LA max vol >33 cm^3.
Conclusions: LV hypertrophy influenced the recovery of atrial contraction after cardioversion of AF. Atrial function was reduced even after short duration of AF.

P368 The effects of 5-HT4 receptor stimulation and blockade, before and following 6 hours of atrial fibrillation

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Aim: Stimulation of atrial 5-HT4 receptors is associated with atrial arrhythmias. Their blockade prolongs the effective refractory period (ERP) following 10 min of atrial fibrillation (AF). The aim of this study was to investigate the effects of the selective atrial 5-HT4 receptor agonism and antagonism on the ERP, monophasic action potential (MAP), ERP/MAP ratio and time to sinus rhythm restoration (TSRR) in pigs, prior to and after 6 hours (h) of AF.
Methods: A quadripolar electrode catheter connected to an external fibrillator and a MAP catheter were percutaneously introduced into the right atrium of 27 pigs (mean weight 18$\pm$4 kg). Atrial ERP, MAP duration and ERP/MAP were assessed at baseline and following the infusion of the 5-HT4 antagonist SB203186 (10 pigs, group A), the 5-HT4 agonist RS67333 (7 pigs, group B) and placebo (10 controls, group C). Then, AF was induced by 0.1 mA extrastimuli at 50 Hz. Following 6 h, TSRR, ERP, MAP duration and ERP/MAP were reevaluated. Differences within and between groups were assessed.
Results: In sinus rhythm, SB203186 prolonged and RS67333 shortened ERP and MAP ($p<0.05$) as shown in the Table. Following AF, ERP and MAP shortening and TSRR prolongation were less in group A than in group B and C ($p<0.01$). ERP/MAP ratio was increased in group B and C ($p<0.01$), while it was unaltered in group A.

	Baseline			Drug infusion			6 h AF		
Group	A	B	C	A	B	C	A	B	C
ERP (ms)	140$\pm$9	135$\pm$5	134$\pm$4	152$\pm$9	125$\pm$5	133$\pm$4	101$\pm$5	77$\pm$2	81$\pm$3
MAP (ms)	180$\pm$10	182$\pm$13	178$\pm$11	201$\pm$11	155$\pm$13	177$\pm$10	143$\pm$7	77$\pm$4	4$\pm$2
ERP/MAP	0.8$\pm$0.1	0.7$\pm$0.0	0.7$\pm$0.0	0.8$\pm$0.1	0.8$\pm$0.0	0.7$\pm$0.0	0.7$\pm$0.0	1.0$\pm$0.0	0.9$\pm$0.0
TSRR (min)							0.4$\pm$0.1	6.0$\pm$1.5	6.3$\pm$0.9

Conclusion: SB203186 prolongs and RS67333 shortens atrial ERP and MAP in sinus rhythm. Following 6h of AF, 5-HT4 blockade attenuates ERP and MAP shortening, while 5-HT4 stimulation has the opposite result. SB203186 is also associated with a decrease in ERP/MAP ratio.

P369 Suppression of the inward rectifier potassium current delays repolarization of electrotonic depolarization around a core region of the spiral waves, preventing cardiac fibrillation

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Background: Suppression of the inward rectifier potassium current (Ik1) tends to prevent cardiac fibrillation. The purpose of this study is to clarify how the suppressed Ik1 acts on spiral waves (SWs), which is myocardial activation sequences during cardiac fibrillation, to prevent cardiac fibrillation, using numerical simulation.
Methods: The electrical behavior was simulated on two sheets of 2-dimensional excitable arrays corresponding to myocardial tissue of 30x30mm, created using the Luo-Rudy-I model. In one array (array1: control), the maximum conductance of the Ik1 (Gk1) was set at 0.750mS/uF in whole units so sustained SWs could be induced. In the other array (arrray2: suppressed Ik1), the Gk1 was set at 0.375mS/uF so sustained SWs would fail to be induced. We tried to induce the SWs in both arrays using crossfield stimulation. The voltage-distribution over the array, and the wavefront and waveback, that is, the leading and backmost edges of the propagating excitation, were represented.
Results: When forming SWs, the wavefront pivoted around its broken end (= wavetip), and the wavetip simultaneously detoured around the region where the excitability was lowered temporarily by electrotonic depolarization. The detoured region became a core of the SWs. The wavetip collided with the waveback (WB1) following after the wavefront, and the wavefront suspended the rotation. Then, the wavetip meandered along WB1 toward the array boundary, and elicited electrotonic depolarization along it. An excitable gap lay between the wavefront and WB1. After a while, another waveback (WB2) emerged from the core region and advanced concentrically, giving rise to another excitable gap surrounded by WB2. The occurrence of WB2 was later in array 2 than in array 1. In array 1, WB2 successfully caught up with WB1 before the wavetip reached the array boundary. Two excitable gaps were united, becoming a broad excitable gap around the wavetip. Then, the wavefront resumed pivoting to sustain the SWs. In array 2, WB2 failed to catch up with WB1 in time. The wavetip collided with the array boundary, and the SWs terminated.
Conclusions: Suppression of Ik1 delays the repolarization of the electrotonic depolarization elicited in the core and along WB1, and which prevents the wavefront from pivoting repeatedly as the SWs.

P370 Comparison of the efficacy of the IKur blocker AVE0118 with the IKr blocker dofetilide in two pig models of atrial arrhythmias

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Background: AVE0118 is a potent blocker of the Kv1.5 channel, the molecular base for the human cardiac ultrarapid delayed rectifier potassium current (IKur). Since the IKur is present in the human atria while it is absent in the ventricles blockade of this channel is highly attractive for the treatment of atrial fibrillation because the typical proarrhyhtmic effects of IKr channel blockade - EADs and torsades de pointes arrhythmias - are not expected to occur. Indeed, AVE0118 prolongs the atrial ERP with no effect on the QTc interval in pigs and goats. We investigated the effect effect of AVE0118 on atrial refractoriness and compared the antiarrhythmic with the selective IKr blocker dofetilide (DO) in two different pig atrial arrhythmia models, left atrial vulnerability and vagotonic atrial fibrillation.
Methods: Experiments were performed in pentobarbital anesthetized pigs weighing 25-30 kg. Atrial ERP was determined with the S1-S2-stimulus method in the free walls of left and right atrium at 240, 300 and 400 ms BCL. Left atrial vulnerabililty (LAV): As previously shown the inducibility of brief runs of atrial tachyarrhythmias by the S2 extrastimulus is very high in the left pig atrium (referred to as left atrial vulnerability (LAV)). The ERPs and incidence of runs of tachyarrhythmias were determined before (vehicle) and after drugs. Vagotonic atrial fibrillaton (vAfib): Atrial burst pacing induced stable vAfib in pigs during bilateral vagal stimulation. AVE0118 or DO were administered after 40 min of stable atrial tachyarrhythmia after a vehicle control.
Results: AVE0118, 0.5 mg/kg, prolonged left stronger than right atrial ERP (32$\pm$6 vs. 18$\pm$5%, $p<0.05$; n=5) at 240 ms BCL and inhibited LAV by 100% (n=5). DO (10 microg/kg) was stronger on the right than left atrium (36$\pm$4% vs. 23$\pm$2; $p<0.05$), and LAV was not significantly inhibited (-14%). AVE0118, 0.5 mg/kg, cardioverted all pigs with vAfib (n=6). DO showed no cardioversion in vAfib (n=5) even at 20 microg/kg.
Conclusion: IKur and IKr blockade showed different atrial effects in pigs. In Afib and LAV IKur blockade was highly effective while IKr blockade showed hardly any effect. Short diastolic intervals are a common feature of Afib and LAV. Since the IKur shows slow inactivation its contribution to repolarization may increase after premature activation at the expense of the IKr explaining the high efficacy of IKur blockade and the weak effect of IKr blockade.

SYNCOPE, LONG QT AND BRUGADA SYNDROME

P371 Molecular genetic analysis of long QT syndrome in 67 Russian families

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Congenital long QT syndrome (LQTS) is an inherited cardiac disorder characterized by a prolonged QT interval, syncope due to polymorfic ventricular arrhythmias ("torsade de pointes") and high risk of sudden death. At least seven genes, when mutated, can produce this phenotype: KCNQ1 (LQT1), HERG (LQT2), SCN5A (LQT3), KCNE1 (LQT5), KCNE2 (LQT6), KCNJ2 (LQT7). Prevalence of disease is stable in different population (1:10 000 – 1:5 000).
One hundred and forty patients from 67 unrelated Russian families with different types of disease were available for DNA and clinical analysis. Diagnoses were confirmed using criterias according by Schwarts (1993). Molecular investigation revealed that not less then 20% of the identified mutations arose de novo. We suggested that such considerable level of mutation de novo could support stability of disorder's prevalence. Using PCR-SSCP analysis and DNA sequencing 20% of the coding region of five ion channel genes KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2 ("hot parts" of this genes) we identified genetic defects in 33 (~50%) probands. Distribution of mutation among there 5 genes was followed: 24 in KCNQ1 (75%), 6 in KCNH2 (16.7%), 1 in SCN5A (2.8%), 2 in KCNE1 (5.5%) and none in KCNE2. We identified 17 novel mutations and the others have been reported. Three probands had two different mutations (the one was inherited and second was de novo). In all these cases probands had graver ill than affected parent. Only these mutations (G306R-2 probands, G314S-3 probands, A341V-3 probands in gene KCNQ1) were detected more than single family. The most severe clinical traits had patients with A341V.
Genotype-phenotypes analysis found that clinical traits and triggers were gene-specific in large part.
We identified 6 polymorphisms in genes KCNQ1(C513T), KCNH2 (A1692G), KCNE1 (G84A, A112G, C252T) and KCNE2 (A22G) which prevalence among patients and healthy individuals were the same. We supposed that these substitutions didn't modified clinical phenotype. Polymorphism G253A (D85N) in gene KCNE1 was found in affected group only (0.03). Clinical significance of this substitution feels the need of verification subsequently.

P372 Slow and fast torsade de pointes – electrocardiogram differences, the mode of onset and termination in acquired long QT syndrome

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As it's known torsade de pointes(TdP)is a clinical arrhythmia not inducible by programmed electrical stimulation. We decided to analyse some ecg variables of TdP, its ventricular rate variability, the modes of onset and termination.
We assessed 54 episodes of TdP in 6 patients(5 female and 1 male)with acquired LQTS. The mean heart rate of TdP was 218/min. We divided all episodes into: slow–TdP(s-TdP)< 220/min(range from 145-220/min)and fast–TdP(f-TdP)>= 220/min (ranged from 221-281/min).There's no differences between s-TdP and f-TdP as regard to: coupling interval(CI)of the initiating beat -488 msec and 472 msec respectively(p=0.48)and prematurity index(PI)-0.47 and 0.53 respectively (p=0.12). The QTc was similar in both groups before TdP: 517msec and 515 msec for s-TdP's and f-TdP's. The faster TdP were longer-p= 0.0003. We assessed parameter called ventricular rate variability(VRV) as a difference between R-R (V-V) intervals in TdP. From all 54 episodes – 9(16.6%) degenerated into VF. Among that only 1(3.2%)from 31 episodes of s-TdP's came to VF.we also analysed first cycle length of TdP(f-CL-TdP).The faster TdP were preceding by faster heart rate - preceding RR interval – 922 msec in compare to slower TdP-preceding RR interval-1062 msec(p= 0.03).Marked U-wave was presented before 63% s-TdP and 60% f-TdP. The initiating beat was of the same morphology as the ensuing course of TdP in 64% episodes of s- TdP and 56% episodes of f-TdP. The most mode of termination of TdP was decreasing the heart rate(slow-mode)– 58% episodes of S-TdP and 39% episodes of F-TdP. The increasing in the heart rate of TdP(accelerate-mode) were observed in 32% S-TdP and 26% F-TdP.

Results

	mean VRV(ms)	onset VRV(msec)	f-CL-TdP(ms)
slow TdP	39.4	46.5	320
fast TdP	19.5	36.9	266
p value	0.0005	ns	0.004

Conclusion: Fast TdP's have shorter first cycle length and decreased VRV. Slow TdP's degenerate into VF in only about 3% of episodes and have longer last cycle length. The fast TdP is preceded by faster basic heart rate before episode of arrhythmia.

P373 Form "fruste of long QT syndrome as a possible cause for unexplained syncope revealed by dobutamine infusion

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Among 455 consecutive patients (pts) referred for syncope, 146 pts (32%) were considered to suffer from unexplained syncope (US) after a targeted work-up including a tilt-test, supine and upright carotid sinus massage, hyperventilation and electrophysiological study when indicated. In 10 pts (6.8%) with incomplete treadmill test and/or cardiovascular risk factors, a dobutamine (dobu) stress echocardiography was proposed and finally performed in 7 pts. Six of them (3 males; mean age: 50±5 years) had a prolonged baseline QTc interval between 450 and 485 ms. With dobu infusion (maximal dosage: 20-30 ug/kg), QTc was prolonged to 540-570 ms without any induced arrhythmia nor ischemia, and returned to baseline values after dobu was stopped. Five pts had a sudden syncope, and 2 females were treated with a known QT-prolonging drug removed before dobu. The only pt with a normal baseline QTc interval didn't show any prolongation with dobu. These findings suggest the possibility of a form "fruste" of long QT syndrome as a possible cause for US.
Conclusion: Dobu infusion significantly prolonged the QTc interval in a selected group of pts with slightly prolonged baseline QTc and US. These results suggest that dobu infusion could be used as a diagnostic test for a "fruste" form of long QT syndrome; however, the effect of dobu on QT interval remain to be determined.

P374 Can history identify Long-QT patients?

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Purpose: The challenge in syncope is to identify the small proportion of patients that are prone to severe morbidity or sudden cardiac death, within the large group of syncopal patients, without excessive testing. History-taking might play a key role. High risk circumstances which are associated with genotype of Long QT Syndrome (LQTS), are syncope during exercise, and emotional stress.
Methods: We used a standardised questionnaire to collect data on syncope from 23 genotyped symptomatic LQTS patients and 114 patients with syncope presented to the Emergency Department (ED). The ED patients had a total history of 368 episodes lifetime, with a median of 1 in the last 12 months. The LQTS patients had 188 episodes lifetime of which none during the last 12 months.
Results: Syncope during sleep or lying in bed was significantly more seen as a trigger in LQTS patients (see table). Furthermore emotional stress was confirmed as a significant trigger in LQTS. Surprisingly syncope during exercise was not a major trigger, but syncope right after exercise was.

triggering circumstances

	114 ED pts	23 LQTS pts	p-value
Sitting	46 (40%)	9 (39%)	0.91
Standing	64 (56%)	8 (35%)	0.06
Lying/sleeping	7 (6.1%)	14 (61%)	<0.0001*
During exercise	14 (12%)	4 (17%)	0.51
After exercise	2 (1.8%)	8 (35%)	<0.0001*
Posture change	24 (21%)	6 (26%)	0.59
Emotion/pain	27 (24%)	13 (57%)	0.005*
Seeing blood	14 (12%)	1 (4.3%)	0.27

* significant

Conclusions: History can guide the attending physician in deciding which patients should receive additional testing. Patients with syncope during sleep and emotional triggers should be considered as high risk for LQTS.

P375 Ventricular conduction in idiopathic ventricular fibrillation without right precordial ST-elevation – comparative study with Brugada syndrome

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To clearify the difference of electrical characteristics on ventricular conduction between idiopathic ventricular fibrillation (IVF) without right precordial ST elevation and Brugada syndrome (BS), electrophysiological test was performed in IVF (without organic heart disease, or right precordial ST elevation and with history of ventricular fibrillation, n=4: 39 $\pm$ 20 years old), BS (without organic heart disease and with right precordial ST elevation and history of ventricular fibrillation or syncope: n=9, 57 $\pm$ 13 years old), and control group (without organic heart disease, history of ventricular fibrillation,also wthout right precordial ST elevation: n=6; 62 $\pm$ 13 years old). The maximum inter-ventricular conduction delay (S2V2-S1V1: Max.CD) from ventricular stimulation to the ventricular electrogram at the distal electrode pair of coronary sinus was measured by using a single to triple ventricular extrastimulations from right ventricular apex and outflow tract.

Results: 1)Effective refractory periods of 600 msec of a basic cycle length at right ventricular apex were 259 $\pm$ 17ms in BS, 248 $\pm$ 26ms in IVF and 225 $\pm$ 21ms in control and that at right outflow were 254 $\pm$ 27ms in BS, 250 $\pm$ 12ms in IVF and 242 $\pm$ 26ms in control. 2) Late Potential was positive in 7/9 (78%) of BS while in 0/4 of IVF and in 0/6 of control. 3) There was no significant difference on the Max.CD at a single ventricular extrastimulation among three groups. However, the Max.CD of double ventricular extrastimulation at right ventricular apex was significantly ($p<0.01$) longer in BS (53 $\pm$ 23 msec) than in IVF (18 $\pm$ 7 msec) and control (27 $\pm$ 7 msec). The Max.CD of triple ventricular extrastimulus at right ventricular apex was also significantly ($p<0.01$) longer in BS (62 $\pm$ 15 msec) than in IVF (20 $\pm$ 5 msec) and control (21 $\pm$ 3 msec). Similar results were shown at a basic cycle length of 400 msec. 4) The Max.CD of triple ventricular extrastimulus at right ventricular outflow tract was also significantly ($p<0.05$) longer in BS (53 $\pm$ 22 msec) than in IVF (21 $\pm$ 12 msec) and control (26 $\pm$ 8 msec). Similar results were shown at a basic cycle length of 400 msec. 5) There was no significant difference on the Max.CD in any stimulation protocols between IVF and control.

Conclusion: These data suggested that Brugada syndrome has relatively larger inter-ventricular conduction delay in more aggressive extrasimulation protocol, comparing with IVF and control. Electrophysiological characteriscitcs on ventricular conduction in IVF without right precordial ST elevation may be different from that in Brugada syndrome

P376 Recurrent unexplained syncope: brain or heart? An observational study of six cases of arrhythmogenic epilepsy

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Background: Despite exhaustive investigations, approximately 15 to 20% of syncope remain unexplained and implantation of a loop recorder is sometimes considered. An under-recognized cause of syncope, however, may occur when epileptic discharges profoundly disrupt normal cardiac rhythm, the so-called arrhythmogenic epilepsy.

Methods and Results: Six patients with a history of multiple unexplained and/or convulsive loss of consciousness underwent a complete cardiologic (including 24-hour Holter ECG, echocardiography, tilt testing and EP study in 4 patients), and neurologic assessment (including standard electroencephalogram [EEG], CT and MRI scan). After this current approach, neurocardiogenic syncope was suspected in 5 patients with tilt-induced hypotension and/or bradycardia. Further investigation consisting of videotelemetry-EEG/ECG monitoring, however, was undertaken because of insatisfactory results and difficulties to interpret the observed abnormalities. While monitored in the epilepsy laboratory, an asystolic pause preceded by partial seizure of temporal onset, reproducing the clinical symptoms, was recorded in all patients. The table summarizes the main characteristics of the studied patients.

Patients characteristics

Sex (age)	Syncope (n)	Asystole duration	Mechanism	Epileptic focus	Management
F (47)	> 20	> 30-sec	SA	temporal right	AE drug + PM
F (50)	5	15-sec	SA	temporal left	AE drug
F (37)	> 20	30-sec	AV block	temporal left	AE drug
F (77)	3	10-sec	SA	temporal right	AE drug
F (21)	> 10	27-sec	SA	temporal left	AE drug + PM
M (52)	3	> 30-sec	SA	temporal left	AE drug

AE: antiepileptic; PM: pacemaker; SA: sinus arrest

Four patients were managed by antiepileptic drugs, and 2 patients have been refractory to antiepileptic drugs and required pacemaker implantation. All the patients remained free of syncope during a mean follow-up of 42 $\pm$ 12 months.

Conclusions: In patients with partial epilepsy who present with loss of consciousness, ressembling syncope, a transient cardiac arrest caused by seizure attack may be the underlying mechanism. Caution should be paid when analyzing electrocardiographic findings derived from implantable loop recorder in young patients with a history of recurrent unexplained syncope.

P377 Prodromes in the investigation of unexplained syncope: fact or fantasy?

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Contradictory results have been reported about the diagnostic yield of prodromes in unexplained syncope (un-Sy).

Aim: Our study is aimed at establishing prospectively the diagnostic value of history in patients (pts) with un-Sy.

Method: 317 consecutive pts referred to a syncope clinic underwent a targeted work-up including the screening for 22 warning symptoms (WS). A putative cause was identified in 79% of the pts. The following diagnostic categories were established: vasovagal (VV) in 24%, bradyarrhythmic (Brady) in 20%, psychogenic (Psy) in 17%, hypotensive (Hypo) in 8%, tachyarrhythmic (Tachy) in 7%, situational in 3% and unexplained in 21%.

Results: The proportion (%) of the 5 most relevant WS in each diagnostic category is reported below. The absence of WS is more common and nausea, diaphoresis and palpitations are less frequent in the Tachy and Brady groups than in the other diagnostic categories respectively ($p<0.05$, Tachy + Brady vs VV + Psy). Nausea, diaphoresis or palpitations have a 65-90% positive predictive value (PPV) and a 70% negative predictive value (NPV) of VV or Psy syncope. In contrast, absence of WS has a 45% PPV and a 80% (NPV) of rhythmic syncope (Tachy and Brady).

Prodromes (% of causes)

	none	nausea	diaphoresis	paresthesia	palpitation
Bradyarrhythmic	48	11	17	2	2
Tachyarrhythmic	50	5	5	0	14
Hypotensive	8	4	21	4	0
Vasovagal	12	39	40	10	17
Psychogenic	4	35	56	53	47
Unexplained	46	12	16	3	10

Conclusion: Prodromes screening may help to define the best investigation strategy for unexplained syncope. In particular, neurovegetative prodromes suggest a reflexogenic or psychogenic syncope, while their absence indicates a high likelihood of rhythmic syncope.

PACEMAKER AND IMPLANTABLE CARDIOVERTER-DEFRIBRILLATOR TECHNOLOGY I

P378 Clinical validation of a new automatic atrial capture verification algorithm

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Introduction: Beside ease of use and increased longevity, automatic atrial capture verification may also facilitate follow-up diagnosis. This study evaluated atrial evoked response (AER) signals during unipolar (UP) and bipolar (BP) pacing from an independent pair of sensing electrodes, between atrial ring and an isolated indifferent electrode (AI).
Method: Patients indicated for DDD pacemaker implantation or replacement were enrolled into this acute prospective study. After routine measurements, an external version of the INSIGNIA™ (Guidant, St. Paul, MN) pacemaker was connected to the leads to record and evaluate the performance of a new autocapture algorithm during UP and BP atrial pacing. Manual step-down (6.5 to 0.1V @ 0.4 ms) threshold tests were performed. Surface ECG and intracardiac EGM from AI, V and A sensing circuits were recorded for off-line validation. Minimum signal to artifact ratios [SARmin, defined as the minimum captured AER amplitude (AERmin, baseline to peak) divided by the maximum non-captured pacing artifact (ARTmax)] were calculated for each patient. Successful capture detection was defined as SARmin $>$ or equal to 2.
Results: Acute data from 20 patients, age 69±17 years, 9 female/11 male, were analyzed. Nine different atrial lead types from 4 manufacturers were included, 4 were chronically implanted (36-126 months), 16 were acute. Routine measurements, using a standard PSA were as follows (mean±SD): A-pacing threshold at 0.4ms UP 0.9±0.4V, BP 1.0±0.4V; P-wave amplitude UP 2.7±0.7mV, BP 2.6±0.8mV; impedance UP 478±107 Ohm, BP 523±134 Ohm. Data from 1 patient was excluded due to incomplete tests. The table shows the averaged (±SD and range) AERmin, ARTmax and SARmin. The automatic atrial pacing threshold measurement was successful in 94.7% (18/19) patients with UP atrial pacing and 21% (4/19) pts with BP atrial pacing.

	AERmin (mV)	ARTmax (mV)	SARmin
UP Pacing	0.9 ± 0.5 (0.2-2.1)	0.1 ± 0.1 (0.1-0.3)	7.6 ± 4.3 (1.7-18.0)
BP Pacing	2.5 ± 1.7 (0.5-7.4)	2.5 ± 2.3 (0.2-7.5)	1.7 ± 1.3 (0.4-5.2)

Analyzed results: mean ± SD (range)

Conclusion: Adequate automatic atrial pacing threshold determination based on AER detection is reliable with unipolar atrial pacing. The lower success rate with bipolar pacing can be explained by the use of a common atrial ring electrode in the pacing/detection circuit.

P379 Digital processing of atrial signals for the detection of far field R-waves

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Purpose: Sensing of far field R wave (FFRW) in the atrial channel of pacemakers and ICD can infer with the correct detection of atrial arrhythmias and led to incorrect mode-switching. Though adjusting of atrial sensitivity and/or refractory period can reduce FFRW sensing, the risk of malsensing of trial arrhythmias.persists. We presumed that digital processing of sensed events in the atrial electrogram (EGM) could better separate FFRWs from P waves while preserving high sensitivity and fast response.
Methods and Results: Bipolar and unipolar atrial EGM recordings were collected during pacemaker implantation. Digital processing of the EGM signals (8 bit, 800 samples/second) included filtering (15-180 Hz), slope and amplitude calculations. For each atrial sense the most negative values of the filtered signals and the value of the belonging slope were measured. and added. This summed value was called the digital morphology parameter. This parameter was used to create histograms of all sensed atrial deflections. The histograms could discrimination between P waves and FFRW when gap of $>$3 histogram bins were applied. For the learning phase intra-operative recordings with varying sensing and pacing settings were made in 31 patients in whom PM replacement was done. The test phase included different parts of these recordings. Two blinded observers established the performance of the FFRW algorithm of 81 rhythm files. A total of 5653 (99.8%) P-waves were classified correctly and 9 (0.2%) were falsely corrected as FFRW. Conversely, 1340 (100%) were classified correctly and none were falsely classified as P waves. FFRW detection had an overall sensitivity of 99.3% and a positive prediction of 99.8%
Conclusion: digital processing of atrial signals shows excellent discrimination of FFRWs in off-line conditions. These results justify the implementation of this algorithm in next pacemaker and ICD programs for the immediate discrimination between FFRWs and P waves avoiding false mode switching and inappropriate anti-tachycardia pacing in the absence of atrial arrhythmias.

P380 In search of the optimal right-ventricular pacing site: a randomized comparison of septal and conventional apical pacing

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Background: Results of non-controlled studies suggest that permanent right ventricular septal (RVS) pacing is technically feasible and may significantly improve cardiac performance as compared to conventional right ventricular apical (RVA) pacing.
Objective: To assess the long term functional and hemodynamic effects of RVS pacing in comparison with RVA pacing.
Methods: 28 pts, aged 63.2 ± 2.0 years with chronic atrial fibrillation and complete heart block induced by radiofrequency catheter ablation, were implanted with a standard DDDR pacemaker connected to two ventricular leads. A screw-in lead was placed at RVS in the site providing the shortest paced QRS duration and was connected to the atrial port. The RV apical lead was connected to the ventricular port. RVS and RVA pacing were achieved by programming the pacemaker in the AAIR mode and in the VVIR mode, respectively. Four months after implant pts were randomized to a crossover single-blind comparison of RVS and RVA during two periods of 3 months each. At baseline LVEF was $>$ 45% in 16 pts and $<$ 45% in 12 pts. Pacemaker programming remained unchanged throughout the study. At the end of each period, NYHA class, LVEF (radionuclides), aortic output (Döppler-echo), exercise time and maximal oxygen uptake (pVO^2) were assessed.
Results: In comparison with RVA pacing, RVS resulted in a significant reduction of QRS duration (145±4 ms vs 1704 ms, $p<0.001$) and tended to normalize the axis (40±10° vs -71±4°). LVEF increased during RVS pacing (48.0±1.4% vs 44.8±1.7%, $p<0.01$). No statistically significant difference was found between the two pacing modalities for all other analysed parameters. Subgroup analysis showed that LVEF improvement was statistically significant in the only pts with baseline LVEF $<$ 45% (42.3±1.5% vs 37.1±1.2%, $p<0.001$).
Conclusion: Within the limitations of this study, permanent RVS pacing significantly improves LVEF in pts with chronic atrial fibrillation and baseline LVEF $<$ 45% as compared to standard RVA pacing.

P381 Rhythm discrimination by QRS morphology analysis: what performance in presence of a wide QRS complex?

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Morphology Discrimination (MD) is a rhythm discriminator based on an analysis of QRS complex morphology, implemented in St.Jude Medical implantable cardioverter defibrillators (ICDs). No data are available on the performance of MD in presence of a wide QRS complex.
The aim of the present study was to assess the discriminator performance in two series of patients (pts): with a wide ($\geq$ 120 ms) and a narrow ($<$120 ms) QRS complex, respectively, in the electrogram (EGM) detected in sinus rhythm and acquired as a template for MD scoring analysis. MD algorithm was programmed to diagnose ventricular tachycardia (VT) if % matching score was $<$65% in comparison with the template.
Results: Overall 26 pts implanted with a dual chamber ICD were analysed: 6/19 pts (31.6%) had a wide QRS complex ($\geq$120 ms) of the template and 13 pts had a narrow QRS complex. Analysis of 988 detected events, occurring during a follow-up of 18.8±5.1 months showed 662 episodes classified by Rate Branch as episodes with ventricular rate $<$ or = the atrial rate. The discriminating performance of MD in terms of sensitivity (SE) and specificity (SP) in VT diagnosis was calculated in both groups of pts.

Morphology Analysis

	QRS$\geq$120 ms	QRS$<$120 ms
N. of pts	6	13
Total Episodes	116	546
Overall SE	49/49=100%	5/5=100%
Overall SP	46/67=68.7%	492/541=90.9%
SP for Atrial Tachycardia	2/3=66.7%	75/98=76.5%
SP for Atrial Fibrillation	31/49=63.3%	20/26=76.9%
SP for Atrial Flutter	0	45/63=71.4%
SP for Sinus Tachycardia	13/15=86.7%	352/354=99.4%

Conclusions: Specificity of MD may vary comparing pts with wide and narrow QRS complex, being lower in pts with a wide QRS complex (overall 68.7% vs 90.9%). Moreover, both in wide and narrow QRS pts, specificity may be different considering different supraventricular tachyarrhythmias, being higher in sinus tachycardia and lower in atrial fibrillation/flutter. These findings are relevant for the clinical use of MD, used as single discriminator or in combination with other discriminators (i.e sudden onset and stability).

P382 Comparison of the atrial defibrillation threshold in patients with and without coronary sinus lead

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A new generation of implantable cardioverter defibrillators (ICD) offers additional therapy options to treat atrial tachyarrhythmias (AT) with either ATP or shock therapy using different shock vectors. The value of a coronary sinus (CS) lead for the selective treatment of atrial tachyarrhythmias by shock therapy remains to be investigated. The aim of this study was to evaluate the potential benefit of the coronary sinus (CS) lead with respect to atrial defibrillation threshold (ADFT), atrial arrhythmia conversion efficacy and safety.

Patients/Methods: In 86 patients (pts) (mean age 64±13 years, 77%male, mean LVEF 45.5±16%, 53% coronary artery disease) with documented episodes of atrial and ventricular tachyarrhythmia the dual-chamber ICD VENTAK PRIZM® AVT™ (Guidant, St. Paul; MN, USA) was implanted in 23 European and one Canadian centre. The additional option of selective atrial shock therapy using A-TRIAD configuration was applied in 21 pts who were implanted with an additional CS lead (Guidant PERIMETER®CS). ADFT was evaluated using different energy steps to conversion failure comparing the A-TRIAD and V-TRIAD configuration after induction of AT episodes at implant or pre hospital discharge test.

Results: A total of 33 episodes of induced AT were analysed, 19 using A-TRIAD, 14 using V-TRIAD configuration for application of atrial shock therapy. Comparison of the demographics of both groups showed no difference in gender, age, NYHA class, ejection fraction and underlying heart disease. There was a significant lower ADFT in pts with A-TRIAD compared with V-TRIAD configuration (4.6±2.7 vs. 10.4±4.7; $p<0.05$). These findings confirm results of previous animal studies. The mean implantation time was 123±57 minutes (min) for A-TRIAD and 99±44 min for V-TRIAD.

	A-TRIAD	V-TRIAD
Implantation time (min)	123 ± 57	99 ± 44
Atrial defibrillation threshold	4.6 ± 2.7	10.4+/4.7

Conclusion: In this patient population, the addition of a coronary sinus shocking lead to a dual-chamber ICD VENTAK PRIZM AVT system (A-TRIAD) significantly reduced the defibrillation threshold for atrial tachyarrhythmias compared to a standard V-TRIAD system. The implantation of a coronary sinus shocking lead may be an option for patients who suffer from frequent episodes of AT, although a longer implantation time has to be taken into account.

P383 Effects of tip-to-ring distance and fixation type on far field R-wave oversensing atrial leads

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Background: It has been suggested that a shorter tip-to-ring distance could reduce the incidence of Far Field R Wave Oversensing (FFRWO) in atrial leads. No data are available about the possible influence of lead fixation type on FFRWO. Aim of this study was to evaluate the incidence of FFRWO in three different groups of leads implanted in the right atrial appendage: 1) Group A: active fixation leads with 10 mm tip-to-ring distance (Medtronic Capsure Fix Novus 5076); 2) Group B: passive fixation leads with 9 mm tip-to-ring distance (Medtronic Capsure SP Novus 5594 and Capsure Sense 4574; 3) Group C: passive fixation leads with 17 mm tip-to-ring distance (control group).

Methods: 110 patients (pts) (41% F, mean age 74 ± 9) were implanted with Medtronic Kappa 700 or Kappa 900 DDDR pacing system and followed for 4.2 ± 4.2 months (range 1-18). 21 pts (19%) were in Group A, 55 (50%) in Group B and 34 (31%) in Group C. Results: Both active and passive fixation short tip-to-ring distance atrial leads had lower FFRWO than those of control group. The differences were statistically significant during the follow-up. No patient of group B showed FFRWO/P wave greater than 50% either at implant or during the follow-up. On the contrary, at least 1/5 of group C patients showed FFRWO/P>50% at the last follow-up. No significant differences could be identified among short tip-to-ring distance atrial leads as a function of active or passive fixation. Pacing thresholds and impedance did not differ among the three groups.

Results are given in the table.

Conclusions: Short tip-to-ring distance atrial leads, regardless of fixation type, may improve atrial signal detection and should be recommended in pts with atrial tachyarrhythmia.

	Group A	Group B	Group C
Mean FFRWO at imp. (mV)	0.22 ± 0.46	0.20 ± 0.32	0.44 ± 0.52
Mean FFRWO at FU (mV)	*0.12 ± 0.29	*0.11 ± 0.24	0.39 ± 0.78
FFRWO/P wave (imp.)	0.08 ± 0.19	0.06 ± 0.11	0.12 ± 0.17
FFRWO/P wave (FU)	0.05 ± 0.01	0.04 ± 0.10	0.13 ± 0.27
Pts with FFRWO/P > 50% (imp.)	5%	0%	3%
Pts with FFRWO/P > 50% (FU)	5%	*0%	18%
Mean atrial thres. at 1 Volt (ms)	0.29 ± 0.14	0.28 ± 0.18	0.23 ± 0.16
Mean atrial impedance (Ohm)	545 ± 76	598 ± 84	571 ± 112

*$p<0.05$ vs Group C

P384 Validation of total atrial conduction time by surface-electrocardiogram at various right atrial pacing sites

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Pacing the right atrium from the appendage (RAA) or free wall (RFW) is known to be the source of delayed intraatrial and interatrial conduction. Electrophysiological studies have shown that right atrial septal (RAS) pacing produces shorter interatrial conduction delay than conventional pacing.

Aim: In the present study we hypothesized that the surface ECG may be a reliable tool to validate shorter total atrial conduction times by septal pacing in pacemaker (PM) patients.

Methods: 62 patients (30 male, 32 female) with a mean age of 73 ± 2 years underwent dual chamber PM implantation for Class I indications. Duration of intrinsic and paced PW, latency [A-Stim to B-PW] and the interval [A-Stim to E-PW] as surrogate for total atrial conduction time were measured during predischarge control on surface ECG lead II (50 mm/s) when pacing at 80 bpm.

Results: Duration of global atrial activation with RAS pacing was significantly shorter ($p<0.001$) compared to RFW or RAA pacing, whereas the latter two pacing sites showed no significant difference. The mean duration (SD) of the interval [A-Stim to E-PW] was 112 (16) ms for RAS, 156 (29) ms for RFW and 157 (29) ms for RAA pacing (see table).

Table 1

Electrode position	A-Stim to B-PW	A-Stim to E-PW	Intrinsic PW	Paced PW
RFW, n = 12	27.3 ± 22.8	155.5 ± 29.1	116.4 ± 24.6	128.2 ± 38.2
RAA, n = 34	41.4 ± 26.3	156.6 ± 29.2	116.7 ± 28.7	113.6 ± 30.4
RAS, n = 16	20 ± 7.3	111.9 ± 15.6	123.1 ± 20.6	91.9 ± 17.2
p-value	<0.0001*	<0.0001*	n.s.	<0.002*

A-Stim = atrial stimulus; B-PW = begin of P-wave; E-PW = end of P-wave; PW = P-wave duration; RFW = right atrial free wall; RAA = right atrial appendage; RAS = right atrial septal; * = RAA compared to RAS; n.s. = not significant; data are mean ± SD (ms).

Conclusion: RAS pacing shortened total atrial conduction time and paced PW duration in PM patients significantly. Despite limitations in the accuracy of measurement technique the effects of pacing on interatrial and total atrial conduction may be derived reliably from surface ECG. RAS pacing appears to be superior to conventional right atrial pacing sites with respect to electromechanical function and interatrial synchronization.

P385 A new and fast echocardiographic method of determination of the optimal atrio-ventricular delay in patients after biventricular stimulation

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The optimization of atrio-ventricular (AV) delay is known to significantly contribute to the maximum cardiac performance. The aim of this study was to validate a new, fast, and simple echocardiographic method of identifying the AV delay which provides the maximum cardiac output (CO).
Methods: Right heart catheterization and Doppler echocardiography of transmitral filling were performed simultaneously in 19 patients with heart failure and at least minimum functional mitral regurgitation treated with atrial synchronized biventricular pacing. CO derived from catheterization and Doppler filling parameters were measured at the predicted optimal AV delay (oAVD), the short AV delay (oAVD - 50 ms), and the long AV delay (oAVD + 28 ms on average/range, +10 ms to +50 ms/) during a constant heart rate. The AV delay was regarded as optimal if the end of atrial contraction (represented by the end of A wave of transmitral filling) coincided with the beginning of ventricular contraction (heralded by the onset of the systolic component of mitral regurgitation). Prediction of the optimal AV delay included the following steps: 1. The maximum AV delay at which full ventricular capture is still preserved was found under electrocardiographic control. 2. This value declined by 5 to 10 ms was designated as "the testing long AV delay", and the time interval from the end of the A wave to the onset of the systolic component of mitral regurgitation (time t1) was measured at this setting. 3. oAVD was simply calculated as "the testing long AV delay" - time t1.
Results: The CO measured at the oAVD (4.5 $\pm$ 0.7 l/min) significantly exceeded those at the short AV delay (4.2 $\pm$ 0.7 l/min, $p < 0.01$) and the long AV delay (4.3 $\pm$ 0.8 l/min, $p < 0.01$), respectively. The method correctly determined the maximum CO in 79% of the patients.
Conclusion: Doppler echocardiography enables very rapid and accurate optimization of AV synchrony in patients after the implantation of a biventricular pacemaker.

P386 Symptomatic occlusion of the access vein after pacemaker or implantable cardioverter-defribrillator lead extraction

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Objective: We studied the incidence of symptomatic venous occlusion of the access vein after pacemaker or ICD lead extraction.
Patients: Clinical follow-up was obtained in 87/89 pts. Group 1: in 65 pts. the access vein was patent before extraction. Indication for extraction: infection in 37 and lead malfunction in 28 pts. Extraction was done with traction in 13 and a laser sheath in 52 pts. An ICD was present in 14 pts. Group 2: 22 pts. with an occluded access vein. Indication for extraction: infection in 18 pts. and lead malfunction in 4 pts. A laser sheath was used in 21 pts. and traction in 1 patient.
Results: The follow-up was 29 $\pm$ 14 months. Group 1: 5 pts. had edema after extraction, although all after laser sheath extraction this was not significantly different with traction (p=0.58). Neither indication (non-functional 4 pts., infection 1 pt.; p=0.15) nor type of lead (pacemaker 3 pts., ICD 2 pts.; p=0.29) influenced the incidence of symptoms. Group 2: 2 pts. had new complaints of cyanosis of the arm after extraction
Conclusion: This study indicates that lead extraction itself might be responsible for venous obstruction after the procedure. These findings should be confirmed by angiographic studies but until then it is prudent to refrain from lead extraction for the sole purpose of preventing venous occlusion.

P387 Is determining the optimal site better for the patient than using the posterolateral site with any position of the right-ventricular lead?

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Introduction Biventricular stimulation is a valuable tool in the treatment of patients with advanced heart failure and prolonged QRS duration. However, the optimal pacing site of biventricular pacing and its hemodynamic effects is not well established. Whether this site is better or not than the posterolateral site is also not known.
Method A group of 75 patients with heart failure class III-IV and QRS>120 msec was studied (mean age 67$\pm$10 years). Temporary pacing leads (Biotronik TC116) were placed in the right ventricular apex (RVAP) and outflow tract (RVOT). Coated guidewires (Galeo Biotronik) were positioned in anterior (LVA) and posterior (LVPL) position in the coronary sinus for unipolar stimulation. Pacing was performed in 5 configurations: RVOT-RVAP, RVAP-LVPL, RVOT-LVPL, RVAP-LVA and RVOT-LVA during VDD pacing. Cardiac index (CI) was determined using echo Doppler flow measurements over the aortic valve and hemodynamic response was determined by a relative increase in CI. For each patient the optimal site was chosen and compared to the posterolateral with RV apex and RV outflow tract combinations.
Results The hemodynamic measurements the optimal site and posterolateral combinations are summarized in the table below.

Comparison of hemodynamic results

Pacing site	Cardiac Index	Cardiac index %	p-value
Optimal site	1.94 SD 0.48	17.6 SD 9.1	-
RVAP-LVPL	1.89 SD 0.47	14.3 SD 9.9	<0.0001
RVOT-LVPL	1.89 SD 0.48	14.1 SD 10.0	<0.0001

Conclusion The optimal site is significantly better than the theoretically best sites of posterolateral position. Therefore, it seems worth while to determine the optimal site for the individual patient for hemodynamic best improvement, in stead of choosing the posterolateral position.

ARRHYTHMIAS IN CONGENITAL HEART DISEASE

P388 Maximum P-wave duration and P-wave dispersion in adult patients with secundum atrial septal defect: the impact of surgical repair

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Patients with atrial septal defect (ASD) have an increased risk for atrial fibrillation (AF).Previously it was shown that maximum P wave duration and P wave dispersion in 12-lead surface electrocardiograms are significantly increased in individuals with a history of paroxysmal AF.
Aims: We studied Pmaximum and Pdispersion in adult patients with ASD during normal sinus rhythm.In addition,the impact of surgical closure of ASD on these variables within one year after surgery was evaluated.
Methods: Thirty-four consecutive patients(21 women,13 men; mean age 35$\pm$11 years)operated for ostium secundum type ASD and 24 age-matched healthy subjects(13 women, 11 men; mean age 37$\pm$10 years) were investigated. Pmaximum, Pminimum and Pdispersion(Maximum minus minimum P wave duration) were measured from the 12-lead surface ECG.
Results: Pmaximum was found to be significantly longer in patients with ASD as compared to controls(115.2$\pm$9 vs. 99.3$\pm$14 ms;p<0.0001).In addition, Pdispersion of the patients was significantly higher than controls(37$\pm$9 vs.29.8$\pm$10 ms p=0.003).Pminimum was not different between two groups (78.1$\pm$11 vs.70.3$\pm$14 ms; p=0.07). After surgical repair of ASD, 10 patients(29%)experienced one or more episodes of paroxysmal AF. Patients with postoperative AF were older(45$\pm$6 vs.30$\pm$10 years; p=0.001)and had a higher preoperative pulmonary artery peak systolic pressure as compared to the those without postoperative AF(51$\pm$11 vs.31$\pm$9 mmHg; p<0.0001). No significant difference in pulmonary to systemic flow ratio was observed preoperatively between two groups(p=0.5).Pmaximum and Pdispersion were significantly higher in patients with postoperative paroxysmal AF at baseline and at postoperative first month, sixth month and first year as compared to those without it(for Pmaximum p=0.02,p=0.01,p=0.001,p<0.0001 respectively;for Pdispersion p=0.03,p=0.02,p=0.001,p<0.0001; respectively). In patients with postoperative AF, no significant changes were detected in both of these P wave indices during postoperative follow-up. However, in the other group, Pmaximum and Pdispersion were found to be significantly decreased at postoperative sixth month and first year as compared to baseline. Pminimum was similar throughout the postoperative follow-up as compared to baseline in both groups.
Conclusions: In patients with ASD,mechanical and electrical changes in atrial myocardium may cause greater P maximum and P dispersion. After surgical closure of the defect, significant decrease in both of these P wave indices may be related to a lower risk for AF in part, for a relatively short term follow-up.

P389 Correlations between connective tissue dysplasia and early repolarization syndrome

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Introduction: The aim of this study was to investigate phenotypic signs of connective tissue displasia (CTD) in patients with different pronouncement of early repolarization syndrome (ERS).
Methods: 119 individuals without apparent disease with ECG signs of ERS (24.97±0.58 years old) and 21 health men were examined for external signs of CTD (dolichomorphia, dolichostenomelia, arachnodactylia, joint hypermobility, skin distension, scoliosis). Two ECG signs were registered: j-point maximal elevation (jmax) and number of ECG leads in which j-point were found (Sum-j-point). With the help of echocardiography cardiac manifestations of CTD were registered (false tendons of ventricle, mitral valve prolaps, Valsalva's sinus aneurism).
Results: The sum of CTD signs in men with ERS was higher than in health men (3.29±0.24 and 2.80±0.24; $p<0.05$). CTD of the heart was significantly more frequent in individuals with ERS than in health men (57.1 and 33.3%; $p<0.05$). Slanting false tendon of left ventricle prevalenced (34.5% - men with ERS; 9.5% - men without ERS), especially in men with syndrom. All health persons with ERS were separated in to 3 groups in relation to the pronouncement of syndrome. In the 1st group (53 patients) there were minimal figures of ECG signs of the ERS (jmax=0.144±0.014 mV; Sum-j-point=2.11±0.09 leads). In the 2nd group (48 patients) there were average figures of the ERS signs (jmax=0.183±0.015 mV, Sum-j-point=3.25±0.2 leads). The 3rd group (18 patients) was characterized with the highest figures of ECG signs (jmax=0.286±0.058 mV, S-j-point=4.86±0.36 leads). CTD manifestations in each group of ERS were studied. The sum of CTD signs increased from 1st to 3rd group (3.053±0.137 - 1st; 3.800±0.563 - 3rd; $p<0.05$). Men with basal-median slanting false tendon had maximal figures of ERS signs ($p<0.05$). Patients with highest sum of CTD signs had CTD of the heart and maximal expressed ERS.
Conclusions: Connective tissue dysplasia is significantly more frequent in men with early repolarization syndrome, especially cardiac dysplasia. Maximal expression of early repolarization syndrome accompanies with slanting false tendons of left ventricle.

P390 Quality of life in implantable cardioverter defibrillator recipients: changes over the first two years after implantable cardioverter-defribrillator

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The implanted cardioverter defibrillator (ICD) has become standard of care for life threatening arrhythmias. Although the ICD has reduced mortality from life-threatening arrhythmias, there has been limited research on the quality of life and health status responses over time to assess long-term adjustment of the ICD recipient. Therefore the purpose of this study was to measure the changes over time in perceived health status, psychological distress, quality of life, and fears/concerns from time of ICD implantation, to 6, 12 and 24 months later.
A prospective, descriptive, repeated measures design was utilized to investigate the changes over two years in health status, psychological distress, quality of life, and fears/concerns in a sample of 70 ICD recipients. Subjects completed the Medical Outcomes Short Form 36 (SF-36), the Ferrans and Powers Quality of Life Index (QLI), and the Profile of Mood States questionnaire (POMS) at time of ICD, 6, 12 and 24 months later and the Brodsky ICD questionnaire (B-ICD) at 6,12, and 24 months. There were 51 males and 19 females with a mean age of 64 years, range 21 to 84 years. The majority (81%) completed at least high school education and 66% were married. Eighty percent had coronary artery disease with a mean NYHA class of 2 and a mean ejection fraction of 37%.
The SF-36 mental (MCS) and physical (PCS) health composite summary scores were significantly different over the first two years. The MCS improved over time ($F=4.8$, $p<0.003$), baseline MCS = 47. 5 increased to 53.6 at two years, indicating better mental health. The PCS decreased over the time, baseline PCS = 43.6 decreased to 39.3 at two years ($F = 9.54$, $p<0.0001$), indicating poorer physical functioning. All of the negative mood states measured by the POMS were significantly better at two years compared to baseline, with anxiety ($F=14.2$, $p<0.001$) and fatigue (15.3, $p<0.001$) contributing the most to the reduction in total mood score ($F=10.8$, $p<0.001$). The QLI was not significantly different over the first two years though there is a trend to improvement over time. On the B-ICD, subjects showed significantly lower scores at year two specifically related to feeling less fear about the ICD firing on the job ($p< 0.024$) or on the highway ($p<0.006$).
These data indicate improvements in mental health though reductions in physical functioning may explain why there is no significant change in the perception of quality of life. These data identify a group of cardiovascular patients who could benefit from a program of rehabilitation to reduce the effects of poorer physical functioning.

P391 Changes in QRS duration during exercise are associated with maximal exercise capacity and peak oxygen consumption in adults with repaired tetralogy of Fallot

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Background: Adult patients with repaired tetralogy of Fallot (TF) have reasonable exercise performance. In a previous study, we found that QRS duration at rest in the presence of a right bundle branch block is a strong predictor of maximal exercise capacity (Wmax) and peak oxygen consumption (Peak VO2). Based on these findings we were interested in the relationship between the changes in QRS duration during exercise and Wmax and Peak VO2.
Methods: Fifty-seven consecutive TF patients were examined. QRS duration on V1 (ms) was measured at rest and at maximal exercise capacity. Wmax and peak VO2 were obtained during a bicycle stress test (protocol: 20 Watt + 20 Watt/min). Cardiac output (l/min) at rest and at submaximal exercise (100 W) were measured by the CO2 rebreathing technique. The corresponding stroke volumes (ml) were calculated. Transthoracic echocardiography was used to calculate the right ventricular diameter in parasternal and apical short axis in rest. Via Doppler residual pulmonary stenosis (PS, mmHg) and via colour Doppler pulmonary regurgitation (scale 0-4/4) and tricuspid regurgitation (scale 0-4/4) could be quantified. Spearman rank correlation was used to describe the relationship between the degree of change in QRS duration during exercise and Wmax and peak VO2. Statistical significance was defined as $P<0.05$.
Results: Seven patients did not pass the anaerobic threshold and the exercise capacity of one patient was extremely outlying (Wmax=340). These patients were excluded from the analysis, resulting is a sample of 49 patients (75.5% male; median age=24 y., IQR=12). QRS duration at rest (median=160 ms, IQR=26) and at maximal exercise (median=153 ms, IQR=25) did not significantly differ. The median change of QRS duration during exercise was -5 ms (range -31 - +83ms). This was negatively correlated with Peak VO2 (2081±577 ml/min; n=-.34, p=.02) and Wmax (182±53 Watt; n=-.33, p=.02). No significant relationship could be found between the echocardiographic variables and Peak VO2 and Wmax. In addition stroke volume at 100 W correlated strongly with Peak VO2 and Wmax (n=.55, p=.002 and n=.62, p=.0004, respectively).
Conclusions: This study indicates that TF patients with QRS shortening during exercise have significantly higher peak oxygen consumption and maximal exercise capacity than patients with QRS lengthening. Lower stroke volumes may be responsible for this difference and could suggest restrictive filling patterns of the right ventricle. Further research will be necessary to determine these findings.

P392 Visualization of the moderator band using ccs-lacz expression in murine embryos; possible implication in the genesis of Mahaim tachycardia?

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Background: Atriofascicular fibers (Mahaim fibers) can sustain atrioventricular (AV)-re-entrant tachycardia. The morphological substrate for initiation of these tachycardias has not been elucidated. The CCS(cardiac conduction system)/lacZ construct is able to delineate the developing and mature cardiac conduction system.
Purpose: The aim of this study was to examine the localization of the developing AV conduction system in the CCS/lacZ reporter mouse, focusing on possible sites of arrhythmogenesis.
Methods: Analysis of lacZ-expression during sequential stages of cardiogenesis was performed in a line of CCS/lacZ transgenic mice (E 9,5-15,5). Embryos were stained for beta-galactosidase activity. An immunohistochemical staining with the myocardial marker HHF35 was performed to produce a double staining with the lacZ reporter construct. Results were constructed into 3-D-images to obtain optimal insight.
Results: After stage E 10,5 lacZ expression became gradually confined to the primitive conduction system. Expression was found in the right atrial sino-atrial node and left and right venous valves, in the right and left AV ring, His bundle and bundle branches. Expression was also evident in the right ventricular moderator band, which extended laterally up to the right AV ring. The latter is an unique finding, allowing for a direct connection between the right AV ring and the apex of the RV, bypassing the AV-node. This may form a substrate for re-entrant tachycardia. There was lack of expression in the RV inflow tract, which may implicate the separate role of this structure in cardiac development. The distal outflow tract also did not show lacZ expression.
Conclusion: Lac Z reporter gene expression is able to delineate the developing murine cardiac conduction system. New details include the presence of lacZ expression in the moderator band of the RV. The latter may have implications in the genesis/perpetuation of Mahaim tachycardia.

P393 Asymptomatic ventricular pre-excitation: electrophysiological evaluation in children and adolescents

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Purpose: Little information exists about the arrhythmic risk of an incidentally found ventricular pre-excitation (VPE) in asymptomatic children. Aim of the study was to evaluate, retrospectively, the role of electrophysiological study (EPS) in the assessment of the arrhythmic risk in asymptomatic pts with VPE.
Methods: Fifty-nine pts (37M/22F, aged 10.1±6.6 years) referred to our Division between 1985 and 2002 with diagnosis of asymptomatic VPE. All patients underwent EPS during the follow-up period. The following parameters were examined: anterograde refractory period of the accessory tract, the inducibility of supraventricular tachycardia (SVT) and the inducibility of atrial fibrillation with measurement of minimal RR between two consecutive preexcitated QRS.
Results: During EPS 32 pts (54.2%) experienced sustained SVT. The tachycardia was initiated in the basal state in 20 pts and after isoproterenol in the other 12. Orthodromic SVT (cycle length 308.4±45.4ms) was recorded in 25 pts. In 3 pts were recorded both orthodromic and antidromic SVT, with different cycle length (CL) as expression of multiple accessory AV pathways. Antidromic SVT alone (CL 239.5±13.7 ms) was recorded in 4 pts. Atrial fibrillation was recorded in 9 pts: in 6 pts it was recorded after the induction of orthodromic or antidromic SVT, in the other 3 cases atrial fibrillation was the first and only arrhythmic event. The minimal RR between two consecutive pre-excitated QRS ranged between 250-230 ms (mean 237.5±9.6ms). In the 27 pts who presented no induced sustained tachycardia in the EPS, the 1:1 conduction over the accessory atrioventricular connection ranged between 210-600ms (mean 281.7±76.1ms)
Conclusions: VPE found on routine ECG in healthy children has generally an excellent prognosis. However the risk of arrhythmic event is not negligible. Electrophysiological evaluation remains the gold standard for assessing risk of life-threatening arrhythmias in patients with VPE. A high number of healthy children and adolescents with VPE can experience sustained SVT and/or AF during EPS. These results raise questions about the necessity of an aggressive treatment approach to prevent "rare" cases of sudden death.

P394 Specialized conduction tracts near the atrioventricular node. Are they linked to the mechanisms of atrial fibrillation?

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Background: experimental studies suggest existence of multiple atrio-AV nodal inputs. However, their structure, complexity and function in regard to the propensity for atrial fibrillation (AF) is unknown.
Objective: To investigate the morphology of intraatrial conductive pathways in relation to AF in humans.
Methods: Fifteen hearts of the patients who died from coronary events were stratified in two age-matched groups in regard to the history of AF (7 AF, 8 non-AF). Atria were excised at the level of the valve plane and separated from interatrial septum (IAS) so as to leave 3-5 mm of the atrial walls both anteriorly and posteriorly. IAS specimens were fixed in paraffin and then sliced into 10-μm thick parallel histological sections with 1-mm step starting from the valve plane, up to the atrial roof (30 to 60 sections per heart). The sections were stained with van Gieson's stain.
Results: 1). Distinct bundles consisting of N-, Purkinje-like and transitional cells surrounded with fibrous matrix and separated from other septal structures were found anteriorly and posteriorly to the fossa ovalis (FO) as well as subendocardially on the right atrial side of IAS. Those bundles entered IAS from the right atrial side and continued downward to the atrioventricular valve plane. 2). All 8 non-AF specimens showed presence of up to 4 bundles in the IAS regions corresponding to the classical locations of the internodal tracts. Six AF specimens (85%) were characterised by more disorganised conductive bundles with additional bundle-like structures (up to 12) located both posteriorly and anteriorly to FO.
Conclusion: specialised conductive bundles exist in the IAS suggesting multiple entries to the AV node in humans. The divergent morphology of these bundles, linked to a history of atrial fibrillation, may represent functional changes of importance for the arrhythmia.

P395 QRS duration at standard or filtered electrocardiogram for arrhythmic risk stratification after repair of tetralogy of Fallot?

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The QRS duration (QRSD) at standard ECG has been proposed to identify patients (pts) at risk of sustained ventricular tachycardia (SVT) during post-surgical follow-up of total correction of TOF, but presence of complete right bundle branch block (RBBB) reduces the diagnostic accuracy of this parameter, particularly the cut-off of 180 ms. The aim of this prospective study was to assess the prognostic value of filtered QRS at SAECG.
Sixty-six consecutive pts (33 m, 33 f), mean age at first visit 26±10 yrs, underwent SAECG during clinical follow-up at 25-40-80/250 Hz. Filtered QRS duration (fQRS), duration of the high frequency low amplitude signal in the terminal portion of filtered QRS (HFLA), root mean square of the mean voltage in the terminal portion of filtered QRS (RMS), and QRSD were evaluated. During a mean period of 7,3±3 yrs, 12 pts (18%) developed SVT and 2 of them suddenly died.
Pts with SVT were characterized by a longer filtered QRS duration at all filter settings. On the contrary, the QRSD did not differ in patients with or without SVT (Table).
The duration of QRS is mainly due to the presence of RBBB, while the filtering procedure magnifies the potentials of low amplitude and high frequency, particularly in the terminal portion of QRS. These potentials probably reveal the presence of an arrhythmogenic anatomic substrate.

	No NSVT, SVT	NSVT, VT	P
QRSD at standard ECG	152 ± 16	159 ± 20	NS
fQRS 25-250 Hz	175 ± 19	188 ± 18	0.02
HFLA 25-250 Hz	24 ± 15	29 ± 13	NS
RMS 25-250 Hz	51 ± 33	40 ± 21	NS
fQRS 40-250 Hz	165 ± 17	179 ± 18	0.01
HFLA 40-250 Hz	37 ± 23	47 ± 30	NS
RMS 40-250 Hz	30 ± 20	26 ± 14	NS
fQRS 80-250 Hz	157 ± 20	170 ± 18	0.04
HFLA 80-250 Hz	42 ± 24	53 ± 36	NS
RMS 80-250 Hz	14 ± 9	12 ± 6	NS

In conclusion, the presence of a prolonged filtered QRS at SAECG seems to be a useful method to identify post-surgical patients with tetralogy of Fallot at higher risk for severe ventricular arrhythmias.

P396 Long-term outcome of ablation of post-operative atrial reentrant tachycardias is complicated by atrial fibrillation

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Introduction Catheter ablation is a possible curative treatment for post-operative atrial reentrant tachycardias (ART) in patients (pts) with congenital heart disease (CHD). 3-D mapping has proven to be an useful aid in the reconstruction of these complex reentrant circuits. However, long-term results of these ablation procedures are unknown. The goal of this study was to evaluate the long-term outcome after ablation of ART in pts with surgically corrected CHD guided by 3-D electro-anatomical mapping (CARTO).
Methods The study population consisted of pts (n=36, age 38±14 yr., 22 male) with ART and 1) tricuspid atresia (7), 2) transposition of the great arteries (5), 3) atrial septal defect (10), 4) aortic valve stenosis (8), and 5) tetralogy of Fallot (6) referred for catheter ablation. The mean no. of failed anti-arrhythmic drugs used prior to ablation was 2±1 [0-6] and the mean no. of surgical procedures performed was 2±1 [1-4]. 3-D electro-anatomical activation/voltage maps were used to identify target sites for ablation in all pts.
Results Successful ablation was achieved after 1 or 2 (n=8) ablation procedures in 75% of the patients. Target sites were located at the cavo-tricuspid isthmus (n=24, CL 286±87 ms, 55%) or between areas of scar tissue/anatomical structures (n=20,CL 279±68 ms 45%). After a follow-up period of 28±15 months, pts were in sinus rhythm (n=33, 91%, anti-arrhythmic drug usage: 88%). However, episodes of AF were documented in 10 pts (27%). Permanent AF was present in 3 pts (8%). AF developed de novo in 5 pts (14%). The presence of AF was associated with the number of surgical procedures performed ($p<0.04$),
Conclusion Ablation of ART in pts with surgically corrected CHD guided by 3-D mapping has a considerable high procedural success rate. During long-term follow-up the majority of the pts are in sinus rhythm, though not "arrhythmia-free". Paroxysmal or permanent AF was present in respectively 27% and 8% of the pts.

P397 Radiofrequency catheter ablation of junctional ectopic tachycardia with preservation of atrioventricular conduction

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Background: Junctional ectopic tachycardia (JET) is an arrhythmia predominantly of infancy and childhood, with a poor prognosis. It is characterised by a normal QRS tachycardia with AV dissociation. Drug therapy frequently fails to suppress the arrhythmia.
Aim: To describe the effect of radiofrequency catheter modification of the arrhythmia focus, while attempting to preserve atrioventricular (AV) conduction, in children with primary JET.
Patients, Methods, and Results: Two patients, a 9 year old girl and a 12 year old boy) with primary JET associated with symptoms (palpitations, presyncope) who had failed a combination of upto 3 antiarrhythmic medications underwent electrophysiologic study. JET was confirmed by the following: absence of dual AV physiology or accessory pathway conduction, inability to induce or terminate the arrhythmia by pacing maneuvers but an incessant character during isoproterenol infusion, presence of AV dissciation, and His bundle electrogram preceding ventricular activation with the same HV interval during tachycardia as sinus rhythm. The following 2 measures were taken to minimise the risk of AV block: 1. the His bundle was meticulously plotted out using the Localisa mapping system, allowing for a reliable measure of the distance between a given ablation site and the site of the proximal His bundle recording (accuracy of 1mm); 2. all ablations were performed using gradually increasing power starting at 5W during atrial overdrive pacing with continuous monitoring of AH interval. Ablation was started midseptally at the tricuspid annulus, at a distance of approximately 20mm from the proximal His bundle, and the catheter moved closer to the His bundle at each successive RF delivery. Successful RF application was performed at a distance of 5mm from the proximal His bundle recording; this site also demonstrated the earliest retrograde atrial activation. Accelerated junctional rhythm was observed at this site, requiring an increase in atrial overdrive pacing rate to insure evaluation of AV conduction. Over a follow-up of $>$6 months, neither patient has had a recurrence of tachyarrhythmia, despite discontinuing all antiarrhythmic medications.
Conclusions: Successful RF ablation of JET with preservation of AV conduction can be performed, using accurate electroanatomical mapping and titrated RF energy delivery during continuous monitoring of AH interval and atrial overdrive pacing.

NUCLEAR IMAGING TO ASSESS CARDIAC INNERVATION

P398 Right-ventricular overload is the main determinant of brain natriuretic peptide elevation in patients with heart failure: a magnetic resonance study

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Brain natriuretic peptide (BNP), secreted by ventricular myocytes, plays a key role in volume homeostasis and its plasma levels are a sensitive and specific marker of myocardial dysfunction. On the other hand, right ventricular dysfunction predicts a worse prognosis in moderate to advanced heart failure. We tested the hypothesis that right ventricular overload might per se influence BNP in heart failure patients. Forty-four patients (38 males, age 61$\pm$2 yrs, body surface area 1.89$\pm$0.02 m^2, mean $\pm$ SEM) with idiopathic (20) or postischemic (24) cardiomyopathy underwent cardiac magnetic resonance imaging (MRI) and resting plasma determination of BNP (IRMA assay, Schering). Left and right atrial and ventricular volumes and function were assessed by MRI (1.5 T, Cvi, GEMS, Milwaukee, USA). A FIESTA sequence was adopted to obtain parallel short axis of the ventricles, and 3D reconstruction was obtained in post-processing.
Left ventricular ejection fraction (LVEF) was 24.8$\pm$1.5, while right ventricular ejection fraction was 37.7$\pm$1.5%. End-diastolic/systolic volumes were 134$\pm$7/101$\pm$7 and 61$\pm$5/40$\pm$4 ml/m^2 for the left and right ventricle, respectively. BNP plasma values ranged from 54 to 1280 with a mean value of 341$\pm$38 pg/ml. BNP positively correlated with either right end-diastolic or end-systolic ventricular volumes (r=0.44, p=0.003 and r=0.51, P$<$0.001, respectively), less with left volumes (r=0.35, P=0.018 and r=0.37, p=0.013, respectively). Moreover, a significant negative correlation was observed between BNP and either LVEF and RVEF (r=-0.31, p=0.03 and r=-0.31, P=0.04, respectively). No significant correlation was found between BNP and dimension of the atria.
In conclusion, right ventricular overload appears the most critical mechanism in plasma elevation of BNP. The role of right ventricular dysfunction, which is known to independently worsen prognosis, could contribute, inducing compensatory elevation of plasma BNP, to its established prognostic power in patients with heart failure.

P399 Early detection of cardiac involvement in patients with familial amyloidotic polyneuropathy by ^{123}I-meta-iodobenzylguanidine scintigraphy

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Background: Familial amyloidotic polyneuropathy (FAP) is a hereditary disorder characterized by deposition of amyloid in several organs and tissues. The clinical picture is dominated by polyneuropathy and progressive insufficiency of the autonomic nervous system. The aim of this study was to assess the cardiac involvement and to correlate the findings with the severity of the neurological status.
Methods: 34 patients with FAP (15 male and 19 female; mean age 43 $\pm$ 15 years)underwent I-123-metaiodobenzylguanidine (MIBG) myocardial scintigraphy, in order to evaluate cardiac sympathetic innervation, 24-hour ambulatory blood pressure (BP) monitoring and two-dimensional and Doppler echocardiography. Their neurological involvement was quantified according to a neurophysiologic score (EMG; 0 = no abnormality and 100% = maximal disability).
Results: Myocardial MIBG uptake for the overall group was 1.75 $\pm$ 0.5 (normal = 2.5 $\pm$ 0.3) and correlated inversely with the EMG score (r = - 0.67; p = 0.001). Twenty-seven of the 34 (79%) patients had a decrease in cardiac MIBG activity, 18 (53%) revealed an alteration in the circadian BP pattern and/or an increase in systolic and/or diastolic BP loads at night and 17 (50%) showed left ventricular hypertrophy and/or diastolic dysfunction. Twenty-two patients were symptomatic and had a mean EMG score of 37.7 $\pm$ 25% (group I) and the remaining 12 were asymptomatic [EMG score = 0 (group II)]. Patients in the group I were older (48 $\pm$ 15 vs. 33 $\pm$ 10.2 years, p = 0.01), had lower MIBG uptake (1.5 $\pm$ 0.4 vs. 2.2 $\pm$ 0.5, p = 0.001), had higher systolic (129 $\pm$ 16 vs. 119 $\pm$ 6 mmHg, p = 0.01) and diastolic daytime BP (82 $\pm$ 10 vs. 76 $\pm$ 6 mmHg, p = 0.05) as well as higher systolic (119 $\pm$ 17 vs. 105 $\pm$ 7 mm Hg, p = 0.01) and diastolic nighttime BP (71 $\pm$ 11 vs. 62 $\pm$ 9 mm Hg, p = 0.01) than patients in the group II.
In 21/22 patients in the group I and in 6/12 in the group II there was a decrease in cardiac MIBG accumulation. Sixteen patients in group I and 2 in group II had abnormal circadian BP pattern. In contrast, hypertrophy was only seen in patients in group I.
Conclusions: Patients with FAP have a high incidence of cardiac denervation and an abnormal circadian BP pattern. These alterations in cardiac autonomic function often antedate the development of clinical and echocardiographic manifestations and may be an important contribution to determine the optimal timing for liver transplantation, which is, nowadays, the only way to control the progression of the disease.

P400 Myocardial beta-adrenoceptor downregulation in idiopathic dilated cardiomyopathy measured in vivo using (S)-[^{11}C]CGP 12388 and positron emission tomography

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Background: In vivo investigation of the beta-adrenoceptor (beta-AR) with positron emission tomography (PET) provides more insight in the pathophysiology of heart failure and the effects of interventions. The radiochemical synthesis of the first developed radiotracer for PET imaging of the beta-AR, [^{11}C]CGP 12177, was very demanding for clinical experiments, preventing widespread use. An easy producible tracer, (S)-[^{11}C]CGP 12388, has been developed and was used to investigate cardiac beta-AR density with PET in patients with idiopathic dilated cardiomyopathy.
Methods and Results: Myocardial beta-AR density was investigated in patients with idiopathic dilated cardiomyopathy (IDC) (n=7) and healthy controls (n=7), using (S)-[^{11}C]CGP 12388 PET and a tracer kinetic model. Patients showed a beta-AR density of 5.4 $\pm$ 1.3 pmol/g, which was significantly lower than healthy controls (8.2 $\pm$ 1.5 pmol/g, p $<$ 0.05).
Conclusion: This study shows that PET with (S)-[^{11}C]CGP 12388 is applicable for the measurement of myocardial beta-AR density in patients. A highly significant reduction in beta-AR density was found in patients with IDC compared to healthy volunteers.

P401 Prognostic value of ^{123}I-meta-iodo-benzylguanidin scintigraphy in patients with long QT syndrome

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Background: Patients (pts) with congenital long QT syndrome (LQTS) clinically present with ventricular tachyarrhythmias, syncopes or cardiac arrest. Currently available data on sympathetic innervation in pts with LQTS is inhomogeneous, partly contradictory and obtained in small pt groups. Therefore, this study was conducted to investigate regional sympathetic innervation in a larger cohort of LQTS pts.
Methods: A total of 30 pts with clinically proven LQTS (mean age 32±12 years) and 10 healthy volunteers (mean age 43±12 years; control group) were examined by means of 123I-meta-iodo-benzylguanidine single photon computed tomography (MIBG-SPECT). Images were acquired four hours post injection and analysed for regional MIBG-uptake in a 33-segment bull's eye scheme.
Results: As compared to the control group, 14 of the 30 pts with LQTS (46%) had a significantly reduced regional MIBG-uptake. However, statistical analysis of all segments of the LQTS group did not depict a consistent defect in a single region. Visual evaluation of MIBG-SPECT images revealed homogeneous MIBG-uptake in controls whereas in LQTS pts a rather inhomogeneous pattern was observed. This was confirmed by statistical analysis of the variance of regional uptake in the 33 analysed segments (variance LQTS 174±89 vs. control group 87±38; $p<0.0001$). However, LQTS pts with an abnormal presynaptic tracer uptake (MIBG+) had more often severe cardiac events compared to those LQTS pts with a normal presynaptic sympathetic innervation (MIBG-): 57% pts with MIBG+ were resuscitated from cardiac arrest (vs. 19% MIBG-). In 57% of MIBG+ pts ventricular tachyarrhythmias were documented (vs. 25% MIBG-), and in 57% MIBG+ pts an automatic cardioverter defibrillator was implanted (vs. 25% MIBG-). However, no significant difference as to parameters of repolarization on 12-lead surface ECG was observed (QTc 498±66ms vs. 490±45ms; QT-dispersion 63±29 vs. 64±33).
Conclusions: Sympathetic innervation defects were observed in 46% of the LQTS pts without a consistent location. MIBG-SPECT may be regarded as an independent indicator for the occurrence of potentially life-threatening complications in LQTS pts in the presence of similar repolarization patterns.

P402 Assessment of myocardial adrenergic innervation in patients with unexplained syncope

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Purpose: Cardiac scintigraphy with I 123 -Meta-iodobenzylguanidine (I 123 -MIBG) is used to evaluate myocardial adrenergic activity. In this study we used this method to investigate myocardial adrenergic innervation in patients with syncope of unknown etiology.
Methods: We studied 25 patients (aged 38 ±19 years, 15 men) with a history of syncopal episodes (>2 during the last 6 months) and a negative clinical and laboratory workout (Group A), while a group of 20 healthy volunteers, with no history of syncope, served as controls (Group B). None of the participants had any disease that may have affected myocardial adrenergic innervation. Both groups underwent a planar and a single-photon emission computed tomography (SPECT) myocardial imaging of the heart after intravenous infusion of 5mg I 123 -MIBG. Heart to mediastinum ratio (H/M) was used for quantitative assessment of adrenergic innervation, 10 minutes and 4 hours after drug infusion. SPECT scintigraphy was used to evaluate the regional distribution of adrenergic activity 4 hours after I 123 -MIBG injection.
Results: The H/M ratio at 10 min and 4 hours in Group A was 1.83 ± 0.11 and 1.80 ± 0.19 respectively; significantly lower than Group B (2.09 ± 0.11 and 2.06 ± 0.10 respectively, $p<0.05$ for both). During SPECT scintigraphy, 20 patients of Group A (80%) showed regional disturbances in myocardial adrenergic activity in inferior wall and 4 patients (16%) in the anterior wall. No regional disturbances were detected in Group B.
Conclusions: A large percentage of patients with unexplained syncope have myocardial adrenergic innervation abnormalities of the left ventricle. The precise contribution of our findings to the elucidation of the pathophysiology of unexplained syncope requires further investigation.

P403 Mechanism of pre- and post-synaptic down regulations of β-adrenergic pathway assessed with neuroimaging techniques in cardiomyopathies

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Objectives: Single photon imaging techniques with 123I-MIBG and positron imaging technique with C-11 hydroxyephedrine or C-11 CGP 12177 have demonstrated in human cardiomyopathies that an altered uptake-1 function and β-adrenergic receptor down regulation was present. However, the relationships between these two alterations and their mechanisms remain unclear. The aim of this study was to evaluate the hypothesis of a chronic elevation of circulating norepinephrine levels as a mechanism for concomitant down regulation of uptake-1 carrier site and β-adrenergic receptors.
Methods: Osmotic minipumps delivering intravenously either norepinephrine (NE) or sodium chloride were implanted in rats for 5 days. The uptake-1 function was assessed in vitro by measuring in excised hearts 3H-NE and 123I-MIBG uptakes and uptake-1 carrier density using 3H-mazindol binding assay. The myocardial β-adrenergic receptor density was assessed in vitro by 3H-CGP 12177 binding.
Results: A 34% decrease in 3H-NE uptake and a 35% decrease in 123I-MIBG uptake were found in the hearts of rats infused with NE pump compared to saline-solution-infused rats (n= 6, $P<0.05$ for both). Moreover, the uptake-1 carrier protein density was decreased by 29% ($P<$O.O5) and 33% ($P<$O.O5) in right and left ventricles of NE-pump rats compared to saline-solution pump rats (n=6 for both). A 36% reduction in β-adrenergic receptor density in the right ventricle ($P<0.05$) and a 31% reduction in the left ventricle ($P<0.05$) of NE- pump rats compared to saline-solution pump rats (n=6 for both).
Conclusion: A chronic elevation of plasma NE may cause a similar and concomitant down regulation of β-adrenergic receptor and uptake-1 carrier sites that can be explored in vivo by using single photon or positron emission tomography.

P404 Left-ventricular restrictive filling pattern is associated with reduced myocardial adrenergic innervation in patients with idiopathic dilated cardiomyopathy

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Purpose: The hallmarks of left ventricular (LV) diastolic dysfunction are slowing of relaxation and reduction of chamber compliance, which may lead to compensatory elevation of LV filling pressure and it is a common finding in pts with systolic dysfunction. The adrenergic nerve system has a major role in regulating cardiac function and 123-MetaIodoBenzylGuanidine (MIBG)cardiac uptake has been used to study myocardial sympathetic activation.
Objectives: We studied the myocardial adrenergic innervation using MIBG cardiac uptake, in relation to LV diastolic filling pattern in pts with idiopathic dilated cardiomyopathy(IDC).
Methods: Thirty -seven patients, 13 women, mean age 56.7+11,3 y, in sinus rhythm, with angiographically proven IDC, NYHA class II-III, LV EF 30.8+ 9.5%, clinically stable during the last month, were studied with planar MIBG. Early (10 min) and late (4 hours) heart to mediastinum uptake ratio and washout was calculated. A complete echocardiographic study was performed on all patients.
Results: According to Doppler transmitral early (E) to late (A) filling Velocity and Deceleration time of E (DTE) patients was divided into restrictive (E/A>2 or E/A=1-2 and DTE<140msec, 15 patients) (Group I) or non-restrictive (22 patients) groups (group II). There were no difference in age(57.1±10.6 vs 53.2±13.6yrs), NYHA functional class(2.2±0.36 vs 2.4±0.44) or LV ejection fraction (33± 9.4 vs 28.1±9.2%)between two groups.Group I pts showed increased left atrial diameter(45.8±4.1 vs 42.5±4.9,p=0.04),and decreased early (1.48±0.12 vs 1.63±0.21,p=0.01)and late (1.38±0.14 vs 1.53±0.23,p=0.01) MIBG uptake compared to group II pts. Late MIBG uptake was significantly correlated with NYHA functional class(r=-0.44,p=0.006),A wave velocity (r=0.37,p=0.02) and DTE (r=0.34,p=0.04) Binary logistic regression analysis revealed that late MIBG uptake was independently associated with the LV restrictive filling pattern (p=0.009).
Conclusions: The transition of diastolic dysfunction from impaired relaxation to restrictive filling pattern is associated with further reduced cardiac sympathetic innervation independently of LV systolic function, in idiopathic dilated cardiomyopathy. A greater percentage of beta-receptors down-regulation may contribute to the aggravation of LV diastolic dysfunction.

P405 The neurohumoral response to exercise stress and its relationship with inducible ischaemia on myocardial perfusion scanning

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Purpose: Recent studies have shown that natriuretic peptides, in particular BNP, are elevated during conditions characterised by cardiac ischaemia, such as acute coronary syndromes or acutely following coronary angioplasty, as well as in situations involving myocardial hypertrophy and volume overload. Natriuretic peptide levels may rise slightly in response to physical exercise in normal subjects. The effect of chronic stable ischaemia, on BNP is not known. We hypothesised that inducible ischaemia, may cause an increase in natriuretic peptides though transient ventricular dysfunction. If the degree of reversible dysfunction (known from isotope and echocardiographic studies to be an adverse prognostic indicator) could be quantified by measurement of natriuretic peptide levels, this could become a useful method of risk stratification in patients with stable coronary disease.
Methods: 36 patients with stable angina without a history or clinical signs of heart failure were included. Baseline bloods were drawn for natriuretic peptide analysis. Patients then underwent maximal exercise using a cycle ergometer. Further blood samples were obtained at peak exercise and 30 minutes post exercise. Thallium was injected during maximal exercise, and stress and resting SPECT images subsequently acquired according to standard protocol. The results were analysed using a semiquantitative method to determine the extent and severity of inducible ischaemia.
Results: Patients with any evidence of ischaemia during either stress or rest had higher levels of BNP than those without. (9.03 vs 2.58 pmol/l) p= 0.07. There was a ANP and BNP levels rose in a non significant fashion from baseline to peak exercise and returned to normal. (10.9, 16.0 and 10.5 pmol/l and 5.0, 6.4, and 5.3 pmol/for ANP and BNP respectively). The absolute increase in BNP during stress was greater in those with inducible ischaemia, compared to those without. (4.85 vs 0.6 pmol/l, p=0.004). 22% of the population had either severe or extensive ischaemia +/- transient left ventricular dilation or lung uptake during stress. But this group did not have significantly higher natriuretic peptide levels at rest or during stress. There was a weak correlation between baseline ANP (r = 3.55 p= 0.08) and the extent and severity of inducible ischaemia, none with BNP.
Conclusions: BNP is elevated in patients with stable ischaemia. Exercise induced ischaemia is associated with a significantly exaggerated rise in BNP, but, the degree of ischaemia does not directly correlate with the quantity of measurable peptide release.

P406 Relationship between iodine-123 metaiodobenzylguanidine myocardial imaging and plasma brain natriuretic peptide concentration in patients with isolated diastolic heart failure

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Background The usefulness of I-123 MIBG myocardial scintigrams has been demonstrated in patients with systolic heart failure. However, that remains to be elucidated in patients with isolated diastolic heart failure.
Methods We enrolled consecutive 21 patients with diastolic heart failure and 13 patients with systolic failure; each patients of either group complained cardiogenic exercise intolerance of NYHA functional class II and III. The diagnosis of diastolic failure was based on the following criteria: LVEF $>$ 45% (measured with modified Simpson methods on echocardiograms); plasma concentration of BNP $>$ twice the normal upper limit (36.8 pg/mL); without significant primary valvular disease; diabetes mellitus of HbA1c fraction $>$ 8.0%. MIBG myocardial scintigrams, Echocardiography, NYHA functional class, and exercise tolerance estimated using specific activity score were compared between the groups of the patients.
Results In either group, plasma BNP concentration correlated with the heart/mediastinum MIBG uptake ratio of delayed image (dH/M): diastolic failure, BNP = 656.9 - 264.4 x dH/M, $p < 0.05$, R = 0.405; systolic failure, 1097.3 – 488.1 x dH/M, $p < 0.05$, R = 0.562. Exercise tolerability described in METs (ET) correlated with dH/M in patients with diastolic heart failure (ET = 2.251 + 1.474 x dH/M, $p < 0.05$, R = 0.355), but not in those with systolic heart failure. In the patients with diastolic failure, dH/M was significantly lower in patients of NYHA class 3 than those of class 2 (1.69 ± 0.17 and 1.85 ± 0.20).
Conclusions The present study suggests that H/M ratio of MIBG imaging is related to neurohumaral activation and exercise intolerance in patients with diastolic heart failure. Accordingly, MIBG scintigraphy may provide useful information for treatment of patients with diastolic heart failure.

P407 Assessment of adrenergic activity using MIBG in patients with left bundle branch block

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Introduction: Patients with left bundle branch block (LBBB) frequently demonstrate left ventricular functional abnormalities. We assessed myocardial adrenergic activity using iodine-123 metaiodobenzylguanidine (MIBG) in pts with LBBB.
Methods: MIBG was performed in 17 patients (pts) with LBBB on ECG and all underwent coronary arteriography (CAR), echocardiocraphy and adenosine-thallium studies (AD-TL). Three pts had coronary artery disease and normal cardiac function (cad-group 1), 13 pts dilated cardiomyopathy with normal coronary arteries (CA) and heart failure (group 2) and one patient valvular disease and normal CA (group 3). All underwent MIBG planar images 5 minutes after the injection of MIBG and single emission tomography (SPECT) 4-5 hours post injection. To evaluate the myocardial accumulation of MIBG the heart/mediastinal (H/M) activity ratio was calculated. MIBG and AD-Tl SPECT images were visually evaluated; We divided into 6 segments: anterior, septal, inferior, posterior, lateral and apical and graded as follows: o=normal uptake, 1=mildly reduced, 2=severe reduced uptake and 3=no uptake obtaining a global score. All pts had abnormal SPECT MIBG imaging. In group 1, H/M ratio was 1.7 ± 0.3, the MIBG score was 7 ± 1.5 and AD-TL was 3 ± 1.5. Group 2 had H/M ratio 0.8 ± 0.1 in pts with LVEF$<$30% and 1.9 ± 0.4 in pts with LVEF$>$30% ($P<0.0005$), the MIBG and AD-TL score was 6.6 ± 1.2 and 0. 2 respectively and Group 3 (one patient with valvular disease) had H/M ratio 1.8, MIBG score 5 and normal AD-TL.
Results: All pts with LBBB had multiple and extensive denervated segments independently of myocardial systolic function; diminished H/M was observed only in the patients with severe heart failure. The limitation of this study is that delayed planar images were not obtained to assess the MIBG washout into the 3 groups.
Conclusion: Ohe major finding of this study is the extensive myocardium denervation in pts with LBBB regardless of the LVEF. The significant decrease of the H/M ratio only in severe cardiac systolic dysfunction can be attributed to the downregulation of neuronal receptors.

P408 Enhanced washout of ^{123}I β-methyl-iodophenyl pentadecanoic acid as a predictor of good left-ventricular functional recovery after acute anterior myocardial infarction

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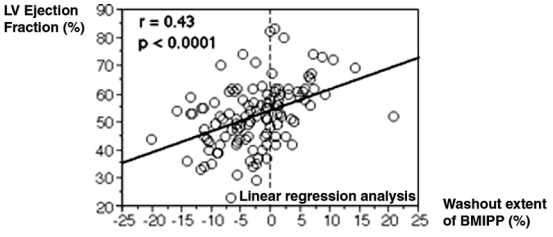
Purpose: The defects in early SPECT images of a free fatty acid analog, I-123 beta-methyl-iodophenyl pentadecanoic acid (BMIPP), may indicate the area at risk in acute myocardial infarction (AMI) patients. Although washout (WO) or fill-in (FI) is seen in the delayed images, the clinical significance of such BMIPP kinetics is unknown. Accordingly, we investigated the link between BMIPP kinetics and left ventricular (LV) functional recovery after reperfusion therapy.
Methods: A total of 114 patients with their first anterior AMI following reperfusion therapy underwent early (30 minutes after injection) and delayed (3 hours) BMIPP quantitative perfusion SPECT imaging on day 8. WO extent was defined as: WO extent (%) = extent of defects in delayed image (%) - extent of defects in early image (%). The patients were divided into either a WO (n=40, WO extent$>$0) or FI (n=74, WO extent$<$0) group. At 3 months, all patients underwent 99mTc-tetrofosmin rest scintigraphy to measure LV volume with a quantitative gated SPECT as well as infarct area that was demonstrated by the extent of defects (%) with quantitative perfusion SPECT.
Results: Patients with WO had significantly lower LV end-diastolic volume indices (60.4 ± 14.1 vs. 75.7 ± 26.2 ml/m^2, p=0.0009) and infarct areas (12.5 ± 13.4 vs. 22.3 ± 13.8%, p=0.0004), and higher LV ejection fractions (59.3 ± 9.5 vs. 49.0 ± 10.8%, $p<0.0001$) than those with FI. Figure 1 also shows the significant link between the WO extent and LV ejection fraction.



Conclusions: BMIPP kinetics may reflect myocardial viability, and WO extent may predict postinfarct LV functional recovery, after reperfusion therapy.

MYOCARDIAL FUNCTION

P409 Value of the assessment of cardiac function of rats with cardiac overexpression of the SR Ca^{2+}-ATPase (SERCA2a) gene with three independent techniques

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We characterized the cardiac contractile function of transgenic rats with cardiac-specific overexpression of the sarcoplasmic reticulum Ca^{2+}-ATPase cardiac isoform (SERCA2a) in 3 month-old transgenic rats (TG) and their age-matched Sprague-Dawley wild type controls (WT). Rats underwent an echo-Doppler examination (systolic LV function assessed upon ejection fraction, fractional shortening and peak systolic velocity of the mitral annulus (Sa); diastolic function assessed upon Doppler transmitral flow parameters (E and A waves, deceleration time, isovolumic relaxation time) followed by invasive hemodynamic measurements using a Millar 3-Fr Mikro-tip pressure transducer catheter immediately followed by sacrifice. LV samples were snap-frozen and kept at -80°C until the measurement of the myocardial SERCA2a protein concentration by Western blotting using specific anti-SERCA2a antibodies. Two other age-matched groups of TG and WT rats were used to assess LV papillary muscle contractility. The heart and LV weight/body weight ratios were similar in the two groups but myocardial SERCA2a protein level was 2-fold higher in TG than in WT rats (11.6±2.1 vs 5.4±0.8 au.; $p<0.01$). Using echo-Doppler, the two rat groups showed similar LV diameters and systolic function but an increased LV relaxation was found in TG compared to WT rats characterised by a shorter deceleration time (34.2±1.1 vs 45.4±1.8 ms; $p<0.001$), an increased E/A ratio (1.46±0.06 vs 1.35±0.05, $p<0.05$), and a shorter isovolumic relaxation time (16.0±0.7 vs 19.6±0.8 ms; $p<0.005$). The LV peak systolic and end end-diastolic pressures were similar in the two rat groups but both + and -dP/dt were markedly increased in TG compared with WT rats (+dP/dt: 7263±467 vs 5531±377 mmHg/s, $p<0.01$; -dP/dt: 5178±198 vs 4121±359 mmHg/s, $p<0.05$). As compared to WT, papillary muscles of TG rats exhibited an increased maximum unloaded shortening velocity (Vmax: 3.44±0.29 vs 3.15±0.18 Lmax/s, $p<0,05$) with no change in the force of the isometric twitch while the maximal lengthening velocity was markedly increased (maxVr: 3.15±0.42 vs 2.62±0.33 Lmax/s, $p<0.01$) with no change the maximal shortening velocity (maxVc), resulting in an decreased maxVc/maxVr ratio (R1: 0.68±0.05 vs 0.76±0.08, $p<0.05$) characteristic of an increased SR function. Taken together, these results indicate that the three techniques provide consistent data for an improved diastolic function in SERCA2a TG rats whereas data on systolic function are less consistent and deserve further investigation.

P410 Semi-quantitative analysis of SERCA2a activity during beta-adrenoceptor stimulation in intact mouse myocardium

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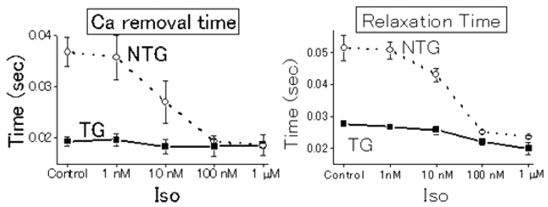
Intracellular Ca is one of the important regulators for contraction-relaxation in cardiac muscles. Ca-ATPase of sarcoplasmic reticulum (SERCA2a) is one of the major players for lowering intracellular Ca concentration. In the present study, we over-expressed SERCA2a to elucidate the contribution of SERCA2a to the changes in the Ca transients and contraction in twitch. We used cardiac restricted-over-expression of SERCA2a transgenic mouse (TG) and non-transgenic littermates (NTG). In western blot analysis, SERCA2a protein in TG increased 1.2 to 1.6 times higher than that in NTG. We used the aequorin method to measure the Ca transients with tension in the left ventricular papillary muscles of mouse. The time courses of the Ca transient and tension in TG were faster than those in NTG. Then, we applied isoproterenol (ISO) to the preparations of TG and NTG. In NTG, the time course of the Ca transient became faster, although no effect was observed in TG. The relaxation time was not significantly shortened by ISO in TG, but was significantly shortened in NTG. The maximally shortened decay time of the Ca transient by ISO in NTG was similar to the decay time of the Ca transient in TG in the absence of ISO. These results suggest that a quantitative increase in SERCA2a shows an equivalent effect of the phosphorylation of phospholamban via beta-adrenoceptor stimulation and that relaxation time is mainly determined by the rate of Ca removal although a slight effect might be due to faster off-rate of Ca from troponin. Thus, under pathophysiological conditions, up-regulation in SERCA2a might be beneficial in lowering the increased intracellular Ca level without phosphorylation of other proteins including troponin-I.



Ca removal time & Relaxation time.

P411 Proteom analysis of rat myocardium: influence of neurohumoral factors and mechanical load

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Introduction: Monocrotaline (MCT) treatment of rats leads to an obliterative vasculitis of the lung with consecutive pulmonary hypertension resulting in an increase of right ventricular afterload. Further neurohumoral stimulation of the left (LV) and right ventricle (RV) could be observed in this model. The aim of this study was the identification of combined load-dependent and neurohumoral-dependent (RV) expressed proteins and the detection of only catecholamine-dependent (LV) expressed proteins.
Methods: Male wistar rats were treated with a single s.c. injection of MCT. In the state of compensated RV hypertrophy 2D-gelelectrophoresis of RV and LV homogenates were performed. Differentially expressed proteins of RV and LV were identified by peptide-fingerprinting with MALDI-TOF-Masspectrometry after tryptic digestion. Myocardium of 5 MCT treated animals and of 5 control animals was analysed. Further calcium cycling proteins (SERCA, NCX, Calsequestrin) were analysed by western-blots.
Results: By 2D-gelelectrophoresis we detected 27 proteins showing a load/neurohumoral-dependent regulation (RV, at least 2-fold regulated, $p<0.05$, 22 down- and 5 upregulated), while 26 proteins showed a isolated neurohumoral-dependent regulation (LV, at least 2-fold regulated, $p<0.05$, 13 down- and 13 upregulated). In the group of combined load/neurohumoral- dependent regulated proteins a variety of metabolic enzymes (i.e. pyruvatdehydrogenase E1 component B-subunit) were found. For calcium cycling proteins only SERCA of the RV showed a significant downregulation in MCT treated animals (-17%, $p< 0.02$)
Conclusion: Neurohumoral stimulation and increased afterload are leading to a striking change of the myocardial proteom even in compensated myocardial hypertrophy. Besides changes in the expression of structure proteins a differential expression of calcium cycling proteins and of enzymes involved in energy metabolism was observed. So even in compensated hypertrophy energy metabolism of the myocardium seems to be impaired.

P412 Increased cardiac interleukin-18 mRNA, pro-interleukin-18 and plasma interleukin-18 after myocardial infarction in the mouse: a role in cardiac dysfunction

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Objective: Interleukin (IL)-18 has previously been reported to be an important predictor for mortality in ischemic heart disease. IL-18 has proinflammatory properties, induces cell death and stimulates nitric oxide production. The aim of this study was to examine the synthesis of IL-18 in the myocardium of mice after myocardial infarction (MI), as well as the effects of IL-18 on cardiomyocyte shortening and left ventricular contractility.
Methods and Results: MI in the mouse was induced by ligation of the left coronary artery. Seven days after MI, myocardial hypertrophy and pulmonary edema were observed. RNase protection assay and Western blot analysis of tissues from the non-infarcted left ventricular myocardium from MI-mice revealed significantly increased abundance of IL-18 mRNA (2.0 fold), pro-IL-18 protein (1.4 fold) and IL-18 receptor protein (3.5 fold). The abundance of cardiac IL-18 protein was, however, reduced by 25%. Since we measured both increased cardiac activity of the pro-IL-18 processing enzyme, caspase-1 and of the IL-18 degrading enzyme, caspase-3 (3.4 fold), it is likely that the observed reduction of cardiac IL-18 protein following MI might be due to increased degradation by cardiac caspase-3. However, the concentration of circulating IL-18 was significantly elevated in MI-mice (90.4±11.7 pg/ml) when compared to sham (47.2 ± 4.2 pg/ml). Following IL-18 (100 ng/ml) exposure, a 19% decrease in fractional shortening of electrically stimulated adult cardiomyocytes was measured in vitro. Additionally, in vivo administration of IL-18 (500 ng/ml) intravenously in mice reduced the left ventricular contractility (+dP/dt max) by 40%.
Conclusions: After MI in the mouse, increased production of cardiac IL-18 mRNA and pro-IL-18, as well as circulating IL-18 occur. Since IL-18 reduces myocyte shortening in vitro and left ventricular contractility in mice in vivo, we suggest a role for IL-18 in the pathogenesis of cardiac dysfunction following MI.

P413 Chronic monotherapy with extended release metoprolol succinate normalizes mRNA gene expression for alpha and beta-myosin heavy chain isoforms in left-ventricular myocardium of dogs with heart failure

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Background: Myosin heavy chain (MHC) is a key component of the cardiac contractile machinery. Recent studies have shown that a switch from the alpha-MHC isoform to the beta-MHC isoform takes place in myocardium of patients with heart failure (HF). In this study, we examined the effects of monotherapy with extended release metoprolol succinate (ER-MET), a selective beta-1 adrenergic receptor blocker, on mRNA gene expression of alpha-MHC and beta-MHC in left ventricular (LV) myocardium of dogs with chronic HF (LV ejection fraction 30%-40%) produced by multiple sequential intracoronary microembolizations.
Methods: Total RNA was isolated from LV myocardium of 14 dogs with HF randomized to 3 months oral monotherapy with ER-MET (50 mg, once daily, n=7) or to no therapy at all (n=7) and from LV myocardium of 6 normal dogs. Using specific primers in reverse transcriptase-polymerase chain reaction (RT-PCR) and restriction enzyme analysis of the RT-PCR product, alpha-MHC and beta-MHC isoforms were measured and normalized to total MHC (alpha-MHC + beta-MHC).
Results: mRNA gene expression for alpha-MHC was significantly reduced and beta-MHC significantly increased in HF dogs compared to normal dogs. Therapy with ER-MET significantly increased mRNA gene expression for alpha-MHC and significantly reduced mRNA gene expression for beta-MHC compared to untreated HF dogs. The data are shown in the table.

	Normal	HF-Untreated	HF + ER-MET
Alpha-MHC (% of total MHC)	23.6 ± 2.5	13.3 ± 0.98*	22.2 ± 0.9**
Beta-MHC (% of total MHC)	76.4 ± 2.5	86.7 ± 0.9*	77.8 ± 0.9**

*=p<0.05 vs Normal; **=p<0.05 vs HF-Untreated

Conclusions: In LV myocardium of dogs with HF, mRNA gene expression for alpha-MHC is decreased and mRNA gene expression for beta-MHC is increased compared to normal dogs. Treatment with ER-MET normalizes mRNA gene expression for alpha-MHC and beta-MHC. Since alpha-MHC is associated with faster velocity of
shortening compared to beta-MHC, this normalization may be responsible, in part, for the observed improvement of LV ejection fraction seen in patients with HF after long-term therapy with ER-MET.

P414 Prevention of myocardial fibrosis by inhibition of the ubiquitin-proteasome system

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Background: Myocardial fibrosis is a hallmark of cardiac remodeling contributing to left ventricular dysfunction. The ubiquitin-proteasome system is the major pathway for intracellular protein degradation and plays a key role in degrading central signal mediators, which are likewise involved in the development of cardiac fibrosis. We have investigated whether inhibition of the proteasome may influence myocardial fibrosis.
Methods and Results: Treatment of primary cardiac fibroblasts of the rat with the specific proteasome inhibitor MG132 revealed concentration-dependent inhibition of fibroblast growth without severe cytotoxicity (determined by proliferation and XTT assays). Interestingly, we observed specific and concentration-dependent downregulation of RNA expression of collagen I alpha 2 and III alpha 1 and of the matrixmetalloproteinases MMP9 and MMP2 as determined by real-time RT-PCR analysis. Moreover, interleukin-1 beta-induced expression of MMP9 and MMP2 was suppressed significantly with different protesasome inhibitors (determined by zymography and western blot analysis). This downregulation was also observed on the RNA level.
The effect of proteasome inhibition on the development of myocardial fibrosis was studied in spontaneously hypertensive rats (SHRs). Long-term treatment over 12 weeks with MG132 (daily 0.1 mg/kg, n=10/group) was well tolerated and resulted in pronounced inhibition of cardiac fibrosis by 38% as revealed by computer-aided morphometry. This correlated well with significantly reduced expression of collagen I alpha 2 and III alpha 1 and of MMP2 and MMP9 in the left ventricle of MG132 treated animals.
Conclusion: We conclude from these proof-of-principle experiments that inhibition of the proteasome system effectively prevents myocardial fibrosis in SHRs. These effects are presumably mediated by reduced growth of cardiac fibroblasts and by a diminished expression of collagens and MMPs.

P415 Long-axis function is impaired in heart failure patients with preserved global systolic function: a colour tissue Doppler imaging study

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Background: Patients with preserved LV systolic function make up a significant proportion of the chronic heart failure population. This study tested the hypothesis that long-axis function is impaired in these patients.
Methods: The study population included 41 patients (aged 67 ± 13 yrs) with signs and symptoms of heart failure (29 of ischaemic aetiology and 12 of non-ischaemic aetiology) who presented with preserved global LV systolic function (ejection fraction > 45%) and 41 age-matched control subjects. The study patients underwent full echocardiographic examination including colour-coded tissue Doppler imaging using a GE Vingmed System Five scanner. Mitral annular systolic velocities (Sm), early diastolic (Em) and late diastolic (Am) velocities were measured at six positions (at the lateral, septal, anterior, inferior, posterior and antero-septal sites of the mitral annulus) and averaged.
Results: Systolic and diastolic mitral annular velocities are presented in the Table. The indices of systolic long-axis shortening (Sm) and late diastolic lengthening (Am) were decreased in heart failure patients compared to age-matched controls, while the velocities reflecting early diastolic lengthening (Em) were not significantly different between the study groups.

	Patients	Controls	P
Sm	4.44 (1.13)	5.45 (1.13)	0.000
Em	4.91 (1.98)	5.27 (2.14)	0.425
Am	5.63 (1.68)	6.95 (1.48)	0.001
Em/Am	1.15 (1.66)	0.86 (0.61)	0.307

In conclusion, long-axis function (systolic shortening and late diastolic lengthening) can be impaired in patients with symptoms of heart failure and preserved global LV systolic function. The role of this phenomenon as a potential mechanism of symptoms, signs and prognosis of heart failure needs further investigation.

P416 Tissue Doppler imaging for the early detection of myocardial dysfunction in patients with type 2 diabetes mellitus

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Purpose: The prevalence of type 2 diabetes mellitus is rapidly expanding, which can cause the incidence and prevalence of heart failure to increase. Myocardial dysfunction may be a consequence of diabetic cardiomyopathy and is an important factor for the poor prognosis in patients with diabetes mellitus. Accordingly early detection of myocardial dysfunction in diabetic patients is extremely important for implementing secondary and tertiary prevention in order to improve the prognosis. This case-control study tested if quantitative Tissue Doppler Imaging (TDI) may be a suitable tool for the detection of myocardial dysfunction in diabetic patients.
Methods: A total of 43 diabetic patients and 34 non-diabetic control subjects without any clinical signs of heart failure and with normal global LV-function by standard 2-D echocardiography were investigated with TDI at rest and during dipyridamol and/or dobutamin stress. Global myocardial function was calculated as mean value from six basal myocardial segments for the peak velocity at systole (Vs), early diastole (Vd) and atrial contraction (Va). The diabetic and control groups were well balanced in respect to demographics and case histories including coronary artery disease.
Results: The rate-pressure product and pulse pressure were significantly higher in the diabetic patients at rest (9363 vs.7840; p<0.01 and 63.1 vs. 49.5;p<0.001)and during Dipyridamol stress (rate pressure product: 11035 vs. 9833; p=0.04 and pulse pressure: 63 vs. 50.8; p=0.001). Compared to controls the diabetic patients had a compromised Vd at rest (8.6 vs. 9.6 cm/sec; p=0.02) and during Dobutamin stress (10.0 vs. 13.1 cm/sec; p<0.01). Their resting Va was higher (10.1 vs. 8.9 cm/sec; p=0.01) and the Vd/Va ratio at rest (0.9 vs. 1.1; p<0.01) and during Dipyridamol and Dobutamin stress significantly lower than in the control group (Dipyridamol: 0.9 vs.1.1; p<0.01 and Dobutamin: 0.8 vs. 1.1; p<0.01). Compared to controls Vs was not reduced at rest in the diabetic patients (p=0.09). It was, however, lower during Dobutamin stress (10.7 vs. 13.6 cm/sec; p<0.05).
Conclusion: Patients with diabetes mellitus have early signs of predominant diastolic and also systolic myocardial dysfunction. This can be identified by quantitative TDI before any clinical signs of heart failure are apparent. Accordingly, TDI may be used for screening diabetic patients for myocardial dysfunction and for monitoring therapeutic strategies.

P417 Dyslipidemic profile of the metabolic syndrome is highly prevalent and under-treated in patients with chronic heart failure – a single-center, electronic medical record clinical experience

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Background: Dyslipidemic profile, such as low high-density lipoprotein cholesterol (HDL-c) level or high fasting triglyceride(TG)/HDL-c ratio, is an independent predictor of clinical outcome in patients with cardiovascular diseases. We sought to determine the prevalence of low HDL-c and high TG/HDL-c ratio in patients with heart failure, and the contemporary patterns of lipid intervention in a busy outpatient heart failure and internal medicine clinic.
Methods: We reviewed 1,557 consecutive patients with chronic heart failure seen at a tertiary care, outpatient internal medicine (IM) and cardiology (CV) clinics between 10/99 and 5/02. Low HDL-c level was defined as </= 40 mg/dL for men and </= 50 mg/dL for women (ATP-III criteria). Clinical, demographic, laboratory data (including fasting lipid panel) and ICD-9 coding data were extracted from electronic medical records (EpiCare, Epic Systems Co.),and compared using univariate analyses.
Results: In our study population (mean age 63 ±14 years, 64% male, 35% diabetics), 35% had total fasting cholesterol of > 200 mg/dL with mean low-density lipoprotein cholesterol (LDL-c) and HDL-c being 103 ±36 mg/dL and 43 ±14 mg/dL respectively. Overall, 58% of the patients had low HDL-c levels (compared with 38% in historical controls of secondary prevention trials), and was similar between men and women (57% vs 59% respectively, p=NS). In addition, 41% patients had a fasting triglyceride/HDL-c ratio of >3.5. Among those with LDL-c >/= 100 mg/dL (i.e. noncachetic), 43% men (mean LDL-c = 127 ±24 mg/dL) and 53% women (mean LDL-c = 136 ±35 mg/dL) had low HDL-c. Patients with low HDL-c levels are more likely to be diabetic and have an ischemic etiology when compared to those with normal HDL-c levels ($p<0.05$). Among all patients with low HDL-c, only 8% of patients were being treated with a lipid-modifying agent, among which only 9 patients (0.6%) were receiving niacin or fibric acid derivatives. Treatment patterns were similar between CV and IM clinics.
Conclusions: Dyslipidemic profile of the metabolic syndrome is highly prevalent in ambulatory patients with chronic heart failure (up to 58% with low HDL-c), even when adjusted for non-cachetic patients. The vast majority of patients with low HDL-c are not adequately treated, and features of the metabolic syndrome were highly prevalent. Further investigation is needed to determine the potential benefits of therapy to improve this dyslipidemic profile in the heart failure population.

P418 The prevalence and determinants of uraemic cariomyopathy in patients awaiting renal transplant measuren using cardiac magnetic resonance

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Premature cardiovascular disease (CVD) is the most common cause of death in patients with end-stage renal failure (ESRF) accounting for 50% deaths. Left ventricular abnormalities such as left ventricular hypertrophy (LVH) and left ventricular systolic dysfunction (LVSD) are thought to be the strongest determinants of CV outcome but echocardiography, especially in this population, is inaccurate meaning as yet, there are no targets for intervention.
The aim of this study was to determine the true prevalence of LV abnormalities in patients with ESRF using the gold standard non-invasive method of measurement, cardiovascular magnetic resonance (CMR) and to identify the predictors of these LV abnormalities.
150 patients with ESRF were recruited from West of Scotland renal transplant waiting list. Information collected included standard CV risk factors, comorbidity, drug history and the aetiology and duration of renal failure. 12-lead ECG, resting BP, 24-hour BP monitor and phlebotomy were carried out as well as CMR. CMR was performed on a Siemen's Sonata scanner operating at 1.5 Tesla and analysed by a single operator. A proportion of the scans were analysed by another observer to ensure inter-observer variability was within normal limits.
147 patients completed the study. The average age of the cohort was 50 years and 66% of the cohort were men. 68% of the cohort had some form of left ventricular abnormality and 65% had LVH, 22% LVSD and 18% had a dilated LV. 15% of the cohort had all three abnormalities. Predictors of LV abnormalities in the cohort were determined using multiple linear regression. The strongest independent predictors of LVH were ambulatory systolic and diastolic BP (p=0.002 & p=0.004) and the strongest predictor of LVSD was a previous history of MI ($p<0.001$). With follow-up the strongest predictors of death or CV event were ejection fraction (p=0.002) and end-diastolic volume (p=0.021).
Conclusion LV abnormalities are common in patients awaiting renal transplant. 68% patients have an abnormal LV and 22% have LVSD. The only modifiable risk factors in this group is BP and ambulatory BP values more strongly predict LV abnormalities. LV abnormalities are the strongest predictors of outcome in this population and therefore BP should be aggressively targeted to improve outcome.

EXPERIMENTAL HEART FAILURE

P419 Increased expression of the syndecan family of transmembranous heparan sulpate proteoglycans following myocardial infarction in the mouse indicates a role in cardiac remodelling

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Purpose: Remodeling of the non-ischemic region after myocardial infarction may involve proteins that link the cytoskeleton to the extracellular matrix. The purpose of this study was to identify essential genes involved in myocardial growth and remodelling.
Methods: Myocardial infarction was induced by ligation of the left coronary artery in anesthetized mice. After one week an increase in heart weight and lung weight was found, indicating myocardial hypertrophy and congestive heart failure. Left ventricular non-infarcted tissue from six mice with congestive heart failure was analyzed by means of cDNA filter hybridization arrays (Atlas, Clontech Laboratories Inc.), and the findings compared to those obtained by analyzing left ventricular tissue from six sham operated mice. To classify as significantly regulated, genes needed a calculated binominal probability of < 0.048, after normalisation for the median value of expressed genes. Further gene expression analyses were carried out using Northern blotting.
Results: Out of a total of 1176, we found that 641 genes were expressed. Twenty-three genes were consistently and significantly upregulated and thirteen downregulated in failing myocardium. Five genes were only expressed in the failing myocardium. Syndecan-3, a transmembranous heparan sulphate, was found to be upregulated together with its transcriptional activator, Wilms tumor protein 1. Based on these findings we hypothesized that also the other three members of the syndecan family are regulated during cardiac remodeling. Northern blotting showed a 124 ± 45% upregulation of syndecan-1, 46 ± 17% upregulation of syndecan-2, 45 ± 16% upregulation of syndecan-3 and 30 ± 9% upregulation of syndecan-4 following myocardial infarction. All four syndecans have been identified in fibroblasts, and syndecan-4 has been demonstrated in cardiomyocytes. Syndecan-4 has been shown to activate PKC-alpha, which is known to be involved in cardiomyocyte growth. Furthermore, the syndecans bind cytoskeletal actin filaments to extracellular matrix components like collagen and fibronectin, and serve as co-receptors for basic fibroblast growth factor (bFGF). Northern blotting also showed an upregulation of fibronectin and bFGF receptor 1 following myocardial infarction.
Conclusions: Since the syndecans link the cytoskeleton to the extracellular matrix and activate intracellular signal regulators involved in cardiomyocyte growth, we suggest a role for all four syndecans in remodeling of the myocardium after myocardial infarction.

P420 Lipopolysaccharides inhibit the angiotensin II-induced proliferation and migration of cardiac fibroblasts via induction of mitogen-activated protein kinase phosphatases

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Activation of ERK1/2- and p38 pathways by angiotensin II (Ang II) plays an important role in cardiac fibrosis. Activity of MAP-kinases is closely controlled by the recently identified group of dual-specific MAP kinase phosphatases (MKPs). Bacterial endotoxins (lipopolysaccharides; LPS) and cytokines are elevated in patients with chronic heart failure and may contribute to disease progression. While some cytokines have been shown to synergistically interact with Ang II to increase cardiac fibroblast (CFB) proliferation/migration, little is known about the potential crosstalk of LPS and Ang II. In the present study, we investigate the effect of LPS on Ang II-induced (1 μmol/L) CFB proliferation and migration. Pretreatment of CFBs with LPS (60 min; 1 μg/mL) inhibited Ang II-induced proliferation (BrdU-assay) by 40% ($p<0.05$). Furthermore, Ang II directed chemotaxis was inhibited by pretreatment (60 min.) of CFBs with 1 μg/mL LPS by 70% ($p<0.05$ vs. controls). To identify the signaling pathways involved, CFBs were pretreated (60 min.) with 1 μg/mL LPS followed by stimulation with Ang II (1μmol/L). Compared to controls, LPS significantly reduced phosphorylation levels of ERK1/2- and p38 kinases (70%, both $p<0.05$), whereas it had no effect on Ang II-induced p70S6-kinase levels. Phosphorylation of MAPK by LPS alone occurred only concentrations $>$ 1 μg/mL, whereas a strong induction of MKP-1 expression was found in CFBs with 1 μg/mL LPS (max. at 60-90 min; both $p<0.05$ vs. controls). Silencing MKP-1 levels with antisense oligonucleotides (1 μmol/L) almost completely reversed the antimitogenic effect of LPS on Ang II-induced CFBs proliferation and migration close to Ang II-stimulated levels (both $p<0.05$ vs. controls). In conclusion, our data demonstrate that lipopolysaccharides have direct cellular effects in cardiac fibroblasts and inhibit Ang II-induced fibroblast proliferation and migration via induction of MKP-1, thereby controlling MAPK-levels.

P421 Differences in serum profiles of matrix metalloproteinases between diabetic and non-diabetic patients with mild left-ventricular dysfunction

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Introduction: Extracellular matrix degradation by metalloproteinases plays a pivotal role in the pathophysiology of adverse left ventricular (LV) remodeling characterizing the progression of chronic heart failure (CHF). This study investigates the differences in serum levels of representative matrix metalloproteinases (MMP-1,-2,-3) between diabetic and non-diabetic patients with CHF symptoms and mild LV dysfunction.
Methods: Serum MMP-1,-2,-3 were measured (ELISA method) in 16 diabetic patients with CHF (NYHA II-III, mean age: 72$\pm$5 years, LVEF: 42$\pm$7%, HbA1c$>$6,5%), in 24 non-diabetic patients with CHF (NYHA II-III, mean age: 75$\pm$7 years, LVEF 41$\pm$5%), and in 22 age- and sex-matched healthy controls. Values are expressed as medians and interquartitile ranges.
Results: We observed that serum MMP-2 and MMP-3 levels in both patient groups were significantly higher than those of control group ($p<0.05$). In contrast, serum MMP-1 did not significantly differ among the three studied groups. Additionally, we observed significantly lower levels of MMP-2 (298 ng/ml, 237-353 ng/ml, p=0.006) and MMP-3 (18.7 ng/ml, 13.6-25.3 ng/ml, p=0.027) in diabetic patients with mild LV dysfunction as compared to respective non-diabetic patients (MMP-2: 395 ng/ml, 316-485 ng/ml; MMP-3: 26.5 ng/ml, 16.8-43.4 ng/ml). Finally, there were no significant differences in serum MMP-1 between diabetic patients (6.5 ng/ml, 3.8-10.1 ng/ml) and non-diabetic patients with mild LV dysfunction (4.2 ng/ml, 3.4-6.7 ng/ml, p=0.141).
Conclusions: Diabetes mellitus affects significantly serum profiles of matrix metalloproteinases MMP-2 and -3 in patients with CHF symptoms and mild LV dysfunction. Our findings suggest that abnormal circulating metalloproteinase activity may play a significant role in the pathophysiology of CHF in diabetic patients.

P422 Antimycin A preconditions in a murine langendorff model in a free radical dependent manner but independent of MAPkinase kinase 3 (MKK3)

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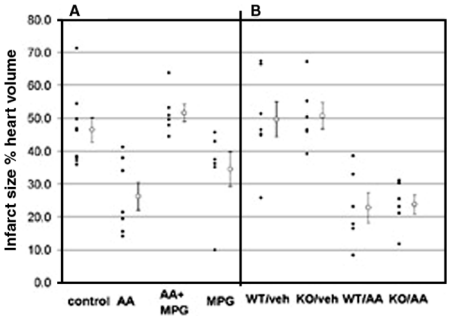
Aim: To show that AA can precondition in the murine langendorff model, to investigate the interaction with MKK3, an upstream kinase of p38 MAPkinase.
Methods: Isolated hearts were Langendorff-perfused and subjected to 30 mins global ischaemia and 2 hours reperfusion prior to infarct size determination using TTC (triphenyltetrazolium). To confirm free radical release from mitochondria by AA, isolated rat cardiocytes were treated with 0.1μg/ml AA and chemiluminescene measured as marker of superoxide production following lucigenin admistration. Untreated cells acted as controls. FCCP (Trifluorocarbonylcyanide Phenylhydrazone), an oxidative phosphorylation uncoupler was added to establish a mitochondrial role for the free radical production.Western blotting probing for p38 activation in AA treated Langendorff perfused hearts was performed.
Results: Infarct size was reduced significantly in the AA treated group 0.1μg/ml (3min infusion,10min washout) compared with control(26$\pm$4 vs 46$\pm$3 $p<0.05$). This protection was abolished by AA bracketed with MPG (200μM) (51$\pm$2 vs (control) 46$\pm$3). The MKK3 wild-type(WT) and knockouts (KO) treated with AA both had a reduction in infarct size compared to vehicle only,(MKK3KO/Vehicle 49$\pm$5, MKK3WT/Vehicle 50$\pm$4 vs MKK3KO/AA 22$\pm$4, MKK3WT/AA 23$\pm$2$p<0.05$). Panel A shows AA protects via a free radical mechanism. Panel B shows this effect is MKK3 independent in the downstream signalling pathway. The chemilumenscence signal was greater in the antimycin A treated cells than contols and the signal in all groups was decreased by FCCP. AA phosphorylated p38 similarily in WT/KO.



Free radical dependent-MKK3 independent.

Conclusion: Antimycin A preconditions murine hearts. Its mechanism of action does not involve MKK3/p38,however there may be a mitochondrial free radical basis.

P423 Myocardial effects of ghrelin and expression of its receptors in the progression to right-ventricular failure

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Ghrelin is an endogenous ligand of the growth-hormone secretagoge receptor (GHSR). Previous studies failed to differentiate ghrelin's direct myocardial action from its indirect effects, mediated by secretion of growth-hormone and vasodilation. This study evaluated direct myocardial effects of Ghrelin and expression of its receptors in normal and hypertrophied right ventricles (RV), due to monocrotaline (MCT) induced pulmonary hypertension. Forty Wistar rats were randomly assigned to receive 60 mg/kg sc of MCT (n=15) or a similar volume of the vehicle (Ctrl group; n=25). Three weeks later RV hemodynamics were studied with a tip micromanometer. RV papillary muscles (Ctrl, n=28; MCT, n=12) were then excised and mounted on vertical bath (modified Tyrodes; 1Hz; 1.25mM Ca^{2+}; 35°C). Effects of graded concentrations (1, 10, 100, 1000 nM) of a pentapeptidic active fragment of ghrelin (fG) were then tested. In two subsets of Ctrl group muscles, fG was added in the presence of indomethacin (indo, 10 μM; n=10) and NG-Nitro-L-arginin (L-NA, 90 μM; n=5). Parameters presented in percentage change from baseline: active tension (AT), maximum rates of tension rise and decline (dT/dtmax and dT/dtmin, respectively), peak shortening (PS) and maximal velocity of shortening (dL/dtmax). In 16 rats GHSR gene expression (concentration of mRNA, no. molecules/ng total mRNA) was estimated using reverse transcription real-time polymerase chain reaction (RT-PCR), in RV transmural free-wall samples (Ctrl, n=7; MCT, n=9). Results expressed as mean$\pm$SEM ($p<0.05$). When compared with Ctrl, the MCT group revealed higher systolic RV pressures (48$\pm$2 vs. 25$\pm$2 mmHg) and dP/dtmax (1602$\pm$91 vs 1228$\pm$67 mmHg/s). In the papillary muscles, fG induced a dose dependent negative inotropic effect maximum at 1000 nM. This effect was similar in Ctrl and MCT groups and was not significantly modified by indo or L-NA. For instance, in Ctrl muscles, in the absence of indo or L-NA, fG decreased 20.3$\pm$7.7% AT, 21.5$\pm$8.1% dT/dtmax, 21.1$\pm$9.9% PS and 23.5$\pm$8.1% dL/dtmax, without affecting dT/dtmin. GHSR mRNA levels were identical between these groups (2.3*10e5$\pm$5.4$*$10e4 vs 3.0$*$10e5$\pm$1.1$*$10e5). Ghrelin exerts a direct negative inotropic effect, independent of its growth-hormone secretagoge potential and most likely not mediated by PGI2 or NO. Its negative inotropic effect and respective subcellular mechanisms are apparently preserved in the progression for RV failure, which is supported by the maintenance of the biological response and level of gene expression of its receptors in RV hypertrophy.

P424 Induction of c-jun mRNA in end-stage human heart failure

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Background: The product of the proto-oncogene c-jun plays a critical role in cell growth and apoptosis in a number of cell types including cardiac myocytes. Apoptosis and cell growth are implicated in the progression of end-stage human heart failure as part of the remodeling process.
Methods and Results: To identify a link between the expression of c-jun and end-stage human heart failure, we used sensitive quantitative RT-PCR analysis to measure c-jun transcript levels in the myocardium of normal donors excluded from heart transplantation and in patients with idiopathic dilated and ischemic cardiomyopathy undergoing cardiac transplantation. In dilated but not in ischemic cardiomyopathy, c-jun transcript levels were approximately six-fold higher than in non-failing hearts (37.05 pg/mg RNA±5.9 versus 6.55 pg/mg RNA±0.48). Significant differences could not be detected in c-jun expression between the four chambers in patients with either dilated or ischemic cardiomyopathy.
These results were confirmed by Western blot analysis of c-Jun protein. Data obtained by gel mobility shift assays showed that AP-1 binding activity to its consensus site was significantly higher in dilated cardiomyopathy than in either non-failing hearts or ischemic cardiomyopathy.
Conclusion: Consistent with animal experiments, these results suggest that c-jun may play an important role in the progression of dilated cardiomyopathy, possibly by modulating rates of apoptosis.

P425 Tumour necrosis factor-alpha and interleukin-6 in diastolic heart failure

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Background: Nowadays, the role of cytokines, specifically of Tumor Necrosis Factor-α (TNFα) and Interleukin-6 (IL6) in pathogenesis of the systolic heart failure(HF) has been well studied. But their role in the development of the diastolic HF and association with functional class of such patients has not been researched.
Methods: We had examined 26 patients (60,2±3,21 years old, 19 males, 7 females). All of them had an diastolic HF (NYHA functional class II-IV, ejection fraction of the left ventricle(LV)>45%) due to arterial hypertension and/or because of chronic ischemic heart disease. The control group was consisted of 10 healthy persons. All of them were subject to echocardiographic study. There were determined commonly used parameters of systolic and diastolic (later-after Doppler parameters of transmitral blood flow) function of the LV, thickness of the interventricular septum (IVS), and posterior wall of the LV (PWLV), end-diastolic size of the LV (EDSLV) and left atrial (LA) volume after Simpson method from apical four-chamber view. Serum levels of the TNFα and IL6 were measured with highly sensitive enzyme-linked immunosorbent assay.
Results: The TNFα and IL6 levels were significantly higher in the group of diastolic HF, in comparison to the control group (347.1±65.5 and 15.8±1.9 pg/ml versus 100.8±51.9 and 7±1.4 pg/ml respectively; $p<0.05$). TNFα and IL6 levels in groups with impaired LV relaxation (219.6±39.7 pg/ml and 14.5±2.2 pg/ml respectively; n=20), and restriction/pseudonormalization (772.3±161.5 and 20±3.2 pg/ml respectively; n=6) were significantly higher than in control group ($p<0.05$). TNFα level was significantly higher in restriction/pseudonormalization group than in the group with impaired relaxation ($p<0.05$), while according to the IL6 level these groups were not considerably different. TNFα level was significantly higher in the group with NYHA class III-IV (519.8±114.6 pg/ml;n=12) in comparison to the group with NYHA class II (199.1±46.6 pg/ml;n=14) ($p<0.05$). IL6 level in these groups was not significantly different (18.3±3.1 pg/ml versus 13.6±2.1 pg/ml). Only LA volume was in strong correlation with TNFα level (r=0.61; $p<0.05$). No association was determined between TNFα level and IVS or PWLV thickness, EDSLV. IL6 level had not correlated with any of the mentioned parameters.
Conclusions: In diastolic HF serum levels of the TNFα and IL6 are elevated. The level of TNFα elevation is in direct correlation with the severity of the HF according to the NYHA classification, LV diastolic dysfunction level and LA volume.

P426 Decreased Ca^{2+}-dependent binding of sorcin to annexin VII and Ca^{2+}-release channel in human failing myocardium

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Modulation of sarcoplasmic reticulum (SR) Ca^{2+} release has been shown for the penta EF hand protein Sorcin (SOR). In rat myocardium, Sorcin binds to the Ca^{2+}-release channel ryanodine receptor (RYR) and the sarcolemmal protein Annexin VII (ANX). Thereby, binding of SOR alters the intracellular Ca^{2+}-relase kinetics.
Currently it is unkown whether the expression and binding of SOR to ANX or RYR is altered in human failing myocardium. Thus, we tested the expression of SOR utilizing immunoblotting in human failing myocardium (dilated cardiomyopathy, DCM, NYHA IV, n=10) and compared to nonfailing hearts (NF, donor hearts, n=10). Furthermore, the binding of SOR to RYR and ANX was examined using immunoprecipitation (IP), Ca^{2+}-dependent incubation and radioligand binding of 3H-ryanodine after incubation with recombinant SOR in homogenates and SR membrane preparations of NF and DCM.
SOR expression was significantly ($p<0.05$) reduced by 35±9% and 25±6% (utilizing IP with SOR) in DCM vs. NF, while total ANX expression and RYR expression remained unchanged. Furthermore, binding of SOR to ANX utilizing IP revealed a diminished SOR binding of 38±10% in DCM compared to NF. Increasing Ca^{2+}-concentration attenuated the diminished binding of SOR to ANX in DCM and was maximal at systolic Ca^{2+} of 10 μmol/l. Incubation with recombinant SOR resulted in a significant inhibition of 3H-ryanodine binding in NF vs. DCM (43±9 vs. 22±4%). Thus, DCM was less susceptible to inhibition of SOR.
These finding suggest a decreased expression of SOR, diminished distribution of SOR and altered modulation of RYA by SOR in human failing myocardium. Therefore, altered SOR availability may contribute to the disturbed Ca^{2+}-homeostasis and diminished systolic and diastolic excitation contraction coupling in failing myocardium.

P427 The activity of the sarcolemmal Na pump determines the functional consequence of adenoviral Na/Ca exchanger overexpression

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Objectives: The functional consequences of Na/Ca exchanger (NCX) overexpression in heart failure have been controversially discussed and may depend on the activity of the sarcolemmal sodium pump.
Methods and Results: We investigated the Na/K-ATPase (NKA) inhibitor ouabain (0.5-16 μmol/L) in electrically stimulated, isotonically contracting adult rabbit cardiocytes overexpressing NCX after adenoviral gene transfer (Ad-NCX-GFP, 48h culture time). Myocytes transfected with adenoviruses encoding for green fluorescent protein (Ad-GFP) served as a control. NCX overexpression was verified by Western-Blots and RT-PCR. Contractions were analyzed by video-edge detection. In the Ad-NCX-GFP group, the maximum inotropic response was significantly reduced by 50.7% ($p<0.05$). This was a result of an enhanced susceptibility to contracture after exposure to the drug (median concentration to achieve contracture (25-75%): 4 (4-8) vs. 8 (6-16) μmol/L, $p<0.05$). When analyzing relaxation before contracture, the maximum relaxation velocity was reduced (0.15±0.04 vs. 0.27±0.04 μm/s, $p<0.05$) and the time from peak shortening to 90% of relaxation was increased (298±39 vs. 185±15ms, $p<0.05$). No differences in systolic and diastolic parameters were observed with the sodium channel modulator BDF9198 (1 μmol/L).
Conclusions: Inhibition of NKA by ouabain induces a combined diastolic and systolic dysfunction in NCX overexpressing rabbit myocytes. This may be the consequence of cytoplasmic Ca overload due to inhibition of forward mode or induction of reverse mode Na/Ca exchange. In end-stage failing human myocardium and during digitalis treatment this mechanism may be of major importance.

OLD AND NEW PROGNOSTIC MARKERS IN HEART FAILURE

P428 Body mass index has an inverse relationship to prognosis in patients with heart failure: data from the IN-CHF registry

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Purpose In community based samples obesity resulted as an independent risk factor of heart failure (HF). However, in HF patients, obesity was not associated with increased mortality, but with a more favorable outcome. Since prevalence and prognostic role of BMI in HF is not yet completely defined, we assessed this issue in the 8622 patients enrolled in a community based registry, the Italian Network on congestive HF (IN-CHF).
Methods Patients were stratified in 4 different BMI groups: Underweight: =<22; Normal: 22-24.9; Overweight: 25-29.9; Obese: ≥30. Univariate and multivariate analysis were performed to assess the prognostic significance of the different BMI strata on total mortality at 12 months.
Results The Table reports the rate of patients in the different BMI strata, their 12 month all-cause mortality and the adjusted RR of death with the 95% confidence intervals.
Underweight patients are more severely compromised than the other categories of patients being older, with more advanced NHYA class, lower SBP, higher HR, lower EF%, higher creatinine levels and more frequent anemia. All cause mortality was inversely related with the BMI level. Adjusted analysis confirmed underweight to be independently associated with a 30% higher risk of all-cause death.

BMI	≤22	22-24.9	25-29.9	≥30	
% of pts	15.2	28.4	42.7	13.7	
% of deaths	17.6	12.4	9.3	7.3	<0.0001
Adjusted RR	1.30	1	0.80	0.66	
95%CI	1.09-1.55		0.68-0.93	0.52-0.84	

Conclusions This analysis of the IN-CHF Registry confirms that BMI has an inverse relationship to prognosis in patients with HF. Further studies are needed to target the nutritional and pharmacologic approach to patients with HF.

P429 Incremental prognostic significance of serial clinical/instrumental assessments in chronic heart failure

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Background: In chronic heart failure (CHF), it is not known whether analysis of serial changes in prognostic parameters provides incremental information with respect to comprehensive isolated clinical and instrumental assessments.
Methods: We analyzed time-related changes over a period ≥6 months in a broad panel of clinical, and instrumental (electrocardiographic, echocardiographic, hemodynamic and cardiopulmonary) parameters in 105 CHF patients (age 53±10 years, 88% male, 55% NYHA III-IV, EF 24±6%).
Results: Among the time-related parameters, QRS widening (adjusted RR per 10 msec, 1.21; 95%CI, 1.10-1.48; P=0.003) and peak oxygen uptake (pVO2) decrease (adjusted RR per ml/kg/min, 1.11; 95%CI, 1.01-1.22; P=0.034) provided independent, incremental information for predicting cardiac death/need for heart transplantation (CD/HT) with respect to the entire panel of isolated readings. CD/HT free-survival after 12 months was overall 60±5%. Clinically stable patients who presented QRS widening and pVO2 decrease values of <10% showed a better CD/HT event-free survival at one year (92±5% vs. 50±6%, P<0.001).
Conclusions: The present study indicates that analysis of time-related changes in prognostic parameters provides relevant incremental prognostic information and may help risk stratification of CHF patients and selection of HT candidates. In particular, clinically stable patients who show QRS widening and pVO2 decreases of less than 10% over a period ≥6 months appear to be characterized by a good prognosis and may not be suitable candidates for HT.

P430 Renal function as a predictor of mortality in patients admitted for decompensated heart failure

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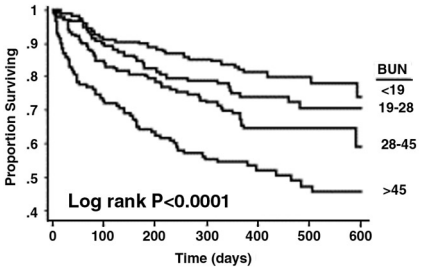
Background: Hospitalization for decompensated heart failure (HF) is associated with a high mortality after discharge. Renal function integrates both cardiovascular and hemodynamic properties. We studied whether renal function is a predictor of mortality in patients admitted for decompensated HF.
Methods: The prognostic significance of renal function was evaluated in 560 patients (mean age 63 ± 14 years, 377 male) with a previous diagnosis of HF (96% with NYHA class III or IV) who were admitted for decompensated HF. Four parameters of renal function were studied: blood urea nitrogen (BUN), creatinine, BUN/creatinine ratio, and creatinine clearance.
Results: During a mean follow-up of 343 ± 185 days, 177 patients (32%) died. The relation between measures of renal function and mortality was evaluated in a Cox proportional-hazards model, adjusting for age, gender, diabetes, primary etiology of HF stratified as ischemic or nonischemic, sodium, and medical therapy (ACE inhibitors, b-blockers, digoxin, and amiodarone). Elevated BUN was strongly associated with mortality. The risk of death increased continuously with each quartile of BUN (Figure), with an adjusted relative risk of 3.4 3-fold increase in mortality in patients in the upper compared to the lower quartile of BUN (95% CI 2.0-6.0, p < 0.0001). Creatinine and creatinine clearance were not significant predictors of mortality after adjustment for other covariates. BUN/creatinine ration gave similar information as BUN.



KM curve according to BUN category.

Conclusion: Renal function is a powerful predictor of mortality in patients admitted for decompensated HF. BUN appears to be the most powerful predictor of post-discharge outcome.

P431 New predictors of in-patient mortality following emergency heart failure hospitalization

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Introduction: Most predictors of clinical outcome in heart failure (HF) have been derived from clinical trials which enrolled only patients with reduced left ventricular systolic function (LVSF). We have studied the characteristics associated with survival in "real-life", hospitalised HF patients, including those with preserved LVSF. We examined the effect of haematological and biochemical measures of recent interest, as well as the effect of concomitant treatment.
Methods: The predictors of in-hospital case-fatality were determined, by multivariate analysis, in all 528 emergency admissions with heart failure to one acute urban University hospital during the year 2000. Echocardiography was undertaken by a single operator. Reduced LVSF was defined as an ejection fraction of <35%.
Results: The average age of patients was 72 (SD 13) years, 50% were male and 88% survived to discharge. 80% had an echocardiogram, 30% of whom had preserved LVSF. The in-patient (IP) case fatality rate was also comparable between those who had preserved or reduced LVSF
On multiple forward step-wise regression analysis, the probability of being alive at discharge was increased by treatment with an ACE inhibitor (odds ratio (OR) 11; 95% CI 0.9,137, P=0.06). Survival was also better in patients with a higher haemoglobin [Hb] (OR 2.8 per SD(2.0 g/dL); 95% CI 1.0-7.9, P=0.05), or a higher glomerular filtration rate (OR 4.8 per SD (52 mL/min/1.73m/2); 95% CI 1,24, P=0.05). Factors associated with a reduced chance of survival included an elevated C-reactive protein concentration (OR 0.2 per SD (61 g/dL); 95% CI 0.1,0.6, P=0.001) or aspartate transaminase level (OR 0.06 per SD (279 u/L); 95% CI 0.005, 0.63, P=0.056), or anti-biotic therapy (OR 0.87 95% CI 0.008, 0.891, P=0.04).
Conclusion: This study has identified two new markers of a better short term prognosis i.e. GFR and Hb concentration. The potentially protective effects of a higher GFR and Hb merit prospective investigation in heart failure.

P432 Prognostic value of hyponatremia in hospitalized patients with heart failure – insights from the outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure

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Purpose: In a post-hoc analysis we thought to describe the incidence of hyponatremia and its impact on mortality and rehospitalizations in hospitalized patients (pts.) with heart failure (HF) enrolled in the OPTIME-CHF trial.
Methods: The OPTIME-CHF trial randomized 949 pts. with systolic dysfunction hospitalized for worsening HF and not requiring intravenous inotropic support to receive 48-72 hours of intravenous milrinone or placebo. Cox proportional hazards regression analysis was used to explore the relationship between baseline hyponatremia (Na≤136 mEq/l) and mortality at sixty days. Logistic regression was used to examine hyponatremia and rehospitalization or death at 60 days.
Results: There were 256 pts. with Na≤136 mEq/l and 687 pts. with Na>136 mEq/l. The results are showed in the table.

Variable	Baseline Na≤136 mEq/l 256 pts. (27%)	Baseline Na>136 mEq/l 687 pts. (73%)	p value
Age (years) *	67 (53, 76)	68 (57, 76)	0.669
Male sex (%)	68	66	0.577
Ischemic etiology of HF (%)	55	50	0.18
NYHA Class III-IV (%)	96	92	0.047
Elevated JVP (%)	72	66	0.1157
Pulmonary rales (%)	83	81	0.444
Baseline HR (bpm)*	84 (72, 96)	84 (72, 96)	0.5654
Baseline SBP (mmHg) *	114 (100, 130)	121 (108, 135)	0.0001
Baseline DBP (mm Hg) *	70 (60, 78)	70 (62, 80)	0.015
Baseline BUN (mg/dl) *	11.8 (7.1, 17.5)	8.6 (6.1, 13.2)	0.0001
Baseline Cr (mg/dl) *	1.4 (1.1, 1.8)	1.3 (1.1, 1.7)	0.0172
Mortality at 60 days (%)	16%	7%	0.0001**
Rehospitalizations/death at 60 days (%)	42%	33%	0.017

* Median, 25th, 75th** Log-rank statistic

Conclusions: Hyponatremia (Na≤136 mEq/l) is common in hospitalized pts. with worsening HF. After adjusting for baseline variables, the Cox regression analysis showed that baseline Na, when modeled linearly, predicts an increased mortality at sixty days: Na (per 5 mEq/l) has a Hazard Ratio of 0.75 with 95% CI 0.6-0.95, p=0.018. Future treatments aimed at normalizing serum sodium might improve the survival and should be evaluated in randomized trials.

P433 Prognostic value of aldosterone in heart failure. Results from Val-HeFT

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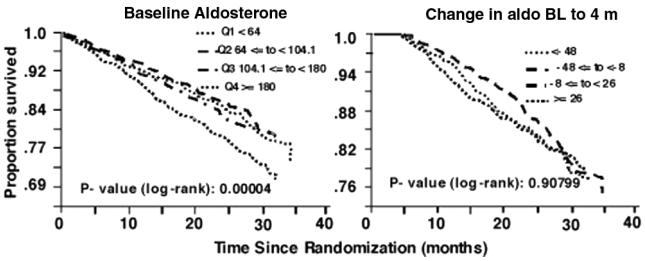
Background: Plasma aldosterone (aldo) is increased in patients with heart failure (HF) and may cause disease progression. Whereas aldosterone receptor blockade with spironolactone has been shown to improve mortality, it is unclear whether baseline (BL) aldo or change in aldo from BL over time relates to mortality. Val-HeFT (Valsartan Heart Failure Trial) provided an opportunity to examine this relationship.
Methods: Plasma aldo (pg/mL) was measured by radioimmunoassay in core labs at BL and during follow-up in over 4000 patients. Cox proportional hazard analyses were made for all-cause mortality with BL aldo classification by median (> or < 104.1 pg/mL) and quartile (Q) groupings used as independent variables in separate analyses. A similar analysis was also made with change in aldo from BL to 4 months in Q for subsequent mortality.
Results: There was an association between aldo > vs < median and mortality (21.1% vs 17.1%, RR 1.284, 95% CI, 1.114 - 1.480, p=0.0006). In the analysis by BL aldo quartile, a uniform Q dependent increase in mortality was not seen. Mortality was similar for Q1, Q2, and Q3, but was significantly higher for patients in Q4. No direct relation between change in aldo from BL to 4 m in Q and mortality was observed.
Conclusions: Only high levels of aldosterone appear to have a significant prognostic relation with mortality in heart failure, and changes in aldo over time are not related to prognosis.



Mortality and aldosterone levels.

P434 Incremental prognostic power of combined triiodothyronine concentration and left-ventricular function assessment in the risk stratification of patients with congestive heart failure

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Background: A decrease in triiodothyroinine (T3) levels has been reported in patients (pts) with dilated cardiomyopathy (DC). Aim of the study was to assess the incremental prognostic effect of an altered triiodothyronine (T3) state over the clinical and functional parameters in a long-term follow-up of pts with DC (LVEF <0.45). **Methods:** 263 consecutive inpts with post-ischemic (PI, n=143) or non ischemic (NI, n=120) DC underwent thyroid evaluation. Patients were followed for 14 months (median) and subdivided in two groups according to the endpoint mortality: Group I, dead pts (n=69; 71 years); Group II, alive pts (n=204; 68 years). **Results:** The two groups differed for LVEF (Group I: 26.2±7.9 vs Group II; 30.8±7.9, p=0.0001), Total T3 (TT3) (Group I: 72, 48, 89 ng/dl vs Group II: 85, 71, 103 ng/dl, p=0.001), fT3 (Group I: 2.15, 1.30. 2.79 pg/ml vs Group II; 2.34, 1.97, 2.73 pg/ml, p=0.037) and NYHA class (Group I: 2.88±1.42 vs Group II: 2.20±1.70, p=0.002). At logistic univariate analysis, TT3 was the strongest predictor of mortality (R= -0.270, p=0.0001), followed by LVEF (R= -0.207, p<0.0001) and both they were the only independent variables at multivariate analysis (LVEF: R= -0.159, p=0.0005; TT3: R= -0.178, p<0.0001). In pts with similar LVEF (0.25) the odds of death increased 4 times when TT3 reduced from 80 to 40 ng/dl. By combining LVEF and TT3 in an integrated prognostic index (IPI), this was different in the two groups (Group I: -0.95 vs Group II: -1.50, p=0.001). The area under the receiver operating characteristic curve (AUC) for IPI (0.759, p=0.0001) was higher than that of LVEF (AUC 0.65, p=0.008) and of TT3 (AUC 0.61, p=0.003).
Conclusions: T3 levels represent a powerful predictor of mortality in pts with PIDC and NIDC, also adding prognostic power to conventional cardiac parameters.

P435 Prognostic importance of elevated circulating levels of heart-type fatty acid binding protein in patients with congestive heart failure

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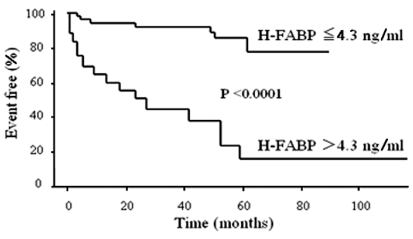
The heart-type fatty acid binding protein (H-FABP) is rapidly released from the damaged myocardium and is used as a biochemical marker of acute myocardial infarction. The purpose of the present study was to examine clinical significance and the prognostic value of serum levels of H-FABP in patients with congestive heart failure (CHF). Serum H-FABP levels were measured 99 patients with CHF, and patients were followed up with an end-point of cardiac death or re-hospitalization for 22±24 months (3-104 months). The serum H-FABP levels increased, as the severity of CHF advanced (control, NYHA I, II, III, and IV: 2.7±0.8, 3.2±1.7, 3.7±2.6, 6.6±3.5*, and 11.3±10.6**# ng/ml, respectively, *p <0.05 vs. control, **p <0.0001 vs. control, NYHA I, II, and #p <0.05 vs. NYHA III). The normal upper limit of H-FABP level was defined as mean + 2SD value of control subjects. Patients with abnormal H-FABP levels (>4.3 ng/ml) had higher age (p <0.0001) and higher plasma lactate dehydrogenase (LDH) levels (p <0.0001) than those with normal levels (≤4.3 ng/ml). Serum levels of H-FABP were positively correlated with creatine kinase MB (R = 0.365, p <0.05) and LDH (R = 0.439, p <0.0001). Patients with high H-FABP levels had lower cardiac event free rate than those with normal levels (p <0.0001). The Cox proportional hazard analysis revealed that high H-FABP level was the independent predictor (chi-square 10.813, p = 0.001).
These findings indicate that elevated levels of circulating H-FABP in patients with severe CHF may reflect the latent ongoing damage of cardiomyocytes. The serum levels of H-FABP can provide important prognostic information in patients with CHF and can be a new marker to predict patients' clinical outcome in CHF.



Cardiac event free rate in CHF patients.

P436 Independent and incremental prognostic value of aminoterminal propeptide of type III procollagen circulating levels in patients with chronic heart failure

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In patients with chronic heart failure (CHF), qualitative and quantitative changes in the extracellular space are responsible for altered organ function. We aimed to assess whether the measurement of PIIINP, a marker of extracellular matrix turnover, might provide incremental prognostic information independently of clinical status and hemodynamics in CHF patients. Methods: 101 consecutive CHF outpatients (mean age 61.7±8.7 years, 88% males) underwent a complete clinical evaluation, including hormonal assessment, exercise testing and an echocardiography and were followed-up for at least six months. The combined end-point of the study was death and hospitalization for heart failure. Results: during a median follow-up of 38.0±11.8 months, there were 15 deaths and 11 hospitalizations for worsening heart failure. At the survival analysis age (p=0.02), NYHA class (p=0.014), s-creatinine (p=0.014), s-PIIINP levels (p=0.005), LVEF (p=0.0002), and a restrictive mitral filling pattern (p=0.0003) predicted event-free survival. At the multivariate analysis, s-PIIINP levels predicted outcome independently of other clinical variables, hormones, echocardiographic and exercise testing variables ($p<0.05$ in all models). In patients with LVEF <31%, the presence of s-PIIINP>4.7 μg/L levels significantly increased the risk of death and hospitalization as compared with the other groups (event-free survival rate at 12 months: 45% versus 95%; at 24 months: 27% versus 88%; at 36 months: 18% versus 85%, $p<0.0001$). Conclusions: in patients with CHF, PIIINP levels predict outcome independently of clinical status, resting hemodynamics and hormonal activation. PIIINP levels provide incremental prognostic information to that of left ventricular function alone, suggesting a possible extracardiac role for this marker.

P437 N terminal B-type natriuretic peptide, but not the putative cardiac hormone relaxin, predicts adverse outcome in patients with chronic heart failure

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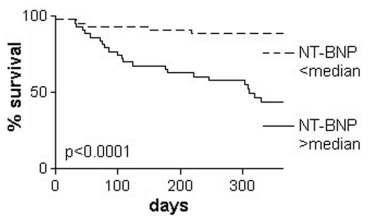
Background: Recently, relaxin, previously regarded as a hormone of parturition, has been found to be secreted by the failing heart. Systemic plasma concentrations are also increased in patients with chronic heart failure (CHF), in proportion to the severity of their condition. We have examined the prognostic importance of relaxin in CHF, comparing it to another cardiac peptide, N-Terminal B-type natriuretic peptide (NT-BNP).
Methods: Plasma relaxin and NT-BNP concentrations, using validated assays, were measured in 87 patients (51 male) admitted as an emergency with CHF due to left ventricular systolic dysfunction. These were related to death and death or readmission with CHF over the following year. The mean age of patients was 75 years.
Results: Plasma concentrations of both relaxin and NT-BNP were markedly elevated. Median plasma relaxin and NT-BNP concentrations were 89 and 2994 pg/ml, respectively (normal relaxin <2pg/ml; normal NT-BNP < 334 for women and <227 pg/ml for men). NT-BNP was a powerful predictor of adverse outcome. Of patients with NT-BNP above the group median concentration, 53% died and 70% died or were hospitalised with CHF. For those with concentrations below the median these proportions were 11% and 27%, respectively ($p<0.0001$ and $p<0.0001$, respectively). Plasma NT-BNP concentration remained an independent predictor of an adverse clinical outcome in a multivariate analysis. Of patients with a relaxin concentration above the median, 31% died and 48% died or were hospitalised, below the median, these proportions were 33% and 49% (p=0.76 and 0.84, respectively).



Time to death related to serum NT-BNP.

Conclusions: NT-BNP is a powerful and independent predictor of outcome in CHF whereas relaxin, also secreted by the heart in increased amounts in CHF, is not.

P438 Value of troponin I in the risk stratification of patients with heart failure

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The outcome of patients (pts.) with severe heart failure (HF) largely depends on the ongoing myocardial damage. Identification of HF pts. who are at increased risk of future deterioration would help in prognosis prediction and therapeutic decision. There are few data on troponin I (TnI) value as a marker of progressive myocardial injury in patients with advanced HF. We intended in our prospective study to assess the validity of TnI as a prognostic marker in patients with severe heart failure and we included 49 consecutive pts. (mean age 57 ± 12 yrs) with HF of NYHA III and IV class. The ischemic etiology was present in 66% of pts. and the mean left ventricular ejection fraction (EF) was 28% ± 3. The pts. were divided in two groups according to the presence of TnI: group A (25 pts.) had positive TnI at presentation (>0.06 ng/ml) and group B (24 pts.) had negative TnI. Both groups were similar regarding NYHA class, EF, gender repartition, etiology and associated conditions as diabetes mellitus, hypertension, atrial fibrillation or smoking. The exclusion criteria were acute coronary syndromes, pulmonary embolism, recent stroke and myocarditis. Pts. in group A had a worse quality of life as assessed by the LVD-36 questionnaire ($p< 0.05$) and were less treated. A greater number of group A pts. received small doses of ACEI or didn't receive ACEI at all than group B pts (75% vs. 41%, $p< 0.05$). Only 28% of group A pts. received beta blockers (vs. 50% in group B). The pts. in group A had higher levels of CRP and lower albumin and cholesterol than the pts. in group B. After a mean of 12 months follow-up 36% of group A pts. died compared with 13% in group B. The number and proportion of hospitalization for worsening HF was greater in group A than in group B ($p<0.03$). Also, the decrease in EF and the increase in left ventricular echografic dimensions were greater in group A pts ($p<0.05$).
Conclusion: Elevated TnI in pts. with advanced HF correlates with the clinical severity and with the amount of treatment. TnI could be a marker of poor prognosis in patients with severe HF pointing to progressive myocardial damage. TnI could help in the stratification of patients with advanced HF.

P439 Association of brachial reactivity with survival in patients at-risk of coronary disease

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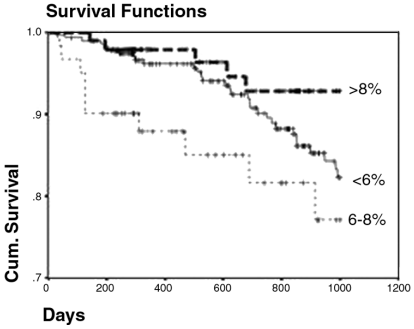
Objective: Impaired flow-mediated vasodilatation measured by brachial artery reactivity (BAR) is commonly used as a marker of impaired endothelial function. BAR is influenced by vascular risk factors and is responsive to various pharmacological and non-pharmacological treatments. However its long term prognostic importance is uncertain.
Methods: 444 pts were prospectively enrolled to undergo BAR and follow-up. These patients were "at-risk" for cardiovascular events based on the presence of risk factors, known or suspected vascular disease, or renal disease, and a full clinical history was obtained. Carotid intima-media thickness (IMT) was measured as a marker of atherosclerotic burden. Pts were followed up for all-cause mortality. Multivariate Cox regression analysis was performed to assess the independent effect of investigation variables on outcomes.
Results: This group of patients exhibited an abnormal mean BAR of 5.3±6.0%. Mean nitrate mediated dilatation was 9.7±9.0%. The average IMT was 0.68±0.12 mm. Forty-six deaths occurred over the median follow-up period of 740 days (interquartile range 307 to 1000 days). Patients in the lowest tertile group of BAR (<2%) had significantly more events then those in the combined group of highest and mid-tertiles (P= 0.035, log rank test). Pre-determined cut-offs demonstrated a trend towards different outcomes (Figure), with 95% survival in pts with BAR >8% ($p<0.01$ vs BAR 6-8%). However, the only independent predictor of an event was mean intima-media thickness.



Conclusion: Vascular function as assessed by BAR provides long term prognostic information for mortality.

IS BRAIN NATRIURETIC PEPTIDE A POWERFUL MARKER OF HEART FAILURE?

P440 The prognostic use of right heart catheter data in patients with advanced heart failure and its relevance in the modern era

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Purpose: Right heart catheterisation (RHC) has long been a routine investigation in advanced heart failure, and has been variably linked to prognosis. However, in the modern era, newer potential markers of prognosis are coming to light. This study reconsiders the use of RHC and compares it to that of NT-proBNP, a neurohormone linked with prognosis in milder forms of heart failure.
Methods: We retrospectively assessed the prognostic potential of baseline right heart catheter data in 97 consecutive patients with advanced heart failure referred to the Scottish Cardiopulmonary Transplant Unit for consideration of cardiac transplantation. As part of the assessment process, each patient underwent baseline right heart catheterisation including cardiac output estimated by the thermo-dilution technique. Patients were followed up for a median of 370 days.
Results: The primary endpoint of all-cause mortality was reached in 17 patients (17.5%) and the secondary endpoint of all-cause mortality or urgent CTx was reached in 21 (21.6%) patients. NT-proBNP concentrations correlated well with right atrial pressure (RAP), pulmonary artery systolic pressure (PASP) and pulmonary artery wedge pressure (PAWP). Univariate predictors of all-cause mortality included PASP (Odds ratio (OR)=4.1, p=0.02), PAWP (OR=2.7, p=0.05) and NT-proBNP (OR=4.2, p=0.01) above their median values and a left ventricular ejection fraction (LVEF) (OR=3.7, p=0.03) below its median value. Univariate predictors of the secondary endpoint included a RAP (OR=4.2, p=0.02), PASP (OR=6.0, p=0.001), PAWP (OR=4.0, p=0.01) and NT-proBNP (OR=6.2, p=0.001) above their median values, and a LVEF (OR=5.5, p=0.002) and cardiac index (OR=4.2, p=0.02) below their median values. In multivariate analyses, however, only NT-proBNP remained an independent predictor of both endpoints.
Conclusion: Despite the useful prognostic properties of right heart catheter data, NT-proBNP is a far superior and non-invasive method of risk stratification in advanced heart failure.

P441 Superiority of N terminal pro-brain natriuretic peptide over interleukin-6 as marker of left-ventricular dysfunction after myocardial infarction

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Activation of natriuretic peptides and cytokines are hallmarks of left ventricular (LV) dysfunction and congestive heart failure (CHF). In the current study, we assessed plasma N-terminal proBNP (NT-proBNP) and interleukin-6 (IL-6) in a head-to-head comparison as markers for LV dysfunction in a large group of patients in the chronic phase after myocardial infarction (MI). NT-proBNP and IL-6 were measured by non-extracted, enzyme-linked immunoassay in 1090 subjects (n=625 outpatients in the chronic phase after MI (MONICA MI register Augsburg; time after MI 1-10 years, mean 5.6) and 465 siblings without MI, control). LV ejection fraction (EF) and mass index (LVMI) were assessed by 2D-echocardiography (Simpson, Devereux, respectively).
NT-proBNP (96.6±13.7 pmol/l vs. control 31.2±1.8, $p<0.001$) and IL-6 (2.57±0.08 pg/ml vs. control 2.09±0.07, $p<0.001$) were both elevated in subjects with MI. These increases were particularly pronounced in the presence of concomitant CHF (NT-proBNP 132.2±38.0 pmol/l and IL-6 2.78±0.16 pg/ml, both $p<0.01$), LV dysfunction (EF<35%, NT-proBNP 182.8±41.9 pmol/l and IL-6 2.94±0.48 pg/ml, both $p<0.05$) and LV dysfunction with concomitant hypertrophy (NT-proBNP 272.6±77.6 pmol/l and IL-6 3.68±0.64 pg/ml, both $p<0.01$). NT-proBNP was highly significantly correlated with EF, LVMI, and history of MI in uni- and multivariate analysis (all $p<0.001$). In contrast, IL-6 was only correlated with LVMI and history of MI in multivariate analysis (both $p<0.001$), but not with EF (p=n.s.). Accordingly, MI subjects with concomitant LV dysfunction and hypertrophy were detected by NT-proBNP with a greater sensitivity, specificity, negative predictive value and ROC-area (90%, 79%, 99.9%, and 0.90, respectively at an optimal cutpoint of 76 pmol/L) as compared to IL-6 (63%, 76%, 99.6%, and 0.76, respectively at an optimal cutpoint of 2.9 pg/mL).
NT-proBNP and IL-6 are both significantly elevated in MI patients and increase further according to severity of LV dysfunction and presence of CHF. However, since NT-proBNP has a closer association with EF and superior predictive values as compared to IL-6, it may provide greater benefit as biochemical marker of LV dysfunction in these patients.

P442 N terminal brain natriuretic peptide versus brain natriuretic peptide for the diagnosis of heart failure in patients over 75 years old

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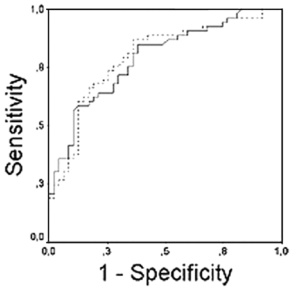
Backgrounds: BNP value is established for the diagnosis of dyspnea in the emergency room in standard population. However, data in elderly patients are scarce and relative diagnostic value of NT-proBNP and BNP have not been reported in this population where renal failure is more prevalent.
Methods: 103 consecutive patients over 75 y.o. who came to the emergency department for acute dyspnea were included. Plasma BNP (Biosite®) and NT-proBNP (Roche diagnostic®) were measured at admission along with other standard biological parameters, and clinical variables were noted. Reference diagnosis was adjudicated by 2 independant cardiologists using all available information at discharge.
Results: 61 were female, 42 were male, mean age was 84.9±6.2 years.
Final diagnosis was CHF in 46 patients (45%), pulmonary embolism in 6 (6%), pulmonary infection in 28 (27%). In 8(8%), dyspnea was considered of both pulmonary and cardiac origin. 21 patients were oriented in pneumology unit, 30 in the cardiology department, and 19 in internal medecine. 10 were not hospitalized, including 3 patients whose BNP was greater than 1300. Creatinin levels were 105 ± 40µmol/l(50-287), indicating frequent renal insufficiency.
However, area under ROC curve (figure) for BNP (continuous line) and NT-proBNP (broken line) as a diagnostic marker for heart failure were similar (0.79 CI:0.70-0.88) and (0.80 CI:0.71-0.89) respectively.



BNP level of 300 pg/ml has similar sensitivity and specificity that NT-proBNP level of 1500 pg/ml.
Conclusions: BNP and NT-proBNP appear to have similar diagnostic value in elderly patients despite the frequent renal failure in this population.

P443 Effects of carvedilol on plasma brain natriuretic peptide concentration and functional capacity in patients with isolated diastolic heart failure

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Background Carvedilol is now a standard regimen for patients with heart failure accompanying systolic dysfunction. However, The benefits of this therapy have not been elucidated in patients with diastolic heart failure.
Methods We enrolled consecutive 43 patients meeting the following criteria: left ventricular EF > 45% (measured with echocardiography using modified Simpson's method); plasma concentration of BNP > twice the normal upper limit (36.8 pg/mL); subjective symptom corresponding to NYHA functional class II or III; no significant primary valvular disease; without obvious contraindications for carvedilol. They were randomly assigned to carvedilol (21 individuals) or conventional therapy (22 individuals) and followed up for 12 to 15 months.
Results Dropout due to treatment failure occurred in one patients on carvedilol and two on conventional therapy. Plasma BNP concentration significantly reduced in patients on carvedilol (186.3 ± 157.7 pg/mL to 100.9 ± 66.3 pg/mL, $p < 0.01$) but not in those on conventional therapy (140.3 ± 68.5 pg/mL to 156.1 ± 119.0 pg/mL). NYHA functional class was also improved in patients on carvedilol (2.45 ± 0.51 to 1.91 ± 0.76, $p < 0.05$) but not in those on conventional therapy (2.10 ± 0.49 to 2.32 ± 0.78). Exercise capacity estimated using specific Activity Scale was increased in patients receiving carvedilol (4.14 ± 1.28 METs to 4.81 ± 1.25 METs, $p < 0.05$) while that was not changed in those on conventional therapy (4.45 ± 0.82 METs to 4.05 ± 1.46 METs). The amplitude of BNP decrease (deltaBNP) was negatively correlated with the heart/mediastinum MIBG uptake ratio of delayed image (dH/M) (delta BNP = 974.4 - 496.1 x dH/M, $p < 0.05$, R = 0.595).
Conclusions Carvedilol may be a treatment of choice for patients with diastolic heart failure. MIBG myocardial scintigraphy may predict the effects in plasma BNP concentration by carvedilol.

P444 mRNA gene expression for B-type and A-type natriuretic peptides is attenuated following chronic monotherapy with extended release metoprolol succinate

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Background: Plasma levels of B-type and A-type natriuretic peptides are elevated in heart failure (HF) and are predictive of poor outcome. Therapy with extended release metoprolol succinate (ER-MET) has been shown to reduce mortality and morbidity in patients with HF. We previously showed that monotherapy with ER-MET increases left ventricular (LV) ejection fraction and attenuates LV remodeling in dogs with chronic HF. In the present study, we examined the effects of monotherapy with ER-MET, a selective beta-1 receptor blocker, on mRNA gene expression of B-type and A-type natriuretic peptides in LV myocardium of dogs with chronic HF produced by multiple sequential intracoronary microembolizations.
Methods: Total RNA was isolated from LV tissue of 14 dogs with HF randomized to 3 months therapy with ER-MET (50 mg, once daily, n=7) or to no therapy at all (n=7) and from LV of 6 normal (NL) dogs. Using specific primers in reverse transcriptase-polymerase chain reaction (RT-PCR), B-type and A-type natriuretic peptides were identified on agarose-ethidium gel; corresponding fluorescent bands were quantified in densitometric units and normalized to glyceraldehyde-3 phosphate dehydrogenase (GAPDH), a housekeeping gene. The results are shown in the table.
Results: Expression of both B-type and A-type natriuretic peptides increased significantly in untreated HF dogs compared to NL. Treatment with ER-MET significantly reduced mRNA expression of both B-type and A-type natriuretic peptides compared to untreated HF dogs.

	NL	HF-Untreated	HF + ER-MET
B-Type/GAPDH	0.54 ± 0.02	1.60 ± 0.10*	0.64 ± 0.07**
A-type/GAPDH	0.48 ± 0.05	1.32 ± 0.03*	0.82 ± 0.03**

*=p<0.05 vs NL; **=p<0.05 vs HF-Untreated

Conclusions: The findings indicate that mRNA expression of both B-type and A-type natriuretic peptides are increased in LV myocardium of dogs with chronic HF. Monotherapy with ER-MET reduces mRNA expression of both B-type and A-type natriuretic peptides. These findings are consistent with the observed attenuation of LV remodeling and with reduced mortality and morbidity in patients with HF treated with ER-MET.

P445 Brain natriuretic peptide plasma levels is a better predictor of sudden death than heart rate variability in mild to moderate heart failure

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Risk stratification with regards to sudden death is of essential impact in chronic heart failure (CHF). BNP plasma levels and heart rate variability (HRV) indices have been shown to predict sudden death in CHF. The aim of this study is to improve the risk stratification using BNP plasma levels and HRV indices.
BNP levels in addition to other neurohormonal (atrial natriuretic peptide, ANP and endothelin, ET1), HRV and clinical variables were obtained from 188 ambulatory patients with mild to moderate heart failure (96% in NYHA class 2 or 3) in sinus rhythm with a left ventricular ejection fraction < 45%. HRV was measured during 24 hours, daytime (9:00 AM-9:00 PM) and nighttime (11:00 PM-6:00 AM) by the standard deviation of normal RR intervals (SDNN), high frequency power (HF): 0.16-0.40 Hz and low frequency power (LF): 0.04-0.15 Hz. HRV indices, clinical variables, BNP, ANP and ET1 plasma levels were related to sudden death by univariate and multivariate analysis (Cox).
During 673 ± 366 days of follow-up, 34 died (16 sudden deaths, 16 pump failure, 2 other causes) and 8 underwent heart transplantation (HTx) and were censored at the day of HTx. Univariate risk factors of sudden death were: NYHA class (p=0.04), SDNN during daytime (p=0.028), ANP levels (p=0.003), BNP levels (p=0.0001). In the multivariate model, the only independent predictor of sudden death was BNP plasma levels (p=0.0001).
BNP was therefore the best non invasive predictor of sudden death in mild to moderate heart failure, whereas SDNN did not add additional prognostic information in risk stratification.

P446 Normal plasma N terminal pro-brain natriuretic peptide levels predicts good short-term prognosis in patients with acute pulmonary embolism

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Objective: Plasma levels of NTproBNP can be helpful in the prognosis prediction of patients with left ventricular congestive heart failure. However, it is unknown if NTproBNP can also predict prognosis in acute pulmonary embolism (APE) frequently accompanied by acute RV dysfunction.
Material and Method: We evaluated 79 pts (28M, 51F, aged 63+16 years) with APE proven by high probability lung scintigraphy or spiral CT. On admission blood samples were collected for NTproBNP assay (Roche, ECLIA). 89% pts were anticoagulated, while 11% pts received also thrombolysis. Fifteen pts died during hospitalization, 24 pts experienced in hospital clinical serious adverse event (SAE) (at least one of: death, thrombolysis, cardiopulmonary resuscitation, intravenous use of catecholamines). On admission plasma NTpro BNP was above reference age and sex specific values (F<50rs <153pg/ml, F>50yrs 334pg/ml; M<50rs <88pg/ml, M>50 yrs 227pg/ml) in 66pts (83,5%). All deaths and SAEs occurred in pts with elevated NTproBNP, while all 13 (16,5%) pts with normal values had uncomplicated clinical course. Thus, normal values of plasma NTproBNP reached 100% NPV for in hospital mortality or complicated clinical course. However, PPV of elevated NTproBNP for death or SAE was only 22,7% and 36,3% respectively. Plasma NTproBNP concentration was significantly higher in survivors than in nonsurviors (median 1939 pg/ml (range: 16-27752) vs median 11491 pg/ml (range: 618-60958), p<0,001). They were also higher in patients with SAE than in pts with uncomplicated clinical course (median 9678 pg/ml (range: 414-60958) vs median 1553 pg/ml (range: 16-27752), p<0,001).
Conclusion: Plasma NTproBNP may be elevated in the majority of patients with acute pulmonary embolism. Normal values of plasma NTproBNP indicate good prognosis, while patients with complicated in hospital course, especially fatal, show elevated NTproBNP levels. Therefore plasma NTproBNP determination may be helpful in risk stratification in APE.

P447 Serum levels of the tumoral marker CA 125 are increased in heart failure patients and correlate with brain natriuretic peptide values

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Recent studies showed that serum levels of the carbohydratic antigen 125 (CA 125),a tumoral marker specifically related to ovarian cancer, are increased in patients(pts) with congestive heart failure(CHF, are related to the severity of clinical picture(expressed as NYHA class) and of hemodynamic abnormalities(i.e. pulmonary artery wedge pressure and right atrial pressure, are predictive of a poor prognosis and change in response to treatment. Aim of this study was to evaluate the relation between CA 125, as measured by a standard assay (Tumor Markers CA 125 AxSYM system, Abbott Laboratories) and brain natriuretic peptide (BNP)serum levels, as measured by a point-of-care method based (Triage,B-type natriuretic peptide test, Biosite Diagnostics),in 58 pts (33 males, 25 females, mean age 68±12 years) with mild-to severe CHF. Upper normal level of CA 125 is < 35 U/mL and of BNP < 100 pg/mL.
Results (see the table): 20 pts were in NYHA class I-II, 15 pts in NYHA class III and 23 pts in NYHA IV; mean value of left ventricular ejection fraction was 24±10%.
A significant inverse correlation was found between the deceleration time of early filling on pulsed Doppler transmitral flow (an indirect measure of left atrial pressure) and serum levels of BNP(r =-0.83,p<0.05) and CA 125 (r= -0.61, p<0.05). There was also a significant relation between BNP and CA 125 serum levels (r= 0.74,p<0.05). In 14 pts BNP and CA 125 were repeated after 5-10 days of aggressive drug therapy with clinical improvement (reduction of at least 1 NYHA Class): BNP levels decreased from 782±361 to 324±300 pg/ml (-58%, p<0.05) and CA 125 levels decreased from 79±37 to 36±23 U/mL (-54%, p<0.05).

	ALL PTS	NYHA I-II	NYHA III	NYHA IV	
BNP (pg/ml)	754 ± 447	229 ± 154	792 ± 222	1120 ± 150	p< 0.05
CA 125 (U/mL)	114 ± 93	28 ± 13	82 ± 39	200 ± 114	p< 0.05

Conclusions: CA 125 serum levels are increased in pts with moderate to severe CHF and significantly correlate with the Doppler measure of left atrial pressure and BNP serum levels. Furthermore, CA 125 changes observed after effective medical treatment paralleled those of BNP. Further studies are needed to clarify the pathophysiological link between BNP and CA 125.

P448 Age/gender-specific referenced high plasma brain natriuretic peptide is a marker for subjects with high risk of heart failure in the general population

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Background: Plasma B-type natriuretic peptide (BNP) measurement is suggested as a useful test for screening for cardiovascular disease. However, the reference value and validity of BNP testing and the precipitating factors leading to abnormal plasma BNP levels are unknown in the general population.
Methods: We have measured plasma BNP concentrations in 4,296 participants (mean 63.6±10.6 yrs, male 1456, female 2840) in northern Iwate area in Japan. For reference value determination, subjects having ECG abnormalities (atrial fibrillation, left-bundle-branch-block), hypertension (≥140 or 90 mm Hg), diabetes, ongoing cardiovascular medication or a history including stroke, symptoms of cardiovascular disease (edema, shortness of breath) were excluded. The remaining 1,498 subjects were eligible for the reference study.
Results: Among the reference subjects, mean plasma BNP increased with to age, and was elevated in female (both $p<0.01$). To verify the BNP screening test, clinical characteristics of subjects showing abnormally high plasma BNP levels above the 95 percentile for each age- and gender-specific reference value from the original cohort were examined. Odd ratio (by logistic regression) to contribute high plasma BNP levels were different between gender (see Table). ECG abnormalities, history of hypertension and ischemic heart disease, and impaired renal function were independent predictors of high plasma BNP levels in male, whereas ECG abnormalities and history of hypertension were the predictor in female.

Odd ratio to contribute high plasma BNP

	HTN	BMI	IHD	DM	Cre	ECG
Male	1.88*	0.73	2.80*	1.36	2.99*	5.66*
Female	2.14*	0.91	0.81	1.51	1.74	3.95*

HTN=hisory hypertension; BMI=obesity; IHD=hisory of ischemic heart disease; DM=diabetes mellitus; Cre=renal impairment; ECG=major ECG abnormalities *$p<0.05$

Conclusion: In the general Japanese population, age- and gender-specific referenced high plasma BNP levels are likely to identify patients with high risks of heart failure especially in male.

NURSING ASPECTS IN HEART FAILURE

P449 Telephonic consultation of a specialized heart failure nurse; an ongoing important component of heart failure care

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Specialized heart failure (HF) programs to guide patients with CHF have been started in many countries during recent years. In majority of these programs a specialized HF-nurse has an important role. One of the tasks can be functioning as a telephonic consultant for the patients when the latter are encountering problems regarding their HF at home. At the Cardiology department in Leiderdorp a HF-program has started in 2000 and is still running. Results regarding the importance of telephonic consultation of the nurse have been presented before. After 3 years of running this program evaluation was made whether there has been a change in number and content of calls and characteristics of patients calling. Therefore all data concerning these questions were collected prospectively. Results: In 2000, 2001 and 2002, 455, 572 and 458 phone calls were made respectively by 96, 125 and 124 individual patients. Content of the calls is shown in the table in consecutive years. Also patient characteristics are demonstrated.

Content of calls, patient characteristic

	2000	2001	2002
weight changes	154 (34%)	154 (27%)	53 (12%)
medication	89 (20%)	66 (12%)	51 (11%)
symptoms of HF	54 (12%)	173 (30%)	143 (31%)
letters/presciption	51 (11%)	54 (9%)	82 (18%)
clinic appointment	35 (8%)	35 (6%)	21 (5%)
other	72(16%)	90(16%)	108(24%)
age(years)	76	75	72
male (%)	56	54	58
LVEF (%)	43	41	41

Conclusion: The possibility to consult the HF-nurse in a CHF-program by phone appears to be an important component to the improved care for CHF-patients. Growing number of individual patients have been calling the nurse during recent years. As shown there has been a decrease in the number of calls made about weight changes concomitant with an increase in the number of calls for other symptoms of CHF. One can speculate that this might results in a decrease in readmissions because of symptoms of HF. Furthermore characteristics of patients have not changed significantly.

P450 Care of the elderly with chronic heart failure in community home care. A record review of nurses assessments and interventions

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Background: Elderly patients with chronic heart failure (CHF) constitute a large group in community home care, they are at high risk for hospitalizations due to worsening heart failure, this may be prevented if early signs of deterioration can be recognized and proper interventions are made.
The aim of the study was to describe nursing care for elderly patients with CHF in Swedish community care, by examining the nurse recording.
Methods: Nursing documentation from 161 records on patients diagnosed with CHF was collected retrospectively from nursing home care units in community care for the elderly. Forty-five % of the patients were age 65-84 and 55% were 85 years or more, 30% were men and 70% women. Records were reviewed for diagnosis specific aspects of nursing care.
Results: Problems related to CHF were poorly recorded which only made it possible to follow fragments of the care process. Only 48% of all the records contained notes related to CHF, of these, the most frequent assessment notes dealt with heart rate and blood pressure (47%), breathlessness (45%) and oedema (44%). Least frequent were notes on the patients' body weight (12%) and their knowledge about CHF (4%). The assessment data seldom resulted in recommended interventions, such as weighing the patient each day. Nursing interventions related to CHF were mainly focused on drug administration (80%). Least frequent were notes about patient information or education (3%).
Conclusion: The findings showed flaws in the recording of assessment data and interventions for patients with CHF. Structured guidelines for nurses may be needed to enhance proper community based home care.

P451 Quality of life of caregivers is worse compared to patients with congestive heart failure

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Background: Congestive Heart Failure (CHF) seriously effects the lives of both patients and their caregivers. The practical and emotional support given by partners of CHF-patient may be essential for the prognosis of these patients, but little is known on the burden experienced by caregivers and how this effects their Ouality of Life (QoL).
Literature in chronic illness suggest gender and role (patient versus partner) differences in psychological distress and QoL, caused by dealing with a chronic illness.
The aim of this study was to describe the QoL in relation to gender and role (patient versus partner).
Method: Data of 40 patients (age 68 ± 8, 80% male, LVEF 30±12, NYHA III-IV) and their partners from a previous HF study were analyzed. QoL was measured by the Cantrils Ladder of Life. This is a self-report, one item scale with 0 reflecting the worst possible QoL a patient or partner could think of, and 10 the best.
Demographic and clinical data of patients were obtained by chart review and partners completed a short questionnaire with demographic data.
Results: The analyzed couples consisted of 32 male patients with their 32 female spouses and 8 female patients with their male partners. The mean age of spouses was 65 years (± 9).
The average QoL score of all patients on the Ladder of Life (6.8 ±1.7, min.3 max. 10) was significantly higher ($t=2.4$, $p<0.05$) than the average QoL-score of their partners (5.9 ±1.6). Female partners reported a higher QoL-score (6.0) than male partners (5.5). Women, whether being a patient or a partner, reported a higher QoL-score (mean 6.7) than men (mean 6.0).
Quality of life of patients was significantly correlated with the quality of life of the partners ($r=.50$, $p<.005$) and to both the age of the patient ($r=-.34$, $p<.05$) and the age of the partner ($r=-.34$, $p<.05$).
Conclusion: The results of this study describe the serious impact of taking care of patients with CHF, with partners reporting a lower quality of life compared to patients. In our attempts to improve patient outcomes, the role and burden of caregivers should not be ignored.

P452 How useful is reported weight gain as a predictor of clinical decompensation in heart failure?

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Background: Guidelines recommend daily weight monitoring in all patients with heart failure. Although a stated component of most disease management programmes (DMPs) as an early warning sign of clinical decompensation, it's value in this role is unsure.
Aims: To assess the usefulness of reported weight gain (defined as >2kg over 2 days) in the identification of early decompensation in heart failure patients.
Methods: All patients entered into our hospital based DMP are advised to immediately report symptomatic deterioration and/or weight gain of > 2kg over 48hours irrespective of symptom status. In an ongoing study we prospectively assess all patients who undergo clinic review for symptom deterioration, with or without reported weight gain (Symp-WG and Symp-NWG respectively). We also review patients who reported weight gain but with no symptom deterioration (No-Symp-WG). Therapy was adjusted where appropriate and patients were reviewed within one week for assessment of response to treatment. The main outcome measure was the sensitivity and specificity of reported weight gain in predicting clinical decompensation in the group.
Results: To date, 35 patients have been included (71.0 ± 9.6 years, 67% male, 68.6% ischemic, 77.1% systolic dysfunction, NYHA Class 2.7 ± 0.6). Twenty-nine patients reported symptom deterioration (11 and 18 in the Symp-WG and Symp-NWG groups respectively). BNP significantly increased from baseline in these patients by 41% (808 ± 509 pg/ml, vs. 570 ± 410 pg/ml, P=0.004) and all but 3 patients had medication adjustment. All but 1 patient was considered to be in early clinical decompensation and 62% of these showed good response to treatment on follow-up. A further 6 patients (No Symp-WG) reported weight gain without any symptom deterioration and had no significant increase in BNP from baseline (608 ± 642 pg/ml, vs. 563 ± 634 pg/ml, P=0.276). Only three of these patients were considered to be in early clinical decompensation and all of these showed good response to treatment on follow-up. There were no significant differences noted between the groups in terms of age, gender, aetiology, heart failure type, NYHA class and medication. Reported weight gain had a sensitivity of 45% and a specificity of 82% in predicting clinical decompensation in this study cohort.
Conclusions: In the setting of our DMP, reported weight gain was not a sensitive indicator of clinical decompensation. While patients should be encouraged to monitor weight gain, it should be recognised that the absence of weight gain does not exclude clinical decompensation.

P453 Qualitative assessment of anxiety in implantable cardioverter-defribrillator patients

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Objective: Implantable cardioverter-defibrillator (ICD) therapy gains its popularity in recent years in Japan. Quantitative measurement of quality of life (QOL) of those patients becomes more important parameter in order to provide better post-implant patient care. This study is a qualitative study to assess anxiety in ICD patients. The result of this study is intended to use for quantitative study in future.
Method: The assessment of anxiety was done by; 1. literature search, 2. analysis of inquiries for patient service phone at Medtronic Japan, 3. patient focus groups. A list of anxiety of ICD patients was obtained by these activities and was sorted out to eliminate generic anxiety which would be measured by a general health questionnaire. The alpha-version of anxiety questionnaire was designed from the list. It was tested for usability in 34 healthy subjects and time to complete the questionnaire and understanding of questions were assessed. The questionnaire was modified according to the usability test results and beta-version was completed.
Result: Two focus groups were held in Tokyo (highly populated area) and Sapporo (less populated local area), and total of 13 patients (9 males, age 19-74, mean 60 years old) and 5 family members participated in the focus groups. They expressed anxiety related to implantable device in general such as electro-magnetic interference (EMI), scar and feeling of foreign body, device reliability, and quantity and quality of given information, as well as ICD specific anxiety such as defibrillation therapy (unpredictable shock), limitation in daily life and mental support. The alpha-version was tested with 34 healthy subjects (17 males), and the mean time to complete the questionnaire was 4 minutes and 35 seconds. Some expressions in the questionnaire were clarified for beta-version.
Conclusion: The qualitative assessment revealed anxiety in ICD patients and the questionnaire was verified to be feasible. Further study is required to test the sensitivity, specificity, and reliability of the questionnaire.

P454 Multidisciplinary intervention in congestive heart failure – does it reduce?

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Background: Nurse led multidisciplinary intervention (MDI) has been shown to improve treatment adherence and improve symptom control/quality of life in patients with chronic heart failure (CHF). In a few relatively small trials, disease specific events (mainly hospitalisation for CHF) have also been reduced. However, it is not known whether this type of intervention definitely reduces more objective end-points such as all-cause hospitalisation or death. Because of the limited power of individual studies to address these end-points we have carried out a meta-analysis of published studies.
Methods: A systematic review of the literature identified 14 randomised controlled trials of MDI in CHF published between 1993 and 2002 which reported on the outcomes of death, death or hospitalisation or the number of patients hospitalised for any reason. The largest of these randomised 282 patients and the smallest 37 (total of 2306 patients). Meta-analysis was performed using the Peto method.
Results: 12 trials reported deaths. There were 172 deaths among the 1091 patients randomised to special intervention (IG) and 222 out of 1117 in the control group (CG), giving an odds ratio (OR) of 0.77 (95% CI 0.61-0.96), P= 0.02. For death or hospitalisation (9 trials) these rates were IG 428/821 versus CG 512/840, OR 0.68 (95% CI 0.55-0.83), P< 0.001. For all-cause hospitalisation (patients not events) [9 trials], the rates were IG 325/813 versus CG 394/797, 0.65 (95% CI 0.53-0.80), P< 0.001.
Conclusions: MDI reduces the risk of hospitalisation from all causes by about 35% in patients with CHF and reduces the risk of death or hospitalisation by 32%. The effect of MDI on mortality is of borderline significance and strongly influenced by one trial. MDI substantially reduces morbidity in CHF and may even improve mortality.

P455 Gender differences in lifestyle exercise following cardiac rehabilitation

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Purpose: Adopting and maintaining long-term aerobic exercise remains a problem for individuals who have had cardiac events. The purpose of this prospective study was to compare men and women's patterns of exercise over 6 months following completion of cardiac rehabilitation (CR).
Methods: A convenience sample of 90 individuals (32 women and 58 men; mean age = 62 years) wore portable wristwatch heart rate monitors during exercise for six months following CR. Exercise behaviors measured were: exercise frequency, exercise amount (# of hours exercised), length of exercise sessions, and intensity compliance (percent of exercise time spent in target heart rate {THR} zone). Data were analyzed by month over the 6-month study period.
Results: Of 90 individuals in the study, 13 (14%) did not exercise at all during Month 1, and by Month 6, 25 (28%) were not exercising. Exercise frequency and amount decreased over the study period for both women and men. Women had fewer exercise sessions than men in Month 1 (9.6 versus 12.1) and in Month 6 (6.6 versus 9.5). Exercise session length stayed consistent over the study period; however, women had a shorter length as compared to men (41 versus 58 minutes; p = 0.02). Women's exercise amount was significantly less than men's at both Month 1 (5.8 versus 10.6 hrs.; p=.02) and Month 6 (4.2 versus 9.5 hrs.; p=.02). Women's exercise intensity compliance decreased over the study period from 37% in Month 1 to 25% in Month 6; whereas, men's intensity compliance remained relatively stable over time. Slope analysis was undertaken to determine if there were differences by gender in the downward trajectory of exercise frequency and amount. Although women's exercise frequency and amount was less than men's throughout the study period, there were no significant differences in the slope changes, thus men and women's exercise behavior decreased at a similar rate.
Conclusions: A significant number of CR participants are not exercising at all at 6 months following CR, and even among those who do exercise, the frequency, amount, and intensity is lower than recommended. These findings suggest that although CR programs do a good job of reconditioning individuals following cardiac events, long term maintenance of lifestyle exercise requires more targeted interventions by clinicians for both women and men.

P456 The recognition and nurse-led modification of cardiovascular risk factors among the coronary disease patients hospitalized in a tertiary center

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Optimal methods of education in patients with coronary disease (CHDpts) are not standardized and the potential of nurses may be underutilized.
Aim of the study was to assess the prevalence of cardiovascular risk factors in CHDpts hospitalized in the academic cardiology center and to evaluate their change during 3 months after nurse-led intensified educational session.
Methods: 100 patients (aged 59±10, 69% male) hospitalized in our Department answered a questionnaire regarding their cardiovascular risk. 50 patients (Group E) were randomized to undergo an individualized 20-minute nurse-led educational session using a custom-designed booklet. The other 50 patients were left with risk education delivered during routine care (Group R). The questionnaire was repeated 3 months after the index hospitalization.
Results: Risk factors in this selected subgroup of CHDpts who reach the tertiary center are still prevalent, including: diabetes in - 13%, hypercholesterolemia - 41%, hypertension -51%, overweight - 46%; obesity- 24%, low physical activity 92%. Only 49% knew the term "risk factors"before the study. 71% are past smokers, 13% continued smoking with decrease to 7% during the follow-up questionnaire. The main specific changes in health behaviour involved the increase in physical activity: patients reporting low activity decreased from 54% to 12% (gr. E) but only 46% to 30% in Gr. R ($p<0,05$ between Groups). Preference for nonsaturated fats in diet increased from 76% to 96% (gr. E) and 84% to 94% in Gr. R ($p<0,05$ between Groups).
Conclusions: Even in the tertiary center, the CHDpts may have insufficient recognition of cardiovascular risk factors. Individualized educational activities can be effectively performed by trained nursesand significantly improve some modifiable components such as physical activity and dietary habits. In this group of patients smoking is already rare due to effective education at earlier stages of medical care.

P457 Patient viewpoint after undergoing coronary angiography/intervention

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Background and Aims: Pts undergoing coronary angiography (cath) and/or intervention (PCI) receive standard oral, written and visual explanations beforehand. Little attention has been focused after the procedure, however, on the patients' point of view regarding the cath experience.
Patients and Methods: Anonymous pre-discharge pt questionnaire was completed by 159 consecutive pts (age 64±11 yrs; 120 males, 39 females) 12-24 hrs after diagnostic coronary angiography (59.2%) and/or PCI (40.7%). In 74 (49%) pts the procedure was first cath procedure. Level of education in 37/144 (25.7%) pts was elementary, in 72 (50%) high school and in 34 (23.6%) university/other higher education.
Results: The major reason for pt concern/fear was the "unknown" (70/145, 48.3%) or in-lab preparation prior to cath (36/145, 24.8%). Also of concern were the femoral puncture (17 pts, 11.7%), staff discussions (12 pts, 8.3%) and pain (10 pts, 6.9%). Pts with higher education were less concerned by discussion, more by punctures. Pain was localized to the chest in 58/133 (43.6%) cases, puncture site in 21 (15.8%), 50 (37.6%) no pain, 4 (3.1%) back or other. 42/156 (26.9%) pts missed having a family member present during the procedure. 43 pts (29.7%) believed that anxiety could be reduced by background music, greater reassurance by cath team (27, 18.6%), more attention to pain relief (19, 13.1%), updating families during procedure (17, 11.7%), not possible/other in the remainder. 123 (78.3%) pts wished to be involved in decisions regarding treatment options. Body exposure was of concern to 15 (38.5%) women and 22 (18.7%) men (p=0.02), and to 7/14 (50.0%) religious pts vs 26/124 (20.9%) others (p=0.03).
Conclusions: 1. The cath/PCI experience was accompanied by fears and anxieties in most pts. 2. Anxiety was related mainly to the unknown and to in-lab preparation. 3. Pts believed that fears/anxieties could be allayed by background music, greater reassurance by cath team, pain relief, involvement of family members. 4. Information from pt oriented questionnaires should allow us to better address pt perspectives/concerns during cath/PCI.

P458 Sex and psychosocial adjustment by 2 weeks and 6 months after myocardial infarction

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Technologic and treatment advances have resulted in large numbers of patients who would previously have suffered mortality now surviving with more or less chronic disorders. The present work investigated sex-based differences in psycho-social outcome at 2 weeks and 6 months after myocardial infarction (MI).
Materials and Methods: The study comprised 243 patients aged 80 years and less. After 2 weeks and 6 months they were mailed two questionnaires. One related to socio-demographic information, the other being the Psychological Adjustment to Illness Scale (PAIS-SR) inventory. The latter assesses the psychosocial adjustment to chronic illness or its sequelae. Higher scores indicate poorer functioning.
Results: Average age at baseline was 66.1 and 63.4 years in women and men respectively. 58% of the women and 87% of the men lived with a partner, and 29% and 50% respectively were working. Apart from previous hypertension (women 35% vs. men 19%, p=0.02) and smoking (women 46% vs. men 35%, p=0.01), demographics were equally distributed between the genders. At baseline women had significant higher scores than men in 2 PAIS domains while the difference was of borderline significance in a third (table 1). After 6 months women had poorer scores compared with men in 2 domains (domestic environment, p=0.016 and extended family, p=0.02).

Table 1

	Women		Men		
	Mean	SD	Mean	SD	p
Health orientation	6,30	2,96	5,95	3,04	ns
Vocational environment	9,50	5,69	5,62	4,67	ns
Domestic environment	3,69	3,16	3,45	2,31	ns
Sexual relationship	3,33	3,61	3,69	3,73	ns
Extended family	1,26	1,47	0,60	1,43	0,03
Social environment	6,08	4,29	4,71	3,68	0,028
Psychological distress	3,76	3,02	2,95	2,69	0,05

Means of PAIS scores for each domain in women and men at 2 weeks post infarction

Conclusions: Results at 2 weeks and 6 months are basically similar, but MI affects different aspects of life of men and women. Health care providers should be aware of these gender differences as intervention to improve psychosocial factors increases in importance.

P459 The Irish experience in rapid access chest pain clinic assessment

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In the Cork and Kerry region 25% of all deaths were attributed to Coronary Artery Disease (CAD) in the years from 1993 to 1997. Tackling the burden of CAD in a geographical hot spot such as this is a major challenge.
To address this problem a Rapid Access Chest Pain Clinic (RACPC) service was set up. It is a Nurse- Led service where clients with suspected Angina are assessed and screened for CAD within 24 - 48 hours of referral by their General Practitioner. It is hoped that by intervening earlier in the presentation cycle that acute coronary episodes in the future may be prevented.
The clinic opened in August of 2002 and to date 184 patients have been screened for CAD. Of those screened 29% are newly diagnosed Angina. The advanced stage of the disease process on initial presentation was particularly striking. To date, twelve clients have undergone coronary revascularisation, seven of which were Coronary Artery Bypass Grafts and five Angioplasties. In the latter group, all were male and under 55 years.
One of the main priorities of the clinic is to identify those at high risk of future coronary events. Once clients individualised risk factors are identified, they are targeted with the use of education, support and medication from the multidisciplinary team. Our initial audit revealed 60% of all patients seen in the clinic had a cholesterol level greater than 5mmol/l, and 64% of clients had Body Mass Index's greater than 25. In this group our main aim is "Prevention rather than cure".
Thus far a wealth of data has been compiled in an area where deaths from CAD are above the national average. To date 89% of our clients are seen within 48hrs of referral, which means we are moving in the right direction. We need to continue fostering and developing links with the community so that primary and secondary care services can work together to tackle the burden of CAD and provide a seamless service to our clients.

P460 Outcomes from the first 2-years of a nurse-led percutaneous transluminal coronary angioplasty follow-up clinic

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Background Percutaneous transluminal coronary angioplasty (PTCA) with or without the insertion of a stent is a widely used and relatively routine practice within cardiology with a mean of 581 per million inhabitants in Europe in 1996. The care of the patient does not end when they leave hospital. Patients need to be reviewed in the out patient department to monitor their progress and ensure timely reinvestigation if problems occur. From January 2001 the Cardiology Nurse Consultant took over the follow-up of these patients at Harefield Hospital in a nurse-led clinic. All patients are now seen at 1, 6 and 12 months and thereafter annually providing they are not having problems. From September 2001 additional nursing staff have been involved in running the clinics. The clinics have facilitated a uniform follow-up for this group of patients. In addition experienced nurses have been able to develop their skills in a previously unfamiliar area. The small group of nurses involved has also increased continuity of care and every effort is made to ensure the patient sees the same nurse at each visit. The reorganisation of the clinic has allowed the collection of a large amount of data on this patient group.
Results Data are available from the first 2 years of the clinics. Between November 2000-October 2002, approximately 1000 NHS patients underwent PTCA performed by one of the in-house cardiologists at Harefield Hospital. 727 were seen in the nurse-led clinic at 1-month post procedure (73%). Patients are offered the choice of being followed up at their local hospital if they prefer. 561 patients were either free from chest pain or had non-cardiac pain (77%). 524 patients (72%) had a systolic blood pressure of $<$140mmHg. 88% of patients were either non-smokers or had stopped smoking. Only 3 patients had resumed smoking having initially stopped. 90% of patients were taking Aspirin, 68% were taking Beta-blockers and 84% were taking a statin.
393 patients have been followed to 1 year. 80% were either free from pain or had non-cardiac pain at this stage. 70% had a systolic blood pressure of $<$140mmHg and 87% were not smoking. 92% of patients were taking Aspirin, 68% were prescribed Beta- blockers and 86% were receiving a statin. The number of patients off sick from work had reduced from 129 at 1-month to 13 at 1 year.
Conclusion The nurse-led clinic is an effective way of monitoring patient progress post PTCA. The numbers of patient receiving Aspirin, Beta-blockers and especially statin therapy compare favourably with those reported in recent studies such as GRACE and EUROASPIRE II.

PREDICTORS OF OUTCOME IN NON-ST-ELEVATION ACUTE CORONARY SYNDROME I

P461 The measurement of whole blood brain natriuretic peptide may detect acute myocardial ischaemia in patients with ongoing chest pain and distinguish them from those with pain not of ischaemic origin

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Background: Plasma Brain Natriuretic Peptide (BNP) levels increase during acute ischemic events. The aim of the present study was to test the hypothesis that plasma BNP levels measured on arrival at the emergency department are higher in patients with an ischemic attack than in patients with other causes of chest pain and that this could be a marker for the detection of ischemia in patients with continuing chest pain.
Methods and Results: Whole blood BNP was measured in 101 patients at baseline, and at 2 and 6 hours after arrival in the emergency department with ongoing chest pain. After a 1-month follow up period patients were classified according to the results of diagnostic tests for myocardial ischemia. In the Ischemic Group median (25th, 75th percentiles) BNP values were 122 (20, 349) pg/ml at baseline, 116 (36, 347) pg/ml at 2 hours, increasing to 148 (52, 428) pg/ml at 6 hours ($p<0.001$ versus baseline). Non-ischemic patients had 12 (5, 32) pg/ml of BNP at baseline, 9 (6, 30) pg/ml at 2 hours, and 13 (5, 29) pg/ml at 6 hours ($p<0.001$ versus corresponding values of the Ischemic Group).
The diagnostic performance of BNP levels was tested using receiver operator characteristic curve analysis. Areas under curve (95% confidence limits) for BNP measurements were 0.81 (0.72, 0.88) at baseline, 0.87 (0.78, 0.93) at 2 hours, 0.90 (0.78, 0.93) at 6 hours and 0.89 (0.81, 0.94) for BNP increase from baseline to 6 hours, all indicating a significant diagnostic ability for the detection of ischemia. Comparisons between areas under curves showed a superior diagnostic performance of BNP at six hours compared to that at two hours (difference between areas=0.04, standard error of difference=0.017, p=0.03) and baseline values (difference between areas= 0.09, standard error of difference=0.02 p=0.000). This is reflected in the augmented specificity that is observed as we proceed from baseline BNP (0.66) to BNP at six hours (0.83) while sensitivity remains reletively unchanged (corresponing values 0.81 and 0.87 respectively).
Conclusions: BNP values may detect acute myocardial ischemia in patients with ongoing chest pain and distinguish them from those with pain not of ischemic origin. Further studies are needed in order to establish optimal cut-off points.

P462 Effect of spontaneous myocardial ischaemia on P-wave dispersion in patients with coronary artery disease

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Background: Increased P wave dispersion (P dispersion=P maximum - P minimum) has been shown during myocardial ischemia induced by coronary angioplasty in patients with coronary artery disease (CAD). The effect of spontaneous myocardial ischemia on P dispersion has not been studied widely. The purpose of this study was to examine the effects of ischemia on P dispersion during spontaneous anginal episodes in patients with CAD.
Methods: Sixty-five consecutive patients with CAD documented by coronary angiography (41 men, 24 women, mean age 62$\pm$13 years), who are admitted to hospital for an episode of typical angina pectoris were enrolled. All patients underwent 12-lead surface ECG during anginal episode and all showed ST segment depression. Immediately after the ECG recordings, sublingual nitrates were administered to all patients. Another 12-lead ECG was obtained when anginal pain was relieved and the ST segment depression had disappeared. P wave duration and P dispersion were calculated in all the 12 leads of the surface ECG simultaneously recorded during both the symptomatic and the painless period.
Results: P maximum values were 126$\pm$18 ms during angina, 116$\pm$17 ms after the relief of angina respectively (p=0.001). P minimum were found to be 79$\pm$13 ms and 78$\pm$14 ms, and the difference between P minimum was insignificant (p=0.7). P dispersion values were 46$\pm$15 ms during angina and 35$\pm$12 ms after relief of angina (p=0.001).
Conclusions: Acute myocardial ischemia during spontaneous anginal episodes causes an increase in P dispersion value, and this increment is the result of an increase in P maximum duration. Therefore, increased P maximum duration and P dispersion may be marker of acute reversible myocardial ischemia.

P463 Inflammation without concomitant myocardial necrosis is associated to a worse outcome in patients with acute coronary syndromes

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Background: There are few prospective data about the prognostic value of C-reactive protein in the absence of elevation of markers of myocardial necrosis.
Methods: We prospectively included 1520 patients with non-ST elevation acute coronary syndromes (NSTE-ACS). Single assays of troponin T(TnT), high sensitivity C- reactive protein (CRP)and myoglobin were performed after a median time of 3 hours from symptom onset. All results were kept blinded until the conclusion of the study.
Results: In a subgroup of 897 patients with neither elevation of TnT ($>$0.03 ng/ml), or myoglobin ($>$58 ng/ml), there were 478 patients with elevated CRP ($>$3 mg/L). These patients with elevated CRP had more common history of diabetes, peripheral vascular disease and tobacco abuse than those with normal CRP. Both groups were similar in age, high risk characteristics at entry (ACC-AHA criteria), baseline ST segment depression $>$0.5 mV, prior history of aspirin use, and prior myocardial infarction. The 6 months rate of death or new myocardial infarction in patients with elevated CRP was statistically higher than the rate in those with normal CRP (6.7% vs 2.6% respectively, p=0.005). In a logistic regression model that included diabetes, smoking habit, and prior history of peripheral vascular disease, CRP$>$3 mg/L and diabetes retained its prognostic value (OR 2.5, 95% CI: 1.2-5, p=0.01, and OR 2.5, 95% CI:1.4-5.1, $p<0.005$, respectively)
Conclusions: In patients with NSTE-ACS and negative markers of acute myocardial necrosis, elevation of CRP is an independent predictor of worse outcome at 6 months. This study suggests that positive C-reactive protein may be a sensitive indicator of severe but potentially reversible myocardial injury.

P464 Plasma level of endothelin-1 in patients with coronary artery disease

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The aim of the study was to evaluate plasma level of ET-1 in patients (pts) with coronary artery disease (CAD). **Methods:** Data of 156 patients (120 men and 36 women, aged 40-76 years mean 55 ± 0,85) were analyzed. The patients were divided in two groups on the basis of the severity of CAD: Group I with unstable angina (UA; n=60) and Group II with stable angina (SA; n=96). Patients with SA were further divided into subgroups according to the presence of a history of myocardial infarction (MI). Subgroup A consisted of 65 pts with SA and with a history of MI; Subgroup B 31 pts with SA and without a history of MI. Plasma level of ET was evaluated in all patients. Mean values of ET in all subgroups were calculated and analyzed. Endothelin level was measured in the EDTA blood using an enzyme immunoassay Kit produced by Cayman Chemical Company and Diagnostic Products Corporation. In a healthy population plasma level of ET expressed in a picomolar range varies between 0,26-5,0pg/ml. **Results:** Plasma level of ET in pts with SA varied between 7,8 and 39,6pg/ml mean 27,71 ± 5,921 and was significantly lower than in patients with UA (range from 6,25 to 62,04 pg/ml mean 17,71 ± 15,15pg/ml.) Mean plasma ET-1 level in subgroup A of SA pts was equal to 23,9 ± 2,96pg/ml, in subgroup B 12,83 ± 1,63pg/ml. ET level was significantly higher in SA patients with a history of MI (Subgroup A) compared to the other patients with SA (Subgroup B). Poor clinical outcome unstable angina pts was more frequently observed in pts with high levels of ET-1. **Conclusions:** 1. Plasma ET level depends on the severity of CAD: it was significantly higher in patients with unstable angina compared to the patients with stable angina. 2. In a group with stable angina, the plasma ET level was significantly higher in patients with a history of myocardial infarction compared to the patients without a history of MI.

P465 Prognostic markers in patients older than 75 years with acute coronary syndromes without ST-segment elevation

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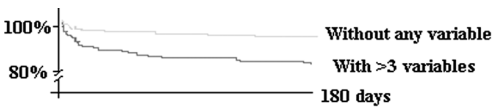
Purpose: the prognostic value of clinical and serum markers in patients (pts.) older than 75 years with non ST elevation acute coronary (NSTACS) are not known.Aim: identify prognostic markers of acute myocardial infarction (AMI) or death at 180 days in pts. older than 75 years with NSTACS. **Methods:** This prospective multicenter study included 1520 consecutive pts., 389 were older than 75 years (25.5%). Single assays of TnT, PCR of high sensitivity and myoglobin were performed after 9 hours (median) from symptoms onset. Results were kept blinded until the end of the study. The association between clinical and serum markers and 180 events was examined by chi square and cox regression analysis. **Results:** Baseline clinical and electrocardiographic data were: media age 80.5 ± 4.4 years, male sex 187 pts. (48.1%), previous AMI 83 pts. (21.2%), previous revascularization 77 pts. (20.2%), diabetes 81 pts. (20.8%) and ST segment depression 95 pts. (24.4%). The combined event rate at 180 days was 15.9%. The variables that suvived multivariate analisys were TnT >0.1 ng/ml (hazard ratio 2.5, p=0.001), PCR > 3 mg/L (hazard ratio 2.4, p=0.007) ST segment depression (hazard ratio 1.85, p=0.03) and diabetes (hazard ratio 1.6, p=0.08). The event rate in pts. wihout any of these variables and with at least one variable was 2.5% and 19.4% respectively (p<0.001, lon rank test). Kaplan Meier curves of both groups are shown in the figure.



Free time of infarction or death.

Conclusions: Pts older than 75 years with with NSTACS are heterogeneous. We identify a model that is predictor of worse evolution at 180 days. The patients without these variables have a reduced event rate and could be handled with a conservative strategy and low cost resourses.

P466 Close correlation between soluble CD40 ligand and soluble CD40 disappears in patients with unstable angina

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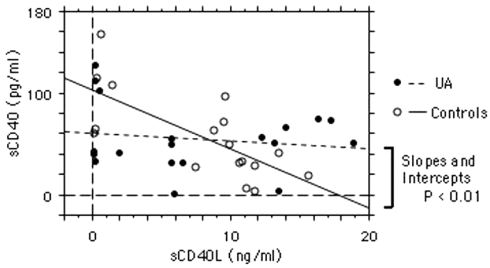
Background: CD40 ligand (CD40L)/CD40 system mediates inflammatory processes important in atherogenesis and plaque instability. It has been shown the expression of CD40L on activated T cells is suppressed by soluble CD40 (sCD40) in vitro. However, the relationship between soluble CD40L (sCD40L) and sCD40 in unstable angina (UA) is still unknown.
Methods: Consecutive 37 patients with recent chest pain or oppression were recruited in this study. The patients with both IB-IIIB of Braunwald Classification and coronary stenosis(es) >75% of AHA Classification were included in UA group (n=19, aged 67.2±8.2 years), and the others in control group (n=18, aged 63.4±8.7 years). Serum levels of sCD40L, sCD40, MCP-1 and interferon (IFN)-gamma were determined by ELISAs.
Results: There was no statistical significance between UA and control groups in terms of age, sex, plasma lipid levels, blood pressure, smoking, HbA1c, CRP or serum amyloid A level. There was also no statistical significance between the two groups in terms of sCD40L, sCD40, MCP-1, or IFN-gamma. As shown below, close negative correlation between sCD40L and sCD40 in controls (r=-0.72) disappeared in UA group (r=-0.16). The differences of the regression slopes and intercepts between the two regression lines were statistically significant (p<0.01, respectively). Similarly, the negative correlations between sCD40L and blood neutrophil and blood monocyte count observed in control group disappeared in UA group. The differences of the slopes and intercepts were also significant (p<0.05, respectively).



Relation between sCD40L and sCD40.

Conclusions: These results suggest that the expression of sCD40L may exceed the supression by sCD40 in patients with UA. This loss of balance may be involved in the pathogenesis of UA.

P467 Very early percutaneous coronary intervention eliminates the adverse prognostic effect of elevated serum markers in non-ST-elevation acute coronary syndromes

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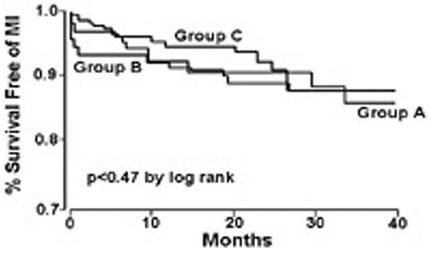
Background: Elevated serum markers of myocyte necrosis indicate an adverse prognosis in patients with non-ST-elevation acute coronary syndromes (NSTACS) that could be influenced by very early percutaneous coronary intervention (PCI) with stenting of the culprit lesion.
Methods: In a cohort of 1047 consecutive patients with NSTACS 601 patients (57%) were treated with PCI at a median of 5.3 (25th and 75th percentile 2.2 and 24) hours from admission. Mean age was 65±11 years and 66% of PCI-patients had multi-vessel disease. Stent rate was 80% and periprocedural use of GPIIb/IIIa-antagonists 11%. PCI-Patients were stratified according to myocardial markers on admission: 196 patients with negative serum markers (Group A), 263 patients with elevated Troponin T (TnT) >0.1μg/L and normal creatine kinase (CK) (Group B), and 137 patients with CK-elevation > twice the upper normal limit (Group C).
Results: Mean follow-up was 24±16 months. For patients treated with PCI Kaplan-Meier analysis showed a cumulative 3-years survival of 95.5% in Group A, 89.8% in Group B, and 91.2% in Group C (p 0.05 by log-rank). Cumulative survival free of MI at 3 years (see Figure) was 85.8% in Group A, 87.2% in Group B, and 87.4% in Group C (p 0.47 by log-rank).



Survival without MI.

Conclusions: Patients with NSTACS treated with very early PCI have an excellent prognosis irrespective of negative serum markers, isolated TnT elevation or CK elevation at baseline.

P468 Synergistic interaction between biomarkers and killip class in patients with acute coronary syndromes: lessons from the pursuit trial

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Purpose: Patients with some degree of heart failure on presentation with acute coronary syndromes are at high risk for future cardiac events. Elevated cardiac enzymes have also been shown to negatively impact outcomes. We sought to determine the interaction between these two variables. **Methods:** We analyzed data on 860 patients who were enrolled in the PURSUIT trial and had Killip Class II or III heart failure symptoms at the time of presentation. We assessed clinical characteristics as well as 7 and 30 day outcomes of death or myocardial infarction in patients with and without elevated myocardial biomarkers defined as CK-MB greater than the upper limit of normal (ULN) value. **Results:** Results are shown in the Table.

	Positive biomarkers (CKMB > ULN) n=594	Negative biomarkers (CKMB < ULN) n=266	p-value
Age	69.3 ± 10.3	67.5 ± 8.9	0.01
Sex (Female)	244 (41%)	97 (36%)	NS
Hypertension	221 (37%)	94 (35%)	NS
Diabetes Mellitus	210 (35%)	81 (30%)	NS
Prior Myocardial Infarction (MI)	251 (42%)	116 (44%)	NS
History of Cerebrovascular Accident	37 (6%)	15 (6%)	NS
Prior Coronary Artery Bypass Grafting	69 (12%)	46 (17%)	0.02
Prior Percutaneous Coronary Intervention	58 (10%)	45 (17%)	0.003
History of Congestive Heart Failure	238 (40%)	89 (33%)	0.06
Tobacco Use	132 (22%)	57 (21%)	NS
ST depression on ECG	317 (56%)	119 (47%)	0.02
Heart rate	79 ± 17	78 ± 17	NS
Systolic Blood Pressure	129 ± 21	134 ± 22	< 0.001
7 Day Death or MI	147 (24.7%)	7 (2.6%)	< 0.001
7 Day Death	53 (8.9%)	6 (2.3%)	< 0.001
30 Day Death or MI	197 (33.2%)	14 (5.3%)	< 0.001
30 Day Death	84 (14.1%)	12 (4.5%)	< 0.001
30 Day MI	148 (24.9%)	4 (1.5%)	< 0.001

Conclusion: Patients who were in heart failure during presentation with acute coronary syndrome and had elevated CK-MB suffered worse outcomes.

P469 Myoglobin elevation predicts angiographic findings in patients with non-ST-elevation acute coronary syndromes. A large prospective cohort study

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Background: Recent reports suggest that myoglobin is a useful marker for risk stratification in patients with non-ST elevation acute coronary syndromes (NSTEACS). Angiographic plaque characteristics have been also associated with adverse prognosis in this setting. However the relation of myoglobin and angiographic findings has not yet been explored. The goal of this study was to relate angiographic data to myoglobin status in NSTEACS patients and determine whether the predictive value of Myoglobin might be associated to the angiographic findings.
Methods: This prospective multicenter cohort study included 1,500 consecutive pts admitted with NSTEACS. Among these, 1,253 patients were prospectively included in the angiographic sub-study. Myoglobin was measured at a median of 9 hours from symptoms onset and the results were kept blinded up to the end of the study. Myoglobin > 80 ng/ml was considered positive. Coronary angiography was performed in 590 patients (47%). Angiograms were reviewed by two angiographers unaware of the lab results and clinical course. Complex coronary lesion (CCL) was defined as the presence of at least one of the following: Thrombus (+), TIMI flow <2 or ulcerated plaque (UP).
Results: Myoglobin (+) was found in 37% of the patients. Patients with (+) myoglobin were older, more likely male and more frequently to present with ST depression and elevation of troponin T and C-Reactive Protein.
Conclusion: In this cohort of NSTEACS patients, myoglobin elevation was significantly linked to morphological complexity of the lesion, abnormal flow and visible thrombus. This association may explain, at least in part, the adverse outcome seen in patients with myoglobin elevation in the setting of NSTEACS.

Myoglobin and angiographic findings

	Myoglobin (+) n=217	Myoglobin (-) n=373	P value
Thrombus	50 (23%)	55 (15%)	0.014
TIMI </= 2	65 (30%)	70 (19%)	0.002
UP	88 (24%)	56 (27%)	0.480
CCL	119 (55%)	147 (39%)	0.000

PREDICTORS OF OUTCOME IN NON-ST-ELEVATION ACUTE CORONARY SYNDROMES II

P470 Sensivity, specificity and predictive value of the echocardiography and troponin-T test combination in non-ST-elevation acute coronary syndromes

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Introduction: Patients with a negative troponin (TnT) result showed 1.4% mortality during a mean follow-up of 9-10 weeks. The mortality was greater in patients with evidence of ischemic ECG changes and a negative TnT test (1.6-4.4%).Few studies have examined the efficacy of echocardiography (2DE) in patients with chest pain. The purpose of the present study was to determine the clinical utility,sensivity and specificity of the combination of the TnT levels and 2DE in patients presenting with chest pain,ST-depression,T-wave negative and no diagnostic ECG. **Methods:** 280 consecutive patients with chest pain and presence of ST depression, T wave inversion, and non diagnostic ECG, acceptable 2DE window, evidence or no evidence of alterations of the segmentary motion, and evidence and no evidence of injury, as assessed by TnT and normal value of CK-CK MB, were enrolled.2DE, blood CK, and TnT levels were performed at entry and subsequent samples were obtained every 4 hours for the first 12 h and then every 12 hours. All patients performed hemodynamic test within 12-72 from admission. PTCA or CABG were performed according to angiographic findings and left ventricular function. **Results:** The 280 patients (98 F/M 182),mean age 59.7+11.9 years, who met the entry criteria, were divided as follows: group 1: ST-segment depression (192 patients); group 2: T wave inversion (36 patients); and group 3: non diagnostic ECG (52 patients). The combination of positive TnT and wall motion alterations showed a higher sensivity, specificity and predictive values in comparison with alone TnT or 2DE. Patients, with the concordance between TnT and 2DE, were at higher risk. Patients with negative combination in all groups (94), showed a low incidence of coronary stenosis (10.6%), as well as negative 2DE alone (102 patients)(12.7%),while patients with negative TnT (128) showed higher incidence of coronary stenosis (39%), p<0.0001. **Conclusion:** Our results suggest that the combination of negative TnT test and negative 2DE in patients presenting to EDs with chest pain either with ECG changes or without ECG changes is a useful tool to identify those who can be discharged safely.We think that our data are important because by the combination we can identify the high risk (when positive) patients,reduce incidence of the false negative, but mostly it allows us to identify true negative patients to discharge safely.

P471 Six-months follow-up of patients coming to the emergency room with chest pain and negative troponin levels

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Purpose: The benign prognosis of patients with chest pain and negative troponin levels is controversial. The aim was to investigate emergency room predictors of poor outcome in this population. **Method:** A total of 439 consecutive patients were evaluated in the emergency room for chest pain with normal troponin I levels (determined upon arrival, and 8 and 12 hours after pain onset). Clinical (chest pain score according to the clinical presentation - maximum of 16 points - and risk factors) as well as ECG data were collected. One hundred and twenty seven patients were discharged immediately after early (<24h) exercise testing, according to a chest pain unit protocol. In hospitalized patients (n=312) the rate of in-hospital catheterization and revascularization were 49% and 21%. All patients were followed-up in an ambulatory setting. **Results:** Within 6-months of follow-up, 25 (5.7%) major events were detected (6 cardiac deaths and 19 non-fatal myocardial infarctions). By univariate analysis the predictors were: chest pain score >11 (p=.006), age >68 years (p=.003), diabetes mellitus (p=.008), previous history of ischemic heart disease (p=.006), ST-segment depression (p=.07) and left bundle branch block (p=.02). By multivariate analysis (C-statistic= 0.77, 0.70 to 0.84 95% CI, p=.0001), 3 independent factors were found: chest pain score >11 (OR=3.5, 1.4 to 8.6 95% CI; p=.008), age >68 years (OR=3.6, 1.4 to 8.9 95% CI; p=.006) and diabetes mellitus (OR=2.7, 1.2 to 6.4 95% CI; p=.02). A risk score proved useful for patient stratification according to the presence of 0 factors (n=119, 0% major event rate), 1 (n=175, 4%), and 2 or all 3 factors (n=145, 12.4%, p=.0001). **Conclusions:** A negative troponin result does not assure a good prognosis in patients coming to the emergency room with chest pain. Clinical data should be carefully evaluated in this population.

P472 Diabetes as the strongest predictor of complications after incident of unstable angina in 2-years follow-up

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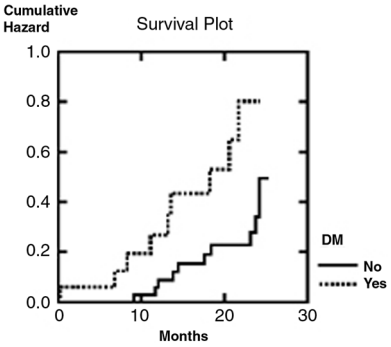
Purpose: Clinical assessment of patients with unstable angina is based not only on clinical symptoms, but also on concomittant diseases. The aim of this study was to investigate the adverse outcome in patients receiving successful treatment and discharged from the hospital.
Methods: The group consisted of 53 consecutive patients after incident of unstable angina (62±11 years, 29-men, 55%), among who 17 patients were diabetics (32%). On admission 61 clinical, electrocardiographic, echocardiographic, angiographic and laboratory features were taken into consideration. We analyzed the frequency of recurent myocardial infarctions, recurent ischemia, need for revascularization, and death during follow-up of 23±2 months.
Results: The mortality rate was 9% and in 38% patients any of above complications occurred. Univariate analysis revealed that age (p=0.005), diabetes mellitus (p=0.017), wall motion abnormalities on echocardiography (p=0.02), ST segment depressions on admission ECG (p=0.033), male gender (p=0.036) and pattern of mitral inflow (p=0.047) were predictors for adverse events. Multivariate analysis showed diabetes mellitus (Figure) to be the strongest independent predictor of complicated outcome (OR=9; p=0.008) beside a filling pattern of mitral inflow (OR=1.9; p=0.03) and lateral wall motion abnormalities (OR=1.5, p=0.05). Left ventricular end-diastolic diameter (p=0.016) and posterior wall motion abnormalities (p=0.051) were the only independent predictors of death.



Conclusion: Diabetes is the strongest prognostic factor in patients after incident of unstable angina. Therefore such patients should be considered for more extensive medical care.

P473 ACC-AHA 2000 guidelines: the need for further stratification of high-risk patients with non-ST-elevation acute coronary syndromes

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Background: Patients classified at high risk by ACC/AHA criteria are clinically heterogeneous, varying from patients with severe angina to those with advanced age, heart failure, ECG changes, or troponin elevation.
Objective: We aimed to improve the risk stratification of the high risk category using simple and objective prognostic variables.
Methods: Prospective multicenter study including 1000 consecutive patients with non ST elevation acute coronary syndromes (NSTE-ACS).
Results: The 6 months rate of death or new myocardial infarction was 1.3%, 6.2% and 11.9% in the low, intermediate and high risk subsets respectively. In turn, in the high risk category (n=649), the rate of events associated with age >75 years(n= 242), baseline troponin T >0.03 ng/ml(n= 341) and ST segment depression >0.5 mV at entry(n= 221), was 17.8%(p=0.001), 16.7% (p=0.0001)and 15.8%(p=0.03), respectively. Conversely, when all these three markers were negative (n=105), the 6 months rate of major events was only 1%. When all three variables were forced in a logistic regression model the following results were observed (table).
Conclusion: The prognosis of patients classified as high risk by ACC-AHA guidelines is heterogeneous. The use of simple and widely available markers might help physicians to select those patients in whom the use of aggressive treatment may not be justified.

Logistic regression model

	OR	95%CI	p
Tn T (+) (n= 122)	3.3	1.89-5.73	0.0001
Age > 75 (n= 341)	2.9	1.74-4.74	0.001
ST-segment depression (n=221)	1.6	0.95-2.57	0.08

P474 IL-1RN (VNTR) gene polymorphism predicts clinical events up to 1 year after a non-ST-elevation acute coronary syndrome: an association independent of troponin T and C-reactive protein

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Background and Aims: We have shown that any carriage of the *2 allele of the IL-1 receptor antagonist gene polymorphism {IL-1RN(VNTR)} is associated with a higher delta vWF and predicts Troponin T (TnT) positive status during Non ST-elevation acute coronary syndromes (ACS).(Ray et al, Clin Sci Sep 2002). Our aim was to determine if this gene polymorphism predicted clinical events after an ACS and if any association was found, to determine whether this was independent of biological markers associated with risk, specifically vWF, CRP and TnT.
Methods: We studied 63 patients with Braunwald class IIIB unstable angina. Blood was taken at 24 & 48 hours after admission for measurement of vWF, CRP and TnT. Change (delta) in vWF and CRP was determined (48-24hour levels). Patients were followed up for 1 year. The clinical events recorded were, urgent in-patient angiography for refractory angina, death and readmission with an ACS. Comparison between carriage & non-carriage of *2 was performed using Fisher's exact test.
Results: At 1 year comparing carriage of *2 with non-carriage, 50% had urgent angiography cf 28.6% (p=0.12, RR 1.63), 3.6% died cf 5.7% (p=1.0, RR 0.74), 57.1% were readmitted with an ACS cf 17.1% (p=0.0014, RR 2.49) & 71.4% had one or more clinical event versus 45.7% (p=0.046, RR 1.88). For each genotype we compared the association between clinical events and TnT positive status using a 2 by 2 contingency table and Fisher's exact test. There was no significant association between TnT positive status and clinical events for either genotype (p=1 for both). Next for each genotype we compared the mean delta vWF levels for patients having a clinical event versus no-event (unpaired t test). There was no significant association between events and delta vWF for either genotype (p=0.66 for allele *2, and p=0.85 for non carriage of *2. Finally we compared mean delta CRP levels in patients having a clinical event versus no events for each genotype. There was no association between delta CRP and clinical events for either genotype (p=0.91 for *2 and p=0.60 for non carriage. These data suggest that the incresed risk of clinical events associated with *2 carriage is independent of TnT, delta CRP and delta vWF.
Conclusion: Carriage of the *2 allele of IL-1RN(VNTR) predicts adverse clinical events after an ACS, independently of TnT, delta vWF and delta CRP after admission. Therefore IL-1RN(VNTR) genotype may be a useful additional marker in the risk stratification of ACS patients. The full clinical impact of this polymorphism and its mechanisms of action warrant further evaluation.

P475 Predictors of in-hospital coronary artery bypass grafting across the spectrum of acute coronary syndromes: an analysis from the Global Registry of Acute Coronary Events

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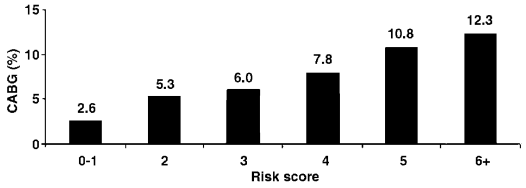
Background: Among patients with acute coronary syndromes (ACS), factors associated with in-hospital coronary artery bypass grafting (CABG) are poorly defined.
Aim: To identify presenting factors associated with an increased use of CABG among ACS patients.
Methods: 12,367 patients with unstable angina (UA), non-ST elevation (NSTEMI) and ST elevation myocardial infarction (STEMI) presenting to hospitals with surgical facilities were included. Patients were grouped according to whether they underwent CABG during hospital admission.
Results: 1119 patients (9.1%) underwent CABG. Significant geographical variation exists in the use of CABG: US 12.4%, Argentina/Brazil 10.5%, Australia/New Zealand/Canada 9.5%, Europe 4.8% (P<.0001). CABG was more likely in NSTEMI or UA than in STEMI patients (12.8% vs 8.8% vs 5.9%, P<.0001). Multivariate analysis identified independent predictors of CABG: history of documented CAD (OR 1.81, 95% CI 1.49-2.2), history of angina (OR 1.77, 95% CI 1.51-2.09), male sex (OR 1.68, 95% CI 1.44-1.96), ST depression (OR 1.36, 95% CI 1.18-1.58), prehospital aspirin (OR 1.24, 95% CI 1.06-1.45), diabetes (OR 1.18, 95% CI 1.02-1.38), history of hypertension (OR 1.24, 95% CI 1.07-1.44). A risk score was derived (OR>1.5= risk score 2, OR1-1.5=1), predicting likelihood of patients undergoing CABG (C statistic 0.71, Fig).



GRACE risk score for CABG (all ACS).

Conclusions: In ACS patients, there is geographical variation in the use of in-hospital CABG. Information available soon after hospital presentation allows prediction of the use of CABG, and may be used to aid selection of initial therapies.

P476 Independent and additive predictive power of C-reactive protein and myocardial damage biomarkers to predict first-month and first-year major events in non-ST-elevation acute coronary syndromes

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Purpouse. C-reactive protein (CRP) and myocardial damage markers are related to prognosis in non-ST-elevation acute coronary syndromes (NSTE-ACS). We analysed whether the analysis of CRP provides independent prognostic information in predicting 1-month (1m) and 1-year (1y) major events.
Methods: During a two-year period 630 consecutive patients admitted to a tertiary hospital with a diagnosis of NSTE-ACS were prospectively studied. Inclusion criteria were: troponin I (TnI) >1ng/ml, dynamic ECG changes, positive stress test in the chest-pain unit (in the absence of the first two criteria) or a high suspicion of ACS (in the absence of the first two criteria and contraindication to stress test). Myoglobin (Myo) and TnI peak levels were determined. CRP was analysed within the first 48 hours. Mean age was 68±12 years and 68% of cases were male. Cut-off values were defined as follows: Myo >70 ng/ml (n=280; 44%), TnI >1ng/ml (n=354; 56%) and CRP >11 mg/l (n=273; 43%).
Results: Within one-year follow-up period 56 (8.9%) cardiac deaths, 85 (13.5%) myocardial infarctions (MI) and 127 (20.2%) first major events were detected. Patients with CRP >11 mg/l showed higher rates of death 1m (7.7% vs 1.4% p <.0001), death 1y (15% vs 4.2% p <.0001), MI 1m (8.1% vs 3.9% p=.04), MI 1y (18.7% vs 9.5% p=.001), major events 1m (15% vs 5% p <.0001) and major events 1y (29.7% vs 12.9% p <.0001). In the multivariate analysis, once adjusted for baseline and ECG characteristics death 1m was related to CRP >11 mg/l (odds ratio (OR) 4.6 p=.003) and to Myo >70 ng/ml (OR 3.3 p=.02); death 1y to CRP >11 mg/l (OR 2.7 p=.003) and to Myo >70 ng/ml (OR 2.2 p=.02). MI 1m was related to TnI >1 ng/ml (OR 2.5 p=.03); MI 1y to TnI >1 ng/ml (OR 2.1 p=.02). Major events 1m were related to CRP >11 mg/l (OR 2.4 p=.006) and to TnI >1 ng/ml (OR 2.5 p=.02); major events 1y to CRP >11 mg/l (OR 1.8 p=.006) and to TnI >1 ng/ml (OR 2.2 p=.002). By subgroups, major events rates at 1y were: CRP >11 mg/l - TnI >1ng/ml 36%; CRP <11 mg/l - TnI >1ng/ml 18%; CRP >11 mg/l - TnI <1 ng/ml 13%; CRP <11 mg/l - TnI <1 ng/ml 9% (log rank 55 p <.0001).
Conclusions: CRP affords independent information to predict short-term and long-term major events in NSTE-ACS. Taking into account the independent and additive role of CRP and myocardial damage markers in the risk stratification of NSTE-ACS it seems worthy the analysis of both parameters in these patients.

P477 Circulating pregnancy associated plasma protein A (PAPP-A) indicates high 6-month risk in troponin negative chest pain patients

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Purpose: Risk stratification in cardiac troponin (cTn) negative acute coronary syndromes (ACS) remains a clinical challenge. We studied whether measurement of PAPP-A, a zinc containing protease present in unstable atherosclerotic plaques, might add to risk assessment in such patients.
Methods: Of 200 consecutive patients hospitalised for ACS, 136 (68%, 69 men and 67 women; mean (SD) age 66 (16) yrs) remained cTnI negative up to 24 hrs. PAPP-A was measured post hoc by a point-of-care time resolved immunoflurometric assay in serum samples obtained at admission, 6-12 hrs and 24 hrs. Cox's proportional hazards model was used to study the associations of prognostic variables and cardiovascular mortality, myocardial infarction (MI) and revascularization during the 6-month follow-up.
Results: Elevated PAPP-A was associated with diabetes (p=0.027), previous MI (p=0.035) and heart failure (p<0.01). 20/26 adverse events (77%) occurred in patients with elevated PAPP-A (cut-off value 2.9 mIU/l). After adjusting for other prognostic variables, elevated PAPP-A was an independent predictor of adverse 6-month outcome (RR 4.6 for the combined endpoint, 95% CI 1.8-11.8; p=0.0016). Also CRP>2.0 mg/l emerged as an independent risk factor in multivariate analysis (RR 2.6, 95% CI 1.1-6.5; p=0.03). There was no correlation between CRP and PAPP-A levels.
Conclusions: We demonstrate for the first time that point-of-care measurement of PAPP-A could be a powerful risk stratifier in cTn negative ACS patients.

P478 Clinical relevance of secondary unstable angina in the elderly

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Purpose: Secondary Unstable Angina Pectoris (UAP) (Braunwald IIIA) is recognised by the presence of extracardiac causes of instability. These conditions are more frequent in the elderly. Because there are only few registries that focuses on Secondary Angina in the elderly, our aim is to compare the clinical characteristics and in hospital outcomes of elderly patients with Primary UAP (Braunwald IIIB and C) and Secondary UAP.
Methods: We prospectively and consecutively included elderly (>75 years old) patients (p) with diagnosis of Unstable Angina admitted to our Coronary Care Unit. Sample was divided in two groups: PUAP: primary UA; and SUAP: secondary UA. Comparisons were analysed with chi-squared and Student t tests.
Results: We included 298 p, mean age 80.3 years, 178 p (59.7%) women. Total in hospital mortality was 21 p (7%). Table bellow shows our main findings. Extracardiac causes of inestability in SUAP were anemia 24 p (46.15%), taquiarrhythmia 13 p (25%), uncontrolled hypertension 13 (25%) and infection 2 p (3.85%).

	PUAP n=246 (82.5%)	SUAP n=52(17.5%)	p	OR (95CI)
Women	144 (58.5)	36 (65.4%)	0.44	1.33(0.71-2.49)
ST depression	82 (33.3)	23 (44.2)	0.18	1.58(0.86-2.91)
ST elevation	11 (4.5)	4 (7.7)	0.53	1.78(0.54-5.82)
T wave changes	37 (15)	1 (1.9)	0.009	0.11(0.01-0.82)
Death	17 (6.9)	4 (7.7)	1.00	1.12(0.36-3.48)
Death/MI	24 (9.7)	4 (7.7)	0.79	0.77(0.25-2.32)

MI: myocardial infarction.

Conclusions: In our population of elderly patients with unstable angina secondary unstable angina has similar outcomes (myocardial infarction and mortality) compared with primary unstable angina, this fact enhances the relevance of this condition.

PREDICTORS OF OUTCOME IN NON-ST-ELEVATION ACUTE CORONARY SYNDROMES III

P479 Gender influence treatment and outcome of patients with unstable coronary artery disease

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Background: Sex bias in management of unstable coronary artery disease (UCAD) has been reported. The aim of this study was to investigate gender differences in treatment and outcome of patients with objective signs of UCAD.
Method: The Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA)contains data including 100 variables for each patient admitted to participating intensive coronary care units (ICCU). 77 354 patients (46 363 men and 30 991 women) with ST-depression on admission-rest-ECG and/or elevated markers (CKMB and/or troponin-T) were included between 1995 and 2000. Pts. with ST-elevation or LBBB were excluded. Adjustment for age and other covariates was done by multiple logistic regression analysis.
Results: Female patients were older (mean age 72.7 vs 68.7 years, p< 0,001), more likely to have diabetes (22.6% vs 19.6%, p<0.001) and hypertension (40.5% vs 34%, p< 0.001),and less likely to be smokers (13.4 vs 18.9,4%, p<0,001) or have a history of AMI (35.4% vs 42.1%, p< 0.001).

Treatment and outcome

	Unadjusted OR	Adjusted OR
Exercise test	1.64 (CI 1.58-1.70)	1.32 (CI 1.27-1.38)
Coronary angiography	1.58 (CI 1.51-1.65)	1.23 (CI 1.18-1.30)
PCI/CABG	1.67 (CI 1.59-1.75)	1.34 (CI 1.27-1.42)
Heparin/LMWH, iv	1.28 (CI 1.24-1.32)	1.14 (CI 1.10-1.18)
Beta blocker, orally	1.27 (CI 1.23-1.31)	1.15 (CI 1.10-1.20)
ASA/thrombocyte inh./anticoag.	1.42 (CI 1.36-1.48)	1.27 (CI 1.21-1.33)
ACE-inhibitor	1.12 (CI 1.09-1.38)	1.22 (CI 1.17-1.28)
Lipid lowering drug	1.33 (CI 1.29-1.38)	1.01 (CI 0.96-1.06)(ns)
30-d mortality	0.95 (CI 0.93-1.01)(ns)	1.27 (CI 1.19-1.35)
1-year mortality	0,91 (CI 0.88-0.95)	1.26 (CI 1.20-1.32)

OR calculated for male patient. All CI at 95% level. All p-values, unless indicated, < 0.001.

Conclusion: In an ICCU population, with objective signs UCAD, the utilization of cardiac procedures and prescription of prophylactic medicine were lower in women. Adjustment for covariates did not change this association.
Unadjusted mortality for women were higher at 30 days and 1 year but after adjustment for age and other risk factors, male sex was significantly associated with a higher mortality at 30 days and 1 year.

P480 C-reactive protein and interleukin-6 increase in acute coronary syndromes could be due to intraarterial thrombosis

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Background: Intraarterial thrombosis and arterial wall inflammation interactions could be responsible for the sharp increase in C-reactive protein (CRP) and IL-6 observed in acute coronary syndromes. Thus, we tested the hypothesis that CRP and citokyne increase in a model of acute coronary syndromes such as coronary angioplasty could be due to intraarterial thrombosis.
Methods: One hundred forty-four patients who underwent a coronary angioplasty procedure at our cath lab were included. We excluded patients with inflammatory, metabolic or neoplastic diseases, and patients with post angioplasty CK/MB elevation. C-reactive protein was analyzed in all patients. In a subgroup of 29 patients IL 6, IL-1b, IL-8, IL-10, IL-12, TNF-alfa and screening for IL-6 production gene 174 GG was also performed. Blood samples were collected pre angioplasty, 24 and 48 hours after the procedure. In 80 patients an eptifibatide perfusion was initiated immediately after the procedure, and continued for only 24 hours. The remaining 64 patients received standard antithrombotic therapy.
Results: CRP figures are shown in the table. From all citokynes studied, only IL-6 increased after coronary angioplasty (6.81±7.04 to 21.15±13.79;p<0.05). This increase was blocked by Eptifibatide in homocigotous (174 GG) IL-6 hyperproduction patients when compared to controls (-1.06±12.79 vs 14.33±14.65; p<0.05).
Conclusions: C-reactive protein and IL-6 increase after coronary angioplasty was suppressed by eptifibatide, a synthetic peptide which is a selective blocker of the platelet GP IIb-IIIa receptor with no known anti-inflammatory effects. Thus, it seems that CRP increase in acute coronary syndromes could be mostly due to intraarterial thrombosis.

CRP after PTCA

	Basal	24 h	48 h
Control	0.63 (0.9)	1.21 (1.23)	1.67 (1.61)
Eptifibatide	0.93 (1.5)	0.91 (1.36)	1.59 (2.76)
p	ns	<0.05	ns

Results are listed as: mean (standard deviation)

P481 Prevalence of heat shock protein 60 homologues in acute coronary syndrome lesions – correlation with serum antibodies to heat-shock protein 65

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Background: Recent studies provide evidence that increased titers of antibodies against heat-shock protein (HSP) 65 are associated with atherosclerois, cross-react with HSP60 and mediate endothelial cytotoxicity. Both chlamydial (c) HSP60, produced during chronic persistent infection, and endogeneous human (h) HSP60, upregulated under stress conditions, contribute to inflammation in atherogenesis and serve as a target for (auto-)immune reactions. However, a correlation between intimal tissue-bound HSP and serum antibodies to HSPs is unknown.
Methods: Coronary atherectomy specimens retrieved from 60 primary target lesions of patients with acute coronary syndrome (ACS; n=30) or stable angina (SA; n=30) were assessed immunohistochemically for the presence of cHSP 60 and hHSP 60. Blood samples from 30 patients were tested for antibody titers to HSP65 by ELISA.
Results: Coronary plaques revealed immunoreactive cHSP60 in 65% and hHSP60 in 79% of the lesions vs. none of 20 undiseased control samples. Intimal predilection sites were regions with macrophages/foam cell accumulation, inflammatory infiltrates and sparse cellularity. Mean expressions were 6.7% for cHSP60 and 6.5% for hHSP60. As the central finding, the expression of both HSP homologues was significantly (p<0.01) higher in ACS lesions compared to SA lesions (8.9% vs. 3.1% and 8.7% vs. 2.1%). Moreover, we found positive correlations in both subgroups (r=0.42, r=0.33; p<0,05). Most interestingly, the serum titers of HSP65 antibodies correlated (p<0.05) with both the intimal cHSP60 (r=0.52) and hHSP60 expression (r=0.44). Mean titers were higher (p<0.05) in lesions associated with both HSPs (1:576) compared to those with one (1:343) or no intimal HSP60 homologue (1:300).
Conclusion: cHSP60 and hHSP60 colocalize within coronary primary atheroma, most prevalent in lesions associated with ACS. For the first time, our data demonstrate a significant correlation between serum HSP65 antibodies and the intimal expression of the HSP60 homologues, thereby suggesting that humoral immune reactions to bacterial and human HSPs may play an important role in coronary atherosclerosis and plaque instability.

P482 Overexpression of cardiac tumour necrosis factor-alpha and interleukin-6 genes and cardiac RAS activation in unstable angina

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Angiotensin (Ang) II is a potent mediator of inflammation and is able to induce the gene expression of several inflammatory mediators. In unstable angina (UA) a selective activation of cardiac renin-angiotensin system (RAS) was recently shown. To investigate whether the increased cardiac Ang II formation induces an inflammatory reaction in myocardium, the gene expression and localization of tissue necrosis factor (TNF)-alfa and interleukin (IL)-6 were investigated in left ventricle biopsies from 2-vessel disease anginal patients. Biopsies specimens were collected from 10 UA and 10 stable angina (SA) patients who underwent coronary by-pass surgery and from 6 patients with mitral stenosis who underwent valve replacement, examined as control hearts (CH). Angiotensinogen (AGTN), angiotensin-converting enzyme (ACE), TNF-alfa and IL-6 gene expression was quantified by reverse transcriptase-polymerase chain reaction (RT-PCR) and expressed as ratios to the costitutively expressed gene for glyceraldeyde-3-phosphatase deydrogenase (GAPDH). RAS and cytokine genes were localized by in situ hybridization procedure carried out with specific cDNA photobiotin-labeled (Vector) probes.
RT-PCR showed that AGTN and ACE mRNAs were expressed in all myocardial ventricular biopsies from anginal patients and controls, whereas TNF-alfa and IL-6 genes were well expressed only in specimens from UA hearts. Importantly, in UA hearts AGTN, ACE, TNF-alfa and IL-6 genes were overexpressed versus SA and controls hearts (p<0.01).Hybridization studies showed that in ventricular myocardium from CH and SA patients AGTN, ACE, TNF-alfa and IL-6 genes were expressed in trace amounts.Conversely, in UA specimens the signal for RAS components and cytokine genes was strong and was almost exsclusively detectable on endothelial and interstitial cells. No signal was detected on myocytes.
In UA heart the selective activation of cardiac RAS components is associated to a myocardial inflammatory reaction.

P483 Time course of markers of inflammation and plaque instability in patients presenting with acute coronary syndromes

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Background: Inflammation within vulnerable coronary plaques may cause an acute coronary syndrome by promoting rupture and erosion. Yet, it is unclear whether 1) the inflammatory process is confined to a single vulnerable plaque, 2) whether markers of inflammation and plaque stability are from a cardiac or extracardiac source and 3) which effect angioplasty exerts on the time course of these markers.
Patients and Methods: Blood samples were taken from patients with acute coronary syndromes (ACS) (n=13), and from healthy controls (n=13). Blood was taken from the femoral vein and from the great cardiac vein before and after coronary angioplasty (day 0). On day 1 and day 120 blood was collected from a peripheral vein. Markers of inflammation and markers of plaque instability were measured by Enzyme-linked immunosorbent assays.
Results: Levels of interleukin-1-receptor antagonist (IL-1-ra) and interleukin-6 (IL-6) were elevated in ACS patients compared to controls in central and peripheral blood from day 0 until day 120. Tumor necrosis factor-alpha (TNF-alpha)- and tissue inhibitor of metalloproteinase-1 (TIMP-1)-levels were higher in ACS-patients on day 0 and day 1 as compared to controls, but showed comparable values at day 120. Monocyte chemoattractant protein-1 (MCP-1) and metalloproteinase-2 (MMP-2) plasma levels were higher in coronary sinus blood and in peripheral blood of ACS patients on day 0, but not thereafter. CD40 ligand (CD40L) and MMP-9-levels showed an increase on day 1 in ACS-patients and were still elevated as compared to baseline levels by day 120. There were no significant differences of the plasma levels of these markers between blood from the great cardiac vein and the femoral vein.
Conclusion: The time course of markers of inflammation and plaque instability may vary according to their role as an either more local or systemic mediator of inflammation. The rapid decrease in concentrations of several markers, such as TNF-alpha, MCP-1, MMP-2 and TIMP-1 indicates their release from a more focally defined process whereas the long-term up-regulation of IL-1 ra and IL-6 suggests to be a systemic reaction in patients having presented with an acute coronary syndrome.

P484 Human heart-type fatty acid-binding protein for diagnosis of unstable angina and non-ST-elevation myocardial infarction

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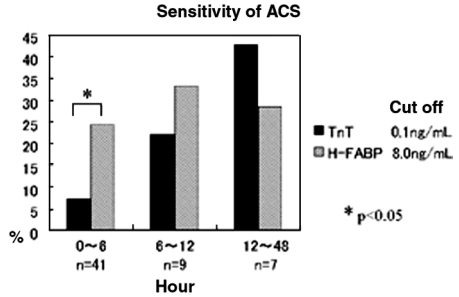
Back ground: H-FABP has been considered as a diagnostic and prognostic marker in acute myocardial infarction (AMI). However, the clinical usefulness for UA/NSTEMI is not well defined.
Method: A total of 57 patients with typical chest pain without ST elevation were enrolled. The patients with renal function abnormality (creatinine clearance $<$50 mL/min) were excluded. We measured H-FABP and Troponin T (TnT) levels, and their diagnostic values were compared in terms of the timing of sampling.
Results: Patients were diagnosed as ACS (n=31) and non-ACS (n=26) by coronary angiography and/or exercise test. The overall diagnostic sensitivity of H-FABP was 41.9%, against was 25.8% with TnT. On the other hand, the diagnostic specificity in the group of patients with non-ACS was 88.5% with H-FABP, against 96.1% with TnT. Within 6 hours of the onset of symptoms, the diagnostic sensitivity of H-FABP and TnT were 24.4% and 7.3% respectively ($p<0.05$, Figure).



Conclusion: H-FABP is more sensitive than TnT for diagnosis of UA/NSTEMI within 6 hours of the onset.

P485 Soluble P-selectin, a marker of endothelial activation

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Background: Atherosclerosis, a chronic inflammatory process, is initiated and perpetuated by activated endothelium. P-selectin, a cell adhesion molecule, is expressed and released by activated endothelial cells and could therefore be a marker of endothelial activation. However P-selectin is also expressed by activated platelets and was often used as a marker of platelet activation. In this animal study we investigated the origin of soluble P-selectin and whether its release can be stimulated by high cholesterol diet.
Methods and Results: Recipient LDLR deficient (LDLR-) mice that were either P-selectin wild type or P-selectin deficient were lethally irradiated at the age of 7 weeks and reconstituted with bone marrow of LDLR- P-selectin deficient or LDLR- P-selectin wilde type mice respectively. By this we obtained one group of mice that expressed P-selectin on their endothelium but not on their platelets (EC+/Plt-) and one that expressed P-selectin on their platelets but not on the endothelium (EC-/Plt+). FACS analysis of activated platelets showed that more than 95% of platelets were of donor origin. Five weeks after transplantation, mice were put on a high cholesterol diet for 18 days. In all the mice cholesterol levels increased from a mean of 210 mg/dl before to 2684 mg/dl after the diet. Soluble P-selectin was measured by sandwich ELISA; mean OD at 450 nm of non-transplanted LDLR-P-selectin wilde type mice (EC+/Plt+) on high cholesterol diet was set 100%. In EC-/Plt+ mice, levels of soluble P-selectin remained unchanged before and after the diet ($20.96 \pm 0.87\%$ versus $23.14 \pm 1{,}4\%$; mean $\pm$ SEM; $p = 0.22$; $n = 5$), whereas in EC+/Plt- mice, levels of soluble P-selectin increased significantly upon high cholesterol diet ($46.01 \pm 3.2\%$ versus $107.37 \pm 8.9\%$; $p < 0.05$; $n = 3$). This increase corresponded quite well to the increase seen in non-transplanted EC+/Plt+ mice ($56.37 \pm 5.6\%$ versus $100 \pm 5.7\%$; $n = 8$).
Conclusions: These data show convincingly that in atherosclerotic prone LDLR- mice soluble P-selectin stems mainly from endothelium and its release can be stimulated by a high cholesterol diet.

P486 Risk prediction in diabetic post-infarction patients

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Background: Diabetic post-infarction patients are at a higher mortality risk than non-diabetic patients. This study was performed to investigate the predictive power of risk stratifiers in post-infarction patients with diabetes mellitus.
Methods: 1,455 consecutive post-infarction patients were prospectively included. Inclusion criteria were acute myocardial infarction $<$4 weeks, age $\leq$75 years, sinus rhythm, Holter ECG duration $\geq$10 hours. 294 patients suffered from diabetes mellitus. Primary endpoint was total mortality. Mean follow up was 22 months. Univariate and multivariate Cox-proportional hazards analyses were performed with respect to age, arrhythmia count, mean heart rate, heart rate variability, history of previous myocardial infarction, LVEF and Heart Rate Turbulence (HRT), all with prospectively defined dichotomy limits. Both parameters of HRT (HRT-TO and HRT-TS) were determined according to the published technology.
Results: During follow up period 5% of the non-diabetic patients and 13% of the diabetic patients died ($p<0.0001$). With the multivariate approach age, LVEF and HRT-TS were the only independent risk predictors in diabetic post-infarction patients. In diabetic patients with an abnormal HRT-TS, 24 out of 84 patients died, the corresponding positive predictive value was 29% at a sensitivity level of 62%. In diabetic patients with a LVEF $\leq$30%, 9 out of 25 patients died, the corresponding positive predictive value was 36% at a sensitivity level of 23%.
Conclusion: In diabetic post-infarction patients HRT-TS is a strong and independent risk predictor. HRT-TS performs particularly well, probably because it identifies patients with relevant autonomic dysfunction.

P487 The long-term prognostic value of elevated cardiac troponins in patients undergoing major vascular surgery is not influence by renal function or skeletal muscle injury

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Background: Perioperative myocardial infarction (MI) is associated with a poor long-term outcome, but diagnosis is often difficult as cardiac symptoms may be absent during surgery. Troponin T (TnT) is a recently developed marker of myocardial necrosis, however it's interpretation in patients with severe renal dysfunction or massive skeletal muscle CK release during surgery is controversial.
Aim: To evaluate the long-term prognostic value of perioperative TnT in patients undergoing vascular surgery without symptoms or ECG changes suggestive of perioperative MI.
Methods: Cardiac enzymes (CK/CK-MB ratio and TnT), serum creatinine and ECG were measured on day 1, 3, and 7 after vascular surgery. Elevated cardiac enzymes were defined as: TnT positive (2nd generation assay), TnT >0.1 ng/ml (3rd generation assay). A creatinine >180 μmol/l indicated severe renal dysfunction, a CK >1000 U/L massive CK release. During follow-up cardiac death and MI was noted. The relation between serum markers and long-term outcome was evaluated by Cox' proportion hazard regression analyses. Results are presented as hazard ratios (HR) and 95% confidence intervals (CI).
Results: 517 consecutive patients were enrolled, and 126 (24.4%) had elevated TnT. During a median follow-up of 4.0 years cardiac death occurred in 22 (4.3%) patients. The composite of cardiac death or MI occurred in 51 (9.9%) patients. Patients with elevated TnT had significant worse prognosis than those with normal TnT (composite endpoint: 20.6% versus 6.4%; HR 3.4, 95% CI 2.0-5.9; $p<0.001$). There was no interaction between TnT and renal function (HR 2.2 [1.1-4.6] in normal renal function, and 4.1 [1.4-12.5] in renal dysfunction; p-value for interaction 0.41) or massive CK release (HR 3.0 [1.7-5.7] if CK <1000 U, and 8.1 [1.0-6.5] if CK >1000 U; p-value for interaction 0.36). After adjustment for age, gender, cardiovascular risk factors, TnT remained an significant long-term outcome determinant (HR 2.9 [1.6-5.2]; $p<0.001$).
Conclusion: Perioperative TnT release is associated with late cardiac death and MI in cardiac asymptomatic patients undergoing major vascular surgery. There was no influence of renal dysfunction or massive CK release on the prognostic value of TnT.

P488 The predictive value of dobutamine stress ecocardiography in the assessment of unstable angina patients with low and moderate risk for infarction and death

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Purpose: In coronary artery disease, dobutamine stress echo (DSE) has been used for the investigation of many conditions including post acute myocardial infarction (MI. However there is concern to use this method in patients with unstable angina. We then thought to evaluate the role of DSE for the risk stratification of patients admitted to the emergency department with chest pain and diagnoses of low to moderate risk unstable angina (UA).
Methods: Ninety-five patients (mean age 59.7 ± 12.2 yo) admitted to the emergency department with unstable angina of low to moderate risk were submitted to an DSE during the first 72 h. We then accessed the combined end point of death, MI, recurrent UA and either percutaneous or surgical revascularization procedures during a 6 month follow-up by univariate and multivariate analysis. Patients had hypertension (67.4%), dislipidemia (54.7%) and previous MI (12.6%).
Results: Most of the patients had UA of moderate risk. DSE was positive for myocardial ischemia in 40 patients (42.1%) and negative in 55 patients (57,4%). We observed 28 end-points at follow-up. So, the positive predictive value and negative predictive value of the test were: [65.0%, IC95%: 48.3 - 78.9%] and [96.4%, IC95%: 86.4% - 99.4%], respectively. Univariate analysis identified UA classification, left ventricle ejection fraction, rest and peak wall motion score index, DSE result and history of previous MI associated to the combined end point. However DSE result was the only independent predictor of cardiac events by multivariate analysis ($p<0.001$) in these patients.
Conclusions: DSE showed an excellent negative predictive value and a positive result for ischaemia was the only independent predictor for cardiac adverse events during 6 month follow-up in these patients.

PROGNOSIS AND RISK ASSESSMENT IN ACUTE CORONARY SYNDROMES

P489 Unstable coronary artery disease – a missed diagnosis?

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Background: Previous studies have suggested that women with unstable coronary artery disease (UCAD) less often than men are subject to risk assessment before discharge. Little is known about differences between men and women in diagnosing unstable coronary artery disease. The aim of this study was to investigate gender differences in diagnosing UCAD in a population with objective signs of UCAD.
Method: The Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) includes all patients from participating intensive coronary care units (ICCU) and collect data including 100 variables for each patient. 76,256 patients with ST-depression on admission-rest-ECG and/or elevated markers indicating myocardial damage (troponin-T and/or CKMB) were included between 1995 and 2000. All patients with ST-elevation or left bundle branch block (LBBB) on admission-rest-ECG were excluded.
Results: Diagnosis at discharge is prsented in the table.

	Men (n=45,606)	Women (n=30,560)	p-value
Unstable coronary artery disease (%)	58.2	48.7	<0.01
Other angina pectoris (%)	18.1	20.6	<0.001
Congestive heart failure (%)	3.9	5.3	<0.001
Arrhytmia (%)	6.5	9.6	<0.001
Other heart disease (%)	1.4	1.7	0.013
Chest pain with unknown origin (%)	7.1	8.4	<0.001
Other disease (%)	4.7	5.7	<0.001

Conclusion: A large proportion of patients with objective signs of UCAD, based on admission-ECG findings and myocardial damage marker levels, were given a non-UCAD diagnosis at discharge. More than half of the women were given a non-UCAD diagnosis.
The relevance of this is unknown but could have implications on treatment and outcome, especially for women.

P490 Are "region based" and "population based" registries comparable? Comparison of reperfusion therapy and 30 day mortality between a region-based and two population-based registries

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Aim: to determine whether large "population-based" registries actually reflect real life situations, as observed in a "region-based" registry. **Methods:** Franche-Comte is a region in eastern France covering 16,200 km^2 and with 1.1 million inhabitants. Between October 1 and March 30, 2002, all patients admitted for acute coronary syndromes in one of the 12 hospitals in the region were entered in a prospective registry. The population and use of reperfusion therapy were compared with the published results of three "population-based" registries (ENACT, GRACE and Euro Heart Survey ACS). **Results:** 882 patients were included, 333(38%) with ST elevation MI, 421(48%) non Q MI and 118(14%) unstable angina (table). **Conclusion:** In comparison with the results of large multinational registries, the results of this region based registry show a lower use of reperfusion therapy and higher 30-day mortality.

	Franche-Comte (a)	GRACE (b)	ENACT (c)	EHS ACS (d)	P (a vs b)	P (a vs c)	P (a vs d)
n	333/873 (38%)	2501/8636 (29%)	1331/3292 (39%)	4431/10484 (42%)	<0.001	0.21	0.02
Male (%)	235 (70%)	1283/1763 (73%)	838/1331 (63%)	3172/4431 (72%)	0.41	0.01	0.69
Admitted<12h	225 (68%)	1763/2501 (70%)	958/1331 (72%)		<0.001	0.11	
No reperfusion	157 (47%)	887/2310 (38%)	559/1331 (42%)	1958/4431 (44%)	0.002	0.09	0.29
Thrombolytic	111 (33%)	987/2310 (43%)	488/958 (51%)	1555/4431 (35%)	<0.001	<0.001	0.51
Angioplasty	38 (11%)	289/2310 (13%)	76/958 (8%)	917/4431 (21%)	0.33	0.05	<0.001
TL & Angio	27 (9%)	147/2310 (38%)			0.03		
30-day mortality				372/4431 (8.4%)		<0.001	0.06
Global	39/333 (12%)	252/3419 (7%)	83/1382 (6%)		0.04		<0.001
Admitted<12h	23/225 (10%)	108/1763 (6%)			0.04		

P491 Recurrence rates of acute coronary syndromes in patients undergoing percutaneous coronary intervention

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Purpose: Patients with acute coronary syndrome (ACS) may have multiple plaques becoming unstable at different times. The study was performed to investigate whether patients successfully treated with percutaneous coronary intervention (PCI) due to ACS have a higher incidence of recurrent acute coronary events due to new plaque instability than patients treated with PCI due to stable angina pectoris (SAP).
Methods: Retrospective study of 526 patients who had a successful PCI. Patients were excluded if they had undergone revascularization prior to the index PCI. Patients were subgrouped into three groups: SAP (SAP-group), ACS (ACS-group) and previous ACS (i.e >1 month prior to PCI) (prev-ACS group). Primary end-points were: occurrence of a new acute coronary event (ST-segment changes or elevated myocardial markers), and occurrence a new acute coronary event in a vessel different from the initially treated. Patients were followed at least 12 months.
Results: The SAP-group included 134 patients; the ACS-group: 236 patients and the prev-ACS group: 156 patients. Median follow-up was 22 months; range 12-36 months. In the SAP-group 4% had a new coronary event compared to 8% in the ACS-group (ns) and 8% in the prev-ACS group (ns). In the SAP-group 6% had a new acute coronary event deriving from a different vessel compared to 8% in the ACS-group ($p<0.05$) and 3% in prev-ACS group (ns). No differences were seen regarding restenosis rate among the three groups; 10%, 12% and 11%, respectively.
Conclusion: Our study shows that after a successful PCI, patients with ACS have a higher incidence of recurring acute coronary events from a vessel different from the one initially treated than patients with SAP or prev-ACS.

P492 Usefulness of TIMI risk score in a non-selected chest pain population. Additive prognostic value of left-ventricular ejection fraction

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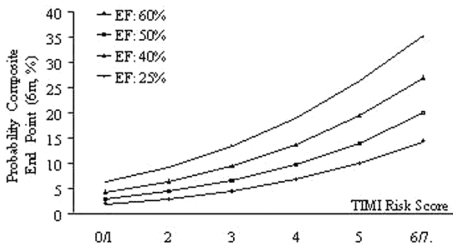
TIMI Risk score has demonstrated to be of prognosis value in selected patients enrolled in clinical trials on unstable angina and myocardial infarction (MI). There is little information about its application to non-selected chest pain population and whether other variables such as ejection fraction (EF) can add prognostic information.
Aim: To evaluate this score in a non-selected chest pain cohort and determine the prognostic value of EF for risk stratification.
Methods: 711 consecutive patients (463 (65%) male, aged 65±12 years) admitted to our hospital with chest pain suggestive of a cardiac origin without ST-segment elevation were included. Patients underwent clinical evaluation, serial ECGs, measurements of cardiac markers, echocardiography and ischaemia testing. Individuals considered to be at high risk underwent cardiac catheterization. All patients were followed-up for 6 months. Logistic regression analysis was employed for prognostic markers.
Results: 61 (8.5%) patients had at least one cardiac event during follow-up (20 (2.8%) death, 22 (3.1%) MI, 28 (3.9%) subsequent revascularization). TIMI risk score [Odds Ratio (OR) for 1 unit increase: 1.52 (95%CI: 1.19-1.95, p=0.001)] and EF [OR for 10% decrease: 1.48 (95%CI: 1.10-1.98, p= 0.009)] were independent predictors of the composite cardiac event (Death/MI/Revascularization) at 6 months. (Figure 1, from Regression Model).



Conclusions: TIMI risk score is an important predictor of prognosis in a non-selected chest pain population. EF provides an additional value in this setting.

P493 Extend of myocardial damage and long-term outcome after non-ST-elevation acute coronary syndromes treated with very early revascularization

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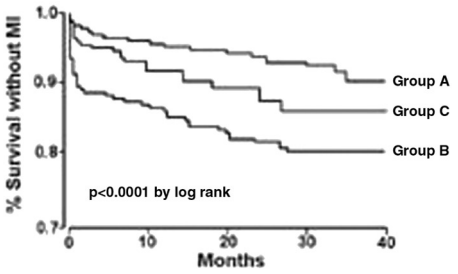
Background: There is limited information about the prognostic implications of the new (elevated troponin) versus the old (elevated creatine kinase (CK) > twice the upper normal limit (2x UNL)) definition for myocardial infarction (MI) in patients with non-ST-elevation acute coronary syndromes (NSTACS) treated with early revascularisation.
Methods: In a prospective study of 1047 consecutive patients (age 64.7±11years) with NSTACS stenting of the culprit lesion within 24 hours of admission was the primary revascularisation strategy. Treatment was percutaneous coronary intervention in 57% (stent rate 80%), coronary bypass grafting in 14% and conservative in 29%. Patients were stratified according to myocardial markers on admission: 420 patients with negative serum markers (Group A), 420 patients with elevated troponin T (TnT) >0.1μg/L and normal CK (Group B), and 205 patients with CK-elevation > 2x UNL (Group C).
Results: Mean follow-up was 24±16 months. Kaplan-Meier analysis showed a cumulative 3-years survival of 97.1% in Group A, 84.4% in Group B, and 90.1% in Group C ($p<0.0001$ by log-rank). Cumulative survival without MI at 3 years (see Figure) was 90.3% in Group A, 80.3% in Group B, and 86.8% in Group C ($p<0.0001$ by log-rank; p 0.019 by log-rank for Group B versus C). By Cox regression analysis elevated TnT at baseline was an independent predictor for long-term mortality (hazard ratio 2.60, 95% confidence interval 1.34 to 5.04; $p<0.005$).



Survival without MI.

Conclusions: Patients with NSTACS who present with an isolated elevation of TnT have a worse long-term outcome after an early invasive strategy than those presenting with elevated CK.

P494 Early invasive strategy for acute coronary syndromes without persistent ST-segment-elevation – 6-month outcome of 401 consecutive high-risk patients from Zabrze registry

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Background: Long-term results of acute coronary syndromes (ACS) depend largely on the early treatment strategy employed. Published data on the late outcome of ACS patients (pts) treated invasively are equivocal and scarce.
Methods: We analysed 401 consecutive pts who fulfilled at least one of the following criteria: 1) Braunwald class III angina, 2) ST segment changes, 3) positive serum cardiac markers. All patients were diagnosed invasively with subsequent revascularisation (PCI or CABG) if appropriate. Analysis of long-term survival and occurrence of major adverse cardiovascular events requiring hospitalisation (MACE) was performed.
Results: Baseline characteristic of the pts: Age: 61,2±10,2 y, >65y 35,4%, males: 67,1%, diabetes: 25%, hypertension: 72,8%, smokers: 41,9%, hyperlipidemia: 78,6%, previous myocardial infarction: 49,9%, previous CABG 6%. Coronary angiography revealed 1-vessel disease in 31% of pts, 2-vessel and 3 vessel disease in 30% and 37% of pts respectively. PCI was performed in 70,9% of pts, 19,2% underwent CABG, 1,5% had combined PCI and elective CABG and 8,4% of pts were treated conservatively. 30-day and overall mortality was 3,9% and 4,7% respectively. MACE were observed in 32% of pts; 9,5% required PCI (7,9%) or CABG (1,6%). In multivariate analysis combined endpoint (death and MACE) occurred more often in pts with previous MI and heart failure (OR 2,14 and 1,44 respectively: p=0,003). Baseline ECG changes and cardiac markers did not influence the combined endpoint.
Conclusion: Invasive strategy in high-risk ASC patients yields good long-term results with low rate of repeat revascularisation procedures. Mortality rate is low especially beyond 30 days from the admission to the hospital.

P495 Beneficial impact of the United Kingdom national refractory angina guidelines on hospitalization

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Background: In 1999 the Scientific committee of the ESC selected the UK national Refractory Angina Guideline (www.angina.org) as a hot outcome from the Barcelona congress. We report on the effect of the fully implemented guideline on hospitalisation rates in a consecutive series of 336 patients referred to the UK national refractory angina centre (NRAC). NRAC is the only specialist referral hospital for a mixed urban and rural population of 2.8 million.
Methods: Since 1995 all hospitals in the NRAC catchment area have recorded all hospital admissions on all patients on local databases. All data was collected and collated on all patients referred to NRAC between 1/1/1997 and 1/10/2001. This time period was selected in order to ensure that at least one year post enrolment follow up was available. Independently predefined periods were used to calculate normalised annual hospital admission rates before and after enrolment. The data was independently statistically analysed using non-parametric tests of significance.
Results: Demographics: 336 patients, aged 34 to 86 years, 70% male, 310 (92%) chronic refractory angina sufferers(of which 260 (84%) had undergone previous revascularisation and 224 (73%) had suffered a previous MI) and 26 (8%) patients diagnosed with syndrome X.

Annual Hospitalisation Rates

	Pre NRAC	Post NRAC	Absolute difference	p (Wilcoxon)
Total number of hospital days	4150	3007	1143	<0.001
Total hospital days/patient	12.4	9.0	3.4	<0.001
Total hospital admissions	676	486	190	<0.001
Total hospital admissions/patient	2.01	1.45	0.56	<0.001

Conclusions: This research demonstrates that full implementation of the UK national refractory angina guidelines reduces hospitalisation. Assuming an average European bed day cost of 300 Euro, this would generate a recurrent annual saving of 1020 Euro per patient.

P496 Inflammation and endothelial dysfunction – correlations with with TIMI risk score in unstable angina patients

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Aim of the study: Antman et al (JAMA, 2000) suggested a new risk score for patients with unstable angina. Trying to elucidate further the role of inflammation and endothelial toxicity in the evolution of patients with unstable angina, we assessed the correlation between the TIMI risk score and the plasmatic levels of C-reactive protein (CRP) and homocysteine (Hcys).
Material and method: 77 patients (pts), 41 men (53.2%), mean age = 57.6±11.9 years-old, with unstable angina. Measurement of Hcys (enzymatic immunoassay) and of CRP was performed (upper limit of normal range 15 μM/L and 5 mg/L, respectively). Patients with infectious or inflammatory conditions were excluded from the study. The patients were assessed using the variables of the TIMI risk score: age >65 y, at least 3 risk factors, >2 anginal events in the last 24 h, ST deviation, coronary stenosis >50%, elevated serum cardiac markers (CKMB/CK, Troponin T), use of aspirin in the last 7 days. We correlated the TIMI risk score with the plasmatic values of CRP and Hcys.
Results: We noted a normal distribution of the TIMI risk score in our study group, with over 77% of pts having a TIMI risk score of 3 to 5. We found a progressive pattern of the values for both CRP and HCys (see table), with higher plasmatic concentrations significantly correlated with the level of cardiovascular risk. CRP had a more significant ascending trend and a better Pearson correlation coefficient with TIMI risk score than Hcys (r=0.73 vs. r=0.51).

Table 1

TIMI score	0/1	2	3	4	5	6/7
No pts (%)	7 (9.1%)	11 (14.3%)	16 (20.8%)	17 (22.1%)	20 (25.9%)	6 (7.8%)
CRP (mg/L)	4.11	6.98	9.34	17.63	21.31	36.2
Homocysteine (mcM/L)	9.27	12.67	16.29	18.03	18.82	17.98

Conclusion: Both inflammation (with CRP as a marker) and endothelial toxicity induced by Hcys correlate well with cardiovascular risk as quantified by the TIMI risk score, with a more significant association for C-reactive protein. Values above normal for both CRP and homocysteine predict quite accurately the presence of a TIMI risk score higher than or equal with 3.

P497 Flu vaccination in acute coronary syndromes: treatment benefits in prespecified subgroups

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The first clinical prospective study Flu Vaccination in Acute Coronary Syndromes (FLUVACS) trial has shown that flu vaccination, to be more effective in addition to standard therapy during the winter season in reducing the risk of death in patients with acute myocardial infarction (MI). However, patients with MI with or without ST segment elevation are a heterogeneous group.
Methods: An analysis using data was performed to examine the efficacy of flu vaccination in different patient subgroups.
Results: Cox regression analyses revealed that Flu vaccination was more effective in reducing the incidence of death, MI or recurrent angina in the majority of subgroups at 6 months after randomization, particularly in patients with non-ST-segment deviation or older than 65 years old, non-smokers and patients with TIMI Risk Score more than 6 (table).

Characteristics	No. of Patients	Control Group with events	Vaccine Group with events	Relative Risk (95% CI)
Overall	301	34	17	0,50 (0,29-0,85)
PCI Group	101	10	7	0,69 (0,28-1,66)
AMI Group	200	24	10	0,42 (0,21-0,83)
Male	138	18	8	0,44 (0,21-0,95)
Female	62	6	2	0,33 (0,07-1,53)
≤ 65 years old	91	10	5	0,49 (0,18-1,32)
> 65 years old	109	14	5	0,36 (0,14-0,92)
ST Segment elevation MI	74	8	8	1,00 (0,42-2,38)
Non ST Segment elevation MI	116	16	2	0,13 (0,03-0,52)
Enzymes elevated at entry	150	14	8	0,57 (0,25-1,28)
Enzymes not elevated at entry	50	10	2	0,20 (0,05-0,82)
Diabetes	39	4	1	0,26 (0,03-2,15)
No diabetes	161	20	9	0,44 (0,22-0,92)
Smoker history	72	7	7	1,00 (0,39-2,56)
Non smoker	128	17	3	0,18 (0,05-0,57)
TIMI Risk Score < 6	168	15	8	0,53 (0,24-1,19)
TIMI Risk Score ≥ 6	32	9	2	0,22 (0,06-0,87)

Conclusions: Secondary prevention against flu during the acute phase of myocardial infarction may be effective in a broad range of patients with acute coronary artery disease.

P498 Relative power of autonomic nervous system high-frequency components and Framingham risk factors in predicting future cardiovascular events. The proof study

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Aim: A prospective cohort of 1011 subjects aged 65 years old at the entry of the study was selected from the electoral register from the town of Saint-Etienne, France.
They were free of symptomatic cardiovascular event. In such a cohort, heart rate variability could be considered as a powerful predictor of cardiovascular risk but was never prospectively compared to the established risk factors.
Methods: Their cardiovascular risk assessment was evaluated from the classical Framingham weighted risk factors which include age, body mass index, presence of diabetes, of hypertension, level of total and HDL cholesterol, triglyceride, and smoking habits.
The subjects were then classified according to these data from the highest to the lowest global risk. Nocturnal heart rate variability (HRV) was simultaneously assessed in the whole cohort. Subjects were again classified according to their high frequency (HF) component power spectral density (Wavelet decomposition) from the lowest to the highest value. The order of the classification of the two lists was then compared using Pearson rank correlation.
Results: The pearson rank correlation coefficient reached 0.995 ($p<0.000$) demonstrating an equivalent ability to summarize cardiovascular risk factors by HF or by the complex set of Framingham risk factors.
Conclusion: The nocturnal HF Power Spectral Density measurement should thus become an easy to use tool to assess global cardiovascular risk and eventually monitor the benefits resulting from medical interventions.

PROGNOSTIC VARIABLE IN ACUTE CORONARY SYNDROMES

P499 Effect of preintervention coronary flow and myocardial perfusion on clinical outcome one year after early post-thrombolysis stenting. An angiographic substudy of the GRACIA trial

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Background and Objective: To address the effect of posthrombolysis culprit-artery flow and myocardial perfusion on prognosis we analysed the relationship between the clinical outcome and the acute angiographic findings of interventional patients of the GRACIA study.
Methods: The GRACIA trial included 500 pts randomly assigned to angiography and stenting within 24 hours of thrombolysis versus conservative posthrombolysis ischemia-guided approach. We studied the angiographic data from the 252 interventional patients (age: 60±12 years, 87% female), which were obtained 6 to 24 hours after thrombolysis. The delay between onset of symptoms and thrombolysis was 3.0±1.9 hours. Angiographic evaluation was carried out by an independent core laboratory.
Results: At 17±6 hours of thrombolysis patency of the culprit artery was documented in 90% of interventional patients, with the following TIMI corrected frame count (CTFC) distribution: CTFC grade 3 in 80%; CTFC grade 2 in 10%; CTFC grade 1 in 4%; and CTFC grade 0 in 6%. However, only 38% of thrombolysed patients had adequate myocardial perfusion (TIMI Myocardial Perfusion [TMP] grade 3 [30%] or grade 2 [8%]). Early posthrombolysis stenting significantly improved myocardial perfusion (TMP-3 from 30% to 83%, $p<0.001$; TMP-2 from 8% to 11%; TMP-1 from 2% to 1%; and TMP-0 from 60% to 5%, $p<0.001$). At one year, patients with baseline impaired flow (CTFC grade 0-1) had worse prognosis than patients with normal or acceptable flow (CTFC grade 2-3): death or reinfarction combined: 25% vs 6% (p=0.009); mortality: 20% vs 2% (p= 0.001). Impaired myocardial perfusion (TMP grade 0-1) had similar effect: on the combined incidence of death and reinfarction (12% vs 1.4%, p= 0.02). Concordantly, multivariate analysis (logistic regression) identified preintervention epicardial flow (OR 1.94, 95% CI: 1.01-3.92, p= 0.047) and myocardial perfusion (OR 3.49, 95% CI: 1.19-10.28, p=0.02) as independent predictors of death or reinfarction at one year. By contrast, flow after stenting did not correlate with one-year mortality or reinfarction.
Conclusions: Although early posthrombolysis stenting improves epicardial flow and myocardial perfusion, pre-intervention CTFC and TMO continue to be strong independent predictors of one-year clinical outcome.

P500 Small creatine kinase-MB elevations after percutaneous coronary intervention in patients with acute coronary syndrome do not have prognostic implications

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Purpose: The new ESC/ACC definition for myocardial infarction (MI) considers that the same discriminative value for each biochemical marker of myocardial necrosis be applied, irrespective of the clinical circumstances (spontaneous acute coronary event or percutaneous coronary intervention), as they reflect the same amount of myocardial damage. However, it remains uncertain whether a similar amount of myocardial necrosis in different clinical settings has the same prognostic implications. The aim of this study was to determine the prognostic value of CK-MB levels after myocardial revascularization procedures in the setting of non-ST-elevation acute coronary syndromes.
Methods: We studied 307 consecutive patients who underwent myocardial revascularization during hospitalization for a non-ST-elevation acute coronary syndrome. The CK-MB level immediately before the intervention was normal in all patients. Further blood samples were obtained after the revascularization procedure and assayed for CK-MB: at 6 and 12 hours after percutaneous coronary intervention and at 12 and 24 hours after coronary bypass surgery. The study endpoint was death or nonfatal MI by 1-year follow-up.
Results: Myocardial revascularization was percutaneous in 230 patients (75%) and surgical in the remainder. During the first year of follow-up, 24 patients died (7.8%) and 25 had a nonfatal MI (8.1%): the combined incidence of death or nonfatal MI was 13%. The table shows the distribution of peak CK-MB levels after revascularization and their relation with the endpoint rate. No significant association was found between the peak CK-MB level and 1-year outcome, whether revascularization was percutaneous (P=0.9) or surgical (P=0.7).
Conclusion: Small CK-MB elevations (up to 3 times the upper reference value) after myocardial revascularization in the setting of non-ST-elevation ACS do not have prognostic implications at 1-year. The definition of procedure-related MI in this specific clinical setting may require a higher discriminative value for CK-MB.

Outcomes by peak CK-MB level

Death/MI (%)	CK-MB<1xULN	CK-MB 1 to 3x ULN	CK-MB 3 to 5x ULN	CK-MB>5xULN
PCI	13.1% (n=168)	10.2% (n=49)	14.3% (n=7)	16.7% (n=6)
CABG	16.7% (n=12)	9.1% (n=33)	18.2% (n=22)	20.0% (n=10)

PCI, percutaneous coronary intervention; CABG, surgical revascularization; ULN, upper reference value

P501 Preprocedural TIMI flow and mortality in patients with acute myocardial infarction treated by primary angioplasty

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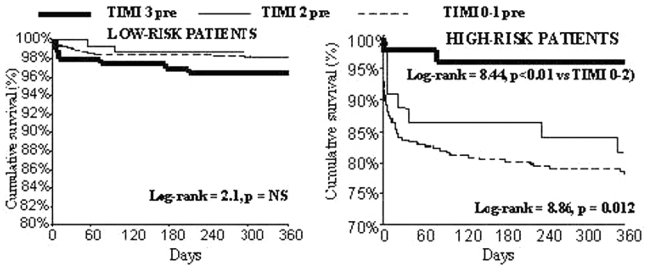
Purpose: Although the excellent outcome conferred by primary angioplasty in patients with acute myocardial infarction (AMI), the prognostic role of early recanalization in these patients has yet to be extensively investigated.
Methods: Our population is represented by a total of 1791 patients with AMI treated by primary angiopalsty at our institution from 1994 to 2001. All angiographic, clinical and follow-up data were prospectively collected. TIMI criteria were used to identify a high-risk population.
Results: Preprocedural TIMI flow was related to postprocedural TIMI 3 flow (p=0.004), myocardial blush grade 2-3 ($p<0.001$), enzymatic infarct size ($p<0.001$), predischarge ejection fraction ($p<0.001$). Preprocedural TIMI flow was significant determinant of 1-year mortality only in high-risk patients (n = 393 patients) (see Figure). Multivariate analysis showed that preprocedural TIMI 3 flow was an independent determinant of 1-year mortality in high-risk patients ($p<0.05$).



Conclusions: This study showed that preprocedural TIMI 3 flow is an independent determinant of 1-year mortality in high-risk patients with AMI treated by primary angioplasty.

P502 Myocardial infarction and patent coronary arteries – is this such an uneventful association?

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Purpose: The evaluation of the clinical course of the patient with myocardial infarction and patent coronary arteries and the post-infarction short-term prognosis.
Methods: A retrospective study based on the cases of acute myocardial infarction (AMI) admitted to the Prof. Dr. C. C. Iliescu Institute of Cardiovascular Diseases, Bucharest, Romania, between 1995 and 2002. The study group consisted of 62 patients with AMI which presented angiographically patent coronary arteries (defined as either normal coronary arteries or non-obstructive coronary disease). They were compared to an age and sex-matched control group of 62 patients with AMI and significant coronary stenoses in terms of cardiovascular risk factors, ventricular function and post-infarction events. In both of the groups, the coronary angiography was performed within the first 30 days after the infarction.
Results: Smoking was represented in the study group in a proportion almost similar to the control group: 47 (66.1%) vs. 54 (87.1%), p=NS. Dyslipidemia was found in 18 patients (29.0%) in the study group vs. 44 patients (74.2%) in the control group, $p<0.005$, and the family history of coronary heart disease (CHD) in 16 patients (25.8%) in the study group vs. 37 (61.3%) in the control group, $p<0.05$.
The post-infarction complications were: ischaemic recurrences in 25 cases (40.3%) in the study group vs. 46 (74.2%) in the control group, $p<0.05$; cardiac failure in 11 cases (17.7%) vs. 26 (41.9%), $p<0.05$; mechanical events (including ventricular aneurysm and new-installed mitral regurgitation) in 12 patients (19.4%) vs. 16 (25.8%), p=NS; arrhythmias in 18 patients (29.0%) vs. 12 (19.4%), p=NS; peripheral embolizations in 5 cases (8.1%) vs. 2 (3.2%), p=NS.
Conclusions: In the population with AMI and patent coronary arteries, smoking was the only well represented risk factor. Dyslipidemia and family history of CHD were less frequently found in this group.
Although there was a significantly lower incidence of the ischaemic events and cardiac failure after myocardial infarction with patent coronary arteries, the mechanical, arrhythmic and embolic complications occurred with the same frequency as in the group with coronary stenoses. This is particularly striking for the ventricular remodelling which was observed to take place also in the presence of an open infarct-related artery, suggesting that the microcirculation may play also an important role in revascularization.

P503 Profile and early outcome of patients admitted for acute myocardial infarction while on antiplatelet therapy: data from the nation-wide French USIC 2000 registry

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The profile and outcome of patients presenting with acute MI while on chronic antiplatelet therapy are not well established. In the French USIC 2000 registry, which included patients admitted to ICUs for AMI $<$ 48 hours from symptom onset in November 2000, 581 of 2320 patients (25%) were on antiplatelet therapy before the index episode. The initial profile of patients on antiplatelet agents was quite specific: older age (70 $\pm$ 13 vs 64 $\pm$ 15 yrs, $p<0.001$), more hypertension (58% vs 42%), current smoking (33% vs 22%), diabetes mellitus (29% vs 18%), more frequent history of cardiovascular disease (prior MI: 46% vs 8%, prior PTCA: 29% vs 3%, prior CABG: 11% vs 2%, prior stroke: 10% vs 3%, prior peripheral artery disease 20% vs 6% and prior CHF: 14% vs 4%). Patients on antiplatelet agents were more likely to receive other cardio-vascular medications (beata-blockers: 44% vs 12%, Calcium antagonists: 24% vs 7%, ACE-I: 29% vs 11%, nitrates: 36% vs 7%, diuretics: 25% vs 14%, statins: 38% vs 12%, all p values $<$ 0.001). Initial presentation was less frequently ST elevation or Q wave MI (60% vs 76%, $p < 0.001$), and less frequently anterior MI (32% vs 37%, $p = 0.01$). More patients on antiplatelet agents were Killip class II or more on admission (31% vs 19%, $p<0.001$). Reperfusion therapy with intravenous thrombolysis or early PTCA was used less often in patients on antiplatelet agents (35% vs 46%). During the hospital stay, all complications except development of heart failure were similar in the 2 groups: ventricular fibrillation (3.8% vs 3.4%, A-V block (4.8% vs 4.6%), VSD (1.6% vs 1.7%), occurrence of stroke (0.7% vs 1.0%), signs of heart failure (38% vs 26%, $p <$ 0.001). Five-day mortality was similar in patients on antiplatelet agents (6.4%) and in those without such therapy (5.6%).
Conclusion: though patients treated with antiplatelet agents have more untoward initial clinical characteristics, their early mortality at the acute stage of MI appears similar to that of patients without such treatment.

P504 The effect of subsequent events on survival following myocardial infarction, stroke or a diagnosis of PAD

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As new preventive interventions for cardiovascular disease emerge, and their benefits are quantified in terms of their ability to prolong quality-adjusted life, it is important to have accurate estimates of the corresponding survival functions and of the effect of subsequent atherothrombotic events and other determinants.
Methods: We obtained the health care records of residents of Saskatchewan who had a myocardial infarction (15,590) or an ischaemic stroke (18,704), between 1990-1995, or a diagnosis of peripheral arterial disease (PAD) (16,440) between 1985-1995. Data on patient characteristics and medical history were available from January 1980 and follow-up was complete to December 2000 or date of death. All subsequent hospitalizations were classified on the basis of primary diagnosis, into ischaemic stroke, myocardial infarction or other. The period-specific hazard was estimated at each death and functions were fit in four periods: hyperacute (first 30 days, Weibull), acute (remainder of first year, Weibull), mid (years 2-5, Gompertz), late (beyond year 5, Gompertz). The resulting hazards over time were used to derive the survival curve, which was then integrated to obtain the mean survival.
Results: The mean age of study subjects (50,734) was 68.3 ($\pm$0.14) years; 55% were male, nearly two thirds died during follow-up, and at least one subsequent event occurred in 8,579. The hazards were extremely elevated following the initial event, dropped over time and then began to rise again after 2 to 4 years. Subsequent events cause a secondary rise in the hazard. Integrating the resulting survival curves led to a mean survival of 12.9 years after the index myocardial infarction, 11.1 after ischaemic stroke, and 13.6 with PAD. An additional myocardial infarction decreased these to 6.4, 4.1, and 4.4 years, respectively and an additional ischaemic stroke to 7.4, 8.9 and 4.7 years. Other factors that significantly affected these estimates were the age at the time of event, the presence of diabetes, or a history of prior atherothrombotic events.
Conclusions: The already shortened life expectancy of patients with atherothrombotic disease is substantially reduced by further events. Thus, preventing these should increase survival. The functions may be customized for use in different patient populations or economic analyses.

P505 Higher mortality in women after myocardial infarction is dependent on the presence of heart failure. A national community study

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Heart failure is associated with poor outcome after myocardial infarction (MI). Women have higher mortality rates as compared to men after MI. It is currently not known if women with or without heart failure (HF) after MI have different prognosis than men.
Aim: To compare the prognosis of men and women with MI complicated by HF
Methods and Results: Among 3,458 consecutive patients with MI (2563 men, and 893 women): 447 men (18%) had heart failure on admission as compared to 254 women (30%). Among MI patients complicated by HF: women were older, had a higher rate of coronary risk factors, and had higher 7-day, 30-days and 1-year mortality rate as compared to men with heart failure. On adjustment to coronary risk factors, MI type (Q vs. Non-Q) and location (anterior vs. non-anterior), and hospital treatment: reperfusion, and medical, women complicated by HF had a 50% higher 1-year mortality risk as compared to men (Table).
Among patients without heart failure on admission to hospital, there was higher crude mortality rate and risk in women at 1-year. However, adjustment for differences in age and other risk factors completely eliminated this association.

	Killip I	Killip II+III
Unadjusted Risk	1.93 (1.42-2.60)	1.89 (1.36-2.64)
Multivariate Adjusted Risk	1.29 (0.92-1.80)	1.48 (1.02-2.16)

Crude and adjusted 1-year mortality risk in women with MI as compared to men

Conclusions: Female gender is independently associated with higher mortality in MI patients complicated by HF, but not in patients without HF. Women with HF on admission are a high risk group which deserves aggressive work-up and management to reduce their risk.

P506 Early assessment of heart rate variability is predictive of in-hospital death and major complications during acute myocardial infarction

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Background: Depressed heart rate variability (HRV) at AMI discharge is associated with poor long-term prognosis. However, its early (< 48 hours) predictive value has not been extensively investigated. Aim of the study was to investigate, during acute myocardial infarction (AMI), in-hospital prognostic value of HRV.
Methods: Twenty-four hour ECG Holter monitoring was prospectively obtained on admission in 413 patients with AMI. Cardiac death and resuscitated ventricular fibrillation were the primary end-points; cardiogenic shock, ventricular tachycardia, post-infarction angina and heart failure the secondary end-points.
Results: A marked reduction in HRV indices but not in LF and HF normalized values was evident. Nine patients died during hospitalization and 13 were resuscitated from ventricular fibrillation. Secondary endpoints occurred in other 91 patients. At univariate analysis, LF, mean RR interval, WMS and family history of ischemic heart disease were predictive of combined primary and secondary end-points. At multivariate analysis, only LF and family history were predictive with a relative risk of 2.01 and 1.84 respectively ($p < 0.003$).
Conclusions: A depressed HRV was present in the early phase of AMI. LF power was an independent predictor of the combined unfavorable short-term events.

P507 Spontaneous ST-elevation resolution in acute coronary syndrome – early and late outcome

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Background: Patients (pts) with spontaneous ST elevation resolution (SSTER) represent a unique subgroup of ST elevation MI (STEMI) pts, which has received limited attention in the literature.
Aim: To examine the incidence, characteristics, and outcome of patients with SSTER in a large national survey of acute coronary syndrome (ACS) pts.
Methods and Results: The ACSIS 2002 survey included all ACS pts (n=2049) hospitalized during a two month period in all cardiology departments (n=26) operating in Israel. Out of 1011 STEMI pts, 588 (58%) were treated with reperfusion therapy (thrombolysis or primary PCI), and are referred to as the "ST reperfusion group". Among 423 pts (42%) in whom reperfusion was not performed, early SSTER occurred in 173 (17%), and they constitute the "ST spontaneous resolution group". The characteristics and outcome of both groups are presented in the table: After multiple adjustment for age, sex, past MI, Killip class and peak CK, the risk of death was lower among the ST spontaneous resolution group in comparison with the ST reperfusion group (7 day OR: 0.33; 95% CI: 0.07-1.10; 30-day OR: 0.34; 95% CI: 0.09-0.99; 6 month OR: 0.48; 95% CI: 0.18-1.16).

SSER versus ST Reperfusion

	ST Spontaneous Resolution Group (n=173) %	ST Reperfusion Group (n=558) %
Men	79	81
Age (mean)	62 ± 13	61 ± 12
Killip 2+	10	18*
Peak CK (median)	303	1344*
Q-wave	47	84*
Re-ischemia	8.1	4.3*
CABG	11	4.0*
Mortality: 7 days	1.7	5.4*
30 days	2.3	6.6*
6 months	4	9.0*

*$p<0.05$

Conclusions: (1) SSTER occurs in a significant (17%) number of STEMI pts.(2) SSTER is a marker of smaller infarction and lower early and late mortality. (3) The higher incidence of re-ischemia and the need for CABG in the SSTER group emphasize the importance of special attention and prompt assessment of this group prior to hospital discharge.

P508 Prognostic value of B-type natriuretic peptide levels on admission in patients with acute ST-elevation myocardial infarction

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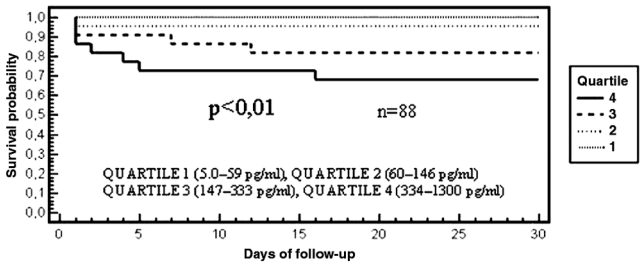
Background: B-type natriuretic peptide (BNP) levels in the first days after the onset of symptoms are predictive of short-term mortality in patients with acute coronary syndromes (ACS). Few data are available for BNP levels obtained on admission in patients (pts) with acute ST elevation myocardial infarction (STEMI).
Objective: To assess the relation between BNP levels on admission in STEMI and short-term, all-cause mortality.
Methods: Blood samples for BNP determination were obtained on admission in 88 pts (mean age 60,6±10,7 years old) with STEMI. In a 15-minute period, BNP was measured by using simple bedside test for rapid quantification of BNP. 30 days follow-up was performed.
Results: During the period of follow-up 12 (13,6%) pts died. Mean for BNP was 228,74±269,98 pg/ml. Lowest value was 5 pg/ml, highest value 1300 pg/ml due to limitation of method. The base-line level of BNP was higher among patients who died than among those who were alive at 30 days (median, 545,6 vs. 178,7 pg/ml; $p<0,05$). Mortality increased among pts in increasing quartiles ($p<0,01$). Kaplan-Meier survival curves according to BNP quartile are shown in figure. The unjustified odds ratio for 30 day risk of death in third quartile was 4,7 (95 percent confidence interval, 0,5 to 46) and in fourth 9,8 (95 percent confidence interval, 1 to 88). When BNP was added to a multivariate Cox regression model including clinical, electrocardiographic, biochemical markers of myocardial damage, BNP levels were independently associated with prognosis ($p<0,05$).



Survival in quartiles according to BNP.

Conclusions: BNP levels obtained on admission are powerful, independent indicator of short-term mortality in pts with STEMI. Rapid tests for BNP assay seem to be new tool in risk stratification of pts with STEMI.

PATHOPHYSIOLOGY AND CLINICAL INTERVENTION

P509 Effects of leonurus heterophyllus sweet on haemorheology and thrombosis on rat with myocardial ischaemia

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Objective The effects of leonurus heterophyllus sweet injection was observed by means of parameters such as hemorheology, platelet aggregation rate and extrasomatic thrombosis on rat with myocardial ischemia.
Methods 20 male SD rats, (body weight 280±35g) were divided randomly into 2 groups: (1) control group (n=10): rats were anesthetized with 1% sodium pentobarbital (1.5ml/100g body weight, i.p.) and fixed on operation table. Sternum was split open with heart exposed. Left anterior descending branch of coronary artery was ligated at the site of 0.3cm from left auricle, which ST segment rising over 0.3 millivolt on electrocardiogram demonstrated the model of myocardial ischemia was successfully constructed. 1 hour later after myocardial ischemia, 1.0 ml of 0.85% NaCl solution was injected into caudal vein. (2) group treated with leonurus heterophyllus sweet (n=10): all procedures were the same as the control group except changing 0.85% NaCl solution into equal volume of leonurus heterophyllus sweet injection (2.0g/ml). 2 hours later after myocardial ischemia, blood sample was collected from carotid artery in both groups to be detected blood viscosity, plasma viscosity, ESR, the content of fibrinogen in plasma, and platelet aggregation rate, as well as the length, wet weight and dry weight of thrombi formed ex vivo.
Results Leonurus heterophyllus sweet decreased blood viscosity, plasma viscosity, ESR and the content of fibrinogen in plasma which increased during myocardial ischemia ($p<0.05$-0.001, compared with control), besides this, it also lowered platelet aggregation rate induced by ADP and collagen respectively ($p<0.05$-0.01, compared with control). In addition, extrasomatic thrombosis was also inhibited, which showed as shortened length, lighter wet weight and dry weight of thrombi ($p<0.05$-0.01, compared with control).
Conclusion Leonurus heterophyllus sweet can improve hemorheology, inhibit platelet aggregation and extrasomatic thrombosis, so it has the effect of improving myocardial ischemia even other thrombotic diseases.

P510 Inflammation and thrombosis interaction in acute coronary syndrome

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Inflammation and thrombosis are important in the pathogenesis of acute coronary syndrome (ACS). Cytokines (interleukin-1b (IL-1b) and interleukin-6 IL-6)) are the inflammation markers which have a great role in coronary heart disease. Experimental data prove cytokine and von Willebrand factor levels increase in unstable angina (UA) and no-Q-wave myocardial infarction (MI) patients and predict adverse outcome.

The aim of the study was to investigate IL-1b, IL-6 and von Willebrand factor levels in ACS (UA, non-Q-wave MI, Q-wave MI) patients.

Method: We examined 60 patients, 49 men and 11 women, aged from 43 to 76. Patients were divided into 3 groups. The first group included 14 patients with UA, the second group – 24 ones with no-Q-wave MI, the third group – 22 ones with Q-wave MI. All patients were given 250 mg aspirin, bolus of 5000 units followed by infusion unfractionated heparin titrated to maintain an activated partial thromboplastin time of 50 – 75 s. Patients with Q-wave MI were given thrombolytic therapy – 1.5 million streptokinase units. IL-1b, IL-6 and and von Willebrand factor levels was measured on patients admission, on the 7-th and 21-st days of illness. 15 stable angina patients were the control group.

Results: As was shown in the Table, cytokines and von Willebrand factor levels were increased at patients admission versus control ($p<0.05$), with the exception IL-6 second group level, which was equal control. On the 7th and 21st days of disease IL-6 and von Willebrand factor levels significantly decreased ($p<0.05$), but IL-1b level increased. It has been found the correlation between von Willebrand factor and IL-6 levels in the third group at the patients admission and at the 7th ACS day (r=+0.74 and r=+0.55). Also the correlation was found between von Willebrand factor and admission the 1st and 2nd group IL-1b and von Willebrand factor levels (r=+0.7 and r=+0.61).

Patients group	IL-1b, pg/ml			IL-6, pg/ml			von Willebrand factor, %		
	adm.	7th day	21st day	adm.	7th day	21st day	adm.	7th day	21st day
1	542.68 ±97.3	609.8 ±98.6	417.8 ±71.6	103.8 ±15.2	90.1 ±21.1	72.1 ±16.2	171.1 ±83.7	154.0 ±92.9	107.6 ±38.0
2	352.5 ±9.3	431.1 ±195.1	497.3 ±121.9	50.7 ±9.3	44.3 ±16.1	47.1 ±8.9	168.2 ±91.1	134.6 ±81.6	77.7 ±39.6
3	84.7 ±18.4	69.9 ±27.5	102.8 ±14.8	84.7 ±18.4	58.6 ±19.4	52.1 ±10.7	102.8 ±14.8	136.0 ±85.8	88.0 ±16.0
Control	51.2 ± 12.6			50.7 ±8.4			44.0 ±16.5		

adm.: admission.

Conclusion: Our data suggests that there is positive correlation between ACS inflammation and thrombosis markers.

P511 Inflammatory response in acute myocardial infarction patients: a long-term follow-up

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Objective: To assess the prognostic long-term usefulness of white-cell blood count (WCBC) and erythrosedimentation (ES) as markers of an inflammatory response in AMI-pts.

Methods: The retrospective analysis of 804 consecutive pts admitted because of AMI within 24hr-period since the onset of symptoms. ROC curves were plotted for WCBC and ES in order to predict death, selecting the cutoff point of each variable; determining sensitivity (S) and specificity (SP) of these ones in order to identify events. Average follow-up: 42mo.

Results: During hospitalization it accounted for 6.7% and 43.2% during follow-up. The area under the ROC curve for WCBC and ES was 0.70 and 0.62 with a cutoff value of 10,000 WCBC and 10mm for ES. The leukocyte count $>$ 10,000 yielded a sensitivity 68% and a specificity 40% in order to predict long-term mortality rate. An ES $>$ 10 showed a sensitivity 75% and a specificity 50%. The cummulative survival rate of 140 mo was 0% for the group with WCBC $>$10,000 vs 57% in the group WCBC$<$ 10,000 (Log Rank Test p= 0.015). In the Cox proportional model, the independent predictors of death were WCBC ($p<$ 0.0001), Age (p= 0.0008), previous infarction (p= 0.01), highest CK-level (p=0.0092) and glycemia (admission) ($p<$ 0.0001).

Conclusion: Considering all the inflammatory markers, which are almost always available during AMI-pts'admission, the WCBC was the only one that yielded a high sensitivity and specificity level in order to identify pts with severe long-term events, showing to be an independent predictor of long-term mortality too.

P512 AGATHA, an investigation of the prevalence and extent of atherothrombosis in patients with or at risk of vascular disease – results of an interim analysis

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Aims AGATHA is a prospective study to assess the prevalence and extent of atherothrombosis in patients with a history of vascular events, current symptoms of vascular disease or who are at an increased risk of suffering a vascular event in the future. The value of ankle-brachial index (ABI) measurements in the routine examination of patients with or at risk of atherothrombosis will also be evaluated.

Methods Patients are recruited if they 1) have a history of vascular events or current symptoms of vascular disease defined as history of ischemic stroke or transient ischemic attack, myocardial infarction, stable or unstable angina, established peripheral arterial disease (PAD) or prior vascular intervention (symptomatic patients) or 2) are at increased risk of vascular disease defined as aged $>$55 years and have at least two cardiovascular risk factors (asymptomatic patients). Recruitment began in March 2002; target total is 8000 patients in 24 countries.

At entry, risk factors, antithrombotic medication, ECG, ABI and carotid echo-Doppler (optional) are assessed. Data analysis will determine the characteristics of patients with atherothrombosis, the extent of the disease and the relationship between this and risk factors, ABI value and treatment.

Interim data (first 4702 patients from 20 countries)

In symptomatic patients (n=3902), 27.8% had two arterial beds affected while 6.0% had three. In symptomatic patients without PAD (n=2963), 34.4% had an abnormal ABI. In asymptomatic patients (n=800), 81.3% had diabetes, 91.0% hypertension, 58.0% dyslipidemia, 15.9% obesity and 20.5% smoking history. Abnormal ABI indicating obstruction was found in 28.0% of asymptomatic patients (Table 1). Globally, 71.5% of patients were treated by antiplatelet agents (79.9% of the symptomatic patients and 31.4% of the asymptomatic patients).

Table 1

	Normal ABI$>$0.96	Mild obstruction 0.7$<$ABI$\leq$0.96	Moderate obstruction 0.3$<$ABI$\leq$0.7	Severe obstruction 0$\leq$ABI$\leq$0.30
Symptomatic patients*	2088 (53.5%)	1031 (26.4%)	609 (15.6%)	173 (4.4%)
Asymptomatic patients	576 (72.0%)	184 (23.0%)	36 (4.5%)	4 (0.5%)

Categorisation of patients according to ABI measurement. * = missing ABI for 5 patients

Conclusions Interim analysis suggests that atherothrombosis is present in many patients with or at risk of vascular disease even if they are asymptomatic. ABI appears to be a useful tool for identifying patients with the disease.

P513 Long-term survival after multivessel surgical or percutaneous revascularization: analysis of high-risk groups

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Background: Randomized clinical trials (RCTs) have reported overall equivalent outcome after percutaneous (PCI) or surgical (CABG) revascularization for multi-vessel coronary artery disease (CAD) in patients suitable for both interventions. Post-hoc analyses suggested significantly worse outcome after PCI in diabetic patients. We investigated the 5-year survival in a large cohort of patients with multi-vessel CAD treated with PCI or CABG at a tertiary institution and focused on the outcome of high-risk groups, including diabetics.

Methods and Results: There were 1,389 PCI and 5,429 CABG patients treated between 1995 and 1999. CABG patients were more likely to have stable angina, 3-vessel CAD, $>$1 total occlusion and left main coronary (LMT) stenosis than PCI patients. Propensity analysis identified unstable angina, higher ejection fraction and absence of total occlusions or LMT stenosis as main predictors for choosing PCI. Mammary grafts were used in 89% of CABG patients, whose peri-operative mortality was one-third of the national average. Stents (65%) and glycoprotein IIb/IIIa antagonists (49%) were frequently used in PCI. At 5 years, survival was 86.0% vs 79.8% for CABG and PCI, respectively, $P<0.001$. These observations were confirmed in an analysis of 2,000 patients matched for propensity score and after exclusion of PCI patients with previous CABG. Among 2,709 diabetics, survival was 81.6% vs 76.2%, respectively, $P<0.001$, not nearly as profound a difference as seen in earlier reports. Similar results were observed in patients with impaired ejection fraction. PCI was an independent predictor of increased mortality (adjusted hazard ratio 2.5, $P<0.001$).

Conclusions: In a cohort of predominantly high-risk patients, 5-year survival appears to be superior after CABG compared with PCI. However, the differences in survival observed in the highest-risk subsets are far smaller than reported in randomized trials.

P514 Hypercholesteremia induces baroreceptro reflex dysfunction

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Purpose: Hypercholesteremic guinea pigs display concentric cardiac remodeling. The autonomic nervous system is likely to play a role in the expression of this remodeling. The purpose of this study was to determine whether the baroreceptor reflex control of cardiac sympathetic and parasympathetic nerve activity was disturbed in cholesterol-fed guinea pigs.
Method: Groups of guinea pigs were fed certified guinea pig chow with or without 1% cholesterol for 13 weeks (n = 4 per group). The guinea pigs were anesthetized with ketamine (120 mg/kg ip)-acepromazine (12 mg/kg ip) and a catheter was placed in a jugular vein to administer drugs and into a carotid artery to determine pulsatile (PAP) and mean (MAP) arterial blood pressures and heart rate. The guinea pigs were allowed at least 4 days to recover from surgery. The guinea pigs received bolus doses of the alpha-1-adrenoceptor agonist, phenylephrine (1-40 mg/kg iv), to elicit pressor responses and bolus doses of the nitric oxide-donor, sodium nitroprusside (1-40 mg/kg iv), to elicit depressor responses. The maximal changes in heart rate in response to the changes in MAP were recorded and subjected to sigmoidal curve fitting analyses.
Results: Resting MAP of cholesterol fed guinea pigs were similar to controls (77 $\pm$ 4 vs 75 $\pm$ 4 mmHg, $P > 0.05$). Resting heart rate of cholesterol fed guinea pigs were also similar to controls (249 $\pm$ 9 vs 269 $\pm$ 13 bpm, $P > 0.05$). The sensitivity (gain, Gave) of the baroreflex was markedly diminished in cholesterol-fed as compared to control guinea pigs (2.63 $\pm$ 0.14 vs 4.08 $\pm$ 0.20 bpm/mmHg, $P < 0.05$). The heart rate range (upper plateau-lower plateau) of the baroreceptor heart rate reflex was markedly impaired in cholesterol-fed as compared to control guinea pigs (69 $\pm$ 6 vs 178 $\pm$ 11, bpm, $P < 0.05$). The maximal increases in heart rate for the cholesterol-fed and control animals were 34 $\pm$ 6 and 92 $\pm$ 10 bpm, respectively ($P < 0.05$) whereas the maximal decreases in heart rate were 35 $\pm$ 6 and 90 $\pm$ 8 bpm, respectively ($P < 0.05$).
Conclusion: Hypercholesteremia is associated with an impaired baroreceptor reflex function. We are currently conducting temporal studies to determine whether the loss of control of cardiac autonomic nerve activity precedes the concentric remodeling in cholesterol-fed guinea pigs in order to provide evidence as to whether the loss of baroreflex function is causal to or results from the cardiac remodeling.

P515 Comparison of beta blockers and calcium antagonists on brain natriuretic peptide reduction after acute myocardial infarction

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Background: Because Japanese patients with acute myocardial infarction (AMI) have a greater incidence of coronary spasm than Caucasians, calcium antagonists are prescribed generally in Japan. A multicenter clinical trial in Japan (The Japanese Beta Blockers and Calcium Antagonists in Myocardial Infarction Study: JBCMI) revealed that beta blockers increased heart failure events compared with calcium antagonists in patients with AMI. The objective of this study was to compare brain natriuretic peptide (BNP) between patients administered with a beta blocker and a calcium antagonist after AMI in addition to angiotensin converting enzyme (ACE) inhibitors.
Methods: We investigated 26 patients with AMI who underwent successful percutaneous coronary intervention. They were divided into 2 groups, one was administered with carvedilol, a beta blocker (13 patients; Group B) and the other with amlodipine, a calcium antagonist (13 patients; Group C). All patients were prescribed with ACE inhibitors. BNP levels before, 3 and 6 months after medication and BNP reduction rate at 3 and 6 months after medication were compared in both groups.
Results: There was no difference of maximum CK levels in both groups (3649 and 2767 IU in Group B and C). There was also no difference of left ventricular ejection fraction at discharge in both groups (63 and 65% in Group B and C). BNP levels before medication showed no difference between 2 groups (138 and 122 pg/ml in Group B and C). At 3 months after starting carvedilol or amlodipine, BNP level was 101 and 36 pg/ml ($p<0.05$), and 101 and 31 pg/ml ($p<0.01$) at 6 months in Group B and C. BNP reduction rate compared with that before medication was 32 and 64% at 3 months ($p<0.05$), 32 and 69% at 6 months ($p<0.05$) after starting medication in Group B and C.
Conclusion: BNP reduction in patients after AMI who underwent emergent successful percutaneous coronary intervention and prescribed with ACE inhibitors are more augmented by calcium antagonist than by beta blocker.

P516 Impact of infarct related coronary artery flow on vagosympathetic interactions in patients with acute myocardial infarction

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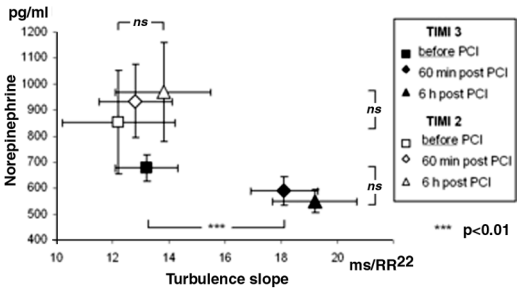
Background: Incomplete reperfusion is associated with an increased risk for life-threatening arrhythmias. It seems likely that these arrhythmias are facilitated by the interaction of neurohormonal activation and autonomic reflexes. However, the relationship between heart rate turbulence (HRT), a surrogate marker for reflex vagal activity, and plasma norepinephrine (NE) concentrations have so far not been studied in patients with acute myocardial infarction (AMI).
Methods: Therefore we prospectively screened 187 consecutive patients undergoing direct PCI for a first AMI. A total of 126 of these patients (TIMI 2, n=28; TIMI 3, n=98) fulfilled the clinical and technical inclusion criteria. Turbulence onset (TO) and turbulence slope (TS) were determined after single ventricular premature beats in the time interval before reperfusion, within the initial two hours after reperfusion, and within the time period from hour 6 to hour 24 after reperfusion, respectively, from 24-hour-Holter-ECG-recordings initiated on hospital admission. Corresponding arterial plasma concentrations of NE were investigated using HPLC method.
Results: There were no significant differences in baseline clinical characteristics between TIMI 2 and 3 patients. TS significantly increased (Fig 1.) and TO decreased (-0.008$\pm$0.04 to -0.023$\pm$0.04%, $P<0.01$) after PCI only in the TIMI 3 subgroup. There were also no significant alterations in NE concentrations in both groups within the observation period (figure).



Conclusion: Complete reperfusion in AMI is associated with a significant improvement of reflex vagal activity, whereas incomplete reperfusion is associated with significant vagosympathetic alterations, reflected by a persistent suppression of reflex vagal activity and increased NE concentrations.

P517 Effects of pravastatin on cardiomyocyte hypertrophy and ventricular vulnerability in normolipidemic rats after myocardial infarction

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Objective: Reactive cardiomyocyte hypertrophy after myocardial infarction is an important risk factor for arrhythmias. Endothelin (ET)-1 has been implicated in the development of cardiac hypertrophy. We investigated the effect of pravastatin on ventricular hypertrophy during remodeling after myocardial infarction and whether the attenuated hypertrophic effect was via reduced regional ET-1 expression.
Methods: After ligation of the anterior descending artery, male Wistar rats were randomized to either vehicle, pravastatin, mevalonate, or a combination of the 2 drugs for 4 weeks. Sham operation served as controls.
Results: Pravastatin decreased cardiomyocyte sizes isolated by enzymatic dissociation at the border zone. The myocardial ET-1 levels at the border zone were 6.3-fold higher ($P<0.0001$) in the vehicle group compared with sham group. The increased regional ET-1 levels can be inhibited after pravastatin administration. Immunohistochemical analysis confirmed the localization of ET-1 mainly in the cardiomyocytes. This was paralleled by a 9.8 2.3-fold upregulation of preproET-1 mRNA assessed by real-time quantitative RT-PCR in the vehicle-treated rats, which reduced after administering pravastatin. Cardiomyocyte sizes at the border zone correlated positive with regional ET-1 levels ($P=0.001$). Arrhythmic scores during programmed stimulation were significantly higher than those treated with pravastatin (3.0 1.3 in the vehicle group vs. 1.3 1.0, $P<0.0001$). In contrast, pravastatin-induced effects were reversed by the addition of mevalonate, implicating 3-hydroxy-3-methyglutaryl-CoA reductase as the relevant target.
Conclusions: The results of the present study suggest that the pravastatin administration after infarction can reduce the inducibility of ventricular arrhythmias as a result of attenuated cardiomyocyte hypertrophy through decreased tissue ET-1 level, which is linked to mevalonate metabolism.

P518 Spatial orientation of ruptured coronary plaques does not correlate with its morphometric appearance

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It has been shown that plaques oriented towards pericardium have more positive remodeling and are exposed to a greater shear stress compared to plaques oriented toward the myocardium. To determine whether this affects the morphometry of plaque rupture, we identified 57 ruptured plaques in 56 patients in which spatial orientation within the vessel was possible. On the basis of vascular and perivascular landmarks we classified ruptured plaques as myocardial (n=28) or pericardial (n=29). Intravascular ultrasound analysis at the site of both the largest plaque cavity and at reference sites included plaque composition; lengths; and measurements of external elastic membrane (EEM), lumen, plaque, plaque cavity, arc of calcium, arc of disease-free vessel wall, and remodeling index (lesion/reference EEM) (Table).

	pericardial plaques (29)	myocardial plaque (28)	P
Rupture length (mm)	4.34±2.48	3.79±3.64	0.49
EEM area (mm^2)	18.64± 5.27	20.41 ± 6.09	0.25
Lumen area (mm^2)	4.01 ± 1.42	4.81± 2.71	0.17
Plaque area (mm^2)	14.62 ± 4.61	15.60 ± 4.91	0.44
Cavity area (mm^2)	2.83 ± 1.40	2.97 ± 1.98	0.77
Calcium arc (°)	30.78 ± 43.23	18.24 ± 27.99	0.20
Curve of free disease wall (mm)	2.19 ± 2.71	2.69 ± 3.73	0.56
Remodeling index	1.17 ± 0.25	1.17 ± 0.14	0.95

15 lesions contained thrombus, 8 in pericardial plaques and 7 in myocardial plaques. 22 plaques were classified as soft, 8 pericardial plaques and 14 myocardial plaques (p=0.071).Reference segments were similar for pericardial and myocardial plaques.

Conclusions: IVUS analysis of ruptured plaques showed that the orientation of a ruptured plaque does not affect its morphometric appearance.

P519 Beneficial effects of dealcoholized red wine on endothelial function and fibrinogen levels in patients with coronary artery disease

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Purpose: The long-term effects of red wine are well investigated in both healthy subjects and in patients with coronary artery disease (CAD). On the other hand, there are few studies, only in healthy individuals, looking at the acute effect of red wine or its antioxidants on endothelial function and haemostatic factors. Therefore, the aim of the present study was to investigate the acute effect of red wine with or without alcohol in CAD patients.

Methods: Fifteen male adults with angiographically documented CAD ingested 250 ml of red wine, or 250 ml of dealcoholized red wine, in a single–blind, cross–over design. Blood samples were collected for lipid (triglycerides, HDL, LDL), apolipoprotein (A-I, B) and fibrinogen determination. High–resolution ultrasounds were used for determination of endothelium dependent flow-mediated dilatation (FMD), as a marker of endothelial function. All measurements were performed at fast, 30, 60 and 90 minutes following the consumption of each beverage. Endothelium independent vasodilatation (nitrate mediated – NMD) was also determined.

Results: Baseline FMD was similar in the two study days. According to repeated measures analysis of variance, regular red wine consumption caused a significant impairment on FMD from 3.83+2.4% at baseline, to 2.81+2.2% at 30 minutes and to 1.51+1.8% at 60 minutes (p= 0.015) and then to 3.14+2.9% at 90 minutes. After ingestion of dealcoholized red wine there was not a significant change in FMD but only a trend to increase (2.37+2.3% at baseline, 5.01+3.8% at 30 minutes, 4.45+3.1% at 60 minutes and 4.80+2.0% at 90 minutes). Incremental areas under the curves were statistically different following the consumption of the two beverages, as FMD was significantly higher following dealcoholized red wine consumption, than following red wine containing alcohol (p=0.0004). Fibrinogen levels, increased following red wine consumption and decreased following dealcoholized red wine ingestion and the two response curves were statistically different (p=0.035). Blood lipid levels were unaltered. NMD was not different in the study days.

Conclusions: In conclusion, acute ingestion of red wine with alcohol impairs FMD and increases fibrinogen levels, compared to red wine without alcohol in CAD patients. The acute effect of red wine on endothelial function of CAD patients may be different than its long-term effect and its favorable effect could be attributed to its antioxidant substances, rather than its alcohol content.

CORONARY STENTING IN CHALLENGING STENTS OR LESIONS

P520 Restenosis is higher after stent implantation for myocardial bridges than restenosis after direct stenting for atherosclerotic lesions. An angiographic follow-up study

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Purpose: To assess the angiographic outcome after stent implantation for symptomatic myocardial bridges (MB) and to compare these results with the results of direct stenting for atherosclerotic lesions.

Methods: Angiographic follow-up results of 12 patients (8 male) who underwent stent implantation for symptomatic MB in mid left anterior descending artery (LAD) were compared with that of 41 patients (25 male) who underwent direct stent implantation for atherosclerotic lesions in LAD (control group), between January 2001 and December 2001. All patients with MB had positive results for ischemia with myocardial perfusion studies. Patients with total occlusions, acute myocardial infarction (AMI) and multiple stents were not included.

Results: Baseline coronary risk factors were not different between the groups. Two patients in MB group and 3 patients in control group had AMI during follow-up. The results are shown in the table.

Angiographic Results

		MB Group (n=12)	Control Group (n=41)	p
Baseline	RD (mm)	3.08 (0.27)	3.18 (0.37)	ns
	MLD (mm)	0.94 (0.25)	0.65 (0.27)	0.004
	DS (%)	69 (8)	79 (8)	0.001
Post Stent	MLD (mm)	2.95 (0.30)	2.97 (0.37)	ns
	DS (%)	4 (5)	7 (6)	ns
6m Follow-up	MLD (mm)	1.18 (1.28)	2.07 (1.03)	0.04
	DS (%)	62 (40)	35 (31)	0.06
	Late Loss (mm)	1.77 (1.1)	0.89 (0.95)	0.02
	Restenosis rate (%)	67	32	0.03

mean (SD). MB:myicardial bridge; RD:reference diameter; MLD:minimal luminal diameter; DS:diameter stenosis

Conclusion: Although intracoronary stent implantation for MB prevents vessel compression early after the procedure, angiographic restenosis rate at 6 month follow-up was higher than restenosis rate after stent implantation for atherosclerotic lesions. This approach should be reserved for symptomatic patients with MB who have objective ischemic findings and who are refractory to the medical treatment.

P521 Sirolimus-eluting stent implantation in very small coronary vessels treated in RESEARCH Registry

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Background: Small vessel size is a well-known powerful risk factor for in-stent restenosis. Sirolimus-eluting stents (SES) have recently proved to reduce restenosis in selected patients with relatively large arteries. However, it is currently unknown the impact of this treament for patients with small vessels. In the present study we evaluated the clinical outcomes of patients treated with SES implantation in vessels with very small diameters.
Methods and Study Population: Since 16th April 2002, a policy of routine SES implantation has been instituted in our hospital, with no clinical or anatomical restrictions, as part of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry. At 6 months of enrollment, 563 patients were treated exclusively with SES implantation (71% of the total number of procedures performed in the period) and composed the present study population, divided into 2 groups: 1) patients treated with implantation of at least one 2.25-mm SES (n=89 pts; 16%) and 2) patients in whom only SES with diameters greater than 2.25mm were utilized (n=474; 84%). The primary endpoint was the occurrence of major cardiac adverse events (MACE) during the follow-up (death, non-fatal MI, or repeat revascularization).
Results: When compared with patients with larger vessels, those with small vessels presented a lower frequency of acute coronary syndromes (39% vs 55%; $p<0.01$) and had a higher prevalence of multivessel disease (77% vs 50%; $p<0.01$), hypercholesterolemia (69% vs 56%; p=0.02), and hypertension 57% vs 38%; $p<0.01$). The presence of diabetes mellitus was not significantly different between patients with and without small vessels (24% and 18% respectively; p=NS). Bifurcation stenting was significantly more common in patients with small vessels treated (35% vs 13%; $p<0.01$). Overall, 65% of patients had completed 6-month follow-up at the time of this evaluation. In a interim analysis, patients treated with very small SES had a similar 6-month MACE occurrence as patients with larger stented vessels (5.6% vs 4.6% respectively; p=NS), with no difference in the need for repeat revascularization (3.4% vs 1.3%; p=NS). Complete 6-month follow-up for the entire cohort will be available at the time of presentation.
Conclusions: Sirolimus-eluting stents implantation in very small vessels was associated with a favorable clinical outcome, similar to that observed in patients with larger vessels. Further analyses with extended follow-up are warranted to confirm these preliminary results.

P522 Sirolimus-eluting stent for treatment of left main coronary artery disease: experience from the German CYPHER registry

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Since the introduction of PTCA, intervention of the LMCA has been an attractive target. The initial acute catastrophic emergencies of dissection with abrupt vessel closure have been overcome by the introduction of coronary stents, yet the high restenosis rate remains the major problem with this procedure. The SES has been reported to be effective in de-novo coronary lesions. We assessed the in-hospital and long term outcomes of SES treated patients for unprotected and protected LMCA stenosis from the German CYPHER Registry.
Methods: A total of 35 Bx-velocity SES treated patients were analysed; 26 treated for protected and 9 for unprotected LMCA disease. The lesions were of type B aqnd C and included thrombus containing, ostial and bifurcational lesions. The primary end point was procedural success defined as in-stent residual stenosis <20% and the absence of in-hospital MACE. The secondary end point was MACE at 6 months follow up.
Results: All the procedures were angiographically successful, no in-hospital deaths nor new Q wave MI occurred. One patient(2.9%) was sujected to a repeat revascularisation which was unrelated to the LMCA SES.
Conclusion: SES for treatment of protected and unprotected LMCA stenosis is technically feasible and safe. Results of the 6 months follow up will be available at ESC 2003.

P523 Sirolimus-eluting stents for the treatment of unprotected left main coronary lesions

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Conventional bare stents have been used to treat unprotected left-main (LM) coronary stenoses. However, restenosis remains the main limitation. Since Sirolimus-eluting stents (SES) appear to inhibit neo-intimal proliferation, their application to this specific site seems promising.
Methods: Since May/02 we have studied a series of 37 consecutive patients (pts), 63±11 years old, with left main coronary lesions treated by SES. Combined treatment of co-existing lesions in the coronary tree was also needed in 11 (30%) pts. The use of bare stents or SES in these lesions was based on our judgement of restenosis risk at each specific site. Clinical presentation was stable angina in 7 pts (19%), unstable in 23 (62%) and peri-myocardial infarction in 7 (19%). At cardiac catheterization, the mean ejection fraction was 56±13%. Eleven pts had multi-vessel disease at remote sites; 4 of them had right coronary artery involvement. The angiographic characteristics of the LM lesions were as follows: reference LM-diameter 3.7±0.3 mm, LM-length 14±5 mm, lesion-length 13±7 mm, stenosis percentage 72±14%. The lesion was native in 32 pts and due to in-stent restenosis in 5. Location of the lesions within the main stem was as follows: ostial 2, body 21 and bifurcation 14. For ostial and body lesions, a single stent was attempted, trying to avoid bifurcation. For bifurcational lesions, the stent was mostly oriented towards the left anterior descending artery, covering the circumflex. Intervention at this site was stepwise oriented, including 2 pts needing full stent covering. Once implanted, the SES was overexpanded to match LM size.
Results: Primary success was obtained in 36 pts (97%). Acute myocardial infarction occurred in one pt (2.7%). At 1-month follow-up, 36 pts (97%) were symptom free. After a mean follow-up time of 4.5±2.4 months, 1 pt with a bifurcational lesion developed restenosis 2 months later at the non-covered ostium of the circumflex and was treated with a new SES. Another pt became symptomatic again because of restenosis at a remote site. Eight pts, who have reached 6-month follow up, have been angiographically re-evaluated. None of them have shown restenosis. All pts are scheduled for late angiography.
Conclusions: Tailored treatment of lesions located at the LM stem by overexpanded SES is feasible and safe. Intermediate-term results seem promising.

P524 Influence of diabetes on small vessel stenting; intracoronary ultrasound sub-analysis of a prospective multicentre randomized CHIVAS (Coronary Heart disease stenting In Vessels with smAll Size)

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It is commonly believed that the superiority of stenting may reduce in small vessel and diabetes. We prospectively performed a multi center randomized trial (CHIVAS study) comparing small vessel stenting or POBA in 302 patients with and without diabetes (DM). DM was defined as patients treated with oral hypoglycemics or insulin. Of the 302 patients 273 with suitable quantitative coronary angiography were divided into four groups based on stenting or POBA in patients with DM and non-DM. The distribution was as follows: DM with stenting, 46 patients; DM with POBA, 44; NDM with stenting, 91; NDM with POBA, 92. Follow-up angiography was performed in 228 patients and intracoronary ultrasound (ICUS) was performed in 115. Restenosis was defined as >50% diameter stenosis at follow-up.
Results:

	Stent	POBA	p
DM			
IRD pre (mm)	2.22 ± 0.41	2.23 ± 0.37	ns
MLD pre (mm)	0.64 ± 0.36	0.74 ± 0.30	ns
MLD post (mm)	1.70 ± 0.34	1.48 ± 0.27	<.01
MLD fup (mm)	1.34 ± 0.51	1.11 ± 0.45	<.05
Restenosis rate (%)	25%	57%	<.01
Lumen gain by ICUS (mm^2)	2.74 ± 1.59	1.26 ± 1.25	<.05
Vessel expansion by ICUS (mm^2)	1.86 ± 1.45	0.11 ± 2.33	<.05
Non-DM			
IRD pre (mm)	2.33 ± 0.42	2.28 ± 0.36	ns
Restenosis rate (%)	33%	31%	ns
Lumen gain by ICUS (mm^2)	2.00 ± 1.18	1.86 ± 1.48	ns

IRD; interpolated reference diameter, MLD; minimal lumen diameter

Conclusions: This ICUS sub-analysis of CHIVAS with an average vessel size <2.50mm indicated that restenosis rate of stenting was significantly lower than POBA in DM, while the restenosis rate of stenting was similar to POBA in non-DM. ICUS indicated that greater lumen gain (mainly due to vessel expansion) in stenting than POBA may explain this phenomenon, while such a beneficial effect of stenting over POBA was not observed in NDM. Small vessel stenting (<2.50mm) could convey more favourable long-term outcome than POBA especially in DM as compared to non-DM.

P525 Sirolimus-eluting stents for the treatment of bifurcation lesions

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Background: Although stents have improved procedural success rate, the treatment of bifurcation lesions still remains problematic with an increased restenosis rate and consequent need for repeat revascularizatin. Sirolimus-eluting stents (SES) have recently shown a remarkable reduction in restenosis rate in selected simple lesions. The aim of this study was to investigate the efficacy of SES in the treatment of bifurcation lesions.
Methods: Since 16 April 2002, a policy of SES implantation for all procedures has been instituted in our hospital, irrespective of clinical presentation and lesion morphology. This study consisted of the patients with bifurcation lesions being treated with SESs in both vessels. The stent deployment technique was left to the discretion of the operator. Clinical and angiographic follow-up will be performed at 6 months after procedure.
Results: Up to October 2002, 74 patients were included in this study. The mean age was 63 years old and 21 patients (28%) were diabetic. The techniques used were as follows: T stenting (55 patients: 74%); crush stenting (14 patients: 19%); kissing stenting (4 patients:5%); Y stenting (1 patient:1%). The baseline QCA data are present in the table. To date, 16 patients have undergone the 6-month follow-up; of those restonosis has occurred in 3 patients (19%). All restenosis were at the ostium of a side branch that was not fully covered with SES. The clinical and angiographic follow-up will be completed at the time of presentation.

QCA data

	Parent vessel	Side branch
Lesion length (mm)	15.0	10.3
Reference diamenter	2.66	2.31
MLD pre (mm)	0.91	0.65
MLD post (mm)	2.35	1.98

Conclusions: This study will provide insights into the treatment of bifurcation lesions with sirolimus-eluting stents.

P526 Drug eluting stent failure: a new challenging therapeutic problem

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The advent of drug eluting stent (DES) technology has the potential promise of dramatic reduction of in-stent restenosis. However, competing with this success, there were a series of failures. Currently, no data is available on the management of DES complications. In our center, we faced few cases of DES failure, a new emerging problem.
Methods and Results: We describe 18 cases of DES failure after DES implantation in a subset of patients presenting with extremely complex lesions in native coronary vessel: 12 patients with de novo lesions (Mean lesion length = 15mm, type B2/C lesion); 6 patients with diffuse recurrent ISR. IVUS guidance was not used during intervention. The reported DES complications, mean time to DES failure and treatment strategy are listed in the table. IVUS evaluation was done for all patients who underwent repeat percutaneous coronary revascularization for in-DES restenois (n=12), in 9 patients the mechanism of in-DES restenosis was neointimal proliferation and in the remaininig 3 was stent malapposition. After a follow-up period ranging from 1-6 months there were no further clinical events, except for one patient with failure of brachytherapy performed for in-DES restenosis and was referred for surgery. Six-month clinical and angiographic follow-up data will be available in August 2003 and will be presented at the meeting.

Cases with DES failure+ their management

	Mean time to event	Treatment strategy
DES for de novo lesions (n=12 pts)		
Focal ISR (n=3)	6 m	POBA (n=3)
Diffuse ISR (n=7)	6 m	Medical (n=1) POBA+ Brachytherapy (n=4) CABG (n=2)
Subacute stent thrombosis (n=2)	3.5 m	POBA (n=2)
DES for ISR (n=6 pts)		
Edge restenosis (n=3)	6 m	SES* implantation (n=2) POBA (n=1)
Complex bifocal edge restenosis (n=2)	6 m	POBA+Brachytherapy (n=2)
Occlusive ISR (n=1)	6 m	CABG (n=1)

*SES = Sirolimus-eluting stent

Conclusion: IVUS evaluation is advisable to define the mechanism of DES failure. The analysis of mid-term clinical and angiographic may allow better understanding of the prognosis of in-DES restenosis and its management.

P527 Randomized comparison of direct stenting and stenting after balloon predilation in acute myocardial infarction (DIRAMI trial)

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The purpose of the study was to assess feasibility, safety and long term effectiveness of direct stenting in acute myocardial infarction (AMI).
Methods: A total of 248 consecutive patients (pts) with AMI (Killip III-IV excluded) were randomized before angiography to direct stenting (DS-125pts) or stenting after balloon predilation (PS-123pts). After angiography 31 pts were excluded due to operators' decision not to perform angioplasty or stenting. Final study groups comprised 110 and 107 pts in the DS and PS groups, respectively. TIMI flow 0-1 was not considered a contraindication for DS. 1-year clinical and angiographic follow-up was performed. Analyses were performed on an intention-to-treat basis.
Results are summarized in the table.

	Direct stenting	Predilation+stent	P value
Procedural data	N=110	N=107	
Cross-over rate, %	11.8	0.0	-
Final TIMI flow grade 3, %	95.4	93.5	0.52
Additional stent(s), %	12.7	14.9	0.63
Fluoroscopy time, min (SD)	12.2 (7.5)	14.9 (7.7)	0.011
Procedure time, min (SD)	59 (22)	72 (31)	0.0006
Minimal lumen diameter after procedure, mm (SD)	2.20 (0.42)	2.25 (0.53)	0.39
Acute gain, mm (SD)	1.97 (0.49)	2.04 (0.54)	0.35
MACE at 1 year	N=110	N=107	
Cardiac death, %	5.5	7.5	0.54
Non-fatal myocardial infarction, %	5.5	3.7	0.55
Target lesion revascularisation, %	8.2	6.5	0.64
1-year MACE, %	14.6	14.0	0.91
QCA at 1 year (in-segment)	N=91	N=95	
Reference diameter, mm (SD)	3.09 (0.51)	3.08 (0.50)	0.93
Minimal lumen diameter, mm (SD)	1.72 (0.83)	1.87 (0.71)	0.18
Late loss, mm (SD)	0.45 (0.87)	0.41 (0.69)	0.73
Loss index	0.21 (0.52)	0.20 (0.38)	0.93

Conclusions: Direct stenting for acute myocardial infarction is feasible and safe in a majority of patients suitable for stent implantation. One-year clinical and angiographic outcomes are similar with both stenting techniques.

P528 Sirolimus-eluting stent Cypher® in patients with acute myocardial infarction

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Background: Recent data showed a significant reduction in restenosis rate with Sirolimus eluting stent Cypher® (SES). However, experience with SES in acute revascularization of infarct related coronary arteries is not available.
Aims: Feasibility and safety of the use of SES in the treatment of acute myocardial infarction (MI, according to the 2003 ESC definition).
Material and methods: Intraprocedural and in-hospital data from 188 patients assigned for SES with acute MI (143 male, 45 female, mean age 59.6 years) were compared to results from 988 patients (743 male, 245 female, mean age 63.4 years) assigned for SES without acute MI, all followed in the German Cypher® Registry.
Results: The ratio of NSTEMI/STEMI was 68/120. Other results are summarized in table 1.

Table 1

		pts. with MI (n=188)	pts. without MI (n=988)
No. of stenosis		213	1074
Mean diameter stenosis (%)		95	90
SES (%)		88.8	92.5
Other stents (%)		10.4	6.2
No stent implanted (%)		0.8	1.2
TIMI flow post angioplasty	0 (%)	0.0	0.6
	1 (%)	1.0	0.4
	2 (%)	1.0	1.4
	3 (%)	98.1	97.6
In-hospital follow-up	death (%)	0.0	0.1
	re MI (%)	1.8	1.1
	stent thrombosis (%)	0.0	0.4
	TVR (%)	2.4	1.4

Procedural and in-hospital follow-up data from patients with or without acut MI assigned for Sirolimus eluting stent

Conclusions: The implantation of SES in patients with acute myocardial infarction is safe. There is no evidence of increasing complication rates (including stent thrombosis) during the in-hospital period. Six months follow-up data and clinical restenosis rate will be reported later in 2003.

P529 Impact of stenting on angiographic outcome in multivessel disease (GABI II study) and comparison with results of the GABI trial

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Percutaneous coronary interventions (PCI) using stents in patients with multivessel disease was evaluated in a prospective multicenter study (GABI II) which served as a third arm of the randomized GABI trial which compared PTCA (n=182) and CABG (n=177) in multi-vessel disease. Patients (Pts) were screened for multi-vessel coronary artery disease amenable for bypass surgery or PCI accord-ing to the GABI trial inclusion criteria in five cardiologic centers. Quantitative coronary angiography of acute and long-term results was done and compared with those of the PTCA group of the GABI trial. Participating in the GABI II study were 134 Pts requiring multi-vessel PCI. The 277 lesions (Ls) (2.1 Ls/Pts) were treated by PTCA in 90, stent in 175, or other devices in 12. Angiographic and procedural success were achieved in 268/277 (97%) Ls. and 118/134 Pts. (88%), respectively. Angiographic success was reduced in small (<2.5 mm) vessels (92% vs. 98%, p=0.04). Control angiography performed in 90/118 (76%) of eligible Pts exhibited restenosis in 43/182 (24%) Ls. Restenosis rates increased with lesion complexity (AHA A 9%, AHA B1 24%, AHA B2 29% and AHA C 41%, p = 0.02). There was no difference in restenosis for Ls re-ceiving a stent or not. Multivariate regression analysis found a diffuse Ls, the Ls and stent lengths and the final luminal diameter predictive for restenosis. Angiographic success was higher compared to PTCA in the GABI trial (98% vs. 92.5%, p = 0.003) and no patient needed emergency bypass surgery compared to 15 in GABI ($p < 0.001$). The need for TLR during follow-up was lower than it was in the PTCA group of GABI (28% vs. 44%, p = 0.005). An obstruction > 50% diameter stenosis of one of the major coronary arteries (>2.5mm) 6 months after the procedure was more frequent in the PTCA group of the GABI trial than after CABG. PCI using stents resulted in an obstruction status comparable to CABG.

Obstruction Status of Main Pathways

	GABI-CABG (a)	GABI-PTCA (b)	GABI II-PCI (c)	p (a vs. b)	p (a vs. c)	p (b vs. c)
Obstruction > 50%	55/255 (21.6%)	83/241 (34.4%)	38/177 (21.5%)	<0.01	<0.01	0.02

Thus, immediate and long-term results of multi-vessel coronary intervention utilizing stents have improved compared to PTCA of multi-vessel lesions. However, in lesion subgroups CABG is still superior to multi-vessl PCI.

CORONARY AND NON-CORONARY PERCUTANEOUS INTERVENTION: MISCELLANEOUS

P530 The effects of prior beta blocker therapy on creatine kinase rise after percutaneous coronary intervations

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Background: There are two retrospective studies investigating the impact of beta-blocker (BB) usage on CK-MB levels after percutaneous coronary interventions (PCI). In one of these studies prior BB usage was found to be the only independent factor that limited CK-MB increase after PCI; whereas in the other study BB did not have any effect on CK-MB levels. On the basis of this data we formulated a prospective randomized study to investigate the impact of BB use on CK-MB in patients who underwent elective PCI.
Methods: In an ongoing, prospective study, 300 patients with coronary artery disease in whom PCI was elected as the revascularization modality were included. The patients were randomized to either BB or to control group at least one week before the planned PCI. Blood samples for cardiac enzymes were obtained before and after 6th, 24th and 36th hours after the procedure.
Results: Of the 300 patients included, 150 received metoprolol 100 mg/day (age 59.0 ± 10,2 years; 106 male, 44 female) and 150 did not receive any BB (age 59.8 ± 9.8 years; 114 male, 36 female) and served as the control group. The baseline clinical characteristics of both groups were similar. The groups did not differ with respect to single or multivessel PCI ($p > 0.05$). The CK-MB and troponin-I levels of both groups were also similar before intervention ($p > 0.05$). We did not observe a significant difference in CK-MB levels between the two groups after PCI (BB group 18%, control group 20%, $p > 0.05$).
Conclusions: Our study is the first randomized, prospective study conducted to evaluate the effect of BB usage on CK-MB levels after PCI. Prior BB therapy seems to have no cardioprotective effect in limiting CK-MB rise after PCI.

P531 Creatine kinase-MB enzyme elevation after percutaneous coronary interventions using sirolimus-eluting stents

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Background: Elevation of serum creatine kinase MB fraction (CK-MB) after percutaneous coronary interventions has been associated with early and late mortality. Procedure and lesion-related variables were reported related to CK-MB elevation. Possible impact of changes in stenting technique in drug-eluting stent era, with intent to fully cover diseased segment, has not been evaluated.
Methods: We studied 320 consecutive patients who underwent the Cypher stent (Cypher, Cordis, Warren NJ) implantation (941 stents) in 740 coronary lesions between April 2002 and January 2003. Univariate and multivariate logistic regression analyses were used to determine predictors of CK-MB elevation and the independent variables selected were clinical, angiographic and procedural covariates.
Results: 81% of patients had multivessel disease, 18% had diabetes mellitus and 25% had unstable angina. 134 patients (42%) received electively platelet glycoprotein IIb/IIIa inhibitors. The mean reference vessel size was 2.68 ± 0.55 mm and the mean lesion length was 17.4 ± 11.9 mm. Total stent length per patient was 63 ± 43mm, with a range 8-205mm. CK-MB elevation >/= 3 times upper limit of normal (normal <5ng/ml for our Institution) occurred in 42 patients (13.1%).
Univariate predictors of CK-MB elevation were: multivessel disease, OR 2.05 (95% CI 1.05-3.99), P=0.032; number of treated lesions, OR 1.43 (95% CI 1.17-1.76), P=0.001; de-novo lesion, OR 1.80 (95% CI 1.02-3.18), P=0.034; total stent length per patient, OR 1.13 (95% CI 1.01-1.20), P=0.001; and elective use of platelet glycoprotein IIb/IIIa inhibitors, OR 0.57 (95% CI 0.34-0.95), P=0.043. Multivariate analysis indicated that total stent length per patient [OR 1.02 (95% CI 1.01-1.03), P=0.001, predisposing factor] and elective use of platelet glycoprotein IIb/IIIa inhibitors [OR 0.22 (95% CI 0.08-0.58), P=0.002, protective factor] were independent predictors of CK-MB elevation.
Conclusions: In patients treated with the Cypher stent, CK-MB elevation correlates with implantation of longer stents. Elective use of platelet glycoprotein IIb/IIIa inhibitors is suggested, especially when long stents are used. Six-month clinical outcome will be available at the time of presentation.

P532 Mortality risk conferred by small elevations of creatine-kinase MB isoenzyme after percutaneous coronary intervention

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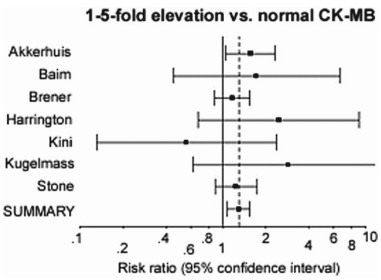
Background: Several studies have evaluated the relationship of creatine kinase- MB (CK-MB) isoenzyme levels after percutaneous coronary interventions (PCI) with the subsequent risk of death. While there is consensus that elevations exceeding 5 times the upper limit of normal increase mortality significantly, there is uncertainty about the exact clinical impact of smaller CK-MB elevations.
The aim of this study was to assess whether small creatine kinase MB isoenzyme (CK-MB) elevations after PCI affect the subsequent mortality risk.
Methods: We performed a meta-analysis of 7 studies with CK-MB measurements and survival outcomes on 23,142 subjects who underwent PCI. Data were combined with random effects models.
Results: Mean follow-up was 6-24 months per study. By random effects, 18% (15-22%) had 1-5-fold CK-MB elevations, while only 6% (95% CI, 4-8%) had >5-fold elevations. Compared with subjects with normal CK-MB, those with 1-5-fold CK-MB elevation had a 29% (95% CI, 7-54%) relative increase in mortality risk (Figure 1). There was a dose-response relationship with relative risk increase 22% (95% CI, 0-50%) in 1-3-fold CK-MB elevations and 50% (95% CI, 12-110%) in 3-5-fold elevations. There was no between-study heterogeneity in the relative risk estimates.



Conclusions: Any increase in CK-MB level post-PCI is associated with a small, but significant increase in the subsequent risk of death.

P533 The "crushing stenting technique: a new technique for treatment of bifurcation lesions with drug-eluting stents

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Background: The use of sirolimus-eluting stents significantly reduced the incidence of angiographic restenosis in the BIFURCATIONS study, but also revealed the prevailing occurrence of restenosis at the ostium of the side branch (SB). Incomplete coverage of the ostium of the SB was a most probable cause of restenosis. To overcome that problem, we designed a new technique for stenting bifurcation lesions: modified T stenting with "crushing".
Methods: new stenting technique was employed in 31 consecutive patients to treat true bifurcation lesions using the Cypher stent (Cordis a J&J Company, Warren, NJ). Technique description: both stents are advanced at the site of the bifurcation. The proximal marker of the SB stent must be situated in the main branch (MB) at a distance of 4-5mm proximal to the carina of the bifurcation and the MB stent must cover the bifurcation as well as the protruding segment of the SB stent. The side branch stent is deployed first and balloon and wire are removed. When deployed, the stent in the main vessel will completely "crush" the proximal segment of the stent protruding from the side branch against the wall of the main vessel. Kissing balloon inflation is not routinely performed especially if complete predilatation of the SB is performed. This fact and full ostial coverage of the SB are major advantages of this approach.
Results: Mean reference vessel diameters of the main branch and of the SB were 2.84±0.51mm and 2.51±0.55mm, with the mean lesion length of 17.4±8.9mm and 9.5±5.8mm, respectively. Glycoprotein IIb/IIIa inhibitors were electively administered in 77.4% of the patients. Following main and side branch predilatation, stents were successfully deployed in all lesions. Final kissing balloon inflation was performed in 12 patients. The acute gain achieved was 1.88±0.6mm in the MB and 1.51±0.6mm in the SB, resulting in final diameter stenosis of 12.9±6.3% and 13.1±7.5%, respectively. Two patients had in-hospital myocardial infarction and one patient underwent in-hospital re-PTCA due to a dissection distal to a stent. No other major adverse cardiac events were observed in-hospital and during one month clinical follow-up.
Conclusion: Treatment of bifurcation lesions using "crushing" stent technique is feasible, with acceptable rate of procedural complications. Angiographic follow-up is necessary to prove the advantage of this specific technique. Six-month clinical and angiographic outcome will be available at the time of presentation.

P534 Has there been any progress in percutaneous coronary intervention treatment of saphenous vein grafts? Evolution of outcomes between 1997 and 2002

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Background: Angioplasty of saphenous vein grafts remains a challenging technique which is associated with a high risk of distal embolization and a non negligible rate of major events.
Method: We retrospectively evaluated the impact of new techniques on the outcome of saphenous graft angioplasty between 1997 and 2002 by comparing two groups of patients treated from 1997 to 1999 (Group 1) and 2000 to 2002 (Group 2). Study population: A total of 197 procedures involving saphenous grafts were performed during the study period; 29 procedures were excluded from analysis due to: acute myocardial infarction in 19 cases, out-of-hospital cardio-circulatory arrest in 3, and in the immediate post-surgery period in 8.

	Group 1	Group 2	p
Patients (n)	81	87	
Male (%)	86.4	78.2	NS
Age (y)	68.2 ± 9.2	71.2 ± 8.2	0.027
Age of grafts (months)	111 ± 61	137 ± 66	0.011
Unstable (%)	56.8	63.2	NS
Saphenous sites treated (n)	1.6 ± 0.7	1.7 ± 0.8	NS
Use of thrombectomy device (%)	4.9	4.6	NS
Direct stenting (%)	24.7	55.2	<0.001
GPIIbIIIa inhibitors (%)	7.4	8.0	NS
Distal protection (%)	6.2	43.7	<0.001
Procedural time (min)	57 ± 34	51 ± 20	NS
Primary success (%)	82.7	96.6	0.006
Death (%)	5.3	0	NS
Mean CPK (IU)	570 ± 2312	152 ± 265	0.012
MACE (%)	16	3.5	0.012

Conclusion: Though the patients in Group 2 were older and had older bypass grafts, their in-hospital outcome after treatment of saphenous vein grafts lesions were significantly improved.
This improvement was associated with a more aggressive strategy involving wide use of direct stenting and protection devices.

P535 Nitric oxide through biodegradable layer elective study for safety and efficacy (NOBLESSE) – first in man pilot trial

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Background: In-stent restenosis may be prevented by drug eluting stents. One pre-requisite for successful drug coated stent development is a biocompatible and biologically inert polymer for drug impregnation to obtain a sustained drug release. The NO preserver loaded Blue Medical stent is a new generation Blue Medical Stent characterized by its particular PEA coating and a NO preserving substance conjugated to the PEA coating. Pre-clinical work showed a similar tissue response and reduced intimal hyperplasia in a porcine coronary stent model using the NO preserver loaded Blue Medical stent. The aim of this study is to evaluate the acute safety and efficacy of the NO preserver loaded Blue Medical stent implanted in patients with de novo single vessel disease.
Methods: In this multicenter trial, 47 patients, 66% were male, average age 61 (range 37 - 86) from 3 study sites were included. Risk factors: 38% had lesion type B2 or C. One 14 mm or 18mm long NO preserver loaded Blue Medical stent was used. Minimal lumen diameter (MLD) and % diameter stenosis (DS) were measured before, immediately after stenting and at 4-month (m) follow-up (f-up). The primary endpoint of the study is 4m in-stent %DS and late loss determined by QCA. The secondary endpoints are binary restenosis rate at 4m follow-up and 30 days, 60 days and one year major adverse cardiac events (MACE) defined as death, MI, CABG & target vessel revascularization.
Results: All the stent implantations were successful except one that resulted in a distal dissection, treated by an additional coated stent implantation. QCA: mean reference diameter: 2.97±0.31 mm, MLD: 1.04± 0.31mm, % DS: 65.08±9.89% and MLD and % DS after stent implantation was 2.74±0.26 mm and 8.52±4.31% respectively. There was no MACE at 30 days and 60 days f-up. Four months angiographic follow-up and 6 month clinical follow-up will be presented.
Conclusion: This preliminary results show that implantation of a NO preserver loaded Blue Medical stent is safe and feasible. It seems a promising approach to prevent in-stent restenosis.

P536 Transcatheter closure of post-infarction ventricular septal defects with the Amplatzer septal occluder

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Background: Clinical experience with transvascular closure of post-infarction ventricular septal defects (MI-VSD) is so far limited. Recently introduced devices provide new potentials and options for treatment of this complication.
Method: Nine pts underwent transcatheter closure of chronic (7pts) or acute (2 pts) MI-VSD with the Amplatzer septal occluder-a device originally used for secundum atrial septal defect closure. The procedures were performed under general or local anaesthesia, with transoesophageal or transthoracic echo guidance, from a femoral arterial and jugular venous approach, with the aid of an arteriovenous guidewire loop. In one patient two occluders were implanted on separate sessions.
Results: (table) The procedure resulted in a complete MI-VSD closure in two pts, in 6 pts the shunt was not significant and in one there was no improvement. Two pts, both in an acute phase of infarction, died from heart and multiorgan failure 2 and 13 days after the procedure. A transient self-limited haemolysis was observed in 3 pts (nr 1,4 and 9) at the periprocedural period. Seven survivors improved dramatically and are doing well at follow-up.

Patients characteristics and results

Patient	1	2	3	4	5	6	7	8	9
Age (years)	52	75	77	71	70	66	81	63	54
MI-implant (weeks)	56; 68	3.5	0.3	14	56	9	2.5	7	10
NYHA	III	IV	IV	III	III	III	IV	II	II
Qp/Qs	3.1	2.9	2.2	3.8	6.2	4.0	3.9	2	1.8
VSD (mm)	8; 15	14	14	21	12	17	17	15	10
ASO (mm)	11; 19	16	24	30	16	22	22	18	16
Result: echo with CD	compl	mild	signif	mild	mild	compl	mild	mild	mild
Follow up weeks	77	142	death	136	74	21	death	14	3
Follow up NYHA	I	II		I	II	I		I	I

Qp/Qs - pulmonary to systemic flow ratio; VSD - VSD diameter; ASO - occluder size; CD - color doppler; compl - complete occlusion; mild - mild residual shunt; signif - significant residual shunt

Conclusions: Transcatheter closure of chronic or acute MI-VSD with the Amplatzer septal occluder is technically feasible. Haemolysis is a possible complication. The successful implantation provided clinical success in pts with completed necrosis. The clinical success is not proven in pts in the early phase of infarction.

P537 Microcoil embolization for ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy

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Background: Percutaneous transcatheter occlusion with ethanol injection of septal arteries is an efficient treatment procedure of hypertrophic obstructive cardiomyopathy (HOCM). The aim of our study is to evaluate the feasibility and efficiency of septal artery embolization with microcoils.
Methods: The microcoils were delivered through the guide-wire lumen of a 2mm-diameter coaxial balloon positioned inside the target vessel as distally as possible. One or more 0.018"-straight microcoils (Hilal straight coils, Cook, USA) were used for each target vessel until complete flow obstruction was noted. The intraventricular pressure gradient was measured before, during and after the procedure. Septal branch occlusion was finally documented by coronary angiography.
Results: We treated 7 patients (pts) (male: 5 pts; mean age: 48±10 years). All pts were symptomatic (NYHA class 3 or 4). The target vessels were successfully occluded in all pts, without complications. Moderate pain was recorded during and after the procedure and the CK level increased five- to ten-fold. The pressure gradient diminished during the procedure from 72±21 mm Hg to 30±15 mm Hg. The number of coils delivered ranged from 3 to 7/patient. The embolized septal branches: 1 vessel in 5 pts; 2 vessels in 1 patient; 3 vessels in 1 case. After the procedure the pressure gradient, evaluated by transthoracic echocardiography, was 34±16 mm Hg and 42±12 mm Hg at 3 month-follow-up. Clinical improvement was recorded in all pts after the procedure (NYHA class 1 or 2). Temporary pacing was necessary in 3 pts during and immediately after the procedure but no patient needed permanent pacing.
Conclusions: Microcoil embolization is an efficient and safe approach for transcatheter ablation of septal hypertrophy in HOCM. This technique induced myocardial necrosis without the toxic effects of alcohol, reducing the risk of complications (permanent pace-maker implantation, ethanol flow to other myocardial regions).

P538 First-line therapy for platypnea-orthodeoxia syndrome with percutaneous catheter-based placement of amplatzer septal closure devices

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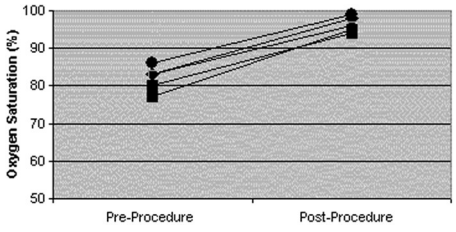
Introduction: Platypnea-Orthodeoxia Syndrome (POS) is a rare syndrome of arterial deoxygenation in the upright but not recumbent position despite normal right heart pressures. While surgical closure of the shunt has been the traditional approach, less invasive alternatives are available.
Methods: Six patients (mean age, 62 yrs) with POS underwent percutaneous atrial septal closure at the Mayo Clinic from 1997 to 2002. We reviewed their clinical presentation, echocardiography and cardiac catheterization studies.
Results: The right-to-left shunt occurred across a PFO (3 patients) or secundum ASD (3 patients). The etiology of POS was status-post pneumonectomy (3 patients), lung reduction sugery for emphysema (1 patient), and other lung injury (2 patients). All patients had normal right heart pressures. Preoperative oxygen saturation (mean, 82%; stdev 3) increased in all patients (mean, 96%; stdev 2) and was statistically significant by paired t-testing ($p<0.0001$). Five patients maintained their response during follow-up; one developed recurrent symptoms with residual flow across the device requiring surgical closure. There were no major procedural complications among the five patients.



Saturations Pre-/Post-Septal Occlusion.

Conclusions: POS can be treated successfully with catheter-based closure of the atrial shunt using an Amplatzer Septal Closure Device. The risk of complications is acceptably low to consider this as first line therapy with the understanding that surgical closure may occasionally be necessary.

P539 Comparison of 9.5 F versus 8.0 F and sheath versus sheathless balloons when treating patients with intra-aortic balloon counterpulsation: data from benchmark registry analysis

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Objective: To study the impact of balloon sheath & size on complications, failure & outcomes during intra-aortic balloon (IAB) counterpulsation
Methods & Results: Benchmark is an international Counterpulsation Outcomes Registry and has collected data on 27207 patients from various centres all over the world. Patients were divided into following groups: Sheath (n=21268) vs. Sheathless (n=5939)& 9.5F (n=17954) vs. 8F (n=9253). There were no significant demographic or procedural differences in all groups. In both groups, IAB related complications, failure & outcomes were compared.
Sheathless vs. Sheath IAB: There were no significant differences in total IAB related complications (7.12% vs. 6.70%;p1) and limb ischaemia (2.83% vs. 2.91%;p0.7) between sheathless & sheath IAB. Sheathless group was associated with higher failure (3.28% vs. 2.80%; p0.049) and higher IAB leak (1.92% vs. 1.28%; p0.0003). Difficult removal (0.69% vs. 0.47%; 0.04) and surgical removal (3.79% vs. 1.72%; $p<0.0001$) was also higher in sheathless IAB group. There was no significant difference in deaths related to IAB therapy in both groups {10 (0.05%) vs. 7 (0.12%); 0.0727}.
9.5F vs. 8F IAB: 9.5F balloon compared to 8F was associated with higher IAB related complications (7.17% vs. 6.03%; p 0.0005) & limb ischaemia (3.42% vs. 1.84%; $p<0.0001$). More patients with 9.5F required balloon removal (3.08% vs. 2.15%; $p<0.0001$) & surgical removal (1.46% vs. 0.79%; $p<0.0001$). It was easier to achieve haemostasis manually in 8F group (9.5F; 57.18% vs. 8F; 59.79%; $p<0.0001$). In 9.5F group higher no. of patients had difficult removal (0.62% vs. 0.31%;p0.0012) & surgical removal (2.131% vs. 1.9%;p0.027) compared to 8F group. There was no significant difference in IAB related deaths in both groups {9.5F; 11 (0.061%) vs. 8F; 6 (0.064%):p0.9}. More IAB failures were reported with 8F compared to 9.5F (3.33% vs. 2.68%;p0.002) eventually leading to higher rate of IAB replacement (1.35% vs. 1.02%;p0.019).
Conclusion Sheathless balloon is associated with higher failure rate and complications. 9.5 F balloon is associated with higher rate of IAB related complications compared to 8.0 F balloon. Therefore on the basis of this study 8.0 F balloon with sheath appears to be a better option when treating patients with intra-aortic balloon counterpulsation.

P540 The microsatellite polymorphism of Heme oxygenase-1 is associated with the inflammatory level but not with restenosis after coronary in-stenting

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Purpose: Vascular smooth muscle cells (VSMCs) can express Heme-oxygenase (HO), a rate-limiting enzyme in the degradation of heme to bilirubin, ferritin and carbon monoxide (CO). VSMC-derived CO can suppress VSMC proliferation and may serve as a antiproliferation factor.The promoter region of HO-1 shows a microsatellite polymorphism with different (GT)n repeats that have been reported to differently induce gene expression, with the short allele being associated with higher gene expression and protection from restenosis following in-stent treatment in peripheral arterial disease. The object of this study was to confirm the effect of this variation on the occurrence of restenosis after in-stent treatment in patients with coronary artery disease.
Methods: 187 patients who underwent successful coronary stent implantation were studied. The genotype for HO-1 promoter microsatellite polymorphism was determined using polymerase chain reaction and automated DNA capillary sequencing.
Results: Repeat length ranged from 22 to 42, with (GT)25 and (GT)32 being the two most common alleles.The allelic repeats were divided into short class(S) with <30 (GT)n, the middle class(M) with 30-37 (GT)n and the long class(L) with >37 (GT)n according to their distribution and previous studies of promoter activity. There was no difference in the prevelance of angiographic restenosis between the genotype groups or between post operation levels of inflammation markers; although carriers of the S allele (n=120) had 33.3% lower baseline IL-6 compared with non-S carriers (n=67)(p=0.0008).
Conclusion: Our results do not confirm an association between the HO-1 promoter polymorphism and restenosis following in-stent treatment, however the association with plasma IL-6 levels suggests that HO-1 S allele might protect from atherosclerotic inflammatory processes.

P541 Thrombospindin-4 gene polymorphism predicting Ala387Pro is associated with an increased risk of angiographic coronary in-stent restenosis

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Background: The risk of in-stent restenosis (ISR) may be modulated by genetic risk factors. Thrombospondins (THBS) are extracellular matrix proteins involved in many vascular wall processes, potentially influencing the process of ISR. Recently, polymorphisms in thrombospondin genes encoding for THBS-1 (A8831G), THBS-2 (T-G substitution in the 3' untranslated region) and THBS-4 (G29926C, predicting Ala387Pro) were associated with an altered risk of premature coronary artery disease or myocardial infarction. We tested the hypothesis of association between three THBS gene polymorphisms and the risk of angiographic ISR.
Methods: Six hundred forty-six patients with stable angina were included in a prospective observational cohort after successful stent placement. Quantitative Coronary Analysis was performed off-line using standard methods (Medis, Leiden). Binary ISR was defined as 50% diameter stenosis or more at follow-up angiogram, using the mean value of two orthogonal views. Genotyping of THBS-1, -2 and -4 gene was successfully performed in 85%, 79% and 83% of patients, respectively.

Thrombospondin-4 genotypes and ISR

Genotype	No ISR	ISR		OR (95% CI)	P
CC	13 (2.9%)	7 (8.0%)	CC vs GG	3.03 (1.15-7.94)	0.019
CG	142 (31.8%)	28 (32.2%)	CG vs GG	1.11 (0.67-1.83)	0.69
GG	292 (65.3%)	52 (59.8%)	CC+CG vs GG	1.27 (0.79-2.03)	0.32
			CC vs CG+GG	2.92 (1.13-7.55)	0.021

Results: There was no association between the THBS-1 or THBS-2 polymorphisms and ISR. Results for THBS-4 are shown in the table as number of patients (percentage).
Conclusion: Individuals homozygous for the THBS-4 C allele have a significantly increased risk of angiographic ISR, compared to wild-type homozygotes.

PERIPHERAL ARTERIES

P542 Prevalence and prognostic role of ABI (Ankle Brachial Index) in patients with high risk of cardiovascular events. The PATHOS (polyvascular atherothrombosis: an observational survey) study

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Background: Pts with known coronary or cerebrovascular disease have high prevalence of further cardiovascular events, and, on the other hand, even pts with symptomatic peripheral arterial disease (PAD) have high prevalence of coexisting coronary artery disease that may strongly influence the prognosis. Nevertheless, the prevalence and prognostic role of PAD in pts with a recent cardiovascular event has not been fully investigated, and the usefulness to detect early markers of PAD (such as ankle-brachial index - ABI) has not been well established.
Methods: PATHOS study is an italian multicenter prospective study, involving 49 centers (Cardiology Div. 49%, Neurology Div. 31%, Internal Medicine Div. 20%)that investigated the prevalence and prognostic role of PAD in a consecutive series of pts admitted for acute coronary syndrome (unstable angina -UA- or acute myocardial infarction - AMI) or for acute cerebral ischemia (stroke or TIA). Coexistence of PAD was diagnosed by means of clinical history of PAD, symptoms of claudication, and abnormal ABI (<0.9 or <0.6).
Results: Preliminary results are referred to 1651 pts, mean age 66.6 yrs, M 69.7%, admitted for UA-AMI in 57.4% and for stroke-TIA in 42.8%. History of PAD was present in 106 pts (6.4%), symptoms of typical claudication were referred in 118 pts (7.3% -left leg) and in 124 pts (7.7% -right leg), respectively, finally, abnormal ABI (<0.9) was detected in 501 pts (30.3%), and severely abnormal ABI (<0.6) in 333 pts (20.1%). The prevalence of abnormal ABI was similar in pts with coronary or cerebrovascular disease.
Conclusions: PATHOS was the first study that prospectively evaluated the prevalence and prognostic role of abnormal ABI, a low-cost, easy test to identify early PAD, in pts with high-risk atherothrombosis disease such as those admitted for coronary or cerebrovascular events. Our preliminary data suggests that abnormal ABI is very frequent involving nearly 1/3 of these pts, while a severely abnormal ABI was detectable in 1/5 of pts. The ongoing follow-up will define the prognostic role of PAD in this population and if ABI could be included among the independent predictors of adverse prognosis.

P543 Novel compound ultrasound imaging for in vitro and in vivo validation of automated carotid intima media thickness measurements

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Ultrasound imaging of carotid intima media thickness (IMT) is an emerging non-invasive screening tool for coronary artery disease. However, it is operator dependent and performed manually, which hinders the broader application of IMT. We hypothesized that novel vascular compound imaging and automated IMT (Q-IMT) would provide accurate measurements and be feasible for automated carotid IMT evaluation.
Methods: We imaged three string phantoms with a linear array epivascular probe (using Sono-CT ® HDI5000, L12-5, Philips Ultrasound) for in vitro validation of compound imaging, which reregisters scatter for improved endothelial image resolution. In vivo validation of Q-IMT (Q LAB ®) was done by imaging the far field IMT of the common carotid arteries (CCA) in three mini-pigs. Q-IMT measurements, performed along the vessel length by 5 independent users on the phantom images (n=33), were compared with the fundamental ultrasound images of the physical diameters of the strings. Q-IMT measurements performed on the left and right carotid arteries of the porcine model were compared with post-mortem histology IMT measurements (n=60) of the excised CCA's.
In vitro Results: Phantom string diameters were 0.50, 0.60, and 0.90 mm, while Q-IMT yielded 0.55 ± 0.02, 0.59 ± 0.02, 0.87 ± 0.05 mm respectively, with $y = 0.86x + 0.11$, $r = 0.95$, SEE = 0.08, $p < 0.001$ by regression analysis with mean difference 0.02 ± 0.01.
In vivo Results: Mean left CCA IMT was 0.39 ± 0.05 mm by histology and 0.41 ± 0.04 by Q-IMT, with $y = 0.96x - 0.009$, $r = 0.67$, SEE = 0.04, $p < 0.05$. Mean right CCA IMT was 0.41 ± 0.07 mm by histology and 0.45 ± 0.04 mm by Q-IMT, with $y = 1.48x - 0.25$, $r = 0.85$, SEE = 0.04, $p < 0.003$. Mean difference in the left and right CCA measurements were 0.02 ± 0.08 mm and 0.03 ± 0.08 mm, respectively.
Conclusions: 1. Compound imaging with automated IMT of string phantoms correlates strongly with physical diameters. 2. Automated IMT in combination with compound carotid imaging accurately measures far field carotid intima media thickness. 3. Automated IMT measurements are feasible in vivo, thus possibly contributing to less operator dependence and use of Q-IMT as a risk assessment tool in the future.

P544 Carotid intima-media thickness as a precursor of carotid atherosclerosis in patients with mitral/aortic sclerocalcification

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It has been previously suggested that aortic valve calcium (AVC) and mitral annular calcium (MAC) can be considered as form of atherosclerosis in the elderly and that these patients are at increased risk for future cardiovascular disease. Several echocardiographic and angiographic studies demonstrated a significant association between AVC, MAC and coronary artery disease, aortic atheroma and arterial atherosclerotic disease. It is also well demonstrated that intima-media thickness (IMT) represents an early phase of atherosclerosis.
Aim: To explore the association between AVC, MAC and the presence of carotid artery atherosclerosis diagnosed by IMT.
Methods: We evaluated 780 consecutive patients who underwent transthoracic echocardiography and echoDoppler of carotid artery for various indication. Patients with important primitive and/or secondary valvular disease were excluded. Consequently, each patient had two qualitative indipendent graduated scores, based on acoustic densitometry (1=no calcium; 2= sclerosis; 3= annular calcium; 4= valvular calcification; 5= valvular calcification without recognition of the leaflets) for mitral and aortic valve; the resulting assigned score was the higher of both. We identified two groups: 1) control group (168 pts; mean age: 43.6±10.5; gender: 88 M/80 F), without AVC/MAC (scores 1); 2) study group (354 pts; mean age: 74,3±8.5; gender: 165M/189F) with signs of AVC/MAC (scores 2-5). All pts underwent measurements of IMT.
Results: Control group (score= 1) showed mean IMT: 0.43±0.06; study group showed the following data: score 2 IMT= 0.61±0.08, score 3 IMT= 0.84±0.07, score 4 IMT= 1.12±0.1, score 5 IMT= 1.40±0.11.
Conclusions: Our preliminary results showed a clear direct correlation between AVC/MAC and IMT; IMT elevation is an important precursor of carotid atherosclerosis in patients with AVC/MAC.

P545 Endovascular stent- graft repair for penetrating atherosclerotic ulcer of the descending aorta

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Background: Penetrating atherosclerotic ulcer (PAU, class 4 aortic dissection) of the aorta is increasingly recognized in patients with acute aortic syndromes. Given the high morbidity and early disease-related mortality rate of 6-20%, endovascular stent-graft repair may be an attractive treatment alternative in selected patients.
Methods: We prospectively evaluated safety and efficacy of endovascular stent-graft placement in 10 patients with PAU of the aorta. All patients were symptomatic and/or presented with complications of PAU. Two patients had contained aortic rupture with left hemothorax. With the patients under general anesthesia, stent-graft placement was performed using a transfemoral approach.
Results: Endovascular stent-graft placement was technically successful in all patients (mean stent diameter 34 mm (24-46 mm), mean length 91 mm (60-130 mm). In one patient with PAU in the aortic arch, the left subclavian artery was covered by the stent-graft, which remained asymptomatic. All patients developed transient elevation of C-reactive protein levels (13.2±5 mg/dl) and mild leukocytosis (11.3±3.6/nl) after the intervention. There were no neurological complications or deaths during the in-hospital period. Within a follow-up period of 24.4±10 months (6-39), one distal endoleak was observed which was successfully treated by additional stent-graft implantation. There were no other aorta-related complications. Two patients died 18 months after the procedure, one of thyroid cancer, one had congestive heart failure.
Conclusion: PAU is a rare but serious acute disease of the aorta with a high rate of bleeding complications. Our experience suggests that endovascular stent-graft placement is a safe and effective therapeutic option.

P546 Percutaneous ultrasound-guided thrombin injection in iatrogenic pseudoaneurysm

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Pseudoaneurysm (PA) is a significant complication after transfemoral catheterization. Ultrasound-guided compression as standard method for non-surgical repair is time-consuming, painful for the patients and has poor success rates. An alternative is the percutaneous ultrasound-guided thrombin injection.
Methods: After transfemoral catheterization 28 PA were diagnosed with colour doppler ultrasound. In 24 patients (14 men, age: 38-84 years, median 70 years) an ultrasound-guided thrombin injection was performed. One patient had a PA at both sides. We injected a single bolus of 1-4 ml (median 2 ml) of thrombin-solution (500 IE/ml). Three patients with significant systolic-diastolic flow underwent surgical repair as primary therapy.
Results: In 20 PA an immediate occlusion was achieved with a single thrombin-injection. Four PA required a second injection, 2 of the 4 PA consisted in at least 2 lobes. A further PA had a spontaneous recurrence at the following day and was treated by a repeated single injection. The overall-success-rate was 100%. The volume of the PA were between 0,7 and 19 ml (median 8,1 ml). At the time of the thrombin-injection 12 patients had an anti-platelet-medication (aspirin and/or clopidogrel), 4 patients received heparin and 5 patients were on a combination of both medication groups. Only 2 patients had no anticoagulation or anti-platelet-therapy, in none of the patients with PA the anticoagulation/anti-platelet-therapy was discontinued. Patients were discharged after 2,6 ± 1,6 days. There were neither allergic reactions nor signs of ischemia following thrombin-injection.
Conclusion: The ultrasound-guided thrombin injection is a safe, simple and effective method for occlusion of PA. Complex PA may require a second injection and a recurrence is rare.

P547 Prospective registry of below the knee percutaneous interventions (cutting balloon application)

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Background: Ten million people in the US alone are suffering from peripheral vascular disease, yet their therapeutic options are very limited. Majority of those patients have serious co-morbid disease, which often prevent them from seeking surgical help. This progressive disease often leads to severe limb ischemia and necessity of amputation, especially in patients with diabetes mellitus. We hypothesized that use of Cutting Balloon (Boston Scientific, USA) during percutaneous peripheral angioplasty (PTI) on vessels below the knee would result in complete dilation of lesions, improvement in the circulation, and resolving of ischemia.
Methods and Results: We are presenting preliminary results on 41 patients, The mean age was 73.7±10.3 years, 58.5% were males. Risk factors included: 87% patients with hypertension, 16% with renal failure, 73% with hypercholesterolemia, 12% tobacco users, 51% with diabetics mellitus, 66% presented with coronary artery disease, and 22% had previous CABG. In most of these patients, affected multiple vessels were affected. Accordingly, 75 arteries were treated with Cutting Balloon in sub optimal PTA. Treated vessels distribution was as follows: 28.6%, anterior tibial artery, 21.4% posterior tibial artery, 23.2% perineal artery, and 26.8% popliteal artery. Average baseline stenosis was 89.4±2.3%, with pedal pulse of 1.2±0.8. Residual post-op stenosis was 3.0±4.2% and pedal pulse increased significantly to 2.3±0.5. The success rate was 100% with no peri-procedure complications. During the follow up only 3.2% of patients developed significant restenosis, majority of the patients remained asymptomatic.
Conclusion: Our preliminary experience suggests that patients with peripheral vascular disease below the knee can safely undergo percutaneous intervention using Cutting Balloon (Boston Scientific). Optimization of the lumen and decrease of elastic recoil results in superior angiographic and clinical outcomes. Percutaneous intervention in lower extremities appears to be safe, carries low risk of restenosis, and should be considered in bifurcations below the knee.

P548 Percutaneous transluminal angioplasty of infrapopliteal arteries in patients with intermittent claudication – acute and 1-year results

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Background: In advanced stages of infrapopliteal peripheral arterial occlusive disease (PAOD) with critical ischemia of the lower limb, the efficacy of percutaneous transluminal angioplasty (PTA) is well established. In contrast, PTA is currently not the therapy of choice in intermittent claudication (IC). In this prospective study, patients with IC were treated percutaneously. Technical aspects and long-term results are presented.
Methods: In 81 patients (61 males [75%], age 71 ± 11 years) with IC (Rutherford grade 2 or 3), 104 interventions (23 patients with bilateral PTA) were performed. At baseline the relative/absolute claudication distance (RCD/ACD) was 49 ± 34/102 ± 57 m, the ankle-brachial index (ABI) was 0.61 ± 0.2 before and 0.49 ± 0.2 after exercise. In 19 interventions (18.3%), the excimer laser technique was used, in 26 cases (25%) a total of 39 stents were implanted and in 59 limbs balloon angioplasty was done.
Results: Primary angiographic success rate (residual stenosis < 30%) was 89.4%. RCD and ACD improved to 107 ± 67 m and 167 ± 74 m ($p < 0.05$ vs. baseline each), respectively, and the ABI at rest and after exercise increased to 0.88 ± 0.13 and 0.72 ± 0.19 ($p < 0.05$ vs. baseline each). Complications: One major groin hematoma requiring surgical repair. One minor hematoma, 1 distal embolic occlusion, 1 arteriovenous fistula, 1 compartment syndrome and one vessel perforation were treated conservatively. After 12 months, the primary patency rate was 66.3%, cumulative primary assisted patency rate was 81.9% and secondary patency rate was 91.5%.
Conclusion: Revascularization of infrapopliteal arteries in patients with IC is feasible and associated with good clinical results and an encouraging long-term patency rate. The complication rate is low.

P549 Duplex ultrasound for follow-up examination after stent-angioplasty of renal artery stenoses

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Purpose: Renal artery stenosis may lead to deterioration of renal function and/or secondary hypertension. Stent-angioplasty has become the method of choice in the treatment of atherosclerotic ostial renal artery stenosis. We describe the changes of the duplex parameters intrarenal resistance index RI according to Pourcelot, and of the renal-aortic flow velocity ratio (RAR) direct after intervention and during follow-up, and the value of the method in detecting restenosis. **Materials and Methods:** We present the results of a prospective study of 241 patients with stent angioplasty for the treatment of 355 severe atherosclerotic ostial renal stenoses (lesions of at least 70% diameter stenosis). Duplex examinations were performed before intervention, before discharge, after 6 and 12 months, and then annually resulting in 1292 examinations. **Results:** RAR could be calculated in 98.9% (1278/1292), RI was calculated in 100% of the examinations. The RAR decreased significantly from 5.9 ± 2.1 to 1.2 ± 0.4 after intervention ($p < 0.00001$) with a slight increase during follow-up. RI increased significantly from 0.64 ± 0.11 to 0.74 ± 0.06 after intervention ($p < 0.00001$) equal to the RI of the contralateral side (0.74 ± 0.07). During a mean follow-up of 27 ± 15 months, 37 restenoses (10.4%) and 12 re-restenoses were, angiographically confirmed, detected by duplex examination resulting in 48 reinterventions. In case of restenosis, RAR increased from 1.3 ± 0.4 to 6.3 ± 2.8 ($p < 0.001$) with a decrease to 1.3 ± 0.6 after reintervention ($p < 0.001$), and RI decreased from 0.75 ± 0.08 to 0.64 ± 0.11 ($p < 0.001$) with an increase to 0.75 ± 0.07 after reintervention ($p < 0.001$). **Conclusion:** In the hand of an experienced technician, duplex ultrasound is a reliable method to follow-up patients after renal artery stent-angioplasty and to detect restenoses.

P550 Comparison of intravascular ultrasound and colour coded duplex sonography for the evaluation of femoral artery stenoses

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The color coded duplex sonographie (CCD) is a well established, non invasive method for the assessment of peripheral artery stenoses. However, the criteria for the quantification are not well defined. Intravascular ultrasound (IVUS) provides the unique ability to exactly measure lumen and vessel parameters with high spatial resolution. The aim of our study was to compare certain CCD derived parameters with the area stenosis as assessed by IVUS

Methods: Patients scheduled for PTA of a symptomatic femoral artery stenosis were included in this study. CCD of the stenoses were performed within 24hs before the planned angiography. CCD (Accuson Aspen 7,5 MHz) parameters comprised peak systolic velocity (PSV) and intra-/prestenotic velocity index (VI). IVUS was performed using a 3.5F 40MHz transducer (Atlantis, CVIS) and an automated pullback device with a standardized pullback speed of 1.0mm/s. Percent stenosis (AS) was defined as the ratio of minimal lumen area and the mean reference lumen area.

Results: Up to now 27 patients entered the study. PSV and VI ranged from 104 to 400 cm/s and from 1.1 to 6.7, respectively. AS ranged from 30.7 to 90%. A close correlation between AS and PSV ($r=0.81$; $p<0.001$) as well as VI ($r=0.89$; $p<0.001$) was observed. All stenoses with AS $>$ 60% showed a PSV $>$ 250 cm/s and a VI $>$2.0. However, in contrast to VI PSV was not useful for further discrimination if AS was $>$60%.

Conclusion: Hemodynamic parameters derived from CCD showed a strong correlation with invasive parameters as assessed by intravascular ultrasound. These preliminary data suggest that VI is superior to PSV for the quantification especially of high grade stenoses.

P551 Relationship of sonographic wall thickness in the carotid, brachial and coronary arteries of coronary artery disease patients

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Background: The association between atherosclerosis among different vascular beds is still unclear. Also, studies comparing the extent of atherosclerosis in peripheral and coronary arteries using ultrasound are lacking. The aim of this study was to investigate the relation of intima-media thickness (IMT) of brachial (BA) and common carotid artery (CCA) with plaque burden of coronary arteries assessed with intracoronary ultrasound (ICUS).

Methods: Intracoronary ultrasound was performed in 42 patients, in whom coronary angiography revealed a $\geq$50% stenosis. An automated mechanic pullback was performed to allow exact volumetric measurements. Manual planimetry was used to calculate vessel area, lumen area and plaque area in an average of 35 images per patient. Plaque burden and plaque volume (using Simpson's rule) were calculated. On the day after angiography, flow-mediated vasodilation (FMD) of the BA and IMT of the CCA and the BA were examined with high-resolution ultrasound.

Results: IMT of the BA correlated significantly with IMT of the CCA ($r=0.56$, $p<0.001$). However, neither parameter showed a significant correlation with ICUS measurements. Endothelial function (FMD) of the BA did not correlate with either plaque volume of coronary arteries or IMT in both peripheral vessels.

Conclusions: In this selected group of CAD patients, we found no significant correlation between IMT of peripheral arteries with ICUS-derived plaque burden. Although peripheral arteries show a close correlation in the extent of IMT, the lack of an association with coronary plaque burden may point towards differences in the progression pattern of atherosclerosis in these vascular beds.

P552 Intravascular ultrasound study in assessment of long-term results of intravascular Gamma brachytherapy of renal arteries after percutaneous transluminal angioplasty

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Background: Intravascular brachytherapy (IVBT) is considered as an effective prevention modality of restenosis after peripherial and coronary percutaneous angioplasty (PTRA). The aim of this study was to assess of the long term outcome of IVBT after PTRA in intravascular ultrasound examination (IVUS).

Materials and 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). Femoral or brachial approach with 8F sheath was used. The PTRA procedure was optimised by an IVUS examination. Both IVBT and ultrasound procedure were uneventful and well tolerated by the patients.

IVBT was performed with PARIS® catheter and MicroSelectron HDR (Nucletron™) system for peripheral arteries. A dose of 15 Gy to adventitia with 7 mm margins from both edges was delivered. Mean irradiation time was 180s (80s –270s range). Baseline, post PTRA and follow-up stenosis were analysed with IVUS and quantitative angiography (QCA).

Results: All 59 pts. were successfully treated with PTRA and IVBT. Post-PTRA IVUS revealed 2 cases of moderate dissection, not compromising renal blood flow. Post-PTRA minimal lumen diameter (MLD) was 4,72$\pm$0,48mm in group I and 4,68$\pm$0,58mm in group II (NS). Angiography and IVUS were obtained in all 59 pts. Mean follow up was 311$\pm$152 days. Control stenosis was 33,9$\pm$11,7% in group I and 25,5$\pm$12,3% in group II (p=0,0096).Minimal lumen area (MLA) was significantly larger in group II than in group I 15,6$\pm$5,4 vs 11,9$\pm$4,4 (p= 0.0053). In IVUS examination late loss of MLD was 1,09$\pm$0,68 and 0,57$\pm$0,68mm in group I and II respectively (p= 0,006). Similarly late loss of cross sectional area was smaller in group II: 3,66$\pm$3,37 vs 7,2$\pm$4,77 (p=0,003).

Conclusions: An intravascular ultrasound is useful method of optimalisation the procedure and assessment of early results and long term effect after precutaneous renal angioplasty

IVUS data proved that IVBT of renal arteries is safe an effective method in prevention of restenosis in long term observation after PTRA.

P553 Prognostic implications of different modalities of presentation in the acute aortic dissection

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Background: Aortic dissection is well recognized as a medical emergency whose clinical presentation at the in-hospital admission can be characterized by a great variety of symptoms and signs, sometimes generic and not very specific, sometimes dramatic.

Aim of our study is to investigate in a large cohort of patients affected by acute aortic dissection the impact of the different modalities of clinical presentation on the in-hospital mortality rate.

Methods: Accordingly, we evaluated 393 patients (pts) with acute aortic dissection, referred to our Division between 1983 and 2002. Study population consisted of 311 pts with type A aortic dissection (79.1%) and 82 pts with type B aortic dissection (20.9%). The modalities of presentation at the admission were classified in: 1) chest pain, 2) worsening dyspnoea, 3) neurological deficits, 4) signs of peripheral hypoperfusion.

Results: The in-hospital mortality rate was of 29.2% (115 pts, of whom 86 pts with type A dissection and 29 pts with type B dissection). The most frequent symptom at the admission was represented by chest pain, present in the 90% of cases, while neurological disorders were the less common modality of presentation (10%). Dyspnoea was present in 34 pts (16.1%) and in 13 of them (38.2%) a pericardial effusion was found. At the univariate analysis in-hospital death was significantly greater in patients showing dyspnoea (p= 0.01) and signs of peripheral hypoperfusion (p= 0.003). At the stepwise multivariate regression analysis both dyspnoea and peripheral hypoperfusion confirmed a significant correlation with early mortality (OR, 2.28; 95% CI, 1.21 to 4.30, p = 0.03, OR, 2.03; 95% CI, 1.28 to 3.2,p= 0.009 respectively).

Conclusions: Although the great improvements in surgical techniques and intensive care management achieved in the last years, acute aortic dissection is still characterized by a high in-hospital mortality. A clinical onset characterized by abrupt and worsening dyspnoea and/or peripheral hypoperfusion syndrome is able to identify a subgroup of patients at higher risk of early death.

STROKE

P554 Do differences between guidelines on stroke prophylaxis in atrial fibrillation have relevant implications for treatment? The GEFAUR-2 Study

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Background: Clinical practice guidelines (CPG)recommendations for stroke prophylaxis in atrial fibrillation (AF) often greatly vary in patient's risk profile stratification. This may contribute to the reluctance of many clinicians to apply this CPG in daily practice and the underuse of anticoagulants(AC) as stroke prophylaxisin this patients (pts). Objectives: To determine the differences of 4 widespread CPG on stratification the risk of stroke and its potential impact on the eligibility for AC in a scenario of routine practice. Methods: Prospective multicenter observational study carried out in 12 emergency departments during July-2000 and Feb-2001. Data was collected on clinical-epidemiological variables, no management recommendations were made. We compared pts classified as having low, moderate and high risk for stroke using published criteria from the Atrial Fibrillation Investigators (AFI), Stroke Prevention in Atrial Fibrillation Investigators (SPAF), the CHADS2 index and the American College of Chest Physicians (ACCP-1998) guidelines. Results: 1220 pts included, age 75±11 y.Prevalence of stroke risk factors: sex (female) 56.1%, age>65y 83.7%, age 66-75y 27.8%, age>75y 55.9%, hypertension 60.5%, diabetes 22.7%, previous stroke 16%, systolic BP>160 mmHg 16.8%, heart failure 21.7% and ischemic heart disease 20.8%. The no. pts stratified as high/moderate/low risk following each CPG was: 70%/22%/8% (AFI), 38%/41%/21% (SPAF), 13%/45%/42% (CHADS2) and 86%/7%/7% (ACCP) respectively. The agreement between the 4 CPG on pts' classification in high/moderate/low risk groups was: 29%/0%/7% (AFI and SPAF), 70%/5%/7% (AFI and ACCP), 13%/3%/8% (AFI and CHADS2), 37%/0%/7% (SPAF and ACCP), 6%/19%/20% (SPAF and CHADS2) and 13%/0%/7% (ACCP and CHADS2). AC prescription in the ED for high/moderate/low risk pts was: 23%/24%/25% (AFI), 16%/30%/26% (SPAF), 16%/20%/28% (CHADS2), and 23%/28%/29% (ACCP). Conclusions: There are profound differences on the stroke risk stratification provided by these CPG (best agreement is observed between AFI and ACCP-1998 and worst between SPAF and CHADS2); therefore the number of pts with AF in whose AC is indicated significantly vary according to the CPG followed. This decision may have a relevant impact on clinical practice so, an effort to homogenise the stroke risk stratification guides is needed to improve their capability to identify high risk pts and clinicians' confidence on their recommendations.Thus CPG would constitute a more reliable and helpful tool for stroke prophylaxis in routine practice.

P555 Improvements in treatment of coronary heart disease and the cessation of the stroke mortality rate decline

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Purpose Many countries observed rapidly declining stroke mortality rates between 1970 and 1990, followed by a slowing or a cessation of this decline. This slowing was seen for both sexes and all ages. Here we test the hypothesis that improvements in coronary heart disease survival can explain this slowing, through an increase in the number of coronary heart disease survivors, at an increased risk for stroke.

Methods We created multi-state life table models based on the survival experience of 46 years of follow-up of the Framingham Heart Study cohort. Improvements in survival post-coronary heart disease were modelled by decreasing mortality rates for those with coronary heart disease. We analysed whether improved coronary heart disease survival could result in a greater than 3% annual increase in stroke mortality rates- enough to eliminate the previously observed decline.

Results Coronary heart disease survival improvements lead to an increase in the number of stroke deaths, but also a concomitant increase in the total population size. Consequently, there was very little increase in the stroke mrtality rate. Under no circumstances was there an increase in annual stroke mortality rates approaching 3% for males or females, the young or the elderly.

Conclusions The hypothesis that increases in the numbers of people with coronary heart disease, as a consequence of improvements in coronary heart disease survival, explain the observed slowing of the stroke mortality rate decline must be rejected. The true explanation is also likely to be a factor that changed markedly around 1990, but with more direct effects on stroke mortality.

P556 The predictive value of white blood cell count and hematocrit measured at admission with in-hospital mortality in acute stroke patients

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Ischemic stroke is associated with increased in-hospital mortality. In the present study we sought to determine which blood morphology variables are helpful in an identification of stroke patients at risk of in-hospital death. Blood morphology was measured at the admission in 400 consecutive acute stroke patients with symptoms starting up to 12 hours prior to hospitalization. Logistic regression adjusted for age, gender, the presence of diabetes, hypertension, atrial fibrillation, previous stroke and ischemic heart disease was used for the calculation of the risk of in-hospital mortality.

Of all analyzed variables, only the white blood cell (WBC) count and hematocrit (HCT) were significantly associated with in-hospital mortality. Odds ratio (OR) for in-hospital death was 1.27 (95%CI: 1.17-1.39; p<0.0001) for every increment of WBC count by 1000cell/μL and 1.14 (95%CI: 1.06-1.23; p=0.0003) for every increment of HCT by 1%. Stroke patients with WBC counts in the 3rd tertile (over 9.7x103/μL) had an 8.26 fold (95%CI: 3.95-17.25; p<0.0001) increased risk of in-hospital mortality and those with HCT in the 3rd tertile (over 43.2%) had a 3.33 fold (95%CI: 1.71-6.48; p=0.0004) increased risk comparing to the rest of patients. The presence of both WBC count and HCT in their 3rd tertiles was associated with more than an 8 times increased in-hospital mortality (OR: 8.34; 95% CI, 4.09-17.02; p<0.0001).

Conclusion: An increased WBC count within the first 12 hours after the onset of ischemic stroke is a strong predictor for in-hospital mortality. An increased HCT is also of predictive value but appears to be less powerful than the value of the increased WBC count.

P557 The role of venous-to-arterial circulation shunts and thrombophilia in ischaemic stroke in young adults

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The cause for ischaemic stroke (IS) in young adults is often unclear. Paradoxical embolism may be a more important cause than previously thought. We investigated the role of venous-to-arterial circulation shunts (v-aCS), such as patent foramen ovale, and thrombophilia in a case-control study of young adults suffering IS and healthy matched controls.

101 survivors of IS aged 16-39 years (cases) were identified from hospital medical records. 101 controls matched by age and sex were drawn from the same GP practice. Testing for v-aCS was performed using transcranial Doppler with agitated saline contrast. Thrombophilia testing included activated protein C resistance, antithrombin III, protein C, protein S, lupus anticoagulant and prothrombin gene variant.

The frequency of v-aCS in IS cases was similar to IS controls (41% vs 40%; odds ratio [OR] 1.04; 95% CI [0.59,1.85]; p=0.88). After adjustment for the confounding effects of smoking, hypertension and hypercholesterolaemia, the risk of IS associated with v-aCS was 1.07. Functionally significant shunts (>50 bubbles spontaneously or >10 bubbles spontaneously with >80 bubbles on provocation) were found more frequently in IS cases compared to controls (25%vs13%; OR 2.1 [0.99,4.46]; p=0.05), with the result becoming more statistically significant after adjustment for confounding factors (OR 2.36 [1.05,5.29]; p=0.037). Hypertension and migraine were more common amongst IS cases than controls (21% vs 8%; p=0.017 and 63% vs 34%; p<0.001 respectively). There was no significant difference in the frequency of smoking, hypertension, hypercholesterolaemia and migraine between v-aCS positive and negative patients. The frequency of major thrombophilia was similar between IS cases and controls (29% vs 23%; OR 1.40 [0.72,2.71]; p=0.32).

This study does not suggest a relationship between presence of a v-aCS and IS. The higher frequency of functionally significant shunts in IS cases compared to controls is an interesting finding, and further research is required to clarify whether these are the patients who should be targeted for transcatheter closure of patent foramen ovale to prevent recurrent IS.

P558 Emboli monitoring in subjects at risk of stroke

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Microembolic signals (MES) monitoring can be considered a good tool of evaluating etiopathogenesis of thromboembolic stroke.
Aims of the present study were: to correlate the number of emboli per hour detected by transcranial Doppler (TCD) monitoring to ischemic acute cerebral event or risk of ischemic cerebrovascular event; to identify the embolic sources; to codify therapeuthical strategy.
The study was carried out in 59 pts, aged between 40 and 75, 43 males and 16 females; 25 pts. affected by acute stroke -group A and 27 pts. affected by carotid artery disease (16 symptomatic and 11 asymptomatic pts) waiting to receive carotid endarterectomy (CEA)-group B. All pts. underwent ECG, Echocardiography, aortic arch Echo-color-doppler, supraortic trunks Echo-color-doppler, standard and monitoring emboli TCD, Neuroimaging.
Results: Comparing pts. affected by stroke to pts. with symptomatic carotid artery disease, the higher rate of cerebral MES was detected in pts. with acute event(X2: 2,208; P: 0,332). Stroke patients presented a higher number of MES per hour when compared to asymptomatic carotid artery disease patients (X2: 4,435; P: 0,350). In surgical pts. the number of MES detected in post-operative was smaller than in pre-operative (X2: 2,790; P: 0,248). Subjects with symptomatic carotid disease showed a higher frequency of MES when compared with asymptomatic subjects (X2: 8,226; P: 0,084). In all pts. affected by emodynamic stenosis we detected an increased rate of emboli in the omolateral middle cerebral artery when compared to pts. affected by not emodynamic stenosis (X2: 0,548; P: 0,770). High intensity MES were found in pts. with stroke and with asymptomatic carotid artery disease (X2: 21,889; P: 0,009). The higher rate of MES was detected in pts with acute event and correlated with worse stroke.
Conclusions: Our results suggests that microembolism is based on an underlying pathology that is a dynamic process not complete after the clinic event. Furthermore, the efforts to identify MES characters that codify the markers of risk for acute cerebral event reveal the significance of high intensity MES.

P559 Mitral valve prolapse and atrial septal aneurysm in young patients with stroke and normal carotid arteries

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Background.Background. The association between mitral valve prolapse and cryptogenic stroke is controversial. The Atrial Septal Aneurysm Multicenter Italian (ASA-MI) Study is a prospective multicenter study evaluating the prevalence of ASA in patients with a recent stroke and normal carotid arteries. The aim of the present research was to evaluate the frequency of ASA and its association with MVP in the stroke population and in the subgroup of young patients (under 55) included in the ASA-MI Study.
Methods: The study group included 245 of the 606 patients referred for TEE (77 women and 168 men, mean age 65.7 $\pm$ 21 years). All patients were selected on the basis of recent unexplained cerebral ischemia and were included in the study if they had normal carotid arteries. Control population included 245 patients (mean age 64.7 $\pm$ 23 yrs) who underwent TEE examination during the same period for indication other than cerebral ischemia. The subgroup of young patients ($<$55 years) included 90 patients (61 men and 29 women, mean age 49 $\pm$ 5 years).
Results: The prevalence of MVP was 18% (95% CI 8 to 21%) in the stroke population and 15% (95% CI 7% to 20%) in control population (X2=2.1, p=n.s.). The prevalence of mitral valve prolapse did not differ between young stroke patients (28.8%) and young controls (20%) (X2 0.835 p=0.3). Mitral valve prolapse was not significantly associated with stroke. We found an association between ASA and MVP: there was an higher incidence of MVP in stroke patients with ASA than in patients without stroke and ASA (40.9% vs 25%: $p<0.05$). There was also a higher frequency of MVP associated with ASA in the group of young patients than in all patients of the ASA-MI study (28.8% versus 18%; X2=20.313, $p<0.001$).
Conclusions: We found an association between ASA and MVP in young patients with stroke and this association between ASA and MVP bore an increased risk than in patients without these abnormalities.

P560 Embolic event rate in patients with atrial tachyarrhythmias: comparison between atrial fibrillation, atrial flutter plus atrial fibrillation and pure atrial flutter

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Recent studies showed controversial results on the prevalence of atrial thrombi and the risk of thromboembolism (TE) after restoring sinus rhythm in (pts) with atrial flutter (AFlut). Primary objective of this prospective observational study, performed on an intention to cardiovert basis, was to evaluate the thromboembolic event rate (TE) in pts with pure AFlut compared to pts with atrial fibrillation (AF). This study comprised 1839 pts (1269 pts with atrail fibrillation (AF), 215 pts with AFlut and AF, 362 pts with pure AFlut).
Results: Transesophageal echocardiography was performed in 845 pts with AF and in 209 pts with pure AFlut. Left atrial thrombi were detected in 65/845 pts with AF(7,7%) compared to 8/209 pts with AFlut (3,8%). Spontaneous echo contrast was observed in 429/845 pts (51%) with AF compared to 43/209 pts (21%) with AFlut. Effective anticoagulation (INR 2-3) was obtained in 85% of pts with AF compared to 63% of pts with AF plus AFlut and 57% of pts with pure AFlut. Acute and long-term TE are listed in the table.

Thromboembolic events

	Atrial fibrillation	Atrial flutter plus atrial fibrillation	Pure atrial flutter
n	1269 pts	215 pts	362 pts
History of TE	134/1269 pts (10.6%)	15/215 pts (7%)	14/362 pts (3.9%)
Acute TE ($<$ 48 h)	2/1269 pts (0.16%)	1/215 pts (0.47%)	0/362 pts (0%)
TE $>$ 48 h - 4 weeks	10/1269 pts (0.79%)	2/215 pts (0.93%)	4/362 pts (1.1%)
Long-term TE (median 20 months)	19/1269 pts (1.5%)	7/215 pts (3.36%)	4/362 pts (1.1%)
Overall TE	13%	11.6%	6.06%

Conclusion: 1) Transesophageal echo revealed 2 times more often left atrial thrombi in pts with pure AF compared to pure AFlut. 2) Pts with AF had 3 times more often history of TE compared to pts with AFlut. 3) The thromboembolic event rate in between 4 weeks after cardioversion was not different between pts with AF compared to pts with AFlut. 4)During a long-term follow up thromboembolic events occurred 2 times more often in pts with AF plus AFlut, compared to pts with pure AF or pure AFlut.

P561 Percutaneous closure of a patent foramen ovale, a possible treatment for migraine?

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Introduction: Recent studies reported an increased prevalence of a patent foramen ovale (PFO) in patients with migraine and a causal relationship has been suggested. We wanted to evaluate changes in the occurrence of migraine before and after percutaneous closure.
Methods: All patients with a right-to-left shunt and/or a history of a paradoxical embolic event through a PFO, who underwent a percutaneous closure in our centre between 1999 and 2002, were included. The medical files were reviewed. Catheterisation data and complications immediately related to the closing procedure were notified. The efficacy of closing was evaluated by transoesophageal echocardiography (TEE) after six months. Late outcome was obtained by reviewing the most recently available medical records. All patients were questioned about headache before, two, and six months after closure. Two neurologists, blinded to the patients' files, diagnosed migraine, according to the criteria of the International Headache Society. McNemar paired chi-square test was used to describe changes in proportions of migraine. Statistical significance was defined as $P<0.05$.
Results: Seventy-six patients were included (43 male, 33 female, mean age 50.7$\pm$12.9 years). Sixty-nine patients suffered from a cryptogenic stroke, seven from a paradoxical peripheral embolism or systemic desaturation. Right-to-left shunt on TEE appeared spontaneously in 28 (37%) or needed to be provoked by Valsalva in 48 (63%) patients. Four types of devices were used (Starflex, n=12, PFO Star, n=25, Amplatzer, n=38, Helix, n=1). Immediately after the procedure, twelve patients developed minor arrhythmias, one a significant inguinal haematoma, one an aspiration pneumonia and one a transient episode of dysarthria. After six months, a trivial right-to-left shunt was found on TEE in 7%. The median follow-up time was 579 days (range 110-1419 days). No recurrent strokes were notified. The prevalence of migraine was 39.4% and decreased to 12.1% and 15.8% two and six months after the closing procedure ($P<0.05$ for both). The prevalence of migraine with aura decreased from 18.2% to 6.5% and 5.6%, respectively ($P<0.05$ for both).
Conclusions: This study confirmed the higher prevalence of PFO in patients with migraine. Percutaneous PFO closure appeared not only to be safe and effective in preventing cryptogenic stroke, but also to decrease the prevalence of migraine. These data suggested a causal relationship between a PFO and migraine. Whether closing a PFO would be an additional treatment of migraine, needs to be determined with prospective randomised trials.

P562 Cardiovascular fitness predicts the risk of stroke among men with or those without common risk factors

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Purpose: Little is known about the association of cardiovascular fitness with the risk of stroke among low and high-risk men in the same cohort. We therefore investigated the relation of maximal oxygen uptake (VO2max) with the risk of stroke in men with and those without common risk factors employing different pre-test probabilities.
Methods: During an average follow-up of 12 years, a total of 137 strokes occurred in a prospective population-based random sample of 2361 men (42-60 years). The standarised testing protocol comprised of an increase in the workload of 20W per minute with the direct analyses of respiratory gases.
Results: There were statistically significant risk reductions and varied from 30 to 40% for 7.5 mL/kg per minute (corresponding to a standard deviation in VO2max)increment of VO2max in healthy and unhealthy (cardiovascular or pulmonary disease), hypercholesterolemic, overweight men, non-smokers and normotensive men, whereas respective increase in VO2max amounted to minor risk reduction in smokers (RR=0.7, 95% CI 0.5 to 1.0) and hypertensive men (RR=0.8, 95% CI 0.6 to 1.0), after adjustment for age, examination year, smoking, alcohol consumption, serum lipids, systolic blood pressure, diabetes and physical activity. However, VO2max as a continuous variable was not associated with the risk of stroke in normocholesterolemic and normal-weight men. Good VO2max was related to reduced risk of stroke in the presence of one or more common risk factors. On the other hand, the cumulative number of risk factors in unfit men was related to a greatly increased risk for stroke. High blood pressure and low VO2max were among the two strongest independent risk factors for any or ischemic stroke.
Conclusion: Unfit men with poor risk factor profile or underlying chronic disease may be the risk groups that will benefit most from the risk factor reduction and other preventive measures with respect to the risk of stroke.

P563 Effects of valsartan on endothelial function and aortic stiffness in hypertensive patients with stroke

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Background: Hypertension (HT) is a major risk factor of atherosclerosis. We compared the effects of valsartan or enalapril on endothelial function and aortic stiffness in hypertensive patients (HT-Pt) between ischemic stroke and non-stroke patient.
Methods: Twenty stroke HT-Pt and twenty non-stroke HT-Pt were randomized to receive valsartan (VAL group, 40-80 mg/day) or enalapril (ENL group, 10-20 mg/day). Brachial artery diameter was measured at rest and during reactive hyperemia (FMD, flow-mediated vasodilation), and then before and after sublingual nitroglycerin (NID, nitroglycerin-induced vasodilation) by using ultrasound system with a 7.5-Mhz transducer to evaluate endothelium-dependent and endothelium-independent vasodilation. Aortic pulse wave velocity (PWV) was measured to evaluate aortic stiffness. Measurements were performed in 12-hour overnight fasting condition at baseline and at 12 months after the treatment.
Results: At the baseline, there was no difference in FMD, NID, and PWV between the VAL and ENL groups of stroke and non-stroke patients. There was no difference on antihypertensive effects between the VAL and ENL groups at 12 months. FMD and PWV were improved in the VAL and ENL groups, but the improvement was much better in the VAL group of stroke patients as compared with ENL group.

Effects on FMD and PWV

			Baseline	12 months
Stroke	FMD	Valsartan	3.2±0.9#	6.8±1.1*†#
(n=20)	(%)	Enalapril	3.3±1.0#	5.0±1.2*#
	PWV	Valsartan	1784±114#	1426±92*†
	(cm/sec)	Enalapril	1794±121#	1685±84*#
Non-stroke	FMD	Valsartan	4.6±1.1	7.8±1.1*
(n=20)	(%)	Enalapril	4.7±1.1	7.5±1.0*
	PWV	Valsartan	1588±123	1416±98*
	(cm/sec)	Enalapril	1609±115	1448±86*

Data are mean ± SD; * p=0.01; †p<0.05 vs enalapril; # p<0.05 vs stroke.

Conclusion: Valsartan is more useful for the improvement of endothelial function and aortic stiffness in HT-Pt with stroke as compared with enalapril.

P564 Intima-media-thickness normal values chart in a French cohort: impact of age, gender and number of cardiovascular risk factors. The PARC study

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Purpose: Intima-media thickness (IMT) of common carotid artery (CCA) is associated with modifiable and non-modifiable cardiovascular risk factors (e.g., age, gender, genetics, or still unrecognized risk factors - RF).It is considered as a marker of early atherosclerosis and may reflect adaptative modifications of the arterial wall. Normal values are likely different from one country to another according to the population characteristics (e.g., geography, nutritional habits, etc.) and are unknown at a country level. In this study, we assessed IMT in a large cohort of French subjects with or without atherosclerotic RF in order to obtain normal values chart. **Material and Methods:** IMT was evaluated using a dedicated software (M'Ath®) with an automatic edge detection algorithm in 6416 subjects with no RF (20%) or at least one RF (80%) recruited by 247 centres. RFs were assessed following a structured questionnaire as well as measurement of blood pressure and blood cholesterol level. IMT was calculated for each subject as the mean value of more than 100 measurements on a length of 10 mm of both CCAs. Subjects were analysed if the quality index (QI) was greater than 0.50 (i.e., more than 50% of measurements available for mean IMT calculation). A centralized reading of IMT measurement was performed by a core laboratory. **Results:** Among 6416 subjects 983 were excluded because of inadequate inclusion or exclusion criteria (n = 212) or a QI < 0,50 (n = 812). In the 1050 subjects without RF, IMT was strongly associated with age and gender ($p < 0.0001$). IMT increased linearly by 0.048 mm for each range of 10-year of age, this increase was not significantly different between men and women (p = 0.97). In the 4383 subjects with at least one RF, the value of IMT was greater than in subjects without RF for the same age and IMT increased with the number of RF at each range of 10-year of age. **Conclusions:** This study provides CCA IMT normal values chart in a French cohort without RF. It also points out the major impact of age and gender, with IMT in subjects with RF being similar to that of subjects without RF but 10 years older. Further analyses will assess the weight of RFs and global cardiovascular risk in this cohort.

P565 Long-term prognosis after transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale in patients with paradoxical embolism

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Background: Atrial septal aneurysm (ASA), which is frequently associated with patent foramen ovale (PFO), has been identified as a risk factor for cerebral ischemia. Patients with both PFO and ASA appear at substantial risk for recurrent embolic events, and may require additional preventive strategies beyond medical treatment. While percutaneous PFO closure has been shown safe and feasible in previous reports, the role of this procedure in patients with additional ASA is less clear. Thus, the purpose of this study was to determine the safety, feasibility, and long-term protective effect of transcatheter treatment of ASA associated with PFO in patients with presumed paradoxical embolism.
Methods: 121 consecutive patients (mean age 49±13 years) with ASA associated with PFO and at least one documented ischemic stroke, transient ischemic attack (TIA) or peripheral embolic event presumably due to paradoxical embolism underwent transcatheter treatment with an atrial septal occluding device. Contrast transesophageal echocardiography (TEE) was performed prior to and 6 months after device implantation. All patients were followed prospectively for up to 8 years.
Results: The implantation procedure was successful in 120 patients (99%) and failed in 1 patient (1%; device embolization). The mean procedure time was 38±20 minutes with a fluoroscopy time of 7±5 minutes. Contrast TEE revealed complete abolition of right-to-left shunt via PFO in 103 patients (86%), whereas a minimal, moderate, or large residual shunt persisted in 8 (7%), 6 (5%), and 3 (2%), respectively. Atrial septal protrusion into the left and right atrium decreased from 9±5 mm and 6±5 mm to 2±3 mm and 1±2 mm, respectively, and maximal atrial septal excursion from 16±4 mm to 4±3 mm ($p<0.001$ for all comparisons) after the intervention. During a mean follow-up period of 2.7±1.6 years (median 2.3 years; total 328 patient-years) 1 ischemic stroke and 5 TIAs were observed. The actuarial survival free from recurrent ischemic stroke, TIA, or peripheral embolism was 97% at 1 year, and 95% at 2 and at 6 years. A residual shunt was a risk factor for recurrence (RR 7.1; 95%CI 1.3-38.9).
Conclusions: Transcatheter treatment of ASA associated with PFO achieves abolishment of right-to-left shunt in the majority of patients, and a marked decrease of atrial septal mobility. The procedure is safe and feasible in patients with presumed paradoxical embolism, and long-term prognosis compares favorably with published data on medical treatment.

NURSING ASPECTS IN INVASIVE CARDIOLOGY

P566 Feasibility of early ambulation after percutaneous coronary interventions using 5 French catheters and low dose anticoagulation

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Health cost containment is becoming a major issue in all countries. Early ambulation after PCI, beside its advantages in terms of patient comfort, may help to shorten the duration of in-hospital stay. The present study was to assessed the feasibility and safety of early ambulation after PCI using 5 French catheters and a femoral access. To assess the optimal time for ambulation, 3 groups of consecutive patients undergoing PCI at a single institution were constituted chronologically, with a progressive shortening of the time duration before ambulation: ambulation was authorized 6 hours after the procedure for the first group (n = 103), 5 hours after the procedure for group 2 (n = 45) and 4 hours and 30 minutes after the procedure for the third group (n = 109). All patients received aspirin, a thienopyridine and heparin before the procedure or, in a few patients, at the time of the procedure. The arterial sheath was removed immediately after the procedure in all patients. The heparin dose was targeted at 50 to 60 U/kg. It was, however, slightly, but significantly lower in group 1 (3822 $\pm$ 925, vs 4267 $\pm$ 870 vs 4137 $\pm$ 709 units, $p < 0.01$; 50 $\pm$ 10 vs 54 $\pm$ 10 vs 55 $\pm$ 10 U/kg). All patients were contacted 7-10 days after hospital discharge to rule out any delayed complication. Mean age (62 $\pm$ 10 years) and weight (77 $\pm$ 12 kg) were similar in the 3 groups. All 3 groups comprised a majority of men (85%, 87%, and 81%), and the risk factors were similarly distributed except for hypertension (61% vs 47% vs 75%, $p < 0.01$) and for treated hyperlipidemia, which was more common in the last 2 groups, reflecting the more widespread use of statins in the most recent period (8% vs 49% vs 43%, $p < 0.001$). Fewer group 3 patients had a history of myocardial infarction (61% vs 64% vs 45%, $p< 0.05$). Group 1 comprised fewer ad hoc procedures (angiography and intervention during the same session) (36% vs 89% vs 66%, $p< 0.001$). The number of treated sites and the number of stents implanted were similar in the 3 groups. Procedural success was achieved in 95%, 96% and 92% of the patients, respectively (p = ns). Only 4 complications occurred, 3 patients developed an haematoma at the femoral access site, (2 in group 3, without clinical consequences and 1 in group 1, which required surgical intervention). No blood or platelet transfusions were required. There were no acute or subacute occlusions at the dilated site. Using 5 F catheters and moderate periprocedural anticoagulation, early ambulation (4h30) after a percutaneous coronary intervention through a femoral access is feasible and safe.

P567 The workload for specialized heart failure nurses of having a heart failure program

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During recent years there has been growing interest in guiding patients with CHF using a heart failure program involving specialized heart failure nurses. As number of CHF-patients is increasing it has not been clear in a regular CHF-population how many patients would get involved in such a program after some years which has implications for the workload of the CHF-nurse. At the Cardiology department in Leiderdorp an intensified program for CHF-patients has started in 2000 and is still running until now. Patients being admitted with CHF as well as outpatient CHF-patients (NYHA class III-IV) have been included in this program. One cardiologist and 1 specialized nurse have been involved in their care. Methods: From 2000 until 2002 data on both the number of patients being admitted each year as well as being seen at the outpatient CHF-clinic have been collected including patient characteristics. Results:In 2000, 2001 and 2002 in total 186, 177 and 230 individual patients were admitted respectively as shown in the table. This table also demonstrates the number of individual patients seen at the outpatient clinic and the patients dying. Patient characteristics during this time-interval are also demonstrated.

Patient characteristics

	2000	2001	2002
Admitted patients(n)	186	177	230
Outpatient clinic pat(n)	227	309	445
Deceased patients (n)	27	38	35
Age (mean)	74	76	77
Male patients (%)	53	49	53
LVEF (%)	43	41	41
Ischemic cause (%)	45	55	54

Conclusion: As demonstrated by the results a specialized CHF-program involving a regular CHF-population results in an impressive load of work especially for the CHF-nurse considering the fact that this person is intensively involved in the guidance and instruction of the patients. Considering the expectations that the number of CHF-patients will increase during the uncoming decade, precautions should be taken to have enough nurses involved in their care.

P568 Which echocardiographic parameters in patients with repaired tetralogy of Fallot reflect their functional status and perceived health?

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Traditionally, the assessment of the left ventricular ejection fraction (LVEF) is used as an indicator of patients' functional status. In congenital heart disease (CHD), and more specifically in patients with tetralogy of Fallot (TF), LVEF measurement is not always reliable. Moreover, sequellae of Fallot repair are located in the right heart. We explored which echocardiographic parameters are associated with TF patients' functional status and perceived health.

Methods: One hundred TF patients (67m/33f) with a median age of 27.6 (Q1=21.3; Q3=34) years were included in this cross-sectional, correlational study. Inclusion criteria were repaired TF, 18 years or older, Dutch speaking and literate. Patients with learning disabilities were excluded. Transthoracic echocardiogram was used to assess the gradient over the right ventricular outflow tract (RVOT) and the right ventricular end-diastolic diameter (RVEDD). Via Color Doppler, pulmonary regurgitation (0-4/4) and tricuspid regurgitation (0-4/4) were appraised. The global right ventricular function was scored as normal, mild or severe dysfunction. Functional class was represented by NYHA and Ability Index (AI). Patients' perception of their health status was measured using a Linear Analogue Scale (LAS).

Results: NYHA and AI were positively correlated with the gradient over the RVOT and the degree of tricuspid valve regurgitation. No association was found between echocardiographic parameters and patients' perception of their health.

Table: Correlation matrix

	NYHA	AI	LAS
RVEDD parasternal	0.120	0.151	0.080
RVEDD apical	0.138	0.103	0.020
RVOT gradient	0.202*	0.232*	0.029
Pulmonary valve regurgitation	-0.003	0.100	0.076
Tricuspid valve regurgitation	0.202*	0.313**	0.025
Right ventricular function	0.094	0.047	-0.178

Spearman's Rho correlation coefficient: *$p \leq 0.05$; **$p \leq 0.01$

Conclusion: Echocardiogram reports may provide nurses with initial information on patient's functioning. In CHD, this is more complicated. This study indicates that echocardiogram, indeed, can offer data that reflect functional capacity, but not perceived health status. For this purpose, a good clinical interview remains crucial to provide appropriate care.

P569 Patients with chronic heart failure rate psychosocial and existential needs higher than physical needs when recently discharged from hospital

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Background: Measuring health status is becoming increasingly important in both clinical practice and research for patients with chronic heart failure (CHF). The Heart Failure Needs Assessment Questionnaire (HFNAQ) is a new, validated, self-administered, 30-item questionnaire that quantifies physical, psychological, social and spiritual domains.

Objectives: To assess the pattern and revalence of needs in patients with CHF recently discharged from hospital following an acute exacerbation of this debilitating syndrome.

Methods: The HFNAQ was administered to patients (n =132; mean age 72.3 (SD 9.69) years; 37% female) consenting to participate in a heart failure cardiac rehabilitation program.

Results: In this sample, the overall mean HFNAQ Score was 67.3 (95% CI = 65.03-69.75), indicating an average level of need around the mid-range of the scale used. In this vulnerable post-discharge phase there was evidence of predominance of psychosocial and existential issues over physical needs. None of the variables that were examined for associations with the measures of needs, reached statistical significance.

Conclusions: The findings of high levels of unmet needs in the psychosocial and existential domains identify this as an important focus for health care interventions in CHF. Failure to identify physical, social or demographic predictors of needs in this sample underscores the importance of assessing the individual's unique perspective of the CHF illness experience. These findings emphasize the importance of the individualized care planning for individuals with CHF following discharge from hospital.

P570 Out-patient intravenous diuretic administration is a valuable part of a hospital based disease management programmme for heart failure

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Background Disease Management Programmes (DMP) for heart failure (HF) help maintain clinical stability and reduce readmission following discharge from hospital. Such programmes frequently respond to patient-initiated unscheduled contacts (UC) due to weight gain and/or clinical deterioration using clinical review and out-patient increase in oral diuretic. An additional benefit of hospital-based DMPs is the ability to give IV diuretic in an out-patient clinic and observe response for a period of two hours in an effort to avoid hospitalisation.
Aim This study reports on the frequency of use and success of administration of out-patient intravenous diuretic in our institution.
Methods Following UC, out-patient IV diuretic was administered to patients with Class IIIb symptoms where augmentation of oral diuretic on one occasion failed to reduce weight or improve symptom and/or where there was marked right ventricular failure. All patients with class IV were admitted and not included in this study. We assessed diuretic/dose administered, subsequent adjustments to regular medication, requirement for repeat administration and impact on weight gain and BNP.
Results In the period between Jan and Dec 2002 there were 86 new patients entered into our DMP for HF. Of these, 12 patients fulfilled the criteria for intravenous diuretic following an average of 81 $\pm$ 71 days of out-patient stability post discharge. Four patients were initiated on IV bumetanide 2mg and eight were intiated on IV frusemide (average dose 64 $\pm$ 17 mg). During the administration of IV diuretic, five patients received oral metolazone. Subsequently, 7 patients had changes to chronic diuretic medication either by increasing loop doses or addition of metolazone. In the majority (8 patients), single dose administration was sufficient, while in 4 patients sequential daily administration was required. In one patient intravenous lasix was given daily for 7 days. All but one patient regained clinical stability without requirement for hospitalisation. The average BNP value of the cohort before outpatient administration of IV diuretics was 1215 $\pm$ 103 pg/ml, which reduced significantly to 408 $\pm$ 264 pg/ml subsequently. Additionally, the average weight of the cohort was significantly reduced by an average of 2.2 $\pm$ 1.2 kg. No clinical or biochemical complications were observed.
Conclusions Intravenous diuretic is an additional safe and effective approach in the outpatient management of decompensating HF patients and is particularly suited to clinic based disease management programmes.

P571 Prevalence and independent predictors for haematoma generation in conjunction with invasive procedures i.e, coronary angiography and percutaneous coronary interventions

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Purpose There are only few international studies concerning the problem of haematoma generation in patients undergoing invasive procedures i.e., coronary angiography (CA) and percutaneous coronary interventioin (PCI).
The purpose of this investigation is to find the prevalence of haematomas in patients undergoing CA and PCI via the femoral artery and to find independent predictors for haematoma generation.
Methods We included 464 patients, 323 patients (69.6%) undergoing CA and 141 patients (30.4%) undergoing CA+PCI or PCI. We defined a haematoma as an accumulation of blood sensible at skin level with a circumference of $>$ 10 cm in accordance to similar studies.
Results Six patients (1.3%) had a haematoma $>$ 10 cm. In order to find independent predictors, this was only possible using a lower cut off value in the definition of a haematoma using $>$ 5 cm of which 46 patients (9.1%) had such. Using 40 variables including sex, age, body mass index (BMI), systolic blood pressure (BTsys), patient medical therapy, sheathsize, way of compression, rest hours; we performed initially univariate succeeded by multivariate statoistical assessment. Independent predictors (Odds Ratio) for haematoma $>$ 5 cm were sex (woman) 1.5; age $>$ 70 years 2.1; BTsys $>$ 160 mmHg 1.4; multiple artery puncture 3.5; ACT $>$ 200 sec.mafter the procedure 3.8; anticoagulant theraphy up to the procedure 2.2. No significance was seen in univariate testing for e.g., BMI, diabetes mellitus, clopidogrel up to the procedure, and multiple people performing compression.
Conclusions We found a prevalence of haematoma after invasive procedures of 1.3% ($>$ 10 cm)/9.1% ($>$ 5 cm). Independent predictors of evolving haematoma are sex (woman), age $>$ 70 years, BTsys $>$ 160 mmHg, anticoagulant treatment up to the procedure, ACT $>$ 200 sec. after the procedure. These risk factords can be used in order to change procedures and minimize generation of haematomas.

P572 Do inpatient cardiac rehabilitation programmes make a difference in quality of hospital practice and patients health?

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Background Well-evaluated cardiac rehabilitation programmes are available for outpatient care, but not for the hospital phase. We investigated if an inpatient programme based on guidelines for cardiac rehabilitation improves quality of hospital practice and patient's health.
Methods An inpatient cardiac rehabilitation programme was initiated by nurses and developed by a multidisciplinary team. It consisted of decision schemes, pre-structured report forms, structured patient education (i.e., video, discharge interview), and agreements regarding consultation of physiotherapist, psychologist, dietician, and social worker.
Before and after implementation of this cardiac rehabilitation programme, we included in total 162 patients hospitalised for myocardial infarction, angina or first diagnosis of heart failure (2x81 consecutive patients). To evaluate the quality of hospital practice, we assessed whether topics in guidelines on cardiac rehabilitation (e.g., secondary prevention, physical exercise, handling chest pain, and psychosocial support) were addressed during hospitalisation. Data on hospital practice were abstracted from medical and nursing charts, after hospital discharge. Three weeks after discharge, patients were asked to fill out questionnaires regarding their health status in terms of anxiety (Hospital Anxiety and Depression Scale), activities of daily living (ADL; Groningen Activity Restriction Scale), and quality of life (Euroqol 5D). Differences in quality of hospital practice and patient's health outcomes between before and after implementation of cardiac rehabilitation were analysed using t-tests and X^2-tests where appropriate, and multiple regression.
Results Baseline characteristics of patients participating in pre and after assessment were comparable for sociodemographic characteristics (except age; mean age 62 (SD 12) vs. 58 (SD 12) years), cardiovascular risk factors, co morbidity, anxiety, ADL, and quality of life.
Improvement in quality of hospital practice between pre and after assessment was observed in terms of attention for mobilisation problems (P=0.03), psychosocial problems (P=0.02), smoking (P=0.04), overweight ($P<0.01$), and timely removal of telemetry (P=0.03). Multiple regression analysis showed an improvement of patient's quality of life ($P<0.01$).
Conclusion Inpatient cardiac rehabilitation programme proved to be beneficial regarding quality of hospital practice as well as patient's quality of life. Application of cardiac rehabilitation guidelines should start in the hospital phase, and not after discharge.

P573 Anxiety level and factors that effect this level in patients who will undergo coronary angiography

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Anxiety is an important issue in medical procedures. It may cause some problems for both the patient and the health care team. Coronary heart disease is especially important from this point of view because anxiety may lead to a lot of problems such as arrhythmias and angina. Coronary angiography is a reference method for both diagnosis and management of these patients. Anxiety of the patients who are to be performed coronary angiography may lead to some unwanted events during the procedure. This study is planned to determine the anxiety levels of these patients and the factors that may influence this level.
Methods: The study consisted of 100 consecutive patients (age=61$\pm$11 years; male:female ratio=69:31). The patients were asked to fill in a data collecting form and also a sheet consisting of situational and continuous anxiety level scale, which was developed by Spielberg et al. (The consistency of this scale in our people was proved.) The anxiety level was determined by averaging the value of each patient. The factors were analyzed by multivariate analysis in SPSS for windows. The statistical significance of p value was set at 0,05.
Results: Both situational and continuous anxiety level of the patients were found to be intermediate. The multivariate analysis revealed that these factors were independently increasing the anxiety level: female gender, having no or very little information about the procedure, having no or very little information about the possible results of the coronary angiography, recent myocardial infarction, first hospitalization because of ischemic heart disease, being performed coronary angiography for the first time, having no relatives who have been performed coronary angiography. The social status, marital status, having noncoronary heart disease, having noncardiac disease and age were found to be ineffective.
Conclusion: The anxiety level of the patients who are to be performed coronary angiography is multifactorial. Among these factors, the modifiable ones are about the informing the patient about the procedure and the possible results of the coronary angiography.

P574 Use of the European heart failure self-care behaviour scale in a heart failure unit in Spain

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Recently the European Heart Failure Self-care Behaviour (EHFScBS) has been developed by Jaarsma et al. and presented in the ESC Congress 2002 and in the AHA scientific sessions 2002. The scale has been tested and validated in 442 patients (P) in 6 European centres from the Netherlands, Sweden, and Italy. In October 2002 we started to use the scale in our P in a heart failure (HF) Unit in Badalona, Spain. We assessed if the self-care behaviour of our P was influenced by sex, age, aetiology of HF and with the time elapsed since they had been admitted to the Unit, assuming that the longer time they had been receiving education and treatment in the Unit the better should be their self-care behaviour.

Results: We studied 267 P, 196 men and 71 women with a mean age of 64.9 years. HF aetiologies were ischemic heart disease 164 P, valvular heart disease 17 P, idiopathic dilated cardiomyopathy 28 P, hypertensive cardiomyopathy 18 P, alcoholic cardiomyopathy 18 P, toxic cardiomyopathy (adriamicin) 4 P, and others 18 P. 48 P were evaluated at the first visit in the Unit, 29 P at 3 months, 22 P at 6 moths, 36 P at 9 months, 79 at 12 months and finally 53 P at 15 months after their first visit. The global score of the EHFScBS in our patients was 22 (median) (range 12-46, P25 17, P75 29). There was no linear correlation with age in global assessment although there was an statistical correlation with age in several items: taking a rest during the day, flu vaccination and exercise. There were no differences between women and men in global self-care behaviour and there was a significant difference only in exercise when each item was analysed individually. We found no significant differences among the aetiologies of HF in any item of the scale nor in global assessment. We found a linear correlation between EHFScBS score and the time elapsed since P had been admitted to the Unit ($p<0.001$). The medians of the score were: 28.5 in P evaluated at the first visit, 22 in P evaluated at 3 months, 24.5 in P evaluated at 6 moths, 22 in P evaluated at 9 months, 21 in P evaluated at 12 months and finally 18 in P evaluated at 15 months after their first visit.

Conclusion: In conclusion the use of the EHFScBS in a HF Unit in Spain has shown a better self-care behaviour in P with a longer follow-up in the Unit, probably due to the education task of the nurse. No differences were found in global self-care assessment relating to age, gender and aetiology of HF.

P575 Nurses observational study on the practice of secondary prevention in a cardiovascular department

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Background: Although it is recognised that Secondary Prevention (SP) measures in patients (pts) with cardiovascular (CV) disease should be started during admissions for acute CV manifestations or interventions, recent reviews invariably show that implementation of SP is unsatisfactory.

Methods: The current practice of SP in the CV department have been the object of "neutral"observation by a group of nurses in our hospital, as part of a quality assurance program: 221 pts (66 $\pm$ 10 y, 23% female) discharged from the intensive cardiac care unit (101 pts), cardiac surgery unit (56 pts), and the vascular surgery unit (64 pts) were prospectively included. Data were extracted from the medical records and the discharge documents. All pts who, during the present admission, showed at least 1 modifiable risk factor (RF) which was previously not known or not corrected, were interviewed on that specific RF and were scheduled for a new assessment 3 months later.

Results: In 72% of pts the diagnosis was coronary artery disease, 22% had diabetes, and 49% had a previous CV major event or intervention; in 69% of pts myocardial revascularisation was performed during admission. Written prescriptions about cessation of smoking and reduction of body weight were given to 7% of current smokers and 3% of overweight/obese pts, respectively. In 17% of pts no lipid measurement was reported, and in 49% of pts with LDL-C $>$ 130 mg/dl statins (S) were not prescribed. In 83 pts with history of MI, aspirin, beta-blockers (BB), both, and angiotensin-converting enzyme inhibitors (ACE-i) were prescribed in 90%, 64%, 59% and 48%, respectively. In pts treated for diabetes, S were prescribed in 50% and ACE-i in 41%. The interview showed that $<$ 50% of pts could tell appropriate levels for arterial blood pressure, body weight, and cholesterol; $>$ 50% of current smokers did not realise the importance of complete cessation. At the 3-month visit (83 pts), treatment with BB and/or S and/or ACE-i had been dropped in 16% of pts; 68% of pts had LDL-C $>$ 100 mg/dl and 29% $>$ 130 mg/dl, and one half of these pts were on S. In 62% of diabetics, glycaemic control was poor, and one third of smokers had not quitted.

Conclusions: This observation by the nurses has shown substantial pitfalls in the implementation of current guidelines, due to incomplete risk assessment, insufficient drug treatment and ineffective pt education. Data from this study are the start point for upcoming actions of quality improvement in the CV department of our hospital.

P576 Drug regimen calculator: a computing software for critical care drugs delivery in the acute setting

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Background: Although it is essential to reliably determine the administration rate (AR) of drugs that must be given by continuous infusion in the coronary care unit (CCU), accurate dosage regimen calculations are not often easy to perform in the acute setting.

Objectives: An infusion rate computing program (Drug Regimen Calculator; DRC) built to facilitate dosage regimen calculations of critical care drugs was developed and tested in critically ill patients admitted to the CCU.

Methods: The DRC package was written using Excel 5.0 and FLASH for Windows; the latter permits the association of data onto cards collected in stacks. After the program has been launched, click upon a button opens a corresponding card which displays the presentation of the drug and requires to set the type of preparation, the number of vials, the patient's weight, the desired dose (DD) and the volume of diluent in the appropriate field. Thirty-tree critical care drugs, including inotropes, vasodilators, anti-thrombotics, anti-arrhythmics, beta-blockers and calcium-antagonists are contemplated in the software. For each compound, the program allows calculation of a wide range of ARs [from the concentration of the solution (CONC) according to the formula: AR (mL/h) = [DD (μg/kg/min) x weight (kg) x 60]/CONC (μg/ml)], time of infusion, total dosage and volume of fluid to be administered over time. To test the reliability of the DRC program, ARs of a number of drugs (dopamine, dobutamine, nitroprusside, nytroglicerin, amrinone, verapamil, diltiazem, amiodarone, lidocaine and non-fractionated heparin) were calculated and then compared to corresponding rates derived from drug nomograms (from ACLS Guidelines) in a group of critically ill patients (n=35).

Results: The use of the DRC computing software allowed rapid and accurate drug regimen calculations for all the drugs. ARs derived from the DRC package and nomograms for drugs delivery showed correlation coefficients between 0.99 and 1 at linear regression analysis. At the Bland-Altman model, the differences between the two methods were close to zero.

Conclusions: The DRC computing package provides a time-saving and reliable means of estimating the AR of critical care drugs in the acute setting. Application of the DRC program to a hand-held computer may be a profitable way to achieve optimal bedside individualization of critical care drugs regimens.

INTERVENTIONS IN CONGENITAL HEART DISEASE

P577 Platelet activation is increased in patients with atrial septal defects suitable for transcatheter closure with the amplatzer device

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Patients with atrial septal defects (ASD)and patent foramen ovale (PFO) often present with features consistent with paradoxical embolism. This study assessed platelet activation in a group of patients referred for transcatheter ASD/PFO closure to determine if increased platelet activation was a contributing factor in the increased thrombotic tendency in this group. Methods: 28 patients with confirmed ASD (n=18) and PFO (n=10) awaiting device closure were recruited. 16 healthy controls had identical venous sampling. All patients with PFO had a confirmed neurological event. Platelet activation was assessed by flow cytometry using surface P-selectin (CD62)expression and antifibriiogen antibody binding. All patients and controls were in aspirin(75-150mg). Results: All 28 patients had successful closure of the defect. Increased Right Ventricular (RV) dimensions (3.6(0.7), 2.3(0.4) p=0.0001) and pulmonary aretery pressure (PAP)(38.4(12.6), 18.8(3.6),p=0.0001) was found in the ASD group compared to the PFO group. Significantly increased CD62 was found in the ASD group compared to the PFO group (2.18(1.6), 1.32(0.5) p=0.05) and the healthy controls(2.18(1.6), 1.1(0.3), p=0.01). Anti-fibrinogen binding was increased in both the ASD's(14.3%(24.5), 3.26(4.44),p=0.07) and PFO's (14.7%(13.6), 3.26(4.44),p=0.05) relative to healthy controls. Repeat sampling at 6 weeks post closure showed a trend for a reduction in CD62 (2.18(1.6), 1.72(1.24) p=0.4) and anti-fibrinogen (14.5(24.5), 10.6(12.4), p=0.1) in the ASD group. Pre-closure RV size and PAP positively correlated with P-selectin expression in the ASD group. (Pearson co-efficient 0.6 and 0.7 respectively). Platelet activation was increased in the presence of a right to left shunt despite normal RV and PAP in the PFO group. Despite anti-platelet therapy with aspirin, right to left shunting results in increased platelet activation which correlated with the magnitude of haemodynamic change. Conclusion:Device closure does not increase platelet activation in the short term and may have benefits in reducing platelet activation. Increased platelet activation may be a contributing factor for paradoxical embolus in this group. This would support the need ofr additional anti-platelet therapy in combination with transcatheter closure as mechanisms to reduce thrombotic risk.

P578 Transcatheter closure of multi-fenestrated atrial septal aneurysm mimiking a secundum atrial septal defect: correct diagnosis and device selection by intracardiac echocardiography

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Purpose: Transcatheter closure of patent foramen ovale (PFO) is an attractive alternative to paradoxical embolism secondary prevention in selected patients. Intracardiac echocardiography (ICE) evaluation of atrial septal anatomy has several advantages on conventional echocardiography and can help the diagnosis and device selection in cases in which standard echocardiography is inconclusive. Aim of our study was verifying the role of ICE in transcatheter closure of PFO mimicking a secundum atrial septal defect.
Methods: Ninety-one cases of transcatheter closure of PFO with the Amplatzer Occluder device were reviewed. The mechanical ICE has been used as primary imaging technique both for choosing the device size and monitoring the procedure. The diameters of the atrial septum and fossa ovalis (FO), and the distance between the guide-wire passage and the limbus of the FO have been determined in two orthogonal planes, the axial "great vessels" and the longitudinal "4-chambers" planes. The device size has been chosen on the criterion of the complete coverage of the FO. Initial standard echocardiographic diagnosis before the procedure and ICE diagnosis during the intervention were reviewed as well as the Amplatzer Occluder device type and size.
Results: Ten patients (6 women, mean age 45±18.0 years) of 91 undergone transcatheter closure of PFO, had a standard echocardiography consistent with a secundum atrial septal defect (7 small ASD, 2 ASD with associated atrial septal aneurysm, 1 polifenestrated ASD) and an ICE diagnosis of multi-fenestrated atrial septal aneurysm. Mean pulmonary arterial pressure and Qp/Qs ratio were 14.8±4.5 mmHg and 1.17±0.28, respectively: these values did not statistically differ from those of the rest of the 91 patients. The intracardiac longitudinal and transverse diameters of the fossa ovalis were 21.8±6.3 and 19.5±3.8 mm, respectively. Six Amplatzer PFO Occluder 35 mm and 4 Amplatzer PFO Occluder 25 mm have been successfully implanted. Mean follow-up was 19.4±7.2 months. In 7 patients the pre-discharge transthoracic echocardiography and 3, 6,12 months transesophageal echocardiography failed to show any residual shunt. Three patients had a "small" residual shunt at 1-year echocardiography. No patients experienced recurrent symptoms during the follow-up.
Conclusion: Sometimes standard echocardiography fails to correctly differentiate a small secundum ASD from a multi-fenestrated atrial septal aneurysm. In such cases, ICE is an effective and safe technique for making the correct diagnosis and selecting the proper device.

P579 Assessment of the markers of platelet and coagulation activation following transcatheter closure of atrial septal defects

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Antiplatelet treatment for 6 months instead of antiocagulants or even no treatment is standard following transcatheter closure of atrial septal defects (ASDs). However, no biological basis supports such an approach in this context. Moreover, some studies have reported an incidence of about 0.5% of cerebrovascular events as well as several cases of device thrombosis within the first weeks following device implantation despite aspirin treatment. The purpose of our study was to prospectively evaluate the presence, degree and timing of the activation of the coagulation and platelet systems following transcatheter closure of atrial septal defects (ASDs).
Methods and Results: A total of 14 patients (9 females, mean age 41±22 years) who underwent successful transcatheter closure of an ASD defect with the Amplatzer septal occluder were included in the study. The procedures were performed under plain anticoagulation, and aspirin (125 mg/day) was administered for 6 months. The activation of the coagulation and platelet systems was determined by measuring the prothrombin fragment 1+2 (F1+2) levels and the percentage of activated platelets (determined by P-selectin expression), respectively. Blood samples were taken at baseline just before the procedure, and at 1, 7, 30 and 90 days following device implantation. F1+2 levels increased from 0.85±0.29 at baseline to 1.18±1.10 nmol/L at 1 day (p=ns), and to a maximal value of 1.20±0.52 nmol/L at 7 days (p=0.006), returning to the baseline levels at 30 days (0.95±0.53 nmol/L, p=ns) and 90 days (0.79±0.53 nmol/L, p=ns). No significant variations of the percentage of platelets expressing P-selectin were detected at any time (1.05±2.12%, 0.28±0.53%, 0.40±0.88, 0.38±0.78%, and 0.62±0.88%, respectively). In a control group of 20 healthy subjects, the mean value for the F1+2 levels was 0.80 ± 0.22 nmol/L (significantly lower than those obtained in the study population at 7 days after ASD closure, p=0.02) and the mean percentage of activated platelets was 0.88 ± 1% (with no differences compared to the values obtained at any time in the study population).
Conclusions: Transcatheter closure of ASDs with the Amplatzer septal occluder was associated with a mild but significant increase of F1+2 levels at least during the first week after device implantation, with no detectable effect on the activation of the platelet system. These results might contribute to a better determination of the type and duration of antithrombotic treatment to be prescribed following ASD closure.

P580 Stenting the neonatal arterial duct in duct-dependent pulmonary circulation

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Objectives To assess the feasibility and safety of a new approach and technique to stent the arterial duct in neonates with a duct dependent pulmonary circulation.
Background Previous attempts to stent the neonatal arterial duct were unsatisfactory: the early generation rigid stents were relatively large, bulky, required stiff wires and long sheaths, and only partially covered the duct. Learning from these failures, we speculated that covering the complete length of the duct with current low profile stents with good scaffolding properties might avoid previous problems.
Methods Ten neonates with duct dependant pulmonary circulations through a short straight duct were treated with stent implantation. The duct was crossed with an atraumatic 0.014" wire. A low profile premounted coronary stent (outer diameter < 4Fr, length 13 – 24 mm, diameter 3.0- 4.0 mm) was positioned within the duct, not protected by a sheath; care was taken to cover the complete length of the duct from the aorta-ductal junction until well within the pulmonary trunk.
Results All stents could safely be deployed with adequate pulmonary flow at early and medium term follow-up. There were no procedure related complications; 1 patient died early from sepsis. All patients had adequate relief of cyanosis for at least 3-4 months. During follow-up the pulmonary vasculature bed had grown without distortion. Acute occlusion of a stented duct was not observed. Ductal flow progressively decreased slowly over several months by luminal narrowing (intimal proliferation or peal formation), until the stented duct either had become redundant, was dilated/restented, or elective staged surgery was performed.
Conclusions With current technology, complete stenting of a short straight duct is a safe and effective palliation, allowing adequate growth of the pulmonary arteries.

P581 Thoracoscopic asd closure is a reliable alternative for percutaneous treatment

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Objective: To demonstrate the feasibility and effectiveness of a totally endoscopic isolated ASD closure technique, thus avoiding median sternotomy.
Methods: Between March 1997 and January 2003, 74 patients underwent an endoscopic ASD closure. Mean age was 43,6±16.4 and 63% were female. Median preoperative functional class was I. Data were collected retrospectively and included patient assessment of scar esthetics, procedure related pain, functional recovery and overall patient satisfaction. Clinical and echocardiographic follow-up was obtained in all patients (mean 37.8±18.7 months).
Results: Successful ASD closure was obtained in all patients (2 ASD type I, 70 type II, 2 type III). Patch repair was performed in 42% of the patients and primary repair in the remainder. Mean aortic cross-clamp and cardiopulmonary bypass times were 54.3±24.5 min and 97.7±35.4 min respectively. Morbidity included one iliac vein stenting, one femoral artery plasty, two revisions for suspected bleeding and atrial fibrillation in 6 patients. There were no hospital mortalities neither early reoperations. Two patients required late reoperation: one for atrial thrombus and another one for tricuspid regurgitation. Echocardiographic control confirmed complete ASD closure in 71 patients and a small residual shunt in 3 patients.
Ninety three percent of the patients were highly satisfied with very low procedure related pain and 97% felt they had an esthetically pleasing scar.
Conclusions: Endoscopic ASD closure can be safely done with a high degree of patient satisfaction. This technique is now our exclusive surgical approach whenever percutaneous treatment is not indicated or failed.

P582 A comparison between surgery and therapeutic catheterization in the management of congenital coronary arteriovenous fistula in children

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Until recent years, the management of congenital coronary arteriovenous fistula (CAVF) in children has been surgical. Advances in interventional catheterization now allow an alternative treatment option with device occlusion. This study reviews the advantages and disadvantages of the 2 modalities.
From 1993 to 2002, 7 children (M=4, F=3) were diagnosed with CAVF (mean age of diagnosis 1.2±2.2 years). Three CAVF were from the right coronary artery, and 4 from the left coronary artery. All drained into the right ventricle, except for 2 (right atrium = 1, superior vena cava = 1). The left to right shunt was 1.9±1.0, and mean pulmonary pressure 20.4±8.3 mmHg.
Two patients presented with congestive cardiac failure and underwent surgery in infancy. Another was operated on at 8 years, before the technique of transcatheter embolization was available in our institution. The average hospitalization was 12±4 days. Overall outcome was good without major complication except for a residual shunt in 1. Transcatheter embolization was performed in 4 asymptomatic patients (including one with a residual flow from surgery) using Cook's and/or interlocking detachable coils. The mean age at procedure was 7.8±7 years, and the patients were discharged the following day. Successful obliteration was achieved in all. One asymptomatic child is awaiting elective therapeutic catheterization at an older age.
Surgery for CAVF is associated with longer hospitalization and therefore higher costs. Transcatheter treatment offers the advantages of cosmesis, less pain and trauma to the child and family, and without the need for cardiopulmonary bypass. Device embolization, being the newer of both methods, demands expertise in interventional catheterization, and is technically difficult to perform in the young infant or with unfavourable anatomy. In selected children, however, transcatheter device occlusion now offers an effective and state-of-art option in the management of CAVF in children.

P583 Uselfulness of a gradual balloon aortic valvuloplasty guided by colour Doppler-ecocardiography strategy for the treatment of severe aortic stenosis in children

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Percutaneous balloon aortic valvuloplasty (BAV) has been demonstrated to be a good alternative to surgical valvulotomy in infants. However, the occurrence of significant aortic regurgitation related to BAV is a worrying complication that occurs in 10 to 30% of cases. This complication is especially dreaded in infants since the solution requires the implantation of a prostheses or the realisation of a Ross procedure, with unknown long-term results. The use of color Doppler-ecochardiography (DE) in the cath-lab has undergone a tremendous increase during the last years, but the systematic use of this technique to guide BAV has not been reported. The objective of our study was to evaluate prospectively, in a series of consecutive children with severe aortic stenosis, the efficacy of gradual BAV guided by DE strategy for relieving aortic stenosis while preventing the appearance of significant aortic regurgitation
Methods: A total of 10 consecutive patients were included (median age 5.5 months, range 28 days to 8 years; median weight 6.8 kg, range 3 to 29 kg). All procedures were performed by retrograde femoral approach. A DE examination was performed at baseline, after crossing the valve with the guidewire, and following each balloon dilation. The gradual approach consisted of choosing the first balloon diameter to obtain a balloon/aortic annulus (BA) ratio of 0.8-0.9, and subsequent larger balloons up to a ratio of 1.0 in case of residual gradient >50 mmHg as determined by DE. The procedure was terminated if residual gradient <50 mmHg with >40% gradient reduction was obtained or significant aortic regurgitation appeared as determined by DE.
Results: BAV achieved a residual aortic gradient <45 mmHg in all cases (from 65±13 mmHg to 26±9 mmHg, p<0.0001), with a final BA ratio of 0.88 (one balloon was used in 6 cases and 2 balloons in 4 cases). Median fluoroscopy time was 18 minutes (range 8 to 39 minutes). Significant aortic regurgitation occurred in 2 cases (moderate in one patient and moderate to severe in another). At mean follow-up of 20±11months, one patient required repeat valvuloplasty because of restenosis.
Conclusions: Gradual BAV guided by DE was associated with a high success rate in relieving severe aortic stenosis. However, despite avoiding valve cusp perforation and massive aortic regurgitation, such a strategy did not preclude the occurrence of significant aortic insufficiency in 20% of cases.

P584 Immediate and intermediate term results of stent therapy for aortic coarctation

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Aims: To assess the immediate and intermediate term outcomes of stent thearpy for aortic coarctation.
Methods: A review of all patients undergoing stent implantation in a tertiary referral center in the Netherlands or Belgium. Coarctation was defined as systolic arm to leg blood pressure gradient of >20mm Hg, and confirmed by echocardiography (n=34), MRI (n=18) and/or angiography.
Patients and Results: Stents were implanted in 34 patients, at a mean age of 21 ± 16 years. Eleven patients had native coarctation, while 23 had recoarctation following previous surgery alone (n=13), balloon angioplasty alone (n=1), or surgery followed by balloon angioplasty (n=9). Stent implantation was elective in 33 patients; one 58 year old patient underwent stent implantation as a bailout procedure for treatment of acute dissection following balloon angioplasty. In 32/34 patients, stents were correctly placed. In 2 patients the stent produced in partial occlusion of the left common carotid artery and right subclavian artery respectively. Apart from one infant who died from a retroperitoneal hematoma related introduction of the long sheath, three other patients had major complications (femoral artery thrombosis requiring streptokinase, cerebrovascular accident, aortic aneurysm upstream from the stent implantation site).
The peak systolic blood pressure gradient decreased from 149 ± 37 mm Hg to 124 ± 24 mm Hg. The diameter of the coarctation segment increased from 7.3 ± 3.8 to 13.3 ± 3.9 mm, while the pressure gradient decreased from 37 ± 16 to 7 ± 7 mm Hg. There was no significant difference in the percentage change of any of these parameters between children (defined as <18 years of age) and adults. Similarly, no difference in outcome was observed between patients with native coarctation and those with recoarctation. During follow-up (range 6 to 63 months) 10 patients (33%)developed recoarctation requiring further therapy. This consisted of redilation of the original stent (n=8), implantation of an additional stent in series (n=1), or surgery (n=1). Twelve patients (36%; 10 adults, 2 children)were still using antihypertensive medications at last follow-up, compared with all 34 patients prior to stent therapy.
Conclusions: Stent therapy provides reasonable immediate and intermediate term palliation in the majority of patients. The incidence of complications associated with the procedure is significant, and may in part be due to the relatively small number of patients treated per center. Longer term follow-up studies are indicated to define the place of stent therapy in young patients.

P585 Transcatheter patch occlusion of adult atrial septal defects: a single institution experience

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The transcatheter patch (TP) is a wireless polyurethane patch used for the occlusion of atrial septal defects (ASDs), supported on the atrial septum by a double balloon catheter for 48 hours.
Since December 1999, 17 consecutive adult ASD patients were implanted by a TP after a previous balloon test occlusion. Balloon size of the ASDs was 17-35 mm (med. 27); deficient rim was present in most of them (anterior 12, inferior 2, superior 1). Qp:Qs was larger than 1.5:1 in all of them and pulmonary hypertension was present in three.
Transcatheter patch implantation was successful in all patients, resulting in effective occlusions (full occlusion in 9 and trivial shunts in 6), in all of them except for two. Both patients had premature balloon deflation resulting in significant residual shunt. One of the patients with residual shunt underwent a second TP implantation with effective occlusion.
On follow-up (1 month - 3 years, med. 14 months) all successfully implanted patients remain well. There were no heart murmurs and the second heart sound was normal. By echocardiography the patch was progressively diminishing in size, becoming indistinguishable from the rest of the septum, approximately a year after the implantation. The good result was maintained in all cases with the trivial residual shunt disappearing in 2 additional cases. No long-term complications were noticed.
In conclusion transcatheter patch occlusion of adult ASDs appear effective and safe; advantages of the method include wide application, lack of wire related complications, no embolizations and progressive normalization of the septal appearance.

P586 Intracardiac echocardiography in the diagnosis and transcatheter closure of secundum atrial septal defect: effectiveness of a mathematical model for defect and device sizing

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Purpose: The standard method for transcatheter closure of secundum atrial septal defect (ASDs) requires balloon sizing of the defect and transesophageal echocardiography (TEE) monitoring. In an effort to shift toward minimally invasive endovascular therapy, we used the mechanical single-element intracardiac echocardiography (ICE) as the primary means for both the selection of the Amplatzer Septal Occluder (ASO) and the guidance of the procedure. This study was aimed to assess the effectiveness of an ICE-derived mathematical model of defect and device sizing.
Methods: Ninety-one patients (mean age 46.4 $\pm$ 16.1 years, range 14 to 76 years) with hemodynamically significant ASDs underwent ICE-guided transcatheter closure. Two standardized orthogonal views, scanning perpendicular to the plane of the atrial septum, were used to obtain ICE-derived measurements of the fossa ovalis and to assess optimal device deployment: the axial view on the aortic valve plane and the long-axis view on the 4-chamber plane.The major and the minor axes of the fossa ovalis (that is, secundum-to-secundum atrial septum distance) on these two orthogonal planes were measured, using end-diastolic frames, assuming its shape to be an ideal ellipse. The ASO waist diameter was estimated on the basis of the r value ($r=/c^2+p^2$, where r is the radius of the ICE-predicted ASO, c is the half focal distance of the elliptical fossa ovalis, and p is its semi-latus rectum distance).
Results: In all cases ICE planes were identified with excellent resolution and detail, providing proper measurements of the fossa ovalis from which to derive geometrical assumption for selection of an appropriately sized device. During the procedure, the 4-chamber plane allowed obtaining clear and easily interpretable images of overall the stages of device placement. Mid-term complete occlusion rate were 97.8% (89/91), 97.7% (88/90), 97.6% (81/83) and 98% (49/50) at 24 hours, 1, 3 months and 1 year, respectively. There were no complications ICE-related.
Conclusions: We conclude that ICE evaluation of ASDs allows quantitative and qualitative information for both proper device selection and optimal deployment during catheter-based closure, eliminating the cumbersome balloon sizing technique and the need for general anaesthesia during TEE monitoring.

P587 Percutaneous treatment of atrial septal aneurysm

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Atrial septal aneurysm are localized saccular deformities associated to patent foramen ovale (PFO) or atrial septal defects (ASD). Patients with this malformation are often asymptomatic. However, in some cases, serious sequellae have been described. Atrial septal aneurysm is considered a potential risk factor for stroke. This study focuses on percutaneous treatment for these complex atrial septal malformations.
Methods: From a total number of 169 patients with ASD or PFO that were treated by percutaneous closure, for the study we selected 23 (18 with ASD and 5 with PFO) that fulfilled the following criteria of atrial septal aneurysm: the malformation measuring >15 mm at the base in adults and 8 mm/m^2 of body surface area in children. The mean age was 36$\pm$26 years (range 5 to 72). Six patients had functional class II or III dyspnea, 1 severe pulmonary hypertension and 7 (30%) a previous event of cerebral ischemia. In patients with ASD the mean pulmonary flow to systemic flow ratio was 1.9$\pm$0.6; 6 patients had a single hole and 12 showed multiple holes. Thirteen patients received a single Amplatzer septal occluder and 5 patients needed 2 or 3 devices. A 35 mm Amplatzer devices was placed in the 5 patients with PFO. **Results:** Complete closure of the ASD defect was achieved in 17 (94%) patients during predischarge transthoracic Doppler ultrasound study. The only complication was a cardiac tamponade successfully resolved by pericardial drainage. After the procedure all patients were treated with low molecular weight heparin for 1 month and aspirin for 6 months. The evolution of residual post-implantation shunt is summarized in the table below. The transthoracic ultrasound study at 6 months follow-up showed defect closure in all patients. At a mean follow-up time of 24$\pm$18 months, all patients remain alive and symptom free.
Conclusion: Patients with atrial septal aneurysm and associated ASD or PFO, can be successfully treated with Amplatzer septal occluders. Despite more technical difficulties, these results are similar to those obtained in patients with ASD without atrial aneurysm.

Evolution of residual shunt

	Angiographic	TE echo in laboratory	TT echo (48 hours)	TT echo (6 months)
No	8	10	17	18
Mild	10	8	1	0

TE: transesophageal. TT: transthoracic

CARDIAC INTERVENTIONS: VALVES, CONGENITAL HEART DISEASE

P588 Is it possible to predict patients quality of life after open heart surgery?

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Using QOLi-NS index, an integral numerical value for measuring disease specific health related Quality of life in cardiovascular patients undergoing open heart surgery, we tried to develop a simple (additive) model for predicting improvement of QOL after surgery.
Target variable was improvement of QOL six months after open heart surgery calculated as difference between QOLi-NS scores before and after surgery. For factors influencing changes in QOLi-NS we chose widely available preoperative clinical data. We collected relevant data for 294 consecutive patients (both risk factors and QOLi-NS scores before and six months after operation).
After applying multivariate stepwise linear regression using QOLi-NS improvement as dependent variable and set of preoperative risk factors as independent ones, a simple linear (additive) model with 18 risk factors was created. Correlation between predicted QOL improvement and observed was very strong ($r=0.78$ $p<0.001$). Patients form training set were stratified into four groups according to the predicted QOLi-NS improvement: The developed method was applied to another group of 465 patients and also has shown strong capabilities of prediction.

QOLi-NS improvement groups	<30	30-45	45-60	>60	0-100
Predicted QOL improvement	11.4	39.3	51.8	64.9	40.7
Observed QOL improvement	11.0	40.5	51.2	65.1	40.7

Obtained method may be used for prediction of patient's outcome after open heart surgery in order to help patients to weight risks and benefits of an operation and as quality monitoring tool for healthcare professionals.

P589 Exercise stress echocardiography enhance diagnostic accuracy in chest pain unit

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Background: Resting ECG, echocardiography (Echo), and myocardial scintigraphy (SPET) showed a poor negative predictive value (NPV) in risk stratification of patients (pts) presenting without ongoing chest pain (CP) at low-risk of coronary events (CE) managed by the chest pain unit (CPU).
Aims: To assess feasibility, NPV and diagnostic accuracy (Acc) of exercise-ECG (ex-ECG), exercise-Echo (ex-Echo), and exercise-SPET (ex-SPET) in pts with low-risk CP.
Methods: We evaluated 503 consecutive pts (mean age 62 y.,36% female,during 2000-02 y.) complying recent (<24h) symptoms suggestive of coronary artery disease (CAD). All pts had CP, non-diagnostic ECG, negative troponins and normal resting left ventricular function on presentation.
End points. Detection of CAD defined as follows: coronary stenoses $\geq$ 50% in pts with $\geq$ 1 positive test at least, and CE at 6-month follow-up in pts with negative tests.
Results: Of 503 pts enrolled, 181(36%) had $\geq$ 1 positive test at least; all these pts underwent angiography and finally 87 pts (17% of the study population and 48% of pts with positive tests) had CAD. In addition 5 pts (0.1% of the study population) with negative tests were recognised as having CAD at follow-up. Thus, overall diagnostic strategy in the CPU had sensitivity 95%, specificity 80%, NPP 99%, PPV 48%, and accuracy 94%. Ex-ECG was positive in 105(21%) pts; ex-Echo was positive in 105(21%) pts; ex-SPET was positive in 155(31%) pts. Among 398 pts with negative ex-ECG, 28(7%) pts were recognised as having CAD (Sens 70%, Spec 90%, NPV 93%, PPV 66%, Acc 86). Among 498 pts with negative ex-Echo, 10(2%) pts had CAD (Sens 89%, Spec 94%, NPV 97%, PPV 77%, Acc 93%). Among 348 pts with negative ex-SPET, 8(2%) pts had CAD (Sens 91%, Spec 83%, NPV 98%, PPV 54%, Acc 84%). In this series of pts ex-Echo and ex-SPET had higher NPV (97% and 98% respectively; P=n.s.) as compared to ex-ECG (93%; P=.004); moreover both these tests had higher sensitivity (89% and 91% respectively; P=n.s.) as compared to ex-ECG (70%; P=.00001). Finally,ex-Echo showed a high accuracy (P=.0003 versus ex-SPET and ex-ECG), high specificity (P=.01 versus ECG and P=.001 versus SPET), and optimal PPV (P<.0001 versus ex-ECG and ex-SPET).
Conclusions: Low-cost and high availability ex-Echo is safe and effective in ruling out CAD in CP pts at CPU, and it is especially valuable for implementation of early discharge. Indeed, ex-Echo showed similar NPV and higher accuracy as compared to high cost and low availability ex-SPET. Thus ex-Echo is particularly appealing for those hospital without nuclear facilities.

P590 Non-invasive bypass angiography with the cardio-computed tomography avoids unnecessary cardiac catheterizations

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Despite all improvements, the patency rate of coronary bypass grafts is still limited: One year after surgery, 12 to 17% of venous and 3 to 6% of arterial grafts are occluded. Since clinical outcome depends on graft patency, more frequent evaluation of bypass anatomy could be performed non-invasively.
Multislice-CT (MSCT) has evolved as a valuable alternative to catheterization of coronary bypass grafts. We therefore examined 80 patients with no angina pectoris and no clear evidence of myocardial ischemia. The mean age was 65 $\pm$ 9 years (5% female). The average time interval since bypass surgery was 4.9 years. Of the 220 bypass vessels, 60% were venous and 40% were arterial. CT-angiography (CTA) was performed using the Philips Mx 8000 4-slice spiral CT in 1 mm collimated sections and retrospective gating within a single breathhold at 120 kV and 300 mAs. Heartrates above 60 per minute were reduced with beta-blockers for better image quality.
36.4% of bypass grafts were occluded. As compared to cardiac catheterization, MSCT was able to identify all occluded grafts. One LIMA bypass presumed to be occluded by the CTA was shown to have a narrow lumen with slow flow. Therefore the sensitivity was 100%; the specificity 96%.
Summary: Non-invasive bypass angiography with the MSCT has excellent sensitivity and specificity in detecting occluded coronary bypass grafts in asymptomatic patients. MSCT can therefore be helpful in avoiding unnecessary cardiac catheterizations.

P591 Role of helical computed tomography and computed tomography angiography in diagnosis of cardiovascular anomalies in infants and children with congenital heart diseases

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Purpose: to evaluate complementary role of helical CT and CT angiography in assessment of cardiovascular anomalies in infants and children with congenital heart diseases.
Methods: 23 patients with congenital heart diseases(12 males,11 females) with mean age of 5 years(range:1 month -15 years)were included.All patients were examined with contrast enhanced helical CT(dose and rate of IV contrast material administration varied according to patient's age and weight).Three dimensional reconstructions with multiplanar reformation and shaded surface display were done for 20 patients.Results were correlated with results of echocardiography(n=23),angiography(n=15),and surgery(n=13).Patients were grouped into 5 groups based on indication for imaging
Results: Coarctation of aorta(n=15;13native and 2recurrent after surgery)CT angiography delineated the anatomic substrate of coarctation as discrete short narrow segment in 11 patients,long segmenttubular hypoplasia in 2 patients,presence of patent arterial duct in 4 patients and presence of collaterals in anterior and posterior chest walls in 7 patients.Also,CT angiography demonstrated extent and location of recurrent coarctation after surgery.Tetralogy of Fallot (n=2)CT angiography identified origin stenosis of left pulmonary artery and right aortic arch with mirror image branching in one patient, and cervical aortic arch in another patient.Aortic pulmonary window (n=1) was suspected by echocardiography and confirmed by CT angiography between ascending aorta and main pulmonary artery.Vascular rings(n=2)were suspected in 2 patients:CT angiography delineated presence of true ring in one patient with pulmonary artery sling, and excluded presence of another one in one patient with right aortic arch and large patent arterial duct.Anomalous pulmonary venous connections(n=3):CT angiography identified the drainage of all pulmonary veins to brachiocephalic vein via ascending vertical vein in 1 patient,right lower pulmonary vein to inferior vena cava at diaphragm inanother patient,and connection of right superior pulmonary vein to superior vena cava in third one.
Conclusion: Helical CT and CT angiography provided enhanced diagnostic accuracy in evaluation of coarctation of aorta,Tetralogy of Fallot associated with central pulmonary arteries and aortic arch anomalies, aortic pulmonary window,vascular rings,and total or partial anomalous pulmonary venous connections.Helical CT and CT angiography helps in thorough preoperative understanding of complex cardiovascular anatomy in infants and children with congenital heart diseases.

P592 Transcatheter closure of atrial septal defect with the amplatzer septal occluder

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Objective: To evaluate short-term the outcomes of transcatheter closure of secundum atrial septal defect (ASD) using the Amplatzer Septal Occluder (ASO).
Methods: Throughout Dec.2000 - Dec. 2002, 27 adult patients (20 F; 7 M; mean age 41.1 "b 13.3; range 18-62 years) were admitted for an attempt at ASD closure with the ASO device. All patients had an isolated secundum ASD with a large left-to-right shunt (ratio of pulmonary to systemic blood flow or Qp:Qs $>$1.5:1). Transthoracic colour Doppler echocardiographic study was performed on all patients before the procedure, 24 hours after, and after one month of follow-up. The echo-calculated diameter of the defect ranged 7 - 24 mm.
Results: The ASO device was successfully implanted in all patients (procedure lasting 25-65 minutes; median 43 minutes; fluoroscopy time 4-40 minutes; median 15 minutes); only 3 patients presenting a trivial residual shunt. The stretched diameter of ASD ranged 11 - 26 mm. The diameter of implanted devices ranged 13 - 28 mm. No predictors for a residual shunt were identified. At one month of follow-up transthoracic echocardiography showed that the device was correctly positioned in all cases. Residual trivial shunt at one month follow-up was confirmed in 3 patients. Septal motion abnormalities normalized in all patients. The right ventricular dimension evaluated by 2D echocardiography decreased in 20 patients (74.1%), mean 5.0 mm (range 1.5-8 mm), the right atrium dimension decreased in 21 patients (77.8%), mean 8.65 mm (range 2-20 mm) and the left atrium dimension decreased in 15 patients (55.6%), mean 6.36 mm (range 2-21 mm). Pulmonary artery systolic pressure decreased in 22 patients (81.5%), mean 5.8 mm (range 1-16 mm). No correlation was found between the ratio of left-to-right shunt before ASD closure and the decrease of right heart, nor indeed any decrease of pulmonary artery systolic pressure.
Conclusions: Transcatheter closure of secundum ASD using the ASO is a safe and effective procedure, characterised by excellent short-term follow-up results. The ASO device corrects the haemodynamic disturbances secondary to the right ventricular volume overload.

P593 Decline in ventricular function and clinical condition after mustard repair for transposition of the great arteries (a prospective follow-up study of 22–29 years)

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Purpose: Great concern exists about the abilities of the anatomic right ventricle to sustain the systemic circulation in patients with transposition of the great arteries who underwent a Mustard procedure. Therefore, the objective of this study was to examine long term survival, clinical outcome and right ventricular function 25 years (range 22-29) after surgery.
Methods: Ninety-one consecutive patients underwent a Mustard procedure between 1973 and 1980 in our hospital. A systematic follow-up study was performed in 1990 and again in 2001.
Results: The cumulative survival was without heart transplantation was 77% after 25 years. Event-free survival was only 36%. Re-operations (46%), pacemaker implantation (28%), and hospital admission for heart failure (9%) were frequent. At last follow-up (54 survivors) 24% of the patients were in NYHA class I, 53% in class II and 23% in class III. Sinus rhythm was present in 69% in 1990 and in 63% in 2001; sinus node disease was observed in 37% and 43% respectively. While all patients had good or only mildly impaired right ventricular function 14 years after repair, 61% of the patients showed moderate to severe dysfunction after 22-29 years. Furthermore, the QRS-complex widened from 94 ms to 110 ms and the exercise capacity decreased from 84% to 72% of normal. At last follow-up only 24% of the patients had a normal exercise capacity. Predictors for systemic ventricular dysfunction were: atrial flutter at the first outpatient visit after repair, and complex Mustard procedure.
Conclusion: The anatomic right ventricle appears unable to sustain the systemic circulation at long-term follow up and clinical condition of patients late after Mustard repair is declining. We may expect more deaths or need for heart transplantation in the next decade. Additional therapy (medication, new pacing modes, double switch procedure) should be considered.

P594 Factors influencing brain natriuretic peptide levels in adult patients after Mustard procedure

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In chronic right ventricular pressure overload BNP is regarded as a marker of heart failure. The influence of medication, underlying concomitant lesions and hypertension on BNP levels still needs to be elucidated.
Patients: In a cohort of 76 patients P(m=46; f=30; 23.3±3.3 years) echocardiographically assessed right ventricular function, AV-valve incompetence, presence of subpulmonary stenosis (SPS), VSD und D. Botalli (DB) occlusion, clinical parameters, medication (ACE-inhibitors, B-Blockers, diuretics, digitalis) and arrhythmias were correlated with BNP levels.
Results: The mean BNP level was 278.5±146.3 pmol/l (normal:<250pmol/l). NYHA III (5P) had significantly higher BNP levels than NYHA II (61 P: $p<0.001$; 566±233 vs.263106 pmol/l). Echocardiographically severely reduced RV-function (11 P) had significantly higher BNP than slightly/moderately reduced RV-function ($p<0.001$; 406±239 vs. 249±98pmol/l). 12 P with VSD and/or DB(9 P) closure had significantly worse RV-function($p<0.03$) and higher BNP($p<0.02$). Without decrease in RV-function 17 P with an operated SPS($p<0.007$) and 9 P with B-Blockers ($p<0.001$) had increased BNP-levels. Arterial hypertension, diuretics, digitalis, the degree of AV-valve incompetence, intermittent supraventricular arrhythmias and pacemaker dependency did not affect BNP levels.
Conclusion: In the chronic pressure overloaded systemic right ventricle BNP is a good marker of RV-dysfunction. In contrast elevated BNP levels are of limited value as a marker of RV-dysfunction in the presence of concomitant SPS and B-Blocker medication.

P595 Transcatheter closure of interatrial communications – one centre experience

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Introduction: Percutaneous closure of the interatrial comuniction became more and more frequent method of treatment.
Patients and methods: Since October 97 till December 2002 - 220 patients(pts), aged 0,4–69 (mean 19,5) years, were catheterized with intent of closure of ASD or foramen ovale apertum (FoA). In all pts simultaneous transoesophageal echocardiography was performed. There were 215 pts with ASD (25 with multiple ASD) and 5 with FoA. Three different kinds of devices were applied: Amplatzer Atrial Septal Occluder (ASO), CardioSEAL (CS) and Starflex (SF).
Results: Implantation of the devices was performed in 192 pts (87,2%). The procedure was abandoned in 28 patients, generally because of too large ASD. There were 183 ASO implanted in 181 pts with ASD (in 2 pts with double ASD 2 ASO were implanted), and CS/SF in 11 pts (in 5 pts with FoA and 6 with ASD). The procedure was effective in 175/181 (96,6%) ASO pts and in 10/11 (90,1%) CS/SF pts. In 7 patients the procedure was unsuccessful with the necessity of withdrawal of the device (6 ASO and 1 SF). The occlusion rate with ASO was 88% after 24 hours, 91% after 1 months, 95% after 1 year, 97% after 2 and 100% after 4 and 5 years. All defects treated with SF/CS were closed successfully after 24 hours. In 2 cases supraventricular tachycardia and in another 2 pts transient left ventricle failure appeared during the first month after implantation of ASO. No late complications were observed.
Conclusion: Transcatheter closure of selected type of ASD using ASO, Cardioseal or Starflex should be offered to patients as a non-surgical alternative. The type of device depends on the size and morphology of the defects as well as the experience of operator. The presence of multiple defects does not exclude successful transcatheter closure.

P596 Is coronariography mandatory as pre-operative evaluation for valvular heart disease?

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Introduction: Coronariography has been usually indicated for valvular heart disease (VHD) patients (pt) over 35 years as a pre-operative evaluation (American Heart Association/American College of Cardiology Guidelines, Circulation 1998:98:1949-84). However, the real prevalence of obstructive coronary disease (CAD) in this population has been poorly studied. The aim of this study was to evaluate the prevalence of and risk factors for CAD in candidates for VHD surgery.
Methods: . We performed coronariography in 3736 VHD candidates for valvular heart surgery in the last 10 years (1992 to 2001) at our Institution, and evaluated the prevalence of obstructive coronary heart disease (CAD) (defined as coronary artery narrowing over 70%) and VHD. Besides, we evaluated the risk factors for CAD in this population.
Results: CAD was associated to VHD in 116 pt (prevalence: 3.42%). In 37 pt there were previous diagnosis of CAD, but in 79 (68.1%) the diagnosis of CAD had only been made by routine pre-operative coronariography. We studied these 79 (2.11% of total) newly CAD diagnosed patients, 55 of these (69.62%) were male, mean age: 64.74±9.23 years. There were 50 (63.3%) isolated aortic valve disease or combined aortic and mitral valve disease and 29 isolated mitral valve disease. Tabagism was seen in 54 pt (68.3%), Hypertension in 34 pt (43.0%), familial history in 24 (30.3%), Hypercholesterolemia in 22 (27.8%), Diabetes mellitus in 15 (18.9%), and obesity in 8 (10.1%). Age over 50 years was observed in 95.7% of the entire study patients (116). Only 5 pt (4.3% of CAD pt or 0.13% of VHD pt) were younger than 50 years and all they had at least one risk factor for coronary artery disease (1 isolated mitral valve disease, 2 isolated aortic valve disease, and 2 combined mitral and aortic valve disease).
Conclusions: Prevalence (3.42%) of CAD in VHD patients was similiar to our general population; 2. Aortic valve disease was the most frequently associated with CAD; 3. Tabagism and Hypertension were the most frequently risk factors of CAD associated with VHD; 4. The majority of CAD pt was over 50 years. Therefore, coronariography as a routine pre-operative exam for candidates to valvular heart disease surgery should be performed particularly in patients over 50 years, with aortic valve disease, and at least one risk factor for coronary artery disease.

P597 Valve replacement for critical aortic stenosis with severe left-ventricular dysfunction: perioperative risk and predictors of outcome

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Background: Natural history of patients [Pts] with symptomatic aortic stenosis [AS] is poor, and accounts for large surgical indications. However, in case of severe left ventricular systolic dysfunction (LVSD), questions remain about the higher perioperative mortality rate and the long-term outcome including LVSD reversibility.The aim of this cohort study was to identify predictive factors of peri- and postoperative mortality and of long-term improvement in LV systolic function.
Methods and Results: between 1990 and 2000, 155 consecutive Pts (72±9 yrs) underwent aortic valve replacement [AVR] for critical (mean gradient: 43±13 mmHg), and symptomatic AS (NYHA class III-IV: n=138, and severe LVSD (LVEF<30%).
The perioperative (30-day) mortality was 12%. Advanced NYHA class (p=0,004), higher cardiothoracic ratio [CTR] ($p<0$, 0001) or pulmonary artery pressure level (p=0,03) and complete left bundle branch block (p=0,03) or renal failure (p=0,001) were predictors of operative mortality in univariate analysis. Using a multivariate analysis, the only predictive factor of perioperative mortality was CTR >0,6 (p=0,002).
Difference (Delta EF) between post- (Day 7) and preoperative EF was >+10% in 55/136 (40%) survivors. Multivariate analysis showed that preoperative CTR (p=0,006) and mean gradient (p=0,045), were independent predictive factors of Delta EF>+10%.
During a mean follow-up [FU] time of 4,6±3 yrs, 50 (36%) Pts died, from non-cardiac cause in 70%. The 3 independent predictors of postoperative mortality were in multivariate analysis: diabetes (p=0,003), age >75 yrs (p=0,004) and Delta EF>+10% (p=0,01). The postoperative clinical benefit was significantly greater in Pts with Delta EF>+10%.
Conclusion: Despite a relatively high but acceptable perioperative mortality risk, the benefit of AVR in Pts with critical AS and severe LVSD, is clearly important. Improvement in both quality of life and LV systolic function is greater when LVEF increases significantly in the early post-operative period.

P598 Transcatheter closure of patent ductus arteriosus – a 10-year single centre experience

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Background: During the last ten years new occluders became available for transcatheter closure of patent ductus arteriosus (PDA). Nowadays percutaneous techniques became a treatment of choice for selected patients. The design of the devices is not ideal and their use has been associated with several drawbacks, especially for large PDAs.
Methods and Results: From 1993 to 2003, 148 pts referred for PDA closure underwent cardiac catheterization and aortography. PDA was confirmed in 128 pts. Seven pts had residual shunt after surgery. In 116 pts transcatheter closure was performed using three types of occluders: Jackson's detachable coils (group1; n=41), Rashkind double umbrella (group 2; n=35) and Amplatzer Duct Occluder (group 3; n=38). Twelve pts with large PDA's, referred between 1993 and 1998 were sent for surgical ligation due to percutaneous method limitations. Mean age of patients was 29.6 years (range 1.8-74; 91 pts $>$ 16 years); mean minimal PDA diameter was 4.54 mm (range 0.9-10.2) 80 pts had PDA larger than 3.0 mm. Duct and/or aortic wall calcifications were seen in 12% of adult patients. Complete angiographic closure of the PDA at catheterization was: 90%, 44% and 95% in group 1, 2 and 3 respectively. 24 hours after the procedure transthoracic echocardiography demonstrated complete occlusion of the PDA in 93%, 57% and 100%. The residual shunt was estimated as significant in 29% of pts (all from group 2), all these pts had a PDA diameter$>$4mm. In 3 pt from group 2 (duct diameters 3.6; 4 and 3.4mm) a coil was implanted but withdrawn prior to release due to a residual shunt. Procedure related complications included device embolization in 1 patient (in group 2), and haemolysis treated by a second device implantation in 1 patient. 96 of 116 pts (82.8%) were observed at 1 to 97 months (mean 34), 6 patients had a second procedure because of residual shunting (2 in group 1, 4 in group 2).
Conclusions: With the use of now available devices percutaneous closure of the PDA is safe and effective procedure with nearly 100% occlusion rate. Follow up data suggest that the successful procedure means complete closure at he end of the procedure. Spontaneous closures during observation are rare. The Amplatzer occluder is the most effective device for patients with large ($\geq$3mm) PDA. For small PDA $<$3mm the single coil is very effective device with very high closure rate. Implantation of Rashkind umbrella results in high rate of residual shunts and no possibility of device withdrawal in case of significant residual shunt.

MYOCARDIAL CONTRACT-ECHO FROM BENCH TO BESIDE

P599 Real time myocardial perfusion in infarcted and sham operated wistar rats by contrast echocardiography

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Background: Myocardial contrast echocardiography (MCE) is in an experimental state for the assessment of myocardial perfusion in humans. For small animals there are further echo associated problems (high heart rate, extreme near field focus without power modulation, difficult contrast agent (CA) application). Therefore, MCE in small animals is not sufficiently evaluated.
Methods: 36 segments (SEG) of short axis view of male Wistar rats (3 with ligation of left anterior descending (LAD), 3 Sham operated) were investigated by MCE in a real time power Doppler mode (Philipps Sonos 5500, 7.5MHz transducer). Examinations were performed under anesthesia (20-30mg/kgBW ketamine + 0.3mg/kgBW xylazine) in a left lateral decubitus position. For MCE the CA (SonoVue, 0.3ml) was injected as bolus in sublingual vein. Loops of enhancement by CA in the left ventricle (LV) were acquired digitally. In blinded off-line analysis every SEG was analyzed by visual assessment of wall motion as well as by signal intensity (SI). SEG were divided in groups of normal and abnormal wall motion.
Results: All rats with LAD ligation had akinesia in the anterior SEG. In addition, hypokinesia in one lateral and one anteroseptal SEG became apparent. Sham operated rats had normal wall motion. All SEG with normal wall motion (n=31) had a clear increase of SI (23.96 $\pm$ 5.00 dB). In SEG with akinesia (n=3) no increase of SI (4.43 $\pm$ 0.98 dB), and in hypokinetic SEG a lower increase of SI was observed (19.88 $\pm$ 8.20 dB). SI between akinetic and normal SEG was significantly different ($p < 0.001$) and also between akinetic and hypokinetic SEG ($p < 0.05$). Heart rate between infarcted and Sham operated rats was not different (350 $\pm$ 35 vs. 390 $\pm$ 30 bpm, n.s.).
Conclusion: Myocardial contrast echocardiography with power Doppler mode makes assessment of myocardial perfusion and perfusion defects in experimental series with small animals like Wistar rats valuable.

P600 Absolute quantification of myocardial perfusion using real-time myocardial contrast echocardiography: an in vitro study and first in vivo results

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Background: Theoretically, myocardial perfusion (ml/min/g) can be quantified using myocardial contrast echocardiography (MCE) by determining ultrasound contrast agent (UCA) kinetics, i.e. refill curves of UCA after its destruction by ultrasound. Video signal intensity generated by the UCA refill follows an exponential curve and statistical correlation between fitting parameters and perfusion has been demonstrated. However, due to the proposed kinetic model, it was not possible to derive absolute perfusion.
Objectives of this study are (1) to derive a model of UCA kinetics allowing the measurement of perfusion and to prove its validity by an in vitro experiment and (2) to demonstrate its applicability in vivo.
Methods: (1) Based on Fick's Law of Mass Transfer, a new kinetic model has been developed yielding perfusion by interpretation of the fitting parameters. A flow phantom comprising a haemodialysis filter was perfused with saline by a peristaltic pump. Two filters with different blood volume fractions were examined with flow velocities ranging within physiological limits. (2) Regional myocardial perfusion (sixteen-segment model) of, so far, one healthy volunteer was assessed by MCE and positron emission tomography (PET, 13N-Ammonium). For in vitro and in vivo studies, UCA refill sequences were recorded during continuous UCA infusion (OPTISON) using real-time MCE. Perfusion data were calculated with the new kinetic model.
Results: (1) MCE perfusion data were converted into volume flow rates (Qmce) for the comparison with pump flow rates (Qpump). For both filters, the relation between Qmce and Qpump demonstrated good linear correlation and comparable precision (filter one: Qmce=0.82*Qpump+6.7ml/min, r^2=0.92, standard error of the estimate (SEE)=15.5ml/min; filter two: Qmce=1.02*Qpump+0.6ml/min, r^2=0.96, SEE=12.6ml/min). Flow rates of filter one were somewhat underestimated (slope 0.82, intercept 6.7ml/min), while the measurements of filter two were very accurate (slope 1.02, intercept 0.6ml/min). (2) Regional perfusion could be quantified in 11 of 16 segments by MCE, mean perfusion measured by MCE and PET was 0.645ml/min/g and 0.622ml/min/g, respectively.
Conclusion: Our model is a valid description of UCA kinetics in haemodialysis filters and, likely, in the human myocardium and yields regional perfusion using real-time MCE. The model generally characterizes the microcirculation the fact of which may also apply to organs other than the heart.

P601 Quantitative validation of intermediate power triggered replenishment imaging as a method to assess myocardial blood flow

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Background: Intermediate mechanical index triggered replenishment myocardial contrast echocardiography (MCE) is a new technique being developed for the assessment of myocardial perfusion. We hypothesised that this technique could be used to accurately assess myocardial blood flow (MBF).
Methods: Twenty six patients underwent MCE using an intravenous infusion of Sonazoid® at rest and following dipyridamole stress. A mechanical index of 0.5 was used for imaging and 1.0 for pulsed bubble destruction. MBF was assessed offline using Qlab™ an automated quantification software package. A region of interest was placed over the apex in the apical 4 chamber view and following microbubble destruction a reperfusion curve was plotted. Values for A (peak video intensity) and β (rate of replenishment) were recorded. MBF was calculated as a product of Aβ at rest and following vasodilator stress. Coronary flow reserve (CFR) was calculated as a ratio of resting/vasodilator stress MBF. All patients underwent coronary angiography within 4 weeks of their MCE.
Results: The mean resting MBF was similar in the 6 patients with normal coronary arteries (10.2, SE=1.9), the 5 patients with moderate (50-75%) LAD stenosis (8.7, SE=2.9) and the 10 patients with severe ($>$75%) LAD stenosis (9.9, SE=1.3). However, the mean resting MBF in patients with documented myocardial infarction (MI) was low (3.3, SE=0.46). Following vasodilatation MBF increased (27, SE=7.1; CFR=2.7) in patients with normal coronary arteries, remained unchanged (8.2, SE=2; CFR=0.94) in patients with moderate LAD stenosis and dropped (4.5, SE=1.5; CRF=0.45) in patients with severe LAD stenosis. In patients with a history of MI there was a small increase in MBF(5.7, SE=2; CFR=1.7). This persistence of CFR may imply myocardial viability.
Conclusion: Intermediate mechanical index MCE is a useful technique for assessing MBF and CFR in humans. This technique can be utilised to quantitate severity of coronary artery stenosis and assess myocardial viability.

P602 Triggered replenishment imaging improves reproducibility of myocardial contrast echocardiography at low emission power: an intra- and interobserver study

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Purpose - We studied variability, reproducibility and validity of quantitative myocardial contrast echocardiography (MCE) in a rest - vasodilatator protocol (adenosine) at two experienced centers using real-time perfusion imaging (RTPI) and triggered replenishment imaging (TRI) at low emission power. Replenishment kinetics following ultrasound induced destruction of contrast microbubbles were assessed applying the mathematical model $f(t)=A*(1-e^{\beta t})$, with parameter β describing mean flow velocity and parameter A representing blood volume.
Methods - 36 patients were prospectively enrolled. Replenishment kinetics were assessed at rest and at peak stress. MCE was repeated at least three times at rest and during stress in all patients. In a subgroup of 6 healthy subjects reproducibility and intraindividual variability of replenishment parameters in different myocardial segments was assessed on three consecutive days. Intra- (IOV) and interobserver (INV) variability (CV) was assessed by repetitive analysis of the same data-sets in both centers. All measurements were obtained in a blinded fashion. To assess validity of MCE to detect coronary artery disease (CAD), myocardial perfusion reserve (MPR) was calculated in both centers and compared with quantitative coronary angiography and Doppler derived flow reserve measurements.
Results - Parameter A was found to be a very robust parameter in all settings (CV $<$ 7.2%$\pm$5.1 for IOV). For β highest IOV was found for RTPI if only one frame per heart-cycle was considered (CV: 32.2%$\pm$18.9). New averaging algorithms (2 frames/cycle) improved CV to 14.6%$\pm$12.6. Variability was lowest for TRI in apical segments (CV: 6.5%$\pm$5.2, $p<0.01$). As expected intraindividual variability of β on consecutive days was higher (RTPI: 29.1%$\pm$14.1, TRI: 36.7%$\pm$14.3). However, MPR in flow-limiting CAD was significantly different as compared to normal subjects ($p<0.01$) and no significant differences were found between both centers (regression MPR/CFR: BN: 1.31x+0.29, r=0.62, $p<0.0001$; SD: 1.61x+0.54, p=0.007). Bland-Altman plots revealed homogeneous distribution around zero.
Conclusions - 1. A is a robust and highly reproducible parameter. 2. TRI improves reproducibility of MCE studies. 3. Although intraindividual variability is relatively high, MCE allows assessment of CAD by calculation of MPR. In summary, quantitative MCE allows user independent assessment of severity of CAD.

P603 Advanced 1.5-harmonic imaging can make possible a visual subtraction image of myocardial perfusion

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Harmonic imaging (HI) using the 1.5 (one and half) harmonics is a new contrast echo technology that images sensitively the signals from the microbubbles. Recently an advanced 1.5-harmonic (TOSHIBA, Japan) based on the rate subtraction image was developed by designating cancellation of all the signals from the background tissue reflection. Thus, this rate subtraction 1.5 HI may achieve a clear visual subtraction image of myocardial perfusion. In order to assess the validity of advanced 1.5-harmonic in intravenous myocardial contrast echocardiography (IV-MCE), 2nd HI and conventional 1.5-harmonic IV-MCE was followed by the rate subtraction HI IV-MCE in 12 patients. Equipment used was APLIO SSA-770A (TOSHIBA, Japan). IV-MCE study of the four-chamber view was performed as follows: intravenous continuous injection of Levovist (125mg/ml, 5ml/min) utilizing 2nd HI (1.4MHz/2.8MHz), 1.5 HI (1.7MHz/2.5MHz) and end-systolic intermittent imaging (1:4). Myocardial staining was scored as strong=3 to none=0 in the septum. Results: 1. Baseline myocardial staining score of 2nd HI, conventional 1.5 HI and advanced 1.5 HI were 1.5$\pm$0.6, 0.6$\pm$0.2 and 0.1$\pm$0.2* (mean$\pm$SD, *$p<0.05$ to others). 2. Peak myocardial staining score was 1.8$\pm$0.6, 2.4$\pm$0.5* and 2.8$\pm$0.5* in the same order (mean$\pm$SD, *$p<0.05$ to 2nd HI). Myocardial staining score was lower in the baseline image and higher in the peak image in advanced 1.5 HI than in 2nd HI and in conventional 1.5 HI. Conclusions: Superiority of advanced 1.5 HI was recognized for a visual subtraction image of myocardial perfusion.

P604 Correlation between real-time myocardial contrast echo parameters of regional perfusion and severity of coronary stenosis by quantitative angiography

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Background: Experimental studies have shown that myocardial contrast echo (MCE) parameters of regional myocardial perfusion are well correlated with the severity of coronary lesions but clinical data in coronary pts are still scarce.
Purpose: To assess whether in pts with coronary artery disease (CAD) the parameters of regional myocardial perfusion derived from real-time MCE are correlated with severity of coronary lesions by quantitative coronary angiography (QCA) and to determine the sensitivity and specificity of MCE parameters in detecting critical CAD.
Methods: 31 pts, 16 males, aged 60$\pm$7 years, 18 with $\geq$ 50% stenosis of left anterior descending artery (LAD), and 13 with normal or $\leq$50% stenosis of LAD underwent real-time MCE with Sonovue® using Power Doppler Armonic Imaging (Vivid 7 GE)at baseline and during Dipyridamole stress (0.84 mg/kg). MCE time-intensity data in 2 regions of interest (proximal (SP) and distal septum (SD))were fitted to the exponential function y= A(1- e-bt)+ c, where A is the peak plateau signal intensity,reflecting myocardial blood volume, b the rate of signal increase, reflecting microbubble velocity and the product A x b is proportional to myocardial blood flow.Baseline and peak stress MCE parameters were correlated with minimal luminal diameter (MLD) and % diameter stenosis (%DS) by QCA.
Results: The product A x b in SD at peak stress was significantly correlated with both MLD (r=.61, p=.0015)and %DS of LAD (r=.66, $p<.0001$); b in SD at peak stress was significantly correlated with %DS of LAD ($r<.61$, p=.0003). No significant correlations were found between baseline MCE variables and QCA parameters. By ROC analysis a value of A x b at peak stress $<$ 2.48 showed a 92%sensitivity (Confidence Interval (CI) 64-99) and a 76% specificity (CI 50-93) for identifying a $>$ 50% stenosis of LAD, and a 82% sensitivity (CI 57-96) and a 85% specificity for a $>$ 70% LAD stenosis.
Conclusions: In pts with LAD stenosis real-time MCE parameters of regional myocardial perfusion during hyperemia induced by dipyridamole are significantly correlated with QCA parameters of coronary stenosis and show a good sensitivity and specificity in identifying a critical LAD stenosis.

P605 Contrast dobutamine echocardiography in the evaluation of coronary artery disease: a comparison with transoesophageal dobutamine echocardiography

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Introduction: Dobutamine echocardiography (DASE) has been shown to be a very useful non-invasive technique for the detection of myocardial ischemia. However, inadequate transthoracic images preclude the use of DASE in a significant group of patients. Transoesophageal approach (TOE) can overcome this limitation and improves endocardial border delineation. Transthoracic contrast echo (CE) has also been shown to improve left ventricular opacification at rest and during stress echo.
The aim of our study was to compare prospectively the feasibility, safety, sensitivity and specificity of dobutamine CE and TOE for the detection of coronary artery disease (CAD).
Methods: Thirty-two poorly echogenic patients scheduled for cardiac catheterisation underwent prospectively both CE and TOE dobutamine tests. All underwent coronary angiography within the 48 h. A lesion $>$ 50% by quantitative analysis was considered significant.
Results: One patient did not tolerate intubation with TOE probe but had developed wall motion abnormalities before the test was stopped. Mean duration of dobutamine TOE and CE was respectively 21.3 $\pm$ 1.0 min and 15.5 $\pm$ 0.8 min ($p<0.05$). There were no major complications with both techniques. Eighteen of 21 patients with significant CAD using TOE and 19 using CE had a positive DASE (sensitivity: 86% vs 90%, NS). One of 11 patients without significant CAD had false positive findings using TOE, 0 using CE (specificity 91% vs 100%,NS).
Conclusions: In poorly echogenic patients, dobutamine CE is a safe, feasible and accurate technique for the detection of myocardial ischemia and compared well with dobutamine TOE.
Because dobutamine CE is less invasive, of shorter duration and more comfortable than TOE, it should be used in patients with suboptimal transthoracic echocardiograms for the evaluation of CAD during dobutamine stress testing.

P606 Quantitative evaluation of regional myocardial perfusion during dipyridamole stress by real-time myocardial contrast echocardiography in patients with and without coronary artery disease

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Background: Experimental studies showed that myocardial contrast echo (MCE) parameters of mycardial perfusion are correlated with the severity of coronary lesions but clinical data are still scarce.
Purpose: To assess whether real-time MCE shows significant differences in regional myocardial perfusion parameters between pts with and without coronary artery disease (CAD)and to define the sensitivity and specificity of MCE parameters in identifying critical coronary stenosis.
Methods: 31 pts, 16 males, aged 60±7 years, 18 with ≥50% stenosis of left anterior descending artery (LAD), and 13 with normal or ≤50% stenosis of LAD underwent real-time MCE with Sonovue® using Power Doppler Harmonic Imaging (Vivid 7 GE)at baseline and during Dipyridamole stress (0.84 mg/kg). MCE time intensity data in 2 regions of interest (Proximal (PSE) and distal septum (DSE)) were fitted to the exponential function y= A (1-e-bt)+c, where A is the peak plateau signal intensity, b the rate of signal increase and the product A x b is proportional to myocardial blood flow. Baseline and peak stress MCE parameters were correlated with quantitative coronary angiography (QCA)minimal luminal diameter (MLD) and % diameter stenosis (DS)of LAD.
Results: see table. The product A x b in DSE at peak stress was related with MLD (r=.61, p=.0015) and %DS of LAD (r=.66, p=.0001); b in DSE at peak was related with %DS of LAD (r=.61, p=.0003). By ROC analysis a value of A x b at peak < 2.48 showed a 92% sensitivity (Confidence Interval (CI) 64-99)and a 76% specificity (CI 50-93) for a >50% LAD stenosis and a 82% sensitivity (CI 57-96) and 85% specificity (CI 54-98) for a >70% LAD stenosis.

Table of results

	Normal	CAD	p value
Basal A x b distal sept	2.16 ± 1.09	1.42 ± 0.71	.0303
Peak A x b prox sept	5.56 ± 2.12	3.03 ± 2.15	.0037
Peak b distal sept	0.68 ± 0.27	0.33 ± 0.28	.0018
Peak A x b distal sept	4.71 ± 2.1	1.92 ± 1.63	.0003

sept= septum; prox= proximal

Conclusions: Quantitative MCE shows significant differences in regional myocardial perfusion parameters between pts with and without critical LAD stenosis. MCE parameters during hyperemia are significantly correlated with QCA parameters and show a good sensitivity and specificity for detecting critical LAD stenosis.

P607 Detection of coronary artery disease in heart failure: role of myocardial contrast echocardiography in patients with first presentation of heart failure without acute myocardial infarction

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Introduction: Identification of significant coronary artery disease (CAD) as the underlying aetiology in patients presenting for the first time with acute heart failure (AHF) and no clinical evidence of acute myocardial infarction (AMI) has important therapeutic and prognostic implications. Both myocardial contrast echocardiography (MCE) and 99mTc-Sestamibi Gated SPECT have the potential to accurately detect CAD.
Methods: Fifty-two consecutive patients (67% males, 33% females; mean age 63±12 years) with first presentation of AHF and no clinical evidence of AMI were assessed with 99mTc-Sestamibi Gated SPECT and low power continuous MCE using intravenous infusion of Sonovue®. Rest studies were followed by dipyridamole stress after the patients were medically stabilised (mean 9±2 days). All patients underwent coronary angiography.
Results: Of the 52 patients, 22 (42%) had significant CAD (>50% diameter stenosis of any major coronary arteries). MCE correctly detected CAD in 18 (82%) patients and SPECT in 17 (77%). Of the 30 patients without significant CAD, MCE showed normal perfusion in 29 (97%) and SPECT in 24 (80%). The overall accuracy of MCE to detect CAD (90%) was higher than SPECT (79%) [p = 0.03]. MCE detected all the six patients who satisfied the criteria for ischaemic cardiomyopathy (i.e. ≥ 75% proximal LAD and/or ≥ 75% proximal RCA and ≥ 75% proximal LCX) and SPECT detected five.
Conclusion: Myocardial contrast echocardiography is accurate for the detection of CAD in patients presenting with acute heart failure without signs of AMI. The better spatial and temporal resolution of MCE could explain the superiority over 99mTc-sestamibi gated SPECT for the detection of CAD in this patient cohort.

P608 Feasibility of the real time myocardial contrast echocardiography during bicycle stress

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Myocardial contrast echocardiography (MCE) after intravenous injection of the ultrasound contrast agent has the potential to evaluate myocardial perfusion and wall motion simultaneously at real time.
Purpose: The aim of this study was to assess the feasibility of MCE during supine bicycle stress echocardiography.
Methods: The study group consisted of 60 consecutive patients (pts) scheduled for coronary angiography. All pts underwent supine bicycle stress echocardiography. MCE was performed at peak stress and 10 min afterwards, during continuous infusion of Sonovue®, administered with a prototype infusion pump (BR-INF 100, Bracco Research). Segmental myocardial opacification (OPAC), replenishment (RP) and wall thickening (WTh) were evaluated for all 3 apical views at peak stress and rest. A 18-segment model of the left ventricle was used for analysis. The segment was considered as diagnostic, if it was evaluable both at rest and at peak stress.
Results: OPAC, RP and WTh were assesed in a total of 1080 segments (seg). WTh wasdiagnostic in 969 seg (89,7%), OPAC in 731 (67,7%) and RP - in 647 (59,9%). The evaluability for apical seg ranged from 100% to 93% for WTh, 85% to 74% for OPAC and 81% to 67% for RP. The respective values for the basal seg were: 93% to 63%, 70% to 30% and 63% to 19%. The mean segmental evaluability for each wall of the left ventricule has been shown below (table).

Wall	Wall thickening	Opacification	Replenishment
Inferior	97,7%	77,6%	70,4%
Septal	96,3%	80,2%	75,3%
Lateral	91,4%	69,1%	61,7%
Posterolateral	91,4%	67,9%	59,3%
Anteroseptal	85,2%	64,2%	55,5%
Anterior	76,5%	46,9%	37,0%

The mean percentage of stress and rest diagnostic segments in every wall of the left ventricule.

Conclusion: The assesement of myocardial perfusion and wall motion is feasible using real time MCE during supine bicycle stress echocardiography. Best results were found in all apical segments and in the inferior and septal wall.

P609 Myocardial microvascular damage contributes to left-ventricular dysfunction in patients with idiopathic dilated cardiomyopathy; usefulness of intravenous myocardial contrast echocardiography

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Background: Myocardial microvascular impairment involves in the progression of heart failure in idiopathic dilated cardiomyopathy (DCM). This study was designed to clarify whether myocardial microvascular abnormalities assessed by intravenous myocardial contrast echocardiography (MCE) were associated with left ventricular (LV) dysfunction in patients with DCM.
Method: Forty-eight patients with DCM and 10 age-matched normal subjects were enrolled in this study. All patients had been treated with a combination of diuretics, angiotensin II type 1 receptor blockers and beta-blockers. MCE was performed at apical 4- and 2- chamber view with a S3 transducer (SONOS 5500, PHILIPS). Intravenous contrast agent (Levovist) was constantly infused with intermittent, incremental and end-systolic triggering method. Background-subtracted myocardial intensity at the plateau (MCI) was measured and MCI was adjusted by intensity at adjacent left ventricle. The extent score (ES) using thallium-201 SPECT was calculated as the value of perfusion defect. LV ejection fraction (EF) was calculated using left ventriculography. Plasma levels of norepinephrine (NE) and brain natriuretic peptide (BNP) were also measured.
Results: Univariate analysis showed that plasma NE and BNP levels, ES and averaged MCI were significantly correlated with EF (NE: r= 0.499, p= 0.0009; BNP: r= 0.583, p< 0.0001; ES: r= 0.499, p= 0.0017; averaged MCI: r= 0.772, p< 0.0001). According to stepwise regression analysis, averaged MCI was the most powerful contributory factor to EF (r= 0.619, p< 0.0001).
Conclusion: Myocardial microvascular abnormalities using MCE may be closely related to LV dysfunction in patients with DCM.

DOPPLER MYOCARDIAL IMAGING, MISCELLANEOUS

P610 Impact of stroke volume on mitral annular velocities derived from tissue Doppler imaging

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Background: Mitral annular velocities assessed by tissue Doppler imaging (TDI) have been shown to complement traditional Doppler variables in evaluating left ventricular (LV) systolic and diastolic performance. The mitral E/E'-ratio has been suggested as an estimate of LV filling pressures in selected subsets of patients. However, the impact of LV stroke volume (SV) on mitral annular velocities has not been clearly defined.
Methods & Results: 18 patients (pts.) with increased SV (defined as SV index (SVI) $>$ 45 ml/m^2) due to either $>$ 2 + primary mitral regurgitation (n=11) or $>$ 2 + aortic regurgitation (n=7, age 53$\pm$15 years, ISV group), 41 pts. with reduced SV (SVI $<$ 25 ml/m^2) due to ischemic cardiomyopathy (n=27), dilated cardiomyopathy (n=14) (age 60$\pm$13 y., RSV group) and 29 asymptomatic controls with normal SV (age 55$\pm$11 y., CON group) underwent echocardiographic measurements of SVI, ejection fraction (EF) and mitral inflow velocities (E, A, E/A-ratio). Peak systolic and diastolic mitral annular velocities (S', E', A') derived from pulsed TDI were obtained at four sites of the mitral annulus and averaged.

Group	SVI (ml/m^2)	EF (%)	E/A ratio	S' (cm/s)	E' (cm/s)	A' (cm/s)	E/E'
CON (n=29)	36$\pm$9	67$\pm$8	1.20$\pm$0.35	8.8$\pm$1.3	11.6$\pm$2.5	11.3$\pm$2.0	6.5$\pm$1.5
ISV (n=18)	62$\pm$18 [1]	70$\pm$10	1.50$\pm$0.56	12.0$\pm$2.2 [1]	14.1$\pm$2.7 [1]	11.8$\pm$3.1	7.3$\pm$4.3
RSV (n=41)	19$\pm$5 [12]	36$\pm$15 [12]	1.44$\pm$1.16	5.7$\pm$1.2 [12]	6.7$\pm$1.5 [12]	8.6$\pm$2.6 [12]	15.5$\pm$4.5 [12]

[1] p$<$0.05 vs. CON group, [2] p$<$0.01 RSV vs. ISV group

Using linear regression analysis, SVI was significantly related to S' (r=0.72, S'= 4.58+ (0.11SVI), p$<$0.001), to E' (r=0.75, E'= 5.11+ (0.14SVI), p$<$0.001) and to A' (r=0.40, A'= 8.26+ (0.06SVI), p$<$0.01).
Conclusion: SV strongly impacts on systolic and diastolic mitral annular velocities. This must be considered, if TDI is used for the evaluation of patients with impaired systolic or diastolic performance, but preserved or even increased SV.

P611 Application of automatic analysis algorithms on tissue Doppler data acquired during dobutamine stress echocardiography

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The subjective, experience-dependent interpretation process is the main limitation of dobutamine stress echocardiography (DSE). Tissue Doppler imaging (TDI) has been used for quantitative analysis of DSE. It requires extensive time consuming analysis. Tissue tracking (TT) and a new analysis algorithm (Q-stress) which allows instantaneous automatic analysis of TDI information by comparison of obtained peak systolic tissue velocities with expected "normal" peak systolic tissue velocities and subsequent color coding of areas reaching normal values have been suggested for facilitated analysis.
Methods: In 55 consecutive patients with normal left ventricular function at rest DSE using only three apical views was performed with color TDI data being acquired in the background. DSE test results were determined by visual analysis of an expert reader and compared to results obtained from three quantitative analysis modalities based on TDI: (1) measurement of peak systolic tissue velocities (PSTV) from TDI tracings, (2) maximal tissue displacement in the basal segments using TT and (3) the new Q-stress analysis algorithm. For the first two modalities previously reported cut-off values were used to determine normality of a study.
Results: 28 DSE were defined to be pathologic and 27 as normal by visual assessment. Non-automatic analysis of PSTV had a sensitivity of 86% and a specificity of 56% to identify a pathologic DSE as defined visually. Sensitivity and specificity for TT were 82% and 56% respectively. For Q-stress sensitivity and specificity were 79% and 44%, respectively. False positive findings were located in the anterior or lateral segments in 75% of cases for TT and in 80% for Q-stress. Impaired Doppler signal quality was found in 53% of these cases.
Conclusion: Recently suggested TDI based modalities allow the detection of pathologic DSE with high sensitivity. TT and Q-stress reach accuracy recently reported for PSTV and are more likely to be used in clinical practice as they allow instantaneous visual semiquantitative assessment. A low specificity due to false positive results affecting mostly anterior and lateral segments in cases of impaired Doppler signal quality has to be recognized.

P612 Changes in mean velocity gradients in patients with left bundle branch block: a Doppler myocardial imaging analysis

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Aim of the present study was to evaluate whether quantification of left ventricular (LV) myocardial function by Doppler Myocardial Imaging (DMI) enhances the assessment of an ischemic cardiac involvement in patients with left bundle branch block (LBBB). 6 with significant coronary stenosis (group A) and 6 patients with normal coronary vessels (group B) by coronary angiografy, all comparable for age (Gruppo A 66$\pm$8,Gruppo B 57$\pm$8) and sex, underwent standard Doppler echo and DMI. By use of M-mode DMI, in 2 different basal myocardial segments (LV septal and posterior walls) both endocardial and epicardial mean velocity gradients were calculated during ventricular ejection (systolic endocardial or epicardial MVG) and during early diastolic filling (diastolic endocardial or epicardial MVG). **Results:** patients of group A showed increased diastolic posterior wall (PW) (p $<$0,05) and increased systolic septal wall (IVS) diameters (p $<$ 0.05). Conversely, heart rate, QRS duration, blood pressure, LV end-diastolic diameter (LVDD),ejection fraction (EF), mass index and end-systolic circumferential stress were comparable in the 2 groups. At the leve1 of PW patients of group A showed reduced both endocardial and epicardial diasto1ic MVG (p 0,05) while they showed impaired both endocardial and epicardial systolic MVG of IVS (p $<$0,05). In patients of group B, significant correlations were found among systolic both endocardial and epicardial MVG and LVEF (r 0,716, p $<$ 0,05), LV index mass (r -0,778, p $<$ 0,05) and PW thickness (r -0,916, p $<$ 0,05) at the level of PW. The same DMI parameters during diastolic filling were strongly associated with septal thickness (r -0,75, p 0,05) and LVDD (r 0,709 , p $<$ 0,05) at the level of IVS. Conversely, in patients of group A with significant coronary stenosis, a close negative association was assessed among both endocardial and epicardial systolic MVG and blood pressure (r -0,961, p $<$ 0,05) and end-systolic circumferential stress at the level of IVS (r -0,945, p $<$ 0,05), and a close negative association among both endocardial and epicardial systolic MVG and LVDD at the level of PW (r -0,84, p $<$ 0,05).In conclusion, DMI is an effective non invasive technique for assessing the severity of regional ischemic involvment of LV septal and posterior.wall in patients with LBBB. Patients with significant coronary stenosis showed impaired diastolic function at the level of PW and reduced systolic parameters at the level of IVS in MVG. Such impairment appeared to be closely related to the degree of both LV preload (i.e.LVDD) and afterload (i.e. wall thickness, end-systolic stress).

P613 Tissue Doppler echocardiography: the new method of right-ventricle preload assessment in patients with atrial septal defect

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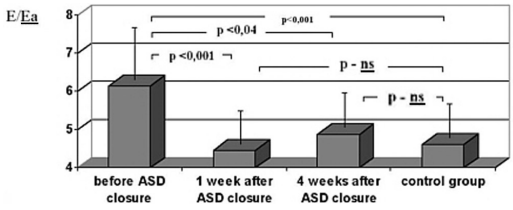
Introduction: Recently the new method of left ventricle preload assessment based on tissue doppler echocardiography was described. The maximal early diastolic mitral inflow velocity (E) depends on diastolic compliance of left ventricle and left ventricle preload. The maximal early diastolic velocity of mitral annulus assessed by tissue doppler (Ea) depends only on left ventricle diastolic compliance. Thus, E/Ea ratio represents left ventricle preload. To assess right ventricle preload by E/Ea ratio, E represents maximal early diastolic tricuspid inflow velocity and Ea represents maximal early diastolic velocity of tricuspid annulus. **Aim of the study:** To assess right ventricle preload in patients with atrial septal defect (ASD) by E/Ea ratio before and after closure of the defect. **Material and methods:** In 27 patients (20 females, 7 males) aged 18-62 years (mean age 41,1) ASD was diagnosed by transesophageal echocardiography. The diameters of the defects were 7-24 mm (mean diameter 16,5mm), the Qp:Qs ratio was 1,5-2,86 (mean 1,9). The control group consisted of 14 healthy, age and sex matched persons. In all the patients maximal early diastolic tricuspid inflow velocity (E) and maximal eary diastolic velocity of tricuspid annulus (Ea) were calculated. The measurements were done before and after the percutaneous closure of the defects by Amplatzer devices. **Results:** Results are shown in the figure below. In the group of patients with Qp:Qs ratio $>$ 2,0 E/Ea was significantly higher than in the patients with Qp:Qs $<$ 2,0 (7,73$\pm$2,01 vs. 5,86$\pm$1,80 respectively, p$<$0,05). **Conclusion:** Significant decrease of E/Ea ratio was observed after the closure of ASD. E/Ea ratio seems to be useful noninvasive method for right ventricle preload assessment.



P614 Arterial-ventricular coupling changes after antihypertensive therapy with angiotensin-II receptor antagonists

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Background: The integration between arterial and ventricular function has been studied by mostly invasive techniques. We considered assessing the influence of angiotensin-II receptor antagonists (AIIRA) on hypertensive patients with the use of a non-invasive method of calculation the arterial-ventricular coupling (AVC) changes.
Methods: A total of 640 patients with essential arterial hypertension, were studied echocardiographically at baseline, and after 6 months of antihypertensive monotherapy with AIIRA. The AVC was calculated by echocardiographic measurements based on the equation: AVC= Ea/Emax = ESP/SV/ESP/ESV= ESV/SV (ESP, End-Systolic Pressure; SV, Stroke Volume; ESV, End Systolic Volume).
Results: AIIRA decreased significantly the AVC values (percentage change: 4.11 ± 3.45%, $p<0.00001$)(see Table). Patients with non-dipping status, microalbuminuria, and left ventricular hypertrophy had significantly higher AVC changes ($p<0.001$ for all). Changes in AVC correlated with baseline characteristics [age (r=-0.115, p=0.004), body mass index (r=-0.108, p=0.006), dipping status (r=0.203, $p<0.0001$)], changes in systolic (r=0.159, $p<0.0001$) and diastolic blood pressure (r=0.143, $p<0.003$), pulse pressure (r=-0.088, p=0.03), heart rate (r=-0.097, p=0.01) and echocardiographically derived parameters such as left ventricular mass index (r= 0.372, $p<0.0001$) and midwall fraction shortening (r= -0.547, $p<0.0001$).

Selected clinical and echocardiographic

	Before	After	% Change
Systolic blood pressure (mmHg)	167 ± 13	132 ± 8	-26.2 ± 7.6
Diastolic blood pressure (mmHg)	102 ± 8	83 ± 5	-23.5± 6.4
Pulse pressure (mmHg)	65 ± 16	49 ± 10	-21.4 ± 13.4
Heart rate (bpm)	75 ± 7	75 ± 6	0.9 ± 4.3
Plasma renin activity (ng/ml/hr)	1.1 ± 1.1	3.4 ± 3.9	310 ± 364
Left ventricular mass index (g/m^2)	140 ± 21	121 ± 15	-13.6 ± 4.1
Midwall fractional shortening	21.3 ± 3.1	22.2 ± 3.0	4.7 ± 4.1

All values are mean ± SD. All p values < 0.0001, except heart rate (p=NS). AIIRA, Angiotensin-II Receptor Antagonists.

Conclusion: AIIRA antihypertensive therapy decreased significantly the AVC values. Baseline characteristics, and changes in clinical and echocardiographic indices were related to AVC changes.

P615 Determination of left-ventricular mass from contrast-echocardiography compared with magnetic resonance imaging

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Background: Patients with LV hypertrophy (LVH) or reduced ejection fraction (LVEF) have been shown to be at high risk of cardiac events. Determination of LVH and accurate and reliable measurement of left ventricular myocardial mass (LVM), left ventricular volume (LVV), and LVEF are crucial to the clinical practice The aim of the study was compared an ultrasound based computer interpreted analysis for the assessment of the left ventricular mass, while using magnetic resonance imaging as the reference standard.
Methods: Contrast enhanced color Doppler and 2D echocardiographic images and MRI data were analyzed in 35 patients. Echocardiography exam was performed with Sequoia C256. LV opacification was achieved by bolus injection of Levovist. Custom software was used to detect the endocardial border from the color information of the echocardiographic image. The epicardial border was traced automatically using the endocardial border and posterior wall and septal wall thickness. LVM was then calculated from the volume occupied by the LV myocardium multiplied by the density of the myocardium. For MRI, a superconducting 1.5 Tesla MR unit was used with 25 mT/m gradients and 0.6 milliseconds rise time, with the patient in the supine position. A segmented ECG-gated breath-hold cine gradient-echo sequence was used for imaging 6-10 short-axis contiguous 10-mm slices covering the whole LV. A standard method of disks (Simpson's rule) was used to calculate the LVM. LVM results from echocardiography and MRI were compared using linear regression analysis.
Results: The mean MRI Simpson's rule LVM was 171,0 g (S.D.52,4 g, range 105,1 to 318,7 g). The mean echo Simpson's rule LVM was 178,2 g (S.D.46,0 g, range 112,6 to 307,6 g). The linear regression correlation between MRI Simpson's and echo Simpson's LVM was excellent (y= 1,022 x; R2 = 0,9860) with a mean difference of 7,20 g (S.D. 20,9 g). Conclusions. LVM may be obtained from contrast enhanced color Doppler and 2D echocardiography reliably. Our results indicated that, the contrast Doppler method-derived LVM produces an accurate determination of left ventricular mass with an excellent agreement with the MRI technique.

P616 Aortic distensiblity and left-ventricular diastolic function are impaired in patients with Adamantiades-Bechets disease

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Adamantiades-Behcet's disease (ABD) is a multisystem disorder characterized by vasculitis leading to vascular complications (VC) such as aneurysm formation, stroke, arterial or venous occlusive disease. We investigated whether ABD is related with impaired aortic distensibility (AoD) and left ventricular (LV) function.
Methods: We studied 82 patients with ABD (age 3811 years) and 24 normal controls by 2D, and Doppler Echocardiography. AoD was calculated using the formula 2 x (pulsatile change in aortic diameter)/[diastolic aortic diameter x (aortic pulse pressure)]. Thoracic aorta diameters (TAO-mm/m^2) were measured 3 cm above the aortic valve by 2D guided M-mode echocardiography and pulse pressure was obtained simultaneously by cuff sphygmomanometry. Abdominal aorta diameters(ABAO-mm/m^2)were also noted. Isovolumic relaxation time (IVRT-ms), deceleration time (DT-ms) and flow propagation velocity (FPV-m/s) were measured to assess diastolic LV function. The duration of disease from diagnosis to time of examination and presence of VC were noted.
Results.Patients had normal systolic LV function and similar age and atherosclerotic risk factor distribution with controls. ABAO, TAO, AoD (cm^2 dyn^{-1} 10^{-6}) ,IVRT, FPV and E/FPV ratio were impaired in patients compared to controls(table).Low AoD was related to the duration of disease(r=-0.48, $p<0.01$) and to prolonged DT (r=-0.37, $p<0.01$). Patients with VC (n=19) had higher LV mass (g/m^2)and DT than patients without (table). DT>190ms predicted VC with 83% sensitivity and 81% specificity (ROC curve area:81% (CI: 65-97%, $p<0.01$) independently of age and risk factors.

	ABAO	Ao D	IVRT	FPV	E/FPV	Vascular complications	LV mass	DT
Patients (n=82)	10.2±1.7	0.79±0.5	87±15	0.43±0.13	1.8±0.6	Yes(n=30)	103±12	220±34
Controls (n=24)	8.9±1.6	2.0±0.9	77±19	0.65±0.19	1.1±0.4	No(n=52)	89±17	180±30
p	<0.01	<0.01	<0.01	<0.01	<0.01	p	<0.01	<0.01

Conclusion: ABD is related with impaired AoD possibly due to vasa vasorum vasulitis leading to increased Ao diameters as disease progresses in time. ABD is related with impaired diastolic LV function likely due to coronary vasculitis or reduction of coronary blood flow during diastole caused by increased aortic stiffness.Diastolic LV dysfunction is linked to presence of vascular complications implying the presence of a common pathophysiological pathway.

P617 Mitral valve prolapse in atrial septal defect patients: a functional disorder

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High incidence of mitral valve prolapse (MVP) associated with atrial septal defect (ASD) has been reported. The study aimed to evaluate the prevalence, etiology and clinical significance of MVP in patients with ASD.
Methods: 47 consecutive patients with secundum ASD (30 F; 17 M; mean age: 37,9±14,0;16-62 years) were enrolled into the study. All patients underwent M-mode and 2-D echocardiography to check for MVP. Pulmonary to systemic flow ratio (Qp/Qs), diastolic right (RV), left (LV) dimensions and left to right ventricle ratio (LV/RV) were measured. Mitral and tricuspid valve insufficiency and right ventricle systolic pressure (RVSP) were evaluated. A cardiopulmonary exercise test (CPX) was performed in every patient. We determined: time of exercise - Time (min), peak oxygen uptake - V02 peak (ml/kg/min), V02 peak expressed as % of predicted value - V02% and anaerobic threshold - AT (as % V02 max). The population was divided into two groups: Group I - with MVP and Group II - without MVP.
Results: MVP was recognized in 17 patients (36%). MVP was not associated with significant mitral regurgitation. There were no significant differences in age, RVSP, RV and LV between groups,but Qp/Qs was significantly higher (p=0.01) and LV/RV significantly lower (p= 0.02) in the MVP group. Moreover, there was a significant negative correlation between Qp/Qs and LV/RV ratio (r = - 0.70; $p<0.001$) in a study group. No significant differences in CPX data were observed between groups.

Table I.

Variables	Group I	Group II	P value
Age	36.6 ± 14.4	38.6 ± 14.0	NS
Qp/Qs	2.95 ± 0.8	2.28 ± 0.6	p=0.01
LV/RV	1.1 ± 0.3	1.3 ± 0.3	p= 0.02
RVSP	36.3 ± 4.9	32.2 ± 2.5	NS
Time	722 ± 347	725 ± 256	NS
VO2peak	22.6 ± 8.6	23.8 ± 7.9	NS
VO2%	62.5 ± 20.6	67.6 ± 16.9	NS
AT	39 ± 8.3	39.7 ± 8.2	NS

Conclusions: MVP associated with secundum type ASD is a functional disorder due to the atrial shunt and leftward shift of interventricular septum. MVP does not affect cardiopulmonary capacity in ASD patients.

P618 Double-chambered right-ventricle: an unexpected echocardiographic finding

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Background: Double-chambered right ventricle (DCRV) is a rare form of right ventricular (RV) outflow tract obstruction in which muscle bundles divide the RV into a proximal high-pressure and a distal low-pressure chambers. The diagnosis is most often made by echocardiography, which also allows the identification of associated lesions and is useful in surgical planning.
Objective: We sought to determine the prevalence of this lesion in our practice and to describe the morphology of the lesion and the associated lesions.
Methods: By reviewing 5800 echocardiographic studies performed in our Institute (tertiary referrral center) during the last year we have identified the cases with a diagnosis of DCRV. All had an initial TTE followed by a TEE study.
Results: Three cases of DCRV, all women, ranging in age from 19 to 22 were identified. The referral diagnoses were: VSD with aortic regurgitation in one patient (pt), tetralogy of Fallot (1 pt) and VSD (1 pt). Two of them had a clinical suspicion of infective endocarditis. TTE clearly showed the existence of a subinfundibular muscular stenosis (giving rise to a DCRV) in 2 pts and raised the suspicion of DCRV in the third pt. TEE confirmed the DCRV in all these 3 pts and offered details about its morphology. In all cases the obstruction was severe with peak gradients of more than 100 mm Hg by CW Doppler. The associated lesions were membranous VSD in 2 pts, both of them presenting with large vegetations (1 pt had a vegetation on the VSD and 1pt at the level of the subinfundibular obstacle), severe aortic regurgitation in 1 pt and PFO with right-to-left shunt in all, due to high RA pressure. The echo findings were confirmed both at cardiac catheterization and at surgery, all pts being successfully operated.
Conclusions: In a highly selected population DCRV is more prevalent (0,05%) than previously reported. Echocardiography (especially TEE) is diagnostic and offers useful information about the morphology of DCRV and its associated lesions. VSD is commonly present and this association is a particular hazard for infective endocarditis.

P619 Value of real time 1.5-harmonic contrast echo for assessing myocardial vascular damage after reperfusion in myocardial infarction

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Harmonic imaging (HI) using the one and a half (1.5) harmonics is a new contrast echo technology that may exclusively image the signals from the microbubbles because the signals from the background tissue reflection become nearly 0 at the 1.5 harmonics. Therefore, peak subtracted contrast intensity of the microbubbles is remarkable at the 1.5 harmonics. We performed 1.5-harmonic (TOSHIBA, Japan) intravenous myocardial contrast echocardiography (IV-MCE) in 15 patients with old myocardial infarction. Echo equipment was APLIO SSA-770A (TOSHIBA, Japan). IV-MCE study was performed before and after dipyridamole stress as follows: intravenous bolus injection of Levovist (300mg/ml, 7ml, 0.5ml/sec) utilizing 1.5-harmonic (1.8MHz in transmit and 2.6MHz in receive) at 10 frames/sec. Myocardial staining was scored using a 4-point scale (strong=3 to none=0) in each segment to provide a staining ratio of the infarct to normal segment (I/N ratio). Results: 1. Myocardial staining score was 2.5±0.5 in the normal segment and 1.7±0.5* in the infarct segment (mean±SD, $p^*<0.05$). Myocardial staining was significantly low in the infarct segment. 2. Dipyridamole stress testing decreased I/N ratio from 0.76±0.16 to 0.59±0.30. Conclusions: Real time 1.5-harmonic made it possible to assess the decrease of myocardial blood flow in the infarct area after reperfusion. In addition, the change in myocardial blood flow distribution in the normal and infarct regions may be assessable using stress 1.5HI.

P620 Echocardiographic quantification of right-ventricular myocardial performance index in the late follow-up of Senning procedure

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Background: The evaluation of the global right ventricular (RV) function has been limited because of its complex geometry. In the Senning procedure this evaluation is of major importance, since the RV is submitted to systemic burden. A Doppler index, combining systolic and diastolic time intervals, has been used to assess ventricular function (named Myocardial Performance or Tei Index). Because this index is independent of geometry it may be particularly useful in the evaluation of the RV function. The aim of this study was to determine values for RV myocardial performance index (RVMPI) to assess global RV function in the late follow-up of Senning procedure.
Methods: Forty four patients submitted to Senning procedure were prospectively studied by echocardiography. Mean age was 16,7 years, ranging from 12 to 26 years. Mean postoperative period was 15,3 years, ranging from 10 to 23,5 years. Forty one patients were in NYHA Class I, and 3 in Class II. RVMPI was calculated using PW Doppler from tricuspid inflow and aortic outflow. RVMPI values were compared to RV ejection fraction (EF) calculated by magnetic resonance imaging (MRI) to establish normal and abnormal values. Both methods were performed within one month.
Results: RVMPI ranged from 0.16 to 1.42 (mean=0.50). MRI showed 32 patients (72,7%) with normal RVEF (≥55%), and 12 (27,3%) with some degree of abnormal RVEF (<55%). A cut off value of 0.475 for the RVMPI was determined (ROC curve), with a sensitivity of 75% and a specificity of 62,5%. The NYHA functional classes of the patients did not correlate with RVMPI or MRI values (Kappa).
Conclusion: The RVMPI could be a good parameter to quantitatively evaluate global RV function in late follow up of a group of patients submitted to Senning procedure. Further experience with a larger number of patients is necessary to establish the real value of this index.

STRESS ECHOCARDIOGRAPHY: NEW DIRECTIONS

P621 Dynamic changes of brain natriuretic peptide during dobutamine stress echocardiography are correlated with induced ischaemia

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Introduction: Brain natriuretic peptide (BNP) is accepted as a marker of heart failure. It is produced by left ventricle and related with regional wall tension thus reflecting LV enddiastolic pressure.We assessed the dynamic changes of BNP induced by dobutamine stress echocardiography (DSE) and interrogated relationships with the outcome of the test.
Methods: We studied 75 consecutive pts (age 60±11, 10 women, a previous infarction was documented in 26, ejection fraction was 40±12%, range 15-60). All underwent conventional DSE for ischemia interrogation. Sampling of BNP was performed at rest (R) and during recovery (Rec), 15 min post discontinuation of DSE
Results: A positive DSE was found in 34/75 pts. BNP changes were not related with EF or score at R.BNP(R)had a weak relationship with both EF (R) (r=-0.24, p=0.07) and wall motion score at peak DSE (r=0.30, p=0.023). Pts with a positive DSE had smaller changes of BNP compared with a negative DSE (p=0.041 and 0.034 for absolute and % changes).
Using ROC analysis, then a %BNP >16 has sensitivity 80% with specificity 50% for prediction of an ischemic DSE (area =0.68, p=0.04). When ischemia in the LAD territory was detected, pts with an ischemic DSE had a significant increase in BNP at Rec (% changes p=0.031).
Using ROC analysis, a 16% increase of BNP at (Rec) had sensitivity 50% and specificity of 91% for prediction of LAD territory ischemia by DSE (area 0.71, p=0.044). Incidence of %BNP>16 among ischemic responces was 6/12 for LAD, 2/9 for RCA and 0/13 for Cx territories ($p<0.05$).
Presence of ECG changes, ventricular extrasystoles, LVH, delayed recovery of regional wall motion abnormalities post a positive DSE outcome were not related with differences on BNP (R) or dynamic changes.
Conclusion: BNP dynamic changes may be induced by DSE. A BNP increase during recovery implies ischemia in the LAD territory, but not in smaller ischemic segments.

P622 Stress echocardiography for liver transplant evaluation

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The detection of coronary disease (CD) by imaging methods has been recommended in the preoperative assessment of patients (pts) proposed to liver transplantation (LT).
Objective: To evaluate the contribution of pharmacological stress echocardiography (PSE) in the preoperative study of cardiac risk in patients proposed to LT.
Methods and Materials: Between July 1996 and September 2002, 46 pts referred to LT were evaluated using PSE, having an average age of 53 ± 8 years and of whom 34 (74%) were male. Ten pts presented with at least 2 cardiovascular risk factors: hypertension 8 pts (17%); diabetes mellitus 11 pts (24%); smoking 11 pts (24%); dyslipidemia 4 pts (9%). In 35 pts (76%) it was used dobutamine protocol and dipiridamol protocol for the remaining 11 pts. A retrospective analysis into angiography evidence of CD and the occurrence of major cardiac events (unstable angina, non-fatal AMI and death from cardiac causes) was done.
Results: A negative PSE was found in 31 pts (67%), it was inconclusive in 12 pts (26%) and positive in 3 pts (7%). Of the inconclusive examinations, 6 (50%) resulted from insufficient chronotropic response (beta blockers effect on 4) and 6 from complications that led to early test cessation: auricular fibrillation (n=1); hypertensive response (n=1); development of significant intraventricular gradient (n=4). Cardiac catheterisation was carried out on 5 pts: 3 pts with positive PSE and 2 pts with inconclusive PSE in whom CD still was suspected. There was evidence of CD in 2 pts, 1 with two-vessel CD and positive PSE and the other with one-vessel CD and inconclusive PSE due to the development of gradient. The remaining 3 pts did not present significant CD. Of this population, 30 pts were submitted to LT, 7 pts are still on waiting list and the rest were excluded. Of the pts submitted to LT, 22 presented a negative PSE, 7 an inconclusive PSE (for not reaching the 85% maximum heart rate, but excluding high risk CD) and 1 patient with positive PSE without evidence of significant CD. Major cardiac events were not recorded in the perioperative period, in which occurred 3 non-cardiac deaths. Based on the evidence of significant CD and/or major perioperative cardiac events, PSE is connected with a negative predictive value of 100% and a positive predictive value of 33%.
Conclusions: PSE showed to be a useful technique in risk stratification of pts proposed to LT with a high negative predictive value.
Based on these results, the systematic use of this test in pts referred to LT might be questionable.

P623 Long-term outcome of patients with high amount of myocardium at risk and stress-induced left-ventricular dysfunction

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Background: Myocardial jeopardy score (MJS) is shown to be very important predictor of survival during interventional procedures, but its impact on long-term mortality rates in the presence of various clinical, angiographic and stress echocardiographic variables is unclear.
Objective: To identify prognostically important clinical variables for 5-year survival among patients who underwent Dobutamine-Atropine (DobAtro), Dipyridamole-Atropine (DipAtro) and Exercise (Ex) stress echocardiography.
Methods: From existing database of stress echo laboratory, 166 patients were identified who all underwent DobAtro (up to 40 mcg/kg/min i.v. Dob with addition of 1 mg of atropine), DipAtro (up to 0.84 mg/kg Dip with addition of 1mg of atropine), Ex (Bruce) and coronary arteriography (analysed by quantitative arteriography). Coronary artery disease (CAD) was present in 114 pts: 91 one-, 23 multi-vessel CAD. Myocardial jeopardy score is calculated for each vessel as a sum of all significant lesions represented as a product of: (1) myocardial kinetic status (0 for akinetic, 0.5 for hypokinetic, and 1 for each normokinetic myocardial segment subserved by the vessel with more than 50% diameter stenosis), (2) diameter stenosis of significantly stenosed coronary vessel (scored from 3-5), and (3) weighting flow factor for particular localisation.
Results: Among clinical, demographical, stress echocardiographic and angiographycal variables, factors strongly associated with high mortality rates were: myocardial jeopardy score >7 (p=0.0003), positive DobAtro (p=0.016), positive DipAtro (p=0.0215) and the number of diseased vessels (p=0.005), while other variables and the results ox Ex stress echocardiography didn't show significant influence on long-term risk of cardiac death (p=ns). Variable most strongly associated with cardiac death was myocardial jeopardy score (RR 1.05; p=0.00054).
Conclusion: Patients with high amount of potentially ischemic myocardium and positive DipAtro and DobAtro stress echocardiography are at high risk for subsequent cardiac death. Myocardial jeopardy score is the strongest predictor of long-term outcome in patents with stress induced myocardial ischemia.

P624 Detection of coronary artery disease using dobutamine stress echocardiography in elderly patients: importance of left-ventricular geometry

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Purpose: The adaptive variations in wall thickness and ventricular size result in different systolic meridional wall stress, which may alter the threshold for demand-based ischemia and may impair the capacity of dobutamine stress echocardiography (DSE) to detect coronary artery disease. The aim of this study was to investigate the effect of the different patterns of left ventricular hypertrophy on the accuracy of DSE in elderly patients.
Methods: Three-hundred and five elderly patients (pts) (age >65 years, mean age 78±4 y, 185 males/120 females) with known or suspected coronary artery disease underwent both DSE and coronary angiography. Mean and relative wall thickness, chamber size, left ventricular mass, and end-systolic wall stress were measured. The patterns of ventricular hypertrophy were: concentric hypertrophy, eccentric hypertrophy and concentric remodeling.
Results: The LV mass was 153±30 g, systolic circumferential wall stress (dyne/cm^2) was 195±36, and the systolic meridional wall stress 68±14 (dyne/cm^2). 108 pts had normal and 197 pts abnormal DSE. Coronary angiography detected significant coronary artery disease in 206 pts (68%). The sensitivity and specificity of wall motion abnormalities for detecting coronary artery disease were 83% and 86%. Sensitivity was higher in pts with abnormal vs. normal resting wall motion (98% vs. 81%, $p<0.001$), but specificity was similar (85% vs. 87%, p=NS). The sensitivity of DSE was comprised only in small subset of pts with concentric remodeling (41%). Specificity was not altered by any hypertrophy patterns. The univariate analysis revealed small chamber size, concentric remodeling, increased wall thickness, single vessel disease as predictors for false negative results. Moreover, the multivariate predictors were concentric remodeling ($p<0.001$) and single-vessel coronary artery disease ($p<0.001$).
Conclusions: Elderly pts with small LV chamber size and increased wall thickness, the pattern called concentric remodeling, exhibit an excessively high number of false-negative DSE studies in the presence of significant angiographic coronary stenosis.

P625 Prognostic significance of left-ventricular contractile reserve in patients with idiopathic dilated cardiomyoptahy: dobutamine versus dipyridamole stress-echocardiography

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Aim: To assess prognostic significance of LV contractile reserve elicited by dobutamine (DOB) and dipyridamol (DIP) stress-echocardiography in patients with idiopathic dilated cardiomyopathy.
Methods: A total of 48 consecutive pts with idiopathic dilated cardiomyopathy was enrolled in the study. DOB was performed using 5, 10, 20, 30, and 40 mcg/kg/min dobutamine infusions in progressive stages lasting 5 minutes each. DIP was performed according to the standard protocol, by using 84 mcg/kg of dipyridamole. Tests were stopped before maximal dose if submaximal heart rate was achieved or complex ventricular arrhythmias were noted. Pharmacologically induced changes in wall motions score index (WMSi) and ejection fraction (EF) were considered as indices of LV contractile reserve. Contractile reserve was considered preserved if there was a change in WMSi of >0.22 and/or in EF$>4\%$ during the test. All patients were followed for 12 months for the occurrence of composite end-point that included cardiac death, partial left ventriculectomy and hospitalization due congestive heart failure.
Results: The study group consisted of 41 men and 7 women (mean age 50$\pm$10 years, 13/48 NYHA class III/IV, mean EF 21$\pm$8%). Combined end-point was noticed in 15/48 pts during the follow-up. Kaplan-Meier analysis demonstrated that DOB induced change in WMSi achieved best separation of pts with respect to composite end-point (log rank=18.83, $p<0.001$), followed by DIP induced change in WMSi (log rank=11.61, p=0.0007), and DOB and DIP induced change in EF (log rank=9.28, p=0.0023 and log rank=8.30, p=0.004, respectively). Cox regression model, that included indices of contractile reserve, identified DOB induced change in WMSi as the only independent prognostic variable.
Conclusions: Contractile reserve elicited by both DOB and DIP can identify pts with dismal prognosis during one-year follow-up. However, it appears that DOB may yield greater prognostic significance.

P626 The prognostic value of myocardial viability recognized by low dose dobutamine echocardiography in chronic ischaemic left-ventricular dysfunction

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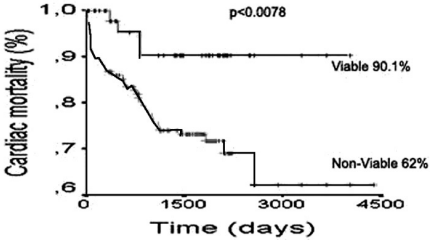
Aim: to assess the prognostic value of myocardial viability recognized as a contractile response to inotropic stimulation in patients with left ventricular dysfunction in a large scale, prospective, multicenter, observational study.
Methods: 425 patients (age= 61$\pm$10 years) with angiographically proven coronary artery disease, previous (>3 months) myocardial infarction and severe left ventricular dysfunction (ejection fraction $<$ 35%; mean: 28$\pm$6%) were enrolled in the study. Each patient underwent low dose dobutamine echo (up to 10 mcg/kg/min). Myocardial viability was identified as rest-stress variation in the wall motion score index (WMSI), each segment scored from 1=normal to 4= dyskinetic in a 16 segment model of left ventricle. Myocardial viability was identified as an improvement >0.40 in wall motion score index. All patients were followed up for a median of 3.1 years. The only end-point analyzed was cardiac death.
Results: One hundred and eighty-eight were revascularized by either coronary artery by pass grafting (n= 118) or coronary angioplasty (n=70). In the revascularized group cardiac death occurred in 4 of the 52 patients with and in 37 of the 136 patients without myocardial viability (7.7% vs. 27.2%, $p<0.003$). Kaplan-Meier survival estimates showed a better outcome for those patients with compared to patients without myocardial viability who underwent coronary revascularization (90.1 vs. 62%, $p<0.0078$). The survival rate in medically treated patients was similar irrespective of the presence of myocardial viability (viable=60% versus non-viable 56%, p=ns).



Conclusion: In severe LV ischemic dysfunction, myocardial viability by low dose dobutamine echo is associated with improved survival in revascularized patients.

P627 Prognostic significance of intraventricular conduction defects in patients undergoing stress echocardiography for suspected coronary artery disease

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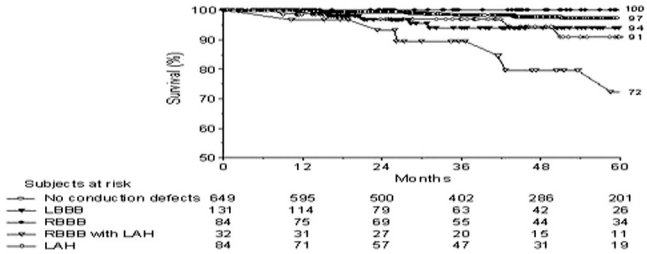
Aim: To investigate the still unclear prognostic implication of conduction defects in subjects without proven coronary artery disease referred for stress echocardiography.
Patients and Methods: The study group consisted of 1230 patients [574 men and 656 women; mean ($\pm$SD) age, 63$\pm$10 years] who underwent stress echocardiography with dipyridamole (n=780) or dobutamine (n=450) to evaluate suspected coronary artery disease. Four-hundred twenty of them presented with intraventricular conduction defects, whilst 810 with normal intraventricular conduction served as control group. A summary wall motion score (on a 1 to 4 scale) was calculated. Overall mortality was the only end point of the follow-up.
Results: Ischemia at stress echo (new or worsening of preexisting wall motion abnormality) was found in 250 (20%) patients. During a mean follow-up of 41$\pm$27 months, there were 56 deaths. Multivariate predictors of mortality were resting wall motion score index [hazard ratio (HR)=6.0 per unit increase; 95% confidence interval (CI), 2.3 to 15.7; $P<0.0001$], ischemia at stress echo (HR=3.9; 95% CI, 2.2 to 6.7; $P<0.0001$), right bundle branch block with left anterior hemiblock (HR=3.7; 95% CI, 1.8 to 7.5; $P<0.0001$), age >65 years (HR=3.2; 95% CI, 1.7 to 5.9; $P<0.0001$), and hypertension (HR=1.8; 95% CI, 1.1 to 3.2; P=0.03). Patients without ischemia showed a lower survival in case of right bundle branch block with left anterior hemiblock (figure).



Conclusion: Right bundle branch block with left anterior hemiblock is an independent predictor of mortality in patients with suspected coronary artery disease undergoing stress echocardiography. In subjects without ischemia, right bundle branch block is associated with an excellent outcome.

P628 Force-frequency relationship in the echo lab: a non-invasive assessment of contractile reserve during exercise

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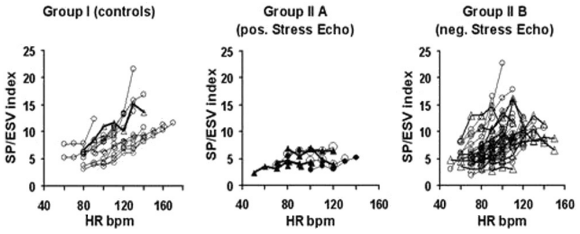
Background: The assessment of force frequency relationship (FFR) is a theoretically robust approach to evaluate left ventricular contractility.
Aim: To assess the feasibility of a totally noninvasive estimation of FFR during exercise stress in the echo lab.
Methods: We enrolled 13 normal healthy subjects (12 males, 38±15 years) as standard controls (group I) and 50 patients (38 males, 64±11 years) referred for exercise-echo (group II). To build the FFR, the force was determined at each step as the ratio of the systolic pressure (SP, cuff sphygmomanometer)/end-systolic volume index (ESV, biplane Simpson rule/body surface area). The slope of the relationship was calculated with the linear best fit of the FFR.
Results: Non invasive SP/ESV ratio was obtained in all patients. The slope of the linear best fit of the force-frequency curve was lower in patients compared to controls (group II = 10.1±9.3 x 10-2 vs group I = 14.9±9.9 x 10-2 group I, p=0.04). By regional wall motion analysis, 2 subgroups were identified in group II: Group II A (n=8) had a positive echo; and group II B (n=42) had a negative echo. The slope of the force-frequency curve was lower in patients with, compared to those without ischemia (Group IIA= 3.5 ± 4.2 x 10-2 vs Group IIB= 11.4 ± 9.5 x 10-2; p=0.012): see figure.



Conclusion: A noninvasive estimation of FFR can be easily determined during exercise-echo. This index of global contractility is exquisitely sensitive to regional ischemia and theoretically appealing for identification of limited contractile reserve and latent global left ventricular dysfunction.

P629 An intensive computer-based interactive training program improves interpretation of dobutamine stress echocardiography

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Objectives: This study aimed to evaluate the effect of an intensive computer-based interactive training course on accuracy of interpretation of dobutamine stress echocardiography (SE).
Methods: 27 cardiologists with minimal experience in SE attended a 2-day training course involving lectures on SE interpretation and computer-based interactive readings of 40 dobutamine studies with experts. Participants completed a test of 10 studies before and after the course. Interpretations to each study were reported in terms of 'Site of Abnormality' and 'Nature of Pathology' and were scored against expert interpretation. The before- and after-training scores are compared using the Wilcoxon signed-rank test. Sensitivities and specificities, defined by comparison with the presence or absence of coronary disease from angiographic data, were compared using the paired t test.
Results: Specificity (mean±SD) improved markedly from 48%±31% to 73%±28% (p=0.002), but sensitivity was changed little from 95%±11% to 98%±5% (p=NS). Overall scores (out of 10) were 4.93 ±1.51 before and 6.24±1.40 after the course (p=0.002). The 'site' scores (out of 5) were 2.80±1.02 before and 3.59±0.82 after training (p=0.003). Improvements were especially made in the RCA territory (Table). The scores for 'nature of pathology' (out of 5) were 2.13±0.70 before and 2.65±0.68 after training (p=0.029). No particular subgroup seemed to benefit more than the others (Table).

Site of abnormality	Before training	After training	Wilcoxon test p value
RCA (3 studies)	64%	83%	0.002
LAD (3 studies)	50%	50%	NS
Multivessel (1 study)	70%	93%	0.03
Nature of pathology	Before training	After training	Wilcoxon test p value
Ischaemia (4 studies)	36%	37%	NS
Viability (1 study)	26%	30%	NS
Mixed (2 studies)	56%	67%	NS

Conclusion: An intensive computer-based interactive training course significantly increased accuracy of dobutamine stress echocardiography interpretation - especially specificity. Accuracy of recognition of RCA and multivessel territory abnormalities improved significantly.

P630 Assessment of longitudinal myocardial function under pharmacological stress in patients with heart failure and preserved left-ventricular systolic function using tissue Doppler imaging

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The mechanisms of signs and symptoms of chronic heart failure (CHF) in patients with preserved left ventricular (LV) systolic function are poorly defined though LV diastolic dysfunction is implicated as a major factor. Systolic (Sm), early diastolic (Em) and late diastolic (Am) mitral annular velocities are increasingly used to assess systolic and diastolic longitudinal LV function and left atrial function respectively. These indices measured with tissue Doppler imaging (TDI) during Dobutamine stress echocardiography (DSE) could be employed to better understand the pathophysiology of CHF in these patients.
Methods: 29 consecutive patients with CHF (mean age 71 years, 72% men, NYHA functional classes II and III) and preserved LV systolic function (LV ejection fraction > 50%) undertook DSE. Colour-coded TDI images were acquired using three standard apical views at rest and during 5, 10, 20, 30 and 40 mcg/kg/min of dobutamine as tolerated using a Vivid 5 scanner (GE Vingmed). All patients reached at least 85% of the age-related THR. At each dose of dobutamine, the Sm, Em and Am velocities were measured at 6 sites of the mitral annulus using Echopac software and averaged. Peak early (E) and atrial(A) velocities of transmitral flow, isovolumetric relaxation time (IVRT) and E wave deceleration time (DT) were also recorded.
Results: The Sm velocities progressively increased from the baseline to the peak dose of dobutamine (from 4.6±1.2 to 7.4±2.1 cm/s, p<0.001) in all patients. The Em velocities increased from 3.8±1.3 to 5.1±1.5 cm/s (p<0.001) in 21 patients (Group1) and decreased from 4.7±1.8 to 2.7±1.4 cm/s (p<0.05) in 8 patients (Group2). In contrast, peak transmitral E velocities did not significantly change in either group (65±30 vs 68±21 cm/s, p=0.46 in Group 1 and 61±14 vs 64±27 cm/s, p=0.76 in Group 2). In both groups the Am velocities increased (from 7.0±1.9 to 8.4±1.8 cm/s, p<0.001 and from 7.3±0.8 to 9.9±1.7 cm/s, p=0.003 respectively). Peak transmitral A velocities also increased significantly (from 97±37 to 110±28 cm/s, p=0.003) in Group 1 but not in Group 2 (85+21 vs 94±29 cm/s, p=0.3). Other conventional parameters of LV diastolic function i.e. E/A ratio, DT and IVRT did not change in either group.
Conclusions: The results of this study suggest that longitudinal LV diastolic function can deteriorate with parallel augmentation in left atrial function under dobutamine stress in CHF patients with preserved LV systolic function. TDI is a more sensitive technique than conventional Doppler in detecting these functional changes.

INTERNET, DATABASE AND TELEMEDICINE

P631 Assessment of a protocol driven, web-based, rapid access chest pain clinic

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We describe a rapid access chest pain referral using web browser technology via the Scottish Health service secure internal internet - NHSnet. The family doctor (GP) refers a patient online using the 6 standard chest pain questions derived by Patterson & Horowitz. These are used to determine the patient's baseline probability of CHD (Diamond & Forrester). The patient's history, risk factors and medication are entered on-line in the GP practice. An appointment is then booked on line. ECG and exercise test data are entered in the hospital. This data further refines the probability of CHD using more powerful equations (Duke Treadmill & Detrano). The final consultant report is available for the GP to view online. 750 referrals were made between 1/12/99 and 30/6/02. The computer classified most patients (>80%) as typical angina (baseline probability of CHD=91%). The Duke Treadmill Score refined the probability of CHD to 60.5%. 42% of patients were discharged, 39% were referred for further investigation or follow up and of these virtually all had a computer probability of typical anginal pain. Only 2% of patients were admitted directly from the service. Of those with atypical chest pain only 7% had a positive ETT. Of the remainder (93%) 22% required further Ix, diagnosis or follow up. No one required angiography. Of those with typical chest pain 36% had a positive ETT, 49% required further Ix, discharge or follow up and 9% required angiography. The probability of significant CHD from Duke Score in those with definite AP=76%, possible AP=57%, not AP=42%. Using <40% probability identified virtually all of those discharged back to the GP with a consultant diagnosis of non or insignificant cardiac diagnosis. This could result in 37% of all referrals not requiring a cardiologist opinion. Similar figures using the Detrano score were definite AP=74%, possible AP=64%, not AP=41%; using <41% probability could discharge 28% to GP. In summary the baseline probabilities of CHD were significantly over-estimated by the Paterson & Horowitz questionnaire. Some "standard" cardiac questions were of no help in risk stratification. The pre-test questionnaire stratification of patients into atypical and typical chest pain separated those who were likely to have a reassuring test from those who required further management. This service represents one of the first web based clinical referral systems between primary and secondary care.

P632 Quality assurance measures in the CONCOR national registry and DNA bank of adults with congenital heart disease in the Netherlands

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Introduction: A national registry and DNA-bank of adults with congenital heart disease has been instigated in the Netherlands to investigate long term outcome in these patients and to allow investigation of the molecular basis of congenital heart defects. All eight academic medical centers in the Netherlands are participating in the CONCOR project (CONgenital CORvitia). After informed consent has been obtained clinical data of patients with congenital heart disease is collected using a web-based application (Promise). For each patient, all clinical events (diagnoses and interventions) are registered using the EPCC (European Pediatric Cardiac Code) coding scheme. Blood samples of participating patients are collected, and DNA is isolated and stored. Data is collected by two trained research nurses from the patient records and by interviewing the patients. To assure the quality of the data in the registry, a large number of quality assurance measures have been implemented.
Methods: All data that are collected are stored in a central Microsoft SQL server database using the Promise Web application. One of the strong features of the Promise system is the unlimited quality control during data entry, based on logical criteria. In addition, on a monthly basis, the full dataset is exported in Microsoft Access format. Various queries on this Access database have been designed to create reports based on the present content of the registry. For instance, based on these data a monthly report is published in the Netherlands Heart Journal. For quality assurance, extra queries are carried out monthly on the CONCOR database to identify possible errors or problems. Some of the standard items that are checked are:
– Identification of patients without main diagnosis
– Correctness of patient-ID and birthdate (checked versus data from the respective hospital information systems)
– Agreement between the information in the DNA-lab database (CONCOR-id, birthdate) and the information in the CONCOR database
Results: The CONCOR registration has officially started in January 2002. One year later almost 2000 adult patients with congenital heart disease are registered; from 49% of these 2000 patients DNA has already been obtained.
Conclusions: The quality checks that have been implemented assure the accuracy of the contents of the registry. Furthermore, based on the results of the montly reports, and on designing the queries to produce these reports, improvements in the database structure of the Promise/CONCOR database have been implemented.

P633 Trends in management of hypercholesterolaemia in the United Kingdom primary care practice from 1998 to 2001

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Introduction: British guidelines recommend that physicians identify patients with and at a significant risk for coronary heart disease (CHD) and offer them statins and dietary counseling to lower total cholesterol (TC) to <5 mmol/L (LDL-C to <3 mmol/L). This study was conducted to assess general practitioner (GP) management of hypercholesterolemia from 1998 to 2001.
Methods: This retrospective cohort study was based on data from the UK MediPlus database, a national GP database. Patients starting lipid-lowering therapy (LLT) between 1998 to 2001 were identified and followed for up to 4 years. Trends in initial LLT, therapeutic changes, TC monitoring before and after LLT initiation and goal attainment were evaluated.
Results: 19,898 patients initiated LLT from 1998 to 2001. The rate of new-start patients doubled from 4.4/10000 in 1998 to 8.5/1000 in 2001. The proportion of patients with prior CHD decreased annually from 44.4% to 34.2% ($p<0.05$) while the proportion with other atherosclerotic disease or diabetes increased from 14% to 24.4% ($p<0.05$). 18,847 (95%) patients were prescribed statins as initial LLT - most commonly atorvastatin 10mg (25.8%) and 20mg (4.2%), and simvastatin 10mg (24.7%) and 20mg (13.7%). Annual average initial doses of atorvastatin and simvastatin increased from 11.4mg to 12.3mg and 13.3mg to 16.9mg, respectively, from 1998 to 2001. Overall, less than 30% of patients titrated to a higher dose. 18% of patients discontinued therapy (median time 2.5mo after initial LLT)and 60% had gaps between prescriptions for 60 days or greater. 8635 patients (43.4%) had no baseline TC record (6mo prior to initial LLT). After therapy initiation, 34.2% of patients had no record of follow-up cholesterol measurements. Among patients with a baseline TC>5 mmol/L, 45% never achieved goal cholesterol (TC<5mmol/L). Those with highly elevated baseline cholesterol (TC>7mmol/L) were least likely to achieve goal ($p<0.05$), with 60% never achieving goal.
Conclusion: Overall, relatively minor changes were seen in hypercholesterolemia management from 1998 to 2001. While more patients initiated LLT from 1998 to 2001, most patients continued to receive low-dose statins as initial monotherapy. Cholesterol monitoring was not performed consistently. Only a small proportion of patients were ever-titrated and a large proportion of patients never achieved treatment goal. More consistent follow-up and use of combination therapy may help more patients to attain goal cholesterol.

P634 The "Have a Heart Paisley coronary heart disease register: using information technology to improve health in those with or at risk of coronary heart disease

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Throughout Scotland and Europe there is great potential to improve the management of, and tackle inequalities in relation to, the primary and secondary prevention of Coronary Heart Disease (CHD). While the practice of evidence based healthcare has, and will continue to, foster improvements in practice and outcomes, it is also important to strengthen the structures and tools that support CHD management. As part of the 'Have a Heart Paisley' Scottish Executive Demonstration Project, an innovative computerised regional CHD Register of those with or at risk of CHD has been developed in Paisley. The CHD Register is a central computerised database that can store, receive and send information from a variety of national and local databases related to people with or at high risk of CHD. The Register contains data, stored over 109 fields, on an individual's demographic profile, CHD risk factors, pharmacological therapies, lifestyle behaviours, access to services and previous CHD-related medical history. Via various established local computer systems, fields stored on the Register can be accessed and modified by health professionals involved in CHD management and prevention. This paper aims to demonstrate the aims and main functions of the CHD Register and its potential benefits to those with CHD, health professionals, researchers and commissioners. The main ethical and data-protection issues that were encountered during the development of the register will also be discussed.

P635 Utility of a telecardiology service dedicated to general practitionairs in the management of patients with hyperlipidaemia

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HL is one of the principle risk factor for cardiovascular diseases; early diagnosis and treatment of HL play an important role in atherosclerosis prevention.
Aim of our study was to assess an TS with co-operation between Cardiologists and GPs, in HL pts' daily management. 1224 GPs resident anywhere in Italian territory received a portable personal 12 leads electrocardiographer which can be interfaced with a fixed or a mobile TACS telephone. The ECG trace was transferred to the receiving station where 22 cardiologists, covering the 24 hours period, were available for the ECG referral and for an interactive teleconsultation. A total of 13796 calls were analyzed, corresponding to an equal number of pts. This study is focused on the subgroup of 1088 pts with known and documented HL.
Results:

	General population	Hyperlipidaemia	p
Patients	13796	1088 (7.9%)	
Sex (%M/F)	44.4/55.6	46.9/53.1	ns
Age (yrs)	61 ± 20	62.4 ± 13.4	0.023
Previous cardiopathy	6173 (44.7%)	635 (58.4%)	0.01
Hypertension	5091 (36.9%)	578 (53.1%)	0.001
Obesity	1388 (10%)	231 (21.2%)	0.001
Normal ECG	8459 (61.3%)	630 (58%)	0.034
Lipid lowering drug	403 (2.9%)	323 (29.6%)	0.000
Action taken:			
– None	9118 (66.1%)	679 (62.4%)	0.008
– Therapy adjustment	1970 (14.3%)	145 (13.3%)	ns
– Further investigation	2030 (14.7%)	224 (20.7%)	0.000
– Referral to ED	678 (4.9%)	40 (3.6%)	ns

HL was present in 7.9% of general population and was significantly associated with previous cardiopathy, obesity and hypertension. Drug treatment of HL is present in a small percentage of pts (29%); cardiological teleconsultation increase this therapy in the 13.3%; laboratory evaluation of lipid assessing was requested in 20.7% to decide drug therapy beginning.
These data evidenced an understimation of this risk factor by GPs and suggest an important role of a TS dedicated to GPs in diagnosis and management of HL.

P636 Atrial fibrillation home management with a telecardiology service

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AF is the most common sustained cardiac tachyarrythmia and frequently is an occasional diagnosis, in particular in older people where the General Practitionairs (GPs) are often alone to care them.
Aim of our study was to investigate how a TS can help GPs in the diagnosis and management of AF. 655 Italian GPs received a portable Card Guard 7100 transferring a 12 lead ecg to a receiving station, where a cardiologist was available 24-hours a day for ecg reporting and teleconsultation.
Results:

	General pop	AF popul	p<	Persistent AF	Paroxys AF	p<
Patients (%)	7516	707(9.4%)		448(63.4%)	259(36.6%)	
M/F	3334/4182	281/426		169/279	112/147	
Mean age (yrs)	61 ± 20	77 ± 12	0.000	76.5 ± 12.7	75.6 ± 11.4	
Pts older >70	2945(39.3%)	562 (79.5%)	0.000			
No cardiopathy	2790(37.1%)	49 (6.9%)	0.000		49 (18.9%)	0.000
Hypertension	2746(36.5%)	283(40%)	ns	167 (37.2%)	116 (44.8%)	ns
CAD	955(12.7%)	122(17.2%)	0.000	78 (17.4%)	44 (17%)	ns
CHF	326(4.3%)	116(16.4%)	0.000	99 (22%)	17 (6.6%)	0.000
Other disease	1585(21.8%)	137(19.4%)	ns	105 (23.4%)	33 (12.7%)	0.000
No symptoms	4017(53.4%)	264(37.3%)	0.000	268 (59.8%)	–	0.000
Chest pain	1634(21.7%)	62 (8.8%)	0.000	24 (5.3%)	36 (13.9%)	0.000
Dispnea	594(7.9%)	139 (19.6%)	0.000	57 (12.7%)	67 (25.8%)	0.000
Palpitation	725(9.6%)	151(21.4%)	0.000	61 (13.6%)	98 (37.9%)	0.000
Syncope	100(1.3%)	11(1.5%)	ns	2 (0.4%)	9 (3.5%)	0.004
Fatigue	446(5.9%)	80 (11.3%)	0.000	36 (8.2%)	48 (18.9%)	0.000
TS problem sol.	5458(72.6%)	469 (66.3%)	0.000	348 (78%)	118 (45.5%)	0.000
Referral to ED	411(5.5%)	168 (23.7%)	0.000	47 (10.5%)	121 (46.9%)	0.000
Further investigat.	1647(21.9%)	70 (9.9%)	0.000	51 (11.5%)	19 (7.6%)	ns

Only 207 (46.2%) pts with persistent AF were treated with aspirin or warfarin and in 130 pts (29%) an uncontrolled heart rate was reported even if 408 pts (91%) were in antiarrhytmic therapy.
TS seems to be a useful tool in diagnosis and management of AF pts. GPs with TS solve the cardiac problem in 66.3% of cases, probably avoiding further cardiac consulence, optimising ED admission, drug treatment and strategies to reduce complications.

P637 Evaluation of an innovative disease management model based on continuous interaction with congestive heart failure patients through teletransmission of data

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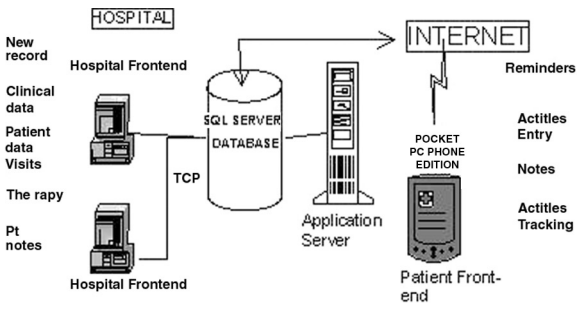
Disease management programs improve the quality and efficiency of care for chronic patients. However some uncertainty still remains. Past disease management programs failed because they were too costly and complicated. Emerging technologies that support the management process through teletransmission of data could be of use.
Aim: Aim of the present study is to evaluate the feasibility of a new palm computer-based approach using a wireless teletransmission of patient's data to the Management Center. A 3 months, Randomized, Parallel Study comparing Usual Specialized Care (USC) from a Congestive Heart Failure (CHF) Unit and an Integrated approach (IA) characterised by remote interaction with CHF patients is ongoing.
Patient Population: III-IV NYHA Class; LVEF <40%; recent hospital discharge (<6 weeks) for HF. 15 patients will be randomized to each group.
Procedures/Software: 1) a pocket PC phone edition device that allows daily, real-time data transmission of the following parameters: weight, DBP, SBP, HR water intake and urine volume. Patient is monitored by the CHF unit team.
2) a dedicated software for the Pocket PC device that prompts Patients to take their medication and to confirm it.
Study objectives: Practical: level of patient acceptance and usage of the device. Clinical: functional status (NYHA class); hospitalizations due to CHF; management of complex therapies, including treatments (especially ACEi and BB) dosage and side effects (hypotension occurrence); Technological: data exchange patterns to/from the CHF unit server.



Architecture.

Conclusions: We describe a new system for remote care of CHF patients using a wireless technology for exchange of clinical data, including vital signs, symptoms, compliance and side effects. Study results will be presented.

P638 Beta-blocking up-titration in patients with stable chronic heart failure: the role of a telecardiology service

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In chronic heart failure (CHF), large clinical trial have demonstrated that beta-blocking agents impact favourably on mortality and on the reduction in rehospitalization, but the beta-blocker will be up-titrated slowly, as tolerated by the patients. For this reason, many cardiac consultations are needed.
Aim of our study was to analyse a home based intervention with a telecardiology system in the Beta-blocking up-titration in CHF stable patients (pts).
One hundred fifty-three CHF stable pts, aged 59±12 years were enrolled. The program consists in a transtelephonic follow-up and ecg monitoring followed by paramedical and medical team. The pts received a portable device, transferring by a mobile or fixed telephone a one lead trace to a receiving station, working 24/24 hours, where a nurse was available for reporting and interactive teleconsultation (providing informations on health status, symptoms, weight, diuresis, drug adjustment and optimization). The nurses have acquired the knolewdge base and practice experiences in the disease, were able to take some diagnostic and therapeutic decision previously arranged. The patient can call the centre when he need (teleassistance), while the team call the patient with scheduled appointment (telemonitoring). The follow-up was of 300 days. During the telephone calls, therapy was changed in 98 pts (64%): Beta-blocking (Carvedilol) in 53 pts (35%) and Ace-Inhibitors in 45 pts (29%). Carvedilol mean initial dosage was 35.9±21.5 mg and was up-titrated till 42.0±20.8 mg. In 53 pts, Carvedilol was: up-titrated in 29 (54%), reduced in 7 (13%), up-titrated and then reduced or vice versa in 14 (27%) and stopped taking the medication in 3 (6%). These modifications were executed with 141 telephone call (2.6±1.9/patient). The one-lead ECG recording had have an important role for these modifications: the trace was similar as the basal one in 37 calls (70%) and different in 16 (30%)(sinus bradycardia in 4, first grade A-V Block in 3, sinus tachycardia in 4, PVB in 5). In conclusion, a telemedicine service permits to follow the CHF patients:- up-titrating Beta-blockers, as tolerated by the patient, in a safe way with the control of the one-lead ECG transferred by the telephone;- permitting the patient to call the healthcare team if he experiences any adverse effects; and permitting the health care team to stop the treatment if any adverse effects or rhythm alterations were present.

P639 Cardiac event recorder yeld more diagnoses than 24-hour Holter monitoring in patients with palpitations

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Palpitation is a common symptom than sometimes results from a substantial cardiac arrhythmia. A 24- hour Holter monitoring is usually used, but the yield of this instrument is low in patients whose symptoms occur infrequently. The aim of this study was to compare the diagnostic yield of transtelephonic event recorder (ER) with those of Holter monitoring in patients (pts) with intermittent palpitations.
200 pts were randomly assigned to receive an event recorder (ER) or 24-hour Holter monitoring. ER were used for 7 days or until two recordings were obtained while symptoms occurred. The main end point was an electrocardiogram recorded during symptoms. The pts with palpitation recorded the one lead ECG trace and send it to the telemedicine call center were a nurse compared the trace with basal one, checked the pt's symptoms, and decided to end the telephone call or, in presence of major arrhythmia to request the cardiologist's intervention.
Results (table 1)

results

	EVENT RECORDER	HOLTER	p
Patients	100	100	
Sex (M/F)	28/72	20/80	ns
Age (yrs)	57.7 ± 18.1	53.1 ± 16.4	ns
Cardiac disease NO/YES	57/43	63/37	ns
Asymptomatics pts	25	51	0.000
Symptomatics pts	75	49	0.000
Tachyarrhythmia (AF, PSVT, nsTV)	9 (12%)	3 (6%)	ns
Supraventricular or ventricular beats	20 (27%)	11 (22%)	ns
No arrhythmia	46 (61%)	35 (71%)	ns

In conclusion, more patients and in real time reached a clear diagnosis when use ER in comparison with Holter for palpitation. For this reason Event Recorder should replace Holter monitoring for this purpose whenever possible.

P640 The TeleMarker™ – A new trans-telephonic blood testing device. Evaluation of feasibility in cardiac patients

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Background: Improved diagnostic accuracy, in the pre-hospital setting, in patients with chest pain would enhance identification of individuals with acute coronary syndromes, conserve resources by appropriate triage when clinical evidence of infarction is incomplete, and improve patients' motivation to seek medical assistance by obviating unessential hospital admissions. **Objectives:** To assess the efficacy, safety and patient acceptability of the TeleMarker™, a compact, personal blood-testing device, for determining the presence of cardiac markers in whole blood. **Methods:** SHL's (a telemedical facility currently seving over 62,000 subscribers) cooperative subscribers who were in stable clinical and hemodynamic condition, independent and with no sensoric or motoric disabilities or being treated with anticoagulants were included. The TeleMarker™ is a hermetically sealed plastic device into which the patient inserts a finger that gets stabbed by a standard lancet at the push of a button. A vacuum created by the device is released after 4 drops of blood (∼190 mic/ml) have dripped into a disposable chemical stat-kit or after 3 minutes had passed. Fifteen minutes later, the test results are photographed by a micro-camera contained within the device and automatically transmitted telephonically via SHL's Home Care Center interphase device to its Monitor Center for review and decision-making. The patients learned to perform the test independently at home by a physician and technician who stood by: the physician then examined the finger-prick for wound condition and, together with the patients, filled out a questionnaire on the testing procedure and acceptability. **Results:** 80 cardiac patients (mean age 66 years, range 33 to 91) were examined. All stabs ceased bleeding within 2 minutes. A sufficient amount of blood (3 to 4 drops) was collected in 96% of the patients. Test time (mean±SD) was 102±60 seconds; 1.3±0.6 (range 1 to 3) attempts were needed, resulting in a 2±2 subjective pain score (0=none, 6=painful). **Conclusion:** The TeleMarker™ was safe and efficacious for independent use by cardiac patients.

MISCELLANEOUS COMPUTER APPLICATIONS

P641 Acute right atrial strain

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P-Pulmonale (P waves $>$ 2.5 in leads II, III, aVF) occurs under a variety of circumstances, including chronic obstructive pulmonary disease. Emergency room (ER) electrocardiograms (ECGs) in patients with acute exacerbations of COPD had suggested that P-Pulmonale tends to resolve subsequent to acute treatment. RA "strain" is defined as a response to RA stress (probably transient pressure rise and/or acute RA enlargement) in COPD patients. Since P pulmonale occurs in a small minority of COPD patients, we investigated dynamic changes in size and mean vector (axis) of all frontal plane P waves in the ER vs. the immediate subsequent ward ECG in patients with acute exacerbations of COPD. **Aim:** To evaluate right atrial (RA) strain as reflected by changes in P wave amplitude and vector in patients with chronic obstructive pulmonary disease (COPD) immediately before and immediately after beginning treatment of exacerbations. **Methods:** We prospectively compared P wave amplitude in the ER with the first in-patient ECG in 50 consecutive patients with acute exacerbations of COPD and in 20 consecutive non-pulmonary control patients, analysing only ECGs showing sinus rhythm and in which P waves were clearly recorded. Despite using a calibrated magnifying graticule, it was difficult to interpret a dynamic change if the initial ER ECG had P wave amplitude smaller than 1.5 mm, in leads II and aVF. We selected lead II because it usually has the largest frontal plane P waves and also aVF to reflect the relative verticality of the mean P vector (axis). We performed a matched pair analysis to compare the equality of means. **Results:** Of the COPD patients, only 7 patients (14%) had classical P Pulmonale on the ER ECG. 48 out of 50 consecutive patients (96%) demonstrated a decrease in P wave amplitude between ER and subsequent ward ECGs. 2 patients showed no change. The mean differences of P wave amplitude between ER and ward ECGs in lead II was 0.78 mm and that in lead aVF was 0.8 mm. The difference of the mean P-axis between ER and ward ECGs was -5.24 degrees. $P < 0.0001$ for all three measurements. There was no P-wave amplitude change in the control group between ER and ward ECGs. **Conclusions:** P-wave amplitude in COPD patients decreases once an acute exacerbation subsides. Thus, P wave amplitude and vector are dynamic and could reflect reduced RA strain. We question the traditional (1935) absolute cutoff of 2.5 mm for P Pulmonale as of limited value due to insensitivity, hence inappropriate for what this investigation demonstrates to be a continuous variable.

P642 QU and not QT measures repolarisation duration due to a TU continuum

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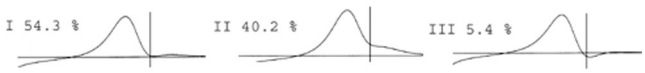
QT prolongation is a harbinger of ventricular rhythm problems and QT dispersion as a sign of myocardial impairment. But the measurement of QT duration is beset by problems. Crucial to its measurement is the methodology and the definition of the end of T wave. We present a model of the repolarisation of the ventricular myocardium, based on known physiological data and established physical principles, from which the course of the repolarisation potentials in an outside point P is calculated. The model shows that the U wave is generated by the last part of the myocardial repolarisation and that T and U together are the resultant of the total repolarisation process: they form a TU continuum and only at the end of the U wave is repolarisation finished. A variety of combinations of T and U amplitudes and durations occur, giving rise to various morphological patterns of the TU wave in the 12-lead ECG. We have studied this in a set of 184 ECGs from healthy volunteers, part of a population study. The ECGs were 1 minute recordings sampled at 500 samples/second. T and U were measured with a special technique, which uses the coherence of small segments in the ECG waveform for signal averaging around the presumed T offset. All recordings showed the repolarisation process to extend beyond the classical end-of-T fiducial point. The TU patterns could be divided into 3 categories (figure), with a prevalence of 54.3%, 40.2% and 5.4%. This reflects the findings of the model that (1) the T and U form a single complex, and (2) measuring the end of the T wave is artificial and leads to ambiguous results.



These findings also show that the concept of QT dispersion is meaningless, and suggest that new parameters to characterize the repolarisation process in the myocardium must be defined.

P643 Empirical simulation model of intravascular ultrasound

O. Rodriguez Leor[1], E. Fernandez-Nofrerias[1], J. Mauri[1], C. Garcia Garcia[1], R. Villuendas[1], V. Valle Tudela[1], M. Rosales[2], P. Radeva[2]. *[1]HU Germans Trias i Pujol, Cardiology, Badalona, Spain; [2]Universitat Autonoma de Barcelona, Computer Vision Center, Bellaterra, Spain*

Extraction of quantitative information through intravascular ultrasound (IVUS) images is a very important goal for the diagnostic and the therapy in atherosclerotic vessels. At the moment this kind of analysis is made without considering the ultrasonic signal principles for the IVUS image generation.
Purpose: We propose a physics-based model for simulating IVUS images, that allows studying the significance and the relation between different tissues, the ultrasound waves and the IVUS image appearance.
Methods: The model uses the transmission and reception principles of ultrasound (US) while crossing the simulated radial artery (fig. 1). The US rotational transducer is located in the centre. It can be the emission signal (P1) and the reflecting signal (P2). US waves are emitted from a rotational trasducer located in the artery centre. We consider that the propagation is radially collimated through the blood and the arterial structure. The reflecting waves are received by the transducer. Subsequently the echo's amplitudes are converted to grey scale for the image generation.
Results: Fig. 2 shows the image generated with a standard IVUS 30MHz equipment, and fig. 3 is a simulated image at the same frequency. For this simulation we have used the cross section average of the blood (120mm^2), tissue (400mm^2), the calcified plaque (550mm^2) and the sound propagation speed (340 m/s) published in the literature.

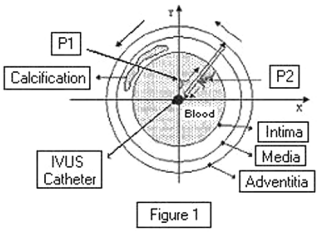


Figure 1

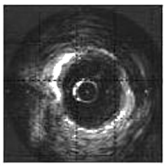


Figure 2

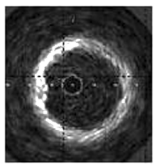


Figure 3

Conclusions: Our physics-based model based on the ultrasonic signal principles allows to study the physics parameters for the IVUS image generation and can be a useful tool for the cardiac dynamics analysis, the elastics properties of the vessels as well as the behavior and the interaction between blood flow and vessel structures.

P644 Reconstruction of a spatio-temporal model of the intima layer from intravascular ultrasound sequences

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Detection of arterial lumen in IntraVascular UltraSound (IVUS) for segmentation demands manual intervention (a tedious and time consuming task that requires experienced observers) or ECG-gating (not available in all centres).
Purpose: To introduce a parametric algorithm that detects the arterial luminal border in in vivo sequences based on a spatio-temporal analysis of the sequence's intensity changes.
Method: Under the assumption that blood presents a chaotic movement compared to the periodic dynamics of the structures of the artery, a measure of the sequence's is computed, calculated as the correlation between the gradient of the sequence and a robust mean based on the image structure tensor. An inverse function of this measure is used as a stopping term in an anisotropic diffusion process that removes irregularities of the level surfaces. To achieve a proper interpolation of the lumen at the side branches and in the presence of artefacts we use a snake parameterised by a cubic B-spline surface to obtain a compact representation of the final model.
Results: Eigth sequences of 500 frames obtained in vivo have been analysed. We compared our automated detected border with a border manually traced by 3 experts, and we made measurements on luminal areas and positioning error between automated segmented and observer defined borders. Statistics show a good correlation between areas (a regression line equal to y=0.9165x-0.3789, with a correlation rate r=0.8452), as well as an average distance of 0.1.94±0.0366 mm between automated and user defined luminal borders. Points of maximum error, in the range of 0.416±0.196 mm, are isolated points difficult to locate even for an expertise observer.
Conclusions: Our three-dimensional analysis of IVUS has proved to succeed in adapting to the intima layer in vivo pullbacks whatever the geometry of the vessel. By tracking the intima in non-ECG-gated sequences we reconstruct a model that recovers not only the morphology of the vessel but also its deformations. Such a model allows a later study of both clinical measurements (severity and location of the coronary lesion, luminal area) and estimation of dynamic parameters (artery's elasticity and cardiac dynamics).

P645 An empiric model for three-dimensional reconstruction of coronary vessels from X-ray angiography

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Three-dimensional (3D) reconstruction of the coronary vessels' structure has many applications as the fusion of data obtained by intravascular ultrasound (IVUS) for the study of the morphology and the real length of coronary lesions.
Purpose: Develop a model of image acquisition and software which allows high precision on the 3D reconstruction of vessel's structure from angiographic images.
Method: First we have determined the distortion introduced by the image intensifier by fixing a calibration grid on the intensifier's screen and acquiring it for different values of rotation and angulation, chosen at random. Once the model of distortion has been estimated, we can correct the distortion for any projection.
Second we have estimated the parameters of the movement of the C-arm and the image acquisition model by acquiring a calibration grid on the table at different values of rotation and angulation.
Then we have estimated the precision of our model by acquiring the grid from different projections and comparing the positions of the intersections of the grid on the image with the one predicted by our estimation model.
Finally, we have acquired 8 different views of a phantom which simulates a coronary artery of 14 mm length; from 2 of these views our software generates a 3D curve of 12.97 mm. In order to validate the precision of this 3D reconstruction, we have projected the curve on the other 6 views.
Results: When comparing the intersections of the grid obtained from different views with the ones predicted by our model, we obtain an error with standard deviation (SD) of 0.86 pixel and maximum of 5.4 pixel. Without applying our model, the SD is of 6.81 pixel and the maximum error is of 33 pixel.
When we project the 3D curve generated by our software on the other 6 views, we obtain a maximum error of 0.3 pixel.
Conclusions: The proposed model allows to obtain the 3D reconstruction of a coronary artery from two views with a high precision, and thus to measure the exact length of the vessel and its different segments.

P646 Mayers waves are shifted toward lower frequencies in patients with cardiovascular diseases – simulation study based on DeBoers model

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Purpose: In healthy subjects, spontaneous baroreflex oscillations of heart rate and blood pressure can be typically found at frequency of 0.1 Hz (Mayer's waves) as a resonance of sympathetic and parasympathetic interaction. Shift of these waves to lower frequencies has been observed in patients with hypertension, diabetes mellitus, and ischemic heart disease. Mechanism responsible for this phenomenon has not yet been described.
Methods: DeBoer's computer model of short-term beat-to-beat hemodynamic fluctuations was used to study the origin of the frequency shift of Mayer's waves. Frequency-domain characteristics of the model were derived analytically. Parameters of the model (sympathetic and parasympathetic modulation, delay of beta- and alpha-sympathetic baroreflex response, peripheral vascular resistance, systolic and diastolic blood pressure) were independently tested to disclose the association of their changes with the shift of Mayer's waves.
Results: Leftward shift of Mayer's waves was predominantly attributed to the prolonged latency of sympathetic component of baroreflex loop. Both longer beta- and alpha-sympathetic delay had similar impact on the frequency of Mayer's waves and their effect was synergic. Other variables of the model failed to have any significant effect.
Conclusion: Sympathovagal balance has negligible effect on the frequency of Mayer's waves. Their shift toward lower frequencies in patients with cardiovascular diseases can be fully explained by more lagging response of sympathetic arm of autonomic nervous system. This finding is compatible with substantial discriminative power of the frequency of Mayer's waves, which is independent of traditional frequency-domain characteristics of heart rate variability.

P647 Interoperable smart-card based system applied in cardiology

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An integrated informatic system, BAGDACARD-CARDIOCARD, has been developed in the Cardiology Department of Bagdasar-Arseni Hospital in order to improve medical data exchange between different health care providers and the medical insurance system. The system was designed for emergency purposes and was enhanced by the strong security features of the smart-card technology.
Aim: In this pilot phase, the aim of the study was to test the interoperability of the system in real conditions.
Methods: Complete medical data concerning a patient were stored in an electronic medical record. BAGDACARD is the database designed for the management and statistical analysis of these records. This database was stored on a server at Bagdasar-Arseni Hospital.CARDIOCARD is a smart-card issued by the Cardiology Department, containing all the information considered to be useful in medical emergencies. Each card has 4 fields: (1)personal and general medical data (blood group, alergies, organ donor etc), (2)medical insurance details, (3)general practitioner's field, (4)hospital physician's field (last 6 hospital admissions available via BAGDACARD). Each field has dedicated read-write permissions. The interface is user-friendly and is adapted to each different health care provider necessities. The data could be recorded on the smart-card only with the full, informed patient consent, and presume general read-only permission. Only authorized physicians could modify or add data in CARDIOCARD (write permission). For security purposes, doctor's smart-card and Personal Identification Number (PIN) and patient's smart-card and PIN code (certifiing his consent) are required concomitently and only the smart-cards issued in the department are accepted by the server.
Results: The acceptance of the system was general among doctors and patients. There were no major problems during interogation of data. Less than 5% handling problems occurred, especially when patients forgot there PIN code number; after 3 wrong PIN numbers consecutively introduced, the card is blocked. 96% of the patients involved, consider BAGDACARD-CARDIOCARD system useful, but only 36% keep the smart-card always with them.
Conclusions: BAGDACARD-CARDIOCARD was perceived as an easy to use informatic system. The main problem was the lack of dedicated hardware-a large number of smart-card reader devices. Health Insurance provider dedicated field, with the possibility of statistic data report, make the system attractive for an extended use. A better education of the patients using CARDIOCARD seems to be necessary.

P648 New baroreflex sensitivity assessment technique dramatically improves clinical applicability in congestive heart failure

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Purpose: Baroreflex sensitivity (BRS) is a prominent nonivasive prognostic parameter in chronic heart failure (CHF) patients. We recently showed that the usual analysis strategy to discard measurements with a blood-pressure-to-heart rate coherence <0.50 can better be replaced by the calculation of individual BRS confidence intervals. This allows for weighted statistical analysis of all patients instead of unweighted analysis of only part of the patients. The following study was meant to test the feasibility of this technique for BRS trend analysis.
Methods: In the experimental CHF rehabilitation programme that we are currently testing, we wanted to detect a possible BRS increase in the first days. We measured BRS in a group of 24 CHF patients (17 male, 7 female, mean$\pm$SD age 62.0 $\pm$ 11.1 yr, NYHA-class 2.2 $\pm$ 0.7) at day 0 (control) and 2 days later (effect) by recording, after 30 min of supine rest, continuous noninvasive blood pressure (Finapres) and ECG during 10 minutes of 15/min metronome respiration. All patients had rehearsed this measurement protocol one week before. BRS was computed offline, by applying the transfer function method in the 0.05-0.15 Hz band to the longest arrhythmia-free episode of each recording. This analysis included computation of the coherence and of the confidence interval.
Results: According to the coherence-based strategy only 5/24 (21%) patients had valid control-BRS values and 10/24 (42%) had valid effect-BRS values. Paired BRS comparison (control-effect) was only possible in 3/24 (12%) of the patients. No meaningful statistical analysis could be made. Contrastingly, paired weighted statistics with the new confidence interval strategy revealed a significant (P=0.004) upward trend in BRS (1.93 $\pm$ 1.83 vs 3.20 $\pm$ 2.83 ms/mmHg, a 66% increase).
Conclusions: Our study demonstrates that the coherence-based strategy excludes greater part of the study group from the analysis (CHF patients tend to have low coherences). Contrastingly, the new confidence-interval based strategy demonstrated a very significant upward BRS trend after 2 days. This methodological improvement hence contributes greatly to the clinical applicability of baroreflex sensitivity assessment.

P649 Structured reporting for cardiology using templates based on recommendations from national societies

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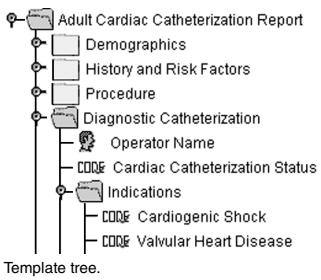
A general purpose structured reporting system has been implemented and is available to provide electronic reporting in a hospital environment. This system uses templates as the basis for the electronic report. Two cardiology-specific templates were developed to support the primary users in the department.
A DICOM working group has developed a draft template based on recommendations from the American College of Cardiology (ACC) for adult cardiac catheterization procedures. The American Society of Echocardiography (ESC) has developed guidelines for the contents of a structured report for adult transthoracic echocardiography procedures. These drafts and guidelines were used as the basis of two templates.
The templates are built from these elements as a tree structure, matching the recommendations (see Template Tree Figure). A site may optionally add, modify, or remove elements to support their reporting requirements.
Element values can be defined to be the result of a calculation based on the value of one or more other elements in the report. Conditional logic can be used to limit the set of values an element is allowed to have (e.g. if heart rate greater than 100, then remove 'bradycardia' from set of values for arrhythmia), and to hide it in the report view. It should be noted that the recommendations sometimes do not always make this logic explicit, and persons familiar with a procedure type have been questioned to infer this for a specific template.
The result of this work was the implementation of two templates for cardiology structured reporting based on recommendations from national societies. Cardiologists using these templates will generate structured reports containing the data deemed important by their peers.



Template tree.

YOUNG INVESTIGATORS AWARD SESSION – POPULATION SCIENCES

651 Brain natriuretic peptide usefulness for diagnosing heart failure in elderly patients (BUD study): about 300 patients over 75

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Background: Because polypathology is the rule in the elderly, differenciating heart failure from pulmonary disease is often difficult on clinical grounds alone over 75. Therefore BNP dosage may be particulary useful in this setting. However, aging of the heart with reduced compliance may increase plasma levels of BNP in the absence of CHF and therefore lower its diagnostic value.
Objective: Evaluate BNP value for dyspnea in elderly subjects
Methods: 300 consecutive patients older than 75 consulting at the emergency department of three hospitals for acute dyspnea were included. Blood was withdrawn for delayed BNP dosage (Triage) at admission before any treatment and patients were managed as usual, BNP plasma level. Reference diagnosis was adjudicated by 2 independent cardiologists using all available information at discharge.
Results: Mean age was 82 $\pm$5, mean LVEF was 45.5 $\pm$15 (51% had an LVEF $>$ 50%), 45% were male and 54% suffering from pre-existent hypertension. Dyspnea was related to heart failure 58% of the patients according to reference diagnosis. 39% of the patients suffering form heart failure previous to the study, 12% were diabetics and 29% had an ischemic cardiopathy. Mean BNP at admission was 714$\pm$ 92 pg/ml. The area under the receiver operating characteristic curve was 0.81. A BNP plasma value of 100 pg/ml had a sensitivity of 92% for identifying heart failure patients i.e. BNP level below 100 pg/ml was associated with a 9% risk of heart failure.
Conclusion: Low BNP level allows confident ruling out of heart failure in elderly patients as it was demonstrated in younger populations. This may be particularly useful in this population where poly-pathology is frequent.

652 Blood pressure, C-reactive protein, and risk of future cardiovascular events: a prospective study among 15,215 women

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Purpose: Accumulating data suggest a link between blood pressure and vascular inflammation. We sought to evaluate the relationship between blood pressure, C-reactive protein (CRP) and future cardiovascular events.
Methods: 15,215 women without overt cardiovascular disease at baseline were followed prospectively over a 8.1 year period for the occurrence of first cardiovascular events, defined as death due to cardiovascular causes, nonfatal myocardial infarction, nonfatal ischemic stroke, or coronary revascularization. Baseline CRP levels and blood pressure were determined. Blood pressure was categorized according to Framingham categories ($<$120/75, 120-129/75-84, 130-139/85-89, 140-159/90-94, and $\geq$160/95 mmHg).
Results: In cross-sectional analyses at baseline, median levels of CRP for those women with blood pressure $<$120/75, 120-129/75-84, 130-139/85-89, 140-159/90-94, $\geq$160/95 mmHg were 0.96, 1.42, 2.20, 2.82, and 3.34 mg/L, respectively (p for trend $<$ 0.0001). In all models, increasing Framingham categories of blood pressure were highly significant predictors of CRP levels (risk factor-adjusted geometric mean levels of CRP = 1.33 mg/L for those women with blood pressure $<$120/75 mmHg vs 1.84 mg/dl for those women with blood pressure $\geq$160/95 mmHg; p$<$0.0001). In prospective analyses, both elevated CRP levels ($\geq$3mg/L) and increasing Framingham categories of blood pressure were independent determinants of future cardiovascular events, and CRP had incremental prognostic value at all levels of blood pressure. The adjusted relative risk for those women with blood pressure $\geq$160/95 mmHg and CRP levels $\geq$3mg/L was over 8 fold greater than for those with blood pressure $<$120/75 and CRP levels $<$3mg/L (hazard ratio = 8.31, 95% confidence interval 4.44-15.55, p$<$0.0001). After dividing the study participants into four groups on the basis of CRP levels ($<$3 or $\geq$3 mg/L) and blood pressure levels ($<$130/85 or $\geq$130/85) the risk factor-adjusted relative risks were as follows: low CRP-low blood pressure, 1.0; high CRP-low blood pressure, 1.87 (95% confidence interval 1.25-2.80, p=0.002); low CRP-high blood pressure 2.54 (95% confidence interval 1.79-3.58, p$<$0.0001); high CRP-high blood pressure 3.27 (95% confidence interval 2.28-4.71, p$<$0.0001).
Conclusions: CRP and blood pressure are independent determinants of cardiovascular risk, and their predictive value is additive. Strategies targeted to lower blood pressure and reduce vascular inflammation may potentially provide increased clinical benefit.

653 The A1166C angiotensin II type I receptor gene polymorphism is a strong predictor of death after acute myocardial infarction

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Purpose: The A1166C polymorphism of the angiotensin II type 1 receptor (AT1R) gene, which appears to be the main receptor mediating the pleitropic vascular effects of angiotensin II in human beings, has been associated with the risk of myocardial infarction (MI), the severity of coronary vasoconstriction and the occurrence of sudden death. The question therefore arises wether the A1166C polymorphism constitutes a hereditary risk factor of survival after an acute myocardial infarction.
Methods: In a large prospective study of 970 consecutive patients with a recent myocardial infarction the A1166C polymorphism was detected using a PCR based protocol. During the follow-up period (median, 2.5 years), 75 patients died and 62 from cardiovascular causes. The prespecified primary and secondary end points considered were total mortality and cardiovascular mortality.
Results: No differences between AA, AC, and CC groups were observed with respect to baseline clinical characteristics. Beyond conventionnal risk factors like age (RR=2.77 [1.55-4.98] 95% CI; p$<$0.001), hypercholesterolemia (RR=2.07 [1.16-3.69] 95% CI; p$<$0.014) or low left ventricular ejection fraction (RR=2.64 [1.45-4.82] 95% CI; p$<$0.002), the AT1R CC genotype was also identified as a strong independent predictor of death after myocardial infarction (RR=3.19 [1.46-7.02] 95% CI; p$<$0.004). After adjustment for mortality causes, the AT1R CC genotype was confirmed to be an independent predictor of cardiovascular death after myocardial infarction (RR=2.75 [1.17-6.49] 95% CI; p$<$0.021).
Conclusions: The AT1R CC genotype is a strong independent predictor of death in post MI patients. This new finding may help to identify high risk post MI patients who may benefit from new therapeutic strategies.

654 White coat hypertension and development of sustained hypertension

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Purpose: To evaluate the development of established hypertension (EH) in patients with white coat hypertension (WCH).
Methods: At baseline 420 mild to moderate hypertensives newly diagnosed by their GP were referred for ABPM, of these 76 were WCH defined by a daytime ABP $<$ 135/90 mmHg and 344 were EH. Furthermore 146 normal controls (NT) were recruited at random from the Danish National Register, however only 92 of these had a daytime ABP $<$ 135/90 mmHg. After 10 years ambulatory blood pressure monitoring (ABPM) and office blood pressure (OBP) was repeated. In the WCH group 70 patients were still alive and in the NT group 87 of those 92 who at baseline had a daytime ABP $<$ 135/90 mmHg were still alive.
Results: 61 (87,1%) in the WCH group and 72 (82,8%) in the NT group accepted to participate in the follow-up examination. In the WCH group 33 (54,1%) had a daytime ABP $>$ 135/90 mmHg
and further 10 had a daytime ABP $<$ 135/90 mmHg but were treated with antihypertensive medication because of a daytime ABP or home BP $>$ 135/90 mmHg performed during the follow-up period, so 43 (70,5%) had developed EH. In the NT group 26 (31,1%) had a daytime ABP $>$ 135/90 mmHg and 5 had a daytime ABP $<$ 135/90 mmHg but were in antihypertensive treatment because of a hypertensive daytime ABP or home BP during follow-up, so 31 (43,1%) had developed EH. The difference between the groups were significant (p$<$0.01). Adjustment for age and gender did not change the result.
Conclusions: We conclude that to a large extent WCH is a prehypertensive state. During a 10-year follow-up period 70,5% developed EH compared to 43,1% in the NT group.

655 Carotid artery plaque burden, stiffness, and mortality risk in elderly men: a prospective, population-based cohort study

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Background and Aim: Indicators of carotid atherosclerosis may confer additional prognostic value and guide clinicians in cardiovascular risk assessment. Carotid artery morphology (plaque burden) and function (stiffness indices) as predictors of all-cause and cardiovascular mortality were prospectively evaluated in elderly men.
Subjects and Methods: In 367 independently living men (mean age±SD, 78±4 years) the cardiovascular risk profile was measured. The number of carotid plaques was assessed by B-mode ultrasound and arterial stiffness was quantified using a wall tracker system. Cox regression and ROC analysis was used for data analysis.
Results: In 84% of the cohort at least 1 plaque was seen, 61% had bilateral plaques. Stiffness indices were 1.5 to 2fold increased compared to 50-year old men. Previous myocardial infarction was prevalent in 16% of the cohort, chronic heart failure in 5%, hypertension in 24%, COPD in 14%, diabetes in 6%. During 48 months of follow-up, 70 deaths (28 cardiovascular) occurred. Total number of carotid plaques was the parameter most closely related to prognosis. Predictors of all-cause mortality in the age-adjusted Cox model were: number of plaques (hazard ratio [HR] per 1-unit increase, 1.35; 95% confidence interval [CI], 1.12 to 1.64) and history of heart failure (HR 2.59; 95% CI, 1.28 to 5.24). Predictors of cardiovascular mortality in the respective model were: number of plaques (HR, 1.18; 95% CI, 1.04 to 1.33), Young's elastic modulus (HR 1.68; 95% CI, 1.26 to 2.26), and use of diuretics (HR 3.19; 95% CI, 1.39 to 7.32). Number of plaques improved the prognostic utility in any prognosis model when added to commonly available cardiovascular risk information. In contrast, stiffness indices had no substantial additive value.
Conclusion: In elderly men, carotid artery plaque burden is a strong independent predictor of all-cause and cardiovascular mortality in the forthcoming 4 years. The additional value of carotid artery stiffness measurements in this age group appears to be limited and, if anything, confined to cardiovascular mortality risk.

YOUNG INVESTIGATORS AWARD SESSION – BASIC SCIENCES

657 The pro-angiogenic factor CYR61 is highly expressed after myocardial stress and depends on activation of protein kinase C and mitogen-activated protein kinases

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CYR61 is a secreted, extracellular matrix associated protein, which induces angiogenesis in corneal implants and ischemic hind limb model. In the present study, we investigated the expression and regulation of CYR61 in the stressed myocardium.
C57BL/6 male mice (12 weeks of age) were subjected to transient (I/R) or permanent coronary occlusion (MI). Both, I/R and MI induced a significant increase in CYR61 expression in ischemic (402, resp. 540%, $p<0.05$) and remote myocardium (226, respectively 202%, $p<0.05$) of left ventricles (LV). Whereas after MI CYR61 expression peaks 6h post MI and remains significantly increased for up to 48h, I/R causes a transient but rapid peak at 1h post I/R. CYR61 protein expression can be localized predominantly to cardiomyocytes (24h post MI; Immunohistochemistry). Similarly, transverse aortic constriction produced rapid increase (after 1 hour) in CYR61 transcripts in LV (402% of sham values $p<0.01$). Infusion of humoral factors, i.e. AngII and norepinephrine (NE), induced CYR61 expression in mice hearts. Similarly exposure of isolated neonatal rat cardiomyocytes (CM) to AngII and NE augmented CYR61 expression. To elucidate signaling pathways involved, CM were treated with phenylephrine (PE) or phorbol ester, a potent activator of protein kinase C (PKC), which both strongly induced CYR61 expression. In contrast, inhibition of PKC with chelyrethrine or PD980598, an inhibitor of MEK1/2, abolished PE and AngII mediated expression of CYR61 completely. The inhibition of p38 (SB203580) and IP3K (wortmannin) attenuated PE induced CYR61 expression moderately, while the JAK2 inhibitor AG490 had no effect.
Thus, the pro-angiogenic factor CYR61 is potently induced in the heart following ischemia and overload. Humoral factors, induced after myocardial stress, contribute to myocardial CYR61 expression in vivo and in vitro. After in vitro stimulation, CYR61 expression largely depends on activation of PKC and MAPKs. The observation that cardiomyocytes are a major source of the secreted CYR61 protein, suggests CYR61 as a part of a paracrine mechanism promoting wound healing and angiogenesis following myocardial stress.

658 Regulation of the growth arrest and DNA damage-inducible gene 45 (GADD45) by peroxisome proliferator-activated receptor gamma in vascular smooth muscle cells

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Peroxisome proliferator-activated receptor gamma (PPARg) is the molecular target for the thiazolidinediones (TZD), a class of drugs widely used as insulin-sensitizing agents for the treatment of type 2 diabetes. TZDs have been shown to induce apoptosis in a variety of mammalian cells. Recent evidence suggests that vascular smooth muscle cell (VSMC) proliferation and apoptosis may be competing processes during the formation of restenotic and atherosclerotic lesions. The precise molecular mechanisms by which TZDs induce apoptosis in VSMC, however, remains unclear. In the present study, we demonstrate that the TZDs rosiglitazone (RSG) and troglitazone (TRO) and a novel non-TZD partial PPARg agonist (nTZDpa) induce caspase-mediated apoptosis of human coronary vascular smooth muscle cells (HCSMC). The ability of the PPARg ligands to induce VSMC apoptosis correlated closely with a dose-dependent and time-dependent induction of GADD45 mRNA, a well-recognized modulator of cell cycle arrest and apoptosis (TRO 4.9 $\pm$ 0.75, RSG 3.2 $\pm$ 0.41, nTZDpa 3.4 $\pm$ 0.53 fold increase at 30 μM afer 24 h, n=3, $p<0.05$). All PPARg ligands tested markedly stimulated the transcriptional activation of the GADD 45 promoter (RSG 2.96 $\pm$ 0.33, TRO 3.9 $\pm$ 0.47, and nTZDpa 3.21 $\pm$ 0.38 fold at 30 μM after 24 h, n=3, $p<0.05$). Deletion analysis revealed that a 153 bp region between -234 and -81 bp proximal to the transcription start site was crucial for the PPARg ligand-mediated induction of the GADD45 promoter. This portion of the 5'-flanking regulatory DNA of the GADD45 gene contains an Oct-1 consensus sequence. Activity of luciferase reporter construct driven by multiple Oct-1 sites was induced by PPARg ligands (RSG 1.86 $\pm$ 0.15, TRO 2.21 $\pm$ 0.19, nTZDpa 2.16 $\pm$ 0.21 fold at 10 μM after 24 h, n=3, $p<0.05$) indicating that the Oct-1 regulatory element might be one of the essential elements involved in the activation of the GADD45 promoter by PPARg. Using adenoviral-mediated overexpression of a constitutively-active PPARg mutant and NIH3T3 fibroblasts that express no PPARg, we provide evidence that PPARg ligands induce caspase-mediated apoptosis and GADD45 expression through a receptor-dependent pathway. These findings suggest that activation of PPARg can lead to growth arrest and induction of apoptosis in vascular smooth muscle cells, at least in part, by inducing transcription of GADD45.

659 Is Skp-2 the missing link between the extracellular matrix and vascular smooth muscle cell proliferation?

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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) regulate SMC proliferation. For example, we previously demonstrated that mitogen stimulated SMCs interacting with native ECM in rat aorta do not proliferate. This is partly because of constitutively elevated levels of cyclin-dependent kinase inhibitors, including p27. These are normally downregulated in proliferating SMC by post-translational mechanisms that may involve proteosome-mediated degradation. Here we sought to further elucidate the link between the extracellular matrix and regulation of SMC proliferation.
We studied the S-phase-associated kinase protein-2 (Skp-2), an F-box protein involved in the ubiquitination and proteosome-mediated degradation of cellular proteins. Skp-2 mRNA and protein expression is significantly (5.7 fold, $p<0.0024$) lower in rat aorta compared to isolated SMCs; it is also strongly induced by serum from undetectable levels in isolated SMCs but remains undetectable in aorta. Furthermore, SMCs cultured in suspension also fail to up regulate Skp-2, which implies that interaction with the ECM regulates Skp-2 expression. Further experiments implicated the protein kinase B/Akt pathway, integrin-linked kinase and small GTPase, RhoA, in upregulation of Skp-2 (results not shown). To confirm the essential role of Skp-2 in SMC proliferation, we constructed a recombinant adenovirus expressing a dominant negative F-box deleted mutant form, Delta F-Skp-2. Expression of Delta F-Skp-2 significantly inhibited proliferation by cell numbers (55%, $p<0.0057$) and ^{3}H-thymidine incorporation (31%, $p<0.0009$). Taken together, this data demonstrates that Skp-2 is essential and participates in the coordinate regulation of SMC proliferation by mitogens and the ECM.

660 Altered phosphorylation status of phopholamban, PLB, and its contribution to the negative $[Ca^{2+}]_i$-frequency relationship in the MLP−/− mouse with heart failure

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Mice lacking muscle LIM protein (MLP-/-) develop dilated cardiomyopathy and reproduce many clinical signs of human heart failure. We examined $[Ca^{2+}]_i$ handling and the mechanisms underlying the frequency dependence of $[Ca^{2+}]_i$ transients in single MLP-/- ventricular myocytes vs. wild-type (WT) during whole-cell voltage-clamp. At 1 Hz, the amplitude of the $[Ca^{2+}]_i$ transients was not different between MLP-/- and WT, but the rate of Ca^{2+} decline, Tau, was faster in MLP-/- (81±9 ms, n=11, vs. 174±30 ms in WT, n=20, $P<0.05$). The protein levels of the sarcoplasmic reticulum Ca^{2+}-ATPase, SERCA, and of phospholamban, PLB, were not increased in MLP-/- compared to WT. The density of the Na/Ca exchange current was unchanged. However, the basal phosphorylation status of PLB was markedly altered in MLP-/-. The PKA-dependent phosphorylation at the Ser16 site of PLB was 233±4% of average WT levels, and the CaMKII-dependent phosphorylation at Thr17 was increased to 289±9% (nhearts=8, $P<0.05$). Increasing the frequency of stimulation resulted in a modest increase of the $[Ca^{2+}]_i$ transient amplitude in WT (n=7), whereas in MLP-/-, the amplitude decreased (n=9), resulting in a negative $[Ca^{2+}]_i$-frequency relation. This was related to a lack of increase in the Ca^{2+} content of the sarcoplasmic reticulum in the MLP-/-. The frequency-dependent acceleration of the rate of $[Ca^{2+}]_i$ decline, observed in WT, was absent in MLP-/-: Tau of $[Ca^{2+}]_i$ decline increased from 81±9 ms at 1 Hz to 94±16 ms at 4 Hz, whereas in WT it significantly decreased from 174±30 ms at 1 Hz to 146±19ms at 4 Hz in WT ($P<0.05$). In conclusion, in MLP-/- sarcoplasmic reticulum Ca^{2+} uptake appears to be increased at baseline, due to increased phosphorylation of PLB at both PKA and CaMKII-dependent sites. This may limit the required increase of sarcoplasmic reticulum Ca^{2+} uptake at the higher stimulation frequencies, and contribute to the negative $[Ca^{2+}]_i$-frequency relation in MLP-/-. These novel findings imply that an elevated basal phosphorylation status of PLB can be an important mechanism limiting contractile function at higher heart rates in heart failure.

661 Matrix metalloproteinases-9 and -12 have opposite effects on atherosclerotic plaque stability

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Matrix metalloproteinases (MMPs) are thought to be involved in the destabilization and rupture of atherosclerotic lesions. We are testing this hypothesis in apolipoprotein E (apoE) knockout mice that have been crossed with various MMP knockouts and fed a high-fat diet for 8 weeks. The present study focuses on apoE/MMP-9 (gelatinase B) or apoE/MMP-12 (macrophage metalloelastase) double knockouts. Plaques in the proximal 150 μm of the brachiocephalic artery were 57% smaller (54181±8358μm v 126026±12161μm; $p<0.0001$) in apoE/MMP-12 double knockouts (n=27) than in age-matched, strain-matched apoE knockout controls (n=24). In marked contrast, plaques were 110% larger (87896±13693μm v 41288±7915μm; p=0.005) in apoE/MMP-9 double knockouts (n=26) than in controls (n=24). The frequency of silent plaque rupture (seen as buried fibrous layers within the plaque) was 64% lower in apoE/MMP-12 double knockouts than in controls (0.44±0.11 v 1.21±0.20; p=0.01), but very surprisingly was 93% higher in apoE/MMP-9 double knockouts than in controls (0.81±0.12 v 0.42±0.12; $p<0.05$). There was no significant difference in the percentage of elastin or lipid in lesions from double knockout mice and their wild-type counterparts ($p>0.05$). These data indicate that MMP-12 plays an essential role in plaque growth and destabilization, but MMP-9 appears to have a protective role: it limits plaque growth and promotes plaque stability. This challenges the concept that MMPs simply degrade matrix and thus destabilise plaques, and suggest instead that different members of the MMP family have differing effects on plaque stability. Notwithstanding this, the present data suggest that inhibition of MMP-12 may be an attractive target for prevention of atherosclerotic plaque rupture.

YOUNG INVESTIGATORS AWARD SESSION – THROMBOSIS

663 Effects of a novel platelet selective NO donor, aspirin + clopidogrel and combined therapy in inhibiting flow and lesion-dependent thrombosis

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Background: Recent evidence shows that the combination of Aspirin + Clopidogrel seems an appropriate treatment for the prevention of acute coronary thrombosis in patients with cardiovascular disease. However, novel approaches such as the use of platelet selective NO donors may also provide appropriate protection against thrombosis.
Objective: To evaluate whether a novel platelet selective NO-donor (LA816) can provide protection against thrombosis triggered by severely damaged vessel wall when administered alone or in combination with the reference treatment of Aspirin+Clopidogrel.
Methods: Thrombogenicity was measured in the porcine experimental model and assessed as platelet-thrombus formation in the ex vivo Badimon perfusion chamber. Pigs were randomly assigned to one of the following groups: I) placebo; II) placebo + LA816; III) aspirin + clopidrogel (oral, 10 mg kg-1 of each, for three days); and IV) aspirin + clopidrogel (oral, 10 mg kg-1 of each, for three days) + LA 816. Animals were anesthetized, heparinized, catheterized and a perfusion chamber was placed in an extracorporeal carotid artery-jugular vein shunt. After baseline control perfusions, both groups of animals with LA816 treatment (groups II and IV) received the iv-infusion of LA816 (6.6 nmols kg-1 min-1 at an infusion rate of 1.25 ml min-1) during 2 hours. Blood pressure, and heart rate were also evaluated.
Results: At high and low shear rates, both LA816 (group II) and Aspirin/Clopidogrel (group III) significantly inhibited platelet deposition. In both cases a 40% inhibition from placebo controls (group I) was achieved by treatment ($P<0.05$). Combined treatment of oral Aspirin+/Clopidogrel and iv LA816 (group IV) produced a significant further reduction in platelet deposition (20% additional inhibition; and 60% from placebo-controls; $P<0.0001$). The iv LA816 treatment (groups II and IV) did not modify systemic blood pressure nor heart rate in the treated animals.
Conclusion: Acute treatment with LA816 inhibits flow mediated thrombosis triggered by severely damaged vessel wall. Interestingly, without modifying blood pressure or heart rate, acute NO donation with LA 816 provides additional benefits in platelet passivation and inhibition of thrombosis to the combinated blockage of COX and Py1,2 with three days treatment with aspirin and clopidrogel.
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664 Increased platelet reactivity in healthy young individuals with a two-generational family history of premature myocardial infarction

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Purpose: While plaque fissuring provides the immediate template for coronary occlusion, the extent of the thrombotic reaction and especially the reaction of platelets to this stimulus may be an important determinant of the clinical outcome. Although studies have shown increased platelet reactivity in subjects with myocardial infarction (MI), it is unclear whether some individuals have an inherent tendency to increased platelet reactivity, which increases their risk of MI. Such a tendency, if inherited, may also partly explain the increased familial risk of MI. The aim of this study, therefore, was to compare platelet function of young healthy individuals (cases (CA), n = 24, 26.10 (6.1) yrs) with a two-generational family history of premature MI (defined as an MI < 50 years in a parent and < 65 years in the corresponding grandparent), with age and smoking matched subjects with no family history of coronary disease (controls, (CT), n=24, 27.08 (6.4) yrs). We also studied whether platelet function in cases correlated with their parent who had had an MI.
Methods: Whole blood flow cytometry was used to measure fibrinogen binding and P-selectin expression in response to stimulation with ADP, thrombin receptor agonist peptide (TRAP) and collagen related peptide (CRP) all at 1 x 10-6 M, and to measure the percentage of monocyte-platelet aggregates (MPAs) in blood samples incubated at 37°C for 4 hours with lipopolysaccharide (LPS 200ng/ml).
Results: There was no significant difference in basal fibrinogen binding, P-selectin expression or percentage of MPAs between CA and CT. However in response to stimulation with ADP, TRAP and CRP, both fibrinogen binding (ADP: CA 67.6±2.5, CT 57.2±2.8, p =0.008; TRAP: CA 78.4±2.2, CT 66.6±3.4, p =0.007; CRP: CA 87.3±1.7, CT 80.4±1.7, p = 0.04) and P-selectin expression (ADP: CA 34.2±2.0, CT 28.0±1.7, p =0.021; TRAP: CA 75.4±1.7, CT 68.9±2.7, p =0.047; CRP: CA 84.7±1.4, CT 77.1±3.3, p = 0.04) were significantly higher in cases compared to controls The percentage of MPAs following LPS stimulation was also higher in cases (22.8±11.2±15.7±4.2 p=0.006). Fibrinogen binding in response to both ADP (r2 = 0.24, p = 0.02) and TRAP (r2 = 0.0.45, p = 0.001) correlated between children and their affected parent.
Conclusions: Healthy young individuals with a strong family history of premature MI have significantly more reactive platelets than matched controls. The results suggest a possible genetic tendency to a prothrombotic state in such individuals, which may partly explain their increased risk.

665 Increased soluble adhesion molecules in patients with slow coronary flow

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Background: The coronary slow flow phenomenon is an angiographic phenomenon characterized by delayed opacification of vessels in the absence of any evidence of obstructive epicardial coronary disease. It is believed to represent coronary microvascular dysfunction. It is well established that endothelium plays an important role in the control of coronary blood flow by regulating coronary vascular resistance. Previously, endothelial activation and inflammation have been reported to be important precursors to atherosclerosis initiation and progression. In the present study, we aimed to evaluate soluble adhesion molecules in patients with slow coronary flow.
Methods: Study population included 17 patients with angiographically proven normal coronary arteries and slow coronary flow in all three coronary vessels (group I, 11 male, 6 female, mean age=48±9 years), and 20 patients with angiographically proven normal coronary arteries without associated slow coronary flow (group II, 11 male, 9 female, mean age=50±8 years). Coronary flow rates of all subjects were documented by Thrombolysis In Myocardial Infarction frame count (TIMI frame count). TIMI frame count method is a simple, reproducible, objective and quantitative index of coronary flow velocity. TIMI frame count was determined for each major coronary artery in each patient. All patients in group I had TIMI frame counts greater than two standart deviation above those of control subjects (group II) and therefore, were accepted as exhibiting slow coronary flow. Serum levels of ICAM-1, VCAM-1, and E-selectin were measured in all patients and control subjects using commercially available ELISA kits (Bender Med Systems, Vienna, Austria).
Results: There was no statistically significant difference between two groups in respect to age, gender, hypertension, diabetes mellitus and cigarette smoking ($p>0.05$). Serum ICAM-1, VCAM-1, and E-selectin levels of group I patients were found to be significantly higher than those of group II patients (ICAM-1: 545±198 ng/ml vs 242±113 ng/ml respectively, $p<0.001$, VCAM-1: 2040±634 ng/ml vs 918±336 ng/ml respectively, $p<0.001$, E-selectin: 67±9 ng/ml vs 52±8 ng/ml respectively, $p<0.01$).
Conclusion: Increased levels of soluble adhesion molecules in patients with slow coronary flow may be an indicator of endothelial activation and inflammation and is likely to be in the causal pathway leading to slow coronary flow.

666 Both ticlopidine and clopidogrel prevent acute phase elevation of von Willebrand factor in non-ST-elevation acute coronary syndromes

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The rise of von Willebrand factor (vWF) is a predictor of unfavorable outcome in non-ST-elevation acute coronary syndrome (NSTEACS). Both clopidogrel (CL) and ticlopidine (TIC) have been shown to reduce the risk of new ischemic events in patients with NSTEACS and CL has become a part of standard treatment. However effects of these mainly antiplatelet agents on acute changes of vWF in NSTEACS have not been elucidated.
Methods: Effects of TIC and CL were investigated in 2 subsequent open randomized studies in aspirin treated pts admitted within 48 hours from last rest pain onset. Patients included into study of TIC (n=19, 500 mg BID for two days loading dose and 250 mg BID day for subsequent 5 days) vs control (no TIC, n=18) received unfractionated heparin (UFH) infusion for at least 48 hours from admission. Patients included into study of CL (n=10, 300 mg loading dose and 75 mg/day for subsequent 6 days) vs control (no CL, n=9) received enoxaparin (ENOX) also for 48 hours or more. Venous blood samples in both studies were obtained at baseline, on days 1,3,7 and 14 (7 days after thienopyridines discontinuation).

Results: vWF %; M±SD, t-test comparison

	TIC (+UFH)	Control (+UFH)	p	CL (+ENOX)	Control (+ENOX)	p
Baseline	162±20	165±32	NS	158±39	165±30	NS
Day 1	163±35	170±41	NS	165±41	181±24*	NS
Day 3	163±27	186±33**	<0.05	152±38	185±20*	<0.05
Day 7	155±20	168±24	NS	141±30*	166±19	<0.05
Day 14	144±22**	173±27	<0.01	145±30	163±22	NS

*p<0.05 and **p<0.01 from group baseline.

Conclusion: TIC and CL used in loading dose regimes in addition to standard treatment for NSTEACS prevented acute phase elevation of vWF without signs of this marker reactivation after study drugs discontinuation. This effect on prognostic marker may contribute to clinical efficacy of thienopyridines in NSTEACS.

667 Using the PFA-100 and serum thromboxane B2 to measure aspirin resistance in patients with cardiovascular disease

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Background: Aspirin reduces the risk of cardiovascular events in patients with pre-existing vascular disease. However there is heterogeneity in the way individuals respond to aspirin with some patients suffering a thromboembolic event despite treatment. "Aspirin resistance" has been used to describe patients who, despite treatment with aspirin, fail to show significant inhibition of platelet function. This study was designed to determine the incidence of "aspirin resistance" and its underlying mechanisms.
Methods: In the first phase of the study 209 patients with a history of coronary artery disease and on aspirin 75-300mg daily were screened using the Platelet Function Analyser (PFA)-100 assay (Dade Behring) and serum thromboxane (Tx) B2 levels (ELISA, Assay Designs Inc.). In the second phase of the study we recalled 25 aspirin non-responders and 25 matched controls 3 to 12 months after initial sampling. Serum TxB2 was repeated and platelet aggregation to arachidonic acid (1.6mM), epinephrine (5μM), fibrillar collagen (0.5μg/ml) and TRAP (5μM) was performed.
Results: 8 patients were classified as non-compliant based on unsuppressed serum TxB2 levels (>50ng/ml). Of the remaining 201 patients 172 (86%) were classified as aspirin responders based on prolongation of the closure time on the PFA-100 (>193 seconds). 29 (14%) did not show prolongation of the closure time on the PFA-100, and were classified as aspirin non-responders. 23 of the 29 aspirin non-responders showed complete suppression of serum TxB2 (<10ng/ml) while the remaining 6 showed partial suppression (10-50ng/ml). 18 of the 172 responders also showed incomplete suppression of TxB2. On retesting, repeat serum TxB2 correlated well with the initial measurement, $r = 0.62$ ($P<0.0001$). 8 of the 25 aspirin non-responders aggregated to arachidonic acid compared to 4 of the 25 responders (p=NS). In addition, 12 of the 25 aspirin non-responders aggregated to epinephrine versus 3 of the 25 responders ($p = 0.01$). There was no difference in aggregation to collagen or TRAP in aspirin non-responders versus responders.
Conclusion: We have shown that 14% of cardiovascular patients have normal platelet function despite confirmed treatment with aspirin. In some cases this is associated with incomplete suppression of serum TxB2 and residual aggregation to arachidonic acid. However, the PFA-100 does not detect all patients who have incomplete suppression of cyclooxygenase during treatment with aspirin. In addition, enhanced sensitivity to epinephrine may explain many cases of "aspirin resistance" detected using the PFA-100.

YOUNG INVESTIGATORS AWARD SESSION – CLINICAL SCIENCE

669 Stem cell homing in myocardial infarction

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Background Stem cell homing to myocardial injury is dependent on cytokine and chemokine mediated cell-trafficking. Using magnetic resonance imaging we demonstrate the preferential homing ability and milieu-specific differentiation of magnetically-labeled bone marrow derived stem cells to myocardial infarction.
Methods Rat mesenchymal stem cells (MSCs) were labeled with micron-scale iron fluorescent particles (IFP). Myocardial infarction was induced in adult Sprague-Dawley rats following 1 hour of ligation of the proximal left anterior descending artery. IFP-labeled MSCs (15-20 million/kg) were administered via the tail vein, one hour after reperfusion. Serial cardiac MRIs were performed up to 8 weeks using an Oxford Instruments 4.7 Tesla/40 cm or Magnex 7 Tesla/20 cm horizontal MRI with Bruker consoles running Paravision. Imaging parameters were as follows: flip angles ranging from 10-40 degrees, TR = 100-200 ms, TE = 2.2 – 3 ms, field of views ranging from 5.3cm – 6.4cm with matrix sizes ranging from 5122 to 256 x 96. High resolution ex-vivo imaging was performed using a 7 Tesla microimaging system. Following euthanasia the heart was examined using fluorescent confocal microscopy for the presence of IFP-labeled MSCs and immunohistochemical markers of cardiomyogenic differentiation.
Results IFP-labeled MSCs appeared as a signal void within the infarct zone. Following euthanasia, high resolution 3D-MRI revealed the IFP-labeled MSCs were distributed throughout the infarct. Using confocal fluorescence microscopy, engrafted IFP labeled cells appeared to be preferentially localized to the infarction zone and were most concentrated in the center of the infarct, with the populations dwindling upon reaching the border zones. In addition, immunohistochemistry showed desmin and connexin 43 coexpression in IFP-labeled cells engrafted within are of infarction.
Conclusion We have non invasively demonstrated the homing ability of iron-labeled mesenchymal stem cells in vivo in the heart at 4.7 and 7 Tesla. In addition engrafted cells appear to differentiate along a cardiomyogenic lineage in response to a milieu-specific differentiation signal. These results may allow further investigation of the chemokine and cytokine axis governing stem cell homing to sites of tissue injury.

670 The pathological basis of Q-waves in myocardial infarction – infarct extent rather than transmurality

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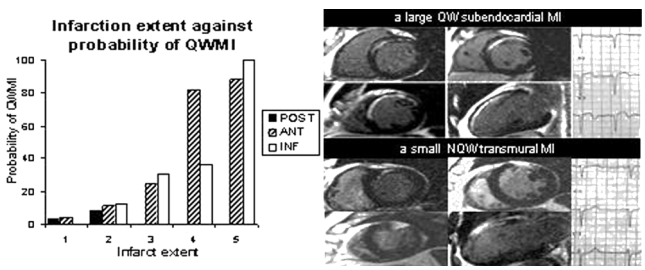
Introduction: For 40 years, the nature of Q-wave and Non-Q-wave myocardial infarction (QW/NQW MI) has been controversial, principally because of debate over the influence of transmurality. Previous study has relied on autopsy data for infarct assessment which has significant limitations. We hypothesised that late gadolinium CMR measurement of infarction would identify the anatomical basis of QW MI because both infarct extent and transmurality is assessed in-vivo.
Methods: 100 consecutive patients with previous infarction (recent, n=33, chronic, n=41, multiple, n=17, 9 excluded for LBBB) underwent ECG and CMR. The total extent of infarction, degree of transmural infarction and ECG classification as QW/NQW MI was determined in 3 territories and correlated.
Results: Non-transmural MI could be QW (28%); transmural MI, NQW (29%). As both MI extent and degree of transmurality increased, the probability of classification as QW increased: (anterior territory, extent chi^2= 53, $p<0.0001$, transmurality chi^2=36, $p<0.0001$; inferior territory, extent chi^2=16, p=0.001, transmurality chi^2=10, p=0.001), but this relationship was better for extent than transmurality, and transmurality was not an independent predictor in multivariate analysis. The QW/NQW classification was a good test for size of MI (area under ROC curve: anterior 0.9, inferior 0.77)and QWMIs had lower ejection fractions (47% vs 55%, p=0.02). None of these findings held for posterior MI which were electrically silent to 12 lead ECG.
Conclusion: The regional extent rather than transmurality of MI determines classification as QW or NQW MI. The presence of a QW MI indicates a larger MI with worse function which is more likely to be transmural, but if you want to definitively determine transmurality, use gadolinium CMR.



671 Biventricular endomyocardial biopsy findings in patients with Brugada syndrome

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Background: Various entities may present with electrocardiographic and clinical features of Brugada syndrome (BS). However no systematic assessment of the histologic substrate has been reported so far.
Methods: We studied 16 consecutive patients (pts) (13 M/3 F; mean age 40.2±13.8 ys) with clinical and electrocardiographic diagnosis of BS. All patients presented with normal cardiac volumes and function and normal valvular pattern at 2D-echocardiography with color-Doppler analysis. At standard ECG, type I depolarization pattern was present in 10 pts, and type II evolving in type I after flecainide challenge in 5 pts. Clinical presentation was cardiac arrest with ventricular fibrillation in 5 pts, documented sustained polymorphic ventricular tachycardia in 7 pts and syncope without arrhythmias documentation in 4 pts. All pts underwent cardiac catheterization, coronary angiography, right ventricle (RV) and left ventricle (LV) angiography with biventricular endomyocardial biopsy. Myocardial samples were processed for histology, immunohistochemistry and electron microscopy studies. PCR for common cardiotropic viruses was performed on frozen endomyocardial samples in all pts. Electrophysiologic study was performed in all pts.
Results: At cardiac catheterisation an increase in left (17.5±3.2 mm Hg) and right (12.2±3.9 mm Hg) ventricular end-diastolic pressure was measured in all cases. All pts showed wall motion abnormalities of the RV (7 pts), of the LV (2 pts) or both (7 pts). Microaneurysms of the RV and of the LV were detected in 10 pts and 6 pts respectively. At histology a focal active myocarditis according to Dallas criteria was present in RV samples of 6 pts and in RV and LV samples in 5 pts. RV fibrofatty replacement diagnostic for arrhytmogenic right ventricular dysplasia was found in 2 pts. In the remaining 3 cases histologic and electron microscopy studies showed non specific cardiomyopathic changes. PCR was positive for parvovirus B19 (1 pt) and enterovirus (2 pts) among the 11 pts with myocarditis (27%). In the 4 pts with syncope electrophysiologic study induced sustained polymorphic ventricular tachycardia, while in the remaining pts reproduced the spontaneous arrhythmia.
Conclusions: Abnormal histological findings consistent with myocarditis, cardiomyopathy and arrhytmogenic right ventricular dysplasia can be observed in pts with electrocardiographic and clinical diagnosis of BS. Endomyocardial biopsy may contribute to the diagnosis and to the definition of treatment and prognosis.

672 Endothelial dysfunction in children with acute infection

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Background: Atherosclerosis begins in early life and endothelial dysfunction is recognised as a key initiating event in the development of the atherosclerotic process. Evidence suggests that infection may be associated with endothelial dysfunction (ED) and vascular injury. However, the impact of the exposure to common infective pathogens in childhood on vascular endothelium is still unknown.
Methods: We studied 262 children, aged 11yrs drawn from the "ALSPAC" population. The children were separated into groups according to documented evidence of infection: current acute infection (AI) group; convalescent (CONV) group, infection in the past two weeks; control (C) group, healthy children. Of the 83 AI children (41 male, 42 female) 73 had chest infection, 3 ear infection and 7 upper airway respiratory infection at the time of study. In the CONV group (44 male, 47 female) 88 had had chest infection, 2 gastro-enteritis and 1 ear infection. The C group had no infection (44 male, 44 female).
Flow mediated endothelial function was assessed in all the children. Using high-resolution ultrasound the brachial artery diameter, at rest and following reactive hyperaemia, induced by forearm cuff occlusion for 5 minutes, was measured. Flow mediated dilatation (FMD) is expressed as the percentage change in diameter from baseline.
Results: Baseline diameter was comparable in all groups; AI: 2.75±0.03mm, CONV: 2.75±0.03mm, C: 2.68±0.027mm. Percentage FMD was significantly lower in both the AI group (6.93±0.326) and the CONV group (7.93±0.291) compared to the Control group (10.74±0.257) ($p<0.0001$). The FMD in the AI group was also significantly lower than in the CONV group ($p<0.02$). Values expressed as mean±SE.
The observed differences between groups remained when multivariate analysis was performed controlling for age, sex and vessel size.
Conclusion: An acute infection in childhood is accompanied by a significant decrease in endothelium dependent vasodilatation. These findings suggest that AI may be involved in the initiation of vascular injury in early life which may have implications for development of atherosclerosis in later life.

673 White cell telomere length and risk of premature myocardial infarction

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Purpose: Biological ageing is distinct from chronological ageing and may contribute to the pathogenesis of age-related diseases such as coronary heart disease. The lengths of telomeres provide an assessment biological age with shorter telomeres indicating increased biological age. We investigated whether subjects with premature myocardial infarction (MI) had shorter leucocyte telomeres.
Methods: Mean terminal restriction fragments (TRF) length, a measure of average telomere size, was compared by Southern blot analysis in leucocyte DNA of 203 cases with an MI under the age of 50 years and 180 age and sex matched controls. Both demographic as well as levels of biochemical markers of cardiovascular risk including fibrinogen, white cell count, C-reactive protein, cholesterol and homocysteine were measured in all subjects.
Results: Age and sex adjusted mean TRF length of cases was significantly lower than that of controls (difference 299.7±69.3 base pairs (bp), $p < 0.0001$). Mean TRF length declined by 26.4±8.1 bp per year in all subjects. Thus, on average mean TRF length in cases was similar to controls 11.3 years older. The difference in mean TRF length between cases and controls was unaffected by adjustment for hypertension, diabetes, smoking, white cell count or plasma levels of C-reactive protein, fibrinogen or homocysteine. Compared with subjects in the highest quartile for mean TRF length, the odds ratios for MI were 1.63 (95% CI, 0.91-2.92, p = 0.102), 3.27 (95%CI, 1.79-5.97, $p < 0.0001$) and 2.79 (95%CI, 1.53-5.11, p = 0.001), respectively in subjects in the second, third and lowest quartile of mean TRF length.
Conclusion: There is a strong and independent association between shorter mean leucocyte telomere length and risk of premature MI. Telomere length has a strong genetic determination. Therefore, apart from describing a novel association the findings could have important implications for our understanding of the genetic aetiology, pathogenesis and highly variable age of onset of coronary artery disease.

ESC LECTURE ON POPULATION SCIENCES

700 Prevalence of coronary heart disease related to passive smoking by self-report and serum cotinine in the Scottish MONICA population surveys

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Purpose: To investigate in never-smokers the relationship between prevalent coronary heart disease (CHD) and passive smoking measured by self-report, serum cotinine and a combination score, in the four random population sample surveys of the Scottish MONICA Project.
Methods: Random samples of men and women aged 25-64 were recruited in North Glasgow in surveys carried out in 1986, 1989, 1992 and 1995 involving questionnaires, risk factor and biochemical measurements. These included questions on passive exposure to tobacco smoke (classified at four levels 1-4 from "none" to "a lot"), and measurements of serum cotinine, an indicator of nicotine exposure, classified at four levels 1-4 in never smokers,from undetectable to just below the level identifying possible smoking deceivers. Results from each of these measures were analysed separately, and then for seven groups produced by adding their category numbers from the two measures into a score. Prevalent coronary heart disease was derived by combining medical diagnosis, the Rose questionnaire and Minnesota coding of the ECG.
Results: 1854 never smokers were identified after excluding a few potential deceivers whose cotinine exceeded the defined threshold of 17.9ng/ml. After combining the sexes and surveys and using multiple risk-factor adjustment the odds ratio (OR) for prevalent CHD showed a gradient from 1.0 self-reported, "no exposure" to 1.8 (1.1-2.8) for "a lot" of exposure. The OR for cotinine groups ranged from 1.0 for undetectable to 1.1 (0.7-1.8) for cotinine 4-17.9ng/ml. The combined score showed a gradient of ORs peaking at OR of 2.6 (1.1-6.0)for group 7. Prevalent CHD related most strongly to exposure at work. It also correlated with length of exposure per day.
Discussion: These results show a gradient of coronary risk associated with passive smoking even after correction for other risk factors. They endorse current policies protecting non-smokers from passive exposure to tobacco smoke.

701 Blood folate levels and subclinical atherosclerosis in Chinese inside and outside China: a report from CATHAY study

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Background: Blood folate level relates to cardiovascular mortality in the White, but its impact on atherosclerotic disease in the Chinese has not been documented.
Methods: To evaluate its impact among the Chinese, we recruited 493 asymptomatic healthy Chinese ethnic (mean age 46.9±12.4 years, 51.3% males) from our on-going Chinese Atherosclerosis in the Aged and Young (CATHAY) study in southern China, Sydney and San Francisco. Carotid intima-media thickness (IMT, surrogate atherosclerosis marker) was measured by high resolution ultrasound, using an off-line validated automated edge-detection and measurement computer package. Blood folate and homocysteine levels were measured by radioassay and immunoassay (IMx) respectively.
Results: Mean carotid IMT was 0.6±0.1mm. The mean plasma folate and homocysteine was 19.1±1.6nmol/l and 7.8±1.3umol/l respectively. The prevalence of methylenetetrahydrofolate reductase (MTHFR) TT genotype was 5.5% and T allele frequency was 24.3%. Carotid IMT was significanlty greater in those with low blood folate levels (<15nmol/l) compared with normal folate levels (0.62 ±0.1mm vs 0.59±0.09mm, $p <0.01$). On multivariate backward stepwise logistic regression, low plasma folate was significantly associated with carotid atherosclerosis (IMT>0.64mm)(odds ratio of 2.1 95% CI 1.24-3.40), independent of age, gender, hypertension (blood pressure >160/90mmHg), hyperglycaemia (fasting glucose > 6.1mmol/l), after adjustment for lipid profiles, plasma homocysteine levels, MTHFR genotype, smoking, body mass index and place of residence.
Conclusion: Low blood folate level is an important determinant of subclinical atherosclerosis, independent of homocysteine, with great implication in primary prevention of atherosclerosis in the Chinese.

Risk factors for atherosclerosis

	Odds Ratio (95% CI)	p-value
Age (yr)	1.09 (1.07-1.12)	<0.001
Sex (male)	2.14 (1.35-3.38)	0.001
Hypertension	2.90 (1.44-5.84)	0.03
Hyperglycaemia	1.96 (1.08-3.58)	0.027
Low folate level	2.06 (1.24-3.40)	0.005

702 Evaluation of the direct and indirect causal effect of risk factor interventions on coronary heart disease. A WHO project

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Background: WHO has established a project on comparative risk assessment for coronary heart disease (CHD) which addresses the overall impact of public health interventions on the risk of CHD. To obtain causal effect estimates, such an evaluation has to consider not only the direct risk factor (RF) effects but also effects mediated through other RFs. As various RFs simultaneously affect and are affected by other RFs (time-dependent confoundig), traditional regression analysis fails. We sought to use causal methods to investigate the expected effect of interventions on CHD risk factors.
Methods: We used the Framingham Offspring Study's longitudinal data (n=5124) with a 20-yr follow-up. We used the parametric g-formula (Robins, 1986) to adjust for time-dependent confounding and to estimate the counterfactual CHD risk under each intervention. First, we fit pooled logistic regression models to predict RF and CHD distributions conditional on given risk factor history. Second, Monte Carlo technique was used to simulate RFs and CHD in 10000 counterfactual subjects. Third, we estimated 95% bootstrap confidence intervals (CI) of relative CHD risks (RR). Evaluated strategies included interventions on smoking, alcohol consumption, body mass index (BMI), low density lipoprotein (LDL), and a combined strategy.
Results: After exclusions, our analyses included 2230 men (47.8%) and 2440 (52.2%) women with 189 and 68 CHD events, respectively. The observed 12-yr risk of CHD in the study population was 8.48% (CI 7.37%-9.73%) for males and 2.79% (CI 2.19%-3.54%) for females. The simulated 12-yr risk of CHD under no intervention was 8.48% for males (CI 6.72%-10.24%) and 2.82% for females (CI 2.10%-3.54%). Smoking cessation at baseline in all male and female smokers had a RR of 0.80 (CI 0.70-0.91) and 0.83 (CI 0.70-1.00), respectively. The RR after shifting the LDL distribution to the distribution of the Chinese population was 0.68 (CI 0.52-0.89) for men and 0.48 (CI 0.35-0.67) for women. Shifting alcohol consumption to moderate alcohol intake or constantly lowering BMI to 22kg/m^2 did not change CHD risk significantly. The combined intervention on smoking cessation, BMI, and LDL reduced the CHD risk by 53% (RR 0.47; CI 0.32-0.69) in men and by 61% (RR 0.39; CI 0.23-0.67) in women.
Conclusions: The parametric g-formula could be applied in a situation with time-dependent confounding, where traditionl regression analysis fails. Highest risk reductions could be achieved by interventions on smoking cessation and LDL. Combined interventions may reduce CHD risk by more than 50%.

EPIDEMIOLOGY OF DYSLIPIDAEMIA

703 Plasma lipoproteins and severity of coronary atherosclerosis in diabetic and non-diabetic patients

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Background: Most studies have related lipoprotein levels only to the presence or absence of coronary artery disease (CAD) but not to its angiographic extent. Whether CAD patients (pts), with or without noninsulin-dependent diabetes mellitus (NIDDM), have similar severity of CAD is in dispute. Furthermore, the determinants of the extent of CAD in pts with NIDDM are not well known. The aim of this study was to evaluate the relationships between risk factors (RF) and the extent of CAD in 282 NIDDM (68±10 years; 70%, men) and 283 non diabetic pts (66±12 years; 65%, men).
Methods: All the 565 consecutive pts underwent coronary angiography and none of them had a previous revascularization. The pt's characteristics, RF, treatment before hospitalization were recorded for each pt. Blood samples were drawn upon admission to the hospital. The extent of CAD atherosclerosis was assessed by 2 different scores, the Gensini score and the Atherosclerotic score, calculated as the average severity [grades 0 (<25%), 1 (<50%), 2 (<75%), 3 (≤95%), and 4 (>95% stenosis)] of all 15 coronary segments.
Results: NIDDM pts had a higher prevalence of hypertension (63 vs 42%), and a higher body mass index (29 vs 26 kg/m^2) than non diabetic pts. HDL cholesterol (0.43 vs 0.48 g/L), LDL cholesterol (1.22 vs 1.30 g/L), and Lp (a) (0.34 vs 0.41 g/L) levels were significantly lower and triglycerides levels (1.66 vs 1.41 g/L) were significantly higher in NIDDM than in non diabetic pts. The Gensini (35 vs 27) and Atherosclerotic (0.50 vs 0.43) scores were significantly higher in NIDDM than in non diabetic pts. In backward stepwise multiple regression analyses, age, sex, admission with an acute coronary syndrome, a previous history of stroke or peripheral arterial disease, a diagnosis of CAD older than 1 month, and hypertension (for NIDDM only) were significantly ($p<0.05$) associated with the 2 scores in NIDDM and non diabetic pts. In the same models, LDL cholesterol ($p<0.05$) levels were associated with the Gensini score in NIDDM and non diabetic pts whereas HDL cholesterol ($p<0.02$), LDL cholesterol ($p<0.02$) and Lp (a) ($p<0.006$) levels were associated with the Atherosclerotic score only in non diabetic pts.
Conclusions: Lipoproteins are more strongly associated with the severity of coronary atherosclerosis in non diabetic than in NIDDM pts. Further studies are needed to study the role of lipoprotein particles as determinants of coronary atherosclerosis in NIDDM pts.

704 Dislipemia in patients with heart failure. Should we treat these patients?

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Purpose: The two main causes of heart failure (HF) are ischemic heart disease (IHD) and hypertension. There is increasing evidence of the benefits of statin use in most of patients with IHD and recently ASCOT trial results suggests a significant benefit for many hypertensive patients. The aim of our work was to investigate the influence of statin use on survival in a cohort of patients hospitalised with descompensated HF.
Methods: From January 1999 until June 2000, all consecutive patients diagnosed during hospitalisation of descompensated HF were investigated (N=1212) by reviewing the discharge letter, and by a structured telephone interview after a mean follow up of 20±2 months. Data regarding past medical history, clinical data and lipid analyses during hospitalisation, as well as treatments on discharge and follow-up were analysed.
Results: Of 1212 patients included (49.8% males; mean age 76.5±10.5 years old), 402 patients (33.2%) had been diagnosed of dislipemia (total cholesterol >200 mgr/dL) (36.9% males vs. 29.8% females, $p<0.001$. Of those patients >75 years-old, 27.1% were dislipemic, vs. 43.4% of patients <75 years-old ($p<0.001$). On discharge, only 7.4% of patients were discharged on statins, that increased up to 17.7% after follow up. Patients with atherosclerotic disease (AD) (ischemic heart disease, diabetes, stroke or peripheral vascular disease) presented a low rate of statin use on discharge (5%), that increased up to 22.8%. On the other hand, statin use in patients without demonstrated AD was 3.5% on discharge and 9% on follow up. Survival analysis by Kaplan-Meier demonstrated in this population that the presence of dislipemia was not an influencing risk factor for survival, but the use of statins was associated with a lower risk of death (log rank p=0.01) and hospitalizations due to HF during follow up (log rank p=0.01). In addition, the lower values of total cholesterol and LDL-cholesterol levels were associated with a higher mortality during follow up ($p<0.01$).
Conclusions: In our study population, although one third of patients with HF had previously diagnosed of dislipemia, the prevalence of statin use was low on discharge and increased slightly during follow-up. In our cohort, statin use on discharge was associated to better prognosis in terms of less mortality and hospitalizations due to HF, although low total and LDL cholesterol levels were associated with poor prognosis.

705 The role of the total to high-density lipoprotein cholesterol ratio to predict myocardial infarction incidence and mortality in a middle-aged southern German population

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Objective: To examine the sex-specific impact of the total/HDL cholesterol ratio (lipid-ratio) on incident acute myocardial infarction (MI) and total mortality.
Material and methods: The study sample included 6,725 men and 6,702 women aged 25 to 74 years who participated in the MONICA Augsburg surveys between 1984 and 1995. Serum lipids as well as other CHD risk factors were measured at the baseline examination. In 1998 a morbidity and mortality follow-up was assessed for all study participants. During a median follow-up of 7.6 years 277 deaths and 234 MI occurred in men (81 and 66 in women). MI incidence and mortality rates per 1000 person years were calculated for three levels of the lipid-ratio: <3.5, 3.5 to 4.9, and ≥5.0. The relative hazard rates associated with lipid status were calculated using Cox regression.
Results: In 1994/95, 49% of men and 21% of women were characterized by a lipid-ratio ≥ 5. Of them, 61% in women and 73% in men were not aware of this risk constellation and were not treated. Screening lidid ratio, more than 80% of the population with at least two main risk factors could be identified. In men, MI incidence was 3,8- and total mortality was 2.1-fold higher than in women. After multivariable risk factor adjustment, MI incidence was 2.5 times higher in men, and 3.1 times higher in women with lipid-ratio ≥5 compared to those with a ratio <3.5. The lipid-ratio showed a u-shaped association with total mortality in men and a j-shaped in women. The high mortality in people with a lipid ratio <3.5 was partly due to an increased percentage of cancer deaths.

MI incidence and mortality rates

Ratio of Total/HDL-C	Men		Women	
	MI Incidence	Total Mortality	MI Incidence	Total Mortality
<3,5	3.74 (1.97-6.29)	13.35 (10.37-16.87)	0.84 (0.28-1.76)	5.03 (3.62-6.75)
3,5-4,9	4.13 (3.14-5.33)	9.14 (7.75-10.70)	0.95 (0.55-1.52)	4.64 (3.71-5.73)
>=5,0	7.94 (6.59-9.47)	12.94 (11.40-14.62)	3.41 (2.17-5.02)	7.01 (5.41-8.90)
All	5.77 (4.98-6.63)	11.49 (10.49-12.54)	1.51 (1.13-1.96)	5.45 (4.75-6.22)

C cholesterol, MI acute myocardial infarction, CI confidence interval

Conclusions: Because of the poor awareness, treatment and control of dyslipidemia in the population, for preventive activities the total/HDL cholesterol ratio should be measured independently from the fasting status of the patient. Doing this routinely, evidence based treatment could start.

706 Cardiovascular events and persistence with statins in primary and secondary prevention: a population-based analysis including 19.178 patients treated between 1996 to 2000

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Purpose: An aim of this study was to investigate the frequency of cardiovascular events (CVEs) in patients with renewed prescriptions for statins compared with that of patients with single prescription (in an intention-to-treat perspective).
Methods: On the whole population listed in the administrative database of the Local Health Unit of Ravenna (population of 356,000) a longitudinal cohort study was conducted. In the period between 1996 and 1999, 19,178 patients receiving prescriptions for a statin were considered eligible for analysis. The exposure to treatment and fatal/non-fatal CVEs were observed up to 2000, with a follow-up period ranged between 1 to 5 years. Pharmaceutical and nosocomial databases were cross-linked to recognise CVEs as well as the pharmacoutilisation profile on a patient-by-patient basis. In order to assess the odds to develop a CVE among patients with renewed prescriptions in comparison with those with a single prescription, a stratified asymptotic odds ratio estimation was performed by type of prevention.
Results: The analysed cohort was composed of 15,927 (83%) and 3,251 patients (17%) treated with statins in PP and SP respectively. In the group of treated for SP, patients experienced a mean of 1.3 events before their index date.
The frequency of renewed prescriptions was significantly lower among patients in PP [9,397 cases (59%)] compared with that of patients in SP [2,613 cases (80.4%); p<0.001]. The persistence rate reached a level over 75% (calculated as proportion of days covered by a treatment with statins) just in 1,717 patients in PP (18.3%) and in 1,089 patients (41.7%) in SP (p<0.001).
In PP, 1,092 CVEs were observed, and the odds to develop an event in patients with renewed prescriptions was 1.42 (95%CI: 1.25-1.62; p<0.001). Conversely in SP, the odds ratio was 0.35 (95%CI: 0.29-0.42; p<0.001), with a level of total CVEs corresponding to 1,251.
Overall, patients with renewed prescriptions showed lower odds to develop CVEs in respect to those with a single prescription (0.88; 95%CI: 0.79-0.98; p<0.001).
Conclusion: Although a general benefit induced by a treatment with statins on the prevention of CVEs was observed, this seems to be mainly attributable to SP. Among patients in PP, a dramatically unexpected increase of CVEs was found. However, this worrying result might be related to a level of treatment persistence with statins which was lower than that observed in SP, and also remarkably less than suggested by landmark randomised clinical trials.

707 Under-treatment of patients with highly elevated cholesterol in UK primary care practices

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Introduction: European and British guidelines recommend lipid-lowering therapy (LLT) and lifestyle changes for patients with or at significant risk for coronary heart disease (CHD) to reduce total cholesterol (TC) below 5 mmol/l (LDL-C<3 mmol/l). This observational study was conducted to assess whether current management in UK primary care practices enabled patients with highly elevated cholesterol (TC>7 mmol/l) to achieve this goal.
Methods: This retrospective cohort study was based on the UK Mediplus Database, a national general-practitioner database. Patients with recorded TC >7 mmol/L prior to initiating LLT between 1998 to 2001 were identified and followed for up to 4 years. Cox hazard models were used to determine factors associated with goal attainment (defined as TC< 5 mmol/L) in these patients.
Results: 4,047 patients with a baseline TC>7 mmol/l initiated LLT between 1998 and 2001. 44.9% were male; mean age was 61.1y (SD 9.8y). Prior to initial LLT, 21.8% had CHD and 21.3% had other atherosclerotic disease (stroke, peripheral vascular disease) or diabetes. Majority of patients were prescribed low to medium dose statin as initial LLT (31.6% atorvastatin 10mg, 6.1% atorvastatin 20mg, 25.3% simvastatin 10mg, 11.4% simvastatin 20mg). During the first year of therapy, 974 patients (24%) doubled their statin dose, 482 (11.9%) reduced therapy dose, and 707 (17.5%) switched to another drug. Less than 1% of patients were initiated or switched to combination therapy. Patients with baseline TC between 7 and 8 mmol/l, 22.2% achieved goal at 6 months and 26.1% at 12 months. Among patients with baseline TC>=8 mmol/l, 13.4% and 15.7% achieved goal at 6 and 12 months, respectively. 896 patients (22.1%) did not have any record of follow-up cholesterol measurement. Patients with >8 mmol/l baseline TC were 50% less likely (HR 0.54, 95% CI 0.44,0.64) and those with >7-<8 mmol/l were 25% less likely (HR 0.74, 95% CI 0.67,0.81) to achieve goal compared to patients with cholesterol between 5 and 7 mmol/L. These effects were independent of initial statin dose (HR 1.10, 95% CI 1.04,1.16), number of therapy changes (HR 1.10, 95% CI 104,1.16) and other patient characteristics.
Conclusion: Less than 25% of patients with highly elevated cholesterol (TC>7mmol/L) achieved treatment goal recommended by guidelines. A majority of these patients were prescribed a relatively low dose of statin and less than 25% ever doubled their initial statin dose. Few patients received combination LLT. Better efficacy and closer monitoring are needed to help these patients achieve treatment goal.

708 Recent trends in (under)treatment of hypercholesterolaemia in The Netherlands

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Purpose: In 1998, un update of the Guideline for Management of Hypercholesterolemia was published in the Netherlands. We assessed the prevalence of pharmacological treatment and control of hypercholesterolemia over the period 1998-2001, and compared it to prevalence figures in two previous periods.
Methods: In the Doetinchem Cohort Study, 4,165 men and women aged 30-70 years of age, were examined for cardiovascular risk factors from 1998-2001. For the period 1987-1992 and 1993-1997 data from two large population based surveys on cardiovascular risk factors were available. In primary prevention, treatment is indicated when the absolute risk for coronary heart disease (calculated with the Framingham risk function) exceeds an age and gender specific threshold. This risk function includes age, gender, smoking, blood pressure, total and HDL cholesterol and the presence of diabetes. In secondary prevention, treatment is always indicated, unless total cholesterol is less than 5.0 mmol/l. All data are standardized to the age and gender distribution of the Dutch population.
Results: For the period 1998-2001, 397 respondents (11%) were eligible for treatment. Only 170 (43%) of those eligible were actually treated. Women were more frequently treated than men (51% versus 39%). Only 15% of those eligible for treatment were both treated and controlled (=total cholesterol below 5 mmol/l). This was equally true for men and for women. Prevalence of treatment was similiar in primary and secondary prevention (45% and 40%), but being treated and controlled was more prevalent among those eligible for secondary prevention than among those eligible for primary prevention (19% vs. 11%). Compared to earlier periods, control of hypercholesterolemia had increased: during the years 1987-1992 only 10% of those eligible were treated and only 1% of those eligible were treated and controlled; from 1993-1997 about 27% of those eligible were treated and 7% were treated and controlled. Treatment especially increased since 1995, the year of publication of a number of landmark trials on statin treatment. Determinants of treatment will be discussed.
Conclusion: Treatment of hypercholesterolemia in the Netherlands has steadily increased during the past 15 years. However, of those eligible for treatment, at present still less than 1 out of 2 is treated, and only about 1 out of 6 is both treated and controlled. Implementation of guidelines of management of hypercholesterolemia should be reinforced to obtain full benefit of lipid lowering drug use in both primary and secondary prevention of coronary heart disease.

EXERCISE TESTING IN HEART FAILURE: CHOOSE THE RIGHT PROTOCOL

709 Comparison between 6 min. walk test and a fixed distance walk test in the evaluation of heart failure patients

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Introduction: Of the walk tests used for functional evaluation of heart failure patients, 6 min. walk test (6 MWT) is the most popular, even if there is not a good correlation with peak VO2 (cycloergometer, treadmill) or left ventricular performance (ejection fraction). That is why we studied the value of a fixed distance (400 m) walk test (400 m WT) in comparison with 6 MWT, in heart failure patients.
Material and methods: There were studied 28 patients with dilated ischaemic or idiopathic cardiomiopathy, 23 males and 5 females, aged 30-65 years. Left ventricular ejection fraction (LVEF) was determined by 2D echo. Each patient performed in three consecutive days a maximal, symptom limited exercise stress testing on cycloergometer, a 6 MWT and a 400 m WT the results of the last test being expressed in seconds.
Results: The mean values of the studied parameter were: LVEF 34$\pm$3.2%; peak VO2 (cycloergometer) 15.2$\pm$1.4 mlO2/kg/min; 381$\pm$37 m (6 MWT), 442$\pm$40 s (400 mWT). There is no correlation between LVEF and peak VO2 (r: 0,20), 6 MWT (r: 0,21) and 400 m WT (r: -0,25). In turn, the correlation between peak VO2 and both 6 MWT (r: 0.58) and 400 m WT (r: -0.57) was good. The correlation between 6 MWT and 400 m WT (r: -0.60) was excellent, suggesting that both tests have the same value in the evaluation of submaximal functional capacity of heart failure patients. Because the peripheral muscular mechanical work is the same for all the patients during 400 m WT, but it is different during 6 MWT, the contribution of periphery to the limitation of the exercise capacity is probably better evaluated by 400 m WT.
Conclusion: It is concluded that 400 mWT is a useful tool for the evaluation of submaximal effort capacity in heart failure patients.

710 Ramp treadmill tests generate higher workload and cardiopulmonary response than bicycle tests in chronic heart failure

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Introduction: Maximal oxygen uptake (peak VO2) is used in risk stratification of patients with chronic heart failure (CHF) and is also considered when prioritizing patients for heart transplantation. On one hand evidence has shown that Upright Bicycle Tests (UBT) may underestimate peak VO2 values and that Standard Treadmill Tests (STT) are more suitable for this purpose. On the other hand Ramp Protocols (RP) on UBT provide an interesting alternative to the STT 2 or 3 minute stage-protocols because they can be created across various levels of difficulty, thus ensuring the patients ability to perform in accordance with individual capabilities. In addition, during RP, VO2 increases linearly with time,allowing a better visualisation of a maximum VO2 or "plateau" if attained. To join these beneficial effects we developed a treadmill RP with a wide range of adjustable speed and inclinations. Mean metabolic equivalents,energy expenditure and oxygen consumption of walking levels deduced from the STT protocols enabled us to create an Adjustable New Treadmill Weighted for Energy Ramp Protocol (ANTWERP)to evaluate the cardiopulmonary response to exercise in patients with CHF. In this study we compared this test with UBT.
Methods: 130 patients with stable CHF(mean Ejection Fraction = 30.5% $\pm$ 9.5, mean age = 59y $\pm$11,and 28% female) with normal pulmonary function underwent in random order both a maximal Treadmill Test with ANTWERP(TTA) and a maximal UBT (at comparable increments of 10W/min or 20W/min) over a one-week period.Respiratory gas analysis and cardiac parameters were assessed during both tests.Body-composition was calculated by bioelectrical impedance analysis.
Results: Peak VO2 (TTA: 19.5 $\pm$ 4.4 vs. UBT: 18.2 $\pm$ 4 ml/kg/min, $p<0.0001$), maximal workload (TTA: 114.5 $\pm$ 39.2 vs. UBT: 109 $\pm$ 41.1 watt, $p<0.05$), oxygen uptake (TTA: 17.8 $\pm$ 4.2 vs. UBT: 15.7 $\pm$ 3.6 ml/kg/min, $p<0.0001$)and workload (TTA: 102.6 $\pm$ 35.3 vs. UBT: 92 $\pm$ 36.4 watt, $p<0.005$)at ventilatory threshold were higher on treadmill than on bicycle test. Moreover, after correction for Lean Body Mass, peak VO2 ($p<0.0001$),maximal workload ($p<0.005$)and both oxygen uptake ($p<0.0001$)and workload ($p<0.0001$)at ventilatory threshold were significantly higher in TTA.
Conclusion: Patients with CHF reach a higher mechanical workload and a higher cardiopulmonary response in TTA than in UBT even after correction for Lean Body Mass.These data suggests that TTA is more suitable for determining peak VO2 than UBT in CHF.

711 Relationship between low workload and maximum workload cardiopulmonary exercise data in chronic heart failure patients

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Background: The use of cardiopulmonary exercise data in the assessment of prognosis for chronic heart failure (CHF) patients is well established. The results of these tests are also used as markers of outcome following intervention. Symptom-limited maximal exercise testing can be uncomfortable for subjects and is often precluded by comorbidities. We compared low-workload cycle ergometer exercise tests with maximal treadmill exercise tests.
Methods: 29 stable CHF patients, NYHA grade II-III, mean age 62 ± 12.1, underwent cardiopulmonary exercise testing. Each subject performed a constant workload bicycle test (BIKE) at 30 watts and, subsequently, a symptom-limited ramped treadmill test (TREAD) where the subject was encouraged to exercise to exhaustion. Subjects also performed a 6-minute walk test (6MW) and a quadriceps strength and fatigue test on each occasion.
Results: Mean cardiopulmonary data for bike and treadmill tests are shown in table 1. VEVCO2 slope was not significantly different between the 2 tests although oxygen uptake efficiency slope (OUES) was lower during the bike test. VO2 (BIKE) correlates with VO2 (TREAD) both for absolute values (r=0.42, p=0.028) and when expressed as a percentage of predicted peak VO2 (r=0.43, p=0.022). VEVCO2 (BIKE) and VEVCO2 (TREAD) are also correlated (r=0.4, p=0.035) as are OUES (BIKE) and OUES (TREAD) (r=0.59, p=0.003). Peak VO2 (BIKE) correlates with 6MW distance (r=0.41, p=0.011), and the VEVCO2 slope (BIKE) correlates with 6MW (r=-0.56, p<0.001), quad strength (r=-0.33, p=0.042) and quad fatigue index (r=-0.33, p=0.046). OUES (BIKE) correlates with 6MW (r=0.41, p=0.011).

	Bike	Treadmill	p value
peak VO2 (ml/kg/min)	10.5 ± 2.23	17.7 ± 3.58	<0.001
% of predicted VO2 achieved at peak	37.9 ± 9.66	64.6 ± 14.4	<0.001
VEVCO2 slope	34.7 ± 15.2	29.2 ± 3.30	0.70
OUES	1.11 ± 0.45	1.93 ± 0.58	<0.001

OUES, oxygen uptake efficiency slope

Conclusions: Peak VO2 and VEVCO2 slope from maximal exercise tests have been identified as predictors of mortality in CHF patients. Data from low-workload tests correlate with data from maximal tests and with tests of functional capacity and should be further evaluated for their usefulness as outcome predictors as they are easier for patients to perform.

712 The relationship between isokinetic muscle endurance and exercise capacity in chronic heart failure

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Aim: This study was designed to clarify the relationship between isokinetic muscle endurance and exercise capacity in chronic heart failure (CHF) patients.
Methods: Subjects comprised 33 CHF patients (27 males and 6 females, mean age of 60.3 years)whose mean left ventricular ejection fraction was 38.9%. Underlying diseases were 19 dilated cardiomyopathy, 9 old myocardial infarction, 4 valve disease and 1 hypertensive heart disease. Symptom-limited cardiopulmonary exercise testing (CPX) using a cycle ergometer with ramp exercise protocol was performed in each patient and anaerobic threshold (AT), peak oxygen uptake (peak VO2), slope of ventilatory equivalent (VE) against carbon dioxide output (VCO2)(VE/VCO2 slope), VO2 increase against work rate (WR)increase (dVO2/dWR), time constant for post-exercise VO2 decrease (tau off)were measured. Prior to CPX, peak leg extension power based on 3 maximal revolutions with 50 cadences per minute (CPM) and strength decrement index (SDI) on 10 maximal revolutions with 60 CPM, an index of muscle endurance, were obtained using Strength Ergo240 (SE240: Mitsubishi Electric C.O. Tokyo), a pedaling type isokinetic device. SDI was calculated by the following formula;
SDI (%) = S9-10*100/S2-3 where S9-10 is an average value in peak power during 9th and 10th revolutions and S2-3 during 2nd and 3rd revolutions.
Result: Average value in SDI was 85.5 ± 4.94%. SDI showed a significant correlation with VE/VCO2 slope(r=-0.55 p<0.001), dVO2/dWR (r=0.63, p<0.0001), not with tau off (r=-0.37). Peak power significantly correlated with peak VO2 (r=0.66 p<0.001) and tau off (r=-0.43, p<0.05), not with VE/VCO2 slope. Both SDI and peak power had significant correlations with AT and peak VO2.
Conclusion: These results suggest skeletal muscle endurance may be a determinant for the ventilatory response to exercise. These observations lend support to the muscle hypothesis of the generation of symptoms in chronic heart failure. In conclusion, measurement of muscle endurance is useful to estimate the severity of dyspnea and mortality in CHF patients.

713 Brain natriuretic peptide levels as marker of enhanced ventilatory response during exercise test in patients with chronic heart failure and intermediate-level peak oxygen consumption

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The aim of this study was to evaluate if brain natriuretic peptide (BNP) levels are associated with the severity of ventilatory abnormalities during cardiopulmonary exercise test (CPx) in patients (PTS) with mild symptoms of chronic heart failure (CHF) and VO2 peak (PVO2) ranging from 10 and 18 ml/kg/min. The enhanced ventilatory response was assessed as ventilation and carbon dioxide production ratio (VE/VCO2) slope > 35.
Methods: 94 CHF consecutive PTS with 10-18 ml/kg/min PVO2 (Age 71±10; F 22%; beta-blocker therapy 53%; ischemic 51%; hypertensive 23%) were considered.9% of PTS were in functional class (FC) I NYHA, 74% FC II, 17% in FC III.The mean echocardiographic ejection fraction (EF) was 41,62 ± 13%. 29% of PTS had VE/VCO2 slope > 35.Mean BNP plasma level, measured by means of the triage system (Biosite Diagnostic Triage BNP Test), was 203,9± 239,2.VE/VCO2 slope, VE/VCO2, ventilation and breathed out oxygen ratio (VE/VO2) were considered for analysis.
Results: A significant correlation between BNP and abnormally high ventilatory response to exercise, expressed as VE/VCO2 slope, (r = 0,265; p <0,01) was observed.A non significant correlation between BNP and VE/VCO2 (r = 0,134) and between VE/VO2 (r = 0,172) was also observed.

table I

PVO2 ml/kg/min	13,06 ± 2,11
VE/VCO2 slope	32,4 ± 5,5
VE/VCO2	36,93 ± 6,93
VE/VO2	43,55 ± 7,89

Conclusions: CPX has become a routine clinical tool for predicting mortality of PTS suffering from CHF. However the prognosis of CHF-PTS with mild symptoms and PVO2 ranging from 10 to 18 ml/kg/min is not well estabilised. In this subset of PTS enhanced ventilatory response to exercise expressed as VE/VCO2 slope > 35 predicts poor prognosis. BNP seems, indeed, to be well correlated to this parameter and might offer a simple and cost-saving alternative in the future to select CHF-PTS for more aggressive therapeutic strategies.

714 Increased exercise capacity and quality of life in patients with chronic heart failure participating in an organized training and special care program

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In patients with chronic heart failure (CHF) both exercise capacity and quality of life (QoL) are reduced in addition to a poor prognosis. The aim of this study is to examine the effects of a standardized exercise program and special care by CHF-nurse on exercise tolerance (ET) and QoL.
Material and Methods: 25 patients (4 females) mean age 70 years, range 45-85 years, with stable CHF in NYHA class II-III B, on optimal medical treatment were randomized to an out-patient training and special care group (T)(n=12) and a control group (C)(n=13). The ejection fraction was 30±11 in C. The training programme consists of dynamic low intensity interval training with strength,endurance,respiratory,stretching exercise(the Ullevaal model),twice a week over a 16-week periode. It is a interval model with 3 peaks of perceived exertion at 15-17 on Borg's scale. At the same time the patients had 4 consultations with a CHF-nurse,including diatory advice, medication adherence, symptom monitoring and social support. The effect was evaluated by: bicycle ergometer test, 6-minute walk test for evaluation of exercise capacity and "Minnesota Living With Heart Failure Questionnaire" for evaluation of the QoL (score 0-105).
Results: At baseline ET was 75±19 watt and exercise time 345±118 seconds in T and 73±17 watt and 331±107 seconds in C respectively. The walking distance (WD) was 468±70 meters in T and 428±98 meter in C. After 6 months both ET (p=0.008), exercise time (p=0.006) and the WD (p=0.007) had increased significantly in the T group without any change in C group. For all parameters a significant difference between the groups was observed. QoL improved in the T group and with significant difference between the groups (p=0.01). A significant negative correlation between ET and QoL was observed in the whole group of patients (r=-0.549, p=0.05).
Conclusion: Our results support the implementation of an organized training program in addition to a nurse based out-patient information program, to improve both ET and QoL in patients with CHF.

RIGHT-VENTRICULAR FUNCTION – NEW APPROACHES, NEW METHODS

715 Prognostic utility of a novel echocardiographic parameter of right-ventricular function in dilated cardiomyopathy

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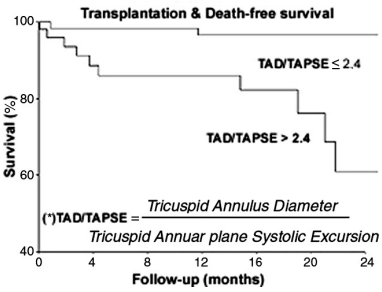
Background: The prognostic value of right ventricular dysfunction in patients with heart failure has been reported in various studies. Some echocardiographic parameters have demonstrated a good correlation with tomographic techniques in this regard.
Objective: To assess the usefulness of echocardiographic markers of right ventricular function as predictors of prognosis in patients with Dilated Cardiomyopathy (DCM).
Methods: 137 consecutive patients (mean age 59 years, [SD 14]; 122 males) underwent two-dimensional and Doppler echocardiography between November 1999 and December 2000 (median follow-up 19 months). Eighty patients (58%) presented with non-ischaemic DCM (NIDCM) and 57 (42%) with ischaemic DCM (IDCM).
Results: Most patients were in NYHA class II (42%) and III (26%). Mean left ventricle ejection fraction (LVEF) was 31% (SD 9). Thirteen patients died and 22 underwent heart transplantation. In multivariate analysis LVEF, NYHA class and Tricuspid Annulus Diameter/Tricuspid Annulus Plane Systolic Excursion ratio; (TAD/TAPSE); were found the independent predictors of outcome. In subgroup analysis, only TAD/TAPSE predicted prognosis regardless etiology. A TAD/TAPSE >2.4 predicted death with an odds ratio of 10.3 ($p<0.01$, 95%CI: 2.2-48.2) after adjusting by NYHA and LVEF.



Transplantation & death-free survival.

Conclusion: TAD/TAPSE was found an independent predictor of survival in DCM. In addition to traditional left ventricular function parameters, this novel parameter, provides a simple and accurate clinical tool in the management of DCM patients.

716 Tissue Doppler myocardial pre-systolic velocity: a reliable marker of right-ventricular systolic dysfunction

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Purpose: Ultrasound approach of right ventricular (RV) function is challenging. Pulsed Tissue Doppler (TD) has been proposed as a reliable method to detect abnormalities of RV function. Aim of this study was to evaluate clinical value and reliability of RV TD in healthy and known pathologic conditions.
Methods: We studied 13 normal subjects (mean age = 41.6 years, 3 women) and 28 patients (mean age = 66.8 years, 5 women) with RV systolic dysfunction, assessed by tricuspid annular systolic excursion (TAPSE). Standard Doppler echocardiography and pulsed TD of RV tricuspid annulus (apical 4-chamber view) were performed. Myocardial systolic (Sm) and diastolic (Em, Am) velocities, Em/Am ratio and myocardial time intervals (pre-contraction time = PCTm, contraction time = CTm, relaxation time = RTm) were measured. Myocardial pre-systolic velocitiy (= PSVm), which precedes Sm during PCTm, was also evaluated. Inter-observer reproducibility of TD measurements was blindly tested in a subset of 20 subjects by 2 independent readers from 2 different echocardiographic laboratories.
Results: TD measures had optimal inter-observer variability: 4.0% for PSVm, 4.5% for Sm, 2.9% for Em/Am ratio, 2.8% for PCTm, 1.7% for CTm, 2.6% for RTm. Patients with RV dysfunction had lower TAPSE and higher Doppler standard tricuspid inflow E/A ratio (both $p<0.0001$) than controls. They also exhibited lower PSVm (0.32 ± 0.3 vs. 0.67 ± 0.4 cm/s, $p=0.006$) and a prolongation of RTm ($p=0.04$). In contrast, Sm velocity and Em/Am ratio were similar between the 2 groups. In pooled groups, PSVm was related negatively with age ($r = -0.60$, $p<0.0001$) and positively with TAPSE ($r = 0.46$, $p<0.002$). This relation remained significant even controlling for age ($r = 0.32$, $p=0.04$). In a multiple linear regression analysis, the association between PSVm and TAPSE ($\beta = 0.30$, $p<0.005$) was independent of the effects of age, heart rate and sex (multiple $R^2 = 0.65$, $p<0.0001$).
Conclusions: Pulsed Tissue Doppler is a reliable, simple method which can be used for the assessment of RV function. In particular, myocardial pre-systolic velocity appears as an interesting marker of RV dysfunction, correlated with longitudinal motion of the right ventricle.

717 Right-ventricular function in patients with left-ventricular myocardial infarction and reduced ejection fraction: analysis by tissue Doppler

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Purpose: Standard Doppler echocardiography has several limitations for the evaluation of right ventricular (RV) function due to difficult ultrasound approach. Aim of the study was to assess RV myocardial function by pulsed Tissue Doppler (PW-TD) in patients with left ventricular (LV) myocardial infarction (MI) and reduced LV systolic function.
Methods: 44 patients (M/F = 36/8, mean age 71 years) with recent (<30 days) LV MI and ejection fraction (EF) <50% were enrolled after excluding patients with RV MI and unstable angina. All patients underwent coronary angiography, standard Doppler-echo and PW-TD, with the sample volume placed at the level of LV lateral mitral and RV tricuspid annuli, in apical 4-chamber view. Myocardial systolic indexes (systolic peak velocity = Sm, pre-contraction time = PCTm and contraction time) and diastolic measurements (early diastolic and atrial velocities = Em and Am respectively, Em/Am ratio and relaxation time = RTm) were determined at both the levels. According to MI location, patients were divided into 2 groups: 22 with inferior MI and 22 with anterior MI.
Results: The 2 groups were comparable for age, body surface area, blood pressure, heart rate, EF and wall motion score index. Standard Doppler mitral and tricuspid indexes and pulmonary artery systolic pressure (PASP) did not differ between the 2 groups. Even by dividing patients according to the angiographic involvement of coronary arteries, no difference in Doppler standard measurements of RV function was found between 12 pts with single-vessel disease and 22 with multivessel disease. PW-TD analysis of RV tricuspid annulus showed lower Sm (9.5 ± 2.9 versus 13.2 ± 2.9 cm/sec, $p<0.01$) and longer PCTm e RTm (both $p<0.01$). In the overall population PASP had negative relation with Sm ($r = -0.60$, $p<0.01$) and positive relation with RTm ($r = 0.55$, $p<0.05$) in patients with inferior MI. PCTm ($r=0.58$, $p<0.01$) and RTm ($r = 0.55$, $p<0.05$) of LV mitral and RV tricuspid annuli were related one each other.
Conclusion: In patients with LV MI and reduced LV systolic function, Tissue Doppler, but not standard Doppler, allows to unmask RV involvement. This involvement is influenced by the degree of pulmonary arterial pressure and by ventricular interaction.

718 Regional right-ventricular function and haemodynamic changes in pulmonary arterial hypertension: ultrasonic strain and strain rate imaging study

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The ultrasonic regional myocardial deformation parameters, strain (S) and strain rate (SR) could be applied to better evaluate regional RV function in pts with pulmonary arterial hypertension (PAH).
Study Aim: To investigate if a relationship exists between changes in regional deformation in the RV free wall (RVFW) and hemodynamic findings in pts with PAH.
Methods: Right heart catheterisation with pulmonary artery pressure (PAP) and thermodilution cardiac output measurement was performed in 11 pts (age 60±14 years) with PAH using a flow directed Swan-Ganz Catheter. In all pts mean PAP was elevated (42±10mmHg) and pulmonary vascular resistance (PVR) increased (588±258 dyne.s.cm-5). The cardiac index was 2.9±0.8 l.min-1.m-2. Blood pool Doppler and S/SR measurements were performed during the same examination. For data analysis, the RVFW was divided into its two morphologically distinct segments: 1) the basal smooth and 2) the apical trabecular segments, and the RVFW longitudinal deformation indices determined for both.
Results: The measured variables are shown in the table. Peak systolic SR measured in RVFW apical segment correlated significantly with mean PAP ($p<0.05$; R=0.7) and PVR ($p<0.01$; R=0.8); the same was found for mean SR ($p<0.01$; R=0.77 and $p<0.05$; R=0.7) and peak systolic S ($p<0.05$; R=0.7 and $p<0.05$; R=0.63). Deformation parameters calculated in the basal RVFW did not correlated with any hemodynamic variable.

	Basal segment	Apical segment
Peak systolic Strain Rate,s-1	-2,2±0,8	-1,5±1,5
Mean systolic Strain Rate,s-1	-0,9±0,3	-0,6±0,6
Peak systolic Strain, %	-28±9	-21±20

Conclusions: For the first time, we have demonstrated that regional deformation parameters derived from the apical RVFW correlate with invasively measured hemodynamic variables. These observations would suggest that deformation in the morphologically distinct apical trabecular portion of the RV better reflects changes in the pulmonary circulation than those in the smooth basal segment inferring that each segment has a different functional response to raised wall stress. Thus deformation parameters measured in trabecular apical RV part could be used as non-invasive indices in the follow-up of pts with PAH.

719 Echocardiographic assessment of left and right heart function in patients with obstructive sleep apnoea

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Purpose: Echocardiographic assessment of right ventricle (RV) morphology and function is technically difficult, and data over right heart alterations and function in patients with obstructive sleep apnoea syndrome (OSAS) are inconsistent. We sought to investigate left and right heart function in OSAS patients by echocardiography and assess the relationship with the severity of OSAS.
Methods: Thirteen patients (M/F: 10/3) with OSAS, and 12 age matched controls (M/F: 7/5) had a routine 2-D and Doppler echocardiographic examination, as well as pulsed wave tissue Doppler (PWTD) mapping of systolic (Sm) and diastolic (early, Em, late diastolic Am) velocities of the mitral (MV) and tricuspid annulus (TA) and the RV free wall. The RV performance index (PI) was determined from the ratio of the sum of the isovolumic times and ejection time, which conceptually combines systolic and diastolic performance. All patients also had lung function tests, arterial blood gas analysis and a polysomnography.
Results: Clinically there was absence of full blown right heart failure in all OSAS patients. There was no significant difference ($p>0.1$) between patients and controls regarding, age: 61±11 versus 57±5 years, and left ventricle ejection fraction: 62±5 versus 66±4%; (values given are average±SD). However significant differences could be seen between, body mass index: 34±7 versus 24±2; systolic blood pressure (BP): 161±26 versus 130±10 mmHg; diastolic blood pressure: 92±21 versus 73±7 mmHg; RV end diastolic dimension: 3.0±0.3 versus 2.1±0.3 cm; pulmonary arterial systolic pressure: 39±10 versus 20±5 mmHg; RV PI: 0.33±0.5 versus 0.21±0.03;; MV Sm: 9±2 versus 12±3; TA Sm: 13±2 versus 15±2 cm/s; and RV Sm: 11±3 versus 13±1 cm/s (for all variables $p<0.02$). The diastolic parameters showed no significant differences. The apnoea hypopnoea index (AHI) was 46±27, tiffeneau ratio 97±11; PCO2 39±3 mmHg and PO2 84±8 mmHg. Regression analysis showed a strong correlation between AHI versus tiffeneau ratio (Spearman correlation, rho: -0.65, $p<0.05$), and between AHI and tissue Doppler derived indices of RV systolic function (TA Sm: r=0.65, $p<0.05$; RV Sm: r=0.70, $p<0.01$).
Conclusions: In these patients with mild pulmonary hypertension, the tissue Doppler derived indices of systolic RV function show a strong correlation with the severity of OSAS. PWTD imaging is a quantitative and technically simple way of assessing RV function, and may be potentially useful in the follow up and assessment of the effects of treatment in OSAS.

720 Right-ventricular tissue Doppler analysis in patients undergoing percutaneous closure of atrial septal defect

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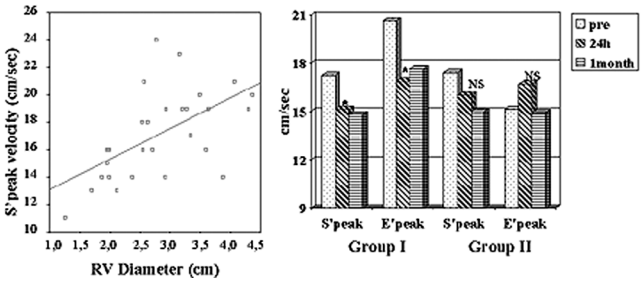
Purpose: To evaluate the effects of preload variations on TDI parameters in patients with RV overload undergoing percutaneous atrial septal defect (ASD) closure.
Methods: Thirty-nine patients with normal invasive pulmonary pressures undergoing percutaneous ASD closure were divided according to lateral RV TDI E/A: Group I (E/A>1, normal relaxation, n=30); Group II (E/A≤1 abnormal relaxation, n=9). Both parasternal M-Mode dimensions and right ventricular border TDI systolic, early and late diastolic peak velocities (S, E, A) as well as E/A ratio were recorded at baseline, 24 h and 1 month after intervention.
Results: No statystically different heart rates were recorded (baseline 85bpm; post 24h 83bpm; post 1 month 78bpm). A positive correlation was found only in group I at multivariate analisys between right ventricular diameter and both S peak (r=0.58 $p<0.01$, Fig.1) and E peak velocity (r=0.53 $p<0.01$). RV myocardial S and E baseline velocities (17.23.2 and 20.63.2cm/sec, respectively) significantly decreased both at 24 h (15.12.6 and 16.93.7cm/sec respectively, $p<.001$) and 1 month follow-up (14.82.5 and 17.63.0cm/sec respectively, $p<.001$ vs baseline) after ASD closure in the group I while no significant changes where found in group II (Fig.2). Early after intervention 66% of group II patients showed normalization of tissue Doppler E/A ratio.



TDI and Atrial Septal Defect.

Conclusions: Both RV systolic and diastolic TDI peak velocities seems to be preload dependent when normal tissue relaxation is found while preload dependence seems to be lost when abnormal tissue relaxation ensues. Furthermore percutaneous ASD closure early reverted TDI E/A in most patient showing abnormal tissue relaxation before intervention.

ENDOTHELIUM, PLATELETS, LIPIDS AND OXIDATIVE STRESS

721 Determinants of platelet nitric oxide response and superoxide levels in diabetic patients with acute coronary syndrome

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Diabetic patients (DM pts)have an increased mortality with acute coronary syndromes (ACS) when compared to non-DM pts. The mechanisms behind this observation remain uncertain. Recently, elevated blood sugar levels (BSL) have been shown to be independent predictors of mortality in DM pts with ACS. Platelets from patients with ACS are hyporesponsive to the anti-aggregatory effects of nitric oxide(NO) a phenomenon partially related to inactivation of NO by superoxide (O_2^-). We assessed the determinants of platelet NO response and O2- levels by a univariate and stepwise multivariate analysis in DM pts with ACS.

Methods: In 76 DM pts with ACS, we measured; (i) ex vivo platelet responsiveness to ADP and its inhibition by NO donor sodium nitroprusside (SNP,expressed as a % inhibition); (ii) whole blood O2- production, assessed by lucigenin derived chemiluminesence (LDCL) and (iii) platelet cyclic GMP (cGMP) generation in response to SNP. Correlates of these parameters were assessed by univariate analysis. Correlates of SNP response and O2- production were sought by a stepwise multiple logistic regression. The parameters assessed are summarised in the table.

Results: The mean SNP response was 39.6%±23.5SD. The LDCL was 20.8mv±21.2. Patient characteristics are summarized in the table.

Age (yrs)	66 ± 12.1	Statin therapy (n)	28
Sex	47M:29F	BSL (mmol/L)	14.3 ± 5.4
Insulin therapy (n)	12	CK (U/L)	332 ± 474
ACE-I therapy (n)	34		

On univariate analysis, increased BSL was correlated with impaired SNP response ($p<0.01$), and increased O2- production ($p<0.001$) but not with ADP induced aggregation or cGMP formation. On stepwise multiple logistic regression, SNP response was inversely related to BSL($P<0.01$) and increasing age($P<0.05$), while O2- production was directly related to BSL($P<0.01$).

Conclusions: These findings are consistent with the concept that extent of BSL elevation is the critical (and potentially correctible) determinant of oxidant stress and NO bioavailability in DM pts with ACS.

722 The influence of simvastatin on the angiotensin type 1 receptor density, oxidative stress and endothelial function in patients with coronary disease

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Aim: Oxidative stress is thought to be a key event in the pathogenesis of endothelial dysfunction and atherosclerosis. Statins are known to improve endothelial function in patients with coronary disease. We tested the hypothesis that in patients with stable angina simvastatin: (i) improves endothelial function by reducing oxidative stress and (ii) that this effect is due to the drug-induced reduction in cellular angiotensin AT1 receptor density.

Materials and methods: Lipid profile, platelet AT1 receptor density, serum F2-isoprostanes (marker of oxidative stress) and nitrate + nitrite concentration, and brachial artery flow mediated dilation (FMD, index of endothelial function) were assessed in 11 patients (LDL cholesterol 103-181 mg%) with proven coronary heart disease, which were not on hypolipemic treatment. These measurements were performed at baseline and after treatment with simvastatin 40mg/24 h for 12 weeks.

Results: At baseline there was a significant linear correlation (i) between AT1 density and F2-isoprostanes concentration (r=0,65; $p<0,05$) and (ii) between F2-isoprostane and FMD (r= -0,75; $p<0,05$). Simvastatin treatment caused a significant reduction in LDL cholesterol (134±28 vs. 78±20mg/dl; $p<0,00001$), AT1 receptor density (13,19±5,31 vs 6,73±1,76 receptors/platelet; p=0,0006), F2-isoprostanes (41,55±14,83 vs. 24,88±9,47pg/ml, p=0,032), a significant improvement in FMD (7,71±3,64% vs 10,41±4,73%; p=0,031), and non-significant increase in nitrite + nitrate (16,92±7,67 vs. 19,96±5,57uM; p=0,17). Among these simvastatin-induced effects, only changes in AT1 receptors and F2-isoprostane concentrations showed strong linear correlation (r=0,72, $p<0,05$).

Conclusions: For the first time we have shown in one study that statin (simvastatin) causes, in addition to LDL cholesterol reduction and endothelial function improvement, reduction in AT1 receptor density and oxidative stress. The results suggest cause-effect relationship between renin-angiotensin-aldosteron system activity and oxidative stress. The cause-effect relationship between LDL cholesterol, AT1 receptors, oxidative stress and endothelial function is not apparent from our study.

723 Induction of oxidative stress and endothelial dysfunction by interleukin-6 via angiotensin type 1 receptor overexpression

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In atherosclerotic plaques, the pro-inflammatory cytokine interleukin-6 (IL-6), the AT1 receptor (AT1-R), and angiotensin II (ang II) are co-localized. Interactions of IL-6 with the AT1-R may play an important role in the pathogenesis of atherosclerosis. Therefore, we investigated whether IL-6 influences AT1-R gene expression and production of reactive oxygen species (ROS) in vascular tissue and cultured vascular smooth muscle cells (VSMC).

Methods and Results: C57BL6 mice were treated with IL-6 for 18d (i.p.). IL-6 led to a significant overexpression of the AT1-R (161%±35% of control mice; real-time PCR) and to an increased ROS production (163%±32%; L-012 chemiluminescence) in the aorta. This was accompanied by an impaired endothelium-dependent vasodilatation and an enhanced ang II-induced vasoconstriction (aortic ring preparations). In AT1-R knock-out mice, these IL-6 effects were completely omitted. Cultured aortic VSMC were incubated with IL-6 for 0-24h. IL-6 led to a significant, time- and dose-dependent upregulation of AT1-R mRNA expression (max. 166%±25% of control; Northern blot) and protein expression (Western blot). IL-6 enhanced AT1-R gene transcription (nuclear run-on assay) but had no effect on AT1-R mRNA stability (transcription blockade). Experiments with specific pharmacological inhibitors revealed that the IL-6-induced AT1-R upregulation involved activation of PI-3-kinase, p38- and p42/44-MAP-kinase, and JAK2. Ang II-induced ROS production in VSMC was enhanced after pre-incubation with IL-6 for 24h (DCF fluorescence laser-microscopy).

Conclusions: IL-6 induces a significant enhancement of AT1-R gene expression and ROS production in vascular tissue and in cultured VSMC, leading to an impaired endothelial function and increased ang II-induced vasoconstriction. This interaction of interleukin-6 with the AT1 receptor may represent an important pathogenetic mechanism in the development and progression of endothelial dysfunction and atherosclerosis.

724 High serum cholesterol levels are associated with increased vasoconstriction and impaired relaxation in human internal mammary arteries

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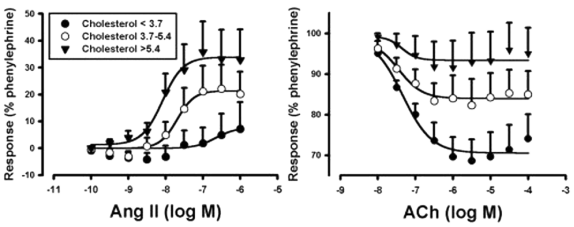
Objective: Increased angiotensin II (Ang II) and Ang II type 1 receptor overexpression of the activated renin-angiotensin system (RAS) plays a crucial role in the development of endothelial dysfunction. Since endothelial (dys-)function is also related to serum cholesterol levels we hypothesised cholesterol is associated with functional responsiveness to Ang II as well as endothelium-dependent relaxation.

Methods: Internal mammary artery segments of 27 patients undergoing coronary bypass surgery were harvested and evaluated in organ baths. Endothelium-dependent relaxation was measured by adding cumulative doses of acetylcholine (ACh, 10nM-100μM). After a washing and stabilisation period constriction to cumulative doses of Ang II were evaluated (0.1nM-1μM). Both were expressed as percentage of response to phenylephrine and correlated with cholesterol by Spearman Correlation (2-tailed). Comparisons between the complete concentration-response curves of Ang II and ACh were made by repeated measures analyses of variances.

Results: Maximal constriction in response to Ang II (r=0.44, p=0.03) and maximal relaxation in response to ACh (r=0.50, $p<0.01$) correlated well with total serum cholesterol. Furthermore, response to ACh was inversely correlated with Ang II response (r= -0.49, p=0.01). Multiple comparisons analysis of variance between concentration-response curves according to tertiles of total cholesterol (<3.7; 3.7-5.4; >5.4 mmol/L) demonstrated increasing constriction in response to Ang II (p=0.04) and decreasing relaxation in response to ACh (p=0.02), respectively (figure).

Conclusion: We demonstrated for the first time a direct beneficial effect of lower cholesterol on Ang II response and observed an inverse correlation with endothelium-dependent relaxation.



725 Deletion of p66Shc gene protects against age-related endothelial dysfunction

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Purpose: Cardiovascular disease increases in frequency with age even in the absence of established risk factors, suggesting that aging by itself alters vascular function. Indeed, an enhanced production of reactive oxygen species (ROS) has been recognized as the major determinant of age-related endothelial dysfunction. P66shc protein modulates oxidative stress response. Recently, it was reported that p66shc knock-out (p66-/-) mice are resistant to oxidative stress and have a 30% increase in total life span. The present study was designed to assess age-dependent changes of endothelial function in this model.
Methods: Aortic rings from young (6 month old) and old (16 month old) p66-/- and wild-type (WT) control mice were suspended for isometric tension recording. Nitric oxide (NO) release was measured by a porphyrinic microsensor. Endothelial NO synthase (eNOS) and total nitrotyrosine-containing protein expression were assessed by western blotting.
Results: The endothelium-dependent relaxations to acetylcholine (10-9 to 10-4 M) were significantly increased in both young and old p66-/- compared to age-matched WT control mice (maximal response: 48±8% vs 32±5% and 38±9% vs 26±10%, respectively; n=9-13 $p<0.05$). Accordingly, higher levels of NO release were found in aortas from young and old p66-/- compared with WT mice (496±34 vs 310±26 nM/L and 415±70 vs 224±29 nM/L, respectively; n=8-13; $p<0.05$). We further investigated the NO pathway by assessing eNOS protein expression in all groups. Only a slight eNOS up-regulation was found in p66-/- compared to WT mice. To determine whether the increased NO availability in p66-/- mice was due to a reduction of ROS-induced NO breakdown, we also quantified the amount of aortic nitrotyrosine-containing proteins as a marker of oxidative stress. Old WT displayed a two fold increase of total nitrated proteins compared to young mice (n=6, $p<0.05$). In contrast, no age-dependent difference in protein nitrosilation was found in p66-/- mice.
Conclusions: Our results strongly suggest that the enhanced oxidative stress resistance of p66-/- mice is protective against age-dependent ROS-mediated endothelial dysfunction.

726 Impaired endothelial vasomotor function in angiographically normal artery after acute coronary syndrom: a transient phenomenon influenced by hs-C-reactive protein and high-density lipoprotein cholesterol levels

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Background: Endothelial dysfunction is an initial event in the development of atherosclerosis and may contribute to the progression of the disease. In previous trials, forearm blood flow measurements or intra-coronary testing at the location of the culprit lesion, have shown a high incidence of abnormal endothelium-dependent vasoreactivity in patients (pts) after acute coronary syndrome (ACS).
Objective and Methods: The present study tests the hypothesis that ACS may be associated with endothelial dysfunction far from the responsible lesion. Serial doses of acetylcholine were infused in an angiographically normal coronary artery to assess endothelium-dependent coronary vasomotor response. Endothelium-independent response was studied by intra-coronary injection of molsidomine. These tests were performed before any coronary angioplasty, at least 72 hours after the last symptom and the withdrawal of vaso-reactive drugs. 43 consecutive male pts (aged 54.3 ± 1.7 years) with one or two focal lesions were included (dyslipidemia, diabetes and malignant disease were exclusion criteria). All the patients had similar tests 6 months later.
At baseline and follow-up a large panel of lipid analyses (total cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C, apoA-1, apoB, apoCIII, apoE, LpA1, Lp(a)) were carried out. Inflammatory markers (fibrinogen, hs-CRP) and adhesion molecules (VCAM-1, ICAM) were assessed.
Results: Of the 43 pts, 35(81.4%) presented initial abnormal endothelium-dependent vasomotricity. The univariate analysis did not show any significant relationships between baseline vasomotor function and clinical or biological characteristics. At 6 months, a significant improvement was observed in 27 (77.1%) of the 35. In univariate analysis, predictors of improvement were: HDL-C and apoA1 6-month levels,delta HDL-C (% change between 6 months and baseline) and 6 months hs-CRP value. In multivariate models, HDL-C, apoA1 and delta HDL-C remained statistically significant. A strong inverse relation was found between % arterial diameter change (baseline to 6 months) and 6-month hs-CRP level ($r = -0.67$, $p < 0.0001$).
Conclusion: Patients with ACS have frequent and severe initial endothelial dysfunction in angiographically "normal" coronary arteries. In most cases, we observe a significant improvement at follow-up, suggesting a possible systemic reaction component in the first few days after ACS. The relationship between improved vasomotor function and HDL-C values shows the need for therapeutic intervention to increase HDL-C and particularly the apoA1 subfraction.

NON-CORONARY PERCUTANEOUS CARDIAC INTERVENTIONS

727 The effect of probucol and brachytherapy (EVBT) on restenosis after angioplasty of the femoro-popliteal arteries: a randomised multicentre trial

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Background: There is an increasing interest of invasive cardiologists in peripheral interventions.We present here the final results of a randomized multicenter trial evaluating the effects of endovascular (EVBT) and/or pharmacological drug prevention using the anti-oxidant P on the incidence of restenosis after (PTA) of the femoro-popliteal arteries.
Methods: A total of 335 patients with claudication Rutherford 2 or 3 undergoing PTA of the femoro-popliteal arteries were randomized according to a 2x2 factorial design to one of the following four groups: EVBT, probucol, EVBT plus probucol and control placebo group. The intravascular gamma-radiation dose was 14 Gy applied from a non-centered endoluminal catheter at a depth of 2 mm. P (1 g/day) given according to a randomized double blinded protocol was started one month before up to 6 months after PTA. Primary endpoint was restenosis defined as > 50% reduction of diameter reduction as detected by duplex ultrasound performed 6 months after PTA.
Results: The actuarial restenosis rate at 6 month follow up was 17% in the group of patients undergoing EVBT, 20% in the patients treated with EVBT and P, 27% in those treated with P and 42% in control patients ($p < 0.01$ for both EVBT and P). The rates of patients free of claudication at 6 month follow up (Rutherford 0) were 79.4 percent in EVBT group, 74,2 percent in the combined-treatment group, 78,5 percent in P group and 56 percent in the control group ($p<0.01$ for both EVBT and P). The rates of repeated angioplasty were 4,7 percent, 7,4 percent, 11,9 percent and 17 percent, respectively ($P< 0.01$ for EVBT). Late thrombotic occlusion occurred in 4,8% and exclusively in patients treated with EVBT after stent implantation.
Conclusions: This randomized multicenter trial demonstrates for the first time that EVBT and P after PTA of the femoro-popliteal arteries reduce the restenosis rate by 50% and by 23% respectively with significant improvement of symptoms and reductions of re-interventions in a range similar to that obtained by drug eluting stents.

728 Different outcome after percutaneous closure of a patent foramen ovale or medical treatment to prevent cryptogenic stroke

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Background: Paradoxical embolism through a patent foramen ovale (PFO) may be one of the causes of a cryptogenic stroke (CS). Nevertheless literature remains inconclusive about the optimal therapy to prevent recurrence: percutaneous closure of the PFO or medical treatment? We were interested in detecting differences in clinical and demographic variables, outcome and safety in both treatment regimens. **Methods:** One hundred and fifty records of patients who were admitted to our hospital with stroke between 1998 and 2001 were reviewed. Patients with CS and the presence of a PFO were included. When no cause was identified, stroke was defined as cryptogenic. Depending on the choice of treatment (medical therapy or percutaneous PFO closure) patients were categorised in group A and B, respectively. Demographic and clinical variables (age, gender, arterial hypertension, diabetes mellitus, hypertriglyceridemia, nicotine abusus, ischemic heart disease or familial cardiovascular antecedents) were obtained. PFO characteristics (hypermobile septum, aneurysm of the interatrial septum) and type of stroke (transient ischemic attack, cerebral ischemia with transient signs or cerebrovascular accident) were noticed. Recurrent stroke or death were considered as primary endpoint and safety of both treatment regimens was evaluated. Student t, chi square and Fisher exact-test were used where applicable. Statistical significance was defined as $p<0.05$. **Results:** Eighty-seven patients (49 male, 38 female; age 52 ± 14 y, mean$\pm$SD) were included; sixty-three patients, who did not match with the criteria of CS, were excluded. Mean follow-up time was 22 ± 13 months. Demographic and clinical variables were comparable in both groups, except for age (58 ± 16 and 48 ± 12 y for group A (n=38) and B (n=49), respectively, $p<0.05$). No differences were found in PFO characteristics. Ninety-two percent of the patients in group A were treated with anti-platelets; all patients in group B were treated with anti-platelets for at least six months. On treatment, stroke reoccurred in 3 patients in group A versus no patients in group B (8% versus 0%, $p < 0.05$). In one patient on aspirin of group A bleeding of a stomach ulcer and in two patients of group B transient atrial fibrillation occurred. **Conclusions:** Although paradoxical embolism through a PFO is considered as one of the causes of CS, percutaneous closure to prevent recurrence remains controversially. This pilot study suggests benefit of percutaneous closure, and proves safety and efficacy. More powered studies will be necessary to confirm these preliminary findings.

729 Percutaneous closure of patent foramen ovale reduces migraine frequency

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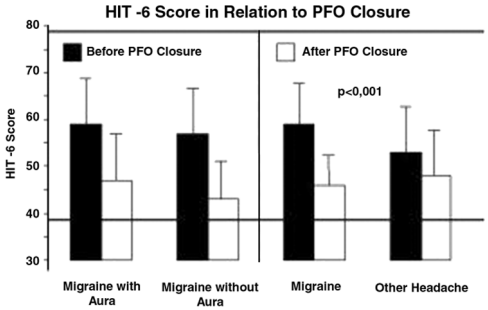
Background: Patients with migraine with aura have a higher prevalence of right-to-left shunt compared with controls, as assessed by transcranial Doppler. Accordingly, paradoxical embolism might be a trigger of migraine attacks. **Methods:** In 215 pts. with patent foramen ovale (PFO) mediated paradoxical embolism, we retrospectively assessed the prevalence of migraine, and the effect of percutaneous PFO closure on its frequency and intensity. Headache was classified according to the criteria of the International Headache Society (IHS). Headache severity before and after PFO closure was assessed using the validated Headache Impact Test (HIT-6; score 36 to 78). A HIT-6 score $>$ 55 indicates substantial impact of headache on daily life.
Results: The one-year prevalence of migraine with aura was significantly higher in patients with PFO and presumed paradoxical embolism (17% [37/215]) compared with the general population (3-4%)($P<0.001$). After percutaneous PFO closure, relative reduction in migraine attack frequency was 56 $\pm$ 41%, compared with 18 $\pm$ 87% in patients with other headache (P=0.02). Attack frequency was similarly reduced in patients with migraine with and without aura 54 $\pm$ 44% vs. 62 $\pm$ 35%, $p>0.2$). Headache impact on daily life as assessed by the HIT-6 score decreased from 59 to 46 in patients with migraine, and from 53 to 48 in patients with other headache (figure, p=0.001). **Conclusions:** In patients with presumed paradoxical embolism across a PFO, the prevalence of migraine, especially with aura, is increased. After percutaneous PFO closure, attack frequency of migraine with and without aura is reduced in 80% of all patients.



730 Patients at risk for recurrent embolism after percutaneous closure of patent foramen ovale for resumed paradoxical embolism

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Background: Percutaneous closure of a patent foramen ovale (PFO) is an alternative to medical or surgical prevention of recurrent embolism in patients with presumed PFO mediated paradoxical embolism. Risk factors for recurrence after successful PFO closure have not been completely elucidated yet. **Methods:** 299 patients with presumed PFO mediated paradocixal embolism were followed after percutaneous PFO closure for a total of 662 patient-years (mean follow-up: 2.2 years, range 0.2 – 8.5 years), assessing postprocedural shunt, recurrent embolic events and device-related morbidity. Freedom of recurrence was calculated according to the Kaplan-Meier method. Predictors of recurrence were calculated using a Cox proportional hazard model. **Results:** Twenty recurrent embolic events were observed (14 transient ischemic attacks, 5 events of peripheral embolism, 1 stroke), resulting in an actuarial recurrence rate of 3.8% (95% CI 1.7-6.4%) at 1 year, 7.9 (95% CI 4.9-12.6) at 2 years, and 8.7 (95% CI 5.5-13.7%) at 4 years. Univariate predictors of recurrence were age at implantation $>$ 60 years (hazard ratio 2.7, 95% CI 1.1-6.5), cardiovascular risk factors (hazard ratio 1.5 for every additional factor, 95% CI 1.05-2.1), and most importantly the number of embolic events prior to PFO closure ($>$ 2 events: hazard ratio 4.1, 95% CI 1.7-9.8; Figure 1). Since patients with multiple embolic events prior to PFO closure were older, only the cardiovascular risk profile and $>$ 2 events prior to PFO closure remained significant predictors of recurrence in a multivariate Cox proportional hazard analysis. There was no relation between recurrence rate and atrial septal anatomy (PFO with or without atrial septal aneurysm), gender, residual shunt after 6 months, type or size of device, and embolic index event. **Conclusions:** Patients with $>$ 2 thromboembolic events prior to device implantation and patients with multiple cardiovascular risk factors are at increased risk for recurrence of embolic events after PFO closure. These findings suggest that alternative mechanisms in addition to paradoxical embolism may be present in this patient group.

731 Transient neurological symptoms in adult patients after transcatheter atrial septal defect closure

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Background: Transcatheter closure of atrial septal defects (ASD) with the Amplatzer septal occluder (ASO) appeared to be safe and effective and has become the treatment of choice for selected patients (pts). However, some of the pts complained of neurological problems after ASO implantation. The incidence, pattern and risk factors of these symptoms were investigated. **Material and methods:** Between XI.1997 and XI.2002, 163 adults (40 male), aged 16-76y (38.7 ± 17.1) underwent successful ASO implantation. Aspirin, 150-300mg was originally prescribed for 3 months. They had follow-up visits at 1 month (163pts), 3 months (163pts), and 12 months (103pts) and yearly thereafter, according to the protocol. **Results:** Neurological episodes - transient vision disturbances (TVD) and headaches (HA), were reported by 22 pts (13.5%). There were no pts with a history of TVD before the procedure. TVD included: temporary bilateral (1 patient), or unilateral (2 pts) loss of vision, reduced field of vision (7 pts) and scotomas (7 pts). These occurred from 1 to 24 weeks (mean 6.11) after the procedure and incidentally recurred (6pts) during 3-12 weeks after the first incident. The single episode duration was from few minutes up to four hours. In four pts episodes of TVD coincided with HA. All the symptoms resolved without neurological deficit. There was a coincidence of TVD onset with aspirin discontinuation in two pts. Intensified (4pts) or new HA without TVD occurred in 5 pts 1 to 4 weeks after the procedure and recurred during 1 to 8 weeks after the first episode. In repeated transoesophageal or transthoracic echocardiogram performed in all pts with HA or TVD the device was in proper position, with neither residual shunt, nor evidence of thrombus. In all pts with neurological symptoms aspirin therapy was prolonged for up to 6 months. Coumadin was added to aspirin in the group of patients with TVD. There were neither differences in terms of gender (82.3% vs 77.4% female) nor ASO size (21.7 ± 7.4 vs 21.5 ± 7.1 mm) between pts with and without symptoms (respectively). The pts with symptoms were younger (31.7 ± 11.5 vs 41.9 ± 16;p=0.005). **Conclusions:** Transient vision disturbances and/or headaches are observed in 13.5% of adults with ASD after ASO implantation. These symptoms may be related to microembolies originating from the occluder and/or platelet activation on the disc. We recommend antithrombotics (Coumadin) in addition to Aspirin for at least 6 months for all adults after ASO implantation.

732 Percutaneous closure of patent foramen ovale: head-to-head comparison of two different devices

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Background: Percutaneous closure of patent foramen ovale (PFO) is an emerging treatment for young patients who suffered cryptogenic stroke or paradoxical embolism. Amongst different devices used for PFO closure, two different types are being implanted at our institution: PFO-Star (Cardia Inc, Burnsville, MN) and Starflex (NMT Medical Inc, Boston, MA). We present the results of an ongoing comparison of both devices.
Methods: We prospectively collected data of 33 patients (females: 33%, age: 23-61 years, mean: 45 $\pm$ 10 y, interatrial septal aneurysm (IAS) $>$ 11 mm: 67%) who underwent percutaneous closure of PFO after cryptogenic stroke (n = 31) or paradoxical embolism (n = 2), divided into two subgroups who received either a PFO-Star (Pop 1, n = 20) or a Starflex occluder (Pop 2, n= 13). Residual shunting after closure is echocardiographically controlled at rest and during a Valsalva maneuver (grade 3 = important, grade 2 = moderate, grade 1 = minor, grade 0 = absent) at 1, 3, 6 and 12 months.
Results: In Pop 1, mean age was 45 $\pm$ 9 years, IAS 60%, mean degree of shunting 2.8 $\pm$ 0.4, and in Pop 2 mean age was 46 $\pm$ 12 years, IAS 78%, mean degree of shunting 2.7 $\pm$ 0.5. The degree of residual shunting was significantly reduced in both populations after intervention. The proportion of pts with no or minor residual shunt after closure was 79% in Pop 1 vs 88% in Pop 2. The degree of residual shunt appears to be higher in the presence of an IAS in Pop 1 but not in Pop 2. No recurrent stroke or paradoxical embolism was seen during a follow-up of 3-28 months (mean: 11.4).
Conclusion: Our datas concerning percutaneous closure of PFO, in a modest number of patients extracted from an ongoing comparison in a highly selected population with a large proportion of IAS, confirm that this treatment is a safe and effective technique. The residual shunting after closure might be influenced by the type of device used, and by the presence of an IAS. The clinical significance of these results remains to be determined by a longer follow-up and extended study population.

ELECTRICAL REMODELLING AND ARRHYTHMOGENESIS: NOVEL INSIGHTS

733 A molecular basis for HCN channel over-expression

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Background: Myocardial hypertrophy and failure is characterized by remodeling of ventricular cardiomyocytes (VCM), leading to electrophysiological abnormalities responsible for severe arrhythmias. A functional over-expression of the f-current occurs in VCM isolated from both hypertrophied rat hearts and failing human hearts, where it might contribute to arrhythmias. Four different genes encoding for the f-channel are known and termed Hyperpolarization-activated Cyclic-Nucleotide-gated Channels (HCN 1-4). No information is available on the influence of cardiac disease on isoform expression, and its relationship with the functional occurrence of the f-current. This study aimed to investigate the effect of hypertrophic factors on HCN expression in primary cultures of adult rat VCM, a well-established model for studying the molecular events involved in myocardial remodeling.
Methods and Results: VCM isolated from the left ventricle of adult rat hearts were cultured either in control condition or in the presence of 0.1 μM endothelin-1 (ET-1) for 4-9 days. Total mRNA was converted to cDNA by reverse transcription. Primers and probes were designed to amplify cDNA of HCN1-4 genes and quantify mRNA by Real-Time PCR. Cultured VCM expressed HCN2, 3 and 4 isoforms, the rank of expression being HCN2$\gg$HCN4$>$HCN3. The specific mRNA for HCN3,4 isoforms significantly increased with time (HCN3: +19.7$\pm$0.9% at 6 days and +24.5$\pm$1.5% at 7 days, $p<0.001$ vs. 0-4 days; HCN4: +48.5$\pm$4.9% at 6 days and +93.2$\pm$7.4% at 7 days, $p<0.001$ vs. 0-4 days). At 6 day of culture, exposure to ET-1 caused a selective and significant increase of mRNA coding for HCN2 with respect to controls (+141.3$\pm$54.8% vs. +38.5$\pm$12.2%, $p<0.001$). These results were in agreement with patch-clamp measurements of f-current in cultured cells. The technique was used to measure (Cm), an index of cell size, and f-current, evoked by hyperpolarization to -120 mV. At 6-9 days of culture, membrane capacitance, an index of cell size (+72%) and f-current density (+171%) markedly augmented as compared to 3-5 days. f-current density was significantly higher in cells exposed to ET-1 (3.7$\pm$0.5pA/pF, n=31) than in control cells (2.3$\pm$0.4pA/pF, n=40) ($p<0.05$).
Conclusions: Ventricular cardiomyocytes express HCN2,3,4 isoforms with a predominance of HCN2. In cultured cells, chronic exposure to ET-1 increases the mRNA expression of the HCN2 isoform and the functional expression of f-current density, with respect to control conditions. These results suggest that hypertrophic factors such as ET-1 play a major role in cardiac electrophysiological remodeling.

734 Increased number of Ca^{2+} sparks and waves in human atrial myocytes from patients with atrial enlargement

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Background: Spontaneous calcium (Ca^{2+}) release from the sarcoplasmic reticulum (SR) is potentially arrhythmogenic and atrial enlargement predisposes to the development of atrial fibrillation. We sought to investigate whether atrial enlargement is arrhythmogenic by altering the spontaneous SR Ca^{2+} release.
Methods: Myocytes were obtained by enzymatic digestion of atrial tissue from patients undergoing open-chest cardiac surgery. Ca^{2+} sparks were detected using the fluorescent Ca^{2+} indicator fluo-3 and confocal microscopy in the line scan mode. Ca^{2+} sparks were detected at rest during 2x10 seconds. The frequency of Ca^{2+} sparks and waves were normalized to the cellular volume scanned.
Results: 109 atrial myocytes from 21 patients were used to analyze the relationship between atrial size and local spontaneous Ca^{2+} release (Ca^{2+} sparks and Ca^{2+} waves). Echocardiographic atrial size was normal in 6 patients (34$\pm$1 mm) and enlarged in 15 patients (50$\pm$2 mm). The frequency of Ca^{2+} sparks was higher in patients with atrial enlargement (88$\pm$8 vs 15$\pm$6 pl-1 s-1, $p<0.001$). Likewise, the frequency of Ca^{2+} waves was increased in patients with enlarged atria (28$\pm$5 vs 0.9$\pm$0.9 pl-1 s-1, $p<0.005$). Permanent atrial fibrillation occurred in 4 out of the 15 patients with atrial dilation, while the arrhythmia was not observed in patients with normal atria.
Conclusions: The increased number of Ca^{2+} sparks and waves in atrial myocytes from patients with atrial enlargement suggest that 1) Atrial enlargement leads to alterations in the Ca^{2+} release from the SR and 2) Spontaneous Ca^{2+} release from the SR could be involved in the genesis of atrial arrhythmias in patients with atrial dilation.

735 Alteration of cardiac connexins in patients with cardiomyopathy

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Cardiomyopathy is a heart disease which is often associated with arrhythmia. Remodeling processes have been described to be involved in the pathophysiology of this disease. The normal heart works as a syncytium the cells of which are connected via low resistance pathways, the intercellular gap junction channels. These gap junction channels are dodecameric channels of connexins. In the heart at least three connexins are expressed: Cx43, Cx40 and -in early stages of development- Cx45. The goal of our study was to investigate in humans whether dilated (DCM) or hypertrophic cardiomyopathy (HCM) is associated with alterations of the connexin isoform expression and localisation. Therefore, biopsies were taken from the ventricle of either healthy controls (n=8), patients with DCM (n=6) or patients with HCM (n=3). Only patients without coronary heart disease (CHD) were admitted to the study. In all patients ejection fraction was assessed using echocardiography. Tissue was quickly frozen and processed for immunohistology and for polymerase chain reaction (PCR). For immunohistological analysis we determined the percentage of the longitudinal membrane length which expressed connexin and the percentage of the cell pole membrane expressing connexin. PCR was performed for Cx43 and Cx40 and was related to the house keeping gene GAPDH. Immunohistological analysis of the biopsies revealed that in DCM the overall expression of Cx43 was significantly diminished if ejection fraction was lower than 50%. More detailed analysis showed that expression of Cx43 at the polar membrane was reduced from 55$\pm$6% to 30$\pm$8% and at the lateral membrane from 10$\pm$4% to 4$\pm$2%. PCR analysis of Cx43mRNA revealed that in DCM Cx43mRNA was significantly decreased to 25$\pm$5%. Cx40mRNA was not altered significantly in these patients. In contrast to DCM in HCM patients we found a significant increase in Cx43mRNA to 225$\pm$34%. Cx40mRNA was not altered in these patients and was at very low levels. Thus, we conclude that in patients with DCM in absence of CHD Cx43 is downregulated, while in patients with HCM Cx43 expression is enhanced. This altered expression of the gap junction channel protein may be involved in the pathophysiology of arrhythmia associated with cardiomyopathy.

736 Chronic beta-adrenoceptor blockade enhances 5-HT effects on calcium current and action potentials in human atrial myocytes

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Purpose: Long-term treatment with beta-adrenoceptor antagonists (beta-blockers) has been shown to enhance the 5-HT induced increase in human atrial contractility but it is not known if this is accompanied by electrophysiological changes. The aim of this study was to compare the effects of 5-HT on calcium current, action potentials and refractoriness in atrial cells from patients treated and not treated with beta-blockers.
Methods: Cells were isolated enzymatically from the right atrial appendage of 30 consenting patients undergoing cardiac surgery who were in sinus rhythm. Procedures for obtaining tissues were approved by the institutional ethics committee, and conform to the Declaration of Helsinki. The whole cell perforated patch clamp technique was used at 37°C to record L-type Ca^{2+} current (ICaL) using depolarising voltage clamp steps from a holding potential of -40 mV. Action potentials and the effective refractory period (ERP) were recorded using current clamp with cells paced at a frequency of 75 beats/min.
Results: 5-HT (1 nM-10 μM) caused a concentration dependent increase in ICaL with a maximum response at 1 μM. This 5-HT induced maximal increase in ICaL was potentiated in cells from beta-blocked (300$\pm$13% increase above control values, n=19 cells from 13 patients) compared with non-beta-blocked patients (220$\pm$6%, n=15 cells from 7 patients; $P<0.05$). Neither the affinity nor the Hill coefficient of the 5-HT dose-response curve was affected by treatment with beta-blockers. In line with this effect on ICaL, 5-HT (10 μM) produced a significantly greater prolongation of action potential duration (APD) measured at 50% repolarisation in the beta-blocked (absolute prolongation of 33$\pm$9 ms, n=20 cells from 11 patients) than in the non-beta-blocked patients (10$\pm$4 ms, n=16 cells from 8 patients; $P<0.05$). However, both the APD90 and ERP, at 193$\pm$20 and 178$\pm$23 ms, respectively, in the cells from the non-beta-blocked patients, and at 235$\pm$21 and 223$\pm$21 ms, respectively, in those from the beta-blocked patients, were unaffected by 5-HT. Abnormal automaticity was observed in response to 5-HT in 25% of the cells studied from beta-blocked, compared with 0% from the non-beta-blocked patients (P=0.056).
Conclusions: These data indicate that in the human atrium, chronic beta-blockade is associated with a potentiated effect of 5-HT on calcium current, early repolarisation and automaticity but not on late repolarisation and refractoriness. Supported by Johnson & Johnson Pharmaceutical Research and Development.

737 The contribution of the human atrial Na^+,K^+ pump current to atrial fibrillation-induced electrical remodelling

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Aim: To assess the contribution of the Na^+,K^+ pump current (Ip) to the action potential duration (APD) and effective refractory period (ERP) in human atrial cells, and to investigate whether Ip contributes to the changes in APD and ERP associated with chronic atrial fibrillation (AF).
Methods: Action potentials and ion currents were recorded using the whole cell patch clamp in atrial myocytes isolated from consenting patients undergoing cardiac surgery, who were in sinus rhythm (SR) or AF (of >3 months duration).
Results: In cells from patients in SR, the Ip blocker, ouabain (10 μM) significantly depolarised the resting membrane potential (Vm) from -80$\pm$2 (mean$\pm$SE) to -73$\pm$2 mV, and lengthened both the APD (174$\pm$17 vs 197$\pm$23 ms at 90% repolarisation) and ERP (208$\pm$22 vs 276$\pm$14 ms; $P<0.05$ for each, Student's t-test, n=7 cells, 5 patients). Ip was measured with an elevated pipette $[Na^+]$ of 30 mM, by increasing extracellular $[K^+]$ ($[K^+]_o$) from 0 mM to 5.4 mM. This produced an outward shift in the holding current at -40 mV, which was abolished by 10 μM ouabain. The K^+ and ouabain sensitive current densities were similar, at 0.99$\pm$0.13 and 1.12$\pm$0.11 pA/pF, respectively ($P>0.05$; n=9 cells, 3 patients), confirming the K^+ induced current as Ip. Ip increased linearly with increasing Vm (between -120 mV and +60 mV) from 0.46$\pm$0.08 to 1.54$\pm$0.13 pA/pF ($P<0.05$; n=25 cells, 12 patients). Stepwise increments in $[K^+]_o$ (between 0 mM and 10 mM) increased Ip at -40 mV in a concentration dependent manner (maximum response, Emax=1.19$\pm$0.09 pA/pF; EC50=1.71$\pm$0.15 mM; n=27 cells, 9 patients). In cells from patients in AF, the sensitivity of Ip to both Vm and $[K^+]_o$ (Emax=1.02$\pm$0.05 pA/pF, EC50=1.54$\pm$0.11 mM; n=44 cells, 9 patients) was not significantly different from that in the cells from patients in SR. Within the group of patients in AF, long term treatment with digoxin (n=5 patients) was associated with a small, but significant, reduction in both Emax (0.92$\pm$0.07 pA/pF) and EC50 (1.35$\pm$0.15 mM), compared with non treatment (Emax=1.13$\pm$0.08 pA/pF, EC50=1.76$\pm$0.14 mM; $P<0.05$ for each, n=4 patients). In cells from patients in AF, but not treated with digoxin, both the voltage and $[K^+]_o$ sensitivity (Emax and EC50) were similar to those in the cells from patients in SR.
Conclusions: The Na^+,K^+ pump current, Ip, contributes to the human atrial cell Vm, action potential shape and ERP. However, the similarity in Ip sensitivity to both $[K^+]_o$ and Vm between atrial cells from patients with and without chronic AF suggests that Ip is not involved in AF-induced atrial electrophysiological remodelling in patients.

738 Atrial contractile remodelling in chronic atrial fibrillation is due to impaired calcium release from a normally loaded sarcoplasmic reticulum

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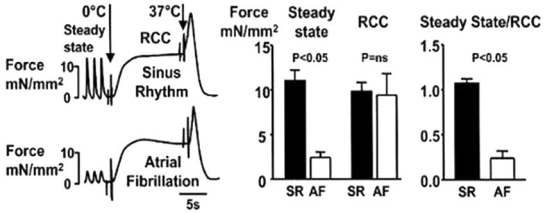
Background: After prolonged atrial fibrillation (AF) the mechanical function of the atria is reduced (contractile remodeling). Apart from a downregulation of the L-type Ca^{2+} current also changes in Ca^{2+}-handling by the sarcoplasmic reticulum may contribute to this phenomenon. We hypothesized that contractile remodeling is due to depletion of the intracellular Ca^{2+}-stores.
Methods: Thin atrial trabeculae were isolated from the right atrial appendages of 40 consecutive patients undergoing open heart surgery. 28 patients were in sinus rhythm, 12 were in persistent AF (>3months). The muscle bundles were transferred to an organ chamber and connected to an isometric force transducer (stimulation at 1 Hz). During cooling of the unstimulated muscle preparations from 37°C to 0°C all Ca^{2+} stored in the sarcoplasmic reticulum is released into the cytoplasm resulting in contracture. The amplitude of this rapid cooling contracture (RCC) indicates the amount of Ca^{2+} stored in the sarcoplasmic reticulum.
Results: Steady state force of contraction (1Hz) was 78% lower in AF patients. Surprisingly, the RCC amplitude did not differ between both groups. The ratio between steady state and RCC amplitudes was clearly reduced in AF patients.



RCC and Force of Contraction in SR vs AF.

Conclusion: Although steady state force of contraction is reduced by 78% in atrial myocardium of AF patients, the Ca^{2+}-load of the sarcoplasmic reticulum is not decreased. Rather, the reduced steady state/RCC ratio strongly suggests that the atrial contractile dysfunction induced by atrial fibrillation is due to an impaired release of Ca^{2+} from a normally loaded sarcoplasmic reticulum.

DIABETES AND CORONARY DISEASE: FROM LEPTIN TO RAGE

739 Leptin, a new target for stimulation of collateral artery growth

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Background: Arteriogenesis is orchestrated by migrating monocytes/macrophages; in previous studies we have shown that GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), a cytokine known to stimulate arterial collateral growth, strongly induces Leptin expression in bone-marrow derived macrophages. These data prompted us to investigate the direct effects of leptin on collateral artery formation in a pump-driven pressure-flow perfusion model in the rabbit hind limb.
Methods and Results: In 12 New Zealand White Rabbits (NZWR) the femoral artery was ligated, leptin (0,1 mg/kg/d) was continuously infused via osmotic minipump into the proximal stump of the occluded artery over 7 days. Body weight and temperature were monitored. After 7 days, a significant increase in net forward flow into the right hind limb (21,33 $\pm$ 1,20 vs. 17,22 $\pm$ 3,40 ml/min, $P < 0,05$) as well as a significant increase in the flow ratio (occluded vs. non-occluded leg) was found upon Leptin treatment (Leptin: 0,674 $\pm$ 0,094 vs. PBS: 0,536 $\pm$ 0,099, $P<0,05$). These data were confirmed by the gold standard method of microsphere perfusion as well as histological markers (Ki-67).
Conclusion: To the best of our knowledge this is the first report about a novel property of the adipocytokine Leptin, augmenting perfusion of peripheral tissue via stimulation of collateral artery growth (arteriogenesis). This multifunctional hormone could constitute a new target for therapeutic arteriogenesis as a treatment modality to treat patients with vascular occlusive disease.

740 Acarbose prevents cardiovascular events in patients with impaired glucose tolerance. Results of the STOP-NIDDM electrocardiogram evaluation

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Purpose: The administration of the alpha-glucosidase inhibitor acarbose to patients with impaired glucose tolerance (IGT) has been shown to delay the development of type 2 diabetes in the randomised placebo-controlled STOP-NIDDM trial. The objective of this analysis was to evaluate the impact of acarbose on cardiovascular events in patients with IGT.
Methods: A total of 1353 patients with IGT were randomly allocated to acarbose or placebo in the STOP-NIDDM study. The mean follow-up was 3.3 years. Cardiovascular events were evaluated centrally and blinded. In addition 12-lead ECGs of every subject were recorded at baseline and at the end of the treatment period. All ECGs were read by two independent cardiologists and changes were classified according to the Minnesota coding conventions.
Results: A total of 1181 patients had evaluable ECGs at baseline and at the end of the treatment. In 74 patients significant changes were observed (Table 1), in 5 patients there was an improvement according to the Minnesota code, all of these occurring in the acarbose group. The total number of myocardial infarctions confirmed by the clinical events committee and observed in the ECG evaluation were significantly higher in the placebo group (2.8% vs. 0.3%, p=0.002). In addition lower rates of angina pectoris (1.7% vs. 0.7%) and coronary revascularization procedures (2.9% vs. 1.6%) were reported in the acarbose treated patients.

ECG Evaluation

	Placebo (n=604)	Acarbose (n=577)
Myocardial infarction	7 (1.2%)	1 (0.2%)
Ischemia	23 (3.8%)	21 (3.6%)
Other findings	8 (1.4%)	9 (1.6%)

Conclusions: By reducing postprandial hyperglycaemia acarbose prevents myocardial infarctions in patients with IGT. This is the first study to support the postprandial glucose hypothesis in cardiovascular disease and this concept should be tested in future trials in higher risk populations.

741 The receptor RAGE as a progression factor amplifying arachidonate-dependent inflammatory and proteolytic response in human atherosclerotic plaques

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Background: Strong evidences suggest a central role for RAGE (receptor for advanced glycation end products [AGEs]) in the accelerated progression of atherosclerosis observed in diabetes.
Recently, we have demonstrated enhanced expression of inducible cyclooxygenase and PGE synthase-1 (COX-2/mPGES-1) in human symptomatic plaques, and provided evidence that it is associated with metalloproteinase (MMP)-induced plaque rupture. However, the specific transmembrane signaling pathway(s) influencing COX-2/mPGES-1 expression in human plaque macrophages is still unknown.
The aim of this study was to characterize the expression of RAGE in human carotid plaques and to correlate it with the extent of inflammatory infiltration, COX-2/mPGES-1 and MMP expression and with clinical evidence of diabetes.
Methods and Results: Plaques were obtained from 60 patients undergoing carotid endarterectomy and divided into 2 groups (diabetic and nondiabetic) according to clinical evidence of type 2 diabetes. Plaques were subjected to analysis of RAGE, NF-kB, COX-2/mPGES-1, MMP-2 and MMP-9, lipid and oxidized LDL (oxLDL) content, and collagen content by immunohistochemistry and Western blot, whereas zymography was used to detect MMP activity. Immunohistochemistry was also used to identify CD68+ macrophages, CD3+ T-lymphocytes, smooth muscle cells (SMCs) and HLA-DR+ inflammatory cells.
Plaques from diabetic group had more ($P<0.0001$) macrophages, T-lymphocytes, and HLA-DR+ cells; more ($P<0.0001$) immunoreactivity for RAGE, activated NF-kB, COX-2/mPGES-1 and MMPs; increased ($P<0.0001$) gelatinolytic activity; reduced ($P<0.0001$) collagen content, and increased ($P<0.0001$) lipid and oxLDL content. Interestingly, RAGE, COX-2/mPGES-1 and MMP expression was linearly correlated with plasma level of HbA1c.
Conclusions: In conclusion, this study demonstrates in humans that RAGE overexpression is associated with enhanced inflammatory reaction and COX-2/mPGES-1 expression in diabetic plaque macrophages, and this effect in turn may contribute to plaque destabilization by inducing culprit metalloproteinase expression.

742 Plasma leptin in a family study: associations with the metabolic syndrome and haemostatic cardiovascular risk factors

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Background: Leptin is synthesized and secreted mainly from adipocytes and correlates with obesity and features of the insulin resistance syndrome. In the WOSCOPS study elevated plasma leptin was predicative for subsequent cardiovascular events, and leptin has been associated with increased vascular stiffness.
Aim and Methods: To investigate the contribution of metabolic and haemostatic cardiovascular risk factors to circulating leptin in a healthy Caucasian family study. Leptin levels were determined by ELISA in 531 individuals from 89 families. Statistical analyses were carried out using the SPSS and SOLAR software packages.
Results: In keeping with previous studies plasma leptin levels were significantly higher in women (13.2 [11.8-14.7] ng/ml compared with men (3.3 [2.9-3.8] ng/ml, $p<0.0001$). Age and sex-adjusted leptin concentrations were significantly associated with fibrinogen ($r=0.20$, $p<0.0001$), factor VII ($r=0.23$, $p<0.0001$), PAI-1 ($r=0.43$, $p<0.0001$), and tPA ($r=0.30$, $p<0.0001$). In addition, in keeping with previous
reports leptin was significantly associated with classical cardiovascular risk factors and features of the insulin resistance syndrome: systolic BP ($r=0.22$, $p<0.0001$) and diastolic BP ($r=0.18$, $p<0.0001$), calculated insulin resistance (HOMA, $r=0.40$, $p<0.0001$), BMI ($r=0.70$, $p<0.0001$), fasting plasma glucose ($r=0.21$, $p<0.0001$), fasting plasma insulin ($r=0.41$, $p<0.0001$), fasting plasma cholesterol ($r=0.19$, $p<0.0001$), triglyceride ($r=0.28$, $p<0.0001$), LDL ($r=0.15$, $p=0.001$), HDL ($r= - 0.18$, $p<0.0001$), and WHR ($r=0.37$, $p<0.0001$). Finally, leptin was significantly lower in current smokers (5.1 [4.1-6.3] ng/ml) compared with non-smokers (8.4 [7.5-9.5] ng/ml, $p=0.01$). In quantitative genetic analyses, additive genetic components explained 13.7% of the variance in plasma leptin whilst BMI, sex, smoking, PAI-1, WHR and fibrinogen together explained a further 51% of the variance in plasma leptin.
Conclusion: Our results indicate that elevated leptin is associated with a prothrombotic phenotype through elevated fibrinogen and PAI -1, occurring in conjunction with clustering of a plethora of cardiovascular risk factors. The mechanisms underlying the association of leptin with cardiovascular disease remain to be elucidated but our data suggest a central role of the adipocyte in determining vascular risk.

743 Rage gene polymorphism study and clinical manifestations of coronary heart disease

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The inflammatory process plays a central role in the development of atherosclerosis and acute coronary syndromes. It has been demonstrated that RAGE, (Receptor of Advanced Glication End products) a multiligand receptor member of the immunoglobulin superfamily, is primarily involved in the process of inflammation and chronicization of disease. RAGE is encoded by a gene located on the short arm of chromosome 6 in the HLA class III region near the junction with class II [6p21.3]. **Purpose:** In our study we decided to analyse a genomic polymorphism of the promoter region, due to a T/A substitution in order to verify whether this RAGE gene polymorphism might play a role in different clinical manifestations of coronary heart disease (CHD).
Methods: We studied this DNA polymorphism in 125 consecutive patients (pts) who were referred for coronary angiography and subsequently underwent exercise stress test. Sixty pts with acute coronary syndromes in history (acute myocardial infarction, unstable angina or restenosis after coronary revascularization) were compared with 65 pts with chronic stable CHD (effort angina, silent myocardial ischemia, asymptomatic pts). Two hundred and thirteen healthy blood donors were considered as a control group.
Results: The study sample consisted of 94 males and 31 females with a mean age of 59± 10 years. Acute and stable pts were similar regarding to age (respectively 58± 19 years vs 59 ±9 years, p= ns), distribution of common CHD risk factors and ejection fraction while they had a different severity of coronary artery disease; 75% of acute pts and 43% of stable pts had less than 2-vessel disease ($p<0.01$). The genotype frequencies of the study sample were 18.4% AA, 48.8% AT, 32.8% TT, similar to the control population 23% AA, 46% AT, and 31% TT. Acute and stable pts had the following genotype frequencies: 30% AA, 46.6% AT, 23.4% TT, and 7.7% AA; 50.7% AT; 41.6% TT, respectively. These data demonstrate that in stable pts the AA genotype was less frequent ($p<0.001$) while TT was more frequent ($p<0.05$) than in acute ones.
Conclusion: Our findings show a strong association between the RAGE polymorphism and clinical manifestation of CHD. We suggest that the T/A polymorphism of the RAGE promoter modulating the quantitative expression of this receptor, might be involved in chronic CHD.

744 Insulin enhances vascular cell adhesion molecule expression in human cultured endothelial cells: a link to the pathogenesis of accelerated atherosclerosis in diabetes

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Hyperinsulinemia is a risk factor for atherosclerosis by mechanisms that are poorly understood. We tested the hypothesis that insulin (I) alone or in concert with other stimuli, can increase monocyte-endothelial interactions, which are implicated in atherosclerosis.
Confluent human umbilical and saphenous vein endothelial cells were incubated in serum-free medium with I (10^{-10} to 10^{-7} mol/L) for 0-24 hours ± tumor necrosis factor (TNF)alpha (0.1 ng/mL), lipopolysaccharide (LPS 0.1 ng/mL), the p38 mitogen activated protein (MAP) kinase inhibitor SB203580 (SB 0.1-20 μg/mL) and the phosphatidylinositol (PI) 3-kinase inhibitor wortmannin (WT 10^{-9} to 10^{-6} mol/L). Vascular cell or intercellular adhesion molecules (VCAM-1 and ICAM-1) and E-selectin were assessed by enzyme immunoassays (EIA), flow-cytometry, immunocytochemistry and Northern analysis. U937 cell adhesion to endothelial cells was determined by a rotational adhesion assay.
At pathophysiological concentrations (10^{-9} to 10^{-7} mol/L) I induced VCAM-1 but not ICAM-1 or E-selectin as shown by EIA, flow-cytometry and immunocytochemistry, and potentiated the effects of TNF-alpha and LPS. I 10^{-8} mol/L with and without TNF increased U937 cell adhesion by 9.2 and 2.7 fold respectively, and markedly induced expression of VCAM-1 mRNA. In the absence of any cytotoxicity WT (10^{-7} mol/L) potentiated the effect of I alone, while SB (1 μg/ml) abolished this effects. Optical density values for VCAM-1 expression at EIA, expressed as mean ± SD % of unstimulated control, for n=3 experiments in each condition, are shown in the Table.

VCAM-1 expression

	I 10^{-10} mol/L	I 10^{-9} mol/L	I 10^{-8} mol/L	I 10^{-7} mol/L
I	96 ± 15	130 ± 10*	150 ± 15*	160 ± 13*
I+WT	124 ± 15	180 ± 17*	198 ± 13*	213 ± 10*
I+SB	96 ± 4	118 ± 16#*	98 ± 12#*	102 ± 6#*
I+LPS	139 ± 11	175 ± 15**	235 ± 23**	238 ± 13**
I+TNF	242 ± 25	489 ± 14***	493 ± 20***	#

p<.05 vs unstimulated control (*), control with I (#), LPS (**), TNF (***). # data lacking because of citotoxicity

Therefore, I promotes VCAM-1 expression by a p38MAPKinase pathway amplified by the PI3-kinase block. This may contribute to atherosclerosis in hyperinsulinemic subjects.

CORONARY VASOMOTION AND COLLATERAL CIRCULATION

745 Coronary vasomotion during dobutamine stress testing in patients with coronary artery disease

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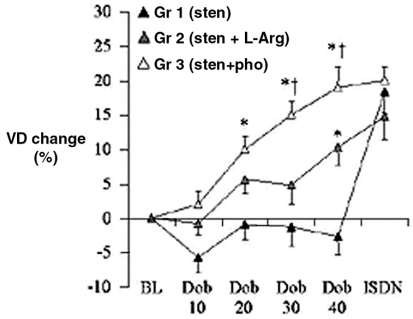
Coronary artery disease (CAD) is associated with endothelial dysfunction and enhanced alpha-adrenergic receptor responsiveness. Dobutamine (DOB), a drug currently used in clinical practice to diagnose CAD, is a coronary dilator acting through both endothelial and adrenergic mechanism. Aim: To study the endothelial and alpha-adrenergic component in the vasomotor response to dobutamine in patients (pts) with stenotic coronary arteries.
Methods: Forty-five pts with at least one coronary stenosis ([>-50%) were recruited. Vessel diameter (VD) was assessed at baseline (BL), during IV DOB (10, 20, 30, 40 y kg-1.min-1) and after IC isosorbide dinitrate (ISDN, 0.2 mg) in 12 patients (Gr 1, 36 coronary segments [cs]). An IC infusion of the NO precursor L-arginine (L-ARG, 150 mM/min, for 20 min) preceded IV DOB in 11 pts (Gr 2, 63 cs). An IC bolus of phentolamine (PHENTO, 12 μg/kg), a non-selective alpha-adrenergic antagonist, preceded IV DOB in 12 pts (Gr 3, 55 cs).
Results: Angiographic stenosis severity was not different among the 3 groups. A similar rate pressure product increase during DOB was observed in all the pts. In Gr 1, DOB did not induce any significant vasomotion, while ISDN did. In Gr 2, L-arginine improved DOB-induced vasodilation. Yet, when pretreated with PHENTO, an even more pronounced improvement of DOB relaxation was observed in Gr 3. ISDN resulted in a similar vasodilation in all three groups. (See graph)
Conclusion: The loss of DOB vasomotion in stenotic coronary arteries is due to both an endothelial dysfunction and alpha-adrenergic receptor hyperresponsiveness. Patients undergoing DOB stress testing on therapy with alpha-blockers and/or endothelial acting drugs might potentially experience false negative results.



746 Nebivolol therapy improves coronary flow reserve in hypertensive patients without coronary heart disease

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Purpose: Nebivolol (NB) is a selective β-blocker with a potent nitroxide-mediated vasodilating properties. In this study, we evaluated the effect of NB on coronary flow reserve (CFR) in patients with uncomplicated arterial hypertension.
Methods: 14 newly diagnosed, never treated, I-II WHO hypertensive patients (M/F = 9/5, mean age = 47 years,) without coronary artery disease (no angina and negative maximal effort test), heart failure, valvular heart disease and atrial fibrillation, underwent standard Doppler echocardiography. CFR was assessed as the ratio between coronary diastolic flow peak velocity after dipyridamole (0.56 mg/kg ev in 4') to resting coronary diastolic flow peak velocity of distal left anterior descending artery using color-guided, harmonic Doppler. The exam was performed at baseline and after 4-week monotherapy by NB 5 mg o.i.d.
Results: At baseline the prevalence of left ventricular (LV) hypertrophy (LV mass index > 50 g/m powered to 2.7) was 64.3% (n=9/14). After 4-week therapy, blood pressure (BP) decreased from 148 ± 8.1/101.4 ± 4.6 mm Hg to 140.7 ± 7.0/91.1 ± 7.4 mm Hg) (p<0.00001) and end-systolic stress was consistently reduced (p<0.0001). Diastolic BP was normalized in 10 of 14 patients (71.4%). Heart rate was also significantly reduced (p<0.01). No change could be detected in LV mass index, relative wall thickness, fractional shortening and Doppler-derived diastolic inflow indexes. LV end-diastolic internal diameter and stroke volume tended to increase (p=0.07 and p=0.09 respectively). After 4-week therapy, CFR increased in 12 of 14 patients (85.7%), from an average of 1.89 ± 0.3 to 2.13 ± 0.3 (p<0.0001). The increase in CFR after therapy was due to enhanced post-dypiridamole, hyperemic diastolic peak velocity (from 47.9 ± 7.3 cm/s to 55.7 ± 6.8 cm/s, p<0.005), resting flow velocities being substantially unchanged. The increase in CFR after NB remained significant even after adjusting baseline and dipyridamole coronary flow diastolic velocities for the respective mean BP (p=0.009).
Conclusions: Coronary flow reserve improves in hypertensive patients free of coronary artery disease after 4-week treatment with Nebivolol. This improvement occurs despite decrease in mean BP and independently of changes in LV mass.

747 Deleterious effect of brachytherapy on vasomotor response to exercise

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Background: In-stent restenosis is one of the major drawbacks of coronary stenting, leading to considerable cardiovascular morbidity and mortality. Debulking strategies, drug eluting stents and brachytherapy have been used with variable success but long-term results with regard to vessel patency, vascular integrity,and vasomotor responsiveness are largely unknown. Thus, the present study was to determine the vasomotor response of stented coronary arteries following brachytherapy, and to assess its influence on vasomotion of adjacent vessels segments during bicycle exercise.
Patients and methods: Biplane coronary angiography was performed at rest and during bicycle exercise in 24 patients with coronary artery disease. Fourteen patients underwent coronary stenting for therapeutic reasons and were restudied ten months after stent placement and served as controls (group 1). Twelve patients were treated with i.c. brachytherapy (Guidant Galileo System) for in-stent restenosis (focal restenosis 4 patients, diffuse restenosis 8 patients) with a mean dosis of 20 Gy. These patients were restudied 6±2 months after radiotherapy (group 2). Coronary vasomotion of the proximal and distal vessel segment of the stented vessel as well as in-stent luminal area and a reference vessel were studied by quantitative coronary angiography. Minimal luminal area, stent area, and proximal and distal vessel areas were determined in all patients at rest, during two levels of exercise (50±5 Watt and 75±10 Watt, respectively) as well as after sublingual nitroglycerin.
Results: The normal vessel segment showed exercise induced vasodilation (+15%±4%, P <0.05) in both groups. Vasomotion within the stented vessel segments was abolished (0%), whereas in the control group the proximal and distal segments showed exercise-induced vasodilation (8±2% and 11±3%, respectively; p<0.005). In contrast, there was exercise-induced vasoconstriction in the proximal and distal vessel segments of the irradiated artery (-6±5% and -14±2%, respectively; p<0.05). Sublingual nitroglycerin was associated with maximal vasodilation of the proximal and distal vessel segments in both groups.
Conclusions: Normal vessel segments show flow-mediated vasodilation during bicycle exercise. As expected, vasomotion is abolished in the stented region. Simple stent implantation does not affect physiologic response to exercise proximal and distal to the stent. However, i.c. radiotherapy destroys normal vessel function although dilatatory response to nitroglycerin is maintained suggesting endothelial dysfunction as the underlying mechanism.

748 Impaired effect of endogenous endothelin-1 on coronary artery stiffness in patients with type II diabetes mellitus

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Vasoconstriction in brachial arteries in response to exogenous and endogenous endothelin-1 (ET-1) is impaired in type II diabetic (NIDDM) patients.
Aim: We examined whether there is differential effect of ETA antagonism on coronary artery compliance in NIDDM compared to non-diabetics (ND).
Methods: We examined 32 patients with atherosclerotic epicardial arteries without significant coronary artery stenoses. BQ-123, 6 μmol, an ETA receptor antagonist, was infused intracoronarily in the proximal part of an epicardial artery, over 20 min. The artery lumen area in the proximal arterial segment was measured at end diastole and end systole before and after BQ-123 administration using an intravascular catheter. Calculations were made of normalized arterial compliance index (NCI, in (mmHg-1 x 103) and of arterial stiffness index beta. Results: Pulse pressure and heart rate did not change after BQ-123. In NIDDM normalized compliance index decreased from 1.79±1.36 at baseline to 1.29±0.82 after BQ-123 administration and in ND increased from 2.10±1.36 to 3.00±2.07 (p<0.05 versus baseline), respectively (F=6.39, p=0.02). In NIDDM beta index increased from 1.97±0.53 to 2.46±0.95 and in ND it decreased from 1.83±0.95 to 1.63±0.84, respectively (F=7.80, p=0.009). Big-ET-1 at baseline was correlated to the baseline beta index (p<0.0001, r=0.68).
Conclusion: Big ET is correlated to the stiffness of the coronary artery stiffness. The coronary artery stiffness effect of endogenous ET-1 is impaired in NIDDM patients. This may have important therapeutic implications with respect to the introduction of ET receptor antagonists as cardiovascular therapeutic agents.

749 Quantitative assessment of collateral derived myocardial perfusion using real-time myocardial contrast echocardiography during elective coronary angioplasty

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Background: Today, coronary collaterals are becoming promising targets for the treatment of coronary artery disease (exercise, growth factors). The efficacy of such therapeutic strategies is demonstrated by the increase of collateral relative to normal flow obtained by invasive methods at the level of epicardial coronary arteries.
Myocardial contrast echocardiography (MCE) can assess myocardial perfusion at the microcirculatory level. Based on a new model of ultrasound contrast agent (UCA) kinetics, we developed a method allowing absolute quantification of myocardial perfusion (ml/min/g) using real-time MCE. The validity of this method has been demonstrated in a phantom study.
We hypothesized that this method can be used to quantify collateral derived perfusion during coronary angioplasty in humans.
Methods: In 13 patients undergoing coronary angioplasty, a collateral flow index (CFI) was determined using simultaneous measurements of mean aortic pressure, intracoronary wedge pressure distal to the stenosis to be dilated and central venous pressure. During balloon occlusion and after successful dilatation, MCE of the collateral receiving myocardial area was performed using a continuous, intravenous UCA infusion. Perfusion data were calculated according to our kinetic model and a collateral perfusion index (CPI) was defined as the ratio of perfusion during occlusion and after dilatation.
Results: 6 patients had a left anterior descending coronary stenosis, 4 had a right coronary artery stenosis and 3 had a left circumflex coronary artery stenosis. The mean CFI was 0.217 ± 0.155. Assessment of perfusion by MCE was feasible in 11 patients, mean perfusion during occlusion and after dilatation were 0.262 ± 0.212 ml/min/g and 1.282 ± 0.397 ml/min/g, respectively. Mean CPI was 0.221 ± 0.189. CPI was linearly related to CFI (CPI=1.11*CFI-0.02, r^2=0.988).
Conclusion: Real-time MCE during coronary angioplasty allows online visualisation of collateral derived myocardial perfusion, which can be quantified using our new model of UCA kinetics. CPI is a valid measure of the coronary collateralisation the fact of which may be important in developing non-invasive methods for the assessment of collateral derived myocardial perfusion.

750 Long-term regression of collaterals after recanalization of a chronic total coronary occlusion

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Background: The collateral circulation has the potential to maintain myocardial function in chronic total coronary occlusion (CTO). Animal data indicate that collaterals regress after revascularization, but casuistic reports showed that collaterals may remain recruitable in man. The present study is the first to systematically investigate to what extent and under what circumstances collateral function (CF) is preserved several months after successful recanalization of a CTO.
Methods: 87 patients with a recanalized and stented CTO (duration >2 weeks) underwent a repeat angiography after 4.5±1.5 months. CF was assessed by advancing intracoronary Doppler and pressure wires through the occlusion before the first balloon inflation (baseline). The average peak Doppler velocity (APVd) and pressure (Pd) distal to the TCO, and the aortic pressure (Pao) were recorded, and antegrade APV was determined at the identical recording site after recanalization. A collateral flow index CFI=APVd/APV and collateral pressure index CPI=Pd/PAo were calculated. Acute recruitable CF was assessed during a balloon inflation at the end of the procedure. Late recruitable CF was assessed in patients with restenosis or reocclusion treated by a repeat PTCA during the first balloon inflation, and in patients without restenosis during a balloon inflation within the stent at low occlusive pressures of 2-4 atm.
Results: Immediately after recanalization APVd decreased from 10.7±5.9cm/s to 6.5±4.4 cm/s (p<0.001), and it was further decreased to 4.7±4.3 cm/s at follow-up. Acutely recruitable CPI was 76% of the baseline level, late recruitable CPI at follow-up reached only 54%. CFI was reduced to 60% acutely, and 51% of baseline at follow-up. A multivariate analysis was applied to determine the factors influencing collateral recruitability at follow-up. Patients with a reocclusion had the highest CFI and CPI at follow-up which reached the baseline levels, whereas there was no significant difference between patients with and without restenosis. The duration of the TCO (< or >3 months), or the regional function of the region supplied by the collaterals had no influence on collateral regression.
Conclusion: Collaterals lose their function immediately after PTCA, and they regress further during follow-up. Collaterals regress independently of the regional function and the duration of the CTO. The loss was similar in patients with and without restenosis, but in those with a reocclusion collaterals reached baseline levels of CF. This indicated that collaterals are gradually recruited in case of reocclusion.

HYPERTROPHIC CARDIOMYOPATHY, TREATMENT AND OUTCOME

751 Abrupt coronary no-flow phenomenon in hypertrophic obstructive cardiomyopathy: no specific adverse effect of alcohol injection in alcohol septal ablation

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Background: Abrupt coronary no-flow (ACNF), a no-reflow like phenomenon, was described by many groups performing alcohol septal ablation in HOCM. The potential of alcohol back flow during the procedure was supposed to be the underlying reason of this severe complication.
Patients: We report on our experience in HOCM pts in whom the new catheter based method (Transcoronary Ablation of Septal Hypertrophy–TASH) was performed (n=415). The ACNF was observed in 11 pts with HOCM (2.6%, 55±14y, 31-72y, 8 males). In 5/11 pts the ACNF occurred already during diagnostic coronary angiography before any alcohol injection. In one pt severe cardiogenic shock developed with sudden, extreme increase of left ventricular obstruction. After immediate rescue TASH and total abolition of intraventricular obstruction stable circulation was achieved. Two patients died from sudden cardiogenic shock (1 pt before, 1 pt after alcohol injection), in one pt TASH was stopped and in 2 pts the procedure was continued after transient ACNF. In 6/11 pts the ACNF occurred after ethanol injection (1.6±0.5 ml), the peak CK activity was 1918±1827 U/l. In all cases there was no evidence of alcohol coronary back flow. Affected vessels were LAD, Ramus diagonalis, RCX or all major branches of the LCA. ACNF resulted in extensive persistent infarction (2/11 deaths), moderate contraction disorder (3/11) or complete recovery of myocardial injury (6/11). A most striking aspect of all pts was an extremely anxious, stressed personality, which might have exacerbated a vasospastic reaction. In 5 pts it occurred in combination with abnormal catheter-induced vagal stimulation (prolonged intuabtion of coronary sinus, clinical study) or difficult catheterisation because of a pronounced kinking of abdominopelvic arteries.
Conclusions: ACNF is a potentially harmful adverse effect in pts with HOCM in whom the new catheter based treatment is performed or intended. It is observed before alcohol injection or after the procedure and may be caused by vagal stimulation or the injection of contrast medium only. ACNF may reflect the common abnormal autonomic function in HOCM leading to abrupt multivessel spasm. Prophylactic deep sedation of patients and intravenous or intracoronary application of verapamil and urapidil for ACNF seems to be helpful.

752 Echo-guided septal ablation for symptomatic hypertrophic obstructive cardiomyopathy: 7 years of experience

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Background and Introduction: Ethanol-induced septal ablation for symptomatic hypertrophic obstructive cardiomyopathy (HOCM) requires the exact definition of the septal myocardium to be abladed. We report on our cumulative experience with septal ablation (PTSMA) guided by intra-procedural contrast echo (MCE) on an intention-to-treat basis in 337 patients (pts.) treated from 1/1996 - 12/2002.
Results: Ethanol could not be injected in 26 of 337 pts. (8%), predominantly due to an unwanted extension of the echo contrast effect away from the septal target region as documented by MCE in 18 pts. (6%). In 33 out of the 311 pts. (11%) who received ethanol, a target vessel (TV) change was necessary for the same reason. In-hospital mortality in 311 pts. was 1.3% (4 pts.). After 3 months, symptoms had improved in 276 pts. (91%) from NYHA class 2.8±0.5 to 1.5±0.6, with an increase of exercise capacity from 94±51 to 115±43 watts, and of peak oxygen consumption from 18±4 to 21±6 ml/kg/min ($p<0.01$ each). 164 pts. (54%) reported to be free of symptoms. A satisfactory reduction of the left ventricular outflow gradient (LVOTG) was achieved in 252 pts. (83%) from 60±33 to 13±18 Hg at rest, and 120±43 to 38±35 mm Hg with provocation ($p<0.0001$). 121 pts. (40%) were free from outflow obstruction. LVOTG with probatory balloon occlusion (PBO) during the intervention was 40±32 mm Hg. There was a weak correlation between the LVOTG with PBO and the residual acute LVOTG during the intervention. After 3 months, however, there was no difference between the pts. with different levels of PBO-induced LVOTG reduction (<30%: n=58, >30%: n=148; or >50%: n=105).
Conclusions: In case of a positive intra-procedural MCE study, PBO adds little information to PTSMA for HOCM. Furthermore, MCE is able to exclude alcohol necrotization of myocardium remote from the septal target area, and thus adds to the safety of the procedure.

753 Abnormal heart rate and blood pressure behaviour after exercise in patients with hypertrophic obstructive cardiomyopathy and recurrent syncope – normalization after catheter interventional treatment

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Background: Syncope is common in HOCM and is associated with an increased risk of sudden death. Surgical or catheter interventional relief of outflow tract obstruction (LVOTG) leads to a reduction of syncopal events, but the precise mechanism contributing to this beneficial outcome remains controversial.
Patients and Methods: Therefore, the hemodynamic response to exercise was investigated in 36 consecutive HOCM pts. (26 male, 53±14y, range 29-73) in a prospective manner before and 6.4±1.3 months after Transcoronary Ablation of Septal Hypertrophy (TASH). Before TASH 18 pts. had unexplained recurrent syncope (Group A), 18 age-matched pts. had no syncope (Group B).
Results: Except of IVS thickness (Group A:21.7±3.6 mm; Group B:18.6±3.8 mm, p=0.034) all subjective and objective measurements were comparable between Group A and B before TASH. In all patients a significant reduction of LVOTG, decrease of IVS thickness and improvement in NYHA functional class could be reached by TASH. During upright bicycle exercise maximal workload, heart rate and blood pressure behavior did not differ between Group A and B. However, early heart rate fall 1min. after exercise cessation was significantly increased in syncopal patients (deltaHR 1.min: -19.7±9.6% (Group A) vs.-15.3±6.9% (Group B); p=0.034). Systolic blood pressure fall 1min after exercise was also significantly increased in Group A (deltaRRs 1.min:-25.5±8.1% (Group A) vs.-19.6±10.5% (Group B),p=0.033).
Within the 6.4±1.3 months follow-up after TASH no pt. experienced any episodes of syncope or presyncope. Early HR fall after exercise in Group A was significantly diminished compared to the pre-TASH results (deltaHR: -19.7±9.6 before vs.-13.8±6.3% after TASH, p=0.015). There were no significant intergroup differences of heart rate and blood pressure behaviour after exercise.
Conclusions: 1) In HOCM patients with recurrent syncope there is a significantly increased heart rate and blood pressure fall during the early recovery period after exercise compared to HOCM patients without syncope 2) In these patients TASH leads to complete relief of syncope during follow up. 3) This relief of syncope after TASH is accompanied by the reduction of prior exaggerated fall of hemodynamics after exercise probably due to a TASH induced normalization of autonomic dysfunction.

754 What is the correct amount of ethanol in the catheter based treatment for hypertrophic obstructive cardiomyopathy?

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Background and Methods: Since 1995 a total of 418 pts (age: 58 ± 14.9 years, male: 49.6%) with severe hypertrophic obstructive cardiomyopathy (HOCM) was treated with transcoronary ablation of septal hypertrophy (TASH) in our institution. The pressure-angiography guided method was performed. To minimise the myocardial injury we systematically reduced the amount of ethanol. In the present study clinical parameters (quality of life (QoL), mortality, complications, peak creatine kinase activity (CK) and intraventricular gradients) were retrospectively analyzed and correlated to the amount of ethanol. In a subset of 329 consecutive pts a standardised and valiated questionaire (23 variables) was used to estimate the quality of life (QoL) before and after TASH (follow up periode 2.1 ± 1.6 years, maximal 6.2 years, 98.8% follow up).
Results: On the average, since 1995 there was no change in the hemodynamic outcome (gradient reduction in different subsets 83% vs. 76%), however, a significant reduction (1st vs. 4th quartile) of the ethanol dosage (3.9 to 1.0 ml), peak CK (690 to 345 U/l), intraprocedural third degree AV-block rate (58.6% to 17.7%) and permanent pacemaker rate (25% to 11.3%). In a different subset (pt No 1-200 vs. pt No 201-418) the in hospital rate of ventricular fibrillation and sustained ventricular tachycardia was also reduced (3.0% vs. 0%). The HOCM-related mortality was significant lower in the group of pts who were treated with low levels of ethanol (< 2.0 ml). The pre/post QoL did not differ in both groups (≤2.0 ml vs. > 2.0 ml ethanol).
Conclusions: The reduction of ethanol in TASH leads to pronounced reduction of arrhythmogeneity and myocardial injury combined with remarkable improvement of prognosis. This effect was achieved by using the pressure-angiography guided method which provides an individual and precise approach regarding the appropriate septal branch selection, the ethanol dosis adaptation and the injection technique predominantly by the consideration of wash out and flow characteristics of the contrast medium injected selectively prior to alcohol instillation.

755 Relation of myocardial scarring to clinical risk factors for sudden death in hypertrophic cardiomyopathy

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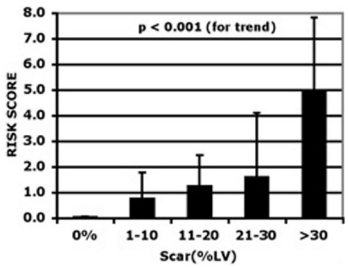
The risk of sudden death (SD) in patients with hypertrophic cardiomyopathy (HCM) is commonly estimated using established clinical predictors. Although myocardial scarring is thought to be an important anatomic component of the arrhythmogenic substrate that leads to SD, the relation between scarring and clinical risk factors for SD is unknown.

Cine and Gd contrast-enhanced MRI (ceMRI) was performed in 45 HCM patients (48 $\pm$ 16 yrs, 27 male) on a 1.5T scanner. For each patient, the clinical risk of SD was assessed using the following additive scale: history of cardiac arrest = 4 points, sustained VT = 3 points, extreme hypertrophy (max wall thickness $\geq$30mm) = 2 points, family history of SD ($\geq$1 first degree relative, $<$50 yrs) = 1 point, unexplained syncope = 1 point, repetitive nonsustained VT ($\geq$2 episodes) = 1 point. Scar volume was assessed by planimetry of hyperenhanced regions on ceMRI.



Scarring was present in 33 pats. (74%). The average amount of scar was 10 $\pm$ 9% LV. Dividing patients into 5 subgroups according to scar volume (Fig 1), we found a progressive stepwise relation between scar volume and clinical risk for SD (P$<$0.001 for trend). For example, in pats. with scar volume $>$30% LV the average risk score was 5 $\pm$ 2 points (range 3-7) whereas in pats. without scar, all had a risk score of zero. Interestingly, of the 25 patients with a risk score of zero, a third (32%) had scar volume greater than 10% LV, suggesting that tissue substrate for SD may be present in some pats. without clinical risk factors.

The extent of myocardial scarring on MRI relates in a progressive stepwise fashion to the clinical risk of SD. Whereas pats. without scar do not have clinical risk factors for SD, the absence of risk factors does not rule out substantiative amounts of scarring.

756 Left-ventricular outflow tract obstruction increases the risk of sudden cardiac death in patients with hypertrophic cardiomyopathy

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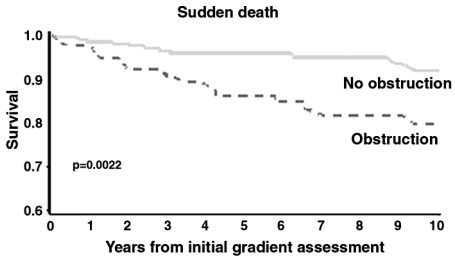
The left ventricular outflow tract (LVOT) obstruction determines disease progression to severe heart failure in patients (pts) with hypertrophic cardiomyopathy (HCM). However, the impact of LVOT obstruction on mortality remains not wholly resolved. We investigated the overall mortality rate and sudden death rate in patients with HCM.

Methods: 492 consecutive pts (263 M, age 38.2 years, range from 6 to 68) were followed prospectively for a mean of 5.1 years. Out of these 133 (27%) had LVOT obstruction with a resting peak gradient of at least 30 mm Hg (HOCM pts).

Results: 51 (10%) pts died of HCM, either suddenly or due to heart failure. In a subgroup of 359 pts without LVOT obstruction 24 pts died, 13 of them suddenly. In the subgroup of 133 pts with LVOT obstruction 27 pts died, 20 of which suddenly. Overal mortality related to HCM was significantly higher among patients with LVOT obstruction compared to those without (P=0.0087). Mortality due to sudden death was also substantially greater in patients with LVOT gradient of at least 30 mmHg than in those without obstruction (P=0.0022).

Conclusion: In patients with hypertrophic cardiomyopathy the left ventricular outflow obstruction increases both the overal mortality and the risk of sudden death.



Risk of sudden death in HOCM.

ACUTE PULMONARY EMBOLISM: MARKERS OF SEVERITY AND TREATMENT

763 Predictors of unsuccessful thrombolysis in acute massive pulmonary embolism

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Rationale: Selection of appropriate candidates for thrombolytic therapy (TT) in massive pulmonary embolism (MPE) is still debated. To date the identification of predictive factors of unsuccessful thrombolysis in patients (pts) with massive PE has never been undertaken.

Methods: 354 consecutive pts with MPE were submitted to TT and a management strategy of systematic echocardiography (echo) and lung scan pre- and post-thrombolysis. Pts were included if they met at least one of the following criteria: (1)cardiogenic shock, (2)syncope, (3)pulmonary vascular obstruction (PVO)$>$50%, (4)$>$=1 echo findings indicating right ventricular (RV) dysfunction (RV/left ventricular end-diastolic diameter ratio $>$1 in the 4-chamber view, paradoxical septal systolic motion or pulmonary hypertension defined as a RV/atrial gradient $>$30mmHg). In-hospital results were determined using a composite endpoint including death, recurrent PE, persistent RV dysfunction at 48h echo and residual PVO$>$40% at 8 days lung scan. Predictors of in-hospital course were identified from among: age, sex, body mass index, heart rate, previous thrombo-embolic disease, cancer, diabetes, obstructive pulmonary disease, deep vein thrombosis, vena cava filter insertion, shock, systemic hypotension $<$90 mmHg, syncope, ECG with RV overload, as well as pre-thrombolysis echo findings and PVO data.

Results: The in-hospital clinical course was uneventful in 211(60%) pts; 35 (9.9%) pts died, of whom 17 died from the PE process (10 pts from refractory shock and 7 pts from recurrent PE). A total of 27(7.6%) had fatal or non fatal recurrent PE. 24(6.8%) pts suffered from major bleeding complications. Initial RV dysfunction was present in 299(85%) pts and was reversible in 260(80%) pts within 48h following TT. By univariate analysis, the variables associated with in-hospital clinical adverse outcome were age$>$80, history of cardiac failure, shock, right heart thrombus, RV dilatation and pulmonary hypertension $>$50mmHg. Age$\gg$80 (relative risk (RR) 2.42 [1.19;4.92]; p=0.01), right heart thrombus (RR 2.95 [1.03;10]) and pulmonary hypertension (RR 2.58 [1.58;4.54]; p=0.004) were independent predictors of poor in-hospital course in multivariate analysis.

Conclusion: Successful thrombolysis is obtained in a vast majority of pts with massive PE. Poor initial outcomes can be expected in pts presenting with age$>$80 or with severe RV afterload as defined by the presence of right heart thrombus and pulmonary hypertension $>$50mmHg. These results warrant the investigation of alternative therapy in such pts.

764 Elevated cardiac troponin I levels in acute pulmonary embolism predict increased long-term mortality

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Background: In the setting of acute pulmonary embolism (PE) an elevated cardiac Troponin I (cTnI) level is the strongest independent predictor of short-term mortality. The purpose of this study was to determine the significance of cTnI elevation on 2 year survival in patients presenting with acute PE.
Methods: Between 1998 and 2000, 176 patients presented to a US tertiary center with acute PE diagnosed by pulmonary VQ scan, spiral CT or pulmonary angiography and had cTnI measured within 24 hrs. Mortality status 2 yrs following diagnosis was determined using the US Social Security Death Index (SSDI) database. Baseline characteristics and mortality status at 2 yrs were compared between patients with elevated vs normal cTnI levels.

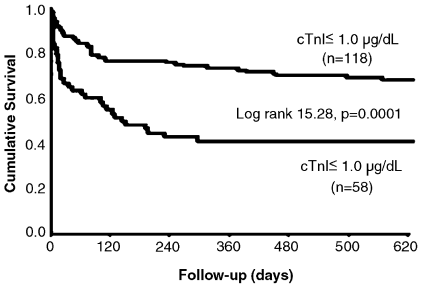

Figure 1. Kaplan-Meier Survival Curve

Results:
At the time of PE diagnosis, 58 patients (33%) had elevated cTnI > 1.0 µg/dL. Patients with elevated cTnI were significantly older (73±13 vs. 65±17 yrs, p<0.01) and had a higher incidence of known malignancy (36% vs. 22%, p=0.05) but had no increased prevalence of CAD (21% vs. 23%, p=0.74). Two years following diagnosis, 34 of 58 patients (59%) with elevated cTnI and 37 of 118 patients (31%) with normal cTnI levels had died (p=0.0001). Kaplan-Meier survival curve analysis demonstrated a significantly higher probability of death for cTnI positive compared to cTnI negative patients (Figure 1). However, 8 to 24 months following acute PE diagnosis the two survival curves paralleled each other.
Conclusions: In addition to predicting short-term mortality, elevated concentrations of cTnI predict increased late mortality 2 years following acute PE. Lack of divergence of cTnI positive and cTnI negative survival curves beyond 8 months suggest that the highest risk period for death following acute PE occurs relatively early.

765 Mobile thrombi of the right heart in pulmonary embolism. Delayed disappearance after thrombolytic treatment

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The presence of a mobile clot in the right heart, distinguishes a particular severe form of pulmonary embolism (PE). The outcome of these mobile clots during or after thrombolytic treatment is poorly known. We described the outcome of right heart mobile clots in patients hospitalized in our cardiology department for PE.
Method: A transthoracic echocardiography was performed on entry in all patients hospitalized for PE. When a right heart clot was seen, echocardiography was repeated twice a day for 48 hours, then once a day, permitting major information concerning outcome of these clots.
Results: From Jan. 1998 to May 2002, 343 patients were hospitalized in our cardiology department for PE. Eighteen patients (5.2%) presented a mobile clot in the right heart. In all this cases, PE was severe: the mean right to left end diastolic diameters ratio was 0.86±0.18; mean systolic pulmonary pressure was 68±17mmHg. All thrombi were located in the right atrium, except one, which was trapped in a patent foramen ovale. All were mobile. Their mean length was 4.2 cm. The treatment chosen was thrombolysis (tPA, 2 hours infusion) in 16 cases (88%); heparin alone in one, surgical removal for the thrombus trapped in the foramen ovale. All patients were alive at day 30. In all cases treated with thrombolysis, the clot disappeared. This happened in 8 cases (50%) just after the end of the infusion, in 4 cases (25%) between the 4th and the 12th hour after thrombolytic treatment, and in the remaining 4 cases (25%) between the 12th and the 24th hour. In the only patient treated with heparin alone, the clot was still present on day 5, then it disappeared on day 6.
Conclusion: A mobile clot can be seen in the right heart in about 5% of patients presenting PE. In our series, thrombolytic treatment gave excellent results. Clots disappeared immediately during or after thrombolytic treatment in 50% of cases and within 24h in 100% of cases. It is noteworthy that the course of the disease was favorable even when the clots did not disappear immediately. The early improvement induced with thrombolytic treatment may have permitted patients to better tolerate later migration of these mobile clots in pulmonary arteries.

766 Plasma N terminal pro-brain natriuretic peptide reflects the severity of right-ventricular overload in patients with acute pulmonary embolism

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Objective: It was proved that brain natriuretic peptide (BNP) released from ventricles upon stretch reflects the severity of left ventricular systolic dysfunction in pts with congestive heart failure. However, there are limited data on plasma BNP in pts with right ventricular (RV) overload. Therefore, we assessed if plasma levels of NTproBNP reflects the severity of RV overload in acute pulmonary embolism (APE).
Material and Methods: We evaluated 74 patients (27M, 47F, aged 63±17 years) with APE proven by high probability lung scintigraphy or spiral CT. On admission blood samples were collected for NTproBNP (Roche, ECLIA) and echocardiography was performed for the determination of RV overload.
Results: Studied group comprised 54 (73%) pts with RV overload (RV+) defined by RV/LV >0,6 and/or tricuspid valve peak systolic gradient (TVPG) >30mmHg, while remaining 20 (27%) pts showed no alteration in RV morphology or function (RV-). When compared to age and sex specific reference values of plasma NTproBNP (F<50rs, <153pg/ml; F>50yrs, <334pg/ml; M<50rs, <88pg/ml; M>50 yrs, <227pg/ml) it was increased in 61 (83,6%) pts, 10 (50%) pts of RV-, and 51 (94%) pts from RV+ (p<0,0001). Moreover, plasma NTproBNP was significantly lower in RV– than in RV + (median 183 pg/ml (range: 16-31168), vs median 4619 pg/ml (range: 161-60958), p<0,001). Interestingly, significant correlations between echocardiographic indices of RV overload and NTproBNP were found (table), while plasma NTproBNP correlated with systemic hemodynamic status to the lesser degree.

Correlations between echocardiographic indices of RV overload and NTproBNP

	RV/LV	IVC exp (mm)	TVPG (mmHg)	RV (mm)	HR (1/s)	RRs (mmHg)	SO2 (%)
Plasma NTpro BNP (pg/ml)	r = 0,53 p<0,001	r = 0,49 p<0,001	r = 0,40 p=0,003	r = 0,38 p=0,003	r = 0,15 p=NS	r = -0,32 p=0,01	r = -0,34 p=0,008

IVC: inferior vena cava expiration, TVPG: tricuspid valve peak systolic gradient.

Conclusions: Plasma NTproBNP can be elevated in majority of patients with acute pulmonary embolism and reflects the echocardiographically assessed degree of RV overload.

767 Clinical experience with the temporary "tulip caval filter for prevention of pulmonary embolism

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Purpose: In patients suffering from recent deep venous thrombosis or pulmonary embolism (PE)and who have a transient contraindication to anticoagulation a Tulip caval filter was inserted into the inferior vena cava. This caval filter (CF)can be retrieved within 14 days or can remain in place serving as a definitive CF in case of persisting filter need.
Method: In a cohort of 118 pts a Tulip CF was implanted, of whom in 42 pts the CF was planned to be temporary. Outcome was prospectively assessed with regard to procedural complications, feasibility of CF retrieval and recurrent embolic events.
Results: Indications for filter placement were contraindications to anticoagulant therapie due to haemorrhage (n=7), perioperative condition (n=24) or prophylactic during venous thrombolysis (n=8) and massive PE (n=3). Implantation was performed via the jugular approach in 6 pts, the left and right femoral vein in 11 and 25 pts, respectively. In 2 pts CF placement was too close to the proximal thrombus end; optimal placement was achieved by repositioning the CF using a retrieval set. No other periprocedural complications were noticed. The CF was explanted in 25 of 42 pts. Reasons for not explanting the CF were failure to grasp the CF at its hook (n=1),new thrombus formation in the inferio vena cava (n=2), captured embolus in the CF (n=1), and persistence of original contraindication to heparin (n=11). One patient refused retrieval and one died of multiorgan failure. Retrieval of the Tulip CF was achieved using the right jugular vein (n=21) or the subclavian vein (n=4). The mean duration of temporary CF use was 9,5 (5 - 17) days. At the time of CF retrieval 13 of 25 pts were treated with heparin in therapeutic dosage. No recurrent PE neither during the protection period nor during the explantation procedure was observed.
Conclusion: The temporary Tulip CF was useful for prevention of PE. The implantation and explantation procedure has a low complication rate. Retrieval of the CF is feasible and could be achieved in all but one case. In approximately 40% the filter has to remain in the inferior vena cava, predominantely due to prolonged contraindication to anticoagulants.

768 Patients after successfully treated acute pulmonary embolism present impaired long-term functional capacity and disturbed echo Doppler parameters

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Background: Right ventricular (RV)pressure overload can be echocardiographically detected in almost 50% of patients with acute pulmonary embolism (APE). In the majority of patients receding of echocardiographic signs of RV overload and normalisation of clinical status occur within several weeks of proper anticoagulation. However, development of CTEPH was reported in some patients after APE. Therefore we assessed whether patients after properly treated APE present limitation in exercise capacity or any differences in echo-doppler indices at long-term follow up.
Methods: We compared 36 asymptomatic patients (23 F, 13 M. age 66 ±10years) after at least 1 year after diagnosis of hemodynamically significant APE defined by the presence of RV strain at TTE in the acute phase and group of 30 age-matched subjects (17 F, 13 M; age 67 ±12 years). In APE group 6 months of oral anticoagulation resulted in normalisation of clinical status. After at least one year after diagnosis of APE all these pts underwent additional examinations including TTE and 6-minutes walking test (6mWT).
Results:

	APE (N = 36)	Controls (N = 30)	p
Echo Doppler			
RV (mm)	26,9±2.5	22,9±1.8	<0.001
RV/LV	0.57±0.08	0.49±0.04	<0.001
AcT (ms)	96±19	122±19	<0.001
TVPG (mmHg)	24±8 (n= 13)	24±7 (n= 9)	NS
6mWT			
HR before test (1/s)	78±11	69±10	0.002
Distance (m)	473±138	527±101	NS
Desaturation after test (%)	3,04 ± 2,08	1,45 ± 0,69	=0.0005

We also found interesting corellations in APE group: (distance vs AcT, r =0.58, p<0.001),(distance vs TVPG n=13, r=-0,67, p = 0.02).
Conclusion: Despite normalisation of PAP (estimated noninvasively as TVPG) and similar exercise capacity, patients after episode of APE presented more pronounced desaturation at exercise what could indicate local ventilation to perfusion mismatch at exertion. Tachycardia, enlarged RV, shortened pulmonary artery acceleration time suggest disturbed RV-pulmonary artery dynamic coupling. This findings warrant further investigation to assess its prognostic significance.

SURGICAL TREATMENT OF AORTIC DISEASE

769 Endovascular stent-graft implantation: a save therapeutic alternative in patients with dissection of the thoracic descending aorta

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Purpose: Endovascular stent-graft placement is a promising therapeutic alternative to treat patients with type B aortic dissection. By abolishing malperfusion syndrome and false lumen expansion via endovascular reconstruction, the concept of aortic remodeling has been proven. This study presents mid-term follow-up of 115 patients with thoracic aortic dissection and endovascular reconstruction.
Methods and Patients: Between October 1997 and December 2002 115 multimorbid patients (75% male, mean age 58.7 years, range 30-81) were subjected to endovascular stent-graft placement using 129 prostheses; 84% of cases suffered from typical type B dissection, 16% were subjected to hybrid procedures in type A dissection combining surgical repair of the ascending and interventional repair of the descending aorta. Mean follow-up was 35 months (range 3 – 62).
Results: Primary success was achieved in 97%; in 7% placement of a second stent was necessary. Early 30-day mortality was 2% and mortality in the entire follow-up period was 8%; 4% of patients died from late rupture of the ascending or descending aorta. Additional 4 fatalities were non-vascular. Neurological complications were observed in 5% during follow-up with minor stroke in 4%, and temporary paraparesis in 1%; persistent paraplegia was not observed. Within mid-term follow-up 5% of patients required a second adjunctive aortic intervention to take care of secondary endoleaks or progressive pathology of the aorta. Elective surgical corrections were necessary in 5% due to progressive aortic diameter or persistent perfusion of the false lumen in dissection.
Conclusion: This retrospective interim analysis after stent-graft placement in thoracic aortic dissection represents the largest published follow-up series of interventional thoracic endovascular stent-grafting. The results confirm procedural safety, the necessity of clinical follow-up surveillance, and a better prognosis than published natural history data with medical treatment.

770 Endovascular stent-graft placement for non-surgical repair of descending aortic perforations – acute and follow-up results

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Background: Perforating lesions of the descending thoracic aorta are a life-threatening condition associated with high morbidity and mortality.
Methods: Between January 1999 and October 2002 a total of 25 consecutive patients (15 male, mean age 63.3 years) underwent percutaneous treatment for perforating lesions in the descending aorta. In 19 cases (group A) the aortic perforation was due to ruptured aortic type-B dissections (n=13) or rupture of preexisting atherosclerotic thoracic aneurysms (n=6); 6 patients (group B) were treated for posttraumatic perforations of the descending aorta. In total 31 endoprostheses were implanted (4 patients with two and 1 patient with three endoprostheses).
Results: The implantation of the endoprosthesis was successfully performed in all cases without periinterventional complications. In one case implantation of a second endoprosthesis became necessary due to incomplete coverage of the lesion with subsequent leakage. Three of the 25 patients died within 30 days, for an early mortality rate of 12%. As all deaths occurred in group A, the mortality rate in this group was 15.8% vs. 0% in group B. Similarly, postinterventional complications were more prevalent with 31.6% in group A (renal failure n=4; ischemic stroke n=2) vs. 16.6% in group B (renal failure n=1). There was no further death or rupture during the average follow-up period of 16 months.
Conclusion: These initial results suggest that percutaneous stent-graft placement offers an effective nonsurgical treatment option for emergency repair of descending aortic perforations. The procedure associated morbidity and mortality is higher for patients with ruptured dissecting or atherosclerotic thoracic aneurysms.

771 Endovascular treatment of type B aortic dissection with multiple stent-graft placement in very high surgical risk patients

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Background: Surgical treatment of descending aortic dissection is associated with high morbidity and mortality, particularly in patients with comorbities and/or in emergency situations. The aim of this study was to evaluate the effectiveness and safety of endovascular treatment of type B aortic dissection with multiple stent-graft placement in high surgical risk patients.
Methods: Between April 2002 and October 2002, 18 patients (16 males; median age=62, range= 21- 84 yrs) underwent endovascular treatment of type B aortic dissection. All patients were at very high surgical risk because of their emergency situation (n=8;44.4%) and/or presence of serious comorbidities, such as CAD (n=5;27.7%), heart failure (n=6;33.3%), renal failure (n=2;11.1%), severe BPCO (n=3;16.6%) and cerebrovascular disease (n=2;11.1%). A numerical risk score (range: 0-11), including clinical and anatomic criteria, was applied to these pts in order to establish their potential risk for endovascular treatment. The median risk score was 9. We used a Talent endograft, a custom-made endoprothesis, made of a self-expanding nitinol stent and a woven polyester fabric. The uncovered proximal and distal extremes allow blood flow in sovraortic and abdominal branches. All patients received more than one endoprothesis (mean = 2.68; range: 2-4), placed with "telescope technic", such as the proximal extreme of the distal endoprothesis on horseback to the distal extreme of the proximal endoprothesis. Patients were clinically followed during hospytalization and they performed a computed tomographic scan at 3 mm intervals two weeks and six months after discharge.
Results: The primary success rate was 94.4%. There was one surgical combined conversion in a patient affected of perypheral vasculopathy, tipe B aortic dissection and abdominal aneurysm, who underwent a double aorto-femoral by-pass and a surgical treatment of the abdominal aneurysm and thereafter an endovascular thoracic placement of two endoprothesis. The average length of hospitalyzation was 8 days. There were no paraplegia and no treatment related organ dysfunctions, such as limb and/or bowel ischemia, cerebrovascular and renal desorders. At six months CT scan a complete obliteration of false lumen was observed in all pts without endoleaks and/or endoprothesis migration.
Conclusion: Endovascular treatment of type B aortic dissection is a safe and effective alternative to surgical therapy in patients at very high surgical risk.

772 Surgically corrected type I acute aortic dissection: what happens to the thoracic descending aorta during the follow-up?

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Introduction: The only effective therapeutic choice in the De Bakey type I acute aortic dissection is actually represented by a prompt surgical intervention of substitution of the ascending aorta with a tubular prosthesis. Little information is available at the moment about the modifications of the descending tract of the thoracic aorta in consequence of such a surgical treatment. Aim of the present study is to evaluate during a long-term follow-up the changes of the thoracic descending aorta in subjects undergone to the surgical intervention for acute type I aortic dissection.
Methods: From our database of 497 patients (pts) with aortic dissection, we examined 67 pts (52 M, 15 F, age 54,8 $\pm$ 10,4 years) affected by type I acute aortic dissection and survived at least 6 months after the surgical treatment, with a complete follow-up. For the evaluation of the aortic diameters a transesophageal echocardiography (TEE) was performed in each patient at 3,6, 12 months from the intervention and successively scheduled once a year, in absence of complications. The aortic diameters at the TEE were calculated at different distances form the incisors and an average value of these was so obtained. The mean duration of the follow-up was 3,8 $\pm$ 3,4 years (range 6 months to 144 months).
Results: During the follow-up there was a progressive enlargement of the thoracic descending aorta. The mean thoracic descending aorta diameter at the baseline was 3,1 $\pm$ 0,4 cm; the increase in dimension was 18,6 $\pm$ 14,5%, with a mean velocity of dilatation of 0,4 $\pm$0,5 cm/year. No significant correlation was shown between the progression of the dilatation and the aortic diameter at the baseline (p= 0,65). The TEE evidenced in the follow-up the presence of intimal tears in the thoracic aorta distal to the prosthesis in 43 pts (64.1%), of whom 2 were re-operated and 2 underwent a stent-graft implantation for the excessive dilatation.
Conclusions: In the De Bakey type I acute aortic dissection the involvement of the descending tract of the aorta is responsible for its progressive dilatation, even after a surgical repair of the dissected ascending aorta. As consequence of this, a careful monitoring during the follow-up is fundamental to guarantee a correct management of such an insidious disease.

773 Treatment of infrarenal aortic stenoses by direct stenting-acute and long-term results

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Objective: Although surgical aortic bifemoral bypass grafting is associated with a high mortality and morbidity risk, it is the gold-standard method in treatment of infrarenal aortic obstructions. Endovascular stenting has been shown to be a highly effective technique in treatment of iliac artery stenoses and occlusions, but the efficacy and long-term patency of infrarenal aortic stenting seems uncertain. The objective of this study was to assess the acute and long-term results of infrarenal aortic angioplasty in aortoiliac obstructive disease.
Methods: In 38 patients (pts.) (male 26, 63 $\pm$11.2 years) with symptomatic claudication (Rutherford class II (n=3) or III (n=35)) infrarenal aortic stenoses (n=25) or combined aortoiliac stenosis (unilateral n=6, bilateral n=7) were treated by direct stenting (n=30) or stent-supported angioplasty (n=8). Coexistent iliac ostial lesions were treated by unilateral stenting (n=4) or kissing balloon dilatation and stent implantation (n=9). Preinterventional mean diameter stenosis of the infrarenal aorta was 77 $\pm$14% with a mean pressure gradient (p mean) of 37mmHg. Excentric, calcified stenoses were found in 27 pts., concentric stenoses in 11 cases. 45 Palmaz stents (length of the stented segment 38-68 mm) were implanted in aortic position (7 pts. with two stents).
Results: Technical success (residual stenosis $<$50%) was achieved in all patients. Postinterventional diameter stenosis was 22 $\pm$18%. In calcified lesions a residual stenosis of 34% vs. 7% in non-calcified concentric lesions was observed. However, in all cases a sufficient hemodynamic result with a mean pressure gradient of 3mmHg could be achieved. A clinical improvement of +2 to +3 according to the AHA criteria was observed in 31 and 7 pts. respectively. Follow-up was performed clinically using standarized treadmill test and colour-coded Doppler ultrasound. After a mean follow-up of 36 months primary patency rate was 92.1%. In three cases significant restenosis was observed in angiography. Two of them were treated successfully by percutaneous transluminal angioplasty, showing a secondary patency of 97.4%. In one patient aortoiliac bypass grafting was performed.
Conclusion: Direct stenting is an effective treatment for infrarenal aortic obstructions providing a high technical feasibility and a long-term patency, especially in patients with severe comorbidity.

COMPUTER APPICATIONS IN CARDIOLOGY

780 Prognostic value of the non-linear dynamicity measurement of atrial fibrillation waves detected by GPRS internet long-term electrocardiogram monitoring

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The extended length (28 days) internet Holter registrations were performed with our mobile ECG system with GPRS transmission. The internet server collected continuously the data for further analysis. The atrial fibrillation waves were detected by the extraction of the QRST segments of the ECG registrations. The dynamics of the atrial fibrillation waves were investigated by estimating the coarse-grained correlation dimension (CGCD) and entropy (CGCE) from the correlation integral. The study population consists of 68 patients (age: 61.1 $\pm$ 7.2 male/female: 31/37) with paroxysmal atrial fibrillation (PAF) and sinus rhythm recurrence within 24 hours. The internet-Holter registration was started within 6 hours after the onset of PAF and lasted continuously for 28 days. At the end of the observation the patients were divided into two groups: (A-group (39 pts): 28 day with recurrent PAF, B-group(29 pts): without it). Nonlinear analysis starts with reconstruction the dynamics of the system from the measured time series and delay vectors ($\vec{x}$) are constructed in the phase space using lagged values of the time series as vector components $\vec{x}(i) = (v(i), v(i + k), v(i + 2k), ... v(i + (m-1)k))$, where k is the embedding delay and m is the embedding dimension of the reconstruction, the phase plots (PP) were also determined. The correlation dimensions (D_m) is estimated as the slope of the correlation integral within the scaling region (in a double logarithmic plot of the correlation integral (C_m (r)) as a function of distance r), the correlation entropy (K_m), the CGCD and the CGE were also calculated. Using the multivariate discriminant analysis three variables (the amplitude values of the 2D plots of the C_m (r) at r value of -1.0 (x1), and -0.5 (x2), of the CGCD at r value of -0.4 (x3)) were determined for the model. The separation of the two groups revealed excellent (Wilks' lambda 0.011 $p< 0.001$), the equation of the discriminant score: $D=0.56*x1+0.42*x2-1.9*x3+15.45$. Our study showed a powerful method for the predicting of PAF recurrence and it would be help in the managing strategy (surveillance of the individual risk, frequency of ECG monitoring, change of drug therapy etc.) of PAF.

781 Continuous 12-lead ST monitoring adds prognostic information to TIMI risk score in patients with non-ST-elevation acute coronary syndromes

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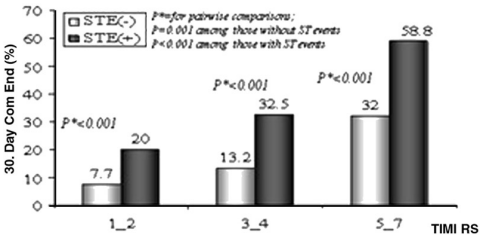
Background: Recurrent ischemia detected by continuous 12-lead ECG ST-segment monitoring early in the course of non ST elevation acute coronary syndromes (NSTACS)has been associated with adverse prognosis. TIMI Risk Score for NSTACS (NSTACS-TIMI-RS) is a simple, accurate and validated tool for early risk stratification. We hypothesize that detection of recurrent ischemia by this device may add prognostic information to NSTACS-TIMI-RS.
Methods: Out of 397 pts underwent continuous ST-segment monitoring with a 12-lead ECG-ischemia monitoring device in the first 24 hrs of NSTACS. An ST ischemic shift was defined as a transient ST-segment depression or elevation in any lead of at least 0.10 mV compared with the reference ECG, lasting for at least 1 min. NSTACS-TIMI-RS was assessed upon admission. The composite of cardiac death, new myocardial infarction and urgent revascularization by 30-days was the primary endpoint.
Results: One hundred and one out of 397 (25.4%) pts had at least one ST shift and the incidence of the composite endpoint in the whole population was 24.2%. There was a significant increased risk for 30-day composite endpoint incidence with increasing of NSTACS-TIMI-RS ($P<0.001$). Moreover the occurrence of $\geq$1 ischemic shift during 12-lead monitoring was associated with increased incidence of 30 days composite endpoint ($P<0.001$). Finally, there was significant difference in 30-day composite endpoint incidence between the several subgroups of NSTACS-TIMI-RS with or without ST-segment shifts (fig.).
Conclusions: The present study suggests that continuous 12-lead ST monitoring early in the course of NSTACS may serve as an affordable tool which adds prognostic information to well established NSTACS-TIMI Risk Score.



782 Towards enhanced, personal, intelligent and mobile systems for early detection and interpretation of cardiological syndromes. The EPI-MEDICS project

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Background: Correct and timely pre-hospital diagnosis of acute ischemia is a very difficult task. Cardiac care strategies are moving towards decision making based on advanced information from the ambulance and on the follow-up of patients at home. But none of the existing trans-telephonic home care ECG recorders embed decision making algorithms, and all need specific receivers and monitoring equipment, which increases the overall cost of possession.
Methods: The solution adopted by the European EPI-MEDICS project(2001-2003)was to design and experiment a novel, affordable and easy to use, portable and intelligent Personal ECG Monitor (PEM) for the early detection of cardiac ischemia and arrhythmia that is able to record, store and derive standard 12-lead ECGs, incorporate intelligent self-adaptive serial ECG data processing and decision-making techniques, generate different levels of alarms, and forward the alarm messages with the recorded signals and the patient's Electronic Health Record (EHR) to the relevant health care providers by means of new generation wireless communication protocols (Bluetooth and GSM/GPRS.
Results: The project has designed an easy to use, pseudo-orthogonal subset of four ECG electrode positions that is adequate for home care or ambulatory use, developed generic and patient specific methodologies for synthesizing standard 12-lead ECGs from the 3-lead PEM ECGs for control by cardiologists, designed robust, neural network based decision-making methods for the detection of ischemic events, and developed a set of twelve PEM devices that are being tested in different clinical settings. The patients ECGs are acquired and processed by the software embedded in the PEM devices and locally stored as SCP-ECG files on a secured personal Smart Media Card. The alarm messages and the EHR are encoded in XML. Major alarm messages are automatically transmitted to the nearest emergency call center by means of GSM or GPRS. Data leading to medium or minor alarms are temporarily stored on a central Web Server and the health professionals are informed by a SMS. The PEM embeds itself a web server to facilitate the reviewing and/or update of the EHR during a routine visit at the GPs or cardiologists office.
Conclusion: EPI-MEDICS provides concretely cost saving solutions to enhance the quality of care: only a standard web browser and internet connectivity are requested, no specific infrastructure is required, and the care providers will be involved only if necessary. A new era has started: health systems will become citizen oriented, personalized, wearable, ubiquitous.

783 Feasibility of seamless remote monitoring of pacemaker patients

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Introduction: Home Monitoring (HM) shall enable remote monitoring of patients with implantable pacemakers by regular automatic transmission of selected implant data to the physician. Technical feasibility and clinical utility of Home Monitoring was investigated in a prospective clinical trial in 11 centers in 4 European countries. We report on the technical feasibility.
Methods: Patients (pts) implanted with the dual-chamber HM pacemaker (PM) BA03 DDDR (Biotronik, Germany) were followed for 3 months. The PM automatically transmitted every 24 hours HM messages to a mobile phone which relayed them to the attending physician per fax in the form of Cardio Report (CR). Primary endpoint of the study was the percentage of pts seamlessly monitored by HM. A pt was classified as "not successfully monitored" for 2 reasons: (A) More than 3 contacts to the pt were necessary to maintain HM; (B) the longest interval without message exceeded 5 days.
Results: 122 pts (44 f, 69.9 $\pm$ 10.0 years, 37 to 87 years) have been included for a mean follow-up time of 76 $\pm$ 29 days. For 6 pts (4.9%) HM transmission could not be established within 5 days after hospital discharge. For 4 pts the reason was insufficient GSM coverage at the patients home, 2 pts were not able to correctly set up the system. These 6 pts were excluded as non-compliant. For the others, 8515 messages were transmitted to the attending physicians. 21 pts (18.8%) were classified as not successfully monitored 41 $\pm$ 25 days (7 to 113 days) after hospital discharge, 17 pts due to criterion (A), 4 pts due to criterion (B). The percentage of not successfully monitored patients ranged from 0% to 67%, with 4 centers having less than 10%, and 2 centers having more than 30% of not successfully monitored pts. For the successfully monitored pts, 92% $\pm$ 7% of the messages were transmitted. 380 interrupts in the message sequence occurred, with 328 (86%) lasting less than 3 days. 56 (61%) of the successfully monitored pts had no interrupts longer than 2 days.
Conclusions: The novel Home Monitoring technology enables seamless remote monitoring for pacemaker patients. Only a small minority of patients cannot be monitored due to technical reasons. Some patients require regular reminders for correct handling of the HM system. The majority of patients, however, can be monitored with minimal maintenance efforts.

784 CARIS-NT: development of a multi-tier, component-based multicentre cardiology information system to support regional healthcare

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Introduction: The Department of Cardiology at the Leiden University Medical Center (LUMC) closely works together with hospitals in the region to provide optimal regional healthcare. Academic care is provided at the LUMC, while routine care is provided by the other hospitals. Patients are therefore often under treatment in the LUMC as well as in the other hospitals. To provide continuous care, it is necessary to have all clinical information about each patient available in either of the hospitals. This is especially important when a patient is admitted at the emergency department of one of the hospitals.
At the LUMC, cardiologists use the Cardiology Information System (CARIS), developed by the IT-group of the department, for entry and retrieval of all clinical cardiology data. CARIS consists of a database server (Oracle) and various application modules built with Borland Delphi. CARIS contains all clinical information specific for Cardiology (on catheterizations, pacemaker implants and follow-up, CCU, etcetera). In addition, information in separate dedicated information systems (ECG management system, DICOM angio and echo image servers) can be viewed in CARIS. Access to CARIS is possible at any location in the department. CARIS is connected to the clinical information systems in the department (ECG's, images, hemodynamics) and to the Hospital Information System (patient demographics, discharge letters, billing).
Methods: As part of a nation-wide project (EPDCAR) we have developed a completely new version of CARIS, CARIS-NT. CARIS-NT is based on a new, multi-tier architecture. Some of the features are: (*) web-based front-end, which will be used to connect to the CARIS database in the LUMC from any of the other hospitals via the Internet (via a secure connection) (*) optimal integration with the electronic patient record system of the LUMC, and also with that in the other hospitals.
Results: The first SOAP/XML based modules (short-stay, stress-ECG, Thoracic Surgery admittance forms) have been implemented. CARIS-NT based versions of the other existing modules will follow shortly, and also new modules.
Conclusion: The new IT architecture that CARIS-NT is based on provides a Cardiology Information System that is accessible via Internet in all regional hospitals. It will be an important step forward in improving regional patient care.

785 A variable valve area lumped parameter model of left-ventricular filling

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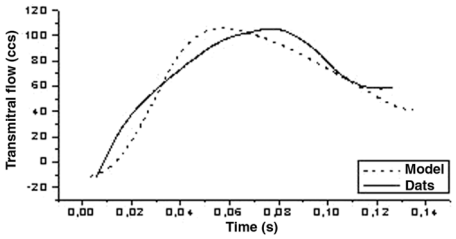
Despite diagnostic advances the quantitative description of left ventricular diastolic filling and mitral valve function remains difficult. We developed a lumped parameter model of left ventricular filling and validated in porcine trials under physiological conditions and valve replacement.
Six animals were instrumented with aortic flow meter, left atrial pressure catheter and combined left ventricular pressure-conductance catheter. Mitral valve replacement was performed with St. Jude Medical prostheses. The model simulates ventricular and arterial pressures and flows during diastolic filling. Input parameters include maximum mitral valve area, blood viscosity and density, atrial compliance, left ventricular active relaxation characteristics and initial pressure and flow values. The outputs of the model are atrial and ventricular pressure and transmitral flow as a function of time. The model primarily consists of a system of four first-order, non-linear ordinary differential equations which are solved with MATLAB software.
Left atrial and ventricular pressure data and model curves were nearly identical under physiological conditions and valve replacement. The figure below shows a very good agreement between measured and model transmitral flow curves. Measured and calculated E-wave (8.86±2.22 vs. 8.45±1.31 ml) and total filling volume (12.1±2.1 vs. 11.9±1.7 ml) were also similar. There was a good correlation ($r=0.97$ $p<0.0000001$) between measured and calculated volume values in a range of 2.5 to 22 ml.



The new lumped parameter model of left ventricular filling allows for the first time a detailed simulation of pressure and flow curves in the left heart including transmitral hemodynamics.

IN-STENT RESTENOSIS: THE REAL WORLD

800 Current percutaneous transluminal coronary angioplasty practice and results in the Netherlands: insights from the GENDER project

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Objective: To document the practice of interventional cardiology and the clinical restenosis rates in an unselected population of patients in the pre-drug-eluting stent era and to provide a perspective for the need of these new devices.
Methods: The Genetic DEterminants of Restenosis (GENDER) project is a prospective cohort study of 3000 patients after successful PTCA (less than 30% stenosis) in four academic tertiary referral centers for interventional cardiology in the Netherlands. Patients with acute myocardial infarction (MI) were excluded.
Results: 3000 patients (age 62±11 yrs) were followed for 10.6±3.7 months. Of them 858 (25.6%) were female, 438 (14.6%) had diabetes and 1378 (45.9%) had multivessel disease. The majority was treated for stable angina, 967 (32.2%) had a non-ST elevation acute coronary syndrome. Multilesion PTCA was done in 768 (25.6%). Stenting was performed in 2888 (76.3%) and IIb/IIIa inhibitors were used in 779 (26.0%). All stented patients received life-long aspirin and ticlopidin/clopidogrel during at least 1 month after the procedure. Target vessel revascularisation during follow-up by either CABG or PTCA was necessary in 309 patients (10.3%). Thirty-eight (1.3%) died of cardiac disease, 20 (0.7%) of other causes. 28 (0.9%) suffered from MI attributable to the originally treated vessel. Overall a need for revascularisation, cardiac death or MI occurred in 378 patients (12.6%).
Conclusion: In this unselected series of patients treated according to the current standards in the pre-drug-eluting stent era clinical restenosis occurred in only 12.6%. A proper selection of patients that benefit from the new devices is warranted, since the vast majority is well treated with standard techniques and proper assignment of expensive new devices obviously is of importance for overall health care.

801 Sirolimus-eluting stents for treatment of in-stent restenosis in the real world: results from the rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital (RESEARCH) Registry

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Purpose: In-stent restenosis (ISR) represents a significant clinical problem following stent implantation. Coronary vascular brachytherapy is, to date, the only effective treatment available. However, complex logistic requirements and the identification of some long-term sequelae have prevented its widespread use. Preliminary studies have shown that sirolimus-eluting stents (SES) are safe and effective for treatment of ISR. We tested the efficacy of this strategy in daily practice.
Methods: Since 16th April 2002 all patients undergoing PTCA at our institution have been treated with SES, irrespective of clinical presentation and lesion morphology. They have been enrolled in the RESEARCH registry. ISR patients were selected to undergo routine 6-month angiographic follow-up, as well as 12-month clinical status assessment. Their outcomes will be compared to the historical cohort of patients treated for ISR in our catheterization laboratory in the preceding six months.
Results: From October 16th 2001 to October 15th 2002, 123 consecutive patients underwent PTCA for ISR at our institution: 66 patients treated in the first six months compose the control group (74 lesions, major treatment: brachytherapy in 31%, cutting balloon in 23%, balloon in 28%, bare stent in 18%), whereas in the subsequent RESEARCH phase 57 patients (with 67 ISR lesions) received SES. Baseline demographics and clinical presentation were similar among the two groups. Severe patterns of ISR (Mehran type III and IV) were more frequently observed in the RESEARCH group (46% vs 22%; p=0.002), as well as the incidence of previous brachytherapy of the target vessel (25% vs 6%; p=0.005). A similar proportion of patients underwent multivessel procedure (23% RESEARCH vs 27% control; p=NS). Procedural success was achieved in 56/57 RESEARCH patients (98%) and in 64/66 (97%) controls. At 6-month follow-up (complete for 67% of the RESEARCH patients vs 100% controls) the incidence of major adverse cardiac events (death, myocardial infarction, revascularization) was similar among the two groups (17% RESEARCH vs 19% control; p=NS).
Conclusions: Preliminary results suggest that SES implantation is as effective as standard treatment (including brachytherapy) to treat ISR in a real-world setting.

802 Long-term outcome of intracoronary radiation to prevent restenosis in diabetic patients after stenting: 6-month results of a randomized trial

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Intracoronary brachytherapy (ICB) has been proven to be effective to prevent recurrence in pts with in-stent restenosis. The role of ICB for the treatment of de novo coronary stenosis remains unknown. Purpose: to assess the efficacy of ICB with beta radiation following successful coronary stenting in diabetic pts with de novo lesions. Methods: This was is a single-center, prospective, randomized, placebo-controlled trial; sub-randomization according to the type of diabetes was also performed. Primary endpoints were: 1) in-stent mean neointimal area as assessed by intravascular ultrasound (IVUS) at 6-month follow-up (primary endpoint of effectiveness), and 2) minimal luminal area of the entire vessel segment as assessed by IVUS at 6-month follow-up (primary endpoint of clinical efficacy). A total number of 92 pts were included: 46 randomized to radiation (R), using the P32 Guidant Galileo system, and 46 to no radiation (NR). IVUS was performed after PTCA and at follow-up. QCA analysis was performed (before, after PTCA, and at follow-up) at 4 segment sites: stented, injured, irradiated, and vessel segments. Results: Angiographic follow-up was performed in 93% of R patients and in 91% of NR patients. No clinical nor angiographic differences were observed at baseline between groups. Insulin-(35%) and non insulin-dependent (65%) pts were equally allocated. During hospital stay, 1 death (non-cardiac)and 1 non-Q wave myocardial infarction (MI) occurred in group R; no events occurred in group NR. In-stent mean neointimal area as assessed by IVUS at 6-month follow-up was 52% smaller in group R (1.04 mm^2 vs. 2.16 mm^2; $p<0.0001$). However, there was no difference in minimal luminal area of the vessel segment at follow-up (4.5 mm^2 vs. 4.4 mm^2). Restenosis rates assessed by QCA varied according to analyzed segments, with a progressive increase in restenosis rate in group R (group R vs group NR): stented (7.1% vs 20.9%; p=0.07); injured (9.5% vs 20.9%; p=ns); radiated (14.3% vs 20.9%; p=ns); vessel (23.8% vs 25.6%; p=ns). At 6 months, 1 cardiac death, 5 MI (due to stent thrombosis), and 10 target vessel revascularization (TVR) occurred in group R; in group NR, there were 11 TVR and no deaths nor MI. Major adverse cardiac events were 13 in group R and 11 in group NR (p=ns). Edge effect accounted for 6 out of 10 TVR of group R.
Conclusions: ICB significantly inhibited in-stent neointimal hyperplasia after stent implantation in diabetic patients. However, this was not translated in any clinical benefit at 6 months due to the occurrence of edge effect and late stent thrombosis.

803 Evolution of late lumen loss after intracoronary beta-radiation – a prospective quantitative angiographic study at 3, 6, 12 and 24 months

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Objective: Vascular brachytherapy (VBT) has proven to reduce restenosis rate (RR) and major adverse cardiovascular events. Yet it has been suspected that radiation does not inhibit but rather delay the process of restenosis. The time course of the restenotic process after beta-VBT of in-stent restenotic lesions (ISR) is unknown. The objective of the study was to investigate the evolution of late loss (LL) and RR after successful percutaneous coronary intervention (PCI) and VBT.
Patients and Methods: The study population consisted of 58 consecutive pts who had undergone successful PCI for ISR and VBT with 90Sr/90Y and who were prospectively enrolled into an angiographic and clinical follow-up protocol at 3, 6, 12 and 24 months (MO) after the index procedure, regardless of their symptomatic status. Restenosis rate was calculated by the Cutler-Ederer-method, and quantitative coronary angiography indexes were determined.
Results: Actuarial RR measured 5,4±3,0% at 3 MO follow-up, 10,7±4,1% (6 MO); 23,2±5,6% (12 MO) and 26,7±6,4% (24 MO), respectively. Minimum lumen diameter at the target lesion was 0,65±0,49mm before PCI and 2,71±0,65mm after PCI. At follow-up, LL of the target lesion (TL) measured 0,15±0,46mm, $p<0,001$ (after PCI/3 MO), 0,18±0,15mm, p=0,003 (3/6 MO), 0,21±0,52mm, p=0,033 (6/12 MO) und -0,04±0,59mm, p=0,599 (12/24 MO), respectively, and LL at the non-target lesion target vessel (nTLTV) was 0,15±0,34mm, $p<0,001$ (post/3 MO), 0,09±0,38mm, p=0,009 (3/6 MO), 0,02±0,41mm, p=0,357 (6/12 MO) und 0,01±0,59mm, p=0,700 (12/24 MO).
Conclusions: The restenotic process after beta-irradiation is not complete within the traditional 6 months interval but sustained up to 1 year. During the second year of follow-up, a significant further late loss could not be demonstrated.

804 Long-term efficacy of intracoronary beta-radiation for treatment of diffuse in-stent restenosis: evidence for late restenosis

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Intracoronary radiation therapy (ICR) using beta or gamma emitters has significantly improved the long-term angiographic and clinical outcome after treatment of in-stent restenosis (ISR) as compared to balloon angioplasty alone. Recent experimental and clinical data, however, indicate a delayed initiation of smooth muscle proliferation following ICR subsequently leading to an onset of recurrent restenosis beyond a 6 or 8 month follow-up.
Data from a systematic mono-center registry including 100 patients (62±11 years, 80% male) undergoing angioplasty and subsequent intracoronary beta-radiation (90Sr Novoste system) for diffuse ISR (lesion length 14±8mm) were analysed. Follow-up angiography (FUA) 6±1 month post intervention was performed in all patients. Thereafter, patients were scheduled for recurrent angiography (RA) when typical angina and/or objective signs of myocardial ischemia were present. Late restenosis was defined as a >50% diameter stenosis (DS) of the target lesion at recurrent angiography in those patients with a <50% DS at 6 month angiography.
FUA documented angiographic restenosis in 28/100 (28%) lesions with the need for target lesion revascularisation due to recurrent ISR in 26/100 (26%) cases. Another angiography was performed in 17/100 (17%) patients 6±3 month (range 2-18 month) after initial FUA (12±3 month post ICR). Late stenosis was present in 6/100 (6%) patients with the need for TLR in all cases. Those 6 patients had a DS of 33±6% at FUA and of 78±7% at RA indicating clinically relevant, delayed neointimal proliferation.
Intracoronary radiation therapy of diffuse ISR in an unselected patient population leads to angiographic restenosis in 28% patients 6 months and in 32%patients 18 month after index procedure as a result of late restenosis. These results complement preclinical data suggesting that intracoronary radiation produces a significant delay in the onset of recurrent restenosis, but does probably not completely prevent the restenosis process. A follow-up period of at least 2 years after ICR seems neccessary to identify late restenosis in patients with ISR undergoing ICR.

805 Sirolimus-eluting stents to treat recurrent in-stent restenosis after brachytherapy

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Purpose: Coronary brachytherapy is the most effective treatment available for complex in-stent restenosis (ISR). However, it is not free from failures and up to one-third of the patients will need a new revascularization over long-term follow-up. We sought to evaluate the safety and efficacy of sirolimus-eluting stent (SES) implantation to treat recurrent ISR after brachytherapy.
Methods: We prospectively collected data of patients treated with SES for ISR at our institution as part of two different studies: the First In Man (FIM), an international, dual-center pilot study, and the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) Registry. Patients with previous target vessel irradiation have been selected for this report.
Results: 18 consecutive patients, enrolled in two different time periods, were treated with SES implantation for recurrent ISR after "failed" brachytherapy (15 catheter-delivered beta irradiation, 1 gamma, and 2 radioactive stents). Acute coronary syndrome was the clinical presentation in 45% of cases. Half of the patients had at least 2 previous episodes of ISR. Previous myocardial infarction was present in 12 patients (67%), and 8 (44%) had had a coronary bypass operation. Multivessel disease was a frequent finding (78%), and 4 patients (22%) had more than one vessel treated. Lesion length averaged 23±20 mm, with an average 2.8±0.5 mm reference diameter. 11 patients (61%) presented severe proliferative pattern of ISR (Mehran classification III-IV). The attempt to entirely cover the lesions is confirmed by device utilization (1.6 stents per patient, 37±30 mm per lesion). All the procedures were considered clinically successful. No episode of subacute thrombosis was reported. During a median follow-up of 5 months, 5 patients (28%) experienced a major adverse cardiac event: one patient died of congestive heart failure (not related to the procedure; angiographic and IVUS control at 4 months did not show neointimal hyperplasia), and 4 patients (22%) presented target vessel failure (3 had clinically-driven re-PTCA, one showed silent reocclusion at elective angiographic control).
Conclusions: Sirolimus-eluting stent implantation is a safe and clinically effective strategy to treat recurrent in-stent restenosis after brachytherapy, although rapamycin efficacy in preventing neointimal hyperplasia in this context seems to be reduced compared with other less complex situations.

HEART FAILURE: INTRIGUING FINDINGS BUT NOVEL MESSAGES?

850 Prognostic impact of matrix metalloproteinases gene polymorphisms in patients with heart failure according to the etiology of left-ventricular dysfunction

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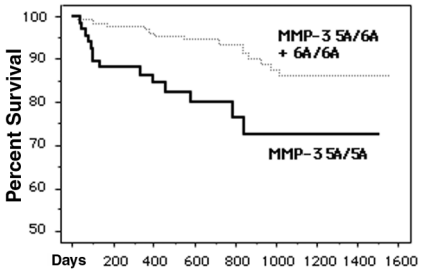
Left ventricular remodeling is a major determinant of survival in patients with heart failure (HF). Changes in extracellular matrix proteins play an important role in this process. We hypothesized that functional polymorphisms in matrix metalloproteinases (MMP) gene promoters could affect the outcome of HF patients.

Methods: We studied 444 consecutive patients who were referred to our center for evaluation of left ventricular dysfunction. We extracted genomic DNA from white blood cells and determined -1306 C>T MMP-2, -1171 5A>6A MMP-3 and -1562 C>T MMP-9 polymorphisms. Clinical follow-up (median 717 days) was obtained for 443 patients.

Results: There was a statistically significant effect of MMP-3 polymorphism on cardiac survival that differed according to HF etiology (interaction $p<0.03$). In patients with non-ischemic cardiomyopathy, the MMP-3 5A/5A genotype was an independent predictor of cardiac mortality (HR 2.92; p=0.01) (Figure). In contrast, there was no evidence for any significant effect of MMP-3 genotype on cardiac survival in patients with ischemic cardiomyopathy. The MMP-9 polymorphism was associated with cardiac survival ($p<0.03$) independently of HF etiology. By multivariate analysis, the presence of at least one MMP-9 T allele was an independent predictor of cardiac mortality (HR 1.81; p=0.02). Finally, there was no evidence for any association between MMP-2 polymorphism and cardiac survival.



Survival in non ischemic heart failure.

Conclusions: MMP-3 and MMP-9 polymorphisms contribute to variability in cardiac survival in HF patients. The more active MMP-3 5A and MMP-9 T alleles are associated with higher mortality. These data suggest that MMP genotyping could provide important additional information to refine risk stratification in patients with heart failure.

851 Elevated myocardial TIMP1 expression correlates with interleukin-6 in patients with deteriorating heart failure, and is stimulated by interleukin-6 in vitro

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Background: Differential regulation of cytokines, matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs), is observed in heart failure. We have previously shown elevated myocardial mRNA levels of cytokines, including TNF-alpha, IL-1beta and IL-6 in patients with deteriorating heart failure requiring LVAD support, compared both to patients with stable end-stage heart failure and to donor organs. Here we have examined mRNA for TIMP1, MMP1 and the MMP inducer EMMPRIN, in the same patients in order to further characterise deteriorating HF at the molecular level and to identify potential regulatory pathways.

Methods: Myocardial samples were obtained from patients requiring LVAD support (deteriorating HF, n=26), donor organs with normal hemodynamic function (donors, n=28) and from stable end-stage heart failure taken at the time of transplantation (ESF, n=17). TIMP1, MMP1 and EMMPRIN mRNA levels were measured by quantitative real-time PCR (TaqMan). Neonatal rat cardiomyocytes were cultured in serum free medium in the presence or absence of human IL-6 for 65 hours, RNA extracted and analysed by real-time PCR.

Results: TIMP1 mRNA was similar in donors (1.47 ± 0.80) and stable ESF (1.00 ± 0.50), but significantly increased in deteriorating HF (5.38 ± 3.63, $p<0.001$). Likewise, MMP1 was similar in donor (0.91 ± 0.79) and stable ESF (1.00 ± 0.63), but elevated in deteriorating HF (6.04 ± 5.06, $p<0.001$). In contrast, EMMPRIN was slightly higher in both deteriorating HF (1.15 ± 0.38) and ESF (1.0 ± 0.27) compared to donors (0.78 ± 0.21, $p<0.05$). Comparing all patients (n=54), TIMP1 and MMP1 levels correlated with each other (R=0.45, $p<0.001$) and to previously determined mRNA levels of IL-6 (R=0.27 and R=0.35 respectively, $p<0.05$), and IL-1beta (R=0.43 and R=0.41 respectively, $p<0.05$). Neither correlated with TNF-alpha or EMMPRIN. Myocardial TIMP1 is predominantly expressed by myocytes and has been previously shown to be up-regulated by IL-1beta in vitro. The effect of IL-6 on expression is unknown. We therefore tested the effect of adding IL-6 to myocytes cultured in vitro. Addition of IL-6 resulted in a dose dependent increase in TIMP1 mRNA reaching 3.7-fold at 1ng/ml.

Conclusions: Elevated TIMP1 and MMP1 mRNA expression parallels that of the pro-inflammatory cytokines IL-6 and IL-1beta. Positive correlation of TIMP1 with IL-6 in myocardium of patients, and the induction of TIMP1 mRNA expression by IL-6 in myocytes in vitro implicates this as a contributory pathway in the pathogenesis of deteriorating heart failure.

852 Borderline myocarditis according to the Dallas criteria of myocarditis in clinical routine endomyocardial catheter biopsies: a problem of continuing clinical and pathological confusion?

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Up to now the Dallas criteria of myocarditis are still the basis of the morphological definition of myocarditis (M). Although additional immunhistochemical methods for the identification of an inflammatory infiltrate are recommended, bioptic diagnosis of M in clinical routine is generally based exclusively on the Dallas criteria of myocarditis (i. e. exclusively based on light microscopic evaluation). Especially the diagnosis of "borderline myocarditis" (BLM) implicates ambiguous terms which seem to cause continuing confusion in clinical routine evaluation of pts. with suspected M.

Methods: Therefore, we investigated for the first time in a prospective study the comparative application of the Dallas criteria of M/BLM in relation to if the pathologist received clinical information (first group) or if the biopsies were judged in a blinded manner (second group) (i.e. biopsy evaluation and the written report of the pathologists were made without any clinical information). EMCB (approximately 4 right ventricular EMCB per pt.) were performed in 2 consecutive cohorts of 100 pts. each with dilated cardiomyopathy, new onset congestive heart failure, regional/global left ventricular dysfunction and/or clinical history of inflammation.

Results: In the first group an inflammatory/interstitial infiltrate was described in 45 of 100 pts.(45%); in 35 of these 45 pts. (78%) a firm or suspected diagnosis of M was stated. In the second group which was judged in a blinded manner an inflammatory/interstitial infiltrate was described in 38 of 100 pts.(38%). However only in 2 of these pts. (82 of 38 pts.;5%) a diagnosis of M was stated. The diagnosis of M with definite myocyte necrosis and adjacent inflammatory infiltrate was stated in 1 pt. in each group (1%); BLM with extensive changes was present in 3 pts. (group 1: 2 pts.; group 2: 1 pt.). In 42 pts. (93%) the diagnosis of BLM was stated on the basis of a sparse infammatory/interstitial infiltrate influenced by information from the clinician about strong clinical suspicion of myocarditis.

Conclusion: These results highlight the ambiguous nature of the term BLM according to the Dallas criteria of M. Difficulties in identification of inflammatory cells, the subjective basis of evaluation, sampling error and high interobserver variability are a cause of diverging diagnosis. Especially in BLM "clinical bias" may lead a pathologist to classify a sparse inflammatory/interstitial infiltrate as BLM. Additional immunhistological investigation is mandatory even in clinical routine EMCB in suspected inflammatory heart disease.

853 In chronic heart failure overactive chemokine system is associated with immune activation, low grade inflammation and predicts loss of fat tissue

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Background: In chronic heart failure (CHF) elevated C-C chemokine levels have been documented, which may be linked to immune activation and inflammatory state. Since in CHF patients who develop weight loss immune and inflammatory reactions are particularly abnormal, chemokines may play an important role.
Aim: To assess whether plasma macrophage chemoattractant protein-1 (MCP-1) level is related to inflammatory cytokines, markers of acute phase response, presence of weight loss and body composition in patients with CHF.
Methods: We studied 29 stable CHF patients (23 men, age: 65 $\pm$ 2 years, peak VO2: 14 $\pm$ 1 ml/min/kg, left ventricular ejection fraction: 33 $\pm$ 2%, New York Heart Association [NYHA] class I/II/III/IV: 1/11/3/4), 6 of which had documented, non-intentional, non-oedematous weight loss $>$ 7.5% of previous normal weight over $>$ 6 months. MCP-1 was measured and correlated with clinical data, cytokine levels (interleukin-6 [IL-6] and tumor necrosis factor [TNF]-alpha), C-reactive protein (CRP, high-sensitivity method), erythrocyte sedimentation rate (ESR). Body composition was assessed with dual energy X-ray absorptiometry (DEXA).The control group consisted of 30 well-matched healthy subjects.
Results: CHF patients had significantly higher MCP-1 levels (443 $\pm$ 34 vs. 209 $\pm$ 8 pg/mL), together with elevated cytokines, CRP levels and ESR (7.0 $\pm$ 1.1 vs. 2.3 $\pm$ 0.2 pg/mL for IL-6; 4.4 $\pm$ 0.5 vs. 1.6 $\pm$ 0.1 pg/mL for TNF-alpha; 7.0 $\pm$ 1.1 vs. 1.6 $\pm$ 0.2 mg/L for CRP, 18 vs. 4 mm/h for ESR; CHF vs. controls: all $p<0.0001$). MCP-1 did not correlate with age, peak VO2 and hemodynamic indices ($r<0.2$, all $p>0.2$) and was only marginally higher in patients with most severe CHF symptoms (371 vs. 490 pg/ml, NYHA class I-II vs. III-IV, p=0.09). We found significant relationships between MCP-1 and cytokines (r=0.46 for IL-6, r=0.36 for TNF-alpha, both $p<0.05$), CRP levels (r=0.63, $p<0.001$) and ESR (r=0.58, $p<0.01$). Interestingly, MCP-1 was markedly elevated in those CHF patients who developed weight loss (631 $\pm$ 59 vs. 394 $\pm$ 34 pg/mL, vs. remaining patients, p=0.004). Additionally, in CHF there was an inverse relationship between MCP-1 levels and fat tissue (r=-0.65 for total fat and r=-0.67 for leg fat, both $p<0.01$) but not with lean tissue mass ($r<0.2$ for total lean and leg lean, $p>0.2$).
Conclusion: In CHF elevated MCP-1 levels are markers of immune activation and inflammation and also closely relate to loss of fat tissue and body weight. This finding may form a novel therapeutic background for the treatment of cardiac cachexia in CHF.

854 Bisoprolol restores the lipopolysaccharide-induced tumour necrosis factor-alpha production in catecholamine-treated whole blood

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Background: Elevated levels of TNF lead to progression of chronic heart failure (CHF). Bacterial LPS might trigger TNF production in vivo. Catecholamines reduce the LPS-stimulated production of TNF. This process is thought to be mediated via beta-adrenergic receptors on monocytes. Beta-blockers reduce morbidity and mortality in CHF. We investigated the TNF suppressive effect of catecholamines and the role of beta-blockers in this setting.
Methods: We studied 11 healthy subjects (33$\pm$1 years, serum creatinine 75$\pm$4 μmol/L, uric acid 241$\pm$10 μmol/L, norepinephrine [NE] 1.7$\pm$0.3 nmol/L, epinephrine 0.29$\pm$0.06 nmol/L, 6 female, mean$\pm$SEM) and 8 male pts with stable CHF (NYHA 2.1$\pm$0.2, 61$\pm$3 years, creatinine 107$\pm$7 μmol/L, uric acid 364$\pm$40 μmol/L, NE 3.6$\pm$0.6 nmol/L, epinephrine 0.45$\pm$0.12 nmol/L). Ex vivo whole blood was stimulated simultaneously with LPS (1 ng/mL) and seven doses of isoproterenol (0.01-1000 nmol/L and control) or NE (identical doses) for 6 hours. Some samples were additionally treated with bisoprolol (2.5 μg/mL). TNF production was detected in the supernatant by ELISA.
Results: Healthy subjects and CHF pts produced substantial levels of TNF after stimulation with low LPS doses (698$\pm$100 vs 1079$\pm$140 pg/mL, $p<0.05$). Isoproterenol and NE reduced TNF-production in healthy subjects and CHF pts dose-dependently (isoproterenol: 698$\pm$100 to 171$\pm$54 pg/mL vs 1079$\pm$140 to 494$\pm$147; NE: 698$\pm$100 to 206$\pm$61 vs 1079$\pm$140 to 570$\pm$154, repeated measures ANOVA all $p<0.05$). The beta1-selective bisoprolol restored the respective pattern of LPS-response in both groups. TNF production was reduced to a lesser extent in CHF pts than in healthy subjects (isoproterenol: 40$\pm$9 vs. 20$\pm$4%; NE: 48$\pm$10 vs. 26$\pm$5%, both $p<0.05$).
Conclusions: Our data show that the suppression of LPS-stimulated TNF production is mediated mainly by beta1-receptors. Beta2-receptors yield an additional effect. Compared to healthy subjects, catecholamines decrease LPS-stimulated TNF production in CHF to a lesser extent. Beta-receptor down-regulation on monocytic cells, which is known to occur in CHF, may account for this phenomenon. Bisoprolol and possibly other beta-blockers restore the normal pattern of responsiveness to LPS.

855 Both ramipril and telmisartan reduce serum levels of high-sensitivity C-reactive protein without affecting low-density lipoprotein cholesterol oxidation in patients with type II diabetes mellitus

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Aim: Growing evidence suggests that activation of the renin-angiotensin-aldosterone system (RAAS) predisposes to vascular inflammation and increased oxidative stress. The aim of this study was to assess the effect of ramipril (an angiotensin converting enzyme inhibitor) and telmisartan (an angiotensin II receptor antagonist) on inflammation and lipid oxidation in patients with type II diabetes mellitus.
Methods: Thirty pts, 57.32$\pm$8.45 years old,13 men and 17 women, with well controlled diabetes (glycated hemoglobin $<$ 8%), of mean duration 6.9$\pm$3.9 years, free of microalbuminuria, with a negative history of hypertension or coronary artery disease and a negative exercise stress test were recruited in this double blind cross-over trial. All pts had a baseline measurement of high-sensitivity C-reactive protein (hs-CRP) with the use of a Dade Boehring Prospec nephelometric analyzer. Moreover, IgG autoantibodies against Cu++-oxidized LDL-cholesterol (aox-LDL) were measured with a commercially available ELISA kit (Biomedica). Subsequently, pts were started randomly on treatment with ramipril (2,5mg/day) or telmisartan (40mg/day) or their combination for 3 months. Every pt was crossed over to the alternative regimen after a 2-week wash out period. Measurements were repeated at the end of each treatment period.Statistical analysis was done with Friedman's analysis of variance.
Results: All types of treatment were associated with a significant fall of the hs-CRP serum levels(0.19$\pm$0.19 mg/dl baseline vs 0.14$\pm$0.16 mg/dl with ramipril vs 0.11$\pm$0.8 mg/dl with telmisartan vs 0.11$\pm$12.5mg/dl with combined therapy, p=0.003).On the other hand, aox-LDL were not affected by the administration of any of the above regimens (273.8$\pm$190.8mU/ml baseline vs 287.1$\pm$214.5mU/ml with ramipril vs 301.1$\pm$224.4mU/ml with telmisartan vs 279.8$\pm$192.5mU/ml with combined therapy, p=0.667).
Conclusions: Both ramipril and telmisartan suppress inflammation without affecting lipid oxidation in pts with type II diabetes mellitus. In view of the accumulating data supporting the current concept that type II diabetes may be associated with a chronic low-grade inflammatory process, blocking of the RAAS may be of great clinical significance. This may be the case even in the early stages of the disease when microalbuminuria or overt macrovascular complications are absent.

HEART FAILURE: OLD FACTS – NEW INFORMATION?

856 Signs and symptoms of heart failure as endpoints for assessing therapeutic response: Val-HeFT data

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Purpose: Signs and symptoms (S&S) are indispensable in monitoring the patient's well-being with heart failure (HF), yet they are not emphasized as endpoints for judging the response to therapy. Val-HeFT which showed a 13.2% risk reduction in morbidity with valsartan (V) formed the database for investigating the usefulness of S&S as measures of therapeutic response.
Methods: From data in 5010 HF patients changes in S&S including fatigue, dyspnea on effort and at rest, paroxysmal nocturnal dyspnea, orthopnea, jugular venous distension, edema, rales and S3 gallop were examined as secondary variables. The numbers of improved or worsened patients were analyzed using the Cochran-Mantel-Haenszel test. A post-hoc analysis was performed in which each of the S&S scores was normalized between best (0) and worst (1) and summed as a totality score. An ANCOVA model adjusted for baseline, site and use of ACE inhibitor and beta blocker was used to analyze treatment differences in change from baseline in totality score.
Results: At endpoint, statistically significantly more patients treated with V showed an improvement and fewer worsened in all S&S compared to placebo (P) with the exception of S3 gallop and orthopnea. At all analyzable timepoints during the trial except for month 24, statistically significant improvements in the totality score were observed in V compared to P patients (table).

Month	V (N)	P (N)	V Change	P Change	V-P	p-Value
4	2294	2323	-0.25	-0.18	-0.07	0.01331
12	2004	2080	-0.34	-0.24	-0.10	0.00084
18	1795	1857	-0.34	-0.24	-0.10	0.00389
24	1197	1235	-0.30	-0.25	-0.05	0.23389
30	609	611	-0.35	-0.23	-0.12	0.03626
Endpoint	2494	2482	-0.23	-0.07	-0.16	<0.00001

Least-Squares Mean Change from Baseline S&S Totality Score

Conclusion: Sustained improvement in S&S in patients with chronic HF was concordant with a morbidity benefit from valsartan and re-emphasized the importance of the history & physical examination.

857 Advanced heart failure among patients with coronary artery disease in absence of myocardial infarcton: prevalence, risk factors and prognosis

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Background: Some patients developing congestive heart failure (CHF) have no history of myocardial infarction (MI), and stable angina pectoris is their principal clinical manifestation of coronary artery disease (CAD). The possible differences in the epidemiology of CAD-related CHF in patients with and without history of MI has not been elucidated.
Methods: The present study was aimed to evaluate the outcome of CAD-related CHF in patients with and without a history of MI over a 7.7-year follow-up. The study sample comprised 14283 coronary patients aged 45 to 74 years. The presence of NYHA functional class II in patients with clinically established heart failure was defined as mild CHF and the presence of NYHA functional class III-IV was defined as advanced CHF.
Results: The patients were divided in 2 groups: 1) With a history of MI – 10307 patients, who formed 3 subgroups: NYHA I – 7551 patients (73.3%); NYHA II–2176 patients (21.1%); NYHA III, IV – 580 patients (5.6%). 2) Without a history of MI – 3976 patients, who also formed 3 subgroups: NYHA I – 2744 patients (69.0%); NYHA – 981 patients (24.7%); NYHA III, IV – 251 patients (6.3%). For patients without history of MI, independent variables associated with advanced CHF were peripheral vascular disease (PVD), higher body mass index and blood glucose level. For post MI patients, in addition to the above-mentioned - female gender, chronic obstructive pulmonary disease (COPD), history of hypertension (but lower current systolic blood pressure) and higher heart rate. Multivariate analysis identified a history of MI as a consistent predictor of increased all-cause and cardiac mortality for patients with NYHA I, II and III+IV subgroups with escalating significance for patients with advanced CHF: hazard ratios of 1.55 (95% CI 1.36-1.75), 1.56 (95% CI 1.30-1.86) and 1.72 (95% CI 1.24-2.40) for all-cause and 1.93 (95% CI 1.60-2.33), 1.73 (95% 1.35-2.20) and 3.22 (95% CI 1.87-5.54) for cardiac mortality, respectively.
Conclusions: The prevalence of advanced CHF was unexpectedly similar among coronary patients with and without a history of MI, but their long-term survival differed substantially in favor of the latter. Therefore, from a clinical point of view, two different types of CAD-related advanced CHF (post MI and non post MI) can be distinguished.

858 Electrocardiographic features of uncomplicated ventricular conduction blocks predict long-term risk of cardiovascular morbidity

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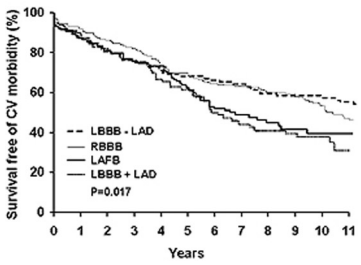
Background: Ventricular conduction blocks (VCB) identified on electrocardiogram predict an adverse outcome in patients with heart failure. The prognostic implications of VCB in asymptomatic patients are not established. The purpose of this study was to evalute the long-term outcome of patients in a community-based population with VCB and documented normal left ventricular ejection fraction and no cardiac disease symptoms or diagnosis at the time VCB was identified.
Methods: A retrospective observational cohort study was undertaken of Olmsted County, MN patients evaluated at the Mayo Clinic during 1975 to 1999 who met the above inclusion criteria. Kaplan-Meier (K-M) analysis of time to development of first cardiovascular morbidity (coronary artery disease, myocardial infarction, congestive heart failure, dilated or ischemic cardiomyopathy, valvular disease, rhythm abnormality, or permanent pacemaker implantation) post-VCB diagnosis was performed with 10-year data.
Results: 706 patients (mean age 64 ± 16 [SE] years) were identified (LBBB with left axis deviation [LAD], 12%; LBBB without LAD, 20%; left anterior fascicular block [LAFB], 26%; and RBBB, 42%). K-M analysis indicated significant differences among groups for the development of cardiovascular morbidity (p=0.017). Patients with LAFB and LBBB with LAD were at highest risk (39% and 31% survival free of CV morbidity respectively).



K-M morbidity analysis.

Conclusions: The diagnosis of uncomplicated VCB is associated with a significantly increased risk of developing cardiovascular morbidity. The majority of the increased risk is associated with the presence of LAD (LAFB or LBBB). These findings suggest that these patient groups should be identified early for preventive management.

859 Long-term survival in diabetic patients with congestive heart failure

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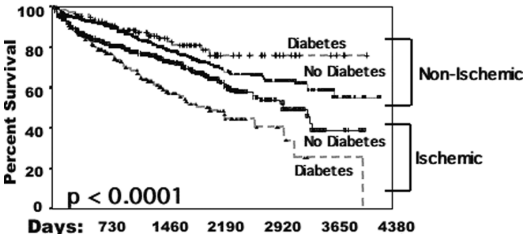
Background: Previous studies have documented an increased risk of heart failure (HF) in patients with diabetes mellitus; a significant proportion of HF patients are diabetic. We designed the present study to test the hypothesis that diabetic status may also be used as a prognostic indicator in HF patients.
Methods and Results: We studied 1246 consecutive patients who were referred to our center for evaluation of left ventricular dysfunction. All patients had a cardiopulmonary exercise test and an echocardiography. Routine cardiac catheterization was performed to define HF etiology. Clinical follow-up (median 1200 days) was obtained for 1241 patients. Twenty-two percent of the patients were diabetic; in diabetics, HF etiology was ischemic in 58% vs 40% in nondiabetics ($p<0.0001$). There was a statistically significant effect of diabetes mellitus on cardiac survival that differed according to HF etiology (interaction $p<0.008$). In nonischemic patients, there was a trend for a better cardiac survival in diabetics; by contrast, in ischemic patients, diabetics had a significantly worse prognosis than nondiabetics ($p<0.004$). By multivariate analysis, diabetes mellitus was an independent predictor of cardiac mortality in ischemic patients (HR = 1.50 [1.10-2.03]) but not in nonischemic patients (HR = 0.62 [0.38-1.01]). Compared to non-ischemic patients, the adjusted hazard ratio for cardiac death was 1.71 [1.32-2.22] in ischemic patients without diabetes and 2.58 [1.91-3.49] in ischemic patients with diabetes.



Cardiac mortality.

Conclusion: Diabetes mellitus interacts with HF etiology to influence the prognosis of HF patients. Further studies are needed to determine whether any specific therapeutic approach may be beneficial in diabetic patients with ischemic HF.

860 Gender differences on current in-hospital management of heart failure by Cardiologists and Internists. Data from the TEMISTOCLE Study

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Background In recent years, epidemiological and clinical reports have shown some differences in medical management and prognosis of men and women with heart failure (HF). We sought to evaluate sex-related differences in the clinical profile, use of resources, management and outcome in a large population of "real world" HF patients.
Methods The TEMISTOCLE survey evaluated 2127 patients discharged from 167 Italian Cardiology Departments and 250 Internal Medicine Units with a primary diagnosis of worsening HF between 14 and 25 February 2000. Gender-related differences were assessed comparing clinical characteristics, frequency in the use of diagnostic tests during hospital admission, therapy, in-hospital and 6-month follow-up outcome.
Results Among the 2127 consecutive pts enrolled, 1000 (47%) were women. Female pts were significantly older (mean age 77 ± 11 vs 72 ± 12 yrs, $p=0.0001$), presented a higher incidence of atrial fibrillation (49.2% vs 40.6%, $p=0.0001$), a more frequent hypertensive or valvular aetiology (48.1% vs 26.3%, $p<.00019$) and a less severe left ventricular dysfunction (mean ejection fraction 41.4% vs 34.8%, $p<0.0001$). Women were admitted more frequently in Medicine units than in Cardiology wards (69.7% vs 30.3%, $p<0.0001$). Among the precipitating factors, myocardial ischemia was less frequent (20.9% vs 28%, $p=0.0004$), while uncontrolled hypertension, anemia and endocrine dysfunction, including diabetes, were more frequent in women (23.5% vs 19.1%, $p<0.02$; 16.0% vs 8.5%, $p=0.0036$ and 15.8% vs 11%, $p=0.0022$, respectively). A significantly lower rate of diagnostic invasive or non-invasive procedures was performed in women. Length-of-stay was similar (11.2 ± 7.4 days in women, 11.1 ± 7.9 in men, ns). At discharge women were less frequently prescribed ACE-inhibitors, amiodarone and spironolactone and more frequently prescribed digoxin. No differences in betablocker prescriptions were found. In-hospital and post discharge (6 months) mortality rate was similar (6.5% in women vs 4.8 in men, ns 13.7% vs 16.9%, ns, respectively). At 6 months follow-up, 45.9% of women and 43.7% of men had a readmission without significant differences between the groups.
Conclusion The "real" woman with HF is usually older than man, more likely to be hospitalized in a Medical Unit and less likely to receive diagnostic and therapeutic procedures. Gender did not significantly influence both mortality (in hospital and 6 months) and readmission rates.

861 Comparing baseline characteristics of patients from 'routine clinical practice and those who enrolled in clinical trials. Information from the EuroHeart Failure Survey

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Background: Randomised controlled trials form the basis of evidence-based medicine and clinical guidelines. However, it is not clear to what extent patients included in trials are representative of the population requiring treatment.
Methods and Patients: We performed a prospective survey in 115 hospitals from 24 countries and identified 10.701 patients (46.788 screened) with suspected heart failure. Baseline characteristics were compared with patients who enrolled in a number of landmark clinical trials (i.e. SOLVD, DIG, MERIT-HF, RALES, ELITE-II, etc.). Left ventricular ejection fraction (LVEF) was an entry criterium in patients enrolled in these trials. Accordingly, we compared only patients in whom LVEF had been measured in the survey (N=5451, 51%).
Findings: The overall mean age was 68 years, 39% were women and the LVEF was <40% in only 2,410 (44%). In the clinical trials, 48-65% had a prior myocardial compared to 40% in the survey population; 0-31% had chronic atrial fibrillation versus 23%; 42-50% had hypertension versus 54%; 24-29% had diabetes versus 27%; while 10% of the survey population had a malignancy, a contra-indication for participation in clinical trials of heart failure. Of the 5451 patients, 15% were eligible for participation in the SOLVD trial, 15% in DIG, 13% in MERIT-HF, 17% in RALES and 17% in the ELITE-II trial. Of the 15% who were eligible for participation in the SOLVD trial, 82% received an ACE-inhibitor, while 52% of the patients who were eligible for MERIT-HF were treated with a bèta-blocker, and 46% of RALES eligible patients received a potassium sparing diuretic.
Conclusions: Patients in randomised clinical trials represent a minority of patients encountered in routine clinical in-hospital practice, limiting the generalisability of these trials to 'real life'. Unfortunately this results in a lack of evidence based recommendations for a substantial number of patients with heart failure. Future trials should either attempt to recruit more representative patient populations or conduct separate trials in different populations. However, for patients fulfilling clinical trial criteria their was a substantial under-utilisation of some treatments.

THE BRUGADA SYNDROME

888 A multicentre histological study of autopsied and biopsied specimens in Brugada syndrome

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Objectives: Histological studies in Brugada syndrome have not been sufficiently documented in the literature. We conducted a nationwide survey from 7 institutions in Japan.
Methods: Three sudden-death autopsied cases with Brugada syndrome (2 of which showed documented ventricular fibrillation: VF) and 22 biopsied cases with clinical evidence of this syndrome (18 of the 22 cases showed VF) underwent conventional gross anatomical and/or histopathological examinations.
Results: In 2 of the 3 autopsied hearts, no gross anatomical abnormalities were observed, whereas, marked fatty tissue infiltrations were noted in the entire myocardial layer and were more prominent in the epicardial side. This pathology was seen only in the anterior site of the right ventricle (RV), and the histology showed a similar picture to that of arrhythmogenic right ventricular cardiomyopathy (ARVC). Another autopsied heart showed gross left ventricular wall thickening and mild RV fatty tissue infiltration. In the biopsied specimens from the RV, pathognomonic fatty tissue infiltration simulating ARVC was observed in 8 of the 22 (36%) cases. One case showed postmyocarditic change. Two other cases showed disorganization of myocytes characteristic of hypertrophic cardiomyopathy. Fourteen (64%) other cases showed various other non-specific or minor findings.
Conclusions: Clinically recognized Brugada syndrome may not be a single disease entity and shows ARVC-like fatty tissue infiltration in at least 30% of cases.

889 Diagnostic yield of the ajmaline challenge for Brugada syndrome in patients with syncope of unknown origin

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Purpose: The Brugada Syndrome (BS) describes a subgroup of patients without structural heart disease associated with atypical right bundle block and coved-type ST-segment elevation in V1-V3 at risk for ventricular tachyarrhythmias. In patients who have already experienced syncope, the implantation of a cardioverter defibrillator seems to be warranted. The diagnostic ECG pattern can transiently normalize and may be unmasked by sodium channel blockers such as ajmaline. Therefore, we studied the diagnostic yield of the ajmaline challenge for BS in patients with syncope of unknown origin (SUO).
Methods: The study population consisted of 89 consecutive patients without evidence of structural heart disease who had experienced syncope of unknown origin. They underwent the ajmaline challenge as part of a routine diagnostic evaluation.
Results: A positive reaction to ajmaline was seen in a total 16 out of 89 (18%) patients with SUO. In the subgroup of 45 pts patients without abnormalities typical of BS in the baseline ECG nor a family history of BS, SUO or sudden death, only 2 (4%) had a positive ajmaline challenge. In another subgroup of 22 patients with SUO and a suspicious baseline ECG, ajmaline unmasked the typical BS ECG pattern in 7 (32%) patients. The diagnostic yield of the ajmaline test was highest, if patients had a family history of SUO or SCD in addition to a suspicious baseline ECG. In this subgroup, 6 of 8 patients (75%) were tested positive.
Conclusions: The diagnostic yield of the ajmaline challenge in patients with SUO is high, particularly if suspicious although nondiagnostic ECG abnormalities are present in the baseline ECG. It is further increased in patients who also have a family history of SUO or SCD. Due to the prognostic importance all patients with SUO without demonstrable structural heart disease should presently undergo drug testing for unmasking BS.

890 Flecainide test for diagnosis of Brugada syndrome: diagnostic accuracy and complications

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Background: Brugada syndrome is characterized by the ECG pattern of high take-off ST-segment elevation in V1-V3 and the propensity to ventricular fibrillation, in the absence of structural heart disease. The ECG abnormalities show dynamic changes over time (including complete normalization) and can be unmasked by sodium channel block.
Methods: We assessed diagnostic accuracy and safety of flecainide test in 92 patients (pts) with suspect Brugada syndrome and 21 control subjects. Among the 92 patients (78 males and 14 females, aged 42 years$\pm$12), 11 were resuscitated from sudden arrhythmic death; 31 experienced syncopal episodes; 18 were asymptomatic family members; and 32 were asymptomatic individuals with borderline Brugada-like ECG abnormalities. Flecainide (2 mg/kg, max 150 mg; in 10 minutes) was stopped if ventricular arrhythmias or significant QRS widening occurred.
Results: Flecainide test was positive in 68 of 92 pts (74%), either symptomatic (29) or asymptomatic (39), by unmasking coved ST-segment elevation in V1-V2/V3 (3.6$\pm$0.6mm); QRS interval was prolonged from 90$\pm$15ms to 115 $\pm$20 ms. Ventricular arrhythmias were observed in 3 pts (3%) and consisted of non-sustained polymorphic ventricular tachycardia that terminated after flecainide interruption in 2 pts and sustained ventricular flutter (260 bpm) that needed DC-schock for cardioversion in 1 pt. Two pts (2%) experienced electromechanical dissociation which was self-terminating in one, and needed prolonged cardiopulmonary resuscitation maneuvers followed by an extracorporeal membrane oxygenation (ECMO) device for recovery in another.The test was negative and uneventful in all control subjects.
Conclusions: Flecainide test showed a good specificity in confirming diagnosis of Brugada syndrome in both symptomatic and asymptomatic patients with borderline ECG abnormalities. Because of the risk of rare (5%) but life-threatening complications the test must be performed in the hospital setting under continuous ECG and blood pressure monitoring as well as defibrillator and advanced life support facilities at hand.

891 Ajmaline versus flecainide: a prospective pharmacological comparision for the detection of Brugada-syndrome in patients with Brugada-like electrocardiogram changes

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Ajmaline and flecainide are used for pharmacological challenge in patients with typical or suspicious Brugada-like ECG changes for the detection of Brugada-syndrome. The drugs are used in different countries, but it is not yet known which of the sodium-channel blocker has the highest sensitivity in order to unmask the typical ECG changes. The aim of the present study was therefore to assess prospectively the inter- and intraindividual response in ECG changes while testing both i.v. ajmaline or flecainide in patients with suspected Brugada-syndrome.
Patients and methods: A total of 110 patients underwent diagnostic work-up for the potential diagnosis of Brugada-syndrome. All of these patients underwent ajmaline testing and 53 of them both ajmaline and flecainide testing. 26 patients were found to have the Brugada-syndrome after full invasive and non-invasive diagnostics. In 22 of these 26 patients ajmaline and flecainide testing was performed.
Results: 25 patients with a Brugada-syndrome had a positive ajmaline test. In 14/22 patients in which an additional flecainide test was performed both ajmaline and flecainide test were positive. 7/22 patients had a positive ajmaline but negative flecainide test. In one patients both tests were negative. This results in a concordance of 64% of both tests and a respective discordance in 32% of the patients with Brugada-syndrome. In comparision of both tests in all 53 patients the sensitivity was 0,67 and the specificity was 1,0.
Conclusion: Ajmaline is superior in the detection of J-point elevations in patients with a Brugada-syndrome. Intraindividually, there is a significant discordance of both pharmacological challenges. These results have significant consequences for clinical phenotyping in family screen of Brugada-syndrome and may combinate the search for the molecular basics of Brugada-syndrome.

892 Diagnostic role of acute NA channel blockage for risk assessment in subjects with type 1-2-3 Brugada electrocardiogram pattern

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Na channel blockage (Na CB) is widely used to unsmask the typical Brugada (B) ECG in subjects (S) with type 2-3 pattern, but predictive value to develop malignant ventricular arrhythmias (B syndrome) is still discussed. Our purpose is to evaluate the diagnostic role of acute NA CB by Ajmaline (A) (50 mg/1 mn intavenous bolus) for risk assesment in S with type 1-2-3 B ECG.
Methods: 69 S with B-compatible ECGs [group I: 10 type 1B (asymptomatic), 1 female, 42 $\pm$ 12.5 years; group II: 27 males type 2B (1 symptomatic), 29.1 $\pm$ 12.1 years; group III: 32 type 3B (asymptomatic), 3 females, 32.2 $\pm$ 16.2 years] consecutively underwent A test. Type 1B ECG was defined as $\geq$ 0.2 mv, coved ST segment elevation (ST-SE) in V1, V2-V3, type 2B ECG as $\geq$ 0.1 mv, saddle back ST-SE, type 3B ECG as $=<$ 0.1 mv, saddle back ST-SE. Signal-averaged ECG (SAECG) (positive if late potentials), programmed ventricular stimulation (PVS) (positive if inducible sustained ventricular arrhythmias) and genetic analysis (SCN5A coding region) were complementary proposed for all S with basal or after A type 1 B ECG.
Results: Group I: A test induced ST segment coved superelevation, SAECG was positive in 6/10 and PVS in 4/10. Group II: 6/27 (22%) had type 1B ECG after A, none of them had positive SAECG and PVS was negative in 5/6; ventricular fibrillation was induced immediatly after A injection in the lonely symptomatic (syncope) S. Group III: 3/32 (9%) had type 1B ECG after A and none were positive for SAECG and PVS. Genetic analysis was positive for one group I S [SAECG(-), PVS(-)].
Conclusion: In asymptomatic S with type 1B or 3B ECG, Na CB had no interest; medical history and PVS are decisive for risk stratification in type 1B. In our experience, acute Na CB had a major positive predictive value for ventricular arrhythmias inducibility and risk assessment in symptomatic type 2 S.

893 Efficacy and effectiveness of implantable defibrillator in Brugada syndrome

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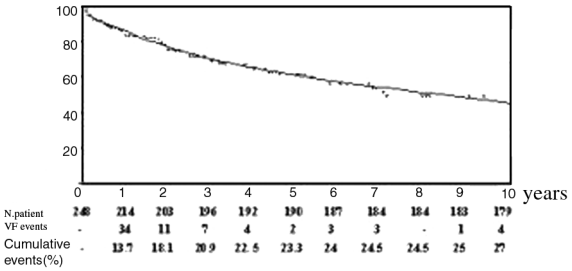
Effectiveness of implantable defibrillator (ICD) in reducing mortality in patients with structural heart disease has already been demonstrated; however the benefit of ICD in a large group of patients with Brugada syndrome has not been evaluated. The objective of the study is to analyze the efficacy and effectiveness of ICD in Brugada syndrome patients.
Methods: From a multicentric cohort of 618 patients with diagnosis of Brugada syndrome, a total of 248 received an ICD because of the high risk for sudden death (SD). The stored electrograms were reviewed to asses the efficacy and effectiveness of defibrillation for ventricular fibrillation (VF) episodes. Efficacy was defined as the ICD ability of reversion of each VF episode. Effectiveness was defined as the probability to receive an appropriate defibrillation due to a VF episode. Only the first VF episode was considered for outcome.
Results: The mean age was 42±13.5 years, there were 204 (82.3%) males. A total of 160 patients were symptomatic before the diagnosis was established. There were 120 patients (48.4%) with a family history of SD and/or electrocardiographic pattern of Brugada syndrome. Inducibility of sustained ventricular arrhythmias at the electrophysiologic study was observed in 178 (72%). During a follow up of 3.1 years (median 2) there were no cases of SD. However, 69 (27.8%) had an appropriate ICD defibrillation therefore, the efficacy of ICD was 100%. The Kaplan Meier curve depicts the probability to receive the first appropriate shock during follow up (figure). At 5 years, the probability to be rescued by the defibrillator is 23.3%



Conclusion: The ICD treatment had a high efficacy in reverting VF episodes and an adequate effectiveness in this group of patients with Brugada syndrome.

EMERGING CONCEPTS IN AORTIC STENOSIS

904 Aortic valve calcification is influenced by gender and associated with polymorphisms of the interleukin 10 and ccr5 gene in patients with degenerative calcific aortic stenosis

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Objective: The study evaluated the relationship between cardiovascular risk factors (CRF), gene polymorphism and calcification and fibrosis of stenotic aortic valves.
Background: Aortic valve calcification might be influenced by CRF. The influence of genetic factors remains uncertain.
Methods: The calcium content of 190 excised stenotic aortic valves was determined using atomic absorption spectroscopy. Hydroxyproline content was quantified. Left heart catheterization was performed. CRF and genotypes of the interleukin 10 and CCR5 polymorphisms were assessed.
Results: Calcification revealed to consist of Ca-deficient hexagonal hydroxyapatite, Ca10-x (HPO4)x (PO4)6-x (OH)2-x; with 0=x=1. Calcification (quintiles) was positively associated with the mean gradient across the aortic valve (44 ± 14, 52 ± 16, 54 ± 16, 61 ± 15, 68 ± 19 mmHg; $p<0.001$). This association was not seen for hydroxyproline content. Males had a higher degree of calcification (26.2 ± 8.9 vs 20.6 ± 9.4 mass%; $p<0.001$), despite the same mean gradient across the aortic valve (56 ± 17 vs 56 ± 19 mmHg; p=0.955). Interleukin 10 polymorphisms -1082, -819, and -592 were significantly associated with the degree of calcification (haplotypes: 17.9 ± 9.0 vs 24.5 ± 8.3 vs 25.4 ± 9.4 mass%; $p<0.001$). This was pronounced if certain allele carriers had also the CCR5 D32 allele (haplotypes plus CCR5: 17.9 ± 9.0 vs 24.5 ± 8.5 vs 27.5 ± 10.9 mass%; $p<0.001$).
Conclusion: Calcification of stenotic aortic valves consists of Ca-deficient hexagonal hydroxyapatite. Gender and genetic polymorphism of the interleukin 10 and CCR5 gene have an impact on the degree of aortic valve calcification.

905 Bone morphogenetic protein-2 and bone sialoprotein are upregulated in calcific aortic stenosis

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Background: Calcific aortic stenosis (AS) is the most prevalent heart valve disease in the elderly. Previous reports suggest that valvular calcification may be an active process resembling bone development. Bone morphogenetic protein (BMP)-2 is a cytokine of the transforming growth factor beta superfamily that promotes bone formation. Bone sialoprotein (BSP) is an RGD-binding bone matrix protein that acts as a nucleator for hydroxyapatite deposition. The pathogenetic influence of BMP-2 and BSP in valvular calcification is unknown.
Methods and Results: Human tricuspid aortic valves with (n=16) and without (n=7) calcific AS were obtained at valve replacement or autopsy, respectively. By histology using hematoxylin-eosin and alizarin red staining, bone-like and cartilage-like areas were observed in calcified valves, whereas no calcification was present in control valves. Immunohistochemistry was performed on cryosections using mouse monoclonal antibodies against human BMP-2 and BSP. BMP-2 was prominently expressed in stenotic valves in association with focal calcifications, but not detectable in control valves. BSP expression was enhanced in stenotic valves as compared to controls by semiquantitative scoring (2.7±0.1 versus 0.6±0.2 score units, $P<0.001$).
Conclusion: Stenotic aortic valves show focal calcification containing bone-like and cartilage-like areas. For the first time, we demonstrate that BMP-2 expression is induced and BSP expression is enhanced in stenotic valves as compared to controls. The data support the concept that valvular calcification may be actively regulated involving mechanisms of bone development. This could be a target for therapeutic modification of calcific AS.

906 Differential expression of receptor activator of nuclear factor kappa B ligand and osteoprotegerin in calcific aortic stenosis

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Background: Recent studies have suggested that valvular calcification in calcific aortic stenosis (AS) may be actively regulated. Receptor activator of nuclear factor kappa B ligand (RANKL) and osteoprotegerin (OPG) are members of a cytokine system involved in bone turnover and vascular calcification. Their role in calcific AS is not known.
Methods and Results: By immunohistochemistry using human aortic valves, RANKL was not expressed at relevant levels in controls but detectable in AS. OPG expression was marked in controls but significantly lower in AS. Areas containing focal calcification exhibited significantly less OPG-positive cells as compared to non-calcified regions. In human aortic valve myofibroblasts cultured for 21 days in promineralization media containing ascorbic acid and beta-glycerophosphate, stimulation with RANKL lead to a significant rise in matrix calcification (2.7-fold), nodule formation (32-fold), alkaline phosphatase activity (2.3-fold) as compared to untreated controls ($P<0.05$), and induced the expression of the bone-type isoenzyme of alkaline phosphatase and of osteocalcin. Moreover, RANKL increased DNA binding of the essential osteoblast transcription factor, cbfa-1.
Conclusion: RANKL and OPG are differentially expressed in calcific AS. In cultured human aortic valve myofibroblasts, RANKL promotes matrix calcification and induces the expression of osteoblast-associated genes, indicating a transition towards an osteogenic phenotype. These results suggest that the RANKL/OPG pathway may regulate valvular calcification in calcific AS.

907 C-reactive protein predicts progression of degenerative aortic valve stenosis

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Purpose: Clinical factors associated with valvular aortic stenosis (AS) are similar to risk factors for atherosclerosis. Thus, several lines of evidence suggest that systemic signs of inflammation are present in patients with degenerative AS. The aim of this prospective study was to examine the relationship between systemic signs of inflammation and the rate of hemodynamic progression of valvular AS. **Methods:** C-reactive protein (CRP) was measured in 43 patients with asymptomatic valvular AS. Echocardiographic data were obtained at the time that venous blood samples were collected and six months later. **Results:** CRP was > or = 0.3 mg/dL in 19 of the patients (44 percent). The rate of progression of stenosis, as reflected by an increase in aortic jet velocity > or = 0.15m/s and a decrease in aortic valve area of > or = 0.05 cm^2, was higher in patients who had levels of CRP > or = 0.3 mg/dL than those who had levels < 0.3 mg/dL (66.7% vs 33.3%, p=0.012 for aortic jet velocity and 62.5% vs 37.5%, p=0.063 for aortic valve area). We did not detect a relationship between CRP levels and the severity of aortic stenosis. **Conclusions:** Elevation of C-reactive protein predicts hemodynamic progression among adults with valvular AS and may reflect an important inflammatory component in the pathogenesis of this condition.

908 Percutaneous aortic valve replacement with a self-expandable stent-valve-device in the beating heart – in vivo stress testing in an animal model

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Introduction: Due to an increasing number of elderly patients with relevant co-morbidity there is need for a non-invasive technique of aortic valve replacement. Therefore, we evaluated the feasibility of percutaneous aortic valve replacement without cardiac arrest in animal experiments. **Methods:** Pulmonary valves from pigs were fixed in a self-expanding stent after low-pressure fixation in glutaraldehyde solution. The Nitinol stent containing the biologiocal valve in its proximal part was implanted in 6 pigs (88-118 kg) by means of a 25F catheter via the left subclavian artery by guidance of fluoroscopy and transesophageal echocardiography (TEE). During the implantation the original aortic valve was pushed against the aortic wall by the self-expanding stent. **Results:** In 4 pigs (67%) it was possible to replace the aortic valve in the beating heart without any complication or even relevant drops in blood pressure (baseline). The procedure failed in 2 pigs (33%) due to failure of the catheter device in one case, and due to problems with the correct positioning in the left ventricular outflow tract in the other case. The first pig died of bleeding complications, the second pig died of an acute aortic insufficiency. In the remaining 4 pigs we infused dopamine (DP), dobutamine (DB), and nor-epinephrine (NE). Under the stress testing we did not observe any relevant aortic insufficiency by TEE, nor an increase of peak aortic flow above 1.7 m/s.

Stress test after stent-valve implant

	Baseline	DP (10 μg/kg/')	DB (10 μg/kg/')	NE (0.2 μg/kg/')
Heart rate (1/min.)	77.3 ± 6.10	97 ± 13.8	158 ± 31.3	119 ± 37.4
Cardiac output (l/min.)	4.0 ± 1.06	6.8 ± 1.38	7.5 ± 1.31	6.8 ± 1.45
Aortic pressure (mmHg)	93 ± 15.3	113 ± 9.9	119 ± 13.4	149 ± 3.4

Results under i.v. infusion of dopamine (DP), dobutamine (DB), and nor-epinephrine (NE) after percutaneous aortic valve replacement with a self-expandable stent-valve-device.

Conclusion: This study proves the feasibility of percutaneous aortic valve replacement in the beating heart, and shows the safety of the device under pathophysiologic stress. By further diameter reduction of the implantation-catheter-device, and chronic animal experiments this concept might become a feasible option for treating patients with relevant aortic valve disease but a high operative risk.

RISK ASSESSMENT OF CORONARY ARTHERY DISEASE: FROM THE CLINICAL TO THE GENES

910 Striking reduction in mortality in patients with acute coronary syndromes in 2002

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We compared the outcome of 2 cohorts of patients (pts) with ACS, hospitalized during 2 months in 2000 (n=1795) and 2002 (n=2049) in all 26 CCU's in Israel. Age (64 vs. 64 yrs), men (75 vs. 76%), prior MI (29 vs. 27%) and diabetes (32 vs. 32%) were similarly distributed in 2000 vs. 2002 pts respectively. A number of guideline-recommended therapies and interventions were used more widely in 2002. [2000 vs. 2002] After multiple adjustment, the 30-day and 6-month OR (95% CI) for death in the 2002 cohort was 0.75 (0.60-0.90) and 0.84 (0.54-0.99) respectively. Mortality was similarly reduced regardless of whether the data were analyzed according to the ECG pattern on admission or the discharge diagnosis.

2000 versus 2002

	2000 (n=1795)%	2002 (n=2049)%
Killip 2+	18	21
ST-elevation	57*	49
Aspirin	94	92
Beta-blockers	66	74*
Statins	37	59*
Coronary angiography	58	69*
Thrombolysys (for ST-elevation)	46*	33
Primary PCI (for ST-elevation)	11	25*
Ib/IIIa antagonist	18*	12
Clopidogrel	27	49*
Any PCI	43	62*
Hospital duration (median 25-75)	7 d (5-9)	6 d (4-8)*
Mortality: 30 days	8.5	5.5*
6 months	11.4	9.1*

*p<0.05

Conclusion: As pts characteristics in both surveys were similar, and since both surveys enrolled consecutive, unselected pts, it seems that the significant mortality reduction between 2000 and 2002 reflects improvement in management. National Surveys play a major role in assessing adherence to guidelines and for evaluation of their impact on health outcome in the community.

911 PAMI risk score for mortality prediction in acute myocardial infarction treated with primary angioplasty

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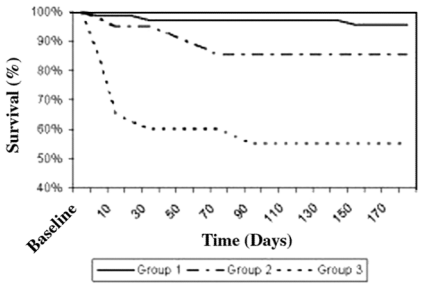
Purpose: Based on PAMI 1 and 2, AIR PAMI, SOS and STENT PAMI trials, a risk score to predict mortality in patients submitted to primary angioplasty (PCI) was recently proposed - the PAMI risk score. It includes only 6 parameters (age>75 years=7 points; age between 65 and 75 years=3 points; diabetes=2 points; anterior acute myocardial infarction (AMI) or AMI with right bundle branch block=2 points; Killip class>1 =2 points; cardiac frequency>100 bpm =2 points). As one of the first tools available to predict mortality in this group of patients, it results from controlled trials, with restricted inclusion criteria. It was our objective to evaluate if the PAMI risk score applies to the "real world" patients.
Methods: 149 patients (mean age 58.2±13.6 years, 113 males) submitted to primary angioplasty were included. Six-month follow-up was available for 113 patients. PAMI risk score was applied and patients were divided in 3 groups: 0 to 2 points (Group 1), 3 to 6 points (Group 2) and >7 points (Group 3).
Results: sixty eight patients (46%) were included in Group 1, 41 (27%) in Group 2 and 40 (27%) in Group 3. There were no significant differences in symptom-to-balloon times between the 3 groups. The immediate mortality (0%, 2.4% and 15%; p<0.001), intra-hospital mortality (2.9%, 7.3% and 37.5%; p<0.001), 30-day mortality (2.9%, 7.3% and 37.5%; p<0.001) and 6-month mortality (4.4%, 14.6% and 45%; p<0.001) was significantly different between the 3 groups. In the figure the survival curves for the 3 groups are presented.



Survival at 6-month curve.

Conclusions: PAMI risk score is a simple prognostic tool, with parameters that can be easily acquired, allowing a reliable prediction of immediate, intra-hospital, 30-day and 6-month mortality in patients with AMI treated with primary PCI.

912 Prognostic value of ST-segment resolution time and electrocardiogram measurement point relations in acute myocardial infarction: 6 months follow-up evaluations

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Background: Early and complete ST segment resolution after primary coronary angioplasty is an independent predictor of successful reperfusion therapy. ST measurement points and resolution time effects on late outcomes are still not clear.
Aim: The study endpoint was relationship between ST segment resolution within 60 minutes after PCI and Major Adverse Cardiac and Cerebral Events (MACCE) at 6 months of hospital discharge.
Material and Methods: From June 2001 to June 2002, 482 consecutive patients between 32-86 years old with STEMI were enrolled in this study. All patients transferred from remote hospitals (3-139 km) to our center, had Percutaneous Coronary Interventions (PCI), and were on continuous ST segment resolution monitoring (Cardiology Review Station, Siemens, Germany). Although risk of its oversensitivity, 20 msec after J point had taken for ECG measurements. Patients with cardiogenic shock prior cathlab admission, previous MI, right ventricular MI, previous coronary artery bypass surgery, prior LV aneurism, multivessel coronary artery disease, longer chest pain time (chest pain to ballon time is $>$ 6 hours), and periferal artery disease were excluded. Patients were divided into three groups; 1- Complete resolution ($>$70%), 2- Partial resolution (30-70%), and 3- No resolution ($<$30%) within 60 minutes after PCI. After 1, 3 and 6 months of hospital discharge, exercise stress tests and echocardiographic examinations have been done.
Results: 217 (45,02%) patients had complete ST segment resolution, 172 (35,68%) patients had partial ST segment resolution, and 93 (19,3%) patient had no ST segment resolution within 60 minutes after PCI. Patients in group 1 had significantly higher exercise tolerance capability, better LV Ejection Fraction, and MACCE free survival than group 3 within 6 months period (p values were 0.014, 0.021, 0.00079 respectively) regardless of primary PCI or prior adjunctive drug therapy. This relation was more significant in diabetic patients. All patients had controlled at least twice, but 454 (94,19%) of them had all follow up examinations.
Conclusion: 1) ST segment resolution within 60 minutes after PCI is an important, strong and independent prognostic indicator for ST elevation myocardial infarction,
2) 60 minutes after PCI procedure is an optimal assessment time for ST segment resolution, and 20 msec after J point should be taken as a measurement point.

913 Elevated tumour necrosis factor-alpha in acute myocardial infarction following primary angioplasty is associated with poor prognosis

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Background: Tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), atrial natriuretic (ANP) and N-terminal probrain natriuretic peptide (NT-proBNP) are upregulated in the myocardium in response to myocardial ischemia-reperfusion. Persistent overexpression of these cytokines and natriuretic peptides, respectively, after ischemia might lead to adverse coronary outcome. The purpose of this study was to assess the prognostic value of TNF-a, IL-6, ANP and NT-proBNP in patients with acute myocardial infarction (MI) following successful angioplasty.
Methods: In a prospective study, 70 pat. presenting with MI (age 58,7$\pm$1,5 y, M$\pm$SEM) undergoing emergency angioplasty (PTCA; TIMI III) were enrolled. The study design allows for a discrimination of procedural effects from MI sequelae. TNF-a, IL-6, ANP and NT-proBNP were analysed for up to 4 days post MI. White blood cell count (WBC) and C-reactive protein (CRP) gave evidence of systemic inflammation. Creatine kinase (CK-MB) detected myocardial injury. In a subgroup of 45 patients LVEF was determined by levocardiography and left ventricular enddiastolic pressure (LVEDP) was measured. The ability of variables to predict the presence of LV dysfunction (LVEF$\leq$45%) was assessed by univariate logistic regression. Prognostic value of TNF-a, IL-6, ANP, NT-proBNP was tested in a Cox proportional hazards regression analysis.
Results: TNF-a values pre PTCA were not different from day 4 (16.3$\pm$3.3pg/ml vs. 12.6$\pm$2.2pg/ml,p=2,382). ANP rose correlated to LVEDP ($p<0.05$) 4 h following PTCA ($p<0.001$) and went down to baseline by 24 h. The increase of ANP was paralleled by a significant rise of IL-6 ($p<0.001$). IL-6 was positively correlated with WBC ($p<0.01$), CRP ($p<0.001$), CK-MB ($p<0.05$), LVEDP ($p<0.05$) and negatively LVEF ($p<0.01$). TNF-a correlated with ANP at any time point ($p<0.001$). NT-proBNP rose continuously up to day 4 ($p<0.001$), and was weakly related to LVEF (p=0.07). Logistic regression analysis showed that IL-6 (p=0.04) and CK-MB ($p<0.04$) were significantly associated with LV dysfunction 4 h post PTCA. During follow up (648$\pm$38 d), 12 pat. died of a cardiovascular cause. Univariate Cox analysis showed that TNF-a ($p<0.001$), ANP ($p<0.005$) and IL-6 ($p<0.05$) were all significant predictors of long-term prognosis 4 h post PTCA. By multivariate analysis, only TNF-a ($p<0.005$) provided independent prognostic information.
Conclusion: Increased plasma levels of IL-6 in patients undergoing successful PTCA in MI are associated with systemic inflammation and left ventricular dysfunction. In those patients TNF-a provide early prognostic information.

914 Elevated N-brain natriuretic peptide predicts death following high-risk anterior myocardial infarction but not following high-risk non-anterior myocardial infarction: an OPTIMAAL substudy

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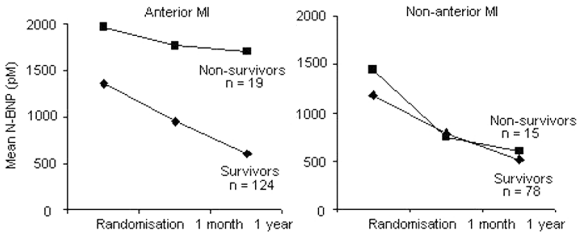
Purpose: Anterior MI is associated with a greater degree of left ventricular remodelling compared with non-anterior MI. Elevated plasma levels of N-terminal brain natriuretic peptide (N-BNP) are related to left ventricular dysfunction and increased risk of death in patients with acute MI and in chronic heart failure. The relationship between localisation of infarction, mortality and N-BNP profile following high risk acute MI is not adequately described.
Methods: N-BNP from the 235 patients who participated in the neurohormonal substudy of the OPTIMAAL trial (losartan vs. captopril in patients with heart failure and/or evidence of left ventricular dysfunction following MI) were assessed at randomisation (mean 3 days following MI), at one month and one year. N-BNP values at each time point in survivors and non-survivors with anterior vs. non-anterior MI were compared.
Results: 61% (n=143) of all patients had anterior MI of whom 88 had new Q-waves. There was no significant difference between anterior and non-anterior MI with regard to age, gender or co-morbidity at baseline. There was no difference in concomitant medication or frequency of revascularisation. There was also no difference in mortality or reinfarctions. N-BNP levels of non-survivors with anterior MI were significantly ($p<0,001$) elevated at all time points compared with survivors (both anterior and non-anterior MI). There was no difference in N-BNP levels between any of the following groups: non-survivors with non-anterior MI, survivors with anterior MI or survivors with non-anterior MI.



MI localisation and N-BNP.

Conclusion: Only non-surviving patients with anterior MI demonstrated significantly elevated N-BNP levels compared with survivors. Among survivors, MI localisation did not influence N-BNP levels any time point.

915 Stromelysin-1 promoter 5A/6A polymorphism is an independent genetic prognostic risk factor in premature myocardial infarction

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Objective: To evaluate the prognostic role of the common multiple polymorphisms with traditional cardiovascular risk factors in premature myocardial infarction (MI).
Background: Plaque rupture is well established as a critical factor in the pathogenesis of acute MI. Several genetic polymorphisms had been reported to be associated with the onset of acute MI in respect to the prothrombotic event, endothelial modulation, vascular function and the stability of plaque. However, little was known about the prognostic and interaction roles of these various polymorphisms in the subsequent cardiac events.
Methods: We studied 150 consecutive patients with acute MI onset at age under 45 (range 27 to 50 years, 84% men, all are Chinese) with MI and 150 sex- and age-matched control subjects of 5A/6A mutation of stromelysin-1 gene, PIA1/PAI2 mutation of the platelet glycoprotein IIIa gene, 4G/5G mutation of the plasminogen activator inhibitor-1 gene, G-33A mutation of the thrombomodulin (TM) gene, C677T mutation of the methylenetetrahydrofolate reductase gene and 27-bp repeat polymorphism of the endothelial nitric oxide synthase gene by using PCR, SSCP and direct sequencing. The cardiac end-points were defined as reinfarction, unstable angina, new revascularization and sudden cardiac death.
Results: Follow-up data were available on 135 (90%) premature MI patients. During a mean period of 4.43 years (from 0.4 to 13 years) follow-up, cardiac events occurred in 40 (30%) patients. There were no significant differences in traditional cardiovascular risk factors between the patients with and without cardiac events except diabetes mellitus (odds ratio [OR] 3.33, 95% confidence interval [CI] 1.69 to 3.55, p=0.0005). In genetic background, there were higher frequencies of 5A/5A homozygous stromelysin-1 gene and the G33-A TM gene polymorphisms (OR 2.33, CI 0.99 to 5.44, p=0.052; OR 1.85, CI 1.08 to 3.17, p=0.025, respectively) in patients with cardiac events. In the multivariate analyses of Cox proportional hazards model, only the 5A/5A homozygous stromelysin-1 gene polymorphism remained the independent predictors of subsequent cardiac events in the premature MI (OR 3.68, CI 1.33 to 10.07, p=0.012).
Conclusion: In this Chinese premature MI population, we found that the 5A/5A homozygous polymorphism in the promoter region of stromelysin-1 gene had significant influence on the prognosis and subsequent cardiac events after the first premature MI.

PLAQUE COMPOSITION AND VULNERABILITY

925 In-vivo coronary plaque characterization in diabetic patients by optical coherence tomography: comparison with non-diabetic patients

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Purpose: Diabetes mellitus (DM) is a major risk factor for coronary artery disease. Autopsy studies showed that coronary plaques in DM patients (pts) are rich in fibrous components, compared to non-DM pts. Intravascular optical coherence tomography (OCT) is a high resolution imaging technique capable of in-vivo plaque characterization.
We performed this study to compare coronary plaque characteristics between pts with and without DM utilizing OCT.
Methods: Intracoronary imaging was performed using a 3.2 Fr OCT catheter in pts undergoing catheterization. OCT images were recorded digitally and reviewed off-line by three investigators blinded to the clinical information. Lipid-rich plaque was defined as a plaque with a lipid area greater than 2 quadrants. Plaques with lipid in less than two quadrants were categorized as mixed plaques.
Results: A total of 64 plaques in 46 pts were examined: 24 plaques in 10 pts with DM and 40 plaques in 33 pts without DM. There were no differences in baseline. The prevalence of lipid-rich plaque and fibrous plaque was similar between the groups.
Conclusion: There is no significant difference in the plaque composition between pts with and without DM.

Coronary plaque characteristics

	DM	Non-DM	p value
Number of plaques	24	40	
Lipid-rich plaque	9 (38%)	22 (55%)	0.18
Mixed plaque	4 (16%)	5 (12%)	0.64
Fibrous plaque	11 (46%)	13 (33%)	0.29
Calcification	5 (21%)	5 (13%)	0.58

926 Importance of plaque composition on the immune-inflammatory response related to coronary stent implantation in stable angina patients

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In order to evaluate the correlation between the acute immune-inflammatory response post-coronary stent implantation (CSI) and plaque composition, specific markers were measured in 30 stable angina patients (67% men, 61±11 years of age) that underwent an elective CSI due to stenoses of >70% luminal narrowing and demonstration of viable myocardium at risk. Immediately before CSI, intravascular ultrasound (IVUS) was performed and target lesions were classified according to plaque composition: calcified (C), fibrocalcified (FC), fibrolipidic (FL), or lipid (L). Angiographic (ACC/AHA) lesion types were also determined. Venous blood samples were collected at baseline (BL) and 15 min after CSI and, afterwards, neopterin (N), interleukin-6 (IL6), tumoral necrosis factor-alpha (TNF) and interferon-gamma (IFN) were measured by ELISA. Results are shown in the Table. FC and FL plaques presented a marked increase on all markers after CSI. In addition, the majority of the lesions were B1 (n=11) and B2 (n=17) and resulted in significant changes only for IL6 and IFN, respectively.
Results:

	N (ng/ml)		IL6 (pg/ml)		TNF (pg/ml)		IFN (IU/ml)	
	BL	15 min	BL	15 min	BL	15 min	BL	15 min
C (n=6)	3.2±0.8	4.6±1.6	1.3±3.0	1.4±1.6	8.0±3.5	7.4±6.5	0.1±0.2	0.08±0.1
FC (n=8)	3.8±2	9.4±1.6*	6.7±3.3	16.1±4.8*	1.9±2	4.4±3.2*	0.1±0.1	2.4±0.3*
FL (n=7)	4±2.4	9.9±1*	0.7±0.9	5.7±4.7*	8.7±4.3	18.8±2.8*	0.1±0.2	3.1±0.2*
L (n=9)	5.2±3.3	5.6±3	1.9±2.8	5.1±8.3	0.9±1.4	3.7±3.5	0.0±0.1	0.1±0.1

Data expressed in mean IL6 (pg/ml) ± SD. Wilcoxin and the non-parametric Kruskal-Wallis one-way ANOVA, with the Mann-Whitney U statistic test. *P<0.02: 15 min vs BL.

Thus, these data suggest that "mixed" plaques are susceptible to a greater acute immune-inflammatory response following CSI in stable angina patients.

927 Identification of plaque constituents using quantitative measurements of tissue optical properties by optical coherence tomography

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Background: Optical coherence tomography (OCT), the optical equivalent of ultrasound imaging, is a high resolution imaging technique, in which the back reflection of light rather than sound is measured. It has been shown that OCT is capable of visualizing the morphology of the arterial wall and of (vulnerable) atherosclerotic plaques. Up to now, the identification of tissue structures and plaque constituents is based on qualitative image analysis (e.g. appearance, structure, delineation). On the qualitative criteria, however, identification of for example the lipid-rich regions in an OCT image, is not always possible. We propose to use quantitative data analysis of the OCT signal to identify tissue structures, based on the intrinsic differences in optical properties (e.g. attenuation of the OCT light) of the tissue components themselves. We hypothesize that by obtaining the attenuation coefficient (μt) of tissue components from the OCT data, quantitative differentiation between plaque constituents is possible.
Methods: Human carotid artery specimens were subjected to high resolution OCT imaging (4 μm resolution, 800 nm center wavelength), and subsequent histological analysis (HE and Picrosirius Red staining). Using histology, regions were identified as intimal, lipid-rich tissue, and thrombus. Using the corresponding OCT images, the μt was determined for these regions, using an algorithm, based on Beers law, in which was corrected for the position and the depth of focus.
Results: The attenuation coefficients of intimal tissue, lipid-rich tissue and thrombus (Table 1) were found to differ significantly from each other ($p<0.01$).

Table 1. Attenuation coefficients of intima, lipi-rich regions, and thrombus. Results were analyzed using ANOVA. The depicted p-values are between groups

	n	attenuation coefficient (mm-1)	st.dev.	p
intima	10	6.52	1.52	<0.01
lipid-rich	5	2.42	0.52	<0.01
thrombus	2	14.92	0.83	<0.01

Conclusion: Quantitative data of the optical properties of plaque constituents can be obtained from OCT data, which in turn can be used to distinguish the lipid-rich regions and thrombi from the intimal tissue. This quantitative analysis can improve the interpretation of OCT images.

928 The more low-density lipoprotein cholesterol decreases by statin, the more fibrous component increases in a coronary atherosclerotic plaque: a prospective randomized study with intravascular ultrasound-radiofrequency analysis

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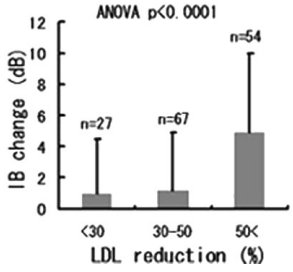
Several clinical trials have demonstrated that statins can reduce coronary events. **Purpose:** To assess whether statins alter the structure of coronary atherosclerotic plaques in a manner clinically detectable by intravascular ultrasound radio-frequency signal (IVUS-RF) analysis.
Methods: 42 consecutive patients undergoing PCI were enrolled. We searched for echo-lucent plaques in non-PCI-targeted coronary vessels using a 40 MHz IVUS catheter after PCI and acquired IVUS-RF. The patients were randomly assigned into two groups: Gr S (n = 20) taking atorvastatin 10 mg/day and Gr C (n = 22) as control. At 6-month follow-up, IVUS-RF were sampled at the same plaque sites (n = 29 in Gr S, n = 30 in Gr C). IVUS-RF parameters were blindly calculated in all regions of interest (ROIs), which were placed on each plaque, and compared between the paired ROIs at baseline and follow-up (n = 148 in Gr S, n = 190 in Gr C). Plaque volumes including the cross-sections sampled by IVUS-RF were measured at baseline and follow-up.



Results: 1) IVUS-RF parameters significantly changed in Gr S (integrated backscatter (IB): - 53.8 ± 4.5 to - 51.2 ± 4.9 dB, $p < 0.0001$; mean-to-standard-deviation ratio: 1.20 ± 0.30 to 1.14 ± 0.29, $p < 0.05$) during 6 months but not in Gr C, the change of which meant increase of fibrous tissue as previously reported. 2) The more LDL cholesterol decreased in blood, the more IB increased (figure). 3) Plaque volumes did not change in both Gr.
Conclusions: Statin may increase fibrous component in a coronary plaque within 6 months without volumetric regression. The change of plaque composition may be related to the amount of LDL cholesterol reduction. IVUS-RF may be useful to evaluate the effect of strategies aimed towards the stabilization of vulnerable plaques.

929 Plaque temperature heterogeneity is associated with macrophage accumulation and metalloproteinase activity

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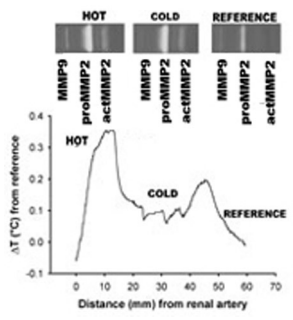
Background: Plaque rupture has been related to a high matrix metalloproteinase (MMP) activity. Recently, regional temperature variations have been observed in atherosclerotic plaques in vivo and ascribed to the presence of macrophages. As macrophages are a major source of MMP's, we examined whether regional temperature changes are related to local MMP activity and macrophage accumulation.
Methods and Results: Rabbit (n=11) aortas were denuded and fed a high cholesterol diet for two months. At the day of sacrifice, a pull back was performed with a novel temperature catheter(Thermocore Medical Ltd,Guildford, GB). Hot,cold (inside the denuded region) and reference regions (outside the denuded region) were dissected and analyzed for smooth muscle cell (SMC), lipids (L), collagen (COL), and macrophage (MF) cell densities (%) and a vulnerability index (VI) was calculated as (VI = MF + L/(SMC + COL). In addition, MMP2 and MMP9 accumulation and activity were determined with zymography. In eleven animals, 12 hot regions were identified with an average temperature 0.4±0.03 °C above cold (0.07±0.03 °C, n=14; $p<0.05$ vs hot) and above reference (0 °C, n=11; $p<0.05$ vs hot). In the hot regions a higher lipid density, less SMC density,and a higher VI index was identified. In addition, inactive MMP2, and MMP9 activity were increased (figure). Regression analysis revealed that temperature heterogeneity was positively related to macrophage density, VI-index, inactive MMP2 and MMP9 activity and negatively related to SMC.



Conclusions: Temperature measurements in vivo enables to detect plaques that contain more macrophages, less smooth muscle cells and a higher MMP9 activity. As these factors have been associated with plaque rupture, temperature measurements may identify rupture prone plaques.

930 Relation between plaque temperature and histology

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Thermal heterogeneity has been reported within atherosclerotic plaques, and increase in plaque temperature has been demonstrated in cases with unstable angina compared with that in stable angina patients. It has been reported that macrophage infiltration is observed in unstable plaques. To assess the relation between thermal heterogeneity and histological findings, intracoronary temperature and histology of the specimen obtained by directional atherectomy (DCA) were compared in 32 patients with angina pectoris (AP) including 9 unstable and 23 stable AP.
Methods: Using a pressure guide wire (Radi Medical Systems Inc., Sweden.), intracoronary temperature was measured with pressure tracings proximal and distal to the stenosis during pull-back the wire through the stenosis. Histological examinations were performed using specimens obtained by DCA.
Results: A significant increase in temperature was observe in the stenotic lesiona in unstable AP compared with stable AP patients (0.34 ± 0.17 vs 0.12 ± 0.11 centigrade degree, $p<0.01$). Macrophage infiltration was demonstrated more often in unstable than stable AP (67% vs 9%, $p<0.01$). Furthermore, plaque temperature was significantly higher in cases with than without macrophage infiltration (0.37 ± 0.15 vs 0.11 ± 0.10 centigrade degree, $p<0.01$). A cutoff value of 0.20 centigrade degree can predict macrophage infiltration histologically with a sensitivity of 80% and a specificity of 100%.
In conclusion, increase in plaque temperature correlates well to histological findings of macrophage infiltration.

COMPUTER DEMONSTRATIONS

931 Functional computer analysis of cardiac phases by regional myocardial pressure-strain loops

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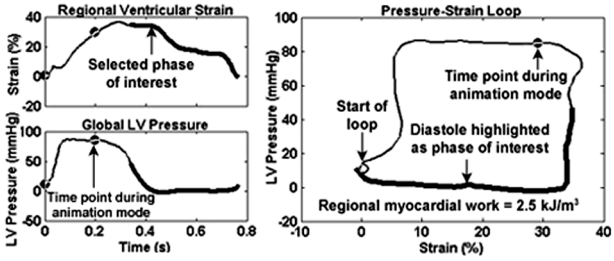
Introduction: Capitalizing on tissue velocity measurements by Doppler echocardiography obtained simultaneously with left ventricular (LV) pressures, we developed a computer application for objective and quantitative analysis of LV function by local strains and myocardial physical work by regional pressure-strain loops.
Methods: Using a Vivid 7 ultrasound system (GE Vingmed), digital tissue Doppler data are converted to regional LV strains. A micromanometer catheter (Millar Instruments, Inc.) measures LV pressures. Data from the two sources are synchronized and the resulting traces are then displayed individually and in combination as a pressure-strain loop (see figure).
Results: The figure presents an example of myocardial functional analysis in which tissue Doppler data were acquired in a short-axis LV projection. The computer system permits interactive selection of cardiac phases on the component pressure and strain traces. Each interactively selected cardiac phase is automatically highlighted by color in the resulting pressure-strain loop plot. The corresponding strain and pressure time points are tracked so that the loop analysis: a) allows qualitative characterization of the pressure-strain relationship and of cardiac phases within the loop; and b) quantitates the regional myocardial work based on the loop area.



Conclusion: We present a software system for objective and quantitative analysis of regional myocardial pressure-strain relationships. A user-friendly computer interface, automated tracking, and an intuitive graphical display make it an efficient tool for the assessment of regional myocardial function. Investigative and diagnostic analyses are often based on multimodality data and our computer application supports such a trend.

932 A computerized system for the percutaneous treatment of thoracic aortic aneurysm

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Background: in the percutaneous treatment of thoracic aortic aneurysm (TAA), the evaluation of the stress distribution in the vessel wall is of fundamental importance to establish the optimal timing for the intervention and to optimize the introduction of stent-grafts.
Aim: to develop a computerized system for TAA evaluation.
Methods: a three-dimensional (3D) finite element model is created assessing the geometry and the material properties of TAA. Processing the DICOM images, obtained by magnetic resonance and by angiography, the 3D morphology of TAA is automatically reconstructed. On the basis of a nonlinear elastic constitutive equation, the material properties are evaluated; a reverse problem is faced, changing the constitutive equation parameters and iteratively solving the finite element model, in order to match observed and computed displacements. The pressure load causing the observed displacement is evaluated during the cath-lab study. Image processing is performed by a MATLAB program, the finite element model is solved by the ANSYS package. The computerized system requires a Pentium platform (2 GHz) and 256 MB RAM.
Results: the material properties and the 3D morphology of the TAA of the specific patient are evaluated, allowing the computation of stress distributions under different pressure conditions. The 3D finite element model has been used to simulate the introduction of nitinol endovascular devices.
Conclusions: the computerized system should furnish a substantial aid in the preoperative assessment and in the follow-up evaluation of TAA.

933 A computerized system for single-beat extraction of ventricular mechanics and neuro-humoral control parameters

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Background: The left ventricle continuously interacts with the systemic circulation network, under the complex control of neural and humoral mechanisms. During the first phase of heart failure, the neuro-humoral factors contemporaneously act on the heart and the vessels, in order to guarantee the needed cardiac output. Heart failure dramatically appears as soon as the compensation mechanisms cease functioning.
Aim: To develop a computerized system for the evaluation of ventricular mechanics and neuro-humoral control, on a beat-to-beat basis, exploiting cath-lab studies.
Methods: A computerized system has been developed to acquire the hemodynamic signals (left ventricular and aortic pressure, left ventricular volume) and the ECG; for the continuous monitoring of ventricular volume, a conductance multileads catheter has been used. A mathematical model has been developed to describe the systole and the isovolumic relaxation. The systolic behavior has been simulated by a time-varying elastance, with a viscous resistance in series. The isovolumic relaxation has been described by the classical exponential model. A program has been developed to fit, the three resulting equations, to the data acquired during pressure-volume studies performed in cath-lab. The inotropic state has been assessed by single-beat elastance, the lusitropic state by the time constant of isovolumic relaxation, the viscous behavior by the ventricular resistance. The sympathetic and vagal activity has been evaluated by the classical spectral analysis of RR interval, as detected by ECG signal, and by the estimation of other nonlinear dynamics parameters, such as Lyapunov exponents and Conditional Entropy. Acquisition and processing software has been developed in LabView environment.
Results: The system has been exploited for the study of myocardial energetics, mechanics and neuro-humoral control in patients with ischemic cardiomyopathy undergoing routine heart catheterization. Particularly, the viscous resistance showed, during each observed ejection, a decreasing course, related to the slope of the elastance function. The analysis of RR interval showed a decrease in the power, within the LF band, correlated with decrease in end-systolic elastance.
Conclusions: The developed system resulted effective in the evaluation of ventricular pump function and simpatho-vagal balance. It is hoped that these parameters, when contemporaneously considered, may one day provide clinicians with another diagnostic tool for early detection of cardiac disorders.

934 The SLOPE software for continuous repolarisation analysis in 24-hour electrocardiogram

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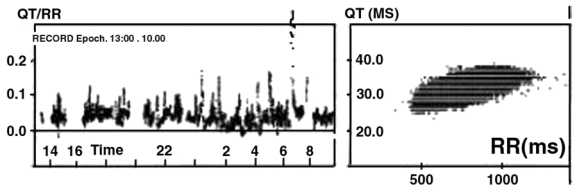
Repolarisation is an important factor in arrythmogenesis. It is analyzed in different way – interval measurement, dispersion assessment etc. QT – RR relationship is various during 24h, however in most of QT software is analyzed in long time periods – 24h, day night. We propose the software for continuous QT-RR relationship analysis in a flexible, user defined way of analysis. QT and RR interval can be implemented as an ASCI file or EVL files from the QT option of DelMar Medical system. The user defines the length (50 to 50000 beats) of sliding QT/RR slope analysis window. The window step (in beats) is also defined. Mean, minimal and maximal QT/RR slope is calculated for every hour, day, night and 24h recording, however any separate period is possible to be defined and analyzed. In this way repolarisation dynamicity can be assessed for example before the onset of VT (see on the figure the abrupt increse in QT/RR slope just before cardiac arrest) or provocative tests.



24h QT/RR slope.

Parallel to QT analysis the dynamicity of Diastolic interval (T end to Q wave) can be also investigated. Supplementary, QT (DI) values are analysed in the narrow heart rate windows (5 beat steps) and compared for day and night differences. The software is written in C++ and is a Windows application.

POSTER DISPLAY II

ACUTE CORONARY SYNDROMES

P935 Long-term follow-up from a national cohort of patients with acute coronary syndrome without ST-elevation: results from the prospective registry of acute ischaemic syndromes in the United Kingdom (PRAIS-UK)

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Background: Non-ST elevation acute coronary syndromes (ACS) are a common cause of hospital admissions. Little data is available on long term outcomes nationally - particularly the causes of mortality.
Methods: Unselected patients (n=1046) with ACS were enrolled from 56 teaching and non-teaching UK hospitals (1998- 99). Causes of death (adjudicated by 2 medical practitioners) were obtained from the Offices of National Statistics.
Results: All pts had 6 months follow-up (fu) and a long-term cohort of 490 pts (47%)had fu to December 2002. Characteristics of the long-term and the full cohorts were similar for mean age (66 yrs), male gender (61%), diabetes (16%), smoking (23%) and prior heart failure (13%). 95/490 (19.4%) pts had died by 45 months and mortality rates at 12, 24 & 36 months were 9%, 14% and 19% respectively. Cardiovascular, cancer and other causes comprised 72%, 15% and 13% respectively. Predictors of all cause mortality (multivariate analyses) are shown. Pts not taking any aspirin [18%] or any of the following: beta-blocker (BB), statin or ACEI [22%] at 6 months were at higher risk of death.

Long Term Mortality Predictors: PRAIS-UK

Parameters	Hazard ratio	P value	95% CI
Age >70 yrs	4.6	<0.001	2.2- 9.6
Men	1.7	0.02	1.1- 2.6
Prior Heart Failure	2.7	<0.001	1.6 - 4.4
ST-dep/BBB	3.9	0.003	1.6 - 9.5
T wave inversion	2.7	0.03	1.1- 6.3
Aspirin at 6 m	0.5	0.001	0.3- 0.8
BB/statin/ACEI at 6m	0.4	<0.001	0.3- 0.7
Revascularisation by 6m	0.3	0.01	0.1- 0.8

Conclusion: Our data showed that following an admission with ACS, 1 in 5 pts had died by 45 months. Nationally this would reflect about 24,000 deaths over 4 years. Cardiovascular causes accounted for almost 3 out of 4 deaths. Cancer was responsible for 1 in 7 deaths. Age > 70, heart failure, abnormal ECG & male gender increased mortality, while evidence based treatments and revascularisation reduced it, either because this is truly the case or there was a bias in providing these treatments to healthier patients. Further studies are needed to investigate this.

P936 Is hyperglycemia associated with worse outcome in non-diabetic patients with non-ST-elevation acute coronary syndromes?

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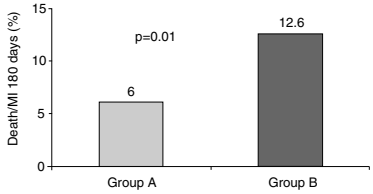
Background: Hyperglycemia has been associated with increased mortality in non-diabetic patients admitted for ST-elevation myocardial infarction. However, it is not known whether hyperglycemia is associated with poor outcome in patients with non-ST elevation acute coronary syndromes (NSTEACS)and no history of diabetes.
Objective: We sought to investigate the relation between fasting glucose level and the occurrence of death or myocardial infarction at 6 months in non-diabetic patients admitted for NSTEACS.
Methods: We selected 787 patients without history of or previous treatment for diabetes from a cohort of 992 consecutive patients hospitalized with NSTEACS. Hyperglycemia was defined as the first fasting blood glucose level greater or equal to 126 mg/dl (1997-ADA classification). Patients were then grouped according to whether they had hyperglycemia or not. The primary endpoint was the 180-day incidence of the composite of death or myocardial infarction (D/MI).



Death/MI at 180 days.

Results: Of the 787 non-diabetic patients, 684 (87%) had glucose level below 126 mg/dl (Group A) and 103 (13%) had glucose level greater or equal to 126 mg/dl (Group B). Patients in Group B were older and had more history of hypertension. There were no differences in the rates of tobacco abuse, prior MI or history of heart failure. Likewise, TnT $>$ 0.01 and the presence of ischemic changes in the EKG at entry were similar in both groups. However more patients in Group B were classified as high risk by ACC/AHA. Patients with hyperglycemia had 2 fold increase risk of death/MI at 180 days than patients with normoglycemia (p=0.01). Even after adjustment for age, troponin T levels and ST segment depression, hyperglycemia was still associated to worse outcome (OR:1.8, 95%IC 0.9-3.9).
Conclusions: This study suggests that hyperglycemia is associated with worse long term outcome in non-diabetic patients admitted for a NSTEACS.

P937 Anti-thrombotic effects of eptifibatide administered following enoxaparin or unfractionated heparin in acute coronary syndrome patients

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Background: Acute coronary syndrome (ACS) patients are increasingly treated early with low molecular weight heparin followed by glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention (PCI).
Purpose: To evaluate the anti-thrombotic effects of enoxaparin followed by eptifibatide as compared with unfractionated heparin (UFH) followed by eptifibatide.
Methods: Twenty-six ACS patients planned to undergo PCI were treated with subcutaneous enoxaparin (n=13) or intravenous UFH (n=13) continued until PCI. All patients received eptifibatide bolus prior to PCI. Antithrombotic effects were assessed as platelet-thrombus formation using the Badimon ex-vivo perfusion chamber. Perfusions were carried out at high and low shear rate (HSR, LSR) conditions typical of mild-moderate coronary artery stenosis. Porcine aortic tunica media with severe arterial injury served as thrombogenic substrates. Patients underwent two perfusion studies: at baseline (under enoxaparin or UFH) and 10 minutes post eptifibatide. Total thrombus area was quantified by computerized planimetry. Platelet function was evaluated by ADP induced aggregation and the Rapid Platelet Function Analyzer (RPFA).
Results: Anti-factor Xa activity did not differ significantly from the pre- to the post-eptifibatide samples in either group. The relative decrease from baseline in ex-vivo thrombus area and in the platelet function assays, following eptifibatide, is shown in the table. The combination of enoxaparin and eptifibatide achieved a significantly higher reduction in thrombus formation than eptifibatide given with UFH.
Conclusions: Eptifibatide administered to ACS patients receiving enoxaparin effectively inhibits platelet function and ex-vivo platelet-thrombus formation. This combination therapy exerts a more potent anti-thrombotic effect than eptifibatide and concomitant UFH.

	HSR Thrombus area	LSR Thrombus area	10 mM ADP Aggregation	20 mM ADP Aggregation	RPFA
Enoxaparin -Eptifibatide	75.6%*	79.7%*	82.9%	89.7%	94.9%
UFH - Eptifibatide	63.9%	66.1%	77.8%	85.5%	92.9%

* p$<$0.01 for difference between the two treatment groups

P938 Early diagnosis of thrombosis by circulationg hepatocyte growth factor in patients with unstable angina pectoris and other deseases

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Plasma concentrations of hepatocyte growth factor(HGF), a powerful angiogenic growth factor inducible by heparin, increased in thrombus-associated disorders. Recently, we have found that mast cell degranulation stimulated by thrombin is necessary for the rapid induction of plasma HGF in intravascular thrombus-associated disorders.
More recently, we have shown that circulating HGF increased in the early stage of arterial thrombosis and that its measurement could contribute to its early diagnosis. The present study was performed to determine whether circulating HGF may assist in the diagnosis of thrombosis in patients with unstable angina pectroris and cerebral infarction. A new enzyme-linked immunosorbent assay detected 10 pg/ml of HGF. Circulating HGF was significantly higher in patients with unstable angina (274 $\pm$ 173 pg/mL, mean $\pm$ SD, n=54) than in healthy volunteers (201 $\pm$ 64 pg/mL, n=250, p$<$0.0001). Individual concentrations exceeded the mean control value +2 SD (329 pg/mL) in 17 of 54 (31%) patients with unstable angina. We also measured HGF in 32 patients with cerebral infarction. Circulating HGF levels exceeded the mean value +2SD measured in controls in 10 of 20 patients (50%) within 6 h after the onset. Increased levels of D-dimar were found in 6 of 11 patients (55%) with high HGF values, although patients with increased HGF did not consistently have elevated D-dimer levels. Because the mechanisms of increase in the concentrations of HGF and D-dimer may be different, combining 2 measurements detected cerebral thrombosis more reliably on admission (18 of 23 patients, 78%) than either measurement alone. The results suggest that circulating HGF is a reliable early marker of arterial thrombosis, and that this new sensitive HGF assay may be useful for diagnosing thrombotic diseases.

P939 Effects of different cut-off values of cardiac troponin I on the prevalence and risk stratification of patients with acute pulmonary embolism

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Background: Recent reports suggest that troponin elevations occur in patients (pts) with acute pulmonary embolism (PE) and contribute to their risk stratification. However, there is still debate as to the most appropriate threshold definition in terms of diagnostic and prognostic capabilites.
Methods: We performed an observational, prospective enrolment of consecutive pts admitted to our CCU, because of confirmed acute PE. cTnI determination was performed on admission and every 8 hours in the first 24 hours. The method used (Dimension RxL system, Dade-Behring) has an upper reference limit of $<$0.07 ng/ml, while the suggested value for detection of myocardial damage is set at 0.6 ng/ml. Pts were categorized based on cTnI levels on admission as having myocardial damage (cTnI$>$0.6 ng/ml), minor elevation (cTnI $>$0.07 and $<$0.6 ng/ml), or normal values (cTnI$<$0.07 ng/ml). Data derived from cTnI assay were analyzed in order to define the prevalence, the clinical correlates and the prognostic impact of cTnI elevations in this condition. The main outcome measure was in-hospital mortality.
Results: The study population consists of 48 patients, 23 males and 25 females, with a mean age of 64 years (range 23 to 90 years). Deep venous thrombosis was present in 17 pts (35%), malignancy in 9 (19%), recent surgery in 8 (17%) and pre-existing chronic obstructive lung disease in 5 (10%). On admission, 14 pts (29%) had cTnI levels$>$0.6 ng/ml (group A), 21 (44%) between 0.6 and 0.07 (Group B), while 13 (27%) had cTnI levels $<$0.07 ng/ml (Group C). A grading of progressive severity was observed among the 3 groups. None of the pts in group A had a normal ecg (compared to 10% for group B and 23% for group C; p=0.1), or a normal echo (vs 10% and 31% in group B and C, respectively; p=0.05). Bilateral massive PE on CT scan was observed in 36% of pts in group A, 24% in group B and 8% in group C (p=0.2). Overall, there were 6 deaths, accounting for a 12.5% in-hospital mortality rate. Five fatalities occurred in group A (36% mortality), 1 in group B (4.8% mortality), and none in group C (p for trend = 0.005). An elevated cTnI on admission was the most powerful independent predictor of mortality at multivariate analysis (p=0.04).
Conclusions: In this cohort of high-risk pts with acute PE, cTnI elevations are frequently detected on admission and are quantitatively related to clinical severity and outcome. Thus, a role for risk stratification and more aggressive therapy in acute PE based on cTnI assay on admission may be foreseen.

P940 Genetic linkage analysis for C-reactive protein in families with myocardial infarction

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Background: C-reactive protein (hsCRP), an inflammatory marker, is an independent predictor of long-term prognosis in coronary artery disease (CAD). In addition to environmental components and cardiovascular risk factors, recent reports demonstrate a significant genetic component to inter-individual hsCRP variability.
Methods and Results: An autosomal genome scan was performed in 513 Caucasian families (1,406 individuals) ascertained for myocardial infarction (MI) in order to identify chromosomal regions linked to serum hsCRP, as measured by a high-sensitivity assay. Employing variance component analysis, 31% of the inter-individual variation in hsCRP levels was explained by genetic factors (p=0.0000015). Subsequently, loci related to hsCRP were identified on chromosomes 10 (at 141cM) and 5 (at 150cM) producing LOD scores of 3.02 and 2.24, respectively. An additional suggestive signal was detected on chromosome 2 in subset analyses. These regions contain clusters of candidate genes known to act in inflammatory pathways.
Conclusions: This genome scan has identified the first chromosomal regions influencing hsCRP levels. The results may facilitate the search for genetic variants involved in the regulation of hsCRP and thus in the development and progression of CAD/MI.

P941 Expression of Toll-like receptors in human atherosclerotic lesions and the relevance to myocardial infarction

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Background: Certain bacterial infections have been linked to progression of atherosclerosis and its complications including myocardial infarction (MI). To explore the molecular mechanism by which recognition of microbes occurs in the artery wall, we characterized expression of Toll-like receptors (TLRs), a family of pathogen pattern recognition receptors, in atherosclerotic lesions. TLR4 is the receptor responsible for cellular activation by lipopolysaccharide of bacterial endotoxin and also recognizes microbial as well as eukaryotic heat shock protein 60. To assess the impact of TLR4-mediated innate immunity on the risk of MI we determined the prevalence of the Asp299Gly polymorphism in TLR4, a mutation causing an impared LPS-response, and its association with MI in a case control study.
Methods and Results: Using semiquantitative polymerase chain reaction (RT-PCR) and immunohistochemical analysis we demonstrated that of nine TLRs, expression of TLR1, TLR2 and TLR4 was markedly enhanced in human atherosclerotic plaques. A considerable proportion of TLR expressing cells were also activated as shown by nuclear translocation of nuclear factor kappa B.
Using TaqMan PCR technology, we determined the prevalence of the Asp299Gly polymorphism in TLR4, a common genetic variant of this gene, and its association with MI in a study of 1213 survivors of a first MI and 1561 controls from the Stockholm region. This missense mutation results in an impaired host response toward LPS due to the substitution of an aspartic acid residue with glycine at amino acid 299 located in the extracellular leucine-rich domain of TLR4.
Compared with wild-type carriers, men with the hyporesponsive TLR4 299Gly allele had significantly increased risk of MI (OR [95% CI]: 1.4 [1.0-1.9]). This was not the case for women. Male carriers of the TLR4 299Gly allele also had a significantly elevated plasma concentration of tumor necrosis factor-alpha. Otherwise there were no associations between Asp299Gly genotypes and inflammatory markers.
Conclusion: Our findings illustrate a repertoire of TLRs associated with inflammatory activation in human atherosclerotic lesions. The associations found between the hyporesponsive TLR4 genotype and risk of MI suggest that the TLR4 genetic variant affects the susceptibility to MI and that a proper TLR4-mediated innate immunity may be implicated in protective mechanisms against MI. Together these findings encourage further exploration of innate immunity on the pathogenesis of atherosclerosis.

P942 Infarct size and mortality after glucose-insulin-potassium infusion in primary angioplasty for acute myocardial infarction

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Background Results of early trials have suggested that combination of reperfusion therapy and high-dose glucose-insulin-potassium infusion (GIK) may be beneficial in acute myocardial infarction (MI). However, very limited patients have been treated by primary angioplasty, and no previous trial in the era of reperfusion investigated the effect on myocardial function.
Methods A randomized controlled trial was performed of GIK (80 mmol potassium in 500 mL glucose 20%, at a rate of 3 mL/kg body weight/h, and short-acting insulin for 8-12 hours) in patients with acute MI, treated with primary angioplasty. End points were 30-day mortality, cumulative enzyme release in the highest quartile and a left ventricular ejection fraction (LVEF) lower than 30%. Infarct size was determined by serial measurements of enzyme concentrations with lactate dehydrogenase as reference enzyme. LVEF was measured before discharge by radionuclide ventriculography using the multiple gated equilibrium method following the labelling of red blood cells of the patient with 99mTc-pertechnate. In the analyses, adjustments were made for differences in previous MI, infarct location, and Killip class.
Results A total of 940 patients was randomized, of whom 476 received GIK. 30-day mortality was 5.8% in the controls compared to 4.8% in the GIK group (p=0.5). In the 856 patients (91%) without signs of heart failure (Killip class I) mortality was reduced from 4.2% to 1.2% ($p<0.05$). Cumulative enzyme release in the highest quartile was observed in 29% in the controls and in 22% in the GIK group ($p<0.05$). After multivariate analyses, GIK resulted in a relative risk of 0.63 (95% CI 0.43-0.91) on a high enzyme release. LVEF <30% was observed in 17% in the controls and in 13% in the GIK group (P=0.2). After multivariate analyses, GIK resulted in a relative risk of 0.69 (0.44-1.0) on LVEF <30%.
Conclusion High-dose GIK in patients treated with primary angioplasty for acute myocardial infarction results in a decrease of 30-day mortality in patients without heart failure and is associated with limitation of infarct size.

P943 Characteristics of 2423 screened patients in the occluded artery trial. International patterns in the care of acute myocardial infarction patients

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Background: Up to 1/3 of stable post-MI patients have an occluded infarct-related artery (IRA). OAT is an international randomized trial designed to determine if benefit exists in opening the occluded IRA 3-28 days post MI in asymptomatic, high-risk patients. As of 1/31/03, 1108 patients were randomized. The purpose of this interim analysis is to define characteristics that correlate with practice differences in the care of acute MI in OAT sites in the US, Canada and other countries. A criterion for selection of an OAT site was the availability of an experienced PCI operator who met rigorous standards.
Methodology: In order to define the population of MI patients from which OAT patients are derived, all OAT hospitals are instructed to screen all MI patients for one-month. Data are entered into a screening log, regardless of eligibility for the trial.
Results: As of 12/31/02, 2423 MI patients (mean age 64 years) were logged in 63 centers in the US, 22 in Canada, and 51 in other countries. Of these, 70% were men and 88% were white. EF was <50% in 54%. ST elevation MI (STEMI) was present in 62%. Patients with STEMI were younger (63 vs. 66 years, $p<0.0001$), more likely to be male (73% vs 66%, p=0.0009) and to have an EF <50% (59% vs 43%, $p<0.0001$) compared to non-STEMI patients. Coronary angiography occurred more frequently in STEMI patients (82% vs. 69%; $p<0.0001$) and more STEMI patients underwent PCI (61% vs 37%, $p<0.0001$). In the US, angiography was more likely to be performed in STEMI patients (86%) than in Canada (80%) and other countries (81%) (p=0.03). Reperfusion strategies were different in STEMI patients with 48% of US patients undergoing primary PCI compared to 31% in Canada and 46% in other countries ($p<0.0001$). Thrombolysis was more frequent in non-US sites (54% in Canada and 34% in other countries) compared with only 31% of US patients ($p<0.0001$).
Conclusions: In hospitals participating in OAT, 62% of patients present with STEMI and the majority of these undergo angiography post MI. In hospitals selected to participate in OAT, thrombolysis is still the predominant mode of reperfusion in Canada and primary PCI is the dominant strategy in the US and other sites.

P944 Acute coronary syndromes complicated by symptomatic and asymptomatic heart failure. Does current treatment comply with guidelines?

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Patients with acute coronary syndromes (ACS) complicated by heart failure (HF) are at high risk of in-hospital and long-term mortality. Treatment with ACE inhibitors (ACEI), β-blockers and early invasive risk stratification are recommended to improve their short- and long-term prognosis.
Aim: To assess adherence to treatment guidelines of patients with ACS complicated by HF in Europe and the Mediterranean basin.
Methods and Results: We analyzed the data of 10,484 patients who participated in Euro-Heart ACS survey. Of the 9587 with known HF status and without cardiogenic shock, 7058 (74%) did not have symptomatic HF, and 2529 (26%) presented with, or developed symptomatic HF during hospitalization. HF patients were older, and had more cardiovascular risk factors. ACEI were more commonly used in HF patients (72% vs. 56%) whereas â-blockers were similarly used (75% vs. 82%). Coronary angiography and in-hospital revascularization rates were lower among HF patients (42% vs. 57% for coronary angiography, and 28% vs. 40% for revascularization). Similar trends were noticed among patients with left ventricular dysfunction (symptomatic and asymptomatic). Adjusted mortality risk at 30 days was higher among patients with ACS complicated by symptomatic HF regardless of electrocardiographic type of ACS: (ST-elevation- ACS; OR – 2.5; 95% CI:1.6-3.9, Non- ST- elevation- ACS; OR - 8.9; 95% CI:4.5-17.8, undetermined-ECG-ACS; OR - 9.3; 95% CI 2.5-34).
Conclusions: Patients with ACS complicated by HF were at increased risk of dying. A relatively high percentage of HF patients were treated with ACEI and â-blockers in accordance with current recommendations. The suboptimal cathetherization and revascularization rates in patients with HF need to be substantially improved, thus possibly ameliorating their prognosis.

PROGNOSTIC ELECTROCARDIOGRAPHIC INDEXES

P945 Heart rate variability and turbulence in hyperthyroidism

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Purpose: To evaluate cardiac autonomic function in hyperthyroidism before and after effective anti-thyroid therapy.
Methods: 405 consecutive unselected patients with hyperthyroidism were recruited with 405 age- and sex-matched euthyroid controls for matched comparisons; all had 24-hour Holter monitoring performed. Patients were reassessed when rendered clinically and biochemically euthyroid. Time domain parameters of heart rate variability (HRV), namely SDNN, HRVi, pNN50 and RMSSD were derived from the Holter data as well as heart rate turbulence (HRT) parameters.
Results: The median age (+IQR) of the hyperthyroid and control cohorts was 50.0 (37-65); 320 females and 85 males were in each group. The cohorts were matched with respect to past history and family history of vascular disease (88 vs 80 and 278 vs 280 respectively, p=ns). The median serum free thyroxine (T4) and tri-iodothyronine (T3) concentrations at presentation were 37.1pmol/L (IQR 27-52) and 11.3pmol/L (IQR 8-18) respectively; serum thyrotrophin (TSH) concentration was undetectable in all patients. Serum free T4, T3 and TSH were normal in all controls. Both SDNN and HRVi were reduced at the first visit compared with matched controls (111msec {IQR 86-136} vs 136msec {IQR 112-164}, $p<0.0001$ and 30{IQR 23-38} vs 38 {IQR 31-46}, $p<0.0001$ respectively). The pNN50 and RMSSD (measures of vagal modulation) were also reduced at presentation compared with matched controls (6% {IQR 2-14} vs 9% {IQR 3-17}, $p<0.0001$ and 28 {IQR 20-39} vs 31 {IQR 22-41}, $p<0.0001$ respectively). Measures of HRT onset and HRT slope (believed to represent vagal modulation) were also reduced at initial visit compared with matched controls (-0.8% {IQR -2.5 to 0.3} vs –1.6% {IQR –3.3 to -0.5}, $P<0.01$ and 5.1msec/RR interval {IQR 2.5-8.7} vs 6.4msec/RR interval {IQR 3.7-10.9}, $p<0.05$). Two hundred and three patients were rendered euthyroid at a median follow up 21 weeks (IQR 15-42); all had serum free T4, T3 and TSH concentrations in the normal range. All HRV and HRT parameters returned to values comparable with matched controls (p=ns).
Conclusions: Overt hyperthyroidism is associated with cardiac autonomic dysfunction with reduced autonomic control and specifically reduced vagal modulation of heart rate; restoration of euthyroidism appears to correct this. Both HRV and HRT parameters convey prognostic significance in ischaemic heart disease. Long-term follow up of our cohort will address whether these parameters convey similar prognostic information in hyperthyroidism.

P946 Prevalent low-frequency oscillation of heart rate probably reflects fractal properties of heart rate variability

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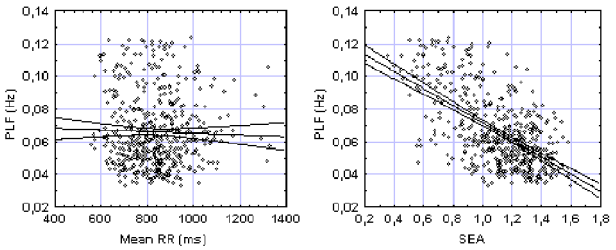
Purpose: Prevalent low-frequency oscillation of heart rate (PLF) is a powerful and independent postinfarction risk stratifier, as shown in the placebo population of EMIAT trial. In the same population, we investigated the relationship between PLF and other risk factors.
Methods: PLF index was calculated by advanced processing of frequency-domain characteristics of heart rate variability (HRV) as previously described. Time- and frequency-domain indices of HRV and HRT were assessed using standard methods. Short-term scaling exponent alfa (SEA) was calculated in all 5-min segments by detrended fluctuation analysis and averaged. Cox's regression analysis was used to establish the univariate association of risk factors with all-cause mortality within mean follow-up of 662 days (n = 633, 87 deaths).
Results: Unlike many traditional HRV indices, PLF did not correlate with mean RR ($r = -0.02$, NS, figure). Weak correlation with HRV index ($r = -0.14$, $p < 0.05$), low-frequency spectral power ($r = -0.33$, $p < 0.00001$), high-frequency spectral power ($r = -0.01$, NS), and Turbulence Slope ($r = -0.21$, $p < 0.0001$) was found. The strongest correlation was observed between PLF and SEA ($r = -0.59$, $p < 0.00001$, Figure). SEA ≤ 1.0 was associated with relative risk for all-cause mortality of 2.1 (95% CI 1.4 - 3.4, $p = 0.001$) while PLF ≥ 0.1 Hz had relative risk of 6.4 (95% CI 3.9 - 10.6, $p < 0.00001$).



Conclusions: PLF probably reflects fractal properties of HRV. However, being considerable stronger predictor than SEA, PLF has to convey additional information relevant to "high-risk" heart rate oscillatory pattern.

P947 The influence of psychological factors on heart rate variability after myocardial infarction

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It is known that the psychological factors encourage the development of life-threating ventricular arrhythmias (VA) in patients (pts) after acute myocardial in-farction (AMI); however, the mechanisms of such interaction are still unclear. On the other hand, the changes in autonomic nervous system in these pts are the predictors for VA. The purpose of the study was to assess the influence of anxiety (A) and symptoms of depression (D) on the heart rate variability (HRV) in pts after AMI. **Material and methods:** The Minnesota Multiphasic Personality Interview (MMPI) and the personal questionnaire of Spielberger and Hanin (S-H) was used to assess pts. Short-term HRV was determined on the 10-14 days of AMI in accordance with the International Standards. 320 patients were investigated. **Results:** According the results of S-H test pts were divided in two groups: 1 - with high level of reaction anxiety (RA - 29 pts) and 2 - with moderate and mild levels of RA (291 pts). HRV in the 1 group was significantly lower then in the 2 group: SD - 19,4±10,3 vs 27,4±12,9 ($p<0,05$); RR -760,8±98,7 vs 915,3±136,2 ($p<0,05$); RMSSD - 6,8±6,3 vs 16,5±9,0 ($p<0,05$), HFnu - 26,8±14,2 vs 46,4±17,7 ($p<0,05$). According to the results of the MMPI, pts were divided in two groups: with elevation in the scales of A and D (I group - 144 pts) and without it (II group - 176 pts). HRV in the I group also was significantly lower then in the II group: SD - 24,5±10,3 vs 31,3±14,0 ($p<0,05$); CV - 2,1±1,4 vs 3,5±1,5 ($p<0,05$); NN50 - 6±10,2 vs 11,4±21,0 ($p<0,05$), PNN50% - 1,2±12,7 vs 6,8±13,8 ($p<0,05$); TP - 456,0±301,8 vs 740,4±670,0, $p<0,01$. During the one year period after AMI, 22 pts died suddenly. Comparing non-survived and survived pts demonstrated that on days 10-14 of AMI 19 (86%) pts who died had high level of personal anxiety (vs 36% survived pts, $p<0,05$), 23% pts had high level of RA and 77% - moderate level RA (vs 8% and 45% survived pts, $p<0,05$). According to the results of MMPI, sudden death pts also had more significant psychological disturbance.
Conclusion: Thus sudden death pts on days 10-14 of AMI had severe psychologi-cal disturbance, including personal and reaction anxiety, as well as, symptoms of depression. At the same time, the patients with high level of anxiety and depression after AMI demonstrated significant alterations of autonomic nervous system, which could be one of the additional causes of life-threating ventricular arrhythmias.

P948 QT and QTc dispersion increase after successful internal cardioversion of chronic persistent atrial fibrillation: clinical implications

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The aim of the present study was to assess the extent and the time course of changes in repolarisation parameters that occur following shock delivery for internal atrial cardioversion.
Methods: Twenty-two patients with chronic persistent atrial fibrillation (AF) (mean AF duration = 17±23 months, range 1-96) underwent transvenous low energy internal atrial cardioversion for restoring sinus rhythm. Shocks were delivered according to a step-up protocol between catheters positioned in right atrium and coronary sinus. Sinus rhythm was restored by shocks at 7.2±4.2 J and a mean of 3 shocks per patient were delivered. Before and after unsuccessful shocks and at sinus rhythm restoration, the following parameters were measured three times and then averaged (recordings at 75 mm/s): RR, QT and QTc interval on 12 leads, QT and QTc interval dispersion on 12 leads.
Results: After an unsuccessful shock (persistence of AF) no significant changes in QT and QTc dispersion were observed. QTc dispersion was 37±19 ms pre-shock and 38±19 ms (NS) at the first minute post-shock. After successful shocks, a significant increase in QT and QTc interval dispersion was observed, with an abrupt increase at 1 min (+44% in QT dispersion vs pre-shock; +30% in QTc dispersion vs pre-shock) and a subsequent return to pre-shock values at 15 min. The following values of QTc dispersion (mean± s.d.) were measured: 40±20 ms pre-shock; 52±32 ms at 1 min ($p<0.05$ vs baseline), 47±27 ms at 5 min, 40±21 ms at 10 min ($p<0.05$ vs 1 min), 40±22 ms at 15 min ($p<0.05$ vs 1 min) [Least significant difference analysis].
In conclusion, in patients with chronic persistent AF, restoration of sinus rhythm by intracardiac shocks is associated with a significant increase in QTc dispersion, with maximal values at 1 min following the shock. In view of the common use of antiarrhythmic agents before and during cardioversion these findings suggest that in the minutes that follow atrial cardioversion an increased vulnerability to proarrhythmic events (especially with class III antiarrhythmic agents) may occur, due to increased dispersion of ventricular depolarization.

P949 Does the sinus node work as a digital-like detector?

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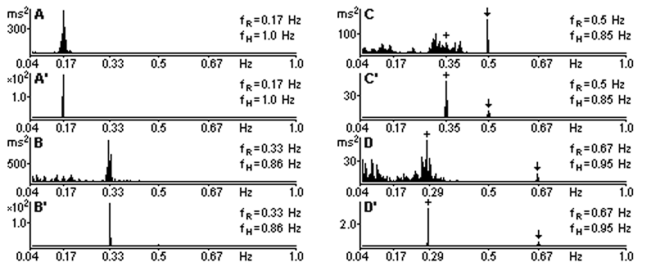
Sinus node (SN) generates heart rate (HR) which is modulated by respiration. The modulation depends both on a frequency and depth of respiration. SN may be treated as a digital detector (DD) that samples a respiratory wave with a frequency equal to an average HR. Each DD possesses some properties: Nyquist criterion, aliasing phenomenon or symmetries in a frequency spectrum. To prove the analogies of SN with DD, we compared signals generated by a model DD (i.e. regular sinusoids sampled with a constant frequency) with signals of the heart rate variability (HRV) (i.e. RR intervals of ecg) of a volunteer breathing regularly with a metronome. We chose four frequencies of the respiration: 0.17, 0.33, 0.5, 0.67 Hz which were accompanied by four average heart beat frequencies (after 50 mg of Metoprolol per os): 1.0, 0.86, 0.85, 0.95 Hz, respectively. Figure shows fast Fourier transform (FFT) spectra of HRV (A, B, C, D) and the corresponding spectra obtained from the model DD (A', B', C', D'). fR is a frequency of a respiratory wave and sinusoid. fH is a sampling frequency of DD and corresponds to an average HR. In: A, A', B, B', where $fR<fH/2$, the main peak is localized at frequency fR. In: C, C', D, D', where $fR>fH/2$ (i.e. fR is greater than the Nyquist frequency), the peaks at fR are reduced (marked by arrows) while additional peaks (marked by crosses) appear at fH-fR which result from the aliasing effect. The presence of the peaks at fR (in: C, C', D, D') is a result of the symmetries of the FFT spectra.



Thus the limitations of DD apply to the analysis of HRV, especially half of an average HR corresponds to the Nyquist frequency which determines the upper frequency band where the HRV spectrum is reliable. To conclude: in some view SN may be treated as a DD.

P950 Predicting sleep apnea from the heart period: a time-frequency domain analysis

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Aim.Heart rate fluctuations are a typical finding during obstructive sleep apnea characterised by bradycardia during the apneic phase and tachycardia at the restoration of ventilation. In this study we evaluated a time-frequency domain analysis of the nocturnal heart rate variability (HRV) as the single diagnostic marker for obstructive sleep apnea syndrome (OSAS).
Methods.The predictive accuracy of time-frequency HRV variables (Wavelet Decomposition parameters from level 2 (Wv2) to level 256 (Wv256)) obtained from nocturnal ECG Holter monitoring were analysed in 147 consecutive patients aged 53.8±11.2 years referred for possible OSAS.
Results: OSAS was diagnosed in 66 patients (44.9%) according to an apnea/hypopnea index > 10. Using ROC curves analysis, the most powerful predictor variables was Wv32 (W=0.758, $p<0.0001$), followed by Wv16 (W=0.729, $p<0.0001$) and Wv64 (W=0.700, $p<0.0001$). Classification And Regression Trees (CART) methodology generated a decision tree for OSAS prediction including all levels of Wv coefficients, from Wv2 to Wv256 with a sensitivity reaching 92.4%, and a specificity of 90.12% (% of agreement: 91.2%) with this non-parametric analysis.
Conclusion: Time-frequency parameters calculated using Wavelet Transform and extracted from the nocturnal heart period analysis appeared as powerful tools for OSAS diagnosis.

P951 Heart rate variability trends in different time intervals over 90-minute period before onset of ventricular arrhythmias in implantable cardioverter-defribrillator patients

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Analysis of trends of heart rate variability (HRV) parameters prior to onset of ventricular tachyarrhythmias (VTA) could serve in predicting risk of VTA. Aim of the work was to find HRV parameters most stably and strongly correlating with occurrence of VTA in patients with ICD.
Methods: 90 sinus rhythm (SR) tachograms preceding episodes of spontaneous VTA retrieved from 37 patients with ICD (Phylax XM, Mycrophylax Biotronik) were analyzed. Time and frequency domain indices were studied in 2-min intervals over 90-min period of SR before VTA. Least-squares curve fit regression test was performed for each index in 40-min window (20 intervals) shifted every 2 min over whole 90-min period. Regression confidence level was used as statistical measure of systematic trend of HRV parameters.
Results: During 30-min period preceding initiation of VTA constant increase in frequency of premature beats was observed, however 2 min before VTA amount of ectopic beats increased suddenly (3.0±0.43% vs. 6.8±0.6%, $p<.000$). This variable had the strongest predictive value for VTA onset. Mean RR interval decreased significantly (786±17 ms vs. 763±17 ms; $p<.000$) in 10-min period before VTA, while other indices, except for RMSSD and pNN50, have changed significantly only 2 minutes prior to VTA. However, while LF power increased, decrease in LF/TP was observed already 8 min before onset of VTA followed by increase in VLF/TP demonstrated 4 minutes before VTA.

HRV values for different window shifts

Index	(-2,0) interval Value	Shift=0 Regr. p	Shift (min)	Value	Regr. p
%ect.beats	6.77 ± 0.62	<.000	30	3.15 ± 0.42	.02
Mean RR(ms)	763 ± 17	<.000	10	786 ± 16	.0001
LF/TP	0.182 ± 0.012	<.000	8	0.202 ± 0.014	.02
VLF/TP	0.696 ± 0.021	<.000	4	0.721 ± 0.019	.001

"Shift=0" indicates (-40,0) window, "Regr.p" nonlinear regression confidence level

Conclusions: 1) In 90-min period of sinus rhythm preceding VTA, trends of most spectral and time-domain HRV parameters can be observed. 2) We suggest the combined analysis of several HRV parameters may increase the predictive power of the observed trends and possibly could serve as a basis for developing new ICD algorithms to predict occurrence of VTA.

P952 Comparison of heart rate turbulence indexes induced by premature ventricular and atrial beats

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Background: Heart rate turbulence (HRT) is a newly established risk predictor that characterizes the early acceleration (TO; turbulence onset) and late deceleration (TS; turbulence slope) of sinus rhythm following ventricular premature complexes (VPCs). HRT presumably reflects a baroreflex trigger by VPC. This study was designed to compare HRT indexes induced by PVC and PAC to provide new insights into the reflex counterparts.
Twelve patients (age 36±16 considered for electrophysiologic test for SVT (no WPW) were involved to compare the effects of prematurity index (PI) of RR intervals induced by VPC vs PAC on HRT indexes. S2 from the right ventricle and atrium was given during sinus rhythm with coupling intervals of 500, 450, 400 for PVC and 400, 350, 300 for PAC. PI is calculated by the formula (1-premature RR/average of the previous 4 RR) and reflects prematurity of the PVC or PAC on RR interval adjusted to the previous sinus rate. PI was matched to obtain similar groups. TO and TS was calculated according to the Schmidt's criteria.
Results and Conclusions: Table summarizes the results. The main difference between the premature beat induced by PVC and PAC is that the later one is physiologic and precedes the QRS. In contrast, PVC induces atrial contraction across closed valves and causes atrial stretch and expected to induce more prominent hypotension. PI is similar in comparison providing the assumption of equal RR prematurity. PAC did not provide long PPI as a result of physiologic response of AV node as prolonged conduction thus retarding the following QRS. PAC did not induced normal TO. In contrary, PAC has the same effect on the TS (late slowing of heart rate) as PVC does. This may be due to lone response of the sinus node to PAC regardless of induced hypotension.

Parameters	PVC (n=50)	PAC (n=34)	p value
PI	0.41±0.06	0.39±0.06	NS
Post pacing interval (msn)	1085±137	998±144	0.007
TO	-2.68±4.79	0.74±4.34	0.001
TS	25±15	23±13	NS

These results raise a question of different mechanistic equivalents in the propagation of TO and TS. TS may represent a combination of different arms of baroreflex response to premature beats.

P953 The evolution of heart rate variability patterns following acute myocardial infarction in the post-thrombolytic era

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Introduction: Abnormality of heart rate variability (HRV) following acute myocardial infarction (AMI) is recognised as an independent adverse prognostic marker. Measurement of HRV is reproducible in normal subjects and in patients with chronic stable heart disease. However, little is known about the evolution and stability of HRV profiles from short term electrocardiogram (ECG) recordings in the acute and convalescent phase following AMI.
Method: 171 patients prospectively underwent 15 minute resting ECG recordings for HRV within 48 hours of admission (day 1) following a first Q-wave AMI. The recordings were repeated at 3 and 18 months. The control group consisted of 20 healthy individuals. Fast Fourier power spectral analysis quantified the total power (TP), very low frequency (VLF, 0-0.04Hz), low frequency (LF, 0.04-0.15Hz) and high frequency (HF, 0.15-0.4Hz) bands and expressed them as mean ln msec^2(SD).
Results: AMI resulted in a significant reduction of HRV in subjects compared to controls across all frequency bands up until 3 months ($p<0.005$) and all values except VLF power up to 18 months ($p<0.005$). There was a gradual increase in power in all bands over the 18 month period, most marked in the first week. The most prominent and early rise was in the HF band of patients with anterior AMI, the HF power on day 1 was 3.64 (1.6) vs 4.50 (0.92) by day 7.

	Day 1	3 Months	18 Months	Controls
TP	6.60(0.9)	7.18(0.6)	7.23(0.4)	8.11(0.87)
VLF	6.03(0.9)	6.60(0.6)	6.79(0.5)	7.29(0.86)
LF	5.17(1.1)	5.35(0.8)	5.52(0.3)	6.78(0.86)
HF	4.20(1.4)	4.73(0.8)	4.99(0.7)	6.60(1.31)

HRV values following AMI

Conclusion: There are major changes in HRV patterns in the 18 months following AMI, most marked in the first 3 months. Knowledge of these evolutionary changes in HRV is important when considering the use of power spectral HRV measures for risk stratification following AMI

P954 The impact of stress on heart rate variability of physicians being on-call

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Introduction: The analysis of HRV has been recommended for the study of the impact of work-stress on the autonomic cardiac control. The literature related to the effect of work stress on physicians on-call is extremely limited. Our study aimed to evaluate the role of on-call stress on the HRV of physicians.
Methods: 26 healthy physicians (11 men- 15 women) undertook a 24-hour Holter-ECG recording while being on-call, as well as on a normal work-day at least 3 days after the day on-call. The mean age was 34±7,49 years (range: 25-51 years). All recordings started at 3 p.m. and lasted 24 hours.
Results: The physicians presented decreased values of SDNN during the day-on call in comparison with a normal workday (SDNN: Standard Deviation of all filtered RR intervals over the length of the analysis): 89.9 and 110.9 respectively, $p<0.05$) The rhythm disturbances during the day on-call were clearly more ($p<0.05$) and included sinus tachycardia and bradycardia, sinus pauses, supraventricular tachycardia, as well as premature atrial and ventricular systoles.
Conclusions: The physicians presented decreased SDNN values. Although it is already known, that decreased HRV correlates with increased morbidity and mortality, the studies about the clinical use of this marker in healthy subjects are few. Our findings show the negative impact of stress on the cardiac function during the day-on call. However, further studies are needed, in order to establish the prognostic value of HRV in healthy individuals as well.

P955 Long-term evolution of heart rate variability after heart transplantation

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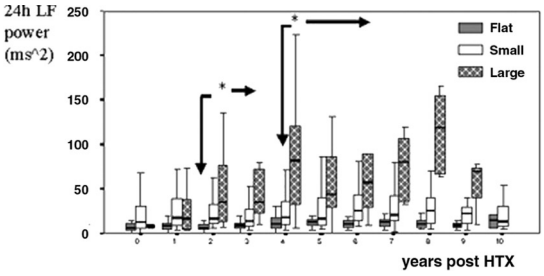
Background: While in dogs reinnervation has been demonstrated, in humans the occurrence of reinnervation remains controversial and many studies have been published in regard to this issue.
Methods: A total of 1009 Holter recordings of 245 heart transplant patients were retrieved from the hospital archives. 206 recordings were excluded due to various reasons. The average age of the patients was 56±13 years at the time of the last recording. In 144 patients 3 or more consecutive recordings were available (average 4.5±1.1 recordings). All patients were on immunosuppressive therapy, consisting of azathioprine, cyclosporine and methylprednisolon. Time after transplantation of the recording varied from 0 to 10 years. Heart rate variability (HRV) was used to assess the evolution in autonomic modulation and as such, possible signs of functional reinnervation.
Results: HRV analysis of all data (not separated into different subgroups) revealed an increase in 24-hour total power starting from 2 years after transplantation, up to 9 years compared to recordings in the first year after transplantation (year 2: $p<0.05$, year 3-8: $p<0.001$, year 9: $p<0.05$; Tukey's post-hoc analysis). 24-hour low frequency (LF) power started to increase significantly from year 3 up to year 8 compared to the early recordings (all $p<0.001$ compared to year 0). High frequency (HF) power did not show a significant evolution. Sub-group analysis showed a clear increase in LF and HF power in 6% of the patients, starting from about 4 yrs after transplantation.



Evolution after heart transplantation.

Conclusion: The vast majority of the patients remain functionally denervated up to 10 years after heart transplantation. However some patients show signs of reinnervation after heart transplantation.

QT DISPERSION AND OTHER ELECTROCARDIOGRAPHY FEATURES II

P956 The reliability of QRS duration and morphology on surface electrocardiogram to identify ventricular dyssynchrony. A Fourier phase analysis of angioscintigraphy

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A long QRS duration (>120ms) with complete left bundle branch block (BBB) has been proposed as a determinant criteria for selecting heart failure patients to cardiac resynchronization therapy because it may be associated with marked intra-left ventricular (LV) dyssynchrony. However, the relationship between the QRS duration, the type of bundle branch block and the importance of regional electromechanical LV dyssynchrony remains somewhat unclear.
Methods: 20 control subjects and 103 patients with idiopathic dilated cardiomyopathy (WHO criteria), underwent equilibrium radionuclide angiography. Fourier phase analysis were examined in both ventricles. Interventricular delay between the mean phase of RV and LV assessed interventricular asynchrony, standard deviations (SD) of the mean phase in each ventricle assessed intraventricular asynchrony and were correlated with the QRS morphology and duration. Dyssynchrony was defined as results >mean + 2 SD of the results obtained in the control group: > 40 ms for interV delay, >45 ms for left intraV dyssynchrony and >50 ms for right intraV dyssynchrony.
Results: 73% of the patients with complete left BBB (n=26) presented with inter-V dyssynchrony vs 26% for the other patients ($p<0.0001$). Intra-LV dyssynchrony was observed in 73% of patients with complete left BBB (and 92% of patients with LBBB on left axis, n=13), 75% of patients with incomplete left BBB (n=8), 52% with left anterior hemiblock (n=23) and 44% of patients with "normal" QRS. There was a significant correlation between the QRS width and inter-V dyssynchrony (R =0.56, p=0.0001) intra-LV dyssynchrony (R=0.57, p=0.0001) and at a less degree intra-RV dyssynchrony (R=0.31, p=0.002). Increase in pulmonary capillary wedge pressure and in SD of LV mean phase were independent predictors of death or heart transplantation during a follow-up of 27 ± 23 months but surface ECG parameters were not.
Conclusions: The QRS width remains a first line parameter to select patient responders to cardiac resynchronization since it is in part correlated to the presence of inter-V or intra-LV dyssynchrony. LBBB on left axis may reflect a high intra-LV dyssynchrony. However, a more precise evaluation of the dyssynchrony is useful since a relatively high proportion of patients with incomplete LBBB as well as "normal" QRS exhibited a marked intra-LV dyssynchrony and might be likely to respond to cardiac resynchronization therapy.

P957 Prognostic significance of late ventricular potentials in the first year after acute anterior wall myocardial infarction in patients treated with t-PA fibrinolysis who had successful reperfusion

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Purpose: To determine the prognostic significance of the late ventricular potentials on signal-averaged electrocardiogram (SAECG) for the occurrence of arrhythmic event (combined sustained ventricular tachycardia and sudden cardiac death), cardiac death and total mortality in patients within first year after anterior wall acute myocardial infarction(AMI), treated with accelerated tissue-type plasminogen activator (tPA) protocol, who had successful reperfusion.
Methods: We prospectively studied 135 patients (80% men) mean age 64 ± 0,5 years, for one year after their first AMI. All patients were treated with tPA and subsequently underwent coronary angiography to ascertain successful reperfusion, which was determined by TIMI grade 3 flow. Serial recordings of both SAECG and 24 hour Holter monitoring were obtained 3, 10, 30, 90 days after infarction. Left ventricular ejection fraction (LVEF) was determined by echocardiography. Multivariable logistic regression was used to examine the effect of SAECG, Holter ECG, LVEF and clinical variables on single and combined clinical outcomes.
Results: An abnormal signal-averaged ECG was seen in 12% of patients. With an abnormal SAECG, the 1-year rates of the arrhythmic events (17% versus 7%, $P<0.01$), cardiac death (31% versus 26%, $P<0.05$), and total mortality (39% versus 35%, $P>0.05$) were significantly higher. In a logistic regression analysis that included clinical variables, EF, ventricular arrhythmia on Holter ECG an abnormal SAECG was the independant predictor for the arrhythmic events (RR=3.2, $p < 0.01$). When combined with EF<40% and complex ventricular arrhythmias on the Holter monitoring positive, negative predictive accuracy and relative risk for arrhythmic event were 23%, 95% and 7.1, respectively,
Conclusions: In our study the signal-averaged ECG independetly predicts arrhythmic event, but not cardiac death and total mortality patients in the first year after first anterior wall myocardial infarction treated with accelerated tPA protocol who had successful reperfusion.

P958 Influence of electrical and electromechanical cardiac asynchrony on exercise capacity in heart failure patients with chronic left-ventricular systolic dysfunction

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Background: The aim of this prospective cohort study was to assess whether electrical and electromechanical cardiac asynchrony may independently affect symptoms and exercise tolerance in patients with left ventricular systolic dysfunction (LVSD) and chronic heart failure.
Methods and results: 103 consecutive patients with echo LV ejection fraction <40% (26±9%) and LV end-diastolic diameter >60mm (71±8 mm) were assessed by 12-lead surface ECG, echocardiography to measure pre-ejection, ejection and post-ejection electromechanical intervals, cardiopulmonary exercise testing and radionuclide angiocardiography. Mean PR and QRS duration were 191±43 ms and 139±39 ms, respectively. PR >200ms and QRS >120ms were documented in 36% and 60% of cases, respectively. Univariate analysis showed that PR was correlated positively with NYHA class ($p<0.001$), and negatively with exercise duration ($p<0.001$) and VO2 peak ($p<0.01$). Significant but weaker correlation were found for QRS with NYHA class and exercise time. Decrease in pulmonary and aortic ejection times, and in isovolumetric relaxation time (IVRT) were associated with higher NYHA class and lower VO2 peak. No significant correlation was found for any pre-ejection parameter.
At multivariate analysis PR prolongation, and shortening in ejection times and/or IVRT were shown to be predictive of more severe symptoms and poorer exercise tolerance independently of baseline LVSD severity. By contrast QRS widening did not appear to be an independent predictor of exercise intolerance.
Conclusion: Electrical and electromechanical cardiac asynchrony are independent predictive factors of exercise intolerance in chronic heart failure patients with left ventricular systolic dysfunction.

P959 Electrocardiographic changes during long-term follow-up in patients with arrhythmogenic right-ventricular dysplasia: relation with age

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Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) is characterized by the progressive replacement of myocites by fibrous and adipose tissue. The ECG as a diagnostic tool is useful, but it has some limitations and may change with the time.
Methods: We have analyzed the long term follow-up of the resting ECG in 38 patients (Pts) with ARVC, (51 ± 16 years; 64% male), excluding those Pts with a follow-up of less than 2 years (3 Pts). Diagnosis was confirmed by right ventricular angiography and cardiac resonance imaging. The first and last available ECG tracing were compared, and we analyzed: The amplitude and width of the QRS complex, the presence of new conduction disturbances and the extension and polarity of T waves in all leads. We defined "massive form" of ARVC as a 50% reduction in a period of time in the QRS amplitude complex in all leads with a complete right bundle branch block (RBBB).
Results: Mean age at the time of first ECG tracing was 41 ± 14 (range 11-68) years. Mean follow-up was 10 ± 6 years (range 2–29). ECG changes were found in 17 Pts (49%). In those Pts with longer follow-up, changes were significantly more frequent (<4 years of follow-up: 0% Pts; 6-12 years 48% Pts; 12-18 years 75% Pts; > 18 years 100% Pts; p< 0,001). ECG changes were: New RBBB in 6 Pts (35%), new negative T waves in precordial leads in 3 Pts (17%), the QRS amplitude is diminished in 2 Pts (12%) and appearance of a "massive form" in 5 Pts (29%). Moreover, changes were significantly more frequent in younger (<35 years; 50%) and older (>60 years; 75%) than in middle age Pts (35-60 years; 29%; $p<0.05$). In older Pts, the most frequent ECG change was the appearance of massive forms of ARVC (55%), and in middle age Pts, the pressence of new negative T waves in precordial leads (60%).
Conclusions: In almost 50% of Pts with ARVC, there are ECG changes in the long term follow-up. The longer the follow-up, the more frequent the changes in the ECG, (100% in ARVC Pts with a follow-up >18 years). Moreover, the sort of ECG changes are different depending on Pts age, with appearance of massive forms in older Pts, perhaps expressing a greater extension of the disease in both ventricles.

P960 P-wave dispersion: can it differentiate atrial fibrillation patients with and without recurrences after electrical cardioversion?

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Background: P wave dispersion (PDisp) has been suggested as a marker potentially able to predict the risk of atrial fibrillation (AF) recurrences after electrical cardioversion (CV).
Aim of the Study: The aim of this study was to assess how different values of PDisp (calculated on 12-lead ECG at 150 mm/s) are associated to AF recurrences, considering two different time periods after CV: short term (< = 1 month after CV) and long term (mean follow-up = 530±278 days).
Patients and Methods: In 37 patients with long-lasting AF (mean duration 21±36 months, range 2-156) with (N=19) or without (N=18) pre-treatment with amiodarone (AMIO), P wave duration (PMax, PMin) and PDisp were measured 1 minute after internal CV.
Results: PDisp was lower in pts with AMIO pre-treatment compared to pts without AMIO pre-treatment (28.3±9.5 vs 21.9±7.3 ms, p=0.029). Pts with AF recurrences at 1 month or at long term did not differ with regard to age, sex, AF duration, left atrial dimensions or ejection fraction. Higher values of PDisp were associated to recurrence of AF at 1 month, but not at long term follow-up (see Table: ECG parameters and recurrence of AF).

ECG parameters and recurrence of AF

	AF recurrence at 1 month	SR maintenance at 1 month	AF recurrence at long term	SR maintenance at long term
Number of pts.	5	30	15	20
PDisp (msec)	33.0 ± 4.6	23.6 ± 9.0*	23.3 ± 8.3	26.1 ± 9.8
PMax (msec)	131.2 ± 7.8	129.5 ± 8.8	129.1 ± 8.2	130.2 ± 9.1

Legend: * = p < 0.05; AF = atrial fibrillation; PDisp = P wave dispersion value; PMax = value of maximum P wave duration; pts. = patients; SR = sinus rhythm.

Conclusions: PDisp may differentiate patients with AF recurrences in the early post-CV period from patients without AF recurrences in the same time period. However, no differences in PDisp exist comparing patients with and without AF recurrences at long term. These findings may be related to different mechanisms and predisposing factors for early and late recurrences. AMIO pre-treatment is associated with shorter values of PDisp.

P961 Abnormal functional Holter late potential analysis with reduced ejection fraction: best prediction of sudden cardiac death in 738 post-infarction patients

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Purpose: Reduced ejection fraction (EF) of < 35% is proposed as criterion for cardioverter-defibrillator (ICD) - implantation in postinfarction patients (MADIT-II). However, the positve predictive value (ppV) for sudden cardiac death (SCD) only based on impaired EF is rather low. We therefore performed a prospective substudy among a large postinfarction trial.
Methods and Results: Among 1120 patients with an acute myocardial infarction, 738 patients both survived the first month and had evaluable high resolution Holter-ECG and RNV-EF. Holter-ECG were subdiveded in 24 segments, 60 min each and late potential (LP) analysis was performed in each segment. During follow-up (2 years) 28 patients had SCD, strictly defined as witnessed, instantaneaous, unexpected death without prodrome or unexpected during sleep. 42 patients had non-SCD by progressive myocardial dysfunction. Predefined risk factors in clinical data, Holter-ECG-parameters and EF were compared to repeated LP-analysis in the high resolution Holter-ECG and related to follow-up. SCD was associated with EF<35%, non-sustained VT and late potentials in more than 75% of analyzed Holter-ECG segments (=abnormal LP75). According to multivariate analysis the only independent significant predictor of SCD was LP75 (p=0.003). Positive predictive value for LP75 was 31%, for EF<35% only 7%. Combined EF<35% with LP75 (n=13) had a ppV of 47%. Non-SCD was associated with age>65years, EF<35% whereas multivariate analysis revealed EF<35% as independent significant predictor (p<0.002).
Conclusions: Thus, repeated, functional LP-analysis in the high resolution Holter-ECG combined with estimation of EF is superior to EF alone in prediction of postinfarction patients at risk of SCD potentially to prevent by ICD.

P962 Electrocardiographic changes in patients with acute ischaemic stroke and their prognostic importance for early mortality

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Background: Ischemic stroke induces electrocardiographic (ECG) changes. The significance of these changes remain unclear as there is limited data. The purpose of this study is to observe the frequency and short-term prognostic importance of ECG changes in ischemic stroke patients without a history of primary heart disease.
Methods: In this prospective study, 162 patients (92 male, mean age: 64±14 years) with first ischemic stroke, verified by computerized tomography (CT) were evaluated during 4 weeks. The ECG changes were assessed and mortality was analyzed by means of clinical parameters (age and gender), ECG findings (ST-segment change, T inversion, U wave, long QT and arrhythmia), and CT findings (lesion location) by using univariate and multivariate analysis.
Results: Ischemia-like ECG changes were observed in 79% of stroke patients, and long QTc in 26% and arrhythmias in 44%. Early mortality (4 weeks) rate was 27% (n:44). Age, ST-segment change, prominent U wave and lesion location (frontal, temporal and occipital lobes) were univariate predictors of early mortality (each p<0.05), whereas the age (OR=1.4, 95% CI: 0.6-3.5, p=0.02) and presence of ST-segment change (OR=2.6, 95% CI: 1.3-5.6, p=0.01) were only independent predictors of early mortality in multivariate analysis. Although sensitivity (61%) and specificity (67%) of ST-segment change were relatively low to identify mortality rate, its negative predictive value was 82%.
Conclusions: The ECG changes are frequently seen in ischemic stroke patients without a history of heart disease. In addition to age, ST-segment change may be an independent predictor of early mortality.

CLINICAL ASPECTS OF DEVICE THERAPY I

P963 Elevation of plasma pro-brain natriuretic peptide concentration in chronic ventricle-based permanent pacemaker implantees: evidence of mechanical asynchrony-related left-ventricular remodelling

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Background: Permanent pacemaker (PM) implantation is effective for symptom relief and survival improvement in bradyarrhythmia patients (pts). Nevertheless, in theory, ventricle-based PM per se represents electro-mechanical asynchrony due to eccentric pacing and is potentially at risk of inappropriate remodeling and functional impairment in the ventricles.
Methods: Plasma N-terminal pro brain natriuretic peptide (proBNP) concentration, a surrogate marker of left heart failure (LHF), together with tissue doppler echocardiographic indices including times to peak sustained systolic contraction (Ts) of 6 basal segments of both ventricles and interventricular time delay (IVTD) derived from difference between aortic and pulmonary flow times were studied in 56 pts with chronic PM implantation (AAI in 13, DDD in 26, VVI in 17) for 4±2 years. They were 69±14 yrs of age, 23 male and 33 female. None had clinical LHF nor significant valvular heart diseases.
Results: The median plasma proBNP concentration was 77.9pg/ml (ln 4.2±1.0) for AAI pts, 109.5 (ln 5.3±1.7) for DDD pts and 880.6 (ln 6.7±1.7) for VVI pts. (p<0.0001, ANOVA or between pairs) For pts with physiological AV synchronized pacing (AAI, DDD), stepwise multivariate analysis disclosed that IVTD (p = 0.019) and age (p=0.023), but not respective Ts difference, were the only independent determinants for proBNP elevation after chronic PM implantation.
Conclusion: ProBNP elevation is prominent in pts receiving ventricle-based PM, with or without AV synchronization. The implicated structural and functional remodeling of relevant left ventricle can hardly be reemphasized, particularly in the mainly aged pts.

P964 Natriuretic peptide profiles are improved after dual compared with single chamber cardiac pacing in patients with high-grade atrioventricular block

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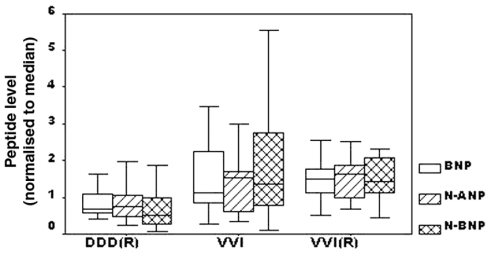
Dual chamber pacing may be associated with better haemodynamic function than single chamber ventricular pacing. Natriuretic peptides are good markers of haemodynamic function and prognosis.
Aim: To measure natriuretic peptide levels in patients randomised to single or dual chamber pacing as a substudy of the UKPACE trial at one centre.
Methods: Patients were aged ≥70 years, in sinus rhythm and receiving their first pacemaker implant for high-grade AV block at trial entry. 84 patients were venesected at their 10-month follow-up visit. All were in their randomised mode (21 VVI, 18 VVIR, 45 DDD(R)). Brain natriuretic peptide (BNP), N-terminal pro-atrial natriuretic peptide (N-ANP) and N-terminal pro-BNP (N-BNP) were measured using in-house immunoluminometric assays.
Results: Median peptide levels at 10 months were 69(BNP), 1094(N-ANP) and 886(N-BNP)pM. Peptide levels normalised to medians are shown in figure 1, with significant differences between groups for all peptides (Kruskal-Wallis test $p<0.002$). Mann-Whitney tests confirmed that BNP, N-ANP and N-BNP were lower in the DDD(R) group than in the VVI group ($p<0.023$, $p<0.025$, $p<0.012$ respectively) or the VVIR group ($p<0.001$ for all comparisons). VVI and VVIR did not differ. Paired samples before and after DDD(R) pacing (n=12) showed significant falls in N-BNP (median 1772 to 1142 pM, $p<0.028$) and BNP (median 122 to 71 pM, $p<0.028$) but not N-ANP (median 2104 to 1727 pM, p=ns). Falls in N-BNP, BNP and N-ANP levels were not significant in 15 VVI/VVIR patients.



Conclusion: Dual chamber pacing is associated with lower levels of BNP, N-ANP and N-BNP, than single chamber ventricular pacing (either fixed or adaptive rate) in elderly patients with high-grade AV block. Dual chamber pacing may confer a haemodynamic advantage.

P965 Atrial natriuretic peptide level is dependent on duration of atrial fibrillation in patients with heart failure and chronic atrial fibrillation

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Atrial natriuretic peptide (ANP) has strong diuretic, natriuretic, and vasorelaxant activities and is released in response to growing frequency of atrial depolarization, hypervolemia and increasing atrial filling pressures. The increased ANP levels are described in patients (pts) with atrial fibrillation (AF) and in pts with heart failure. The aim of this study was to evaluate plasma ANP concentrations in pts with heart failure and concomitant chronic AF and to analyze the determinants of ANP levels in this group.
Methods: The study group was comprised of 42 pts with mild to moderate heart failure and chronic AF. All pts were in controlled AF, normalized blood pressure and clinically stable heart failure. Echocardiography examination was performed in every patient. Plasma samples of ANP were obtained at rest, were prepared by refrigerated centrifugation and stored until radioimmunoassay. Heart rate was assessed from ECG at the same time as plasma sample collecting. Echocardiography parameters (left atrial and left vetricular sizes, left ventricular ejection fraction) and clinical data (age, sex, NYHA functional class, heart rate, systolic and diastolic blood pressure and duration of AF) were analyzed as the determinants of ANP values. Univariate and multivariate regression analysis were used. Pearson's test was used to calculate correlation coefficients.
Results: Median ANP level was 57 (range 21 to 102) pg/ml. Median AF duration was 7 (range 1 to 24) months. Twenty six out of 42 pts (62%) were in NYHA I-II class., 16 pts (38%) were in NYHA III class. Mean heart rate was 85 beats/minute. The mean left anteroposterior atrial, left ventricular enddiastolic, endsystolic dimensions and ejection fraction were: 48,0; 54,6; 38,7 mm and 54% consecutively. The univariate and multivariate regression analysis revealed significant negative correlation between duration of AF and plasma ANP level (r=-0,41, p=0,02) and identified duration of AF as an independent predictor of ANP.
Conclusion: Plasma ANP levels in pts with heart failure and chronic AF are dependent on time of AF duration. Longer duration of AF is associated with lower ANP level.

P966 Utility of home monitoring for surveillance of pacemaker patients

C. Stellbrink[1], J. Gill[2], M. Santini[3], A. Hartmann[4], E. Wunderlich[5], K. Wallbrück[6] on behalf of Home Monitoring technology for pacemaker therapy. *[1]Univ. of Aachen, Clinic for Med. I - Cardiology, Aachen, Germany; [2]Guy's & St. Thomas' Hosp., Cardiology, London, United Kingdom; [3]Osp. S. Filippo Neri, Cardiology, Rome, Italy; [4]St. Georg Hosp., Intern. Med., Leipzig, Germany; [5]Hosp. Dresden-Friedrichstadt, Intern. Med., Dresden, Germany; [6]BIOTRONIK, Technology & Service Center, Erlangen, Germany*

Introduction: The novel Home Monitoring (HM) technology enables automatic, regular transmission of selected data from the pacemaker (PM) to the attending physician. Technical feasibility and clinical utility of HM was investigated in a European multicenter trial. We report on the utility findings.
Methods: 122 patients (pts) were enrolled following implantation of the BA03 DDDR pacemaker (Biotronik, Germany). PM data were transmitted from the implant to the clinics every 24 hours per fax in the form of Cardio Report (CR). CRs indicated mean and maximal ventricular rate, percentage of intrinsic atrial and ventricular rhythm and of intrinsic and PM-mediated atrioventricular conduction, and counters of ventricular extrasystoles (VES), couplets, triplets, runs and of ventricular tachycardia. The physician examined CRs gathered in the periods from 0-2 weeks (w), 2-4 w, 4-8 w, and 8-12 w of implantation, to figure out if HM data would indicate the need for a supplementary medical examination or therapeutic intervention necessitating the patient's referral to the hospital.
Results: 95 pts were "successfully monitored" according to the pre-defined technical criteria. A total of 318 examinations of CR clusters were received from the investigators. In 50 examinations (15.7%), a patient visit to the hospital was considered necessary. The reasons were: frequent VES (33 cases), ventricular (4) or atrial (3) tachyarrhythmia, lead problem (2), or other situations (8 cases). 79 interventions or medical examinations (table) were deemed necessary based on CR analysis, yet not all interventions were classified as requiring immediate patient referral to the hospital. The measures were implemented during the subsequent follow-up visits in 81% of patients.

Interventions/Examinations	No. of cases	No. of pts	Implemented for affected pts
24-h-Holter-ECG	53	31	26
PM reprogramming	12	11	11
Change in medication	10	8	5
Stress-ECG	1	1	1
Others	3	2	0

Measures proposed based on HM data

Conclusion: HM enables remote transmission of data from the PM to the physician, offering the possibility of intensified monitoring with respect to clinically relevant events.

P967 Correlation between closed-loop stimulation, quality of life and vital capacity

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Introduction: The improvement of the patient's quality-of-life (QoL) is currently one of the major goals for development and optimization of cardiac stimulation. The CLS integrates the pacemaker with the autonomic nervous system, and thus, sensitive to the physical and mental stress.
Objectives: To evaluate the CLS and its relationships with the life quality (QoL) and vital capacity.
Methods: This prospective, randomized, controlled, single-blinded and crossover study includes patients (P) with Sinus Node Disease, who were implanted Inos2+ pacemaker. The patients were randomized in 2 groups (DDD and DDD-CLS). First evaluation after 30 days with application of QoL Single Form-36 (SF-36) questionnaire and ergometric and espirometric test performed. Patients were crossed-over and after 1 month a new evaluation was accomplished with the same parameters. Test T of Student and ANOVA were used for validation of the data (alfa=5%, CI=95%)
Results: It has been enrolled 34 patients 50 patient, 27 male, with mean age 62±8 years old. The patients with DDD-CLS demonstrated significant improvement ($p<0,05$) of the physical and emotional aspects through QoL questionnaire. Significant difference was demonstrated ($p<0,05$) also when the indexes of vital capacity obtained through the Ergo-espirometric test was compared (VO2max, Myocardial consumption of O2 - MVO2, and Heart Output) between the DDD-CLS and DDD patients.
Conclusions: The CLS stimulation provides a pronounced variation of the heart frequency, approaching to the normal physiologic answer at physical and emotional stress, and, with that, improving not only the resistance to the maximum exercise but the quality of life either.

P968 10-year single centre experience with VDD pacing

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Purpose: Current guidelines suggest the use of single lead VDD pacemakers (VDD-PM) in patients with heart block and normal sinus node function. Nevertheless, DDD systems are often preferred, because later system upgrades for sinus node dysfunction and/or atrial undersensing are feared. Therefore, we aimed 1) to evaluate long-term performance of VDD-PMs with regard to proper atrial sensing and maintenance of AV-synchronicity, and 2) to determine the natural incidence of secondary sinus node dysfunction in this population.
Methods: Retrospective analysis of follow-up data from all patients (pts) who had a VDD-PM implanted at our clinic between 1992 and 2000 with regard to appropriate atrial sensing, necessity for reprogramming to the VVI mode for atrial fibrillation (AF) or atrial undersensing, incidence of pacemaker revisions and DDD upgrades, respectively.
Results: 265 consecutive pts (74±13 yrs; 56% men) with VDD-PMs were followed for 4.1±2.4 yrs (range 6 days to 10.1 yrs). The indications for pacemaker implantation were second-degree AV block in 92 pts (35%), third-degree AV block in 144 pts (54%), bifascicular block with first-degree AV block in 17 pts (6%) and other indications in 12 pts (5%). Death occurred in 95 pts (36%), with a mean period after PM implantation of 3.2±2.1 yrs. At the latest follow-up, 228 pts (86%) were in the VDD mode, including 9 pts who had intermittently been programmed to the VVI mode for transient AF-episodes. 33 pts (12%) remained permanently in the VVI mode (26 pts for AF, 4 pts for atrial undersensing, 3 pts for other reasons). Two pts (0.8%) received DDD upgrades during follow-up due to chronotropic incompetence. Two other pts received a DDD-ICD for serious ventricular arrhythmias. Revision of the VDD lead had to be performed in 11 pts (4%) (atrial undersensing 3, ventricular lead dislocation 4, insulation defect 1, fracture 1, perforation 1 or infection in 1, respectively). Battery depletion led to elective replacement in 27 pts (10%) after 6.9±0.8 yrs.
Conclusions: VDD pacemakers in patients with heart block and normal sinus node function exhibit an excellent long-term performance with a very low incidence of lead revisions for atrial undersensing (1.1%) and an even lower rate of DDD upgrades for secondary sinus node dysfunction (<1%). The rate of reprogramming to the VVI mode (12% at 4.1 yrs) is comparable to that in the DDD literature (17% at five yrs in the large C-TOPP trial).

P969 The effects of pacing and pacemaker mode on anxiety and fear of falling

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Purpose: Symptoms of dizziness and syncope can increase anxiety and the fear of falling. Pacing prevents bradycardia and syncope, and improves dizziness. The effects of pacing and different pacemaker modes on anxiety and the fear of falling however have not been evaluated. This study was undertaken to assess the impact of pacing and pacing mode on cardiac symptoms and psychological variables in patients with symptomatic bradycardias.
Methods: A subgroup of patients from the UKPACE and STOP-AF studies randomised to AAI(R)/DDD(R) or VVI(R) pacing were evaluated at the time of pacing and 1 and 24 months afterwards using the Activities Balance Confidence (ABC), Geriatric Depression (GD), Hospital Anxiety (HA), and Karolinska Cardiovascular Symptom (KCS) scales.
Results: Data for those patients who completed the 3 stages of the assessment are shown in the table as the change in score expressed as a % of maximum possible score. A negative change in score in GD, HA or KCS indicates an improvement. Levels of depression, anxiety and balance confidence improved significantly after pacing as did the cardiovascular symptoms of chest pain, breathlessness, dizziness and palpitation. Baseline scores had significant effects on 24 month scores ($P<0.001$ for each of the 4 scales) but pacing mode had no independent effect on 24 month scores ($P>0.4$ for each of the 4 scales).

Scale	D 1 month	D 24 Month	N1	P	N2
ABC	10.2	1.2	118	0.002	75
GD	-12.0	-0.7	129	0.02	81
HA	-24.4	-5.2	79	<0.001	50
KCS	-59.2	-15.6	115	<0.001	81

Key: D1 month, the change from baseline to 1 month; N1, number of patients with baseline and one month data; P, significance of change from baseline to 1 month; N2, number of patients with baseline, 1 and 24 month data.

Conclusion: Pacing improves balance confidence and decreases anxiety, depression and cardiac symptoms in the first month after pacing. Baseline scores were the major predictors of subsequent scores. Pacemaker mode had no significant effects on levels of balance confidence, anxiety, depression or cardiac symptoms.

P970 Female gender predicts longer survival despite higher age at pacemaker implantation

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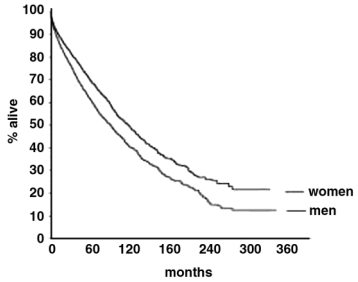
Implantation of cardiac pacemakers (PM) is the treatment of choice in symptomatic bradycardias, however, little is known about the impact of gender on very long term survival, as this might influence the device-selection.
Methods: Analysis of a database containing 6505 PM patients in a university hospital implanted from 1971-2000. Survival analysis was based on standardized 6-12 months control intervals and telephone follow up, the Kaplan-Meier method was used for estimation of survival.
Results: A total of 6505 pts was analyzed (3078 female, 47,3%; age: 72,1y ±11,8; mean follow-up period: 56,9 months). Women (W) were significantly older than men (M) at PM implantation (73,3 ±11,2y vs. 71,0 ±12,3y) Despite this, their median survival time (MST) after PM implantation was still longer than men (118,0 vs. 91,7 months, $p>0.0001$, fig 1). Subgroup analysis showed that in pts with atrial fibrillation (AFIB) no age difference was found between W and M (74,4 ±8,8 vs. 73,5 ±9,4 months; p=n.s.) and MST differed markedly (93,6 vs. 70,7 months, $P<0.01$). In AV-block (> 2nd degree), the age difference was more pronounced (73,2 ±12,9 vs. 71,3 ±13,0; $p<0.0001$) and MST differed by 22,4 months (106,3 vs. 83,9 months, figure). In sick-sinus syndrome (SSS) we observed the highest difference in age (72,8 ±10,3 vs. 68,5 ±12,8y), but the survival advantage was still seen for W (MST: 145,7 vs. 115,5 months, $p<0.05$)



Conclusion: Women have a markedly longer survival after PM-implantation for all indications. Despite the markedly higher age of W at implantation for AVB and SSS, this age difference does not offset their better survival. This difference needs to be considered when selecting PM-devices for women.

P971 Telemetric homemonitoring: can it replace routine contolls of implantable defibrillators?

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Implantable defibrillators (ICDs) are the treatment of first choice concerning survived sudden cardiac death (SCD) or symptomatic ventricular tachycardias (VT). Routine controlls are performed every 3 to 6 months after implantation. Technical progress now offers telemetric performed longdistance interrogations and controlls including information about the system status, episodes detected and treated via homemonitoring (HM). Since May 2002 27 patients (pts.; age 64±14.8 years, ejection fraction: 35±20.4%, underlying disease: coronary artery disease: n=19, dilative cardiomyopathy: n=7, hypertrophic cardiomyopathy: n=1) received ICDs with HM (Biotronic Inc.: single chamber ICDs, Biotronic Belos VR-T: n=23; dual chamber ICDs, Belos DR-T: n=4). Indications for ICD implantation: survived SCD: n=9, sustained VT: n=11, syncope and inducible VT: n=6, prophylactic indication: n=1. Directly after implantation implementation and testing of HM was performed. Routine interrogations and controlls of ICDs were performed 4 weeks after surgery followed by controlls every 3 months. HM-interrogations and reports were obtained every 2 wks. including information regarding battery status (battery), lead impedance (LI), shock impedance (SI), counts of episodes (VT/VF (ventricular fibrillation)) and therapies aborted/delivered (ATP (overdrive stimulation)/shocks. Event triggered reports were delivered in case of episode detection and treatment, system status changes, i.e. LI>2000 Ohms, battery status ERI, etc. HM can be performed on request, every 24 hours, weekly or every 2 weeks. Out of 289 scheduled reports 273 were received, 11 event reports due to episode detection and termination. Missing report delivery was caused by transmission failure of the cellular net. Data of HM versus routine controll at 6 months (n=27): battery [V]: 6.21±0.03 vs. 6.20±0.01; LI [Ohm]: 447±13 vs. 451±38; SI [Ohm]: 51±2 vs. 54±4; VT/VF: 1/2 vs. 1/2; ATP/shock: 1/1 vs. 1/1.
Conclusions: Close ICD interrogations and controlls including information regarding system status, episode counts and therapies aborted/delivered can be performed reliably via longdistance telemetric HM offering the possibility of immediate data transfer in case of necessary consultation and reduction of routine controlls in outpatient clinics or hospital admissions.

P972 The prospective predictive power of 24-hour ambulatory electrocardiogram markers in determining implantable cardioverter-defibrillator discharge

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Twenty four hour ECG markers of cardiac autonomic function (heart rate variability (HRV) & heart rate turbulence (HRT)) are known to stratify the risk of arrhythmic death in cardiovascular disease, but their utility in selecting candidates for an implantable cardiodefibrillator (ICD) has not been studied. Whereas the analysis of HRV is limited by frequent ectopic beats, common in ICD candidates, HRT quantifies fluctuations in sinus cycle length after such ectopic beats to assess cardiac autonomic control. We have prospectively studied the utility of 24-hr HRV and HRT in predicting appropriate use of an ICD implanted according to current selection criteria.

Methods: 69 consecutive patients selected for ICD implantation according to MADIT-I or AVID criteria, underwent 24 hr digital holter recording 1 day after their procedure. After a follow-up period of 20[9-30](mean[range])months patients were divided into 2 groups: utilisers had received at least one appropriate therapy from the ICD; non- utilisers had not.

Results: 24 hour HRV analysis was not possible in 8(12%) of patients due to a high percentage of ectopic beats, whilst HRT analysis was successful in all cases. Utilisers and non-utilisers could not be separated by 24-hr SDNN. In contrast, mean values of HRT in the two groups dichotomised either side of the previously validated prognostic thresholds, with non-utilisers falling into the better prognostic stratification (i.e. higher HRT: slope >2.5 ms/mmHg and a negative value for onset). No patient with a slope of >5.8 ms/mmHg received any ICD therapies. This identified 15% of the non-utilisers.

	24-hour SDNN (ms)	HRT Onset (ms)	HRT Slope (ms/mmHg)
Utilisers	86 (4)	0.1 (0.2)	2.2 (0.3)
Non-utilisers	90 (8)	- 0.3 (0.2)	3.6 (0.7)
Good Prognosis	> 70 (ATRAMI 1997)	< 0 (Schmidt 1999)	> 2.5 (Schmidt 1999)

24 hour ECG markers (mean (SEM)) in users and non-users of ICD.

Conclusion: HRT was easily obtained from all patients and unlike conventional 24 hour HRV distinguished those who benefited from ICD implantation. A high HRT slope (>5.8 ms/mmHg) may identify low-risk patients who would otherwise receive ICD according to current criteria. The addition of HRT to current selection criteria should be examined in future trials.

PULMONARY VEIN ABLATION

P973 Substrate modification by left atrial linear lesions as an alternative in patients with recurrence of atrial fibrillation despite pulmonary vein isolation

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Trigger elimination by pulmonary vein (PV) isolation has been demonstrated to cure atrial fibrillation (AFib). Despite initially successful PV isolation, AFib may recur during follow-up.

Methods: Of a total of 347 pts (mean age 57±9 yrs) who underwent PV isolation resulting in acute elimination of the PV spike potential (max. 30 W, 50° C over max 180 sec), a subgroup of 15 pts (12 m, mean age 56 ± 12 years) underwent additional ablation procedures aiming at a compartmentalization of the left atrium (LA) interrupting possible reentrant circuits to treat their unchanged arrhythmia (4 intermittent AFib). Despite a mean number of 2.5 ± 0.9 acutely successful PV isolation procedures, PV spike potentials were demonstrated in 9/15 pts at the beginning of the linear ablation session. Two linear lesions in the LA were deployed by point-by-point radiofrequency current applications: one connecting the superior right to the superior left PV ("roof" line) and a second line from the middle of the roof line to the anterior aspect of the mitral annulus to interrupt atypical flutter ("anterior line"). Mapping and ablation (irrigated tip 14/15 pts with max. 30-35 W) were performed using the CARTO system during SR or coronary sinus pacing.

Results: A mean number of 37.4 ± 17.7 RF applications were used to deploy the two lines. Procedure duration amounted to a mean of 478± 113 min and 29.6 ± 9.8 min of fluoroscopy. Validation of line completeness was performed using both conventional stimulation criteria and the CARTO system (local activation time and voltage amplitude maps).

During follow-up (mean 130 ± 90 days), 10/11 (91%) pts with complete lines were in SR, whereas in the group with persistent gaps 3/4 pts experienced recurrence of AFib or incessant scar-related atrial tachycardia. In one pt a significant PV stenosis eventually necessitated stent implantation.

Conclusion: One explanation for AFib relapse after demonstrated complete PV isolation might be re-conduction of the previously interrupted conducting fibres into the PV. However, even after repeat "successful" pulmonary vein isolation, AFib does recur in a subset of patients. Additional modification of the atrial substrate by left linear lesions resulted in SR in 91% of these pts when lines were completely deployed. Incomplete linear lesions resulted in AFib recurrence or scar-related reentry tachycardia.

P974 Anatomic particularities of human atrial myocardial extensions into pulmonary veins

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Purpose RF ablation of paroxysmal atrial fibrillation initiated in one or more pulmonary veins (PV) specifically targets the electrical disconnection of PV - left atrium junction. This emphasizes the importance of precisely understanding the anatomical particularities of this junction.

Method Twelve human hearts without known cardiopathy were obtained at autopsy. Left atrium with PV and adjacent right atrial tissue were excised then fixed in formaldehyde. Macroscopic analysis of the fiber structure was carried out, with special attention to the myocardium extending at least 5 mm into the PV junction from the left atrium myocardium (LAM).

Results 44 PV and a unique Left PV could be examined. Myocardial extensions were observed in 100% of Left Superior PVs (LSPV), 70% of Right Superior PVs (RSPV), 55% of Left Inferior PVs and 50% Right Inferior PVs. All extensions consisted of circular muscle bundles, parallel to each other and perpendicular to the PV axis.

All LSPV extensions were directly linked to the LAM by distinct myocardial bundles, originating from Bachmann's bundle (60%) or from organized muscular fibers always surrounding both left PVs. All of these were in the high posterior quadrant of the PV.

60% of RSPVs were directly connected to the myocardium surrounding the superior vena cava – right atrium junction by distinct myocardial fibers.

Inferior vein extensions did not present with recurrent features.

Conclusions Left Atrial Myocardium is always connected to the LSPV by specific muscular bundles. These are derived from either Bachmann's bundle or structured muscular fibers. The RSPV often present distinct structures linking the muscular extensions to the right atrial myocardium.

P975 Evaluation of the anatomy and the diameter of the pulmonary veins before and after ablation for atrial fibrillation

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Background: Isolation of the pulmonary veins (PV) by ablation (ABL) for cure of atrial fibrillation (AF) carries a potential risk of stenoses of these veins with consequent pulmonary hypertension and sometimes serious complications. Furthermore, anatomical variants of PV are encountered in some patients (pts).

Methods: Since february 2002 we performed systematically a contrast spiral CT scan of the PV, 3 to 4 days before ABL, after 1 week and during follow-up (FU) after ± 2 months in order to calibrate the diameter of the PV ostia and to detect possible PV stenoses. The diameters were measured at 5 mm from the extrapolated border of the left atrial cavity. After a transseptal puncture, ABL was performed systematically in the first mm of the ostia of the PV. ABL was guided by spontaneous or paced PV potentials, detected at the ostia on a 10 pole Cordis Lasso® catheter. A maximum energy of 30 W was used and a temperature of 40 to 50°C. Ten pts had an electro-anatomic (CARTO®) circumferential exclusion with an 8 mm or an irrigated 3.5 mm catheter with a power setting of 50 W and a temperature of ± 50°C.

Results: Thirty two consecutive pts (10 CARTO® pts) were eligible for this study. All PV were successfully isolated during the procedure (mean procedure time: 4.2 ± 0.7 hours). Seven pts had more than 2 right PV ostia (7 x RMPV). The diameters (mm) of the PV were shown in the table. No pt had a clinically significant (maximal narrowing observed: 30%) reduction of the diameter of the ostia. For the 16 pts having completed the follow-up, the mean difference of the diameter of the 4 veins were respectively: 1.5(LSPV), 0.6(LIPV), 0.6(RSPV), 0.4mm(RIPV). No pt had complaints suggestive of PV stenosis, pulmonary involvement or pulmonary hypertension.

Diameters (mm) of the PV

	n	LSPV	LIPV	RSPV	RIPV	P
(1) before	32	14.4 ± 3.3	12.1 ± 2.2	14.5 ± 3.6	12.6 ± 2.7	/
(3) 2 months	16	12.9 ± 2.5	11.1 ± 1.7	13.1 ± 2.8	12.7 ± 1.7	P=NS (1vs2)

Conclusion: ABL of the PV with a maximum power setting of 30 Watts and a temperature limited to 50°C with the classical Lasso® catheter method seems to be safe without significant stenoses of the ostia of these veins after ABL. No clinical events related to this possible complication were noted. This was also the case in the ten pts with circumferential electro-anatomic approach.

P976 Usefulness of phased array intracardiac echocardiography during pulmonary vein isolation with radiofrequency catheter ablation in patients with atrial fibrillation

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Purpose: to assess the usefulness of phased array intracardiac echocardiography (ICE) during pulmonary vein (PV) isolation in patients (pts) with AF.
Methods: Twenty-four pts (22M, 2F; mean age 55±11 years) with symptomatic paroxysmal (13 pts), persistent (7 pts), and permanent (4 pts) AF, underwent to ICE-guided PV isolation. The mean AF duration was 6 years (range 1.5-30) with daily or weakly episodes for pts with paroxysmal AF. All the pts were on anticoagulation therapy and tried at least 3 antiarrhythmic drugs (AAD) without success. Structural heart disease was present in 17 pts. The mean left ventricle ejection fraction was 58±7% and the mean left atrial diameter was 45±6 mm. The transesophageal echocardiography (TEE) was performed in all pts 1-3 days before ablation. AAD were discontinued at least 5 half-lives prior to the procedure. The ablation was performed under ICE-guide to visualize the intra-atrial septum during the transeptal puncture, to define the left atrium (LA)-PV junction for the circular mapping catheter positioning and to guide energy titration by monitoring micro-bubbles formation. The power was titrated upward until bubbles limited to the area around the ablation catheter (type 1) were observed and was terminated if shower of dense bubbles extending to the LA cavity (type 2) appears. PV isolation was considered acutely successful after abolition of all ostial PV potentials. All pt were followed with history, ecg, Holter recording at 1 and every 3 month. TEE was repeated at 1, 3, 6 and 12 month. In case of symptom recurrences ECG and Holter recording were also performed. Complete success was defined as the absence of AF recurrences in the follow up (FU) without AAD. Pts with recurrences of AF during the FU that remain in sinus rhythm with AAD previously ineffective, were considered as partial success.
Results: Four PV were isolated in all pts. After a mean FU of 3±1.5 months the success rate was 79.5% (19 pts)with a complete success in 16 pts (67%) and a partial success in 3 (12.5%). The radiofrequency energy delivered during the ablation ranged from 30 to 100 W. The procedure was complicated in 1 case with cerebrovascular embolic event. No severe PV stenosis were observed during the procedure and in the FU.
Conclusions: The PV isolation guided by ICE seems to be effective to prevent the AF recurrences. The ICE is a useful tool to guide the titration of radiofrequency energy by direct visualization of micro-bubbles formation reducing the risk of PV stenosis in a short-term FU.

P977 Impact of the duration of cryoablation application on the clinical efficacy of pulmonary vein isolation using transvenous cryoablation

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Background: Recent studies have demonstrated that transvenous cryoablation (Cryo) is a safe and feasible method for pulmonary veins (PVs) isolation for treatment of atrial fibrillation (AF). However, a significant limitation of this technique is cryoablation requires a much longer ablation time. Whether decrease the duration of Cryo affects the clinical efficacy for PV isolation remains unclear.
Methods: We compared the procedure time and clinical efficacy of Cryo (CryoCorTM, San Diego, USA) for PV isolation in 25 pts (mean age 51±13, 18 men) with paroxysmal AF using either double-5 mins (5x2, n=15) or double-2.5 mins (2.5x2, n=10) freeze delivered with a 10 F deflectable transvenous catheter. PV isolation was performed as guided by identification of PV potential recorded with a circular catheter (Lasso, Webster). All pts underwent Holter and event recorder at 3 and 12 months to evaluate for AF recurrence. Antiarrhythmic drugs were discontinued at 3 months if pts had no AF recurrence.
Results: Successful electrical isolation was achieved with Cryo in 76 of 78 (97%) targeted PVs in 25 pts (mean: 3.1±0.7 PVs per patient). A mean of 47±21 (range 12 to 79) Cryo were delivered per pt, and there was a median of 12 (range 2 to 40) applications per vein (7.5 ± 3.2 sites). The overall mean percentage of effective Cryo applications was 75 ± 10% (range 25 to 100%). The mean temperature achieved at target sites during effective applications (-77.8 ± 5.5 °C). After 12±6 months, 15 (60%) pts had no recurrences of AF. There were no significant differences in the mean number of PV isolated and Cryo application, percentage of effective Cryo, the acute and long-term clinical efficacy and fluoroscpy time between using 5x2 and 2.5x2 freezes (Table). However, the procedure time of using 2.5x2 freezes was significantly reduced compared with 5x2 freezes (380±131 vs. 510±115 mins, p=0.01).
Conclusions: Transvenous catheter Cryo is an effective method to create PV electrical isolation for the treatment of AF. The use of 2.5x2 freeze protocol significantly reduces the procedure time without affecting the acute and long-term clinical efficacy of Cryo.

Comparison Between 5x2 vs. 2.5x2 Freeze

	No. of PV isolated per pt	No. Cryo applications per pt	% Effective Cryo	Acute efficacy	Chronic efficacy	Fluoro-scopy time	Procedure time
5x2 freeze (n=15)	3.1	51	69	47/48 (98%)	8/15 (53%)	138	510
2.5x2 freeze (n=10)	3.3	52	73	29/30 (96%)	7/10 (70%)	117	380*

*p=0.01

P978 Pulmonary vein isolation using a novel circular cryoablation catheter: early changes in pulmonary vein activation predict effectiveness

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Background: Pulmonary vein (PV) isolation by cryoablation can be time-consuming, predominantly due to the duration of each application. We hypothesized that the likely effectiveness of each application can be predicted by early changes in PV activation during cryo-delivery.
Methods: Using a novel 7F steerable circular tipped cryoablation catheter (Artic CirclerTM), we targeted 32 PVs (diameter 19±5mm) in 17pts (12M, age 52±12yrs) with drug refractory paroxysmal atrial fibrillation. The cryoablation catheter was placed at the ostium of each targeted vein, proximal to a circumferential mapping catheter (LassoTM). Cryoablative lesions were created at -80°C for ≥4min. PV isolation was defined as either the elimination of PV electrograms or their dissociation from left atrial (LA) electrograms. An effective application was defined as one causing a significant change in PV activation.
Results: Twenty-five (78%) PVs were successfully isolated, 16 using the circular cryoablation catheter alone, and 9 after additional cryoablation with a 6mm tipped catheter. Of 371 (12±8 per PV) applications delivered using the circular catheter, 107 (29%) were terminated within 60s due to suboptimal catheter position resulted from catheter expansion or technical problems. The remaining 265 applications (71%) were continued for >60s (mean 200±64s), of which 92 (35%) were effective. To detect a possible cumulative effect, applications for each PV were divided into tertiles. Effective applications were evenly distributed across these (32, 30 and 30 for the 1st, 2nd, and last tertile, respectively), so that the index of effectiveness was independent of total energy delivered. All but one effective application caused a >/=10% prolongation of LA-PV conduction time or a significant change in PV morphology, within the first 40 (17±13) sec of the delivery.
Conclusion: Effective application using a circular cryoablation catheter can be predicted by early changes in PV activation. This may avoid prolonged applications at ineffective sites and shorten procedure time.

P979 Cartilage, bone, and marrow formation as a marker for unintended energy deposition post-ablation in the canine heart

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Background: Laser energy ablation to create circumferential lesions at the PV orifice has shown promising results in treating AF, but the chronic effects of endocardial injury, both intended and unintended, from laser energy ablations have not been well described.
Methods: To assess the chronic effects associated with the use of circumferential laser energy balloon ablation, 42 PV lesions were created in 19 dogs. Laser energy ablation was performed at power levels of 3.5, 4.5, and 5.5 W/cm, for durations of 120 to 600 seconds in 14 PVs each. To assess subsequent chronic effects, 16 dogs were randomly survived to 4 months, and 3 dogs survived to 6 months.
Results: Post-mortem investigation demonstrated extensive cartilage formation both grossly and histologically at the orifice in 36 out of 42 (86%) of the ablated PVs. Cartilage was seen in 8/14 PVs (57%) ablated at 3.5 W/cm, 14/14 PVs (100%) at 4.5 W/cm, and 14/14 PVs (100%) at 5.5 W/cm. In each case, cartilage was formed superior to either the left or right superior PVs. In 2 cases, there was also extension of cartilage inferior to the affected PV. The main site of cartilage formation in all cases was the point of previous contact between the superior aspects of the non-ablating part of the balloon and the superior aspect of the PV and left atrium. Bone formation was found in 13 of 36 PVs with cartilage, and bone-marrow formation was seen in 10 of these 13 PVs. There was no regression of cartilage or bone formation at 6 months compared to 4 months.
Conclusions: Cartilage, bone, and marrow formation within the canine atrium after laser energy balloon ablation at the pulmonary vein orifice is seen in most of the PV ablations in this study. Nevertheless, cartilage formation may be a species-specific phenomenon.

P980 Usefulness of a new radiofrequency thermal balloon catheter for pulmonary vein isolation to treat atrial fibrillation

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Background: A triggering ectopic focus originated from the pulmonary vein(PV)or its ostial lesion induces atrial fibrillation (AF). We evaluated the safety and efficacy of a new radiofreqency thermal balloon catheter for PV isolation to treat atrial fibrillation.
Methods: We treated 50 patients with drug resistant paroxysmal AF using this catheter. By trans-septal approach,the inflated baloon with a diameter 5-10mm larger than that of PV ostium, was wedged at the left atrium(LA)-PV junction, which was heated by a very high frequency current(13.56 MHz) applied to the coil electrode inside the balloon for 3-5 minutes repeatedly up to 4 times. The ballon center temperature was maintained at 60-75 degree Celsius by regulating the output of the generator.
Results: Successful PV isolation was performed in 49 of 50 left superior PVs, in all of 50 right superior PVs, in 18 of 20 left inferior PVs, and in 18 of 20 right inferior PVs, associated with a significant reduction of the amplitude of the ostial potentials. Total procedure time was 1.5-3.2 hours, including 25-46minutes of fuluoloscopy time. After 6-12 months follw-up period, 45 patients were free from AF, including 35 not taking and 10 taking the same antiarrhythmic agents before ablation. Electron beam tomography revealed no PV stenosis. There were no major complication associated with this thermal balloon ablation.
Coclusion. Using a radiofrequency thermal balloon catheter, we can safely and quickly isolate the PV and its ostial lesion from the LA to treat paroxysmal AF, through circumferential ablation around the PV ostium.

P981 Morphologic study of the pulmonary veins by three-dimensional magnetic resonance angiography: implications for the electrophysiologist

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Radio frequency ablation (RFA) of focal atrial fibrillation has renewed the interest in the morphological study of the pulmonary veins (PVs). Transesophageal echocardiography (TEE) is semi-invasive and limited technique in readily visualizing the more distal part of all PVs draining into the left atrium. The wide field of view of cardiovascular magnetic resonance imaging (CMRI) allows the fully depiction of PVs anatomy, and 3D contrast enhanced magnetic resonance angiography (3D-CEMRA) is an outstanding method to identify PVs anatomical details and relationships and the position of the ostia in the left atrium.
Purpose: To report our experience in the anatomical study of PVs by means of 3D-CEMRA
Methods: The study group consisted on 23 patients scheduled for a CMRI study for different reasons (5 of them pre-RFA studies) and who presented without significant left atrial dilatation on the initial CMRI sequence of pilot scans. In them, a 3D-CEMRA sequence was performed after the completion of the study protocol in every case. The MRI system used was a Philips Intera 1.5 T, and the contrast agent administered in the 3D-CEMRA study was gadoteridol (0.2 mmol/kg) at an infusion rate of 3 ml/s. Reconstructions on maximal intensity projection (MIP) and 3D volume rendering of the images were displayed for analysis on a dedicated workstation. A measurement of the diameter of all vessels was performed on coronal slices of the 3D volume set at the section nearest to the ostium.
Results: In all cases, adequate images from all PVs were obtained. Diameter ranged from 11-21 mm. In 17 cases (74%) 4 independent ostiums were observed, and in 5 patients (22%) 5 independent ostiums were present (3 left PVs and 2 right PVs in 3 patients and 2 left PVs and 3 right PVs in 2 patients), while in 1 patient (4%) – this case corresponding to a pre-RF ablation study- only 3 ostiums were detected because of the presence of a unique left PV ostium. In 13 patients (56%) the right lobar veins converged distally forming a very short common trunk. In 5 patients the PV ostium was formed from the direct convergence of the lobar veins into the left atrium (right upper PV in 3 cases, left upper PV and right inferior PV in one case respectively).
Conclusions: 3D-CEMRA is a non-invasive diagnostic technique allowing the complete morphological study of the PVs pre and post-RFA. Knowledge of the anatomical details of the PVs distal part and the position of the ostia in the left atrium is a very useful information for the electrophysiologist to make easier the RF ablation procedure.

P982 Isolation of pulmonary veins during sustained atrial fibrillation: efficacy of combined treatment with ultrasound balloon ablation and radiofrequency ablation

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Aims: Pulmonary veins (PVs) isolation can be achieved easily by targeting the PV potentials during sinus rhythm and/or atrial pacing, but during an ongoing episode of atrial fibrillation (AF), the PV potentials may be difficult to differentiate from the left atrium (LA) potentials. The purpose of this study was to determine the efficacy of combined treatment with ultrasound balloon ablation and radiofrequency ablation during sustained AF.
Methods and Results: Fifteen patients with markedly symptomatic and drugs refractory AF were included in this study. In each patient, cardioversions have been performed but with prompt recurrence. Mapping of PVs was performed with a circumferential mapping catheter (A-focus/Lasso). Ultrasound PV ablation was performed anatomically until complete isolation of the PV or the PV activity allowing secondarily a more localized ablation with a radiofrequencyt (RF) catheter. Right inferior PV mapping and ablation was performed with a RF catheter. In total, 57 PVs were ablated. Complete PV isolation was achieved in 54 (94.7%) of them. Ultrasound balloon ablation was performed in 45 PVs. After a mean of 6.4±3.1 (2-17) ultrasound energy applications were delivered, 34 PVs (75.6%) were complete isolated and 11 PVs were partial isolated. Ostial ablation with RF was performed in these PVs. The total procedure duration and fluoroscopy times were 138±21min and 38±9min, respectively. There were no PVs stenosis or other complications in this study. After a mean follow-up of 6.9±2.9 (5-13) months, 7 patients (46.7%) were AF free without any antiarrhythmic drugs and AF can be controlled by drugs in 4 patients (26.7%).
Conclusions: Isolation of multiple PVs during sustained AF is feasible and safe. Combined treatment with ultrasound balloon ablation and RF ablation had a high efficacy in PVs isolation during ongoing AF.

P983 Circumferential pulmonary vein ablation as a new anatomic approach for atrial fibrillation and predictive criteria for succesfull radiofrequency ablation

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Background: Circumferential radiofrequency (RF) ablation of all 4 pulmonary vein (PV) ostia has recently been described as an effective and safe anatomic approach for the treatment of atrial fibrillation (AF). It seems that the amount of post-RF low voltage encircled area is the only predictive criterion for a successful ablation.
Objectives: Our aim is to report the outcome of this approach in a small cohort of patients with highly symptomatic drug-recurrent paroxysmal AF (PAF) and investigate possible predictive criteria for a successful ablation.
Methods: We studied 39 patients (32 male, mean age 59,9 yr.) with PAF who underwent Circumferential PV ablation deployed transseptally predominantly during sinus rhythm, using 3D electroanatomic guidance. We determined the total left atrial volume (LAvol), the amount of encircled area around each PV, the number of RF lesions and the number of PVs with complete lesions. These were complete when distances between 2 consecutive lesions were less than 10mm.
Results: No PV stenoses were detected by transesophageal echocardiography or magnetic resonance. Among 144 lesions surrounding individual PVs, 79% were defined as complete. After a mean of 8,5 months, 31 patients were AF free and 5 had AF recurrence. Patients with (Group A) and without (Group B) AF recurrence did not differ in age, prevalence of heart disease, ejection fraction or LA diameter. Ablated area around Left PV/LAvol was significantly smaller in patients from Group A (p=0,032). The percentage of PV with incomplete lesions did not differ between groups. There was no significant difference considering the amount of low voltage encircled area on the right PVs, the total number of RF lesions and LAvol, although patients from Group A presented with larger LA volumes (p=0,057).
Conclusions: Circumferential PV ablation seems to be an effective and safe treatment for paroxysmal AF. Present experience suggests that the amount of encircled area around the left PVs may be regarded as a possible predictive criterion for a successful RF ablation.

ANTICOAGULATION IN ATRIAL FIBRILLATION

P984 Nadroparin versus unfractionated heparin for anticoagulation of all cause atrial fibrillation: preliminary results of the NADROPAF trial

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Background: Few studies were conducted to test the safety and efficacy of low molecular weight heparin (LWMH) as an anticoagulation modality in new onset atrial fibrillation (AF) before cardioversion and most of those studies excluded patients (pts) with high risk for systemic embolism particularly those with valvular heart disease.
Methods: The NADROPAF trial (Nadroparin for Atrial Fibrillation) is a prospective randomized open label multicenter study comparing Nadroparin versus unfractionated heparin (UH) in pts with all cause atrial fibrillation of more than 48 hours duration. Pts $>$ 75 year-old, with a history of $<$ 6 months systemic embolism, cerebral or gastro-intestinal hemorrhage, prosthetic valve, left atrial thrombus or renal failure were excluded. Pts were given LMWH or UH at a body weight adjusted dose.
From Oct 2001 to Dec 2002, 179 pts were included: 107 pts in the LMWH group and 72 in the UH group. Age, sex, and distribution of AF etiology were similar between the 2 groups as shown in the table below:
Treatment duration was of 5.7 $\pm$ 2.8 days in the LMWH group versus 6.37 $\pm$ 2.8 in the UH group (p: NS)
Results: There was only one death that occurred in the UH group 10 hours after inclusion, most likely related to ventricular arrhythmia. There was no major stroke in either group. Transient ischemic attack was observed in one pt with mitral stenosis in the UH group. There was no major hemorrhagic events in either group. However, minor hemorrhage was observed in one pt of each group.

Comparison of demographic characteristic

	LMWH	UH	p
Age (years)	58.9 $\pm$ 13.5	60.0 $\pm$ 13.2	NS
Sex (Female)	72 (67%)	52 (72%)	NS
AF Etiology			
– Valvular disease	28 (26%)	23 (32%)	NS
– Hypertension	34 (32%)	23 (32%)	NS
– Other	13 (12%)	7 (10%)	NS
– Lone	32 (30%)	19 (26%)	NS

Conclusions: Anticoagulation of AF from all cause including valvular heart disease can be safely and effectively accomplished by LMWH. These findings need to be confirmed as the study progresses before recommending an outpatient management of all pts with AF.

P985 Risk of cerebral embolism in patients with left atrial thrombi and atrial fibrillation: a prospective and serial study using transesophageal echocardiography and cerebral magnetic resonance imaging

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Background: Patients (pts) with left atrial (LA) thrombi and atrial fibrillation (AF) have an elevated risk of cerebral embolism. The aims of this prospective study were (1) to evaluate the fate of LA thrombi in anticoagulated AF pts and (2) to determine predictors of thrombus resolution and cerebral embolism.
Methods: The study group consisted of 20 pts with LA thrombi (age 62$\pm$12 years). All pts received oral anticoagulation therapy and underwent serial transthoracic and transesophageal echocardiographic examinations, serial assessment of the anticoagulation level (an INR $>$ 2 was defined as effectively anticoagulated) and cranial MRI including diffusion- weighted imaging to determine the presence of cerebral embolism at the beginning of the study, at 4 weeks, at 3 months and at 1 year.
Results: Seven pts had cerebral embolism at the index admission. Three pts had cerebral embolism with neurological deficits during the follow up period. One patient died. 4 out of 20 thrombi resolved within 4 weeks. An additional 9 thrombi disappeared within 12 months (65% resolution within 12 months). Pts with and without thrombus resolution did not differ for ejection fraction (51$\pm$20 vs. 45$\pm$18%; p=0.60), LA size (5.2$\pm$1.0 vs. 4.5$\pm$0.4cm; p=0.13), mobility (62% vs. 43%; p=0.26), protrusion (15% vs. 29%; p=0.48) and echogenicity of thrombi (77% vs. 86%; p=0.64), whereas the thrombi were smaller in pts with thrombus resolution (1.0$\pm$0.5 vs. 2.5$\pm$1.8; p=0.02). Pts with cerebral embolism had larger thrombi (3.2$\pm$2.7 vs. 1.1$\pm$0.62; p=0.02) and a higher incidence of previous cerebral embolism (2 vs 5; p=0.03) as compared to pts without embolism.
Conclusions: Most LA thrombi disappear within 12 months under continued anticoagulation therapy. Thrombus size is the only predictor for thrombus resolution. Cerebral embolism may even occur under continued anticoagulation therapy (15%). Thrombus size and previous embolism are predictors of cerebral embolism during follow-up.

P986 A post-cardioversion transoesophageal echocardiography strategy with the use of enoxaparin for brief anticoagulation in atrial fibrillation patients: a pilot trial study

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Transeosophageal echocardiography (TEE)-guided cardioversion (C) of atrial fibrillation (AF) foresees post-C oral anticoagulation theraphy (OAT) of four weeks, as empirically determined, due to the possibility of an atrial/left atrial appendage stunning (S) related thromboembolism. Many studies agree that in most patients (pts) post-C S lasts about one week. The aim of this work is to evaluate the feasibility and safety of a new TTE-guided strategy that entails a 2nd, 7 days post-C, TEE in order to select those pts who, without S, can benefit from a one week period of anticoagulation. For a rapid and brief anticoagulation we use enoxaparin (E) in alternative to OAT.
Methods: We enrolled into a multicenter, randomized, prospective, clinical trial 206 pts with AF $\geq$ 2 days eligible for electrical and/or pharmacological C. They were randomly assigned to two groups, A and B. Group A pts received E at a dosage of 100 IU antiXa/kg twice a day and underwent TEE-guided C. After seven days a 2nd TEE was carried out and, in the absence of S, E was stopped. Otherwise, E was embricated with OAT for three weeks. Group B pts carried out a conventional TEE-guided C with heparin and four weeks of OAT post-C.
Results: Of the 105 group A pts, 98 underwent the 1st TEE. Of these 2 (2.1%) did not undergo C due to thrombi (T) and 7 (7.1%) due to dense spontaneous echocontrast (SEC). C was efficacious in 76 pts. After 1 week 53/61 pts in SR underwent the 2nd TEE. In the 43/53 pts (81.1%) who showed no signs of stunning, E was stopped. Of the 101 group B pts, 87 underwent TEE. C was not carried out in 5 pts due to T (5.7%) and in 5 pts due to dense SEC (5.7%). C was efficacious in 75 pts. At one month follow up 84 group A pts and 84 pts group B pts were evaluated.
In group A one patient (pt) who had shown complex plaques in the aortic arch at 1st TEE had a stroke during E anticoagulation treatment.
In group B there was one death, non treatment-related, and a TIA. A severe hemorrhage occurred while on OAT in a group A pt with atrial S.
There was 1 minor hemorrage in group A and B respectively. In the 43/53 pts who showed no signs of stunning at 2nd TEE the mean duration of antithrombotic therapy was 8.7$\pm$1.47 days compared to 33$\pm$2.45 days in group B.
Conclusions: These results suggest that the POSTEC strategy for AF may constitute a feasible and safe therapeutic alternative to the conventional TEE-guided approach with undoubted clinical advantages. If a larger trial, currently under way, should confirm these data, the management of pts undergoing C for AF could be greatly simplified.

P987 Whats "lifelong anticoagulation in patients with chronic atrial fibrillation?

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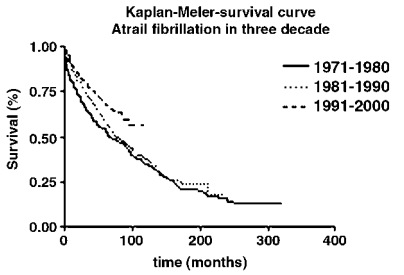
Chronic atrial fibrillation (AFIB) is the most common arrhythmia in patients (pts) >60y with benefit from oral anticoagulation. There is a lack of prognostic data in terms of life expectancy in this group of pts.
We analysed 1627 pts (886 male [55%]; 741 female [45%]) with chronic AFIB and pacemaker (PM) therapy in terms of mortality, and a non-selected subgroup of these pts in terms of morbidity (ischemic stroke) and status of oral anticoagulation. Between 1971 and 2000 pts were followed in standardized 6-12 months intervals. In the first decade (D1; 1971-1980), we included 571 pts (mean age 72,3y), in D2 (1981-1990) 676 pts (mean age 74,2y) and in D3 (1991-2000) 380 pts (mean age 75,7y).
Female PM-recipients lived significantly longer than male ($p<0.01$, mean survival: 93.6 vs. 70.7 months) despite older age at time of inclusion. Mean time of survival was 66.8 months in D1 and 75.9 months in D2 (p=ns). In D3 however, survival time was significantly longer than in D1 ($p<0.001$) and D2 ($p<0.005$) despite older age at implantation in D3.



Kaplan-Meier survival curve.

Life expectancy in pts with chronic AFIB has increased in the last three decades to now more than 10y. Only 34% of these pts were effectively treated with oral anticoagulation with a total incidence of ischemic cerebral events of 26.4%.

P988 Conversion of atrial fibrillation to sinus rhythm could induce hyperclotting state: the relationship with the atrial fibrillation duration

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Introduction: It is well known that thromboembolic events are likely to occur in patients(pts) with long-lasting atrial fibrillation (Af) but not in pts with Af of recent onset. However, the correlation between the duration of Af and the cardiovascular clotting level after cardioversion (CV) is not clarified.
Aim: The aim of the study was to determine whether the duration of Af could be a risk factor for the hyperclotting state after CV of Af.
Methods: Fourty-two pts undergoing CV of Af. There were divided into two groups. In Group A (24pts,14 male, 56±11 years), the duration of Af was 72 hours or more (142.7±103.8 hours). In Group B (18 pts, 10 male, 61±13 years) the duration of Af was less than 72 hours (25±16 hours). Plasma D-dimer levels (an index of hyperclotting levels) were measured before and 36 hours after CV by the enzyme immynoassay. The changes of plasma D-dimer levels n 36 hours after CV were calculated as Alpha- D-dimer.
Results: There were no significant dfferences n age, sex, hematocrit, hemoglobin, plasma fibrinogen level, underlying heart disease, the success ratio of electrical CV and the presence of diabetes mellitus or hypertension between the two groups.
Alpha D-dimer levels were significantly higher in Group A than in Group B (48.5±72.9 ng/ml vs. -19.2±47.8ng/ml, p=0.005). There were no significant differences in plasma D-dimer levels before and 36 hours after CV between the two Groups.
Furhermore, plasma D-dimer levels 36 hours after CV and Alpha D-dimer showed significant correlations with the duration of Af (D-dimer 36 hours after CV;r=0.52, p=0.0016, Alpha D-dimer;r=0.73, $p<0.0001$).
Conclusions: Our results show that the longer Af duration could lead to the more prominent cardiovascular hyperclotting states after CV and that the duration of Af might be a risk factor for the high occurrence of the post-CV thromboembolic events.

P989 The safety of clopidogrel for the prevention thromboembolic events in patients with atrial fibrillation

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Aim: Atrial fibrillation (AF), the prevalence of which reaches 6% in those aged over 60 years, carries an increased risk of thromboembolism. The aim of this study was to determine the applicability of clopidogrel therapy and the value of clopidogrel as an altenative therapy in preventing thromboembolic complications in patients with AF.
Material and method: The study group consisted of 118 consecutive patients with chronic nonvalvular atrial fibrillation in whom warfarin/aspirin can not be used for different reasons. The study population included 50 men and 68 women aged 63.1 ± 10.3 years. Mean AF duration was 28.2 ± 5.3 months. Of these patients 72 had hypertension, 34 coronery artery disease, 22 diabetes mellitus type II, 28 congestive heart failure, 15 chronic obstructive lung disease, 3 hypertiroidism and 4 prior cerebral events. Six patients had mitral valve prolapse and 14 had mitral annulus calcification. Left atrial spontaneous echo contrast (LASEC) was present at baseline in 55% patients. After clinical evaluation and echocardiographic examination, all patients received clopidogrel 75 mg/day. Five patients with left atrial thrombus were excluded. All patients were followed-up for a miminum of one year (mean followin duration: 15.8 ± 2.7 months).
Results: One patient had a thromboembolic event at the secondary day of the treatment (0.9%). The thromboembolic event was transient ischemic attack. The patient had prior cerebrovascular event. Only one patient had a bleeding complication (minor) during followed up. There was no major bleeding inthe group. Five patients (4.5%) stopped the study due to adverse effects of clopidogrel. Two of them (1.8%) have gastric complaint and nausea and vomiting were occurred. Pruritic reaction was seen at one patient (0.9%). There were 2 patients (1.8%) with significant reduction in neutrophils ($<4.000/mm^3$), but there was no major severe neutropenia ($<450/mm^3$). There was no death in the group.
Conclusion: In patients with nonvalvular atrial fibrillation clopidogrel is a safe and efficient as aspirin preventing thromboembolic complications and can be used as an alternative regimen in patients with contrendications to aspirin or warfarin.

P990 Population prevalence of atrial fibrillation and factors associated with use of warfarin

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Atrial fibrillation (AF), a major risk factor for thrombotic stroke, has an estimated population prevalence of around 1%. We have undertaken a cross-sectional, community-based study (36 general practices, population base 186,000) of AF patients in the Glasgow area, to study factors associated with warfarin use and concordance with Scottish national guidelines.
1466 patients with documented AF were identified (48% aged >75y), giving a population prevalence of 0.79%. There was a positive correlation with age (45-54y, 0.25%; 55-64y, 1.3%; 65-74y, 3.1%; >75y, 5.9%). Overall 53% of patients were receiving warfarin, but fewer of the elderly (age "> 85y, 19%; 75-84y, 53%; 45-74y, 70-80%).
Detailed clinical information was available on a subgroup of 1034 patients, of whom 65% were taking warfarin (8% with aspirin), 25% aspirin alone and 10% no antithrombotic therapy. Traditional risk factors for AF-related stroke were common (ischaemic heart disease 44%, hypertension 42%, diabetes 16% and prior stroke or TIA 27%), as were relative contra-indications for warfarin, (e.g. alcohol, falls, haemorrhage and likely non-compliance) 20%. 85% of those receiving warfarin had no identifiable contra-indication, while of those not on warfarin, 22% had one relative contra-indication and 8% >2 contra-indications. However, 69% of those not receiving warfarin (24% of all AF patients) had no apparent contra-indication and may have benefited from warfarin treatment.
Compared to historical estimates the prevalence of AF is not increasing. Following publication of guidelines, more AF patients are receiving warfarin. However, up to one quarter may be eligible for warfarin, but not yet receiving it.

P991 Interleukin-6, endothelial activation and thrombogenesis in chronic atrial fibrillation

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A prothrombotic or hypercoagulable state is present in AF, which could increase the risk of thromboembolism. As inflammation has been related to thrombogenesis and endothelial activation, we hypothesised that the prothrombotic state in AF (as assessed by an index of thrombogenesis, prothrombin fragment 1+2 [F1+2]) and endothelial activation (soluble E-selectin, sEsel) could be related to an index of inflammation (interleukin-6, IL6).

Methods: We studied 191 consecutive patients (98 male; mean age 72.3±9.2years) with chronic non-rheumatic AF who were not on anticoagulant therapy. Plasma IL-6, sEsel and F1+2 were measured by ELISA. Research indices were compared to 74 controls in sinus rhythm matched for age and sex. In 43 patients with AF, the effects of introducing anticoagulation (INR 2.0-3.0) were also studied. Results are expressed as median [IQR].

Results: Patients with AF had elevated levels of F1+2 and IL6 (table), but not sEsel. There were no significant correlations between F1+2 and IL6. In multivariate analysis (linear regression), only F1+2 levels were independently associated with the presence of AF (p=0.001). After oral anticoagulation, plasma levels of F1+2 and sEsel were significantly decreased: F1+2 1.24[1.00-2.03] vs 0.42[0.35-0.49], $p<0.001$; and sEsel 50.0[38.0-70.0] vs 31.6[20.0-46.0], $p<0.001$.

Research indices

	Patients	Controls	p value
F1+2 (nmol/L)	1.35 (1.02-1.92)	1.05 (0.88-1.25)	<0.001
IL6 (pg/mL)	5.0 (2.5-11.0)	3.2 (2.5-8.5)	0.045
sEsel (ng/mL)	44.0 (31.2-62.4)	42.0 (32.4-58.0)	0.566

Conclusion: High levels of IL6 in AF suggest an inflammatory state, which appears to be more related to clinical variables of the patients, rather than to the presence of AF per se. There was no association of inflammation (IL6)with endothelial activation (sEsel) or the presence of abnormal thrombogenesis (high F1+2 levels) in AF. Moreover no changes in IL6 levels were found despite the reduction of the other markers by anticoagulant therapy.

P992 Raised plasma levels of interleukin-6 predict stroke or adverse outcome in atrial fibrillation

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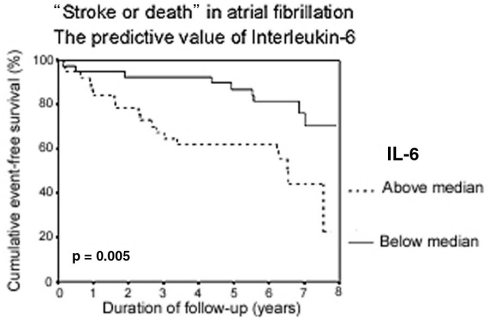
Background: Atrial fibrillation (AF) is associated with an increased risk of stroke and death. Evidence exists of an inflammatory state in AF, but the relationship to prognosis is unknown. We hypothesised that inflammation may be associated with stroke or death in AF.

Methods: We measured plasma interleukin-6 (IL-6) and C-reactive protein (CRP) among 77 AF cases (mean±sd age 67±10; 57% male) regularly attending our hospital outpatient clinic in the early 1990s. Using hospital records, we identified subsequent stroke or death among our cohort and used Cox proportional hazards to identify the predictive value of IL-6 and CRP for the composite endpoint 'stroke or death'.

Results: Median (IQR) IL-6=20 (9-61) pg/ml; median (IQR) CRP=0.31 (0.17-0.95) mg/ml. High (above median) IL-6 was associated with an increased risk of stroke or death (OR 2.99 (95%CI 1.34-6.65), see figure). High (above median) CRP was associated with a non-significant trend towards increased risk (OR 2.09 (95%CI 0.97-4.47). Age was the only clinical characteristic significantly associated with increased risk (OR 1.05 (95%CI 1.00-1.10) per year, p=0.046). Gender, heart failure, diabetes, prior stroke, ischaemic heart disease, hypertension and blood pressure were not significant predictors of outcome in this cohort(all $p>0.05$, data not shown here). High IL-6 remained a significant predictor after adjustment for age (OR 2.91 (95%CI 1.20-6.51), p=0.007).



Kaplan-Meier survival curve.

Conclusion: High plasma levels of IL-6 were associated with an increased risk of stroke or death in AF. Similar trends were also seen for plasma CRP, but did not reach statistical significance. The role of inflammation in the pathogenesis of stroke and thromboembolism in AF deserves further study.

P993 Increased platelet expression of P-selectin (CD62P) in atrial fibrillation

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Purpose: In order to define the range of intravascular platelet activation the expression of CD62P (P-selectin) molecule on the surface of platelets in patients with atrial fibrillation (AF) was determined. Expression of CD62P is a consequence of intravascular platelet activation and subsequent degranulation of á-granules containing CD62P and other procoagulant factors. Thromboembolism is well known frequent complication of atrial fibrillation. We tested the hypothesis whether increased intravascular platelet activation is related to clinical parameters such as structural heart abnormalities and frequency regulation. These data may be usefull in stratification of patients at higher risk of thromboembolism.

Methods: We measured platelet CD62P expression by flow cytometry using anti-CD62P monoclonal antibody method in the platelet population defined by CD41 (alpha-chain of integrin molecule GPIIb/IIIa, CD41/CD61) specific for platelets and megakaryocytes. AF group comprised of 35 patients (mean age ± SD: 64.43 ± 11.89 y) and control group of 30 subjects with sinus rhythm (63.10 ± 16.23 y).

Results: There is significant difference in expression of CD62P between these two groups (AF: 8.41 ± 3.31, control: 3.56 ± 2.65; $p<0.05$). Criteria for intravascular platelet activation were defined as more than 5% of platelets expressing CD62P on their surface. These criteria were present in 8 patients with AF, and in 7 control subjects ($p>0.05$). Aortic root diameter (<0.001), platelet number (<0.001), left ventricular ejection fraction (<0.05) and heart rate (<0.05) were defined as significant for platelet activation by multivariant discriminant analysis. Conclusion: These preliminary data suggest increased activation of platelets in patients with atrial fibrillation greatly caused by advanced structural heart changes and poor frequency regulation.

P994 Impaired flow-mediated dilatation as evidence of endothelial dysfunction in atrial fibrillation

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Hypothesis Endothelium-dependent flow-mediated dilatation (FMD) has been used to demonstrate endothelial dysfunction in hypertension, diabetes mellitus, hypercholesterolaemia and heart failure, as well as to identify individuals at risk of atherosclerosis. We hypothesised that endothelial dysfunction exists in atrial fibrillation (AF) and could contribute to the risk of stroke and thromboembolism seen in these patients.

Methods High-resolution ultrasound was used to measure the diameter of the right brachial artery at rest, during reactive hyperaemia (with increased flow causing endothelium- dependent dilatation), and after sublingual GTN (to assess endothelium-independent dilatation) in 49 fasted subjects (29 outpatients with chronic AF and 20 healthy controls). All readings were performed over 5 cardiac cycles, and patients with AF were rate-controlled and stable on cardioactive medications (excluding nitrates). Successful scans were undertaken in all patients.

Results Groups were matched for age, sex and systolic blood pressure.

	AF	Controls	P value
Age (years)	68.7 (8.7)	65.7 (8.7)	0.258
Systolic BP (mmHg)	139.9 (17.8)	137.8 (20.5)	0.694
Brachial artery diameter (mm)	4.1 (0.6)	3.8 (0.8)	0.309
Flow-mediated dilatation (mm)	0.0 (-0.2 - 0.1)	0.4 (0.23 -0.5)	<0.001
Flow-mediated dilatation (%)	0.0 (-5.1 - 2.6)	9.0 (6.4 - 14.6)	<0.001
GTN-induced dilatation (mm)	0.43 (0.19)	0.53 (0.23)	0.115
GTN-induced dilatation (%)	11.1 (7.2 -14.1)	10.9 (8.8- 19.3)	0.158

All indices expressed as mean (SD) except flow-mediated dilatation and GTN-induced dilatation (mean, IQR).One-way ANOVA used for all except flow-mediated and GTN-induced dilatation where Mann-Whitney test used.

FMD was significantly impaired in AF compared with healthy controls ($p<0.001$). There was no significant difference between the groups in relation to GTN-induced (endothelium independent) dilatation.

Conclusion Our data suggests that FMD can be used to assess endothelial function in stable outpatients with chronic AF, who demonstrate evidence of endothelial dysfunction.

EXPERIMENTAL HEART FAILURE II

P995 Spontaneous development of heart failure in mice overexpressing protein phosphatase 2 (PP2A)

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An increased activity of protein phosphatases has been described in failing human myocardium. We studied the spontaneous development of heart failure and response to stress in transgenic mice with cardiac specific overexpression of the catalytic subunit of PP2A (PP2A, increased mRNA levels, protein levels increased by 110%, PP2A activity increased by 68%) Echocardiography was performed in age and sex matched littermates using a 15 MHz transducer at the age of 8, 16 and 52 weeks (w, n=10 per group). Cardiac dilatation and dysfunction were already present in young (8 w) mice, reflected by reduced fractional shortening (FS, WT 35±2 vs. PP2A 26± 3%*, *: $p<0.05$) and left ventricular diameter (WT 4.0±0.1 vs. PP2A 4.8±0.0 mm*). While impaired contractility remained constant between 8 and 16 w, left ventricular dilatation progressed (WT4.1±0.1 vs. PP2A 5.4±0.2 mm*). In senescent PP2A (52 w), contractility further declined to 53% of WT, and challenge with isoproterenol (2 μg/g intraperitoneally) increased fractional shortening in WT mice from 36±1 to 70±1% and in PP2A mice from 19±2 to 39±4% (* for WT vs. PP2A and for baseline vs drug in each genotype). In intact catheterised mice, 42% less maximal rate of left ventricular pressure development and 47% less rate of maximal pressure decline were measured compared to WT. In vivo and ex vivo, absolute and relative heart weight was increased in PP2A (calculated LV mass 8w: WT 71±4 vs. PP2A 89±3mg, 16w: WT 82±6 vs. PP2A 146±10*, 52w: WT 93±6 vs. PP2A 165±22 mg*). Diameter of cardiomyocytes was enlarged in PP2A at the age of 16w (WT 16.2±0.3 vs. PP2A 21.4±0.6 μm*). Phosphorylation of phospholamban and troponin I was reduced in PP2A mice.

Conclusions: Cardiac-specific overexpression of PP2A results in progressive decline in cardiac contractility, progressive ventricular dilatation and reduced response to maximal stress in vivo. Increased activity of PP2A may contribute to the development of impaired cardiac function in human heart failure (Supported by SFB556 B2 and Z2).

P996 Left-ventricular dysfunction and molecular remodelling in pulmonary hypertension

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Pulmonary hypertension (PH) represents increased afterload to the right (RV), but not to the left ventricle (LV). Both ventricles however are exposed to endocrine and paracrine activation. Impaired LV function in PH was attributed to impaired filling due to ventricular interaction. The present study evaluated the occurrence of intrinsic LV haemodynamic and molecular abnormalities in a monocrotaline (MCT) model of PH.

Wistar rats were instrumented with RV and LV tip manometers and ultrasonic crystals to measure intracavitary pressures and LV septal free wall diameter 4 and 6 weeks after random injection with MCT (60mg/kg, sc) or vehicle. Four groups were investigated: i) Control 4th week (C4; n=6); ii) MCT 4th week (M4; n=6); iii) Control 6th week (C6; n=6); iv) MCT 6th week (M6; n=6). Graded single beat constrictions of ascending aorta increased systolic LV pressure from baseline to isovolumetric (LVPiso). Transmural LV samples were collected to quantify SERCA2a and phospholamban (PLB) proteins (Western blot, normalised to calsequestrin), and myosin heavy chains (MHC) isoforms (SDS-PAGE). Results presented as mean±SEM; $p<0.01$.

MCT increased systolic RV pressure (C4: 20.8±1.3; M4: 39.1±1.9; C6: 21.2±1.6; M6: 51.4±4.1 mmHg) and RV/LV weight ratio (C4: 0.23±0.02; M4: 0.37±0.03; C6: 0.22±0.02; M6: 0.58±0.03), whilst end-diastolic LV dimensions decreased (C4: 8.2±0.6; M4: 6.9±0.7; C6: 8.3±0.7; M6: 5.4±0.9 mm). LV systolic function was severely impaired in the M6 group: dP/dtmax (C4: 4953±550; M4: 5263±393; C6: 5197±567; M6: 2205±272 mmHg/s); LVPiso (C4: 194±7; M4: 208±4; C6: 202±7; M6: 132±7 mmHg). No slowing of pressure fall nor upward shift of the end-diastolic pressure-dimension relation were observed in response to afterload elevations, in C4 and C6, while such alterations became apparent with afterloads exceeding 78-82% and 50-55% of LVPiso in M4 and M6 groups, respectively, reflecting progressive diastolic intolerance to afterload. SERCA2a (C6: 0.6±0.1; M6: 0.3±0.1) and PLB (C6: 2.2±0.3; M6: 1.3±0.2) protein levels were decreased in M6. Relative expression of beta-MHC was increased both in M4 (C4: 10.6±1.8; M4: 25.4±3.6%) and M6 (C6: 10.0±2.0; M6: 28.2±3.1%).

PH induced dysfunction and molecular remodelling of the LV. Diastolic disturbances and increased beta-MHC preceded systolic dysfunction and SERCA2a and PLB down-regulation. These results suggest that myocardial overload is not essential for inducing haemodynamic and molecular phenotypes found in congestive heart failure.

P997 Age-stage specific of p-38β mitogen-activated protein kinase and apoptosis in hypertensive rats

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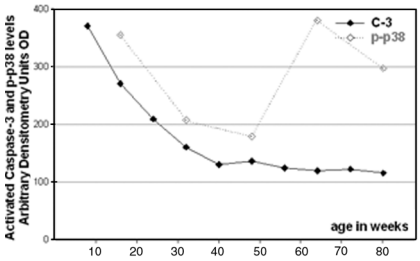
Mitogen activated protein kinases (MAPKs) are involved in the early development of cardiac hypertrophy, but their roles are still unclear in cell fate decision. Recently we determined the differential activation of caspase-3 (C-3) in spontaneously hypertensive rats (SHR) and its specific role in hypertrophy (H) and heart failure(HF). In this regard we correlated the activation of C-3 and p38 MAPKs in SHR.

Methods: Western Blotting: Left ventricles were removed, lysed, and proteins were separated by SDS-PAGE and electroblotted onto nitrocellulose. An antibody that recognises 32kDa inactive procaspase and 20kDa C-3 fragment as well as specific antibodies for p-38 beta and phosphorylated p-38 (p-p38)beta were detected by chemiluminescent autoradiography. Digitised images were analysed with Diversity Database image analysis software.

Results: p38 beta activation (determined as p-p38 beta/p-38 beta ratio) was found to be highly elevated in the early period of hypertrophy (20 weeks of age) where C-3 activation (cleaved 20kDa caspase/procaspase)was also increased and remained so during the decompensation period (60-80 weeks of age) during which C-3 activation was attenuated.



Caspase-3, p-38beta activation timecourse.

Conclusions: In SHR chronic pressure overload induces C-3 dependent apoptosis in the early hypertrophic period probably due to p38 activation. During this period the role of p38 beta phosphorylation suggests a pro-apoptotic effect in contrast to the late decompensation period suggesting an anti-apoptotic one. This mismatch of p-38 and C-3 induced apoptosis may be age related.

P998 ETA receptor antagonism, angiotensin type 1 receptor antagonism, angiotensin-converting enzyme inhibition and combined treatments after experimental myocardial infarction in stroke-prone spontaneously hypertensive rats

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Objectives: We investigated the effects of combined treatments with the endothelin ETA-receptor antagonist, darusentan (ETA-RA, 30 mg/kg/d) with either the ACE-inhibitor, trandolapril (ACE-I, 0.1 mg/kg/d), or the angiotensin II AT1-receptor antagonist, irbesartan (AT1-RA, 50 mg/kg/d) in comparison with monotherapies (equal doses for combined treatments and monotherapies) with darusentan, trandolapril, irbesartan and vehicle on cardiac function and left ventricular (LV) structure, in stroke-prone spontaneously hypertensive rats (SHRSP) after myocardial infarction (MI).

Methods: SHRSPs were treated from 4 weeks prior to 6 weeks after induction of MI. (n=90-200 per group).

Results: In comparison to vehicle, the two combined treatments of the ETA-RA with the ACE-I (combination 1) or with the AT1-RA (combination 2) showed substantially different influence on myocardial remodelling: combination 1 followed the pattern of monotherapy with ETA-RA, (1) the infarcted area featured vital, diffusely fibrotic myocardium and transmurality of the infarction scar was prevented, (2) interstitial collagen content (ICC) was reduced to a high extent ($p<0.001$) and LV was dilated, and (3) LVEDP and dP/dtmax were significantly ($p<0.05$-0.001) improved despite marked ($p<0.01$) LV-dilation. In contrast, combination 2 followed the pattern of monotherapy with AT1-RA, (1) a compact transmural collagen-fibrous scar of the infarcted area, (2) ICC was reduced to a lesser extent and LV was not dilated, and (3) dP/dtmax was improved to a lesser extent despite the absence of LV-dilation.

Conclusions: In rats, these findings point to (1) a hitherto undescribed early protection of infarcted myocardium by chronic pretreatment with ETA-RA, (2) a correlation of improved LV-hemodynamics with reduced ICC but not with LV-dilation, and (3) a differentially modulated crosstalk between the cardiac renin-angiotensin system and the endothelin system by the use of ACE-I or AT1-RA.

P999 Effects of IKr block on myocardial repolarisation in pacing-induced heart failure

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Background: Sudden cardiac death due to life-threatening arrhythmias is a major problem in chronic heart failure (CHF). CHF is associated with action potential prolongation due to downregulation of potassium channels and may therefore increase the proarrhythmic side-effects of cardiovascular and non-cardiovascular drugs. We aimed to examine underlying mechanisms in a model of pacing-induced heart failure. Methods and results. In 12 rabbits, heart failure was induced by 4 weeks of rapid pacing (400 beats/min). 10 of 12 rabbits (83%) developed clinical signs of congestive heart failure. The mean ejection fraction decreased from 72±14% to 17±5%. In the failing Langendorff-perfused hearts, the QT-interval (31±15ms) increased significantly as compared to 13 sham-operated control hearts. Eight simultaneously recorded endo- and epicardial monophasic action potentials showed a significant homogenous prolongation of repolarization (APD 90) of 17±6ms to 9±4ms after induction of AV-block and stimulation at cycle lenghts between 900 and 300ms. There was no increase in dispersion of repolarization. After infusion of the IKr-blocker erythromycin (150-300μM) there was a further increase in action potential prolongation in failing hearts as compared to control hearts. (mean increase: +58ms vs. +43ms; $p<0,05$). The increase in dispersion was significantly higher in the heart failure group than in the sham group (39ms vs. 16ms; $p<0,05$) Conclusions: In pacing induced heart failure, a homogenous prolongation of action potential duration occurs. Block of IKr results in a further increase of action potential duration and dispersion of repolarization in failing hearts. These findings may contribute to arrhythmogenesis in heart failure. Thus, administration of repolarisation prolonging drugs should be monitored especially careful in heart failure.

P1000 Inhibition of the Na^+/H^+ exchanger attenuates the functional deterioration in pacing-induced heart failure in rabbits

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In rats, inhibition of the Na^+/H^+ exchanger (NHE) reduces myocardial infarct size and attenuates hypertrophy and left ventricular (LV) dilatation following myocardial infarction. Whether or not inhibition of the NHE also attenuates LV dilatation and functional deterioration in heart failure (HF) of non-ischemic origin - especially when treatment is started after LV dysfunction has already developed - is unknown. We therefore investigated the functional consequences of NHE inhibition with BIIB 722 (sabiporide), a compound which competes with sodium at the NHE, in pacing-induced HF in rabbits. HF was induced in 25 rabbits by LV pacing at 400 bpm for 3 weeks. Eighteen sham-operated rabbits served as controls. In sham rabbits, 9 animals received placebo while the other 9 received BIIB 722 at a concentration of 30 mg/kg po once a day. In HF rabbits, 9 animals received placebo, 9 animals received BIIB 722 prior to pacing while the remaining 7 animals received BIIB 722 following 1 week of pacing.
In sham rabbits treated with placebo or BIIB 722, LV end-diastolic diameter (LVedD), echocardiography) and systolic fractional shortening (FS) remained unchanged. In HF rabbits, LVedD increased and FS was reduced from 31.5±1.4 to 8.1±1.0% ($p<0.05$). The activity of the 90 kDa NHE kinase was significantly ($p<0.05$) greater in HF (2.25±0.20 AU) than in sham (1.56±0.15 AU) rabbits. Morphologically, the extent of fibrosis and apoptosis and, biochemically, the extent of p38 MAPK phosphorylation (66.9±9.0 vs. 28.9±5.9% of total p38 MAPK) and iNOS protein expression (168,382±34,845 vs. 68,944±20,624 density AU; both $p<0.05$) were significantly increased in HF compared to sham rabbits.
In HF rabbits receiving BIIB 722, FS was significantly better preserved than in HF rabbits when treatment started before (18.1±2.2%) or at 1 week of pacing (15.5±1.6%; both $p<0.05$ vs. HF). Along with the improved LV function, the extent of fibrosis, apoptosis, phosphorylation of p38 MAPK (20.4±6.1% of total p38 MAPK) and iNOS protein expression (62,623±17,957 density AU; both $p<0.05$ vs.HF) were significantly reduced in HF rabbits receiving BIIB 722.
In conclusion, inhibition of the NHE attenuates the functional and biochemical derangements in pacing-induced heart failure in rabbits, even when treatment is started after LV dysfunction developed.

P1001 Angiotensin type 1-receptor blockade preserves baroreflex sensitivity in experimental heart

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Depressed baroreflex sensitivity (BRS) and marked activation of the renin-angiotensin system are common features characterizing the congestive heart failure (CHF) syndrome. Since angiotensin (AT) is known to blunt baroreflex function, we examined whether blockade of AT1 receptors preserves BRS in rats with post-coronary artery ligation CHF. Eight week-old Sprague-Dawley rats were subjected to i) left anterior descending coronary artery ligation (Lig) to produce a large myocardial infarction (MI) and dysfunction of the left ventricle (LV), or sham ligation (Sh), and ii) administration of irbesartan (Irb, 40 mg kg^{-1} day^{-1} in the chow) or placebo (Pl). Four weeks later the animals were chronically instrumented and arterial blood pressure (BP), pulse interval (PI) and BRS (slope of the regression of the rises in PI to the rises in BP in response to graded iv injections of phenylephrine, 0.5, 1 and 2 μg kg^{-1}) were evaluated in conscious state. LV end-diastolic diameter (LVEDd, mm/g body weight, BW) and fractional shortening (FS) were measured by echocardiography whereas indices of heart weight and lung weight (HWI, LWI) were measured post-mortem.
Results are shown in table.

	Veh-Sham (n=16)	Veh-Lig (n=17)	Irb-Sham (n=10)	Irb-Lig (n=12)
BW, g	380±24.2	403±22.7	298±15.0#&	313±18.7#&
HWI, mg/g	2.9±0.3	3.6±0.4&	2.6±0.1#	2.8±0.2#
LWI, mg/g	5.2±0.4	7.5±0.4&	4.4±0.3#	4.9±1.1#*
LVEDd, mm/g	1.8±0.2	2.6±0.5&	1.9±0.4#	2.7±0.4*&
FS, %	45.2±6.2	22.6±4.6&	50.4±3.6#	33.5±5.4*#&
MAP, mmHg	99.6±10.1	92.2±10.3	92.2±6.5	91.8±5.8
PI, msec	161±17.5	154±16.2	190±14.4#&	169±14.2*
BRS, msec/mmHg	0.86±0.11	0.44±0.09&	0.92±0.06#	0.75±0.06#*

*, $p<0.05$ vs Irb-Sham; #, $p< 0.05$ vs Veh-Lig; &, $p<0.05$ vs Veh-Sham.

Conclusions: AT1-receptor blockade almost entirely prevents the impairment in BRS observed in rats with post-MI LV failure. This may relate to the ability of AT1 blockers i) to abolish the baroreflex-depressing effect of angiotensin II, and/or ii) to prevent the development of the heart failure syndrome in spite of a clearcut impairment of LV function.

P1002 Validation of a conductance system to determine left-ventricular volumes in rats after myocardial infarction: comparison to cine-magnetic resonance imaging

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Background: Studies investigating the use of a conductance catheter in rats with left ventricular (LV) chamber dilation and hypertrophy after myocardial infarction (MI) are lacking. To validate the conductance system (CS) in rats with MI we compared conductance with cine-fast low-angle shot (FLASH)-magnetic resonance imaging (MRI) data.
Methods and Results: LV end-systolic volume (ESV), LV end-diastolic volume (EDV) and ejection fraction (EF) were analyzed in sham-operated rats and rats with MI (size range: 35-58%), 12 weeks after surgery. MRI was done on a 7-T scanner using an electrocardiogram-triggered cine-FLASH sequence. Pressure-volume loop data were obtained by a pressure-CS (miniaturized catheter SPR-774, unit MPCU-200, Millar Instruments), acquired by BioBench software (National Instruments) and analyzed by PVAN software (Conductance Technologies). Hypertonic saline method was used to determine parallel conductance volume (Vp). ESV (range: 240,2-1279,3μL) and EDV (range: 476,3-1688,3μL) were calculated for each rat from conductance volume corrected by the relative Vp. In sham-operated and MI rats volume and EF values obtained with CS were similar and highly correlated (NMR vs CS ESV: r=0.96, $p<0.001$; NMR vs CS EDV: r=0.94, $p<0.01$; NMR vs CS EF: r=0.90, $p<0.01$) with those derived from Cine-FLASH-MRI.
Conclusion: Miniaturized conductance system can accurately measure LV volumes in rats with moderate to extensive LV chamber remodeling following myocardial infarction.

P1003 Identification of proteins differentially expressed in normal and experimentally infarcted mouse myocardium

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Background: The molecular mechanisms underlying ischemic injury and myocyte death in the infarcted myocardium are largely unknown. It is likely, that significant alterations in myocardial protein expression underlie these disease processes and determine their progression and outcome. The combined use of 2 dimensional gel electrophoresis (2-DE) and mass spectrometry enables the characterization of alterations of protein expression in the infarcted myocardium.
Methods: Changes in protein expression in the experimentally infarcted mouse myocardium were investigated. Protein spots displaying significantly different intensities in silver-stained 2-DE gels of infarcted and normal myocardium were visually located. The proteins within these spots were identified by high sensitivity matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS).
Results: Two of the identified proteins - isocitrate dehydrogenase 3 and enolase 3 - are glycolytic enzymes and were down-regulated in the infarcted myocardium whereas another enzyme - ATP synthase, H^+ transporting F1 complex, beta subunit - which also displayed a reduced abundance in the infarcted tissue, is an enzyme of the respiratory chain in mitochondria. The changed expression of these enzymes probably reflects the metabolic difference between the normal and the infarcted myocardium. Whereas the former is characterized by a fast rate oxidative metabolism, the metabolic rate of the latter is much lower.
Conclusion: The identification of further differences in protein expression between normal and infarcted myocardium will be presented. Such data may lead to new insights into the molecular mechanisms involved in myocardial infarction and will likely result in the discovery of novel diagnostic markers and new targets for therapeutic interventions.

P1004 Transplantation of HUVEC after myocardial infarction results in improvement of left-ventricular function and neovascularization

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Introduction: The concept of tissue-restricted differentiation of postnatal stem cells has been challenged by recent evidence showing pluripotency for hematopoetic, mesenchymal and neural stem cells. Recent reports showed that endothelial cells, either freshly isolated from embryonic vessels or establishes as homogenous cells in culture (human umbilical vein endothelial cells HUVEC) differentiate into cardiomyocytes and express cardiac markers when cocultured with neonatal rat cardiomyocytes. It opens perspectives for replacement therapy after myocardial infarction.
Method: HUVEC (1x10E6) were injected in the margin zones of 4 week old myocardial infarctions, done by occlusion of the left coronary artery by a suture after thoracotomy in 12 rats, 12 control rats received sham operation with injection of culture medium. To identify transplanted cells in myocardial infarction, cells were labeled with bromodeoxyuridine. Cyclosporine (20 mg/kg KG/d) was administered orally to all rats to avoid rejection. LV function was assessed by 2D echocardiography using a 12 Mhz pediatric tranducer 2 and 8 weeks transplantation. Thereafter, left ventricular pressure was measured by perfusion of the hearts in a Langendorff perfusion system by a thin-wall balloon. After 30 min of stabilisation the balloon size was increased by 0.005 ml increments by addition of saline solution.
Results: BrDU showed survival of transplanted cells after 2 weeks, but not after 8 weeks in margin area of myocardial infarction. Further investigation showed development of endothelial cells with neovascularisation without transdifferentiation to cardiomyocytes.
Transplanted hearts developed higher pressures (70 $\pm$ 10 mm Hg in transplanted hearts, controls 40 $\pm$ 8 mm Hg) with normal balloon size and after volume balloon size increase after 8 weeks ($p<0.05$ for all balloon sizes).
Conclusion: This study shows for the first time in an experimental setting that transplantation of HUVEC improves global left ventricular function after 8 weeks follow-up after myocardial infarction. HUVEC-transplantation results in neovascularisation without transdifferentiation to cardiomyocytes.

STUNNING, HIBERNATION, PRECONDITIONING

P1005 Apical ballooning of the left ventricle: first series in Caucasian patients

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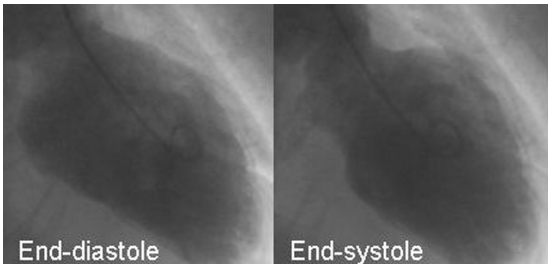
Introduction: Recently, a cardiac syndrome of "apical ballooning" was described, consisting of an acute onset of transient extensive akinesia of the apical and mid portions of the left ventricle, without significant stenosis on the coronary angiogram, accompanied by chest symptoms, electrocardiographic changes and a limited release of cardiac markers. Until now, this syndrome has only been reported in Japanese patients.
Methods: We describe 13 Caucasian patients who presented with this syndrome at our institution over the last 4 years.
Results: All patients but one were of female gender, with a mean age of 62 years. Eight of them presented with chest pain, of whom 6 with cardiogenic shock. In 9 patients a triggering factor was identified: emotional stress in 3, trauma in 1, pneumonia in 1, asthma crisis in 1, exercise in 2, and cerebrovascular accident in another. On left ventriculography, all patients showed very extensive apical akinesia ("apical ballooning") in the absence of a significant coronary artery stenosis, not corresponding with the perfusion territory of a single epicardial coronary artery. Mean maximal creatinekinase MB and troponin rise were 27.4 μg/l (range 5.2 to 115.7, median: 16.6) and 18.7 μg/l (range 2.0 to 97.6, median: 14.5) respectively. Six patients were treated with intra-aortic balloon counterpulsation. One patient died of multiple organ failure. On autopsy, no myocardial infarction was found. In the 12 survivors, left ventricular systolic function recovered completely within 3 weeks.



Conclusions: We report the first series of "apical ballooning" in Caucasian patients. Despite dramatic initial presentation, left ventricle function recovered completely within 3 weeks in the survivors.

P1006 Evidence of pharmacologic preconditioning during percutaneous transluminal coronary angioplasty by intravenous pretreatment with ATP-sensitive K^+ channel opener nicorandil

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Background: The IONA study, a recently completed randomized placebo control trial, clearly demonstrated a significant reduction in major coronary events after the oral administration of nicorandil to patients with stable angina.It is not known whether pretreatment with nicorandil, an ATP-sensitive K^+ channel opener, induces a preconditioning effect independent of increased collateral recruitment.
Methods: Forty-four patients with angina who underwent PTCA to proximal LAD stenosis were randomly allocated for pretreatment with an intravenous injection of nicorandil 5 minutes before initial ballooning or saline. 99mTc tetrofosmin was injected during balloon inflation, and quantitative analysis of occlusion images by SPECT was conducted. The defect severity score (SS) was calculated and compared with ST elevation(sigma ST) during ballooning. Results:sigma ST levels were significantly reduced in patients with nicorandil pretreatment compared with control patients (control:1.89 $\pm$ 0.85 mV nicorandil:1.24 $\pm$ 0.57 mV, p=0.0052). However, no difference was observed in defect severity(control:79.0 $\pm$ 32.5, nicorandil 98.7 $\pm$ 48.9). A close correlation was observed between SS and sigmaST in both groups. A multivariate regression model demonstrated that both defect severity ($p<0.0001$) and pretreatment with nicorandil($p<0.001$) were significantly related to the level of sigmaST, suggesting a cellular protective effect against ischemia by nicorandil, independent of myocardial blood flow.
Conclusion: Nicorandil pretreatment resulted in the induction of myocardial preconditioning independent of the severity of ischemia. The results of this study strongly support the hypothesis that nicorandil has a cardioprotective action, suggesting that the drug is effective for pharmacological preconditioning. The attenuation of ischemic damage by pretreatment of nicorandil appears to confer protection in patients undergoing PTCA and CABG.

P1007 Predictors of myocardial recovery in hibernating myocardium

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Factors that influence functional recovery of hibernating myocardium after revascularization are at present under investigation. From 3/2000 to 8/2002 we prospectively analyzed 41 patients with ejection fraction (EF)< 30% who underwent coronary artery bypass grafting (CABG). All patients received low-dose dobutamine echocardiography (DE), dobutamine myocardial scintigraphy with SPECT, dobutamine magnetic resonance tomography (MRI), contrast-enhanced MRI and when necessarry positron emission tomography. Hibernating myocardium ("area of interest") was thus identified preoperatively and biopsied intraoperatively. The early operative mortality rate was 2.4%. Three patients died during follow-up. Six months postoperatively DE, MRI and SPECT were repeated. LVEF increased in 23 patients (group I) by at least 5%, and in 14 patients (group II) it did not improve. The wall motion score in the "area of interest" significantly increased during preoperative DE in group I. The score did not change in group II. The diastolic-systolic wall thickness increase in the "area of interest" rose by >15% during DE in group I preoperatively; the increase was < 15% in group II. MRI hyperenhancement was measured with a mean of 16.7±11.6% of the left ventricle in group I compared to a mean of 27.4±14.4% in group II ($p<0.05$) preoperatively. SPECT showed myocardial viability in the "area of interest" in all 41 patients. There were no significant differences between groups I and II. When the "area of interest" was located in the anterior wall the patients showed more frequent ventricular improvement postoperatively than patients with an "area of interest" located in the inferior, lateral or posterior wall. Light microscopy showed more severe myocardial cell hypertrophy (<19μm) and less severe destruction of myocardial cell architecture in biopsies of group I compared to group II (<17μm). Gene expression of pro-apoptotic genes such as BAK and BAX was lowered (0.5±0.1/0.8±0.1) compared to "normal" myocardium (1.0±0.1)($p<0.05$). The anti-apoptotic gene BCL-XL was more expressed in the "area of interest" of patients of group II (1.34±0.10) than of group I (1.0±0.1)($p<0.05$). We conclude that in patients with endstage coronary artery disease myocardial recovery after CABG can be predicted using DE and MRI preoperatively. Myocardial regions without any potential for functional recovery show less adaptive process (less pronounced myocardial cell hypertrophy), a more severe degree of myocardial architecture destruction and a higher degree of anti-apoptotic gene expression.

P1008 Tissue expression profiling in patients with pressure overload hypertrophy due to aortic stenosis

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Microarray profiling is a new tool to elucidate complex genomic pathways in LV hypertrophy (H)/failure. We used the DNA microarray technique to study the expression of multiple transcripts in patients with LVH due to aortic stenosis (AS). At surgery, LV biopsies were obtained in 9 patients with AS and in 4 pts with coronary artery disease and normal (N) LV function. Invasive hemodynamics was obtained at cardiac catheterization. Doppler echocardiography was performed within 24 hours prior to surgery. Expression levels of 12 565 transcripts were determined by Affymetrix HG-U95 Av.2 microarrays.

Results: AS pts had higher LV mass index vs N (133±10 vs 72±9 gm/m^2, $p<0.01$). Statistical filtering identified significant changes in 419 genes (3.9%, delta = 0.24). We observed altered expression of genes related to 1) cytoskeletal and myofibrillar remodeling (troponin I and T, myosin binding protein C, actinin, microtubule-associated protein 4); 2) extracellular matrix proteins (vitronnectin, thrombospondin 2 and 4, collagens 1, 16, 21 and connective tissue growth factor); 3) signal transduction (janus protein kinase 2, genes of the MAP kinase cascade); 4) cell growth and survival (insulin growth binding protein 5, heat show protein 25/27) 5) transcription regulators (four and half LIM domain protein, AE binding protein, myobrevin). Yet, 30% of the genes had unknown function. In patients with reduced LV ejection fraction (<60%,n=3), transition from compensated hypertrophy to failure was associated with downregulation of 90 genes mostly related to energy production/handling and mitochondria (cytochrome C ad C1, COX 7, creatine kinase, aldose reductase) and signal transduction (IP3 receptor, MAP kinase 3, MEK2 and 5, calmodulin kinase II).

Conclusion: This detailed transcriptional profile of human pressure overload hypertrophy indicate that LV remodeling due to sustained pressure overload is related to changes in genes governing critical pathways of the cell growth and survival. In contrast, transition from compensated hypertrophy to LV dysfunction is associated with downregulation of genes related to signal transduction and energy production/utilization. Thus, our data define sets of gene changes that could lead to a novel molecular description of human cardiac hypertrophy.

P1009 A critical role for protein kinase C-epsilon in the protection induced in the myocardium by delayed ischaemic preconditioning of the in vivo mouse heart

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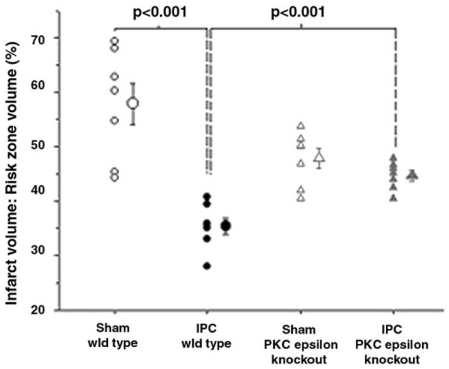
Background: The critical role of PKC-epsilon in early ischaemic preconditioning (IPC) is undisputed. However, its signalling role in late preconditioning has not been explored. Furthermore, controversy surrounds the role of HSP70 which is induced in late IPC.

Method: In this study we performed an in vivo IPC protocol of 3 cycles of 5-minute coronary artery occlusion/5-minute reperfusion followed by 24-hour recovery or a sham procedure followed by 24-hour recovery in male wildtype (WT) and PKC-epsilon knockout (KO) mice. The coronary artery of these mice was then re-occluded for 30 minutes followed by 4 hours of reperfusion. Infarction volume (I) was quantified by TTC and risk volume (R) by dye.

Results: Delayed preconditioning resulted in a significant reduction in sensitivity to ischaemia reperfusion injury in WT mice (I/R% 57.9±10.1v 35.4±4.2% in sham v IPC, $p<0.001$, n=7). However, in KO mice late IPC was lost (I/R% 47.9±4.9% v 44.7±2.6% in sham v IPC, p=ns, n=7). Immunoblots of WT and KO hearts homogenised 24-hours after IPC showed similarly increased HSP70 accumulation.



Comparison of myocardial infarct size.

Conclusion: In sibling mice the presence and absence of late IPC depends on the presence or absence of PKC-epsilon suggesting a causal relationship. Furthermore, the high expression of HSP70 in the unprotected PKC-epsilon deficient mouse hearts dissociates its expression from protection against ischaemia reperfusion injury.

P1010 Ischaemic preconditioning increases HSP-72 protein expression and reduces elevation of creatine kinase-MB following coronary artery bypass graft in man

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Background: Ischemic preconditioning, ie, the reduction of infarct size development during prolonged and severe myocardial ischemia by one or more preceding short episodes of ischemia and reperfusion, is the most powerful endogenous cardioprotective effect. We investigated whether a stress activated signal-transduction via heat shock protein 72 (HSP-72) mediated activation of p38 Mitogen activated protein kinase (MAPK) is involved in the creatine kinase-MB (CKMB) release reducing effect of ischemic preconditioning in patients undergoing CABG.
Methods: 19 patients were grouped according to their ischemic episodes within 24 hours before CABG: Patients with angina CCS III or IV were classified as preconditioned (IP, n=9), whereas patients with angina CCS I or II formed the control group (CON, n=10). The effect of IP on the CABG induced maximal release of creatine kinase (CK) and CK-MB was examined. Intraoperative biopsy specimens taken from ischemic and control regions in each patient were processed to analyse protein expression of HSP-72 and the calcium handling proteins phospholamban (PL), sarcoendoplasmic Ca-ATPase 2a (SERCA), calsequestrin (CSQ), the inhibitory subunit of troponin (TnI) and as well as the activation of MAPK.
Results: While IP significantly reduced CKMB (18.7±1.3 vs. 13.8±1.5 U/L, CON vs. IP, mean±SD, p=0.02) it only tended to reduce CK (292.7±32.8 vs. 274.1±31.1 U/L, CON vs. IP, mean±SD, p=0.68). Results of biopsy specimens are depicted in the table.

Relative changes of *protein expression and #MAPK-activation (phosphorylation): differences of values from individual ischemic and control biopsy specimens normalised by individual control values

mean±SD	PL*	SERCA*	CSQ*	TnI*	HSP-72*	MAPK#
CON	0.24±0.12	-0.26±0.07	-0.09±0.04	-0.12±0.07	0.09±0.12	0.05±0.28
IP	0.06±0.35	0.33±0.19	-0.02±0.07	0.12±0.18	0.44±0.11	0.84±0.43
t-test: P	0.626	0.008	0.354	0.212	0.045	0.141

Conclusion: Cardioprotection during CABG can be improved with IP. Possible mechanisms are the induced expression of HSP-72 and/or SERCA.

P1011 Cardioprotection with exercise training during ischaemia-reperfusion in senescent heart

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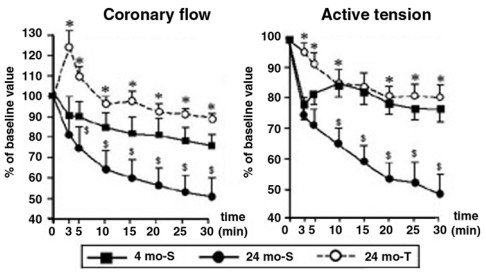
Aging is associated with a high vulnerability to myocardial ischemia-reperfusion (I/R), associated with a major calcium overload. Exercise training in aged rats improves diastolic function and limits calcium-regulating protein alterations. However, beneficial effects of exercise training on functionnal post-ischemic recovery of aged heart is presently unknown.
Methods: 2.5 and 21.5 month old (mo) rats (4 mo-S, n=10 and 24 mo-S, n=9, respectively) were maintained in sedentary conditions whereas 21.5 mo rats (24 mo-T, n=11) were treadmill trained (1h/day,5days/week,5% grade,16m/min) for 10 weeks. Isolated perfused hearts from 4 mo-S, 24 mo-S and 24 mo-T rats were submitted to 45 min of low-flow ischemia, by reducing coronary flow (CF) at 15% of its initial value, and to 30 min of reperfusion. Active and resting tensions (AT and RT respectively; g.g-1 of heart weight (HW)) and CF (ml.min-1.g-1 of HW) were recorded at baseline and after 1,5,10,15,20,25 and 30 min of reperfusion.
Results: Mean±SEM. *p<0.05 vs 24 mo-S group, $p<0.05 vs 4 mo-S group. At baseline, training, in contrast to aging, does not significantly modify AT and CF (respectively 11.6±0.4;6.8±0.3$;7.4±0.5 and 10.1±0.6;8.3±0.4$;8.9±0.4 in 4 mo-S, 24 mo-S and 24 mo-T groups). See figure: results in % of baseline value during reperfusion. After 30 min of reperfusion, RT (% of baseline value) is lower in 24 mo-T group (107±5* vs 137±8 in 24 mo-S group).



Conclusion: Post-ischemic recovery of contractile function and coronary perfusion is reduced in senescent heart, indicating a major vulnerability to I/R during aging. Contractile dysfunction and coronary vasoconstriction during reperfusion is fully prevented in trained senescent hearts indicating major cardioprotection by exercise training during aging.

P1012 The influence of hypercholesterolaemia and HMG-CoA reductase inhibitor on contractility of guinea pigs papillary muscle subjected to simulated ischaemia-reperfusion injury

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Aim: Effect of hypercholesterolemia and HMG-CoA inhibitors on contractility in response to ischemia-reperfusion injury remains questionable. The aim of the present study was to examine whether hypercholesterolemia and cerivastatin influence contractility of guinea pigs papillary muscle, subjected to experimental ischemia-reperfusion (IR).
Material and Methods: Animals were divided into three subgroups fed for 4 weeks with standard (StD), hypercholesterolemic (HD) and hypercholesterolemic diet with low-dose cerivastatin (HD+CE). HD (containing 0.05% cholesterol) was prepared by Research Diets, INC (NY, USA). The mean cerivastatin concentration in HD+C was 0.0005% (0.1mg/kg b. w.). Experiments were performed on right papillary muscles that were perfused with Krebs-Henseleit solution at 37 ° C±0.5°C and paced using two silver electrodes at 0.5Hz with stimulus duration 3 ms and 20% over threshold voltage. IR was achieved due to 60 minutes of hypoxia followed by 60 minutes of reoxygenation. Force of contraction (Fc), velocity of contraction (+dF/dt), velocity of relaxation (-dF/dt), time to peak (ttp) and relaxations at 10% of total amplitude (tt10) were measured during the experimental procedure. Data were compared with the use of ANOVA followed by Newman-Keuls test.
Results: The total cholesterol in HD, HD+CE and in StD was 119, 99 and 39mg/dl, respectively. Lipids concentrations were significantly higher in HD and HD+CE groups in comparison to StD group (p<0.001). The cerivastatin added to HD did not lower the lipids level in HD+CE. Baseline Fc and -dF/dt were significantly higher in HD+CE comparing to HD and StD (Fc: 1.4, 1.1 and 0.9 mN, respectively; -dF/dt: 2.2, 1.7 and 1.5 mN/s, respectively). After IR injury the Fc and +dF/dt were significantly lower in comparison to baseline values in all experimental groups (Fc: 35, 25 and 43% of the control value for HD and HD+CE and StD group, respectively; dF/dt: 41, 51 and 40% of the control value in HD, HD+C and StD group, respectively). -dF/dt was completely reversed only in HD group after IR. Baseline ratio ttp/tt10 was similar in all groups and decreased during ischemia and recovered at the end of reperfusion.
Conclusions: HD alone and HD+CE did not change the systolic function of guinea pig papillary muscle after EHR. However, recovery of diastolic function was observed only in HD group. The reason of this phenomenon remains unknown.

P1013 Angiotensin II activates NADPH oxidase in isolated rat hearts subjected to ischaemia-reperfusion

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The role of Angiotensin II in functional and metabolic alterations associated with myocardial ischaemia-reperfusion is not clearly defined and, in this respect, the implication of NADPH oxidase remains to be determined. The aim of this study was 1) to evaluate the cardiac effects of AT1 receptor stimulation in non-ischaemic conditions of perfusion or during ischaemia-reperfusion, and 2) to measure the concomitant activation of NADPH oxidase.
Isolated perfused rat hearts underwent 45 min of non-ischaemic perfusion, or 30 min of total global ischaemia followed by 30 min of reperfusion. Angiotensin II (0.1 μM) and/or the AT1 antagonist: Losartan (1 μM) were perfused during the preischaemic and postischaemic periods. Our results showed that, in non-ischaemic hearts, Angiotensin II induced rapid and prolonged vasoconstrictive and negative inotropic effects, which were antagonized by Losartan co-administration. After ischaemia, partial recovery of functional parameters was confirmed. The development of post-ischaemic heart failure was associated, in control group, with a substantial increase in the mRNA expression of AT1 (643 ± 81 vs 100 ± 17 Arbitrary Units) and AT2 receptors (293 ± 34 vs 100 ± 2 Arbitrary Units). During reperfusion, Angiotensin II administration 1) reduced the incidence of arrhythmias and the amount of lactate dehydrogenase activity released, 2) increased NADPH oxidase mRNA expression (p22phox subunit: 164 ± 24 vs 97 ± 12 Arbitrary Units in control group; gp91phox subunit: 225 ± 26 vs 94 ± 18 Arbitrary Units in control group) and NADPH oxidase activity (264 ± 14 vs 194 ± 10 Arbitrary Units/g of proteins in control group). Losartan co-administration totally antagonized these effects of Ang II.
In conclusion, our study demonstrates that ischaemia-reperfusion induces adaptative cardiac modifications which allow exogenously added Angiotensin II to stimulate myocardial NADPH oxidase through AT1 receptor activation.

P1014 Varying susceptibility to myocardial infarction among C57BL/6 of different genetic background

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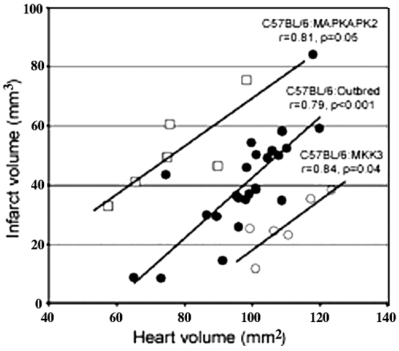
Genetically manipulated mouse lines are invaluable to investigate the effects of a single gene on sensitivity to ischemia. When choosing appropriate controls, we were concerned that intrinsic, strain-independent but colony-dependent differences may influence the susceptibility to ischemia. We therefore compared the infarct:risk volume ratio (I:R%) after 30 min global ischemia in Langendorff-perfused hearts from outbred C57BL/6 mice with that in wild-type mice derived from heterozygote x heterozygote crosses of two different in-house C57BL/6 mouse lines with targeted disruption of an MKK3 or MAPKAPK2 allele.



Despite similar hemodynamic characteristics, I:R% in outbred C57BL/6 hearts was significantly smaller (40.8 ± 2.8%) than in C57BL/6 MAPKAPK2 wild-types (65.8 ± 4.5%, p = 0.0003) and significantly larger than in C57BL/6 MKK3 wild-types (23.7 ± 2.9%, p=0.002). Therefore, inherent colony substrain dependent differences appear to influence the susceptibility to infarction in response to global ischemia, underscoring the importance of using colony matched wild-type controls in murine studies of myocardial ischemia.

P1015 Angiotensin II inhibition increases cellular glucose transport during reperfusion but not ischaemia in pig hearts

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Objective: To study whether ACE-inhibition modulates myocardial glucose uptake during ischemia and reperfusion.
Design: We developed a method for in vivo sampling of large trans-myocardial tissue samples from beating pig hearts and in vitro measurement of sarcolemmal glucose transport, in a series of experiments in which hearts were exposed to stimuli (glucose/insulin and pacing) known to promote cellular glucose transport. In the subsequent study we compared three experimental groups: 1) ACE-inhibition (ACE-I, n=6): increasing oral doses of benazepril up to 40 mg daily for three weeks, 2) Angiotensin II receptor antagonist (AT II-A, n=7): increasing oral doses of valsartan up to 320 mg for three weeks, 3) Control (n=7). Samples were harvested at baseline, following 20 minutes of regional ischemia, and following 5 and 15 minutes of reperfusion. The samples were incubated with 3-O-methylglucose (MeGlu), and cellular MeGlu uptake was measured.
Results: insulin/glucose, pacing and ischemia increased cellular MeGlu transport 2-4-fold ($p<0.001$). Sarcolemmal MeGlu transport was increased in ACE-I and AT II-A animals during reperfusion ($p<0.001$), but not at baseline or during ischemia, compared to controls.
Conclusion: Enhanced capacity for glucose transport during reperfusion may be a mechanism underlying the beneficial effects of ACE-inhibition and AT II-antagonism in ischemic heart disease.

HAS THE PROGNOSIS IN HEART FAILURE IMPROVED?

P1016 Mechanism of death in the valsartan heart failure trial

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Background: With 979 total deaths, the Valsartan Heart Failure Trial (Val-HeFT), provides one of the largest databases to examine mechanism of death with modern heart failure (HF) therapy in an international trial. Valsartan (V) added to prescribed HF therapy, reduced morbidity/mortality (m/M) by 13.2% (p=0.009) and mortality (M) was unaffected. In subgroups based on background neurohormonal (NH) therapy, those taking ACE inhibitor (ACEI) or beta blocker (BB) or neither had a favorable M trend with V. Those taking ACEI plus BB unexpectedly exhibited higher M with V than placebo (P). Distribution of mechanism of death was explored in the whole population and in the NH subgroups.
Methods: Causes of death were adjudicated by a central committee using a standardized classification system after examining all available data relating to the terminal event. Follow-up averaged 2 yrs.
Results: In the overall population (V, 2511 pts; P, 2499 pts), cardiovascular (CV) causes were 86.4% of deaths, occurring in 17.0% of V pts and 16.8% of P pts. The most frequent causes of death were sudden death (SD-53% of deaths) (9.2%, 8.5% [V vs. P, respectively]), pump failure (PF-24.8%) (4.7%, 5.0%), and myocardial infarction (MI-2.8%)(0.7%,0.4%). Non-CV accounted for 12.7% of deaths (2.7% V, 2.6% P). Table shows NH subgroup data.

Causes of Deaths in NH Subgroups, %

	ACEI-/BB-		ACEI+/BB-		ACEI-/BB+		ACEI +/BB+	
	V	P	V	P	V	P	V	P
N=	112	114	1532	1502	73	67	794	816
All-cause deaths	17.0	31.6	21.8	22.5	17.8	19.4	16.3	11.9
CV	16.1	27.2	18.4	19.6	15.1	13.4	14.6	10.4
SD*	8.0	12.3	10.7	11.9	9.6	7.5	10.3	7.4
PF	5.4	13.2	5.4	6.1	2.7	3.0	3.5	2.0
MI	1.8	0.9	0.9	0.5	0	1.5	0.3	0.1
Non-CV	0.9	4.4	3.2	2.7	2.7	4.5	1.5	1.4

*includes SD with and without premonitory worsening HF

Conclusion: In Val-HeFT, in a mild-moderate HF population, SD was the predominant mechanism of death overall and in subgroups treated with a NH blocker. ACEI or V reduced pump failure M which was further strikingly reduced by the addition of BB. Further benefit on survival would require targeting SD.

P1017 Risk of worsening renal function in patients admitted with decompensated heart failure: results of a multicentre European study

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Little is known about the frequency, causes or consequences of worsening renal function (WRF) in patients hospitalised with decompensated heart failure. We report the results of a prospective multi-centre European study designed to determine the proportion of patients who developed WRF during such hospitalisation, the risk factors for WRF, and the association with outcome.
Methods: 241 patients hospitalised with decompensated heart failure were enrolled in 16 centres in 8 countries in Europe between Oct 2001 & Nov 2002. Heart failure was defined according to the ESC criteria but recruitment was limited to those with documented systolic dysfunction (Ejection fraction $\leq$ 40% on echocardiography or other imaging). Data on patient's history, physical examination, medication use, complications, and mortality during the index hospitalisation and at 30 and 180 days were recorded. Serum creatinine and electrolytes were measured on day 1 and 3 of the index hospitalisation and then every other day up to 15 days or discharge, whichever came first. WRF was defined as an increase in serum creatinine $>$ 25 umol/l ($\sim$0.3mg/dl) during the admission.
Results: The cohort included 180 (75%) men & 61 women with a mean age of 68 yrs (95% CI 45- 91). Follow up was 92% complete to 30 days. 81 patients (34%)[95%CI: 28-40%] developed WRF during the hospitalisation. The median time to the occurrence of WRF was 4 days from admission (median length of hospital stay 9 days). Mortality in subjects with WRF was 12.4% during hospitalisation, rising to 16.0% by 30 days compared to 1.9% during hospitalisation and 4.1% by 30 days for those without WRF (p=0.001 and p= 0.004, respectively). Factors associated with WRF on univariate analysis were NYHA Class (p=0.05), a history of peripheral artery disease (p=0.03), atrial fibrillation (p= 0.05), insulin treated diabetes mellitus (p=0.07) and serum creatinine levels at admission (p= 0.007). On multivariate analysis, factors independently associated with WRF were a history of peripheral artery disease (OR 3.2 [1.3 - 8.3]), atrial fibrillation (OR 0.5 [0.2-0.9]) and serum creatinine levels at admission (a 6% [1-12%] increase in the risk of WRF for a patient with a baseline serum creatinine 10umol/l higher than another patient).
Conclusion: WRF is common in patients admitted to European hospitals with decompensated heart failure, and is associated with a substantially increased mortality. Simple clinical features can be used to identify patients at the highest risk of WRF.

P1018 Clinical prediction rule of mortality in ambulatory patients with chronic heart failure

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Background: Chronic heart failure (CHF) is associated with different mortality risks. However, there are no validated predictive rules that could be used prospectively to identify patients at higher risk.
Methods: To identify independent prognostic variables for mortality, we performed a multiple stepwise logistic regression on a prospective and multicenter registry of out-patients with CHF. The derivation set included 1341 patients (pts), with at least one year follow-up. A scoring system was created based on coefficients.Subjects from the validation set were grouped into risk categories. Observed and expected mortalities within categories were compared. Calibration of the model was evaluated with goodness of fit (GOF) test, and discrimination with ROC curve. The validation was performed with an independent prospective group of 598 pts followed for one year, through calibration and discrimination.
Results: A- Derivation set: 1) Independent variables and their scores are shown in table 1. 2) GOF: Chi2 = 3.28, p= 0.91. 3) ROC area= 0.77 (CI 95% 0.73-0.81).B- Validation set: no significant differences were found between coefficients values, and their signification tests; 5) GOF test: Chi2= 10.54, p= 0.25; 6) ROC area= 0.74, (CI 95% 0.68-0.80). Patients with a score $\leq$19 had a 4.14% mortality, compared to 42.05% in patients with a score of $\geq$40.

Observed and expected mortalities

A – Score	Observed mortality. %		Expected mortality, %
	derivation set	validation set	
0-19	4.14	5.68	3.42
20-29	8.23	9.67	8.89
30-39	19.33	19.88	19.29
$\geq$40	42.06	41.81	41.80

Variables included in the model

Variable	Scores	Variable	Scores
Age (y)	$\leq$60 = 0 60-70 = 3 >70 = 8	Ventr. arrhythmia	No = 0 Yes = 6
Diabetes	No = 0 Yes = 4	Comorbidities	No = 0 Yes = 8
BMI (kg/m^2	<24 = 7 $\geq$24 = 0	Natremia (meq/L)	<130 = 17 $\geq$130 = 0
NYHA class	I = 0 II = 6 III-IV = 11	Urea (mg %)	<45 = 0 $\geq$45 = 5
SBP (mmHg)	$\leq$110 = 7 >110 = 0	LV dysfunction	mild = 0 mod. = 4 severe = 8

Conclusion: In out-patients with CHF due to systolic or diastolic dysfunction, the GESICA risk score is a simple scheme, built on easily available clinical variables, that categorizes ambulatory patients' risk of death. This information may be useful for clinical decision making and for identifying patients who warrant more careful follow up.

P1019 Baseline predictors of adverse events with chronic valsartan therapy in symptomatic heart failure. Results from Val-HeFT trial

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Background: Valsartan (V) decreased the combined endpoint of morbidity and mortality in pts with chronic heart failure (CHF) enrolled into Val-HeFT. Despite its satisfactory tolerability (84% of V pts received the target dose of 160 mg bid vs 92% of P pts), adverse events (AE) were associated with treatment discontinuation in 249 V pts (9.9%) and in 181 (7.3%) P pts (p<0.001).
Methods: Descriptive and multivariate logistic analyses were used on the Val-HeFT database (5010 pts) to explore the existence of baseline predictors of the main AEs (hypotension, hyperkalemia, renal impairment, as reported by investigators) independent of treatment discontinuation in 5000 pts (2506 V, 2494 P; safety data were not available for 10 pts).
Results: Over a mean follow-up of 23 months, the rates of index AEs for V and P were: hypotension 13.8% vs 8.1%; hyperkalemia 6.5% vs 3.2%, renal impairment 5.4% vs 3.0% (for all: p<0.0001). Nevertheless, the outcome of pts with hypotension, the most frequent treatment-related AE was better in those on V vs those on P (e.g. combined endpoint of morbidity and mortality 42.4% in V vs 57.7% in P for pts with hypotension, p=0.015, chi-square for interaction).

Baseline independent predictors

Hypotension	OR (95% CI)	Hyperkalemia	OR (95% CI)	Renal impairment	OR (95% CI)
Valsartan	1.84 (1.53-2.21)	Valsartan	2.08 (1.58-2.75)	Valsartan	1.80 (1.34-2.40)
NYHA III-IV	1.28 (1.07-1.54)	Male sex	1.53 (1.05-2.23)	NYHA III-IV	1.51 (1.13-2.02)
DBP	0.96 (0.95-0.97)	NYHA III-IV	1.46 (1.11-1.91)	DBP	0.97 (0.96-0.99)
LVEF	0.98 (0.97-0.99)	DBP	0.95 (0.94-0.96)	Serum Cr >	
		K^+ > 5 mEq/L	1.89 (1.35-2.64)	115 umol/L	3.93 (2.87-5.37)

Independent predictors of AEs are reported in the Table. Concomitant exposure to ACEi and/or BB was not associated with an increased risk of AEs, even in univariate analysis.
Conclusions: In the context of the significant clinical benefit by V, this in depth analysis of the Val-HeFT database suggests that V is the main predictor of hypotension, hyperkalemia and renal impairment but the other independent predictors of AEs coincide with the profile of more severely ill pts. In addition, candidates for V therapy should be carefully controlled for K^+, creatinine and blood pressure.

P1020 Cardiovascular prognosis of patients with beta-thalassemia major in the current era: an 8-year (1995–2003) clinical follow-up study of young adults

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Background: Despite intense iron chelation therapy, life expectancy of patients with beta-thalassemia major (b-TM) is still limited by the occurrence of heart failure. In the present study we aimed at assessing the significance of several clinical and echocardiographic factors regarding the prognosis of cardiovascular events in Greek patients with b-TM.
Methods: The study group consisted of 131 consecutive patients with b-TM (71 males aged 21$\pm$4 yrs; 60 females aged 22$\pm$5 yrs) who were examined initially in our department during 1995. The original charts of all patients were reviewed (2003) and their current clinical status was assessed during a hospital visit, by telephone interview or by review of hospital records. Cox proportional hazards models were applied to assess the association between the investigated outcome (cardiac death or non-fatal events: congestive or subclinical heart failure, arrhythmia), and, clinical (systolic and diastolic blood pressures), echocardiographic (left and right ventricular diameter, left atrial and aortic route dimensions, left ventricular ejection fraction (EF), and diastolic mitral Doppler flow indexes), electrocardiographic (T-wave inversion in leads V1-V3, QRS abnormalities, heart rate) and laboratory (last trimester serum ferritine) factors, after controlling for age, gender, body mass index, and medication).
Results: During the 8-year follow up, 11 (16%) young men and 5 (8%) young women had a cardiac event (men vs. women, p = 0.212). The age-adjusted 8-year event rate was 16 events per 913 person-years (2%). At baseline only 6 (5%) of the patients had low EF (<50%). Cutoff point analysis revealed that EF<63% was highly associated (p < 0.01) with an adverse cardiac event in young adults with b-TM. Moreover, we observed that T-wave inversion 3-folds (hazard ratio = 3.06, 95% CI 1.1 – 8.8) the risk for an adverse event, 5-beats/min difference in heart rate is associated with 28% (hazard ratio = 1.28, 95% CI 1.03 – 1.58) higher risk for cardiac event, and decreased levels of ejection fraction are associated with 5% (hazard ratio per 1% change = 1.05, 95% CI 1.01 – 1.09) higher risk for cardiac event.
Conclusions: In young patients with b-TM, EF<63%, the presence of T-wave inversion in right precordial leads and increased heart rate, appear to confer higher risk for cardiac events.

P1021 In-hospital cause of death in patients with heart failure

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Purpose: Since 1995, the in-hospital healthcare expenditure in Italy has been based upon the so-called Diagnosis Related Groups (DRGs). The DRG 127 includes all the cases in which the main clinical diagnosis is heart failure (HF) and, therefore, it can be used to obtain data concerning such a syndrome.
The aim of the study was to analyse the in-hospital cause of death in patients (pts) hospitalised for HF in 1997 in the district of Trieste and deceased between 1997 and 2001.
Methods: From the analysis of the Data Base of "Regional Health Registry", we selected 1,010 pts hospitalised for DRG 127 in the district of Trieste during 1997. Of them, 572 (56.6%) died between 1997 and 2001; 301 (52.6%) pts, who died in-hospital, underwent autoptic examination.
Results: From the time of first hospital admission for HF, 1-, 2-, and 3-year in-hospital survival was 92, 80, 68, and 56%. Of 301 pts who underwent autoptic examination (117 males, median age 82 years; 184 females, median age 85 years), 263 (87.4%) pts (99 males, 164 females) died from cardiac causes, 30 (10%) from various types of cancer and 8 (2.7%) for other causes. One hundred and eighty-three (69.6%) pts had ischemic heart disease (IHD) (104 (56.8%) with previous myocardial infarction (MI), 64 (35%) with total occlusion of 2 of 3 coronary vessels), 85 (32.3%) pts had hypertensive (HHD) and 49 (18.6%) valvular heart disease (VHD). Two hundred and five (77.9%) out of 263 pts dying from cardiac causes had multifactorial disease etiology, especially among pts with more advanced age. The most frequent intermediate causes of death were acute pulmonary disease (n=139, 46.2%), acute MI (n=53, 17.6%), or worsening decompensation of other heart disease (n=33, 11%). Refractory HF (n=173, 57.5%), cardiogenic shock (n=45, 15%), and thromboembolic events (n=37, 12.3%) resulted to be the main final causes of death while an arrhythmia related death was documented in 30 pts (10%).
Conclusions: In HF pts, the most important predisposing factor to death appears to be the ischemic etiology of the disease frequently with a previous MI. A concomitant acute pulmonary disease represents a precipitating factor in about 50% of cases. Among hospitalised pts, most cases die for worsening HF, while only a minority for arrhythmic causes.

P1022 A prospective registry of patients hospitalized for worsening heart failure: observations from the IMPACT-HF registry

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Background: Hospitalizations for decompensated heart failure (HF) occur frequently with over 3 million patients admitted annually in the United States (US). A similar rate of HF hospitalization is observed in Europe. The IMPACT-HF registry was designed to collect observational data in patients hospitalized for worsening HF.
Methods: The IMPACT-HF registry was conducted concurrently with the IMPACT-HF study, a randomized trial of in-hospital initiation of carvedilol compared to the standard practice of post discharge beta-blocker initiation. The primary objective of the IMPACT-HF study was to determine if in-hospital initiation was associated with a higher rate of beta-blocker use at 60 days after randomization. Patients were eligible for registry enrollment if they were admitted with a primary or secondary diagnosis of HF regardless of ejection fraction. There were no exclusions to participation. Data describing clinical history, demographics, medications, symptoms, and clinical outcomes at 60 days were captured.
Results: The characteristics of the registry population (n=567) are shown in teh table. The majority of admissions were due to progressive volume overload; only 1% were attributed to low cardiac output. The 60 day rate of re-hospitalization or death was 31%.
Conclusions: The IMPACT-HF registry enrolled elderly patients admitted for worsening HF primarily due to progressive volume overload. Despite the use of evidence based therapies, the 60 day rate of death or re-hospitalization remains alarmingly high. These data demonstrate the urgent need to identify new treatments for this population to decrease the morbidity and mortality associated with decompensated HF.

	n=567
Mean (SD) age (years)	71 (12)
% Men	52
% Caucasian	82
Mean (SD) LVEF (%)	36 (17)
% Ischemic Etiology	59
% ACEI or ARB at discharge	72
% Digoxin at discharge	41
% Beta-blocker at discharge	62

P1023 Has the natural course of heart failure finally improved?

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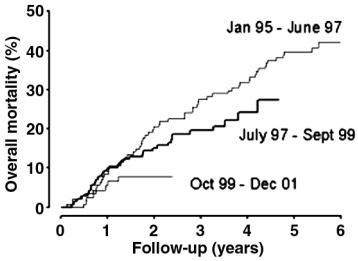
Background: The use of recommended drugs for chronic heart failure is discouragingly low in clinical practice. We studied the implementation of heart failure drug titration (mainly ACE-inhibitors and beta-blockers) regarding tolerability and survival in the setting of a nurse directed outpatient heart failure clinic.
Methods: Data on patients referred to the clinic for drug titration, 1995-2001 (n=454), were entered in a database. The type and doses of treatment, as well as clinical and laboratory data were registered. The outcome of titration was assessed, and all patients were followed regarding overall mortality until February 2002.



Survival during different periods.

Results: A high percentage of all patients was discharged with an ACE-inhibitor (during 2001, 88%). The use of beta-blockers increased significantly during the observation (from 43 to 88%). Patients started on treatment continued with an ACE-inhibitor in 89%, and in 95% when started on a beta-blocker. There was a significant improvement in temporal survival, constituting a reduction in mortality of 15% per year (95% confidence interval 3 to 26%), p=0.016 (Figure). In a multivariate Cox regression analysis, overall survival was significantly associated with renal function, ejection fraction, the use of beta-blockers and ACE-inhibitors, and negatively with NYHA-class and the use of digitalis.
Conclusions: Drugs for heart failure treatment could successfully be introduced in the setting of a nurse directed outpatient clinic. A high degree of treatment with beta-blockers and ACE-inhibitors was associated with a striking increase in survival during the observation period, reducing two-year mortality from 21 to 8%.

P1024 2-year prognosis of 1346 patients with heart failure, scheduled for guideline-based treatment

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The prognosis of patients (P) with heart failure has been shown to improve in controlled studies with ACE inhibitors and/or beta blockers. The extent to which treatment guidelines isussed by professional organisations are implementable in daily clinical practice is unknown, as are the effects on prognosis and mortality predictors.
Methods: 1346 consecutive patients (64 $\pm$10 years, 27% women) with an ejection fraction (EF) $<$ 45% (mean EF 36,3$\pm$6%) were enrolled in the study (between 1/98 and 12/00). The etiology of the cardiomyopathy was ischemic in 77%, valvular in 6,5% and due to other causes in 16,5% of the cases. 15,5% of the patients had atrial fibrillation. During inpatient rehabilitation resting ECG, exercise testing, Holter monitoring with heart rate (HR) variability, echocardiogram to determine LV diameter, LV filling (E/A), mitral insufficiency and pulmonary hypertension, and a 6-minute walk-test were performed. The drug therapy was noted at the time of discharge. The patients were followed for 731 days.
Results: 89/10% of the patients received ACE inhibitors/AT1-blockers, 82% beta blockers, 8% amiodarone, 57% diuretics, and 35% digitalis. Overall mortality was 11%, cardiac mortality was 6%. Significant differences were observed in sinus rhythm (85,3% survivors vs. 68,4% nonsurvivors), number of VES/h (140 vs. 205), heart rate variability (SDANN 71,2 vs. 65,7), systolic diameter on 2 D-echo (LVSD 47,7 vs. 51,5mm), E/A in the transmitral flow pattern (1,46 vs. 1,79), maximum exercise capacity (76,3 vs. 57,9W) and 6-minute walk test (375 vs. 302m). Statins and BMI (kg/m^2) did not differ. Multivariate analysis showed that age, pulmonal hypertension, atrial fibrillation, mitral insufficieny, higher NYHA grade, necessity of diuretics and digitalis, a short distance in the 6-minute walk test, and low exercise capacity were associated with a significantly higher mortality.
Conclusion: Guideline-based therapy could be established in approximately 90% of patients with heart failure and was associated with improved prognosis. While physical fitness was beneficial for the prognosis, symptomatic therapy was related to poorer outcome.

P1025 Mortality of patients in the UK community with left-ventricular systolic dysfunction and heart failure due to other causes

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Purpose: Heart failure and left ventricular systolic dysfunction (LVSD) are common and important conditions. Some indication of the prognosis of sufferers in the era of modern therapy is available from recent large therapeutic trials, but it is not known how well such studies represent patients in the wider community, who are often older and have more concomitant illnesses.
Methods: Over a 4 year period (1995 to 1999), the ECHOES (Echocardiographic Heart of England Screening) study established the prevalence of left ventricular systolic dysfunction (LVSD) and symptomatic heart failure due to this and other causes, in 3960 subjects aged 45 and older chosen at random from the community in the West Midlands region of England. Participants underwent clinical assessment and echocardiography. Treatment with an ACE Inhibitor was recommended for all those with an LV ejection fraction (EF) of <40%. Mortality data are now available for all participants, a minimum of 3 years from the initial assessment.
Results: Of the 3749 from the population sample who had normal LV function (EF, >50%), survival at 3 years was 97%. Survival at 1 year of the 72 with definite impairment of LV function (EF <40%) was 92%, and at 3 years 86%, with 92% 3 year survival for the 139 with borderline function (EF 40-50%). 3 year survival in those with EF <40% was slightly worse (82%) in those who were symptomatic with dyspnoea than those with asymptomatic LVSD (88%). Those with the syndrome of heart failure (symptoms plus objective evidence of cardiac dysfunction) had a similar prognosis whether the main cause was LVSD (82%) or other causes (atrial fibrillation or valve disease, 85%).
Conclusions: The prognosis of those with LVSD and heart failure in the wider community is not as poor as some previous studies have suggested. This may reflect the widespread use of ACE Inhibitor therapy. Further improvement might be expected as beta-blocker use becomes more widespread. The prognosis of those with asymptomatic LVSD is considerably worse than the general population and identification by echocardiographic screening of those at risk should be considered.

HOW TO PROPERLY IDENTIFY A HEART FAILURE PATIENT

P1026 Individual symptoms and signs of heart failure. The Reykjavík study

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Background: The definition of heart failure has been inconsistent in various epidemiologic studies. The purpose of this study was to examine the prevalence of individual manifestations of heart failure and their independent effects on cardiovascular mortality in a large population-based cohort study.
Methods: A general population sample of 9328 men and 10062 women aged 33-85 at entry was followed for 7-29 years. In addition to a questionnaire, physical examination and blood tests, a chest X-ray was obtained and cardiomegaly defined as a relative heart size exceeding 550 ml/m^2 in men and 500 ml/m^2 in women. By Cox multivariate regression analysis those signs, symptoms and X-ray features of heart failure independently predicting cardiovascular mortality were calculated and their age-dependent prevalence determined.
Results: The prevalence of exertional dyspnea ranged from 9,6 in the youngest age group of men (33-39 years) to 27,9 in the oldest (70-85). For women the corresponding numbers were 16,9-31,4. The prevalence range for cardiomegaly was 1,7-17,5 in men and 1,0-11,8 in women.

	Prevalence	RR	Confidence interval	p
Men				
Exertional dyspnea	13.5	1.75	1.60-1.01	<0.0001
Diuretics	1.23	1.72	1.32-2.24	0.0001
Digitalis	1.51	1.81	1.45-2.27	<0.0001
Edema	0.2	2.01	1.23-3.21	0.014
Cardiomegaly	6.67	1.40	1.23-1.58	<0.0001
Women				
Exertional dyspnea	20.9	1.53	1.38-1.69	<0.0001
Diuretics	6.1	1.32	1.12-1.56	0.001
Rales	0.7	2.06	1.37-3.09	0.0005
Rhonchi	1.9	1.59	1.23-2.06	0.0004
Cardiomegaly	5.2	1.37	1.54-1.61	0.0002

Conclusion: Individual manifestations of heart failure independently predicting cardiovascular mortality could be detected. Exertional dyspnea was the most common manifestation in both sexes with cardiomegaly and use of heart failure drugs also statistially significant predictors of cardiovascular mortality.

P1027 SHAPE (study of heart failure awareness and perception in Europe): a pan-European general public survey on awareness and perception of the clinical, social and economic importance of heart failure

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Background: Appropriate heart failure (HF) care and adequate resourcing of HF treatment and research require recognition of its clinical, social and economic importance by the general public and by health care authorities and providers. It is conceivable that HF is in unknown by the general public and its severity considered less important than well known diseases such as cancer. SHAPE is the first study aimed at documenting community awareness and perception of HF in Europe.
Methods: 7,958 subjects were randomly selected from 9 countries (France, Germany, Italy, Netherlands, Poland, Romania, Spain, Sweden and UK) on the basis of gender, age (25-45 and 65-85 years, respectively) and urban versus rural domicile (minimum 100/group/country). Each subject completed a 32-question survey covering recognition, impact on health, comparative prevalence and severity, treatment and costs.
Results: Although 86% of respondents claimed to have heard of HF, only 3% could correctly identify HF after a description of typical symptoms and signs ("a condition causing breathlessness, tiredness and swollen ankles"), whereas 31% identified a description of angina and 51% a TIA/stroke. Only 29% thought HF signs and symptoms as a "severe" complaint. Whereas, following an explanation of HF, most respondents expected that modern drugs can improve well-being and prognosis of HF patients (76% and 73%, respectively), most respondents also thought HF patients should live quietly and reduce all physical activity. As regards etiology, 34% thought HF was a normal consequence of ageing. Only 40% believed that quality of life was more affected by HF, closely followed by diabetes and arthritis. When asked to compare cancer to HF, the majority thought that cancer was more common and 67% thought HF patients lived longer (versus 17% who thought cancer patients lived longer). 82% thought that HF was more common than HIV infection and 66% thought survival was better in HF than in HIV (whereas 21% thought HIV patients lived longer). As regards the economic consequences of HF, only 9% of the population believed that HF leads to greater health care expenditure than cancer (40%), HIV (27%) and diabetes (11%). Overall, the responses were comparable between countries.
Conclusion: In Europe, community awareness and perception of heart failure is low. Under these conditions, the general public is unlikely to demand appropriate measures by health care authorities and providers. Strategies to better educate the public about the importance of HF are needed and could lead to better funding of HF health care and research.

P1028 Heart failure acute precipitants: frequence and prognostic value

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Background: Factors that acutely precipitate heart failure are well known and include non-cardiac causes(non-compliance to prescribed drug or adverse drug interaction and effects, alcohol abuse, renal dysfunction, infection, pulmonary embolism, thyroid dysfunction, anaemia) and cardiac causes(arrhythmias, appearance or worsening of valve regurgitation, myocardial ischaemia, excessive preload reduction). It is generally assumed that an episode of heart failure with a discernible worsening cause has a better prognosis than one without it. However few reports have systematically studied worsening causes frequence and prognostic value. Aim of this work is to study heart failure precipitants and to verify their prognostic value.
Methods: From January 2000 to June 2002 clinical records of all consecutive cases of heart failure admitted to our Cardiology Department were studied. We performed a complete follow-up recording all major adverse events (including all causes death, heart failure and myocardial infarction).
Results: A total of 300 episodes of heart failure occurred in 217 patients(67.4 $\pm$ 11.7 years, 65.3% males, 50% of cases with ischemic cardiomyopathy, mean ejection fraction 33.5 $\pm$ 8.0%).
A precipitating cause was identified in 169 out of 300 cases(56.3%): 39 cases(13.0%) with a non-cardiac precipitant and 130 cases(43.3%) with a cardiac precipitant. We recorded myocardial ischaemia in 80 out of 300 cases(26.7%), atrial fibrillation in 22 cases(7.3%), other supraventricular or ventricular arrhythmias in 17 cases(5.7%), infection in 14 cases(4.7%), drug interaction or therapy compliance problems in 14 cases(4.7%), anaemia in 9 cases(3.0%), appearance or worsening of valve regurgitation in 7 cases(2.3%), bradycardia in 3 cases(1.0%), alcohol abuse in 2 cases(0.7%) and thyroid dysfunction in 1 cases(0.3%). Prompt recognition of heart failure precipitants was very useful for correct management of the episode. After a mean follow-up of 18 months patients with a non-cardiac precipitant had a longer survival without major adverse events than patients with a cardiac precipitant or patients without precipitating factors(respectively 17.8 $\pm$ 9.6 months vs 13.6 $\pm$ 9.7 months vs 14.2 $\pm$ 9.4 months; for all $p<0.05$).
Conclusions: A worsening cause of heart failure is very frequent. Its detection is very important for optimal treatment of the episode. Moreover precipitants early recognition and a correct patient education could be useful to prevent further exacerbations. Patients with a non-cardiac precipitant has a better short-term prognosis than other patients.

P1029 The digital stethoscope: transforming a historic art into a reproducible technique

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Background: Auscultation was one of the first approaches for the diagnosis of heart disease. Although very valuable in the hands of the experienced, its value has been steadily declining due to problems of training that led to poor accuracy and reproducibility in the non-experienced. However, its universal availability, low cost and ease of repeated examinations argue for a revival of this historic art. We hypothesized that performance of auscultation with a digital stethoscope that allows electronic storing in the patient chart, comparing and analyzing findings objectively would improve diagnostic accuracy as well as interobserver variability of auscultation.
Methods: 100 nonselected patients underwent heart auscultation with a conventional stethoscope and a novel electronic stethoscope by two clinicians. Auscultation findings corresponding to current practice were taken from the clinical exam sheet at admission. Echocardiograms were performed on all patients within one day to assess diagnostic accuracy. Digital auscultation findings were stored on the hospital network for ready access. Digitized data were read by three independent observers. Comparisons were done by chi-square tests and ANOVA.
Results: We found that storing and interpreting data from digital auscultation is feasible without prolonging the clinical exam. Digital auscultation improved the interobserver concordance (F 10.2, $p<0.0001$ vs. F 7.7, p 0.0007 for systolic murmurs). Intraobserver agreement of the two methods was 75%. Sensitivity for relevant valve pathologies was unchanged with digital auscultation. Interobserver agreement on systolic murmurs in digital auscultation was high (85-89% and 73-78% in patients with and without relevant valve disease), as well as sensitivity for detecting relevant valve disease (70-80% depending on the examinator). Similar results were found for splitting of the 2nd and presence of a 3rd heart sound.
Conclusion: The digital stethoscope is a new instrument in the hands of the clinician that has the potential to revive the historic art of cardiac auscultation by rendering it more objective and more reproducible. It allows reliable monitoring of auscultation changes over time and objective reporting of findings. The didactic value of reviewing auscultation findings and the potential for quality improvement of the clinical exam is of great promise in an era of cost constraints and declining clinical judgment.

P1030 Clinical assessment of pulmonary congestion using estimates of gas exchange parameters

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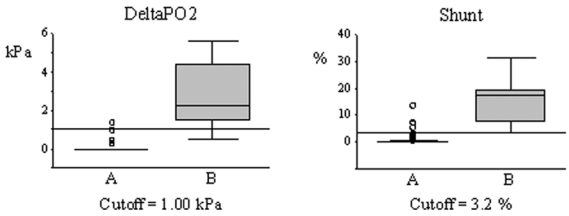
Purpose: Assessment of pulmonary congestion is part of the evaluation in heart failure and involves X-ray and clinical examination. These methods are semi-quantitative and insufficient. The aim of this pilot study is to evaluate the possible use of a new clinical method to quantify pulmonary congestion using gas exchange parameters.
Methods: Eleven patients (74years, 46years - 81years; median, range) with pulmonary congestion on X-ray and 51 healthy volunteers (48years, 20years - 75years) were examined using the Automatic Lung Parameter Estimator (ALPE). The subjects were breathing spontaneously while the inspiratory oxygen fraction was changed giving an arterial blood saturation (SpO2) within 90% to 100% measured by pulse oximetry. The ALPE-system estimated the subjects pulmonary shunt and ventilation/perfusion-mismatch (DeltaPO2) from the obtained relation between the expired oxygen fraction and SpO2 and a mathematical model on oxygen transport.
Results: The DeltaPO2 and shunt were higher ($p < 0.001$) in patients with pulmonary congestion compared to healthy volunteers (Fig 1). Replicate measurements in 11 healthy volunteers showed a good reproducibility with small numerical differences in DeltaPO2 (0.00kPa, 0.00kPa - 0.63kPa) and shunt (0.0%, 0.0% - 2.1%). The sensitivity and specificity for pulmonary congestion were 91% and 98% for DeltaPO2 (cut-off = 1.00kPa) and 100% and 90% for shunt (cut-off = 3.2%) when compared with chest X-ray.



ALPE-estimates of ventilation/perfusion-mismatch (left) and shunt (right) in 51 healthy volunteers (A) and 11 patients with pulmonary congestion (B)

Conclusions: The results of this pilot study suggest that it might be possible to quantify pulmonary congestion by non-invasive estimation of gas-exchange parameters. The ALPE-method is reproducible, sensitive and specific. The method might be a tool to improve treatment in heart failure.

P1031 Mediastinal lymphadenopathy in congestive heart failure: a sequential computer tomography evaluation

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Aim: To evaluate the frequency and evolution of mediastinal lymphadenopathy associated with congestive left heart failure on computed tomography (CT) scans in correlation with clinical and echocardiographic findings.
Materials and methods: 31 consecutive patients with acute left heart failure underwent a clinical evaluation using the NYHA class, a transthoracic echocardiography and a CT examination at the time of initial presentation (T1). Within 8 days after initiation of medical treatment (T2), follow-up CT scans were obtained with a clinical evaluation.
Results: At T1, patients showed severe (NYHA III: n=12 (39%); NYHA IV: n=12 (39%)) to moderate (NYHA I: n=1 (3%); NYHA II: n=6 (19%)) dyspnea with a mean ejection fraction of 39%. On initial CT scans, enlarged mediastinal lymph nodes were seen in 14 patients (45%) with blurred contours in 5 patients (16%) and hazy mediastinal fat in 1 patient (3%). Significant decrease in the size of mediastinal lymph nodes was observed between T1 and T2 (T1: n=14; 45% vs T2: n=10; 32%; $p<0,01$) with a concurrent decrease in the severity of dyspnea (NYHA class III-IV at T1: n=24;78% vs NYHA class I-II at T2: n=26;83.5%). Patients with enlarged lymph nodes at T1 showed: i) a significantly lower ejection fraction than those without lymphadenopathy (mean $\pm$ SD value: 33 $\pm$ 12.6% vs 45 $\pm$ 14.8%; p=0.03); ii) a larger diameter of the right superior pulmonary vein (mean $\pm$ SD value: 16 $\pm$ 2.9mm vs 14 $\pm$ 4mm; p=0.09); iii) a higher frequency of abnormal peribronchovascular thickening (n=5 vs n=1; p=0.06) and increased lung attenuation (n=13 vs n=11; p=0.09).
Conclusion: This pilot trial emphasize the frequency of mediastinal lymphadenopathy in patients with left heart failure (identified in 45%). From a practical standpoint, follow-up CT scanning should be considered after initiation of adequate treatment in order to search for their regression, identified in 69% of those patients with enlarged lymph nodes at T1 in the present study. Awareness of such anomalies and their changes over time should lead to avoid mediastinoscopy at first intention, and to demonstrate noninvasively their cardiogenic origin on sequential CT scan examinations

P1032 Stress echocardiography is an insensitive test to diagnose coronary artery disease in patients with chest pain

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Aim: To assess the sensitivity (Se), specificity (Sp), positive (PPV) and negative (NPV) predictive values and positive (LR+) and negative (LR-) likelihood ratios of stress echocardiography to diagnose significant coronary artery disease in patients referred for the evaluation of chest pain avoiding the verification bias.
Methods: We evaluated 279 consecutive patients between november 2001 and september 2002 submitted to our echo laboratory for symptoms suggestive of coronary artery disease. An exercise echocardiogram was performed to 89.6%, dypiridamole-echo to 8.6% and dobutamine/atropine-echo to 1.8% of our patients. A stress echo was considered to be demonstrative of myocardial ischemia when at least 2 adjacent myocardial segments worsened their contractility during the test. Coronary disease was defined as present if there was 1 or more vessels with at least 50% luminal diameter narrowing on the coronary angiogram.
Results: The mean age was 64$\pm$11 years, 43% females. The distribution of the risk factors for coronary heart disease was: arterial hypertension 48%, diabetes mellitus 18%, hypercholesterolemia 50%, current smokers 20%, early familiar history of ischemic heart disease 14%. Twenty-nine percent were hospitalised and in 26% the cardiologist considered the chest pain as "typical". Sixty-eight percent reached the submaximal heart rate (exercise-echo and dobutamine/atropine-echo) and 16% were taking beta-blockers 48 hours before the test. Forty-six (17%) patients were submitted to the cardiac catheterization laboratory, 62% of those who had a positive stress echo and 6% of those who had a negative stress echo (verification bias, $P<0,0001$). In this subset of patients (biased sample), the Se was 82%, Sp was 54%, PPV=82% and NPV=54% with LR+=1.8 and LR-=3.0. Using the 2 reported methods for debiasing the results, we calculated a Se=30%, Sp=92% (Begg and Greenes method) and Se=32%,Sp=94% (Diamond method). LR+=3.8 and LR-=1.3 for both methods.
Conclusions: The sensitivity of stress echocardiography to detect significant coronary artery disease in patients referred for the evaluation of chest pain is low avoiding the verification bias. However, the specificity is very high and the positive predictive power is higher than the negative predictive power.

P1033 A more effective algorithm using brain-type natriuretic peptide for the diagnosis of congestive heart failure in acute dyspnea

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Background B-type natriuretic peptide is a neurohormone synthesized predominantly in ventricular myocardium as a result of increased wall tension, and has proven to be very valuable in the etiologic diagnosis of acute dyspnea. The purpose of this analysis was to increase its predictive value.
Methods: The "Breathing Not Properly Multinational Study" included a total of 1586 patients who came to the emergency department with acute dyspnea and whose B-type natriuretic peptide was measured with a bedside assay. The clinical diagnosis of congestive heart failure was determined by two independant cardiologists who where blinded to the results of the BNP assay.
Results: The mean age was 64 years. The final diagnosis was CHF in 744 pts, no CHF but LV dysfunction in 72 pts, no CHF in 770 pts. A cutoff of 100 microgrammes per milliliter was proposed (sensibility = 88%, specificity = 75%, likelihood ratio (LR) + = 3,6). In multiple logistic regression analysis, 3 independant factors appeared to predict which patients had dyspnea related to CHF: history of CHF, BNP level and diuretic treatment.
Conclusion: We propose a more effective diagnostic algorithm with different B-type natriuretic peptide cutoff (sensibility 90%, specificity 84%, LR + = 5,6).

P1034 Do changes in the incidence of heart failure contribute to the heart failure epidemic?

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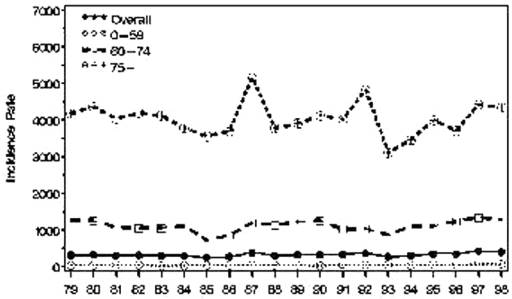
Heart failure (HF) has been designated as an emerging epidemic with undisputed clinical and public health importance. The reported increased hospitalization for HF might be due to prolonged survival, more resource utilization or higher incidence of HF. Yet, little is known on the incidence of HF and its secular trends in the population. This study was undertaken to test the hypothesis that the incidence of HF in Olmsted County, MN increased between 1979 and 1998. All in- and outpatient first clinical diagnoses of HF were assembled using the Medical Index system (which does not rely on billing), maintained by the Rochester Epidemiology Project. The graph shows overall and age- specific 20-year trends in the incidence of first diagnosis of HF. The incidence rates per 100,000 in age strata 0-59, 60-74 and $>$75 years are 51, 1117, and 4032 respectively. Using Poisson regression, men and women aged 0 to 59 had a 26% and 20% increase, respectively, in the relative risk (RR, 95 CI) in 1993-1998 compared to 1979-1986 (men: 1.26; 1.11-1.43. women: 1.20; 1.02-1.34). For persons age 75 years or older, the incidence of HF decreased over time in men (RR 0.90, 0.82-0.99) and women (RR 0.86, 0.79-0.94).



Thus, while HF is more frequent in older individuals, its incidence increased over time among younger persons. However, these data do not evoke an overall increase in the incidence of HF implying that the HF epidemic cannot be fully explained by increased HF incidence.

EXERCISE TESTING IN HEART FAILURE

P1035 Critical appraisal of the prognostic value of the VE/VCO$_2$ slope in chronic heart failure

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Introduction: The slope of increase of ventilation relative to carbon dioxide production (VE/VCO2) has been shown to have a high prognostic value in patients with chronic heart failure (CHF). However, there is no consensus on how to calculate it, as the relation between VE and VCO2 becomes non-linear near the end of exercise, when ventilation is driven both by CO2 output and by decrease in plasma pH. **Methods:** Ninety seven CHF patients with ejection fraction<45% (mean 27±9%), in NYHA class II-IV underwent cardiopulmonary exercise test. VE/VCO2 slope was assessed by linear regression using all the data points (Sl), using only points before the non-linear part of the curve (Sli) and using only the first 3 minute data (Sl3min). Peak oxygen uptake (VO2), circulatory power (VO2 x systolic arterial pressure) were also assessed. Death and transplantation were the end-points considered (mean follow-up 22 months). **Results:** Mean value of VE/VCO2 overall slope (Sl) was 39.3±11.6 (22-78). In 64% of the patients, two distinct slopes could be found: an initial, linear slope (Sli: 31.8±7.5, 18-62) and a final (Slf), steeper slope (48.6±15.7, 24-101). Patients in whom no rupture of slope was observed were sicker. There was a relation between Sli and Sl slopes (r=0.915, p<10-4) and between Sl and Sl3min slopes (r=0.808, p<10-4). VE/VCO2 slope (Sl) correlated with peak VO2 (r=0.55, p<10-4) and peak circulatory power (r=0.49, p<10-4). Univariate analysis showed that the prognostic value of VE/VCO2 Sl (Chi2 25.4, p<10-4) was greater than Sli (Chi2 22.8 p<10-4), Sl3min (Chi2 14.6, p<10-4) or Slf (Chi2 6.7, p=0.009). By multivariate analysis, the peak circulatory power had slightly greater pronostic value (Chi2 5.6 p=0.02) than the VE/VCO2 overall slope (Sl) (Chi2 2.27, p<0.07). **Conclusion:** The VE/VCO2 slope should be computed from all the data points to have its highest prognostic value. Peak circulatory power has similar prognostic value.

P1036 Oxygen uptake kinetics faithfully reflect the presence and extent of left-ventricular dysfunction in dilated cardiomyopathy patients with preserved functional capacity

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Peak VO2 measured at exercise testing with respiratory gas analysis is poorly correlated with left ventricular ejection fraction (LVEF). In practice, some of patients with LV dysfunction exhibit normal or near-normal peak VO2, however, parameters indicative of VO2 kinetics (DVO2/DWR = an increase in VO2 to work rate increment, VO2 Recovery half-time; HT) may be impaired in those patients, especially when LV dysfunction is severe. Since these parameters may be affected by aging, we determined normal ranges in controls, and then examined the above hypothesis. **Methods:** Among 237 consecutive patients with mild to severe heart failure due to dilated cardiomyopathy (DCM) who underwent symptom-limited exercise (upright bicycle, ramp protocol), we selected 77 patients with preserved peak VO2 ≥70%. According to LVEF, patients were divided into Group-1 (30<LVEF≤45%, 38 ± 4%, n=39) and Group-2 (LVEF≤30%, 24 ± 5%, n=38). Normal 203 subjects (%Peak VO2>=75%) served to determine the age-related changes in DVO2/DWR and HT. **Results:** In normals, both DVO2/DWR and HT significantly correlated with age (r=-0.35, r=0.47, respectively). When we defined normal limits as the range where 95% of normal fell, a reduction of 25% or greater in DVO2/DWR and a prolongation of 13% or greater in HT were considered abnormal. By these criteria, patients with DCM but with preserved functional capacity (peak VO2 = 80 ± 9%) often showed abnormal VO2 kinetics: attenuated DVO2/DWR in 27% and prolonged HT in 35%. Furthermore, these abnormalities were more frequently found in Group-2 than in Group-1: DVO2/DWR(40 vs. 15%, p=0.018) and HT(47 vs. 23%, p=0.026). **Conclusion:** Abnormal VO2 kinetics are often seen in DCM patients, even when functional capacity (peak VO2) is preserved. These indices may faithfully reflect the presence and extent of LV dysfunction.

P1037 Combined analysis of VE/VCO$_2$ slope and slow periodic oxygen uptake oscillations accurately predicts future cardiac events in patients with dilated cardiomyopathy

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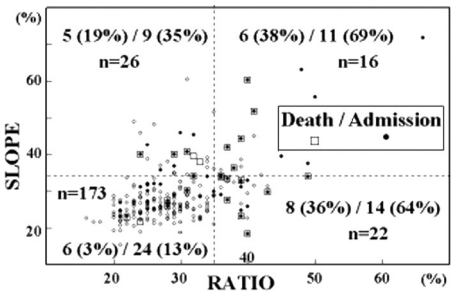
Although an elevated VE/VCO2 slope (SLOPE) during exercise provides important information in predicting prognosis in patients with heart failure (HF), its power is not necessarily sufficient. To improve the predictability of prognosis, we concomitantly analyzed SLOPE with slow periodic oscillations in VO2 (OSC) often observed in severe HF, and then evaluated its performance.
Methods: We analyzed VO2 data during symptom-limited exercise testing with respiratory gas analysis in 237 consecutive DCM patients (LVEF = 30±11%). Since we have no available method for quantifying OSC, we estimated low-frequency (LF) components of VO2 measured during testing. LF (0.5-1.25 cycle/min) and total power were computed by FFT (4-min time-window, overlapping every 30sec), yielding RATIO (LF power/total power). According to the cut-off values of SLOPE (=34) and RATIO (=35), determined by the comparison between patients and 188 controls, patients were divided into 4 groups. Long-term follow-up was performed.
Results: During 40±18 months, 58 hospital admissions for HF and 25 cardiac deaths occurred. When both SLOPE and RATIO were normal, event rates were markedly low (death 3%, admission 13%). A subgroup with abnormal levels of both parameters had high event rates (death 38%, admission 69%), which were similar to those in a subgroup with normal SLOPE but with abnormal RATIO (death 36%, admission 64%).



Events rate.

Conclusion: Combined analysis of VE/VCO2 slope and slow VO2 oscillation quantified by computing low-frequency components may serve to accurately predict cardiac events in DCM patients.

P1038 Ventilatory response to exercise and recovery oxygen kinetics are similar in cardiac transplant recipients and patients with mild chronic heart failure

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Background: Exercise capacity is a widely used and accepted criterion for the selection of patients for heart transplantation. However, exercise capacity does not return to normal after cardiac transplantation. The purpose of our study was to evaluate the ventilatory response to exercise and recovery oxygen kinetics in cardiac transplant recipients and compare them with those measured in healthy subjects and in patients with mild or severe heart failure (HF).
Methods: Cardiopulmonary exercise treadmill testing was performed in 18 endstage HF patients (Group 1), 12 patients in mild HF, matched for peak oxygen consumption (pVO2) (Group 2), 12 cardiac transplant recipients (Group 3) and 12 healthy subjects (Group 4). pVO2, O2 consumption at the anaerobic threshold (AT), the first degree slope of O2 consumption decline during early recovery (VO2/t), carbon dioxide output (VCO2), ventilation (VE), the slopes VE/VCO2 and VE/VO2, the time required for a 50% fall from pVO2 (T1/2VO2) and the difference in the heart rate between peak exercise and 1st min of recovery (dHR), were measured.
Results: The results are summarized in the table. * p<0,05 vs Group 1, @ p<0,05 vs Group 1, & p<0,05 vs Group 2, # p<0,05 vs Group 4, % p<0,05 vs Group 1, ^ p<0,05 vs Group 2.

Effects of exercise testing

	Group 1 (severe HF)	Group 2 (mild HF)	Group 3 (transplant recipients)	Group 4 (normal subjects)	F/p
pVO2 (ml/kg/min)	9,4 ± 0,9	17,3 ± 4,8*	18,5 ± 5,7@#	28,4 ± 6,9%^	37,9/<0,001
AT (ml/kg/min)	6,7 ± 1,8	14,5 ± 5,5*	13,8 ± 4,8@#	19,8 ± 4,5%^	15,9/<0,001
VO2/t (l/min/min)	0,33 ± 0,21	0,60 ± 0,32	0,61 ± 0,21#	1,04 ± 0,39%^	12,5/<0,001
T1/2VO2 (min)	2,36 ± 1,06	1,28 ± 0,39*	1,45 ± 0,3@	1,03 ± 0,18%	11,4/<0,001
VEmax (l/min)	43 ± 19	57 ± 14	63 ± 16@	79 ± 21%^	9,1/<0,001
VE/VCO2	39,2 ± 9,9	34,8 ± 8,5	31,4 ± 3,8@	23,6 ± 2,7%^	11,0/<0,001
VE/VO2	29,1 ± 14,7	26,1 ± 4,9	26,7 ± 4,9	17,2 ± 5,0%	4,0/<0,013
dHR (bpm)	16 ± 10	20 ± 10	5 ± 9@&#	27 ± 7%	12,8/<0,001

Conclusion: Heart transplant recipients, despite their improvement in exercise tolerance, continue to have impairment of the ventilatory response and recovery oxygen kinetics, similar to those observed in patients with mild HF.

P1039 Changes in oxygen uptake oscillations after 3-month concurrent therapy with beta-blocker and exercise training in patients with heart failure

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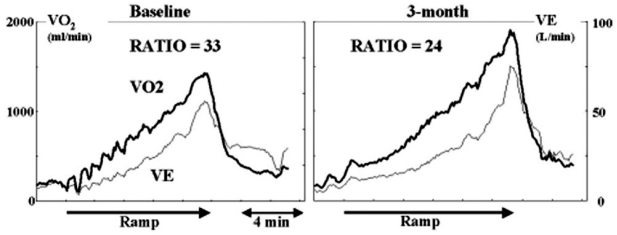
Although periodic oscillations of respiratory parameters during exercise have important clinical and prognostic implications, how the short- to mid-term improvement in the status of heart failure by medical therapy affects oscillations (OSC) remains poorly understood. We examined this issue in patients with heart failure (HF) treated with the 3-month concurrent therapy with beta-blocker administration and exercise training.
Methods: We analyzed VO2 during symptom-limited exercise testing (bicycle, ramp) in 28 HF patients (LVEF<40%) before and after the 3-month concurrent therapy with beta-blocker and exercise training. Since we have no available method for quantifying OSC, VO2 oscillations were quantified by power spectrum (PS) analysis with FFT (4-min window, serially shifting every 30 sec), yielding the relative ratio (RATIO) of low-frequency VO2 PS (0.5-1.25 cycle/min) to total VO2 PS.
Results: Peak VO2 significantly increased (1207 ± 423 to 1374 ± 532 ml/min, p <0.001), while RATIO remained unchanged (32 ± 7 to 30 ± 8%, NS). When patients were divided into 2 groups according to the increase in peak VO2 (≥15% in 16, <15% in 12), RATIO was significantly attenuated only in a subgroup with an increase ≥15% (30 ± 8 to 27 ± 7%, p <0.02).



A representative case.

Conclusion: Despite a significant improvement in peak VO2 after 3-month therapy, VO2 oscillations did not significantly changed. Significant attenuation in VO2 oscillations was observed only in a subgroup with an apparent increase in peak VO2 (≥15%).

P1040 Chronic beta-blocker therapy: effects on exercise left-ventricular function and cardiopulmonary exercise capacity in patients with chronic heart failure

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Beta receptor blocking agents belong to evidence based therapy in patients with chronic heart failure (CHF). For better understanding of the effects of beta blocker therapy on left ventricular function and cardiopulmonary exercise capacity in patients with CHF we performed echocardiographic left ventricular function analysis at rest and during dynamic exercise and treadmill spiroergometry.
28 patients (NYHA class II–IV) were investigated before and after 12 months of double-blind randomized treatment with bisoprolol, carvedilol or metoprolol. Digital echo image loops were acquired at rest and during exercise at 20 Watts and at 15 Watt levels above 20 Watts. Storage and off-line analysis was performed by means of the software package EchoPac 6.3.4™ (General Electric Vingmed). The digital image loops acquired at rest and at levels of 20%, 80% and 100% of maximum exercise capacity (MEC) were analyzed by an experienced and blinded echocardiographer by means of manual boarder detection. The biplane Simpson method was used to calculate left ventricular systolic and diastolic volumes.
Results:

	Before treatment	After treatment	p
RQ at identical exercise level	0.97	0.91	.013
Max. output [Watt]	105	125	n.s.
LVEF at rest [%]	31	34	n.s.
LVEF at 20% MEC [%]	33	39	.007
LVEF at 80% MEC [%]	34	38	.021
LVEF at 100% MEC [%]	32	39	.002

Chronic betablocker therapy improves cardiac function during exercise in patients with chronic heart failure. Significant improvement of left ventricular ejection fraction during mild, submaximal and maximal exercise could be shown. The significant decrease of the respiratory quotient during identical exercise before and after treatment with beta blockers shows the improvement of the circulatory system during exercise. After therapy the patients were able to reach the same exercise level under more favourable metabolic conditions than before beta blocker treatment.

P1041 Mild anemia as an indicator of functional impairment and worsened functional capacity in patients with chronic heart failure

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Anemia is well known to be associated with functional impairment due to abnormalities in O2 transport. Recent reports have suggested that mild to moderate anemia is a prevalent condition in chronic heart failure (CHF). This study was designed to evaluate the relationship between anemia and exercise capacity, and to investigate whether anemia is associated with functional impairment, worsened functional capacity, and worsened heart failure in CHF patients.
Method: Thirty-eight clinically stable patients admitted to our hospital for congestive heart failure and LV systolic dysfunction were enrolled in this study. Cardiopulmonary exercise testing (CPX) was performed using a ramp protocol. The levels of hemoglobin, noradrenaline (NA), and brain natriuretic peptide (BNP) were measured. Patients were divided into three groups based on the obesity index (OI=body mass index/22): body wasting (BW n=8) OI<0.95, normal body weight (NB n=18) 0.96<OI<1.10, and overweight (OB n=12) OI>1.11. The levels of hemoglobin, NA, and BNP were measured for reevaluation 3 months after the initial test.
Results: There were no significant differences among the three groups in the peak VO2, VE/VCO2 slope, or hemoglobin level. In the overall study population, the hemoglobin level was significantly correlated with the body weight (r=0.37), obesity index (r=0.41), peak VO2 (r=0.35) and VE/VCO2 slope (r=-0.29). In patients with body wasting, the hemoglobin level was significantly correlated with the obesity index (r=0.47), peak VO2 (r=0.76), VE/VCO2 slope (r=-0.62), and BNP (r=0.41). The hemoglobin level in the overweight group was not correlated with any parameters.
The change in the hemoglobin from the initial evaluation to the second evaluation was correlated with the changes in the peak VO2 (r=0.42), VE/VCO2 slope (r=-0.46), and NA (r=-0.63).
Conclusion: In CHF patients with body wasting, hemoglobin levels may play an important role in the development of functional impairment and aggravated severity, in spite of the mild anemia. Hemoglobin levels are associated with functional impairment, worsened functional capacity, and neurohormonal abnormalities in CHF patients These results suggest that CHF patients with mild to moderately low hemoglobin levels can expect to develop neurohormonal abnormalities and worsened functional capacity, conditions that contribute to the process of severe chronic heart failure.

P1042 Influence of exercise on arterial distensibility in congestive heart failure

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Introduction: Patients with congestive heart failure (CHF) have limited exercise capacity because of depressed left ventricular (LV) function. Arterial distensibility is inversely correlated to pulse wave velocity (PWV), and plays an important role in determining LV function because increased arterial stiffness leads to greater cardiac workload.
Aim: The aim of the study was to evaluate the response of arterial distensibility on exercise in patients with CHF vs normal subjects.
Material and Methods: The study population consisted of 20 patients with CHF (NYHA II-III) and 8 normal subjects. Normals were comparable to CHF patients according to age and gender. Treadmill exercise test was performed. PWV was assessed before the test and up to 10 minutes after exercise using a computer system COMPLIOR-Colson. For automatic measurements of PWV pressure waveforms were digitized at rate 500 Hz for carotid – femoral distance.
Results: During exercise systolic blood pressure (SBP) increased by 20% in CHF group and by 40% in normals, p<0,05) Initial PWV was higher in CHF group (10,4 ± 0,8 m/s) than in normals (8,0 ± 0,6 m/s), p<0,05. After exercise the significant changes of PWV were observed. In normals PWV decreased to 7,0 ± 0,4 m/s. In contrast, CHF patients presented with significant increase of PWV (11,8 ± 0,7 m/s). The possible explanation of observed results could be an endothelial dysfunction in patients with CHF.
Conclusions: 1. Exercise provokes the decrease of arterial distensibility in patients with CHF in contrast to normal subjects. 2. Postexercise decrease of arterial distensibility could affect cardiac function in patients with CHF.

P1043 Oscillatory changes of oxygen uptake during exercise in cardiomyopathy: relationship with clinical status

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Oscillatory changes of the parameters of gas exchange during exercise, have been reported in patients (pts) with congestive heart failure and have been ascribed to hemodynamic dysfunction. The aim of the present study was to analyse if this phenomenon is also observed in pts with cardiomyopathy (CMP).
Patients: 14 children with CMP (7 dilated CMP: DCMP, and 7 hypertrophic CMP: HCMP) were selected for this study. The pts were compared to 29 normal controls (Nl) of the same age range, and 8 pts with a ventricular septal defect (VSD).
Methods: All pts underwent exercise testing on a treadmill. Gas exchange was measured breath-by-breath by mass spectrometry. Variability of VO2 was determined as the difference between all single breaths during one minute and the mean of those breaths, expressed as a percentage of the mean value for VO2 during that minute.
Results: The oscillatory changes in VO2 (difference individual breaths-mean value for VO2 for each exercise level) were significantly ($P<0.05$) higher in pts with DCMP compared to nl, HCMP and VSD. In pts with DCMP, the highest variability for VO2 (exceeding the 95% CL of normal) was found in pts with the lowest value for fractional shortening determined on echo (15-17%).

Oscillations for VO2 during exercise

Patients	N	Age	2%	4%	6%	8%
DCMP	7	9.6 ± 3.6	11.8 ± 8.3*	11.1 ± 5.4*	9.5 ± 4.2*	7.6 ± 2.5*
HCMP	7	11.4 ± 3.3	6.5 ± 2.6	6.7 ± 1.8	5.7 ± 2.1	5.1 ± 1.0
VSD	8	12.1 ± 2.4	7.7 ± 1.6	6.4 ± 1.2	6.3 ± 1.5	5.6 ± 1.0
NL	29	10.4 ± 2.9	7.1 ± 2.0	6.2 ± 2.0	6.3 ± 2.7	5.4 ± 1.8

Values (mean ± SD) represent oscillations of VO2 (single breaths- mean value for VO2) for each level of exercise, expressed as % of mean value for VO2 for each level of exercise. 0%, 2%,4%,6% indicate inclination of treadmill. * $P<0.05$: DCMP vs NL.

Conclusion: Increased oscillatory changes of VO2 during exercise in DCMP correlate with hemodynamic dysfunction of the left ventricle and suggest inadequate oxygen delivery to the exercising tissues.

P1044 Attaining energy equilibrium in proxies assessing human bioenergetics

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Purpose: During the last two decades human bioenergetics have been largely assessed by means of cardiorespiratory fitness field tests. The validity and accuracy of such protocols is questionable, however, when the exercise mode used in each field protocol does not closely simulate the movement patterns utilized when bioenergetics are evaluated in laboratory conditions. When designing proxies assessing human bioenergetics scientists should be aware of the energetic specificity factor. The purpose of this study was to investigate on the bioenergetics of the 15m Square Shuttle Run Test (15mSST), a novel field test designed to predict treadmill maximal oxygen intake (VO2max) values and compare it to that of the classic 20m Multistage Shuttle Run Test (20mMST) and a treadmill test (TT) in the laboratory.
Methods: A repeated-measures randomized block design required 45 male volunteers to perform within a 20-day period three VO2max assessments using a TT, the 20mMST, and the 15mSST. Workload throughout all tests was identically regulated according to the classic 20mMST protocol. During testing VO2max and total oxygen deficit (O2def) were recorded via a portable gas analyzer, maximum heart rate (HRmax) was recorded via telemetry, and peak blood lactate concentration (PLac) was obtained 5 minutes after each assessment. Data were also obtained from knee flexion and extension isokinetic dynamometry at 60 and 120 d°/sec.
Results: The 20mMST demonstrated lower correlations with TT VO2max compared to 15mSST ($r=0.931$, $p<0.001$ vs $r=0.681$, $p<0.05$). Unlike between TT and 15mSST ($p>0.05$), significant bias was detected between the mean VO2max values from TT and 20mMST ($p<0.05$) using repeated measures ANOVA. The '95% limits of agreement' analyses indicated 20mMST to have a wider range of error in predicting VO2max (±6.51 ml/kg/min) than the 15mSST (±2.9 ml/kg/min). Mean PLac and O2def from the 20mMST were found to be significantly elevated comparing with TT whereas the equivalent values from TT and 15mSST were not significantly different ($p>0.05$). The mean HRmax recorded during 15mSST and 20mMST was significantly elevated ($p<0.05$) compared to that of TT. No significant relationship was detected between the examined strength variables and performance in any of the VO2max protocols.
Conclusions: It is concluded that the novel 15mSST is a valid and reliable test and it is generally a more efficacious proxy in predicting VO2max compared to the classic 20mMST.

EXERCISE TESTING IN HEART FAILURE, TRAINING AND OUTCOMES

P1045 ExTraMATCH: exercise training meta analysis of trails in chronic heart failure patients. Effects on mortality and hospitalization in different subgroups

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Objectives: To determine the effects of exercise training programme on mortality and hospitalisaton among heart failure (HF) patients and left ventricular dysfunction in pre-specified subgroups, namely male versus female sex, NYHA functional class I-II vs. III-IV, ischaemic versus non-ischaemic aetiology, age, peak O2 uptake (peakVO2<15 vs. >15ml/kg/min), left ventricular ejection fraction (LVEF<27 vs. >27%), and training programme duration (<28 vs. >28 weeks). **Review methods:** Randomised trials of an exercise training programme versus control in patients with chronic HF and LV dysfunction, from which results were available before December 2000, were identified from Medline, search of abstracts of presentations at international congresses, examination of reference lists. Only the original individual patient data-sets of trials constituted the data source. **Results** Nine data-sets satisfying the entry criteria were identified, including 801 patients. In the patients with ischaemic aetiology the training programme reduced the combined endpoint (OR 0.49, 95% CI: 0.34-0.70, $p<0.05$), but not in those with non-ischaemic aetiology. There were significant benefits on survival and reduced hospitalisation from exercise training only in the male sex (OR 0.64, 95% CI 0.47-0.87) and in those patients with more severe HF as categorised by NYHA class III or IV (OR 0.48, 95% CI 0.32-0.72), by LVEF< 27% (OR 0.58, 95% CI 0.39-0.85) or by peakVO2<15 ml/kg/min (OR 0.54, 95% CI 0.37-0.78) ($p<0.05$). Only training programmes lasting >28 weeks reduced the combined endpoint of mortality and hospitalisation (OR 0.53, 95% CI: 0.36-0.77, $p<0.05$).
Conclusions: Exercise training affect hospitalisations and survival in HF patients. Significant larger benefits in patients with poorer functional status, more depressed exercise tolerance and impaired heart function are evident.

P1046 Which exercise training intensity is better for dilated cardiomyopathy patients concerning functional and muscle oxidative capacity: low or high? A prospective randomized study

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Background: Exercise training improves functional capacity in chronic heart failure(CHF). However, there are concerns regarding what exercise training intensity is better for CHF patients(pts). **Methods:** 31 men, 54 ± 2 yrs (mean ± se), with non-ischemic dilated cardiomyopathy, class II-III, LVEF 28 ± 1%, peak oxygen consumption(VO2)= 17.43 ± 0.55 mL/kg/min randomized into 3 groups: low intensity exercise training (LO) - 9 pts, high intensity exercise training (HI) - 11 pts, and control (CO) - 10 pts, under optimal medical treatment. At baseline and at 6 months, all pts underwent maximal treadmill cardiopulmonary exercise testing, six minutes walking test,rest and peak exercise type B natriuretic peptide (BNP),rest echocardiography (echo), skeletal muscle biopsy and quality of life score (QLS). Low intensity training was prescribed using the heart rate corresponding to that immediately below the anaerobic threshold (67 ± 3% of peak VO2) and HI using the HR immediately below the respiratory compensation point (88 ± 2% of peak VO2). **Results:** Significant differences from baseline are in the table (* = $p < 0.05$, ** = $p < 0.01$). Oxidative enzymes increased similarly in HI and LO but not in CO. Cardiac function and dimensions by Echo did not change in any group. **Conclusions:** HI and LO enhanced maximal and submaximal exercise capacity and muscle oxidative enzymes. Only LO improved respiratory efficiency and QLS and reduced rest and peak exercise BNP levels. LO program is efficacious and would be stimulated in dilated cardiomyopathy.

Variables before and after training

Variables	HI - Before/After	LO - Before/After	CO - Before/After
Peak VO2 - mL/kg/min	18.2±0.5/21.8±1.4*	15.9±1.2/20.4±1.2**	18.0±1.0/18.6±1.4
Peak VO2/HR mL/beat	8.8±0.6/9.9±0.6	8.8±1.1/11.1±1.3*	9.9±0.9/10.4±1.2
Peak VE/VO2	56.2±7.1/50.5±3.3	56.2±7.0/43.9±2.8*	56.8±4.7/51.1±-5.1
Peak VE/VCO2	45.4±2.8/43.5±2.6	49.4±4.0/40.2±2.0*	50.9±3.4/45.7±3.9
Peak VD/VT	0.28±.02/0.24±.01	0.28±.02/0.23±.01**	0.26±.02/0.25±.02
6 min. Walking - meters	470±20/570±18**	503±24/557±22**	503±23/512±16
Rest BNP - pg/mL	491±146/315±123	451±112/176±37*	494±91/338±105
Peak BNP - pg/mL	525±/135/327±110	599±122/255±50*	643±110/406±116
QLS - Minnesota	413.±8.8/26.2±8.9	43.7±7.9/24.8±7.4**	38.3±8.3/36.5±6.8

Peak = Peak exercise, VO2/HR = oxygen pulse, VD/VT = Dead space/tidal volume ratio.

P1047 Continuous training maintains positive cardiopulmonary effects of a cardiac rehabilitation programme in patients with chronic heart failure

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Purpose: Rehabilitation of patients with Chronic Heart Failure (CHF) is one thing. Maintaining their achieved physical performance is another. Many advices have been given to keep up the positive cardiopulmonary effects of such a programme. To determine what kind of advice should be given after being rehabilitated, different methods should be compared.
Method: We therefore trained 40 patients with stable CHF for 6 months in a combined endurance-resistance training programme. At the end of this programme patients were randomly assigned either to continue in this Trained (T) group or given a Home Trained (HT) programme, others were advised not to train at all and were considered as Untrained (UT) the last group was asked to maintain their physical fitness by themselves and were considered as Self-trained (ST). During rehabilitation all four groups were evaluated at baseline, at 4 and at 6 months. After rehabilitation they were evaluated every 3 months. Evaluation was done by cardiopulmonary exercise testing on treadmill, assessment of biometric and linear isokinetic(LIK) measurements. Patients in T group where closely monitored in a supervised programme the HT group by monthly controlled home-monitoring.
Results: Three months after rehabilitation we found that UT patients lost 6% of their Peak Oxygen Consumption (PeakVO2) while T and HT groups didn't change significantly. ST group gained 20% of Peak VO2. Maximal Workload went down with 15% in UT group en did not change significantly in T, HT and ST groups. All groups had a higher Ventilatory Response during maximal exercise test. LIK measurements did not change in T, HT and ST groups. In the UT group LIK measurements such as Maximal Isokinetic Force (-12%) and Mean Explosive Force (-6%) decreased significantly.
Conclusion: Patients with stable CHF, trained in a 6 month cardiac rehabilitation programme, lose almost 15% of all cardiopulmonary, biometrical and LIK benefits they gained within three months if they don't maintain regular physical exercise. Therefore maintenance of physical fitness is crucial.

P1048 A randomized study of the effects of physical training in chronic heart failure

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Supervised physical training has proved to be safe and beneficial for patients after myocardial infarction and following coronary bypass surgery. This type of rehabilitation has been practiced for many years in Iceland in these particular groups of patients. Until recently, physical training has not been considered to be useful or safe in patients with chronic heart failure (CHF). The aim of this study was to evaluate the efficacy of physical group training in patients with CHF
Methods: Patients with CHF (NYHA class II and III, age 50-71 years, mean 67 years, 75% male) were randomized to either a control group (n=20), that continued regular treatment and lifestyle, or a training group (n=21), that in addition to regular treatment attended supervised exercise classes two times a week (50 min.) for five months. Initial measurements included exercise testing on bicycle with maximal oxygen uptake (V02max), six minute walk test, spirometry, muscular strength test (1RM), analysis of plasma ANP and BNP, 2-D echocardiography with evaluation of left ventricular ejection fraction (LVEF) and quality of life questionnaire. All these measurements were repeated after five months. Each exercise class consisted of warm up exercises, bicycle training, weight training, breathing exercises, muscle stretch and relaxation.
Results: No training related adverse events were reported. Within group changes between baseline and five months were compared between the two groups. Significant improvement was found in the six minute walk test (+37.1 meters vs. +5.3 meters, $p<0.01$), work load on the exercise test (+6.1 watts vs. 2.1 watts, $p<0.05$) and quadriceps muscle strength (+2.8 kg vs. +0.2 kg, $p<0.01$) in the training group compared to the control group. Quality of life factors that reflect exercise tolerance and general health improved significantly in the training group compared to the control group. No significant changes were found between groups for the other parameters.
Conclusion: The training programme used in this study improved physical capacity, submaximal exercise tolerance and some aspects of quality of life in patients with CHF but did not significantly affect V02max, LVEF, plasma ANP, BNP or respiratory function.

P1049 Physical exercise training in patients with end-stage chronic heart failure: effects on exercise capacity and left-ventricular function

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Randomized trials showed that exercise training represents a safe and effective adjuvant therapy to improve physical work capacity and hemodynamic parameters in patients (pts) with stable chronic heart failure (CHF) and moderate symptoms. It remains unclear, whether pts in a more advanced stage of CHF (NYHA III-IIIb) also benefit from a training intervention. Aim of the present study is, therefore, to evaluate the impact of an individually tailored exercise training on maximal oxygen uptake (VO2max), left ventricular ejection fraction (LVEF) and end-diastolic diameter (LVEDD) in pts with severe CHF fulfilling the inclusion criteria of the COPERNICUS trial.
Methods: Eighteen male pts with CHF (NYHA III-IIIb) were randomized either into a training group (4-6 times bycicle ergometer training per day) or an inactive control group. At begin and after 6 months all pts performed a symptom-limited spiroergometry to determine VO2max and maximal exercise time. LVEF and LVEDD were assessed by echocardiography.
Results: After 6 months, pts in the training group showed a significant improvement of VO2max by 24% (from 16.3±1.6 mL/min/kg at begin to 21.5±1.2 mL/min/kg after 6 months, $p<0.05$ vs. controls), whereas VO2max remained unchanged in control pts (14.8±2.4 vs. 16.3±2.5 mL/min/kg) In the exercise training group LVEF increased by 16% (from 27±2% at begin to 32±4% after 6 months, $p<0.05$ vs. controls) compared to no change in control pts (24±2% vs. 24±3%). Exercise training led to a reduction of LVEDD by -8% (-7±3 mm) and remained unchanged in controls (+3%, +2±3 mm).
Conclusion: These data suggest that a carefully designed aerobic exercise training in pts with end-stage heart failure fulfilling the inclusion criteria of the COPERNICUS trial is not only associated with an increase of functional work capacity but also with a small but significant improvement of cardiac function.

P1050 Exercise training in women with chronic heart failure and its influence on clinical parameters and quality of life

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Introduction: There is now evidence that moderate training plays an important role in the treatment of chronic heart failure (CHF). But little is known about how such training programs should be carried out for women. The aim of our study was to assess the outcome of a training program and its influence on quality of life for women.
Methods: Women with stable chronic heart failure took part in a 4-week training program including muscle strength training, bicycle ergometer and the six-minute walk test as a training unit. Quality of life was measured using the German Version of the Short Form-36 questionnaire (SF-36). Women were studied before (T1) and at the end (T2) of the training program.
Baseline data: 46 women, mean age: 70±9 years, cause of CHF: coronary heart disease (n=29, 63%), valvular heart disease (n=6, 13%), non-ischemic heart disease (n=11, 24%), LVEF: 32±9%, LVED Volume: 103±38ml and VO2max: 9.6±3.5 ml/kg.
Results: see table.

	T1	T2	p-value
LVEF (%)	32±9	39±10	p=.001
LVED (ml)	103±38	96±30	p=.01
VO2max (ml/kg)	9.6±3.5	11±4.5	p=.05
Work load (Watt)	45±21	50±20	p=.001
Physical summary scale (SF-36)	31±9	40±8	p=.001
Psychological summary scale (SF-36)	49±11	54±8	p=.01

Conclusion: Our results show that a standardized training program is beneficial for women, improving clinical parameters and quality of life.

P1051 The effect of physical training on exercise capacity and left-ventricular function (estimated by magnetic resonance) in patients with congestive heart failure: preliminary report

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Physical training is an accepted method of treatment in congestive heart failure (CHF). There are some controversies concerning the influence of physical training on left ventricular (LV) function. The aim of this study was to assess the effect of 6-month physical training with progressively increasing workload on exercise capacity and LV function in patients with CHF.

Material and methods: 28 patients with ischemic CHF, NYHA II and III class, EF $\leq$ 35% and a duration of CHF 2.4$\pm$1.5 years, receiving standard pharmacotherapy. Patients were randomized into 2 groups: A (trained - 14 patients) and B (not trained - 14 patients). Groups were comparable in terms of age, sex, duration and severity of CHF. Physical training was conducted at the rehabilitation center 3 times a week, 60 minutes daily. At the start and after 6 months cardiopulmonary exercise test (Sensor Medics Vmax 29C-2130 spirometr system) and magnetic resonance (Magneton Vision Plus Siemens with use of Leonardo Workstation Siemens Argus Software) of the heart with estimation of LV parameters were performed in both groups. At baseline analyzed parameters of exercise tolerance and LV function were comparable in both groups. Until now control examinations were done for 16 patients (8 from group A and 8 from group B). After 6 months we observed in group A (trained) a marked increase of exercise capacity: VO2peak was 14.4$\pm$2.8ml/kg/min (at baseline) and 19.1$\pm$3.6ml/kg/min (after 6 months); VCO2/VE 38.8$\pm$3.6 vs 34.5$\pm$4.1 l/min; duration of exercise 370.8$\pm$45.0 vs 690$\pm$85.6sek; maximum workload 3.5$\pm$1.0 vs 6.2$\pm$1.4 MET respectively. All these changes were statistically significant. In trained group a slight tendency to improvement of LV function was observed: ejection fraction increased from 28.9$\pm$5.6% to 31.2$\pm$6.8%, LV end-diastolic volume decreased from 198$\pm$43 to 184$\pm$55ml and LV end-systolic volume from 123$\pm$34ml to 116$\pm$28ml, but these changes were not statistically significant. In group B (not trained) both exercise tolerance and LV function parameters have not changed during this study.

Conclusions: Physical training with progressively increasing workload has a positive influence on exercise capacity and LV function (tendency to improvement) in patients with ischemic CHF.

P1052 The use of cytokine parameters tp evaluate the severity of chronic heart failure

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Some investigators have recently reported that measurements of proinflammatory cytokines such as tumor necrosis factor-alpha soluble receptors (TNFR-1 and TNFR-2) are useful to evaluate the severity of heart failure. This study was designed to evaluate the relationship between cytokine levels and classical prognostic parameters.

Method: Forty-five clinically stable patients with chronic heart failure (CHF) were enrolled in this study. All patients underwent cardiopulmonary testing (CPX) using an ergometer with a ramp protocol. Plasma concentrations of brain natriuretic peptide (BNP), noradrenaline (NA), TNFR-1, and TNFR-2 were measured prior to CPX. Left ventricular ejection fraction (EF) and left ventricular diameter at diastole (LVDd) were measured by an echocardiogram. Patients were divided into three groups by the obesity index (OI=body mass index/22): body wasting (BW n=11) OI$<$0.95, normal body weight (NB n=24) 0.96$<$OI$<$1.10, and overweight (OB n=20) OI$>$1.11. Three months later, CPX and blood sampling were performed once more for reevaluation.

Results: In the patients of the BW group, TNFR-1 was related to NA (r=0.52), BNP (r=0.59), peak VO2 (r=0.84), VE/VCO2 slope (r=0.66), LVDd (r=0.72), and EF (r=0.63), and TNFR-2 was related to peak VO2, VE/VCO2 slope, LVDd, and EF. In the OW group, TNFR-1 was not significantly correlated with any clinical prognostic variables other than BNP (r=0.48). TNFR-2 showed similar correlations with all clinical prognostic variables in the OW group. The change in BNP during three months follow up period was correlated with the change in EF (r=0.53), but not with the changes in peak VO2, VE/VCO2 slope, and NA. In contrast, the change in TNFR-1 during three months was correlated with the changes in peak VO2 (r=0.47) and VE/VCO2 slope (r=0.48), but not with the changes in EF and BNP. The results for TNFR-2 were similar to those for TNFR-1.

Conclusion: Proinflammatory cytokines were related to clinical prognostic variables in the patients with body wasting, but not in the overweight patients. And the change in cytokine abnormalities may be associated with the change in functional capacity rather than the change of EF. These results suggest that the proinflammatory cytokines provide important prognostic information only in patients with body wasting associated with cardiac cachexia and/or severe heart failure.

P1053 Elevated C-reactive protein predicts reduced exercise capacity in patients undergoing diagnostic treadmill exercise testing

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Introduction: Maximal exercise workload (Mets) predicts late cardiovascular events in pts referred for diagnostic stress testing. Measurement of high sensitivity C-reactive protein (CRP), a marker of underlying inflammatory activity, identifies pts with a predisposition for future coronary events. The relation of CRP to exercise performance in this population has not been examined.

Patients and Methods: High sensitivity CRP was measured (Roche particle enhanced immunoturbidimetric assay) in 288 non-hospitalized pts undergoing diagnostic, symptom limited, treadmill stress testing. Student's t-test was used to compare Mets for upper and lower quartiles of CRP (QCRP)distribution. Correlation of a positive stress test ($>$1mm horizontal or downsloping ST segment depression) with upper and lower QCRP was examined (2x2 table). Multiple logistic regression was performed to determine independent predictive value of QCRP for stress test outcome.

Results: A significant inverse correlation was found between QCRP and Mets (p=0.001), and between QCRP and maximal heart rate (HRmax)(Table). Neither positive stress test nor ischemic threshold (HR at 1 mm ST depression (HR1mmST)) correlated with QCRP (Table). In multiple linear regression models correcting for age, diabetes mellitus, hypertension, smoking and body mass index, high CRP remained a significant predictor of reduced exercise workload and of lower HRmax (Table) but did not predict an ischemic stress test.

Exercise Performance and CRP Quartiles

CRP correlates	Age	HRmax*	Workload (Mets)	DP#	HR1ST	GXT+ve
Lower qtl CRP	58.6 $\pm$ 12.5	150 $\pm$ 22	9.6 $\pm$ 3.6	27.2 $\pm$ 6.3	142 $\pm$ 21	31 (41%)
Upper qtl CRP	59.3 $\pm$ 11.1	143 $\pm$ 21	7.7 $\pm$ 2.9	26.5 $\pm$ 5.6	134 $\pm$ 22	24 (33%)
p (univariate)	0.73	0.04	0.001	0.54	0.2	0.32
p (multivariate)	-	0.015	0.0001	-	-	-

*maximal heart rate attained; #Double product(HRmax x maximal systolic BP)/1000

Conclusions: In a non-hospitalized population referred for diagnostic treadmill stress testing 1. High CRP was an independent correlate of lower estimated exercise workload (Mets) and lower maximal heart rate. 2. CRP did not predict ischemic stress test or ischemic threshold.

DILATED CARDIOMYOPATHY: BACKGROUND

P1054 Association of myocardial adrenergic denervation to elevated proinflammatory cytokines levels in heart failure, secondary to idiopathic dilated cardiomyopathy

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Purpose: Experimental studies showed that cytokine production might be regulated in part, by sympathetic nervous system (SNS) stimulation of cardiac beta-adrenergic receptors. The cardiac fixation of 123-MetalodoBenzylGuanidine (MIBG) has the potential to mirror the whole myocardial adrenergic pathway disintegrity, while heart rate variability (HRV) is thought to measure autonomic nervous system activity. In CHF, the cardiac response to sympathetic stimulation is impaired and this may contribute to elevated levels of circulating cytokines. We evaluated the relationship between MIBG cardiac uptake and HRV with circulating levels of proinflammatory cytokines in patients(pts) with idiopathic dilated cardiomyopathy(IDC).
Methods: Fifty one pts, mean age 54±11,3 y, with angiographically proven IDC, functional NYHA class II-III, with Left Ventricular ejection fraction (LVEF) 31,1 ± 8,1%, and twenty age-matched normal (N) individuals were studied with planar MIBG. Early (10 min) and late (4 hours) heart to mediastinum MIBG uptake ratio and washout was calculated. Circulating plasma levels of Interleukin-1(IL-1), Interleukin-6(IL-6),TNF-a and its soluble receptors sTNFr1 and sTNFr2 were measured by Elisa method while 24 hours rhythm recording performed and HRV parametres assessed in all patients. None of study pts were on beta-blockers or suffered from diabetes mellitus.
Results: The IDC pts group had significantly reduced values in MIBG uptake at 10 min (1,6±1.15 vs 1,91±0,08, $p<0,001$) and 4 hrs(1,48±0,17 vs 1,84±0,12, $p<0,001$) and increased WO (7±4%vs3±3%, $p<0,005$) compared to control group. Late MIBG uptake was correlated with NYHA class (r=-0.42, p=0.02), LVEF (r=0.34, p=0.01), LV systolic wall stress (r=-0.40, p=0.05), IL-1 (r=-0.55, $p<0.001$), TNF-a (r=-0.33, p=0.02) and sTNFr2 (r=-0.44, p=0.001). Multivariate regression analysis revealed that MIBG at 4 hours was independently associated with IL-1 levels (p=0,01). Additionally IL-6 was correlated with SDDNind (r=-0,658, $p<0,001$) and RMSSD (r=0,658, $p<0,001$) both indexes of autonomic nerve activation.
Conclusions: Cardiac sympathetic innervation is related to proinflammatory cytokines levels in IDC, suggesting that the reduced myocardial innervation, in addition to its cardiovascular consequences, has a potential inflammatory effect via modulation of the production of multiple inflammatory mediators. The association of IL-6 to autonomic nervous activation suggests its mainly peripheral production in these patients.

P1055 Cardiac peroxisome proliferation-activated receptor alpha expression in patients with dilated cardiomyopathy

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PPARalpha is a central regulator of myocardial fatty acid and glucose metabolism implicated in the pathogenesis of heart failure. Hypertrophic cardiomyopathy is associated with decreased cardiac PPARalpha activity resulting in reduced fatty acid- and increased glucose-uptake/utilization, whereas a converse regulation is seen in the diabetic heart. The role/activity of PPARalpha in other types of cardiomyopathy, particularly in humans, is mostly unknown.
We studied PPARalpha expression levels in left ventricular biopsies from patients with dilated cardiomyopathy (DCM, n=16) and control subjects (n=19). PPARalpha mRNA was quantitated using real-time sybr green PCR. Target gene mRNA was related to the stably expressed GAPDH mRNA from the same sample. Tissue samples from DCM patients were obtained at orthotopic heart transplantation, and the control group was composed from donor hearts which were not used for logistic reasons. Mean left ventricular ejection fraction (LVEF) in the DCM group was 19.8 ± 6.5%. The control group had normal systolic cardiac function, and no cardiac history. Left ventricular PPARalpha mRNA level were significantly increased compared to the control group (1.3 ± 0.1-fold vs. control, $p<0.01$). No correlation between cardiac PPARalpha mRNA levels and age/LVEF was observed.
Elevated cardiac PPARalpha level may result in increased fatty acid metabolism for cardiac energy production in DCM, suggesting a specific cardiac metabolic programm in DCM compared to other types of cardiomyopathy.

P1056 Accumulation of a bradykinin type-2 receptor promoter polymorphism in human end-stage heart failure

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Objectives - To study the presence of a -58T/C promoter polymorphism in the bradykinin type-2 receptor (BK-2R) gene in human end-stage heart failure. Background- Accumulating work in experimental animals suggests that bradykinin (BK) exerts cardioprotective effects through specific BK-2Rs. We have recently shown that, in human end-stage heart failure, the number of BK-2Rs is significantly downregulated. However, nothing is presently known about the mechanisms involved. Methods- Human heart tissue was obtained from excised hearts of patients undergoing cardiac transplantation (n=15) or from normal hearts (n=12) unsuitable for donation. The patients had heart failure due to idiopathic dilated cardiomyopathy (IDC; n=8) or to coronary heart disease (CHD; n=7). The presence of a -58T/C polymorphism in the BK-2R gene was analyzed in both normal and failing left ventricles by means of SSCP. Results- Here we show that in normal hearts BK-2R expression increases with age. In IDC hearts, the BK-2R expression also increases with age, but the relative increase is significantly lower as compared to normal hearts. Using SSCP analysis, we found that the homozygous form of the C-allele of the -58T/C promoter polymorphism, previously linked to a reduced BK-2R expression and to hypertension, is accumulated (75%) in the IDC hearts, but not in the CHD hearts. Conclusions- The present results suggest that the C-allele of the -58T/C promoter polymorphism may be involved in the progression of heart failure in IDC patients.

P1057 Role of polymorphisms in the beta1-adrenergic receptor in susceptibility to idiopathic dilated cardiomyopathy

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Beta-adrenergic signal transduction is markedly altered in idiopathic dilated cardiomyopathy (DCM). Genetically based changes in beta-adrenergic receptors (beta-AR) may favour the occurrence of the disease by altering receptor function. Considering the beta1-AR predominance in the myocardium, we assessed whether the known functionally relevant beta1-AR are associated with an increased likelihood of developing DCM.
A total of 165 consecutive unrelated patients (pts) (49±14 years, 125 males, NYHA functional class 1.8±0.7) with DCM (WHO criteria) and 203 unrelated controls, coming from the same geographic area, were included in an association study. Allele and genotype frequency distributions of the Ser49Gly and Arg389Gly polymorphisms in the beta1-AR were compared between pts and controls. For purposes of comparison, we also evaluated the Arg64Trp polymorphism in the beta3-AR and the Arg492Cys polymorphism in the alpha1a-AR. All the polymorphisms were characterised on the basis of PCR-amplified DNA using RFLP analysis. The allele and genotype frequencies in the pts and controls were compared using chi-square test. There was no deviation from Hardy-Weinberg equilirium for any of the considered polymorphisms. Single locus analysis revealed that the polymorphism at position 49 in the beta1-AR showed significant difference in genotype and allele frequencies between patients and controls (table). The OR for DCM associated with the beta1-AR Ser49Gly genotype was 1.87 (95% CI: 1.1-3.1). We did not find different distribution in genotype and allele frequency between pts and controls for the other analysed polymorphisms.

Genotype	Controls (n=203)	DCM patients (n=165)	p
Ser49Ser	170 (84%)	121 (73%)	
Ser49Gly	33 (16%)	44 (27%)	0.015
Gly49Gly	0 (0%)	0 (0%)	
Ser49 allele	0.92	0.87	0.022
Gly49 allele	0.08	0.13	

In conclusion, the Ser49Gly genotype of the beta1-AR is associated with an increased likelihood of developing DCM.

P1058 Potential role of IgG-3 in cardiac dysfunction of patients with dilated cardiomyopathy

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Background: Immunoadsorption (IA) capable of removing circulating autoantibodies represents an additional therapeutic approach in dilated cardiomyopathy (DCM). The role played by autoantibodies belonging to the immunoglobulin (Ig) subclass G-3 in cardiac dysfunction remains to be elucidated.
Methods and Results: Patients with DCM (left ventricular ejection fraction [LVEF] $<$ 30%) participated in this case control study. 18 DCM patients were treated by different treatment regimes of protein-A IA. Nine patients underwent protein-A-IA with effective IgG-3-reduction (IgG-3 reduction $>$75%) and nine patients were treated with ineffective IgG-3 elimination (IgG-3 reduction $<$40%). IA was performed in 4 courses, at one-month intervals until month three. Hemodynamics did not change in the group with ineffective IgG-3 reduction. In the group with effective IgG-3 reduction during the first IA course, cardiac index (CI) increased from 2.3 $\pm$ 0.1 to 2.9 $\pm$ 0.2 l/min/m^2 ($p < 0.01$ vs. ineffective IgG-3 reduction). After three months before the last IA course, CI was 2.2 $\pm$ 0.1 l/min/m^2 in the group with ineffective IgG-3 reduction, and 2.8 $\pm$ 0.2 l/min/m^2 in the group with effective IgG-3 reduction ($p < 0.01$ vs. ineffective IgG-3 reduction). LVEF increased only in the group with effective IgG-3 reduction from 23 $\pm$ 3% to 31 $\pm$ 3%($p < 0.05$ vs. ineffective IgG-3 reduction).
Conclusion: Autoantibodies belonging to IgG-3 play an important role in cardiac dysfunction of DCM.

P1059 A novel mutation, Ser143Pro, in the lamin A/C gene is found in several families with dilated cardiomyopathy

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Purpose Dilated cardiomyopathy (DCM) is familial in approximately 20-35% of cases. The most frequent DCM associated gene defects have been detected in the lamin A/C gene. In this study we screened for variants the lamin A/C gene in Finnish patients with dilated cardiomyopathy.
Methods All 12 exons of the lamin A/C gene were screened by PCR-SSCP method in 13 well-characterized familial patients with familial DCM from Eastern and Southern Finland and in 45 sporadic patients with DCM from Eastern Finland.
Results A novel mutation, S143P, was detected in the lamin A/C gene in 20 subjects from 3 unrelated families and in one sporadic case with DCM. The Ser143Pro mutation locates in the rod domain of the lamin A/C protein. Almost all previously reported DCM associated mutations in the lamin A/C gene have been located in the same domain. Clinically the Ser143Pro mutation was characterized by sinus or atrioventricular nodal dysfunction, atrial fibrillation and heart failure. Conduction defects were progressive in nature and need for pacemaker became common at older ages. Several cases (5/25%) with S143P mutation died suddenly or of progressive heart failure or underwent heart transplantation. The S143P mutation explains 7% of unselected and 23% of familial cases of DCM in our study population.
Conclusions A novel mutation S143P in the lamin A/C gene was found to be common among Finnish DCM patients. The phenotype is characterized by severe heart failure, progressive AV conduction defects and sudden cardiac death. The screening of the S143P mutation seems warranted particularly when patients with DCM have conduction system disturbances.

P1060 Frequent detection of parvovirus B19 genome in the myocardium of adult patients with idiopathic dilated cardiomyopathy

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Purpose: The present study was performed to assess the frequency of B19 (PVB19) genome, aside from the prevalence of enterovirus (EV) and adenovirus (ADV) genomes, in the myocardium of adult patients with idiopathic dilated cardiomyopathy (IDC) and to analyze the significance of PVB19 with regard to the course of the disease, as compared to the other cardiotropic viruses.
Methods: In 52 adult patients (mean age 50$\pm$11 years) with IDC endomyocardial biopsy samples were investigated for EV RNA using polymerase chain reaction (PCR) and Southern blot hybridization of the PCR product. Specific nested PCR was used to assess the prevalence of ADV and PVB19 DNA in addition to sequencing of the latter. The clinical and echocardiographic course of the disease was followed for a mean [$\pm$ SD] period of 23$\pm$9 months.
Results: Fourteen of the 52 patients (27%) were EV-positive, 2/52 (4%) were ADV-positive, 14/52 (27%) were PVB19-positive, 8/52 (15%) patients were EV plus PVB19-positive, and in 14/52 (27%) patients no viral genomes were found. A total of six patinets died during the follow-up period without any significant difference between the patient groups: 1/14 (7%) in the EV-positive, 0/2 (0%) in the ADV-positive, 2/14 (14%) in the PVB19-posiitve, 1/8 (12.5%) in EV plus PVB19-positive and 2/14 (14%) in the virus-negative group (p=NS).
Conclusion: In the myocardium of adult patients with IDC, PVB19 is detectable as frequently as EV genome. PVB19-positive patients with IDC seem to have a rather favourable prognosis and do not differ significantly from the other virus-positive or virus-negative patient groups with respect to survival.

P1061 Increased activity of the regulatory site of the calcineurin/NFAT pathway in human heart failure

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Background: Cardiac hypertrophy may initiate progression to a compromised cardiac function. While the clinical consequences of hypertrophy are well understood, only little is known on the underlying molecular pathways. As reported from animal experiments, the Ca^{2+}-calmodulin activated phosphatase calcineurin and its downstream transcriptional effector NFAT have been implicated as transducers of the hypertrophic response.
Methods and Results: To study whether the calcineurin pathway is activated in human heart failure, we investigated samples of human left ventricular myocardium from patients with dilated (idiopathic) cardiomyopathy (DCM, NYHA IV, n=9) in comparison to non-failing controls (NF, n=8). We analyzed the pathway by measuring the calcineurin activity, and also by determination of the protein expression of the calcineurin B subunit and additional key markers of the calcineurin signaling cascade (NFAT-3, GATA-4). Calcineurin enzymatic activity was increased by 80% in human dilated cardiomyopathy compared to non-failing human hearts (135.42 $\pm$ 11.69 and 83.48 $\pm$ 1.81 nmol Pi/min/μl). This was in line with increased protein expression of calcineurin B in DCM (71.18 $\pm$ 9.11 vs. 46.41 $\pm$ 11.23 densitometric units (DU)/μg protein). In order to verify the activated calcineurin pathway as described in animal models, we compared the protein expression of NFAT-3 in homogenates within nuclear extracts. In nuclear extracts the protein level of NFAT-3 was increased in dilated cardiomyopathy compared to non-failing myocardium (104.01 $\pm$ 8.85 vs. 71.47 $\pm$ 8.79 DU/μg protein). In contrast, in homogenates the expression of NFAT-3 was higher in the non-failing tissue indicating subcellular distribution (19.56 $\pm$ 3.36 vs. 25.84 $\pm$ 3.16 DU/μg protein). The protein expression of GATA-4 was increased in DCM (43.14 $\pm$ 2.89 vs. 29.87 $\pm$ 2.17 DU/μg protein).
Conclusion: In human heart failure (DCM) the calcineurin signaling pathway is activated not only by an increased activity of calcineurin and expression of GATA-4, but also by the shift from dephosphorylated NFAT-3 to the nucleus indicating subcellular distribution and regulatory activation as well as activation of cell growth.

P1062 Dilated cardiomyopathy caused by lamin A/C mutation: need for a prospective study to prevent sudden death in lamin A/C mutation carriers

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Background: Approximately one third of cases of idiopathic dilated cardiomyopathy (DCM) is inherited. Lamin A/C mutations can cause DCM associated with cardiac conduction-system disease (CCD) and have been often reported in small families, so that uniform clinical expressions of laminopathy are difficult to evaluate. However, larger families allow to judge uniform clinical features of lamin disease.
Findings: We report on a large 3-generation family with DCM-CCD due to an Asn195Lys mutation in exon 3 of the lamin A/C gene which has been associated previously with DCM-CCD. Four family members progressed to terminal cardiac failure requiring heart transplantation (HTX) within three years after initial diagnosis of DCM. Strikingly, atrial arrhythmias or conduction disturbances developed in all during disease progression. Five family members died suddenly at the age of 48, 47, 42, 41 and 36 yr. Data on underlying disease were available in one patient who presented with multiple VES, intraventricular conduction disturbance and first-degree AVB at the age of 39 yr; she developed DCM 1 year later and died suddenly 8 years later. Two other patients show similar conduction disease and DCM at this moment. Because of the malignant familial history, implantation of an ICD seems warranted. However, no studies are available on the predictive factors for sudden cardiac death and on the risk in lamin A/C mutation carriers in general.
Conclusion: The clinical data of this large family with a lamin A/C mutation confirm its association with malignant presentations of DCM. Moreover, they indicate that sudden death may be as important as clinical endpoint as congestive heart failure. Risk identification in lamin A/C mutation carriers in general and in individual affected patients is unknown and ask for a multicenter prospective study. Such a pan-European effort is underway, including evaluation of conduction disturbances on the 12-lead ECG, atrial arrhythmias, Holter recording of ventricular arrhythmias and an invasive electrophysiological study. It may help to devise a strategy for risk-stratification and prophylactic ICD implantation.

P1063 Clonal T-cell composition, detected by analysis of the T-cell receptor beta chain, is exclusively present in dilated cardiomyopathy, and not associated with enteroviral or adenoviral infection

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Background: Autoimmunity, resulting from molecular mimicry between viral and cryptic cardiac antigens, is postulated for the pathogenesis of dilated cardiomyopathy (DCM). Autoimmunity directed against distinct antigens evokes expansion of specific T-cell clones infiltrating the target tissue, which can also result from chronic presentation of foreign (e.g. viral) antigens. This phenomenon leads to a clonal predominance of T-cells harboring an identical rearranged T-cell receptor gene (TCR), which can be reliably identified by family specific PCR for the Vβ-N-Dβ-N-Jβ-region of the TCR gene in combination with the GeneScan-analysis (Assaf et al., Blood 2000).
Methods: DNA extracted from explanted DCM hearts (n=17, 1 female; 49±13 years; LVEF: 18±5%) were investigated for clonality of the TCR-Vβ-gene. Non-DCM-hearts (ischaemic cardiomyopathy: n=2, valvular heart disease: n=3, donor hearts: n=3) served as controls. The TCR-PCR-products analyzed by high-resolution fragment analysis (GeneScan), displayed a Gaussian-like distribution profiles in polyclonal and single dominant peaks in monoclonal T-cell populations. Clonal TCR-β PCR-products were directly sequenced. Cardiotropic viral (enteroviral and adenoviral) genome was amplified by PCR as published (Pauschinger et al., Circulation 1999).
Results: The GeneScan analysis of the TCR-β PCR-products demonstrated a clonal T-cell population in n=9/17 (53%) of the DCM hearts. In contrast, exclusively polyclonal composition of the TCR-Vβ PCR-products were obtained from the non-DCM hearts. Sequence analysis of the clonal TCR-Vβ PCR-products from the n=9 DCM hearts determined Vβ19.01 in n=6 cases (67%), and Vβ6-1.01, Vβ6-3.01 and Vβ10-3.04 in each of the remaining cases. Monoclonal TCR-composition was not significantly ($p>0.05$) associated with PCR amplification of viral genome.
Conclusion: Clonal T-cell composition is exclusively present in DCM, as detected by PCR and GeneScan analysis of the TCR-Vβ rearrangement. This phenomenon indicates a clonal T-cell proliferation due to specific antigen, which confirms the autoimmune hypothesis of DCM, since viral perstistence was not associated with viral persistence. Our results, demonstrating a clear predominance of Vβ19.01 T-cell clones in DCM, warrant the molecular analysis of the respective immunogenic sequence. Eventually, a TCR-based immunotherapy in DCM (e.g. with anti-TCR antibodies or DNA vaccines) might be a feasible therapeutic option in DCM with monoclonal TCR-composition.

DILATED CARDIOMYOPATHY, CLINICAL ASPECTS

P1064 Renal function in ischaemic and non-ischaemic cardiomyopathy: effects on survival and neurohormones

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Background: Renal dysfunction, as presented by glomerular filtration rate (GFR) is a strong predictor of mortality in CHF. However, most patients have atherosclerotic vascular disease, and it has been suggested that impaired renal function is not induced by a reduced renal blood flow but only a marker of advanced atherosclerotic disease. We compared in a large survival study (PRIME-II), patients with CHF and a history of proven myocardial infarction and coronary artery disease (CAD, n=995), to those with idiopathic dilated cardiomyopathy (IDC, n=429). In a substudy, neurohormones, including natriuretic peptides, were also determined (IDC: n=37; CAD: n=270).
Methods: The population consisted of patients with NYHA class III-IV; at baseline the mean age was 64±10 yr, mean LVEF 0.26±0.08 and 83% of the patients were male. Baseline GFR was calculated using the Cockcroft Gault equation (GFRc). Relations between GFRc with survival and plasma neurohormones were performed within etiology groups.
Results: In a multivariate Cox regression analysis, GFR was significantly related to survival in both groups, but this relation was stronger and more pronounced for IDC (table below; $P<0.001$ in IDC vs $P=0.01$ in CAD). Regarding neurohormones, all natriuretic peptides showed a relation with the GFRc in both ICD and CAD. However, this relation was stronger for IDC. For IDC, the relation between GFRc and natriuretic peptides varied from r= -0.72 (N-terminal BNP; $P<0.01$) till r= -0.49 (ANP; $P<0.01$) and for CAD, r= -0.59 (N-BNP; $P<0.01$) till r= -0.37 (ANP; $P<0.01$).

GFRc in IDC (ml/min)	RR-multivariate for IDC (95% CI)	GFRc in CAD (ml/min)	RR-multivariate for CAD (95% CI)
>90		>73	
90-69	0.87 (0.36-2.10	73-55	1.02 (0.63-1.63)
69-53	1.83 (0.83-4.06)	55-42	1.07 (0.68-1.71)
<53	3.04 (1.43-6.44)	<42	1.81 (1.14-2.87)

Multivariate analysis of GFRc quartiles in IDC and CAD. RR= relative risk. CI= confidence interval.

Conclusions: GFRc is strongly related to survival and neurohormones in both ICD and CAD. This relation is even more pronounced in patients with IDC than with CAD. These results suggest that the prognostic and clinical value of renal dysfunction in CHF is more related to hemodynamics, rather than local renal atherosclerotic disease.

P1065 Predictive models of moderate or severe systolic dysfunction in Chagas disease based on clinical, electrocardiographic and radiological data

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Clinical trials have shown the benefits of pharmacological interventions to increase the survival of patients with moderate or severe ventricular dysfunction, even asymptomatic. The purpose of this study is to generate predictive models of systolic dysfunction in Chagas' disease based on clinical, electrocardiographic and radiological data to be used when it is not possible to evaluate the left ventricular function by the echocardiogram (like in poor areas where Chagas' disease is most prevalent). **Methods:** 604 Chagas' disease patients were underwent to a prospective investigation of clinical, electrocardiogram, thoracic X-ray and two-dimensional echocardiography evaluation. By logistic regression, we derived a system score that predicts the probability of dysfunction (ejection fraction<45%). The cutoff points that identifies dysfunction were defined by the receiver operating characteristic (ROC) curve.
Results: The normal electrocardiogram displayed a 100% negative predictive value that excluded the dysfunction. The model featuring sex and electrocardiographic variables (model A) showed a sensitivity of 81% and a specificity of 78% for a diagnosis of dysfunction with a positive predictive value of 61% and a negative value of 91% to patients with an abnormal electrocardiogram. Area under ROC curve from this score system model was 0.891 (95% CI 0.86-0.92). Cardiothoracic ratio>0.5 showed a specificity of 93%. The addition of this variable to the electrocardiographic model (model B) resulted in an increase in its accuracy, with a positive predictive value of 70% among patients with an abnormal electrocardiogram and area under ROC curve equal 0.926 (95% CI 0.9-0.95). Addition of other clinical variables (symptoms, model C and comorbidities, model D) did not result in a significant increase in accuracy. The model A was validated through its employment in 263 Chagas' disease patients from a rural cohort with an excellent reproducibility (sensitivity=83.3%, specificity=71.4% and area under ROC curve=0.824).
Conclusion: The employment of predictive models made it possible to identify moderate or severe dysfunction in Chagas' disease based on clinical, electrocardiographic, and radiological data.

P1066 Familial dilated cardiomyopathy: an international registry

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Background: Dilated cardiomyopathy (DCM) is a heart muscle disease characterized by progressive ventricular dilation and systolic dysfunction. More than 50% of cases of DCM are familial forms. Familial DCM (FDC) can be inherited in an autosomal dominant (AD), autosomal recessive (AR) or X-linked (XL) pattern. Family screening is essential to perform molecular genetic studies for the identification of disease genes and helps in the understanding of the full phenotypic and genotypic spectrum of FDC. The specific aims of our study are to establish a comprehensive clinical and genetic Registry of families with DCM (both FDC and sporadic pedigrees), to study known FDC-genes, to further understand the molecular basis of FDC, to test new candidate genes and to define genotype/phenotype correlations in FDC.
Methods: Patients are enrolled from the University of Colorado Hospital and Children's Hospital, Denver and the Maggiore Hospital of Trieste, Italy. All participants undergo detailed family history analysis, physical examination, ECG, echocardiogram, serum CK and other laboratory investigations. DNA is extracted and systematically screened for disease causing mutations. Special studies are also performed, if indicated, to define the phenotype, including SAECG, stress test, Holter monitoring, chest x-ray and MRI. Informal consent has been collected for all subjects.
Results: Our population is composed of 153 families (535 subjects). To date 90 families (207 subjects, 58.8% of the whole population), have been completely screened for FDC and are enrolled in the study. Screening of other families is in progress. Twenty-eight families have a sporadic DCM, while 62 have a FDC. The latter group includes 173 subjects: 82 subjects are affected by the disease, 78 are healthy relatives and 13 have an unknown status. Sixty-seven percent of these families present an AD pattern of inheritance, while 5% an AR one. No families have an XL pattern and 27.4% are unclassifiable at this time. Screening of family member participants has also revealed evidence of early echocardiographic signs of DCM in 11 otherwise healthy individuals. The analysis of genotype/phenotype correlations is in progress.
Conclusions: This Registry represents one of the largest efforts in the DCM field. Informations about phenotypic features and family history provides valuable data that can be translated into gene discovery, characterization, and genotype-phenotype correlations. Finding early asymptomatic cardiac disease in clinically unaffected relatives has important ethical and therapeutic implications.

P1067 Does idiopathic dilated cardiomyopathy represent an autoimmune-disease?

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Background: Today, dilated cardiomyopathy (DCM) represents the main cause of severe heart failure and disability in younger adults. Although up to 30% of dilated cardiomyopathies may be genetic in origin, the large majority are sporadic, and a viral or immune pathogenesis is suspected. Following the classical postulates for autoimmune diseases in our present study we attempted both to generate (indirect evidence) and then to transfer (direct evidence) experimental immune-cardiomyopathy in a rat-model in order to analyze whether antibodies against the the second extracellular loop of the beta1-adrenergic receptor (beta1-ECII; 100% sequence-identity human/rat) might be causally involved in the pathogenesis of DCM.
Methods and Results: According to the above postulates, first, we immunized inbred rats against the second extracellular beta1-receptor loop (beta1-ECII; 100% sequence-identity human/rat) every month over a 15 months-period. All rats developed receptor-stimulating anti-beta1-ECII-antibodies (functional cAMP-assay) and after nine months progressive left ventricular dilatation and dysfunction (echocardiography and left heart catheterization, confirmed by histology/morphometry of the excized hearts).
Second, we mimicked autoantibodies by transferring anti-beta1-ECII-positive sera every month to healthy rats of the same strain. All anti-beta1-ECII-transferred rats also developed a cardiomyopathic phenotype within a similar time-course (again determined by echocardiography, left heart catheterization, and histology/morphometry of the excized hearts).
Conclusion: Thus, our data furnish direct evidence that beta1-adrenergic receptor-targeted autoimmune-DCM should now be roughly categorized with other known receptor antibody-mediated diseases, i.e. Graves' disease or myasthenia gravis. This fact further encourages development of therapeutic strategies that combate harmful anti-beta1-ECII-antibodies.

P1068 Autoantibody profiles in patients with peripartum cardiomyopathy: a distinct entity to idiopathic dilated cardiomyopathy

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Peripartum cardiomyopathy (PPCM) represents a specific cause of heart failure in which the underlying putative factors of the disease are largely unknown. We have previously identified a distinct immunoglobulin (Ig) class/subclass profile against cardiac myosin in patients (pts) with idiopathic dilated cardiomyopathy (DCM) compared with ischemic cardiomyopathy (IHD) and healthy blood donors. Levels of IgG3, a potentially damaging Ig, were specifically raised in DCM pts despite equivalent levels of total IgG-reactivity in both disease states. The current study sought to characterise Ig-class and subclass responses in PPCM pts from two geographical locations (GL), and compare them to pts with DCM.
Twenty four pts with PPCM from Haiti and 15 PPCMs including 15 age and parity matched healthy mothers from South Africa (SA) were evaluated for Ig-class and subclass (IgG1, IgG2 and IgG3) reactivity against cardiac myosin heavy chain. PPCMs from either group did not differ in age; 32y (28-41) vs 32y (28-38) or left ventricular ejection fraction (LVEF); 25% (20-29) vs 22% (18-25), p=0.17, although end-systolic dimensions were greater in the latter group (SA). Parity (median) in PPCMs from Haiti 4.5 (2.25-7), higher than in PPCMs from SA 2 (2- 4), p=0.015, did not correlate with LVEF. Levels of total-IgG, 1,2 and 3 did not differ in PPCMs from either GL sought or correlate with parity. Frequency of Ig-G1,G2 and G3 in PPCMs from haiti was 58%, 66% and 54% respectively. In PPCMs from SA, Ig-frequency was 53% for all the subclasses whereas the age and parity matched healthy mothers were negative. Compared with Ig-levels in DCM pts (UK: IgG1; 11%, G2; 8.8% and G3; 22%), frequency of all the Igs in PPCMs was much higher: IgG1; p=0.0001, G2; p<0.00001, G3; p=0.0004 (Haiti) and p=0.005 (SA). Unlike the selective up-regulation of IgG3 in DCM pts and its correlation with LV-dysfunction, approx. 90% of the auto-Ab significant PPCM pts were positive for two or more of the subclass-Igs. Levels of C-Reactive Protein, available in the PPCMs from SA (raised in 45% of the pts), showed no correlation with the Igs.
From an humoral-autoimmune perspective PPCM may represent a clinically distinct entity compared to DCM. The differential distribution of the Igs in the heart failure pts of different etiologies may contribute to a better understanding of their evolution and biopathology of disease. The very high incidence of the Igs in PPCMs raises concerns that warrant larger longitudinal studies to determine their course in disease and clinical outcome.

P1069 Meta-analysis on the histological and immunohistological proof of intramyocardial inflammation in myocarditis and dilated cardiomyopathy

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Background: Myocarditis, often evoked by cardiotropic viruses, can transit from the acute stage to dilated cardiomyopathy (DCM), which is in parts due to chronic persistence of the intramyocardial inflammation, denoted inflammatory cardiomyopathy. Since the standardized histological Dallas Criteria are prone to considerable sampling error and interobserver-variability, several immunohistological evaluation techniques have emerged as more specific diagnostic approaches. To summarize the current status on the immunohistological diagnosis of myocarditis and inflammatory cardiomyopathy, we performed a meta-analysis.
Methods & Results: 25 studies were enrolled with a total of 5,635 patients (males: 67%, mean age: 45±13 years) by Medline®-query on immunohistological diagnosis of myocarditis or inflammatory cardiomyopathy. The clinically suspected diagnosis was myocarditis in n=4, DCM in n=19 and DCM or myocarditis in n=2 of these studies. No histological or immunohistological proof for intramyocardial inflammation was confirmed in the n=216 control hearts reported in these studies. Myocarditis according to the Dallas Criteria was found significantly ($p<0.01$) less frequently (total: 14±18%; active: 5±13%; borderline; 8±9%) compared with immunohistochemical criteria (positive in 52 ± 18%). As much as 12 different diagnostic criteria (pan-leukocytes, T-lymphocytes, cytotoxic T-cells, macrophages, cell adhesion molecules in various combinations) were applied for the immunohistological diagnosis of intramyocardial inflammation.
Conclusions: Despite some divergence in the applied diagnostic criteria, intramyocardial inflammation is detected substantially more often and with less variances between the research centers by immunohistological evaluation techniques than by the histological Dallas Criteria. These data warrant a standardization of the immunohistological criteria for the diagnosis of inflammatory cardiomyopathy.

P1070 Growth hormone treatment modulates circulating cytokine network and improves left-ventricular contractile performance in patients with dilated cardiomyopathy

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Background: Previous studies have shown that abnormal inflammatory cytokine activation contributes to the development and progression of chronic heart failure (CHF). This study investigates whether growth hormone (GH) administration modulates peripheral immune responses in CHF secondary to dilated cardiomyopathy (DC) and whether these effects are associated with the improvement of left ventricular (LV) contractile performance in DC patients.
Methods: Plasma inflammatory cytokines TNF-a, IL-6, GM-CSF, its soluble receptor sGM-CSFR and MCP-1, soluble adhesion molecules sICAM-1 and sVCAM-1, and anti-inflammatory cytokines IL-10 and TGF-b2 were measured (ELISA) in 12 DC patients (NYHA III; LVEF:24±3%) before and after a 3-month subcutaneous administration of GH 4IU every other day (randomized crossover design). Peak oxygen uptake (VO2 max), end-systolic wall stress (ESWS), mean velocity of circumferential fiber shortening (Vcfc) and contractile reserve (change of Vcfc/ESWS after dobutamine infusion) were also determined.
Results: GH produced a significant reduction in plasma TNF-a (7.8±1.1 vs 5.4±0.9 pg/ml, $p<0.01$), IL-6 (5.6±0.5 vs 4.6±0.3 pg/ml, $p<0.05$), GM-CSF (27±2 vs 23±2 pg/ml, $p<0.05$), sGM-CSFR (4.0±0.4 vs 3.2±0.3 ng/ml, $p<0.05$), MCP-1 (199±5 vs 182±6 pg/ml, $p<0.05$), sICAM-1 (324±33 vs 274±27 ng/ml, $p<0.05$) and sVCAM-1 (1237±88 vs 1043±77 ng/ml, $p<0.05$), as well as a significant increase in ratio IL-10/TNF-a (1.9±0.3 vs 3.5±0.9, $p<0.05$), IL-10/IL-6 (2.6±0.6 vs 3.2±0.5, $p<0.05$) and TGF-b2/TNF-a (3.1±0.6 vs 4.4±0.6, $p=0.05$) in DC patients. A significant reduction of ESWS (840±43 vs 634±41 gr/cm^2, $p<0.005$), and a significant increase of contractile reserve (0.0003±0.0001 vs 0.0005±0.0001 circ*cm^2/gr*sec, $p<0.001$) and VO2max (15.2±0.7 vs 17.1±0.9 ml/kg/min, $p<0.001$) were also observed.Good correlations were found between GH-induced increase in contractile reserve and the increase in VO2max ($r=0.62$, $p<0.05$), ratio IL-10/TNF-a ($r=0.66$, $p<0.05$) and TGF-b2/TNF-a ($r=0.58$, $p<0.05$), as well as the reduction in TNF-a levels ($r=-0.86$, $p<0.001$).
Conclusions: GH modulates beneficially circulating cytokine network and soluble adhesion molecules in DC patients.These immunomodulatory effects may be associated with the improvement in LV contractile performance and exercise capacity of patients with CHF secondary to DC.

P1071 Amiodarone preserves cardiac sympathetic function to hold norepinephrine in heart, as well as suppressed left-ventricular remodelling and improves cardiac function

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Background: Recent studies suggest that amiodarone improves the prognosis of chronic heart failure, but the mechanism remains uncertain. We investigated the effect of amiodarone on left ventricular remodeling and the cardiac sympathetic function in chronic heart failure. **Method:** Autoimmune myocarditis was induced in Lewis rats by injection with porcine cardiac myosin. In the phase of chronic heart failure from 28 day until 70 day, we treated normal rats and rats with CHF by oral administration with amiodarone (50mg/kg). At 73 day, we examined hemodynamic parameter, pathological findings, plasma concentration and tissue mRNA levels such as ANP, IL-6, TNFalpha, TGFbeta-1, sarcoplasmic reticulum Ca-ATPase and myosin heavy chain(MHC) isoform. After a dose of 0.8 MBq 125I-metaiodobenzylguanidine(MIBG) was intravenously injected, the rats were sacrificed at 3 min, 10 min and 240 min. The myocardial uptake in each phase was measured by a scintillation counter.
Results: LV weight/body weight ratio were reduced in treated rats($p<0.005$). Myocardial fibrosis was not different significantly. Amiodarone improved hemodynamics in LV pressure, central venous pressure and +dP/dt. Serum thyroid hormone level was not different. Amiodarone decreased ANP and collagen III and TGFbeta-1 mRNA levels compared with non-treated rats ($p<0.05$). TNFalpha and Ca-ATPase mRNA level were not different in 3 groups. The MHC phenotype (alpha MHC mRNA level/beta MHC mRNA level) was improved to be normal in treated rats ($p<0.01$). The initial uptake of MIBG was decreased(CHF:7.8 ± 1.0 vs normal:11.5 ± 0.8, $p<0.001$) and the washout rate was higher (CHF: 73.8% vs normal:33.0%) in chronic heart failure. Whereas amiodarone also more decreased the initial uptake (CHF+Amio: 7.5 ± 0.8 and normal+Amio: 8.3 ± 1.0) but the washout rate was lower than non-treated rats (CHF+Amio: 29.9% vs CHF: 73.8%). In result amiodarone kept the late accumulation of MIBG compared with non-treated rats (CHF+Amio: 5.2 ± 1.2 vs CHF: 2.0 ± 0.3, $p<0.01$).
Conclusions: Amiodarone suppressed LV hypertrophy and improved cardiac hemodynamics. In cardiac sympathetic function, amiodarone decreased the cardiac uptake and the washout rate was lower to hold norepinephrine in heart.

P1072 C-reactive protein and hypercholesterolaemia do not influence myocardial immune response in patients with dilated cardiomyopathy

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C-reactive protein (CRP) and hypercholesterolemia occurred as important components of chronic systemic inflammation. The aim of this study was to investigate whether these components were related to endomyocardial immune response in dilated cardiomyopathy (DCM).
Methods: 258 consecutive pts with idiopathic DCM (125M, 40F, aged 40 ± 11 years), hypertensive DCM (66M, 9F, aged 47 ± 7 years) and ischemic DCM (13M, 5F, aged 47 ± 12 years) with NYHA class II underwent coronary angiography (82% of pts) and RV endomyocardial biopsy (all subjects). All pts were taking standard therapy for heart failure at the time of the study. The expression of cell adhesion molecules (HLA, ELAM-1, ICAM-1), CD3 + lymphocytes and macrophages counts were studied on cryostat biopsy sections (EnVision method and monoclonal antibodies from DAKO). A highly sensitive latex-based immunoassay was used to determine the CRP levels. Lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) were measured by standard procedures (Cobas Integra 700, Roche).
Results: Pts with ischemic DCM had significantly higher CRP values (median, 8.86 mg/L, IQR, 2.62 - 13.99) as compared with idiopathic DCM (median, 2,09 mg/L, IQR, 1.03 - 5.59, $P = 0.002$), and hypertensive DCM (median, 2.42 mg/L, IQR, 1.19 - 4.77, $P = 0.002$). Spearman's correlation testing showed no association between serum CRP levels and immunohistological markers of inflammation studied. Both expression of cell adhesion molecules and inflammatory cell counts did not differ statistically between groups (Kruskal-Wallis test). Among serum lipids, triglyceride concentration was significantly higher in the hypertensive DCM as compared with idiopathic DCM, only (2.09 ± 1.46 vs. 1.67 ± 0.99 mmol/L, 95% CI, 0.08 - 0.75, $P = 0.015$; ANOVA). There was no correlation between serum lipid concentrations and immunohistological markers of immune response in the biopsy specimens.
Conclusions: These results demonstrate the lack of direct relationship between serum CRP levels, lipid levels and local endomyocardial immune response in pts with ischemic and non-ischemic DCM. The present data provide evidence that immune response in the biopsy specimens pts with chronic heart failure due to DCM is modulated by local factors.

P1073 The benefit of immunoadsorption in dilated cardiomyopathy on the level of gene expression

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Purpose: Disturbances of the humoral immune system may play a pathogenic role in dilated cardiomyopathy (DCM). Removal of cardiac autoantibodies by immunoadsorption (IA) induces hemodynamic improvement of DCM patients. The mechanisms of IA remain to be elucidated. We analysed the effects of IA on myocardial gene expression of lumican and annexin I, which are known to be upregulated in DCM. In addition, we measured the changes of gene expression of the genes beta-actin, SLIM1 and SERCA, which are known to be reduced in DCM.
Methods: In 9 DCM patients (LVEF<30%, NYHA III-IV) IA was performed in monthly intervals until month 3. Endomyocardial biopsies were obtained before and after IA treatment (after 3 months). The gene expression of lumican, annexin I, beta-actin, SLIM1 and SERCA were compared in biopsies of 9 patients before and after IA by real-time PCR.
Results: During IA therapy LVEF increased from 21.2 $\pm$ 2% to 29.4 $\pm$ 3% ($p<0.05$). During IA lumican and annexin I, which are known to be upregulated in DCM, were reduced by 45$\pm$7% and 41$\pm$6% ($p<0.01$). In addition, after IA the genes beta-actin, SLIM1 and SERCA, which are known to be reduced in DCM were upregulated by 180$\pm$25%, 240$\pm$140% and 220$\pm$120%.
Conclusions: IA therapy not only improves LVEF but also modulates gene expression in myocardial tissue of DCM patients.

ANTITHROMBOTIC TREATMENT IN ST-ELEVATION ACUTE MYOCARDIAL INFARCTION

P1074 Subacute stent thrombosis in acute myocardial infarction: insight from the abciximab and carbostent evaluation (ACE) trial

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Background: It is unknown if a carbon coating stent may decrease the incidence of stent thrombosis in patients with acute myocardial infarction (AMI), and if the adjunctive use of abciximab may have a benefit in the reduction of the incidence of stent thrombosis.
Methods: To determine the impact of abciximab therapy as adjunct to infarct artery stenting in AMI, 400 pts without any restriction based on age or clinical status on presentation were randomized at 4 sites to primary stenting alone (n =200) or stenting plus abciximab (n=200). The stent used was the Carbostent (Sorin, Italy). There were no angiographic exclusion criteria except for a reference infarct related artery diameter $<$ 2.5 mm. Patients with diffuse disease, left main disease, ostial location of the target lesion, major side branch involvement in the target lesion, massive thrombosis were included. Randomization had to be done after angiography and before the procedure. Protocol 1-month angiographic follow-up was sheduled in a 264 patient subset in order to assess asymptomatic stent thrombosis and the infarct artery patency. Unscheduled angiography was performed in all patients with recurrent ischemia or reinfarction.
Results: Overall, stent thrombosis occurred in 11 pts (2.75%). Out of these, 9 pts underwent urgent repeat coronary angioplasty, one asymptomatic patient underwent coronary surgery, and one had conservative treatment. Subacute stent thrombosis was complicated by reinfarction in 10 pateints despite successful repeat emergency revascularization. Stent thrombosis rate was 0.5% in the abciximab group, and 5% in the stent alone group (p=0.006). Patients with stent thrombosis had at least 2 of the following unfavourable characteristics: diabetes, shock, stent lenght $>$ 20 mm, final inflation pressure $>$ 18 atm, and crossover to bailout abciximab treatment. There were no deaths due to stent thrombosis. One-month angiography in 217 pts (F-U rate=82%) did not show any evidence of stent thrombosis in all but one patient.
Conclusion: Overall, the Carbostent is associated with a low thrombosis rate in patients with AMI. However abciximab provides a strong protective effect against stent thrombosis.

P1075 Safety and efficacy of low versus very low dose of unfractioned heparin in patients treated with facilitated percutaneous coronary intervention for acute myocardial infarction

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Background: Frequency of bleeding events after administration of combined thrombolytic therapy in acute myocardial infarction (AMI) is strongly related to heparin's dose. The aim of this study was to asses the safety and efficacy of various doses of unfractioned heparin (UFH) in patients treated with combined thrombolytic therapy undergoing subsequent percutaneous coronary intervention (PCI) for AMI.
Methods: 438 patients (pts.) with AMI $<$ 12 hours, $<$ 75 years old with anticipated transfer time to an interventional cardiology center $>$ 90 min. were enrolled to the study. All pts. received aspirin (325 mg), alteplase (15 mg i.v. bolus, followed by i.v. infusion of 35 mg/60 min), abciximab (0.25 mg/kg i.v. bolus, followed by i.v. infusion of 0.125 μg/kg/min). Pts. were divided into two groups according to UFH dose: 60 U/kg (max. 5000 U) - group I (291 pts.); 40 U/kg (max. 3000 U) - group II (147 pts). All pts. were transferred from the remote center to reference cardiology center for diagnostic angiography and immediate PCI. We evaluated occurrence of major adverse cardiac events (MACE) (death, recurrent MI (re-MI), recurrent PCI (re-PCI)) and combined bleeding complications (severe, moderate, minor) in 30-days follow-up.
Results: There was no difference in baseline clinical and angiographic characteristic of pts. in both groups. Occurrence of MACE and combined bleeding complications at 30 days for both groups is shown in the table.

	Group I (291 pts.)	Group II (147 pts.)	
MACE (death, re-MI, re-PCI)	5.5%	3.4%	NS
combined bleeding complications	20.9%	12.3%	0.03

Conclusions: Use of reduced dose of heparin in pts. treated with facilitated PCI decrease occurrence of bleeding complications without any affection of clinical outcome.

P1076 Use of IIb/IIIa receptor blockers before and during percutaneous coronary intervention for acute coronary syndromes versus stable angina in consecutive patients in Europe: results of the international SHAKESPEARE registry

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Background: In early 2001, the ACC/AHA Task Force on Practice Guidelines published revised guidelines for percutaneous coronary interventions (PCI). At this time, no data exist to help understand how these guidelines are implemented into clinical practice, especially the use of IIb/IIIa receptor blockers (IIb/IIIa). The SHAKESPEARE registry has been designed to fill this informational void.
Methods: Since February 2002 consecutive patients undergoing PCI have been included in the international SHAKESPEARE registry to document clinical practice in 30 centers in different countries of the European Society of Cardiology (France, Germany, Israel, Italy, Portugal, UK). We examined the use of IIb/IIIa for PCI in acute coronary syndromes (ACS) as well as in stable angina.
Results: Out of 4913 consecutive patients undergoing PCI 2881 patients (59%) had ACS, 20.1% acute STEMI, 8.5% acute NSTEMI, 30.0% unstable angina, 1251 patients (41%) underwent PCI for stable angina. Patient characteristics, acute treatment and outcome are summarized in the table.

ACS versus stable angina

Parameter	ACS (n=2881)	Stable Angina (n=1944)	p-value
Age (years)	65	65	ns
Male gender	74.2%	77.3%	<0.01
Prior MI	19.5%	32.9%	<0.01
IIb/IIIa before PCI	21.5%	3.2%	<0.01
IIb/IIIa during PCI	48.7%	24.4%	<0.01
Stenting	75.7%	74.8%	ns
Bleeding complication	6.6%	5.1%	<0.01
Hospital mortality	3.1%	0.2%	<0.01

Conclusion: The use of IIb/IIIa was high in consecutive patients undergoing PCI for ACS with 21.5% even before the start of the intervention and 48.7% during the procedure. In consecutive patients undergoing PCI for stable angina IIb/IIIa was given in only a minority before the intervention but in one quarter of the patients during the PCI procedure.

P1077 Differential benefit of abciximab as adjunct to infarct artery stenting in patients with acute myocardial infarction: insight from the abciximab and carbostent evaluation (ACE) trial

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Background: Previous randomized studies have produced conflicting results about the benefit of abciximab as adjunctive treatment to infarct artery stenting in acute myocardial infarction (AMI). However, these studies enrolled mainly low-risk patients, or were done with first generation stents.
Methods: To determine the impact on outcome of abciximab therapy as adjunct to infarct artery stenting in AMI, 400 patients without any restriction based on age or clinical status on presentation, were randomized at 4 sites to primary stenting alone (n =200) or stenting plus abciximab (n=200). The stent used was the Carbostent (Sorin, Italy). There were no angiographic exclusion criteria except for a reference infarct artery diameter $<$ 2.5 mm. The primary endpoint of the study was the 1-month composite incidence of death, reinfarction, repeat target vessel revascularization (TVR), and stroke (MACCE).
Twenty-two prespecified subgroups with fixed characteristics were examined. A test of interaction was used to identify factors that were associated with a differential treatment effect within subgroup.
Results: There were no differences in baseline clinical and angiographic characteristics between the randomized groups. The incidence of the primary endpoint at one month was lower in the stent plus abciximab group (4.5% vs 10.5%, p=0.023). In the subgroups analysis the variables that positively interacted with treatment at one-month were: age $<$ 75 yrs (HR 0.29, 95% CI 0.01-0.90, p=.032), non-anterior AMI (HR 0.07, 95%CI 0.0-0.58, p=0.014), diabetes mellitus (HR 0.10, 95%CI 0.01-0.82, p=.032), hypertension (HR 0.33, 95%CI 0.11-0.95, p=.041), no previous myocardial infarction (HR 0.38, 95%CI 0.16-0.90, p=0.027), preprocedure TIMI 0-1 (HR 0.31, 95%CI 0.12-0.81, p=.016), coronary collateral grade Rentrop 0-1 (HR 0.36, 95%CI 0.16-0.84, p=.019), single stent implantation (HR 0.12,95%CI 0.03-0.56, p=0.006), stent length $<$ 20 mm (HR 0.22, 95%CI 0.06-0.80, p=.022), and time to reperfusion equal or less than 6 hours (HR 0.33, 95%CI 0.11-0.93, p=.036).
Conclusion: Abciximab treatment interacted significantly with most of the predefined subgroups of patients with AMI undergoing routine infarct artery stenting.

P1078 Infarct size limitation with abciximab as adjunctive therapy to infarct related artery stenting: data from abciximab and carbostent evaluation (ACE) trial

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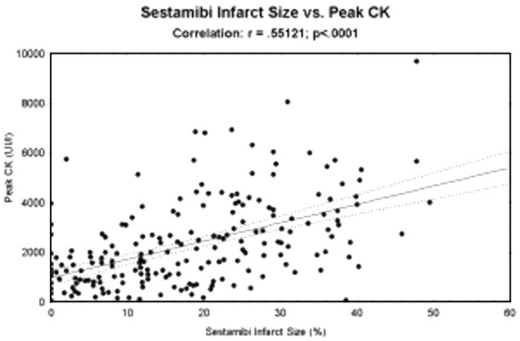
Background: Previous randomized studies have produced conflicting results about the benefit of abciximab as adjunctive treatment to infarct artery stenting in acute myocardial infarction (AMI).
Methods: To determine the impact on outcome of abciximab therapy as adjunct to infarct artery stenting in AMI, 400 pts without any restriction based on age or clinical status on presentation, were randomized to primary stenting alone (S) or stenting plus abciximab (Abx). The primary endpoint of the study (composite incidence of death, reinfarction, repeat target vessel revascularization, and stroke) was reached in 4.5% in Abx group and in 10.5% in S group, p=.023. One key secondary end point of the study was the infarct size as assessed by 99Tc-sestamibi SPECT at 1 month in a prespecified subgroup of 250 patients. Creatine kinase (CK) value was evaluated every 3 hours for 24 hours. Results: Median infarct size and interquartile ranges were smaller in the Abx group as compared to S group (12.5% [IQ 3.0-24.9] vs 16.6% [IQ 6.5-26.1], p=.067). The difference reached significance in the subgroup of patients with early ST-segment resolution (11.1% [IQ 1.5-22.5] vs 18.3% [IQ 11.7-24.4], p=.007). Morover the occurrence of no detectable defect was more frequent in Abx group than in S group (18.2% vs 8.4%; p=.032). In A group there were less patients with CK over the median value than in S group (45% vs 57%, p=0.18); similarly time-to-peak CK was shorter in A group than S group (median value: 10.1 vs 14.1 hours, p$<$.001). Finally, infarct size was correlated with peak CK value (see Figure).
Conclusion: In patients with AMI, abciximab as adjunctive treatment to stenting provides a more effective reperfusion and myocardial salvage as compared to stenting.



Correlation infarct size vs CK value.

P1079 Substitution of coagulation factor XIII partially restores scar healing after myocardial infarction in factor XIII KO mice

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Background: Clotting factor XIII has been shown to have a role in healing processes in tissues as skin, bone and cartilage. Because this role may be universal in the organism, we studied healing after coronary artery ligation in factor XIII knock out (FXIII KO) and wild type (WT) mice.
Methods: Magnetic resonance imaging was performed 1 day, 7 and 42 days after myocardial infarction (MI) in a 7 T-Biospec using an ECG-triggered Cine-FLASH-sequence: slice thickness 1 mm, echo-time 1.2 ms, resolution 230 μm. Cardiac volumes and index, ejection fraction, scar thickness and left ventricular mass were determined. To minimize bleeding from the thoracotomy wound, FXIII-free fibrin glue was applied. 5 groups of 6-12 mice were studied: WT MI, FXIII KO MI, FXIII KO sham operated, FXIII KO MI with iv. substitution of factor XIII (200 U/kg via tail vein for 5 days).
Results: All FXIII KO mice died within 3 to 5 days after MI, whereas wild type mice, sham operated KO mice and KO mice with MI and iv. substitution of factor XIII survived the subacute period (7 days). Histology revealed rupture of the infarct area with little inflamatory response to ischemia in the KO group. Substituted KO mice survived, but the infarct scar was thinner than in WT 1 week after MI (WT 0.66 $\pm$ 0.03mm, KO plus iv. FXIII 0.37 $\pm$ 0.06mm, p$<$0.005). LV dilatation was more pronounced in KO than in WT (increase of end-diastolic volume from day 1 to 42 after MI, WT 33.2 $\pm$ 5.2μl, KO plus iv. FXIII 68.3 $\pm$ 10.2μl, p$<$0.05). LV mass and cardiac index were not significantly different between WT and KO 42 days after MI. Ejection fraction of KO was not significantly lower (WT 51.7 $\pm$ 5%, KO 43.8 $\pm$ 8.9% p=ns).
Conclusion: These data show that FXIII may have a major role in healing processes post myocardial infarction. When compared to WT, scar healing in substituted KO was not completely restored as indicated by a thinner scar. This may be explained by the fact that the largest part of FXIII in WT is transported inside platelets which home in at sites of injury, whereas in substituted KO mice FXIII was transported in the plasma.

THROMBOSIS, THROMBOLYSIS AND BLEEDING: THERAPEUTIC AND PROGNOSTIC IMPLICATIONS

P1080 Statins impair the antiplatelet effect of clopidogrel – a flow cytometry study

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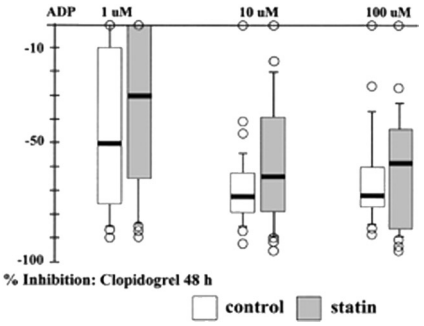
Purpose Clopidogrel is a pro-drug which is converted to an active, unstable drug by cytochrome P450 (CYP). The active drug irreversibly modifies one specific platelet adenosine 5'-diphosphate (ADP) receptor (P2Y12). Conflicting data have been presented whether the most abundant human CYP isoform, 3A4, activates clopidogrel or not. Since certain lipophilic statins (i.e. simvastatin, atorvastatin, lovastatin) are a substrate of CYP3A4, we were interested in potential drug interactions between clopidogrel and statins
Methods In patients with coronary artery disease (n=60) in whom clopidogrel treatment was initiated for balloon angioplasty and stent implantation, blood samples were taken at 0, 5 and 48 hours after oral administration of clopidogrel (loading dose 300 mg, followed by 75 mg daily). ADP-stimulated (1-100 μmol/L) expression of p-selectin on platelets was measured by flow cytometry, and used as a marker for the antiplatelet effect of clopidogrel.
Results Pre-treatment with statins (atorvastatin, simvastatin) reduced significantly the antiplatelet effect of clopidogrel during the loading phase and, to a lesser extent during the maintenance phase (Figure 1). In addition, 5 patients (~5%) were identified in whom clopidogrel exerted almost no antiplatelet effect.



Conclusion Certain statins which are substrates of the CYP 3A4 isoform competitively inhibit the metabolic activation of clopidogrel. As a result the relative antiplatelet effect of clopidogrel (p-selectin-expression) is diminished by about 22% - but still clopidogrel has an effect (relative inhibition of more than 75% after 48h). It may be reasonable to test the therapeutic efficacy of clopidogrel in those patients who require long-term treatment.

P1081 Long-term prognosis of patients with myocardial infarction and normal coronary angiography: impact of inherited coagulation disorders

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Background: Prevalence of inherited coagulation disorders including factor V Leiden is higher in pts with myocardial infarction (MI) and normal coronary angiography (NCA) than in pts with MI and coronary artery stenosis. Despite a good long-term prognosis of patients with NCA, the prognosis of those with inherited coagulation disorders is unknown.
Objectives: The purpose of this study was to compare the clinical thrombosis outcome of patients with (GpI) or without (GpII) an inherited coagulation disorders who suffered from an acute MI with NCA.
Methods: From September 1994 to November 2000, 82 consecutive patients (mean age 49±15 years; 29 females) with MI but NCA were recruited.
Results: Twelve patients (15%) had an inherited coagulation disorder: APC resistance in 8 pts, factor XII deficiency in 3 pts and protein C deficiency in 1 pt. GpI and GpII were statistically similar regarding age (45±11 vs 50±16 years-old), gender (33 vs 36% female), tobacco (50 vs 53%), diabetes mellitus (8 vs 10%), hypertension (25 vs 17%), obesity (8.3 vs 14%), coronary heart disease family history (33 vs 19%), hypercholesterolemia (50 vs 21%; p=.08), and left ventricular ejection fraction (58±13 vs 61±13%). Prevalence of coronary spasm did not differ significantly (8.3% vs 17%) between the two gps. All patients were initially treated with antiplatelet agents with the exception of one (8%) in GpI and 6 (9%) in GpII who were taken oral anticoagulant therapy (ns). The mean follow-up was 57±26 (range from 2-91 months). Four patients were lost of follow-up, 0% in GpI and 5.7% in GpII (ns). During the outcome, 12/78 (15.4%) thrombotic events occurred, including venous thrombosis or pulmonary embolism (1/12 vs 1/66), reinfarction (2/12 vs 4/66), and stroke (2/12 vs 2/66), two events in one patient (GpI). Kaplan-Meier event-free survival, with combined end-point defined as venous thrombo-embolic event, reinfarction, or stroke differed between the two groups: 4/12 (33.3%) in GpI and 7/66 (10.6%) in Gp II ($p < .02$).
Conclusions: Patients with MI, NCA and congenital coagulation disorder present a high risk of thombotic recurrence under antiplatelet agent. This new finding supports the hypothesis that anticoagulation therapy should be recommended in this selected situation.

P1082 Prior use and withdrawing of oral antiplatelet agents affect both the clinical presentation and the clinical outcome of acute coronary syndromes

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Background: Aspirin can prevent myocardial infarction, stroke, and death in cardiovascular disease. How prior use or recent discontinuation of treatment affect the severity and the prognosis of acute coronary syndrome is unclear.
Aim: To investigate whether prior use or withdrawing of oral antiplatelet agents (OAA) influence the severity of acute coronary syndromes (ACS) presentation and the clinical outcome (death, MI).
Methods: A cohort of 1358 consecutive patients admitted for a suspected ACS of whom 930 were non user (NU), 355 were prior user (PU) and 73 had recently withdrawn (RW) OAA, was carefully characterized regarding hospital diagnosis on admission and clinical outcome at 30 days.
Results: PU were at higher risk than NU with a significantly higher proportion of diabetes, hypertension, past history of myocardial infarction (MI), stroke, coronary revascularization and severe renal dysfunction. NU had more frequently STEMI on admission and Q-MI at discharge than PU (36.6% vs 18.0%, $p<0.001$ and 47.8% vs 27.1%, $p<0.001$, respectively). There was no difference regarding the incidence of death or MI at discharge between NU and PU at 30-days (10.3% vs 12.4%, p=ns). However, PU experienced significantly more major bleeds at 30-days compared to NU (3.4% vs 1.4%, $p<0.01$, respectively). RW were admitted within 2 weeks after OAA withdrawal (average of 11.9±0.8 days). OAA was discontinued on a patient decision (n =20) or on a physician decision for scheduled surgery (n =47) or bleeding complications (n=6). Despite a similar risk cardiovascular risk profile, RW had a higher rate of death or MI (21.9% vs 12.4%, p=0.03) and bleedings (13.7 vs 5.9, p=0.02) at 30 days compared to PU. In multivariate annalysis, aspirin withdrawal was found to be an independent predictor of major ischemic events and of bleedings at 30-days.
Conclusion: Prior use of OAA is associated with NSTE-ACS in comparison to patients not pretreated by OAA. Although patients with a recent interruption of OAA resembles those chronically treated by OAA, they displayed a much worse clinical outcome.

P1083 The effect of subjective and objective methods of data collection on bleeding rates in the A to Z trial

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Purpose: Assessment of bleeding risk across trials involving anti-thrombotic agents is known to be confounded by the non-uniform application of standardized definitions of bleeding. Data from two independent bleeding evaluations within the A-phase of the A to Z study indicate the method of data collection is a second potentially important confounder.
Methods: The A-Phase of the A to Z study randomized 3987 patients with non-ST elevation acute coronary syndromes to either enoxaparin or unfractionated heparin as adjunctive therapy to baseline tirofiban and aspirin. During the trial an unexpectedly low aggregate bleeding rate from case report form data (CRF) led to a second independent bleeding evaluation. The original CRF evaluation relied on investigators reporting TIMI bleeding using prespecified definitions (major = Hemoglobin (Hgb) change $>$ 5g/dl or intracranial hemorrhage or cardiac tamponade; minor = Hgb change of $>$ 3g/dl to 5g/dl with a site or with spontaneous gross hematuria, hematemesis or hemoptysis; or Hgb change of $>$ 4g/dl but $<$ 5 g/l without a site). The second independent inquiry retrospectively evaluated Hgb values between enrollment and 24 hours after cessation of study tirofiban. Drops in Hgb of $>$ 3mg/dl generated a second query to evaluate key clinical circumstances associated with the Hgb change. An independent reviewer adjudicated bleeding using the same TIMI criteria provided to the investigators.
Results: The independent bleeding evaluation yielded 3723 evaluable patients from the 3987 enrolled. (30 had no data and 234 had indeterminate values due to early CABG or inadequate Hgb reporting). The CRF data yielded TIMI major and minor bleeding rates of 0.33% (13/3976) and 1.13% (45/3976). The independent assessment's TIMI major and minor bleeding rates were 0.51% (19/3723) and 0.83 (31/3723). The aggregate bleeding rate for the trial (defined as worst identified bleed in either analysis) yielded TIMI major rate and minor rates of 0.70% (26/3724) and 1.45% (54/3725). There were only 7 concordant major bleeds between the two analyses. The analysis for any effect of subjective versus objective data collection with regard to the specific type of antithrombotic awaits imminent data unblinding.
Conclusion: Two independent analyses of bleeding yielded differing results, suggesting that accurate assessment of bleeding risk during antithrombotic therapy requires the incorporation of both subjective and objective measures of bleeding.

P1084 Bivalirudin versus heparin plus protamine in off-pump coronary artery bypass surgery: improved graft flow rates without increased bleeding

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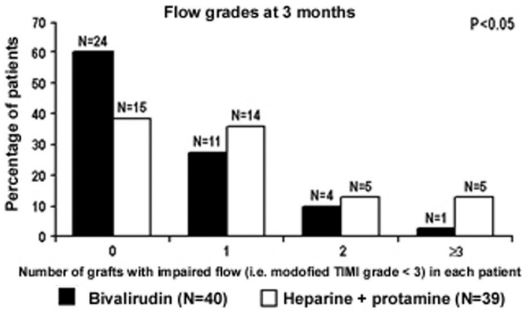
Purpose: Bivalirudin is a short-acting direct thrombin inhibitor which may overcome some of the limitations of unfractionated heparin plus protamine reversal (bleeding, heparin-induced thrombocytopenia, prothrombosis) in cardiac surgery. In this first randomized comparison of a new anticoagulant with heparin in cardiac surgery, we tested the hypothesis that bivalirudin does not increase bleeding compared with heparin plus full protamine in off-pump coronary artery surgery. We also assessed flow in the grafted arteries using a modified TIMI flow grading system.
Methods: 100 patients (pts) were randomized to bivalirudin (0.75 mg/kg bolus plus 1.75 mg/kg/hour infusion) or heparin (150-300 IU/kg bolus). Blood loss was measured for 12 hours after starting the study drug.



Results: Three (range 1-5) grafts were inserted per pt. The median 12-hour blood loss was 793 mL (interquartile range 523-1,214) in bivalirudin pts and 805 mL (517-1,117) in heparin pts (p=0.33). Angiography was performed in 79% at 109 (range 46-200) days. The group medians of the individual mean graft grades per pt were 3.0 in the bivalirudin group and 2.67 in the heparin group ($p<0.05$). Analysis of pts with grade 3 flow in all grafts (p=0.06), pts with grade 3 flow in at least 1 graft (p=0.04), or individual grafts with grade 3 flow (p=0.03) showed better outcomes in bivalirudin pts.
Conclusions: Anticoagulation with bivalirudin is feasible in pts undergoing off-pump coronary surgery. Bivalirudin improved graft flow without increasing bleeding.

P1085 The importance of pharmacogenetic factors in the occurence of bleeding complications in patients receiving oral acenocoumarol anticoagulant therapy

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Background/Objective: The oral anticoagulants, in Hungary acenocoumarol, are widely used for the primary and secondary prevention of thrombotic events. The low therapeutic index and the frequent bleeding complications are characteristic side effects of these drugs. Establishing the proper therapeutic dose for different patients is complicated by a variety of conditions, such as the comorbiditation, age, other drugs used, diet, and pharmacogenetic factors. One of these factors is the polymorphism of the cytochrome P450 CYP2C9 enzyme, which metabolises a wide range of cardiovascular drugs, including oral anticoagulants and statins. The enzyme CYP2C9 has 3 alleles and 6 phenotypes. The wild type CYP2C9*1 allele has the normal enzymatic activity, while the CYP2C9*2 and CYP2C9*3 alleles carry only 12% and 5% of this activity, respectively. In this study, we investigated the influence of CYP2C9 polymorphism on the occurrence of bleeding complications related to acenocumarol therapy.
Patients and Methods: Genotyping of 421 patiens including 183 men and 238 women, (mean age 66.2$\pm$11.8 years) who took acenocoumarol for at least 6 months was performed. Based on anamnestic and laboratory data, the correlation between the genotype and the acenocoumarol dose and bleeding complications were retrospectively analysed.
Results: The frequency-distribution for the CYP2C9*1, CYP2C9*2, and CYP2C9*3 alleles were found to be: 0.814, 0.110, and 0.076, respectively. In the 145 patiens bearing the alleles with reduced activity (CYP2C9*2 and/or CYP2C9*3), the optimised dose of the acenocoumarol was significantly ($p<0.001$) lower than in patients with the wild type allele (2.12$\pm$0.96mg/day and 2.90$\pm$1.45 mg/day, respectively). Although the occurrence of minor bleeding complications in the former group was significantly ($p<0.005$) higher (OR=1.99 [CFI: 1.20–3.33]), there was no difference in major bleeding complications. In patients taking an acenocoumarol dose lower than 2 mg/day, the occurrence of an INR value higher than 6 in the anamnese was significantly ($p<0.05$) more frequent, but there was no correlation with the frequency of bleeding complications.
Conclusions: The frequency-distribution of the CYP2C9 alleles was as reproted by others. In patients bearing alleles with reduced enzymatic activity, the occurrence of minor bleeding complications was significantly more frequent. In patiens with a lower acenocoumarol demand at the introduction of this therapy, a caution is required, but the determination of the CYP2C9 genotype is not necessary.

P1086 The association between anticardiolipin antibodies and left-ventricular thrombus formation in patients with first acute anterior myocardial infarction

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Background: Anticardiolipin antibodies (ACA) are immunoglobulins that react with phospholipids of prothrombin activator complex. The effects of phospholipids on pathophysiology of venous and cardiovascular thrombotic events are well known. Some previous studies reported that high ACA IgG levels increase the risk of left ventricular (LV) thrombus formation after acute myocardial infarction (AMI). We evaluated the importance of ACA IgM and IgG on left ventricular thrombus formation after acute anterior MI.
Methods and Results: Seventy patients with a first anterior AMI were prospectively and consecutively enrolled. Patients with previous MI, autoimmune disease, collagen vascular disease and arterial or venous thrombosis history were excluded from this study. At the time of hospitalization, key demographic and clinical characteristics were collected including age, gender, ethanol intake and presence of traditional risk factors for atherosclerosis (hypertension, diabetes, smoking, hyperlipidemia, positive family history). Patients were evaluated for echocardiographic data, blood chemistry and ACA. Two-dimensional and Doppler echocardiographic examinations were performed in all patients within the first week and at 14, 30, 90, and 180 days after MI. LV thrombus was detected in 30 (42.8%) patients. ACA IgM levels were significantly higher in the patient group with LV thrombus than in the group without thrombus (12.44±4.12 vs. 7.69±4.25 mpl, p=0,01). ACA IgG levels were also found higher in the group with LV thrombus (24.2±7.5 vs.17.98±6.45gpl, p=0.02). Univariate analysis showed that LV thrombus formation was associated with a higher ACA IgM levels (beta=0.02, p=0.01), a higher ACA IgG levels (beta=1.75, p=0.02), a lower initial ejection fraction (beta=0.04, p=0,001) and a higher initial wall motion score index (beta=-0.86, p=0.01).
Conclusions: Our data demonstrate that beside the low ejection fraction and higher wall motion score index, higher ACA IgM and ACA IgG levels are associated with LV thrombus formation in patients with anterior MI.

P1087 New rapid ecarin clotting time assay stongly correlates with bivalirudin concentration among percutaneous coronary intervention patients

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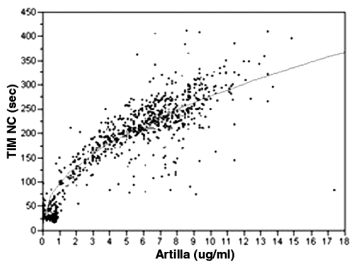
Background: Bivalirudin, a direct thrombin inhibitor (DTI), has recently been approved for anti-coagulation during percutaneous coronary intervention (PCI). Clinical monitoring of the anti-coagulant effect of DTI's is limited due to the uncertain correlation between DTI concentration and both the aPTT and Activated Clotting Time (ACT). A new point-of-care assay based on the Ecarin Clotting Time (RapidPoint Thrombin Inhibitor Management(TIM-ECT), Pharmanetics), has been developed to more accurately assess the level of anti-coagulation with DTI use.
Methods: We enrolled 233 consecutive patients at five clinical centers undergoing PCI using bivalirudin for anti-coagulation. Blood samples were collected at five pre-specified time points in each patient. For each sample, ACT (Hemochron, Hemochron Pro, or ProDM), TIM-ECT (citrated and non-citrated), and anti-Factor IIa levels (a direct measure of bivalirudin concentration) were determined. The correlation coefficients between assessments of anti-coagulation were calculated by log transformed regression. Results: Of the 233 patients, 172 were male. The mean age was 67± 11 years. Glycoprotein IIb/IIIa inhibitors were used in 52% of cases. In 993 samples (i.e. mean 4.3 samples per patient, there was a very strong correlation between both citrated and non-citrated TIM-ECT and anti-Factor IIa levels (r^2=0.89 and 0.85, respectively). The correlation between ACT and anti-Factor IIa levels was moderately strong (r^2=0.72).
Conclusion: This study demonstrates that the TIM-ECT test reliably measures the anti-coagulant effect of bivalirudin and is superior to ACT. This test may have important application in the clinical monitoring of patients receiving direct thrombin inhibitor therapy.



P1088 No clinically significant interaction between ximelagatran, an oral direct thrombin inhibitor and amiodarone

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Purpose: Ximelagatran, an oral direct thrombin inhibitor, is currently in clinical development for the prevention and treatment of thromboembolism. After oral administration, ximelagatran is rapidly absorbed and bioconverted to its active form melagatran. This study investigated the potential for interaction during coadministration of ximelagatran and amiodarone.
Method: In this single-blind, randomized, placebo-controlled, parallel-group study, 26 healthy male subjects (age, 20-45 years) were randomized to receive either 36 mg oral ximelagatran or placebo bid for 8 days. On day 4, a single dose of 600 mg oral amiodarone was administered with the morning ximelagatran dose. On days 3 and 4, plasma concentrations of melagatran were determined at intervals up to 12 h after the morning dosing. Plasma amiodarone and desethylamiodarone (DEA; active metabolite of amiodarone) concentrations were measured up to 120 h after amiodarone dose. Blood samples were also taken at specified times on days 3 and 4 to measure the activated partial thromboplastin time (APTT).
Results: Mean melagatran AUC0-12 and Cmax estimates following ximelagatran+amiodarone treatment were 2.29 μmol.h/L and 0.44 μmol/L, respectively, compared with the AUC0-12 and Cmax values of 1.89 μmol.h/L and 0.36 μmol/L following ximelagatran alone. The ratio of the mean melagatran AUC0-12 and Cmax estimates for ximelagatran+amiodarone versus ximelagatran was 1.20 (90% CI, 1.16-1.25) and 1.23 (90% CI, 1.18-1.28), respectively. The concentration-effect relationship of melagatran on APTT was not altered by amiodarone coadministration. Geometric mean ratios of the AUC0-120 values for amiodarone+melagatran versus amiodarone+placebo were 0.87 (90% CI, 0.69-1.08) for amiodarone and 1.00 (90% CI, 0.89-1.12) for DEA. For Cmax, the geometric mean ratios were 0.86 (90% CI, 0.66-1.11) for amiodarone and 0.92 (90% CI, 0.77-1.09) for DEA. These 90% CIs, except for amiodarone Cmax, were within the predefined no-effect boundary of 0.70-1.43. The minor decreases in exposure to amiodarone and DEA are not likely to be clinically relevant, given the high variability of their pharmacokinetic properties.
Conclusions: This study showed no evidence of a clinically significant interaction between ximelagatran and amiodarone with respect to melagatran, amiodarone and DEA pharmacokinetics or the effect of melagatran on APTT; and there is unlikely to be a need for dose adjustment of either drug when used in combination.

REPERFUSION WITH THROMBOLYTIC THERAPY

P1089 Prehospital thrombolysis accelerates myocardial reperfusion compared to percutaneous coronary intervention for STEMI: results of the START in Berlin pilot study

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Randomized trials had proven superiority of PCI over thrombolysis (TL) in AMI when performed with similar time delays. However prehospital (p) initiation of fibrinolytics saves critical time compared to in hospital administration. START is the first prospective, randomized study measuring the extent of earliest possible myocardial reperfusion by pTL compared with PCI.
Methods: Patients (Pts) with STEMI less than 6 hours, enrolled by MICU physicians, were randomly asigned to pTL with reteplase or PCI with stenting. 12-lead ECGs were obtained in both groups at MICU arrival (MICU 0), after 90 min (MICU 90) and 180 min (MICU 180) as well as just before start of TL or PCI, after 90 min and 180 min.
Results: From October 2000 to March 2002, 88 Pts were enrolled (44-pTL, 44-PCI). There were no differences between the two groups regarding baseline characteristics. Median time delay from symptom onset (SO) to MICU arrival was 70 (45-125) min, from SO to first bolus of TL 85 (61-137) min and from SO to first balloon 143 (110-195) min. Rates of complete ST resolution (>70%) 90 min and 180 min after the first diagnostic ECG (MICU 0) were higher in the pTL group compared to PCI (MICU 90: 46% vs 29%, MICU 180: 60% vs 52%) while no differences were observed 90 min and 180 min after start of pTL or PCI.
Conclusions: Initiated very early in the prehospital setting, mainly < 2 hours after symptom onset, TL is associated with a higher extent of early myocardial reperfusion compared to PCI. Considering facilitated PCI as a future strategy for optimal management of AMI, pTL should be included in the pharmacological pretreatment.

P1090 Association between fibrinogene on platelet surface and restenosis after thrombolysis

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Purpose: Increased platelet activation is known to be responsible for failure of thrombolysis due to thrombotic reocclusion. Platelet activation is known to be an independent risk factor for acute ischemic events after Percutanous Coronary Intervention (PCI). Beneficial effects on restenosis by thrombolysis due to removal of residual thrombus as site for ongoing local platelet recruitment are less well understood. Our study aimed to investigate, whether thrombolysis in patients with Acute Myocardial Infarction (AMI) influences platelet reactivity and restenosis after stent-implantation during rescue PCI.
Method: In patients with AMI (n=63) platelet activation and blood thrombogenicity were obtained by flow cytometry. 47 patients were referred to our hospital for primary PCI, 16 patients for rescue PCI after failed thrombolysis. Intravascular Ultasound (IVUS) detected plaque rupture in all patients. Blood samples were taken before intervention in all patients and after 5 months, when IVUS was repeated during control angiography in 33 patients treated with heparin coated coiled wire stent. No patient received GP IIb/IIIa receptor antagonists.
Results: Before intervention platelet activation was significantly increased in patients treated with thrombolysis compared to control patients as indicated by 11% (6,1;15,6) versus 7,5% (6,5;10,5) P-selectin positive, 42,2% (30,3;52,5) versus 30,3% (24,7;38,1) CD 63 positive and 12,2% (8,1;16,2) versus 10% (8,2;13,1) thrombospondin positive platelets. Fibrinogene bound to platelet surface was detectable in 39,7% (27,2;51,3) after thrombolysis versus 42,4% (31,3;50,4) in control patients. 24 hours after intervention fibrinogene positive platelets were even more decreased in patients treated with thrombolysis and heparin coated stent. There was no difference in patients treated with stenting only. After 5 months no restenosis was found in patients treated with thrombolysis and heparin coated coiled wire stent while 33% of patients treated with stent implantation only presented with instent restenosis.
Conclusion: P-selectin, CD 63 and thrombospondin are independent predictors for acute ischemic events while changes in fibrinogene bound to the platelet surface seem to predict in stent restenosis. For improving short and long term results a combination of thrombolysis with platelet blockade might be reasonable for all patients with AMI.

P1091 Impact of reocclusion on long-term survival following fibrinolytic therapy: 10-year follow-up of the APRICOT-1 Trial

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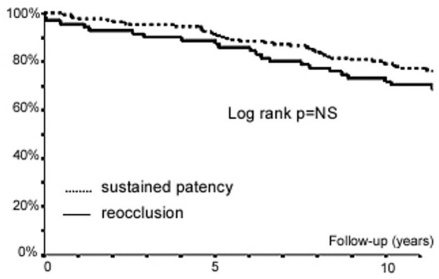
Background: Reocclusion after successful fibrinolysis occurs in about 30% of patients, the majority in the absence of clinical reinfarction: asymptomatic reocclusion. Whereas early symptomatic reocclusion has been associated with a twofold increased risk of mortality, the prognostic impact of reocclusion after the acute phase remains to be determined.
Methods: In the APRICOT-1 trial 248 patients had an open infarct related artery at 24-hour angiography, with follow-up angiography at 3 months. Outcome was recorded using medical charts and information from the general physician and municipal registries.
Results: Reocclusion was observed in 71 patients (29%). Mean clinical follow-up was 9.8+3.4 years, 71% having more than 10 years follow-up. No difference in death from any cause was observed between patients with and without reocclusion. However, 10-year cardiac death was higher in those with reocclusion: 22% vs. 11% (Figure, p = 0.06). This difference was primarily caused in the subset of patients in whom 3-month reocclusion had occurred asymptomatically.



Reocclusion and 10-year cardiac death.

Conclusions: After demonstrated coronary patency following fibrinolytic therapy, patients who survived the first 48 hours had an excellent 10-year prognosis. Whereas reocclusion was associated with a markedly increased risk of cardiac mortality, even in case of asymptomatic reocclusion, all cause mortality did not differ from patients with sustained patency.

P1092 Primary angioplasty versus intravenous thrombolysis with a reasonable amount of early angioplasty in acute myocardial infarction

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Background: Several studies for the treatment of acute ST elevation myocardial infarction (AMI) showed that primary angioplasty (PA) is superior to thrombolysis (TL). However, the use of early angioplasty for failed thrombolysis has been very low in these studies. Therefore we investigated if the benefit of PA over TL will still be present, if early (<24 hours after TL) angioplasty is performed in a reasonable amount after TL.
Methods: We analysed the data of the Acute COronary Syndromes (ACOS) registry, which was performed at 154 hospitals from 7/2000-11/2002.
Results: Out of 7603 patients (pts) recruited in ACOS, 1453 pts with ST elevation AMI were treated with PA and 608 with TL within 12 hours after symptom onset. Out of the pts treated with TL 130 (21.4%) were treated with angioplasty (PCI) within 24 hours after start of TL. Pts characteristics and hospital data are shown in the table.
By multivariate analysis after adjusting for confounding parameters, PA remained an independent predictor of a lower death rate (multivariate OR: 0.52, 95%CI: 0.35-0.78, p=0.002).

	PA	TL+-PCI	p-value
	n=1453 (100%)	n=608 (100%)	
age (years)	62.7	62.5%	ns
female gender	25.2%	22.4%	ns
anterior wall infarction	45.2%	47.9%	ns
heart rate <100/minute	12.0%	15.3%	0.041
systolic BB <100mmHg	12.3%	11.2%	ns
events until discharge			
death	5.7%	9.2%	0.004
non-fatal reinfarction	1.8%	6%	<0.001
non-fatal stroke	0.3%	0.9%	0.075
death/MI/stroke	7.6%	15.1%	<0.001

Conclusions: Early PCI after initial TL was performed in 21.4% of pts in ACOS. However, PA was still associated with a lower mortality (5.7% versus 9.2%, multivariate p = 0.002) as well as a lower morbidity compared to TL ± PCI.

P1093 Double bolus of 0.75 MU streptokinase plus enoxaparin versus front-loaded alteplase plus unfractionated heparin in ST-segment elevation myocardial infarction

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Background: We have previously reported a significantly higher rate of coronary reperfusion (CR) and a lower in-hospital mortality with a new 'accelerated' streptokinase (SK) regimen (double bolus of 0.75 MU in 10 min) in combination with unfractionated heparin (UFH), as compared with the traditional SK regimen of 1.5 MU in 60 min plus UFH, in patients with ST-segment elevation myocardial infarction (STEMI).
Objective: The efficacy and safety of the combination SK double bolus of 0.75 MU in 10 min plus enoxaparin (Enox) was compared with the combination of front-loaded alteplase (t-PA), given 100 mg/90 min, plus UFH.
Methods: In a prospective, open study, 162 patients (age 20-74 years) admitted within the first 6 hours after the onset of STEMI were divided in two subgroups: (1) ASKEnox subgroup (n=102) received an i.v. bolus of 40 mg Enox followed by 0.75 MU SK in 10 min. A second bolus of 0.75 MU SK was administrated only if no bedside signs of CR were detected within the 50 minutes following thrombolysis. Enox was administered 1 mg/kg subcutaneously every 12 hours for 5-7 days. (2) t-PAUFH subgroup (n=60) received front-loaded t-PA: 15-mg bolus followed by 50 mg in 30 min and 35 mg within the next 60 min; the t-PA infusion was followed by UFH 1,000 IU/hour for the next 48-72 hours. All patients received aspirin 325 mg/day. Three criteria for noninvasive CR were used: rapid cessation of chest pain; rapid reduction of the sum of ST-segment elevations by more than 50% of the initial value; rapid increase of the plasma CK and CK-MB concentrations with a peak within the first 12 hours. The incidence of haemorrhagic events, the rate of CR, and the in-hospital mortality were evaluated.
Results: Two patients from the t-PAUFH subgroup had non-fatal stroke (one haemorrhagic, one ischemic). No other major haemorrhagic events were registered in either subgroup. The rate of CR was 78.4% in the ASKEnox subgroup and 70.0% in the t-PAUFH one (P=0.311, NS). Six patients (5.88%) from the double bolus SK group and 3 patients from the t-PA one (5.0%) died (P=0.906, NS).
Conclusions: ASK plus Enox is at least as safe and efficacious a combination as front-loaded t-PA plus UFH. Larger comparative studies are needed for a definitive conclusion.

P1094 Coagulation activation induced by full dose reteplase is blunted by half dose reteplase and abciximab

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Background: Fibrinolysis in acute myocardial infarction activates blood coagulation and may favour reocclusion or ischemic complications. The aim of the GUSTO V Italian Hematologic Substudy was to compare the effects of full-dose reteplase versus half dose reteplase combined with full dose abciximab on the markers of coagulation activation soon after myocardial infarction.
Methods and Results: We measured the plasma levels of prothrombin fragment 1+2 (F1+2, a marker of prothrombin activation) and the thrombin/antithrombin complex (TAT, a marker of thrombin generation) in 67 patients participating in the GUSTO V study who were randomised to receive full-dose reteplase (34 patients) or the combination of half- dose reteplase and full-dose abciximab (33 patients), in addition to heparin. Blood samples were obtained at baseline, and after 90 minutes and 24 hours. There was no difference in the baseline plasma levels of F1+2 or TAT between the two groups. Median F1+2 levels at 90 minutes were significantly lower In the patients receiving combination therapy than in those receiving reteplase alone (2.0 vs 3.2 nmol/L; P=0.006), the median increase being significantly greater in the latter (P=0.007); the same was true in the case of median 90-minute TAT levels (6.7 vs 7.9 ng/L; P=0.016), with a significantly higher median increase in the patients receiving reteplase alone (P=0.005). There was no between-group difference in the plasma levels of either F1+2 or TAT after 24 hours.
Conclusion: In patients with acute myocardial infarction, the combination of half-dose reteplase and full-dose abciximab blunts the increase in prothrombin activation and thrombin generation observed with full-dose reteplase.

P1095 Antecedent thrombolytic therapy followed by planned rescue percutaneous coronary intervention for acute myocardial infarction, compared with primary percutaneous coronary intervention

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Objective: We investigated the clinical benefit of prior thrombolytic therapy with mutant t-PA, monteplase, before percutaneous coronary intervention (PCI) for early reperfusion in patients with acute myocardial infarction (AMI). Method: Forty patients who presented within 12 hours of symptom onset with ST segment elevation consistent with AMI at admission were enrolled and randomly assigned to treatment with mutant t-PA followed by rescue PCI (group M) or primary PCI (group P). PCI was performed if there was TIMI 2 flow or less at the first coronary angiograpy. Results: There were no significant differences in the baseline characteristics including age, sex, coronary risk factors, and infarct area between the two groups. TIMI 3 flow was observed higher in group M than in group P (43% vs 15%; p=0.013),and resulted in undergoing fewer PCI in group M. Peak creatine kinase values were lower in patients with anterior myocardial infarction in group M (2265 $\pm$ 1739 vs 3958 $\pm$ 2658 IU/L, p=0.013), though no difference for inferior wall myocardial infarction. There were no differences in hemorrhagic complications (5% vs 8%) and the other in-hospital complications between the two groups. Conclusion: These findings suggest that administration of mutant t-PA prior to PCI for AMI is an effective modality of facilitating early recanalization in patients with AMI without augmentation of adverse events, especially in patients with anterior wall myocardial infarction.

P1096 Activation of the contact system and inflammation during thrombolytic therapy in myocardial infarction

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Background: Thrombolytic therapy activates the contact system, and factor XII activation may in turn activate the coagulation cascade and produce inflammation. It is not known whether an early inflammatory response is induced by thrombolytic therapy in acute myocardial infarction.
Methods and Results: We prospectively measured the plasma levels of activated factor XII (FXIIa), prothrombin fragment 1+2 (F1+2)(as indices of the contact phase and factor Xa activity), interleukin 6 (as an index of inflammation) in 39 patients hospitalised for acute myocardial infarction within 12 hours of symptom onset: 26 receiving thrombolytic therapy and 13 heparin alone. Blood samples were collected at baseline, and after 90 minutes and 24 hours. The patients undergoing thrombolysis showed a significant early increase in FXIIa (from 2.2 ng/ml at baseline to 4.7 ng/ml after 90 minutes; P=0.0001), and F1+2 (from 1.4 ng/ml to 2.1 ng/ml; P=0.0001), whereas the 24-hour levels were not different from baseline levels. The levels of interleukin 6 significantly increased during the first 90 minutes (from 3.9 mg/ml to 6.3 mg/ml; P=0.001), and were even higher after 24 hours (11.9 ng/ml, P=0.0001). There were no changes in these parameters in patients receiving heparin alone, except for a 24-hour increase in interleukin 6 levels.
Conclusions: In patients with acute myocardial infarction receiving thrombolytic therapy, early signs of inflammation parallel the activation of the contact system and of the coagulation cascade and might contribute to microvascular obstruction and reperfusion injury.

P1097 Activated factor XII levels do not influence the outcome of thrombolytic therapy

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Introduction: Factor XII is a component of the contact system of blood coagulation. When activated (XIIa), it has been shown to initiate the intrinsic clotting pathway, as well as to participate in kinin formation. The exact physiological function of XIIa remains unclear. Factor XII deficiency does not result in excess bleeding but is instead associated with increased thrombotic risk. It is now believed that Factor XII is in fact an anti-thrombotic protein and has an important role in fibrinolysis. It has been shown that XIIa will convert plasminogen to plasmin and that XII can inhibit thrombin-induced platelet aggregation. We tested the hypothesis that XIIa levels may be one of the many factors influencing the success or failure of thrombolytic therapy when used in the treatment of acute myocardial infarction.
Methods: Patients studied were those presenting within ten hours of the onset of typical cardiac chest pain, and found to have characteristic ST elevation on a 12 lead ECG. Failure of thrombolysis was defined as failure to obtain at least 50% resolution of ST elevation at one hour after the initiation of thrombolytic therapy with streptokinase. This was applied to the lead showing the most ST elevation on the 12 lead ECG recorded just prior to thrombolysis. Patients with new left bundle branch block or a contraindication to thrombolytic therapy were excluded. Venous blood samples were obtained immediately prior to thrombolytic therapy (Time, T=0), and eighteen hours later (T=18). XIIa levels were calculated by means of ELISA by a technician blinded to the ECG findings.
Results: 82 patients were studied. XIIa levels were successfully obtained in 78 patients at T=0, (mean level 2.33ng/ml, range 0.5-10.5), and 74 patients at T=18, (mean level 2.52ng/ml, range 0.8-7.5).In 38 patients thrombolysis was successful (T=0 mean level 2.36ng/ml, range 0.90-10.50, T=18 mean level 2.56ng/ml, range 0.8-4.7). In 44 patients thrombolysis was unsuccessful (T=0 mean level 2.31ng/ml, range 0.50-6.60, T=18 mean level 2.49ng/ml,range 0.8-7.5).
Conclusion: XIIa levels did not differ significantly between patients where reperfusion was successful and in those in whom it failed. This was true both at T=0 and T=18. XIIa levels did not change significantly between Time=0 and Time=18. Levels of XIIa had no influence on the success or failure of thrombolytic therapy.

P1098 Failure of thrombolytic therapy to reopen the infarct related vessel in non-smokers: results of the TATAMI study

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Background: Intravenous administration of thrombolytic therapy and primary percutaneous transluminal coronary angioplasty (PTCA) are the two validated coronary artery reperfusion strategies in the treatment of acute myocardial infarction (MI). Smoking status has shown to have an impact on outcome of myocardial infarction, smokers receiving thrombolytic therapy having better immediate and short-term outcome than nonsmokers. Whether this could be explained by a different efficacy of the reperfusion strategies according to smoking status on admission has never been evaluated prospectively. Such was the aim of the TATAMI study.
Methods: Patients with an acute ST-elevation MI were randomly assigned in a 1:1 ratio to receive thrombolytic therapy (reteplase) or to undergo an immediate PTCA. Efficacy of the treatment was defined as 1) the presence of a TIMI grade flow =3 on the infarct related artery within days 5-8 after admission and 2) no need to undergo a rescue revascularization procedure (either by PTCA or coronary artery bypass grafting) within 8 days after admission.
Results: A total of 75 patients (64 men, mean age= 68.6±15.0 years) were included in the study: 36 were randomised to receive reteplase (group A/15 smokers – 21 nonsmokers) and 39 to undergo a primary PTCA (group B – 23 smokers – 16 nonsmokers). The procedure was successful in 58.8% of group A pts and 91.7% of group B pts (p=0.02). Percentages were respectively 89.5% for smokers and 59.4% for non smokers (p=0.03). No significant interaction was observed between treatment arm and tobacco (p=0.83). In the multivariate analysis, the odds ratio of having a successful procedure is multiplied by 7.6 for the use of PTCA and by 5.5 for smokers.
Conclusions: This randomized trial shows that smoking status on admission is a key-factor associated with a higher reopening rate of the infarct related vessel in the acute phase of myocardial infarction. Since nonsmokers do not benefit from a thrombolytic treatment, they should be offered to undergo an immediate PTCA.

P1099 Benefical effects of r-PA in combination with abciximab: platelet-/leukocyte-interactions and coagulation system

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A hypercoagulable state and the involvement of platelets and leukocytes (monocytes and granulocytes) play a pivotal role in the pathogenesis of acute myocardial infarction.
Methods: We investigated the effects of full dose reteplase (r-PA, 2x 10 IU) versus half dose r-PA (2x 5 IU) in combination with a standard abciximab infusion on activated factor XII (FXIIa), on prothrombin fragment 1+2 (F1+2), on percentage of CD41-positive monocytes and granulocytes in 38 patients with acute ST-segment elevation myocardial infarction. 28 healthy persons served as control group.
Results: In the r-PA/abciximab group, there were lower FXIIa, F1+2 levels and a marked decrease of the percentage of CD41-positive monocytes and granulocytes vs. the r-PA group.
Conclusions: In vivo, the thrombolytic regime with r-PA in combination with abciximab causes a lower extent of procoagulatory effects and lower platelet-monocyte- and platelet-granulocyte-aggregates vs. the r-PA group. The combination regime thereby could have benefical effects on platelet-induced leukocyte activation and leukocyte-induced proinflammatory- and cytotoxic effects. This could be, at least in part, a possible explanation of the observed significant lower rates of reinfarction, recurrent ischaemia and the lower use of percutaneous coronary interventions within 6 hours in the combination group in the GUSTO-V trial.

CORONARY ANGIOPLASTY IN ACUTE AND CHRONIC CORONARY SYNDROMES

P1100 Angioplasty in cardiogenic shock due to myocardial ischaemia: a 5-year follow-up study

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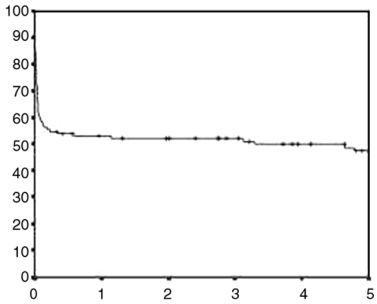
Background: Up to 10 percent of myocardial infarction are complicated by cardiogenic shock (CS) with a high mortality rate. Early revascularization improved survival at 6 months and the results were sustained at one year. No long-term data are available, we report our experience of late outcome after angioplasty (PTCA) in patients (pts) with CS due to myocardial ischemia (MI).
Materials and Methods: Between 1986 and 2001, all pts suffering from CS due to MI who underwent PTCA were reviewed. CS was defined as vasopressors infusion, systolic blood pressure <90 mmHg, the use of intraaortic balloon counterpulsation or clinical evidence of end-organ hypoperfusion. We analyzed their five year follow-up outcome.
Results: 115 pts fulfilled the study criteria, there were 83 males with a mean age (±SD) of 63±11, 47 pts received thrombolysis. The culprit lesion was mainly present in the left coronary arteries (left main 5, LAD 43, circumflex 19%). Although the number of diseased vessels was equally distributed, only one artery was treated in 90% during the emergency procedure, corresponding to the treatment of 1 to 4 lesions/pts (78.3, 19.1, 1.7 and 0.9%, from 1 to 4 lesions respectively). PTCA was successful in 96/143 lesions treated (84%), and since 1991, mainly since 1997, stents were implanted in 54/136 procedures (successfully in 53 cases). One month, 1 and 5 years survival were 59±5, 53±5 and 47±5%, respectively [fig]. The survival was significantly (p=0.008) improved with a successful PTCA at 1 (58±5 vs 26±10%) and 5 years (52±5 vs 26±10%).



5 year survival (Kaplan-Meier).

Conclusions: Prognosis of pts suffering from cardiogenic shock due to MI and who underwent PTCA is favorable up to five years if they survived one month after PTCA. Therefore, early PTCA should be strongly recommended in these pts.

P1101 Simple predictors of outcome in acute myocardial infarctiontreated by primary percutaneous coronary intervention

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Background: Although the outcome of patients with acute myocardial infarction (AMI) has improved significantly with the advent of primary percutaneous coronary intervention (PCI), it is of great importance to predict patients who cannot be saved by primary PCI. The present study was undertaken to verify indicators that could predict the outcome of AMI patients treated by primary PCI.
Methods: A total of 635 consecutive patients with AMI who underwent primary PCI within 12 hours of onset were studied. Hemodynamic changes were monitored by right heart catheterization, left ventricular ejection fraction (LVEF) was evaluated on admission, and serial creatine kinase (CK) was measured for 48 hours. The end point of this study was 30-day cardiac mortality. Multivariate logistic regression analysis was applied to examine the determinants of 30-day mortality. Variables, which were assessed simultaneously, included age, gender, previous AMI, prodromal angina, coronary risk factors, coronary anatomy on admission, results of PCI including no-reflow, time from onset to PCI, peak CK, LVEF, and post-PCI Killip class, left ventricular filling pressure (LVFP), cardiac index (CI) and heart rate/systolic blood pressure (HR/SBP).
Results: Forty-five cardiac deaths occurred during the 30-day period. The following measurements assessed at the end of primary PCI were significantly effective in predicting 30-day mortality as analyzed by multivariate logistic regression: LVFP (LVFP >18 mmHg, OR; 11.98, p=0.0006), HR/SBP (HR/SBP >1.0, OR; 17.64, p=0.0007), Killip class (Killip class >2, OR; 10.36, p=0.0028), and CI (CI <2.2, OR; 6.22, p=0.0128). However, right heart catheterization was not performed in 28% of patients. In contrast, post PCI Killip classification (sensitivity 82%, specificity 91%, c statistic 0.923) and HR/SBP (sensitivity 67%, specificity 97%, c statistic 0.868) were available in 100% of patients, and appeared to be excellent practical predictors of 30-day mortality. Moreover, post-PCI HR/SBP was the critical value in the setting of post PCI coronary care: there were 30 patients with HR/SBP >1.0 at 24 hours after onset, 19 of whom (63%) died within 30 days, whereas 11 of 13 patients (85%) who had post-PCI HR/SBP >1.0 that improved to <1.0 within 24 hours after onset survived.
Conclusion: Post-PCI Killip class and HR/SBP are excellent predictors of 30-day mortality in AMI patients treated by primary PCI.

P1102 Mechanism of pexelizumabs mortality benefit in acute myocardial infarction patients treated with primary percutaneous coronary intervention

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In the COMMA (COMplement inhibition in Myocardial infarction treated with Angioplasty) study of 814 patients with ST elevation acute myocardial infarction presenting within 6 hours of symptom onset, pexelizumab (Pex) bolus 2.0mg/kg over 10 minutes, plus an infusion of 1.0 mg/kg over 20 hours, significantly reduced all cause mortality at 90 days 5.9% (16/271) placebo versus 1.8% (5/281) bolus plus infusion (p=0.014); whereas patients receiving only a bolus of Pex had an intermediate mortality of 4.2% (11/262).
Although the primary hypothesis was that Pex would reduce infarct size, no significant difference was observed in this principal outcome assessed by serial CKMB release over 72 hours. We, therefore, explored alternative mechanisms that might provide insights into the survival benefit. The table (left panel) shows 90-day mortality (%) in each of the 3 treatment groups categorized by time to treatment. Pex's impact on mortality appeared to be not only independent of time to treatment, but also of ultimate infarct size as quantified by CKMB ng/[mLh]. Interestingly, the survival benefit of Pex was not accompanied by improved angiographically defined TIMI perfusion post-PCI, nor influenced by territory at risk as measured by ST segment elevation (mm) on admission, nor the extent of ST segment resolution (% pts) following PCI [right panel of the table].

Mortality (%) and Other Outcomes

Time to Rx	0-2 h	2-4 h	>4h	n	Infarct size	% of 3 TIMI 3	Sum ST	>70% ST resolution
n=	263	316	133					
Placebo	5.6	3.9	10.4	271	4393	87%	9.0	49
Bolus Px	3.3	2.7	9.7	262	4526	87%	10.5	54
Bolus/Infusion Px	1.2	1.9	1.9	281	4713	88%	10.0	48

These unexpected data imply an effect of Pex which appears to be independent of conventional treatment modulators including time to treatment and raise the possibility of unrecognized mortality benefits of complement inhibition on inducible nitric oxide synthase, cardiac remodeling and apoptosis that warrant confirmation and further investigation.

P1103 High in-hospital and 1-year mortality regardless of infarct location in patients with ST-elevation myocardial infarction not receiving reperfusion therapy. Results of the MIR+ registry

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Purpose: Recent large randomised clinical trials in patients with acute ST elevation myocardial infarction (STEMI) receiving thrombolysis or primary percutaneous coronary intervetion report about a significant higher mortality in patients with anterior infarct location compared to patients with inferior infarcts. We have evaluated the "real world" mortality in patients with STEMI < 24 hours enrolled in the large German MIR+ registry with respect to reperfusion therapy, age and infarct location.
Methods: A total of 28,913 patients with STEMI were enrolled into this registry and in-hospital mortality was obtained in over 99% of the patients. In a predefined subgroup of 7,141 patients 1-year mortality could be evaluated. We have divided the patients into 6 subgroups according to age (<75 and > 75 years) and the use of reperfusion therapy (thrombolysis, primary PCI, no reperfusion therapy).
Results: Thrombolysis was used in 51.1% vs. 53.8%, primary PCI in 14.3% vs. 14.0% and no reperfusion therapy in 33.7% vs. 31.1% of patients with anterior and inferior infarct location, respectively. The in-hospital (1-year) mortality rates are shown in the table.
Conclusions: In contrast to patients treated with thrombolysis or primary PCI patients not receiving reperfusion therapy have a high in-hospital and 1-year mortality with no difference between patients with inferior and anterior infarcts. In particular patients > 75 years have a very high mortality. Therefore all efforts should made to increase the use of reperfusion therapy in patients with STEMI regardless of infarct location.

In-hospital (1-year) mortality

	Anterior < 75 yrs	Inferior < 75 yrs	Anterior > 75 yrs	Inferior > 75 yrs
Thrombolysis	11.0 (17.8) %	6.4 (10.0) %	25.4 (47.4) %	21.8 (35.8) %
Primary PCI	5.1 (9.2) %	3.8 (7.7) %	14.2 (26.5) %	10.3 (18.6) %
No reperfusion	12.5 (24.5) %	11.1 (21.5) %	28.1 (60.5) %	29.7 (64.1) %

P1104 Continuous 12-lead ST monitoring and long-term prognosis following successful coronary stenting: four years follow-up in GENERATION study

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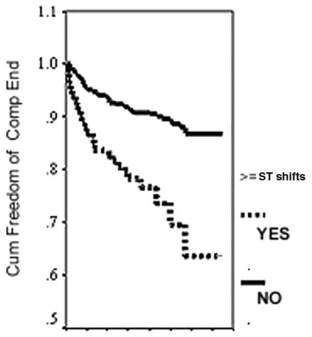
Background: 12-lead ECG monitoring of the ST segment is more sensitive than patients' symptoms for detecting ischemia after catheter-based interventions. However, its usefulness for the prediction of long-term prognosis after successful coronary stending (CS) was not thoroughly investigated.
Methods: The present study was part of the prospectively designed GENERATION study which investigated the impact of several factors including continuous 12-lead ECG monitoring on the long-term prognosis following successful CS. All patients underwent continuous ST segment monitoring for 24 hours following successful CS with a computer-assisted 12-lead ECG-ischemia monitoring device. An ST ischemic episode was defined as a transient ST-segment depression or elevation in any lead of at least 0.10 mV compared with the reference ECG, lasting for at least 1 min.



Results: One hundrend and one (101/483, 20.7%)patients had at leats one ST shift during the 24 ECG monitoring. The incidence of the composite of cardiac death or myocardial infarction by the 4 years of follow up in the whole population was 13.9%. Pts with ≥1 ischemic shifts during continuous ST segment monitoring were on significantly higher risk for the composite endpoint than those without ST shifts (25.5% vs. 10.9%; P<0.001) (figure).
Conclusions: The results of the GENERATION study suggest that continuous ST segment monitoring is a useful tool for the prediction of long-term ischemic complications following successful CS.

P1105 Late percutaneous transluminal coronary angioplasty of occluded infarct-related arteries promotes myocardial electrical stabilisation

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Background: Long term patency of infarct related artery (IRA) is an independent predictor of survival in patients with previous myocardial infarction (MI), however it is unclear if myocardial electrical stabilization play a role in this late mortality reduction.
Aim of the Study: to assess QT dispersion (QTd) and late potentials (LP), two indexes of arrythmic risk, in patients with previous myocardial infarction undergone to late reopening of occluded IRA.
Methods: We studied QT/corrected-QT (c-QT) dispersion and LP before and 1,3, 6 months after an attempt of late recanalization of IRA in 31 consecutive patients (26 males, aged 57± 8 years) with previous MI and single vessel disease of IRA (occlusion or sub-occlusion) diagnosed ≥ 4 weeks after the acute myocardial infarction. Patients underwent PTCA 131± 94 days after acute MI. IRA reopening was successful in 24 patients (77%) (Group A), but failed or it was impossible for technical reasons in 7 patients (33% – Group B). QTd of QT and c-QT was calculated by 3 blinded expert and independent investigators on 3 consecutive cardiac cycles. Signal averaged ECG analysis (Arrhythmia Research Technology 1200 EPX System) was considered positive for LP when two of the following conditions were present: fQRS>114 msec, RMS40<20mV, LAS > 38 msec.
Results: The two groups were similar for age, IRA, ejection fraction, risk factors, pharmacological therapy, distance from MI, basal QTd/QTcd and basal LP prevalence. Group A showed a statistically significant lower LP prevalence after one month from PTCA than before procedure (3/24 vs. 9/24 pts, p<0.03) and reduced QTd and c-QTd (51±9 vs. 72±11 msec, p<0.00001 and 51±10 vs. 76±15 msec, p<0.00001, respectively). LP prevalence, QTd and c-QTd did not vary significantly at 3 and 6 months after the procedure compared with 1 month control. Conversely Group B showed a similar LP prevalence, QTd and c-QTd before and 1,3,6 months after failed PTCA.
Conclusions: IRA patency obtained ≥ 4 weeks after acute MI play a significant role in myocardial electrical stabilization. This phenomenon may contribute to the better outcome of patients with previous MI and long term patent IRA.

P1106 Observations from the registry of the occluded artery trial. Patient and physician preferences for therapy of an occluded infarct-related artery late after myocardial infarction

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Background: OAT is an international randomized trial of late percutaneous coronary intervention (PCI) of an occluded infarct-related artery (IRA) in asymptomatic patients after a myocardial infarction (MI). In a 1997 pre-study registry we reported that 53% of patients with a recent MI underwent a non-primary PCI of an occluded IRA in the absence of a standard clinical indication. Our aim is to report on current clinical practice in trial-eligible but non-randomized patients and compare patient and physician preferences for late revascularization in a prospective registry conducted concurrently with OAT.
Methods: The inclusion criteria for OAT include 1] MI 3 to 28 days prior; 2] no recurrent symptoms or ischemia; 3] IRA with antegrade TIMI flow 0-1 and EF<50%; or, if EF>/=50%, a proximal occlusion of a major artery. Patients are randomized to PCI plus medical therapy or to medical therapy only. Eligible non-randomized patients are entered into the registry.
Results: As of 12/31/02, 1065 patients were randomized and another 210 were registered in 226 centers in 27 countries. Randomized and registry patients had a similar mean age (59 vs. 58 years), proportion of women (22% vs 26%) and % LAD as the culprit artery (37% vs 32%). Patient refusal was the reason for non-randomization in 72%, physician refusal in 19% and other in 10% of cases. These groups were similar in age, sex, IRA, and early MI therapy. Overall, 47% of registered patients had a planned PCI; [31% of patients who refused to participate and 90% of patients whose treating physician had refused participation ($p<0.001$)].
Conclusions: Randomized patients and nonparticipating eligible patients have similar clinical characteristics and proportion of LAD culprits. In patients with an occluded IRA late post MI the rate of selection for PCI has not changed since 1997. OAT-eligible patients who refuse randomization generally do not undergo PCI, which may reflect their apprehension regarding an invasive procedure in the absence of proven benefit. In contrast physicians who refuse enrollment for their patients generally exhibit a strong pro-PCI bias.

P1107 ST-segment elevation in the intracoronary electrocardiogram and the occurrence of angina during angioplasty for detection of myocardial viability

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Distinction of viable, but dysfunctional, myocardium from scar tissue in patients with previous myocardial infarction (MI) has both prognostic and therapeutic significance. The aims of this study were to evaluate the diagnostic value of ST-segment elevation in the intracoronary electrocardiogram (ICE) and the presence of angina pectoris during coronary angioplasty for detection of myocardial viability in patients with recent MI. **Method:** Seventy-one patients (60 men, 54±11 years) with recent Q-wave MI and nonocclusive significant stenosis (>70% diameter stenosis) in the infarct related artery who were referred for angioplasty were included. Myocardial viability was assessed by dobutamine echocardiography. ICEs were recorded from 0.014-inch angioplasty wire before and during the balloon occlusion of the coronary artery. Significant ST-segment elevation was defined as a new or worsening ST segment elevation of at least 1 mm at 80 msec after the J point. During the procedure, patients were questioned about presence or absence of angina pectoris. **Results:** Significant ST elevation in the ICE and angina pectoris were observed 56 (78.9%) and 49 (69%) of the 71 patients. Viability occurred in 52 (92.9%) of 56 patients with and 3 (20%) of 15 those without ST elevation. Viability was detected in 45 (91.8%) of 49 patients with and 10 (45.4%) of 22 those without angina pectoris. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ST elevation for viability were 94.5%, 75%, 92.9%, 80%, and 90.1%, respectively. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of angina pectoris for viability were 81.8%, 75%, 91.8%, 54.5%, and 80.3%, respectively. There were a positive correlation between the number of viable segments and the presence of significant ST elevation in the ICE ($r=0.520$, $p<0.001$) or the presence of angina pectoris ($r=0.344$, $p=0.003$). There was also a good correlation between the number of viable segments and the magnitude of ST elevation in the ICE ($r=0.592$, $p<0.001$). **Conclusion:** This study demonstrated that a simple assessment of ST segment elevation in the ICE or angina pectoris during coronary angioplasty can be used to assess myocardial viability in patients with previous MI. This approach requires no extra cost, and the presence or absence of myocardial viability could be particularly relevant for clinical decision-making regarding adjunctive stent implantation and use of more sophisticated methods to evaluate the result of the procedure.

P1108 Reperfusion therapy in ST-elevation myocardial infarction: results from the Franche-Comte registry of acute coronary syndromes. Reasons for non-reperfusion therapy

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Rationale: In 30-45% of cases, reperfusion therapy in acute ST elevation MI is not performed.
Aim: To determine the reasons for not using reperfusion therapy in patients admitted for ST elevation myocardial infarction, and incidence on 30 day mortality.
Methods: Franche-Comte is a region in eastern France covering 16 200 km^2 and with 1.1 million inhabitants. Between October 1 and March 30 2002, all patients admitted for acute coronary syndromes in one of the 12 hospitals in the region were entered in a prospective registry. Demographic, clinical and ECG data were entered in a logistic regression to determine independent factors for non-use of reperfusion therapy.
Results: Among the 882 patients included, 333(38%) had acute MI with ST elevation. Reperfusion therapy was used in 176/333(53%), 111/333(33%) by thrombolysis, 38/333(11%) by angioplasty and both strategies in 27/333(9%). The main reasons for non reperfusion in 157/333(47%) patients were older age (OR = 1.05/year, $p<0.01$) and delayed admission (OR = 1.05/hour, $p<0.01$). Among the 185/333(56%) patients admitted within the first 6 hours, reperfusion strategy was used in 72% (thrombolysis 50%, angioplasty alone 10% and both 12%) and older age was related to non use of reperfusion therapy (OR = 1.05/year, $p<0.001$). Independent predictors for in hospital death were age (OR = 1.09, $p<0.001$), heart rate (OR = 1.03/beat.min-1, $p = 0.007$). Availability of on site angiography did not influence the rate of reperfusion therapy.
Conclusions: In a population based registry, reperfusion therapy for ST elevation acute MI is performed in 53%; older age and delayed admission are the main reasons for non use of reperfusion therapy.

P1109 Myocardial contrast echo quantitative analysis in acute myocardial infarction treated with successful primary angioplasty: heterogeneity of myocardial perfusion patterns

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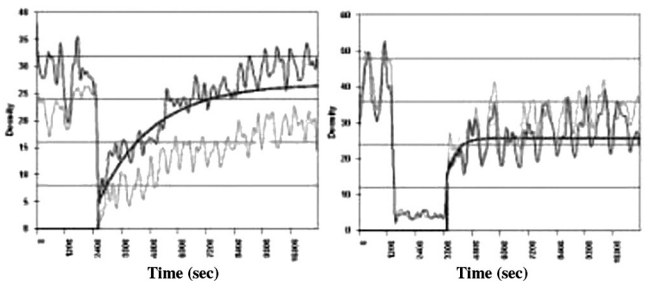
Recanalization of an occluded epicardial coronary artery is not equivalent to restoring myocardial perfusion, due to the possibility of microvascular damage. The aim of our study is to analyse myocardial perfusion patterns in patients (p) with acute myocardial infarction (AMI) treated with successful primary angioplasty (PPTCA) with myocardial contrast echo (MCE).
Methods: Real-time MCE studies were performed in 24 p admitted to hospital for first episode of AMI after PPTCA. MCE were performed in apical views with contrast pulse sequencing (CPS), a new non-destructive method implemented in a Acuson-Siemens Sequoia equipment and digitally stored. Sonovue was administered in continuous infusion. Quantitative analysis was performed in 15 p with TIMI 3 flow in the infarct-related artery and good or acceptable acoustic window. In each p, VDI plateau (A), slope of VDI ascending curve (B) and product AxB were calculated in an akynetic segment (AK) with patchy or homogeneous opacification and compared to the normokynetic segment (NK) with the highest VDI in the same echocardiographic view.
Results: Mean VDI plateau was higher in NK than in AK segments (19.6±1.8 dB and 11.6±1.6 dB, p=0.003) and so were mean VDI slope (1.08±0.24 and 0.70±0.23, p=0.04)and product AXB (22.6±5.7 and 10.8±5.4, p=0.04). Three flow patterns could be defined: AK segments with A and B >50% from corresponding values in NK (40%), AK segments with A or B <50% from control values (40%) and AK segments with depressed A and B (both values <50% from NK) in 20% of the cases.
Conclusions: In spite of succesful PPTCA, different grades of impairment of microvascular perfusion can be identified with quantitative analysis. These findings could be related to myocardial function recovery during follow-up.



Different myocardial perfusion patterns.

P1110 Detecting myocardial salvage after primary angioplasty: comparative study of coronary flow velocity pattern immediately after primary angioplasty and perfusion- metabolism mismatch

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Background: It has been known that perfusion-metabolism mismatch using thallium-201/radioiodinated 15-iodophenyl 3-methyl pentadecaenoic acid (Tl/BMIPP) dual scintigraphy is an indicator of viable myocardium in acute myocardial infarction. Coronary flow velocity (CFV) patterns immediately after primary angioplasty are predictive of recovery of regional and global left ventricular function. In this study we investigated salvaged myocardium from the Tl/BMIPP mismatch and CFV patterns in patients with acute myocardial infarction.
Methods and Results: We studied 21 pts with a first anterior wallmyocardial infarction who underwent primary coronary angioplasty and achieved reflow within 8 hours of onset. By using a Doppler guide wire, CFV pattern were assessed immediately after primary coronary angioplasty. Tl/BMIPP dual single photon emission tomography (SPECT) performed within 48 hours after onset. The left ventricle was divided into 20 segments, and regional myocardial uptakes of the tracers in each segment were scored from 0 (normal) to 3 (no activity). A severity score was determined from the extent of the score. The extent of discordance in severity score between Tl and BMIPP defined as the Tl/BMIPP mismatch. We investigated the relationship between Tl/BMIPP mismatch and CFV pattern. By regression analysis, Tl/BMIPP mismatch correlated well with deceleration time of diastolic flow velocity ($r=-0.61$, $p<0.001$).
Conclusions: CFV patterns were correlated well with Tl/BMIPP mismatch. CFV patterns measured immediately after reperfusion may be useful indicator for early prediction of myocardial salvage.

MYOCARDIAL TISSUE CHARACTERIZATION/FUNCTION

P1111 The assessment of cardiac toxicity of high-dose continuous infusion 5-fluorouracil with ultrasonic myocardial tissue characterization

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Aim: A prospective clinical study was performed to determine the incidence of cardiac toxicity under treatment of high-dose continuous 5-fluorouracil (5-FU) infusion with calcium leucovorine. The mechanism responsible for cardiac toxicity of 5-FU is classical coronary spasm without formal evidence. Since acoustic properties of the myocardium are sensitive to the myocardial structure and the contractile conditions of myocyte, cardiac toxicity is evaluated based on cyclic variation of myocardial integrated backscatter (CVIBS).
Method: We examined 16 cancer patients (mean age 65±9) with normal cardiac functions, who had received 5-FU bolus (400 mg/m^2) plus continuous infusion (600 mg/m^2) with calcium leucovorine in 48 hours. Clinical examination, ECG, laboratory tests and transthorasic echocardiography (TTE)was monitored in all cases. The parasternal long-axis view was used to obtain the 2-dimensional image of integrated backscatter. Two regions of interest were chosen in the parasternal long-axis image (septum, posterior wall). Baseline and post 5-FU infusion measurements of CVIBS were performed. During the post infusion period on 15th day a third measurement was performed as control. We determined the magnitude of CVIBS in decibels as the difference between the maximal and minimal values in a cardiac cycle.
Results: None of the patients developed symptoms suggestive of cardiotoxicity. Also pre and post-treatment no significant difference was detected on ECG and TTE. There was a statically significant decrement in the magnitude of myocardial CVIBS after 5-FU infusion which was equal in all myocardial segments. On 15th day CVIBS values was returned to normal and did not show any difference from baseline ($p>0.05$).

Table-I

	Before5FU-1	After 5FU-2	Control-3	P(1-2)	P(1-3)	P(2-3)
CVIBS IVS	9.1 ± 1.3	7.7 ± 1.4	9.0 ± 1.2	0.003	NS	0.003
CVIBS PW	9.0 ± 0.8	7.4 ± 0.9	8.9 ± 1.1	0.002	NS	0.003

CVIBS: Cyclic Variation of Integrated backscatter, IVS: Interventricular septum, PW: Posterior wall, NS: Non-significant.

Conclusion: The mechanism of 5-FU induced cardiotoxicity is still not clear. This study suggested that a new echocardiographic method, "integrated ultrasonic myocardial backscatter" may be a useful tool for determination of asymptomatic cardiac events as well as in further evaluation of the underlying mechanisms of 5-FU induced myocardial toxicity.

P1112 Ultrasonic tissue characterization predicts left-ventricular remodelling in patients with acute myocardial infarction after primary coronary angioplasty

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Objectives: The aim of this study was to assess the role of cyclic variation(CV) of myocardial integrated backscatter (IBS) in the prediction of left ventricular (LV) remodeling in patients with acute myocardial infarction (AMI) after primary coronary angioplasty.
Background: Some studies have shown that the CV of myocardial IBS, which reflects intrinsic contractile performance, predicts myocardial viability in patients with AMI.
Methods: We recorded short-axis IBS images within 24 hours after revascularization in 37 patients with anterior AMI. IBS curves were obtained by placing the region of interest on the anterior wall and 2 parameters were obtained; the magnitude of CV and normalized time delay. The former was the difference between the minimal and maximal values in a cardiac cycle averaged over at least 2 consecutive beats. The latter was determined by dividing the interval between the upstroke of the QRS complex and the nadir of the IBS curve by QT interval. The increase in LV end-diastolic volume (LVEDV) at 4 weeks was defined as LV remodeling (>15% increase from baseline).
Results: The patients were divided into 2 groups according to LV remodeling; remodeling group (n=11) and non-remodeling group (n=26). Baseline clinical and angiographic characteristics were similar between the 2 groups. However, remodeling-group had a higher peak creatine kinase (8021 ± 4990 vs 3734 ± 3443 IU/l, $p<0.005$). There was no significant difference in the magnitude of CV between the 2 groups (5.83 ± 1.34 vs 6.42 ± 1.87 dB, p=NS). Whereas, there was significant difference in the normalized time delay (1.61 ± 0.32vs 1.24 ± 0.35, $p<0.005$). There was significant correlation between the normalized time delay and the increase in LVEDV at 4 weeks($r=0.445$, $p<0.01$). Normalized time delay >1.35 as the optimal cutoff value had a sensitivity of 83% and a specificity of 70% for the prediction of LV remodeling.
Conclusions: CV of myocardial IBS, especially normalized time delay is useful for predicting LV remodeling in patients with AMI after primary coronary angioplasty.

P1113 The influence of growth hormone therapy on ultrasound myocardial tissue characterization in patients with childhood onset growth hormone deficiency

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Objective: In GH deficiency (GHD) a reduction in left ventricular mass (LV-mass) and impairment of systolic function has been shown. GH therapy was associated with a decrease in ventricular diameter and increases in wall thickness, ejection fraction, and myofibrillar content. In this study, we investigated the effects of 12 months GH replacement therapy on cardiac structure and functional indices measured by echocardiographic techniques including acoustic quantification with cyclic variation (CV) of integrated backscatter (IB). Several studies have shown that the IB signals from the myocardium are affected by both structural and functional properties of the myocardium, such as sarcomere length, size and function of the myocyte, architecture and geometry of the muscle fibers, collagen contents, myocardial thickness, and cardiac contractile performance.
Patients and Methods: Sixteen patients with childhood onset GHD (age 42,3 ± 13,1 years, 10 males) were investigated before and after 12 months of GH treatment at a dose of 0,02 IU/kg/day (7 μg/kg/day). The GH dose resulted in a serum IGF-I level in the normal range in all patients. Echocardiography of the heart was performed including acoustic quantification techniques with CV of IB.
Results: Left ventricular diameter and wall thickness did not change after GH treatment, although percent of left ventricular walls thickening increased significantly (IVS% 52,15±31,94% vs. 67,25±30,38% and PWT% 48,71±20,15% vs. 57,96±17,68%, $p<0,01$, $p<0,01$, respectively). Ejection fraction calculated by the Simpson's rule increased from 0,56±0,07 to 0,63±0,06 ($p<0,01$). LV-mass index increased after GH treatment (103,33±29,4 vs. 108,19±28,1 g/m^2), although it did not reach significance ($p>0,05$). CV-IB increased significantly after GH treatment ($p<0.05$), in both the interventricular septum and the left ventricular posterior wall (4.7±1.5 vs. 5.8±1.9 dB for the interventricular septum, 4.9±1.8 vs. 6.5±2.4 dB for the left ventricular posterior wall, $p<0.05$, $p<0.05$, respectively). The calibrated integrated backscatter (cal-IB) also increased significantly after GH treatment (-23.5±4.1 vs. -21.8±4.2 dB for the interventricular septum, -23.0±4.4 vs. -21.8±4.3 dB for the left ventricular posterior wall, $p<0.01$, $p<0.05$, respectively).
Conclusion: 12 months GH treatment in adults with childhood onset GHD resulted in improvement of cardiac contractile performance. Observed changes in cal-IB and CV-IB suggest that GH treatment in this patient group can lead to a further somatic maturation of the heart, probably not accomplished previously.

P1114 The relationship between regional integrated backscatter levels and regional strain in normal, acutely ischaemic and reperfused myocardium

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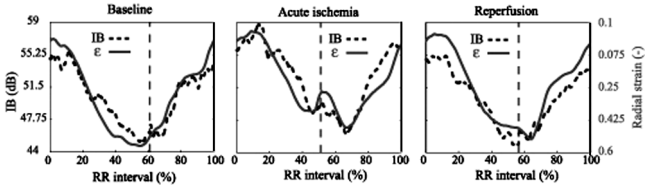
Integrated backscatter (IB) and its cyclic variation (CV) are parameters used for myocardial tissue characterization. Prior work of our group suggested that IB is directly related to scatterer density while its CV could be induced by myocardial strain. The aim of this study was to further test this hypothesis by simulateneously recording changes in IB and strain in normal, acutely ischemic and reperfused myocardium.
In 10 closed-chest pigs acute ischemia was induced by inflating a PTCA balloon in the left circumflex. Radiofrequency (RF) M-mode data of the ischemic region were acquired before, during and immediately after the balloon occlusion. IB and radial strain, i.e. the temporal integral of the spatial velocity gradient, were calculated from the same RF data sets. End-systole was defined on a simulataneously recorded LV pressure trace. Negative radial strain (NRS) was plotted on top of the IB curve.
Results are shown in the figure. At baseline, both the NRS and IB pattern paralleled and showed to be minimum at end-systole. During acute ischemia, post-systolic thickening was observed which resulted in a post-systolic peak in both the NRS and IB traces: the overall minimum in both curves was phase shifted. Moreover, the mean IB level increased acutely. At reperfusion, NRS showed some remaining characteristics of acute ischemic myocardium in contrast to IB that merely showed an hyperemic but normal response.



IB and NRS thus paralleled over the whole cardiac cycle in normal and acutely ischemic myocardium. At reperfusion the IB curve normalized immediately while the NRS showed some remaining ischemic characteristics. These observations might be explained by the hypothesis that changes in integrated backscatter are induced by regional three-dimensional strain.

P1115 Early assessment of cardiac contractile performance in patients with Thalassemia Mayor by ultrasonic tissue characterization and magnetic resonance imaging

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Early cardiac dysfunction has been demonstrated in patients with Thalassemia Mayor (ThM) by conventional transthoracic echocardiographic-Doppler techniques (TE) as a consequence of myocardial iron overload. Previous reports indicated the relationship between myocardial iron deposition and impaired standard echocardiographic parameters. Aim of our study was to evaluate the accuracy of the analysis of cyclic variations in integrated backscatter (IBScv) to identify the initial impairment of cardiac contractility.
Material and Methods: We studied 10 young ThM patients with good quality ecocardiographic imaging, no clinical signs of cardiac dysfunction, no abnormalities of regional or global systolic function at TE. Patients were receiving blood transfusions and chelation therapy with desferroxamine. All patients underwent to two-dimensional and M-mode TE to measure left ventricular dimensions, thicknesses and functional parameters. The quantitative analysis of IBScv was performed in parasternal long-axis and short-axis views with IBS software available on echo system. Real time IBS images were acquired placing the region of interest in the midmyocardium of anterior and posterior wall during 2 to 3 consecutive cardiac cycles. Magnetic resonance cine gradient echo (MR) was acquired for each patient in short-axis and long axis slices imaging. The heart/skeletal muscle signal intensity ratio (SIh/SIm) was calculated positioning the regions of interest within the myocardium and the skeletal muscle. The results from ThM patients were compared to a control group (C) of 10 normals.
Results: Differences in mean values of ventricular dimensions and function between ThM and normal subjects were not significant. SIh/SIm in ThM patients was lower than in C (0.63 ± 0.3 vs 1.20 ± 0.2, $p<0.001$). IBScv in patients with ThM showed significant difference compared to C for anterior (4.7 ± 1.6 vs 7.6 ± 1.5 $p<0.001$) and posterior wall. A significant correlation was found between the SIh/SIm ratio and the IBScv in ThM patients.
Conclusions: This study indicate that IBScv is a sensitive index with a potential in the identification of early contractile impairment in patients with ThM before the appearance of echocardiographic cardiac dysfunction.

P1116 The relation between right-ventricular isovolumic contraction velocity and end diastolic pressure: a Doppler tissue imaging and cardiac catheterization study

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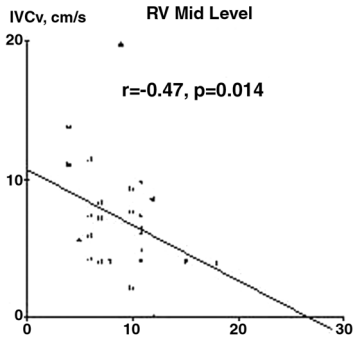
Purpose: Importance to assess right ventricular (RV) behaviour in acquired and congenital heart disease is well known. Echocardiography and MRI were used but not without certain limitations. A reliable load independent parameter is needed.Doppler tissue imaging (DTI) of the longitudinal velocity during isovolumic contraction phase (IVCv) is proposed as a potential measurement of intrinsic myocardial properties. However, this is not adequately tested in clinical studies and available data was studied from one site of the RV. The aim of this study was to validate IVCv, measured from different RV sites, in relation to golden standard technique.
Methods: Twenty-seven consecutive patients with different cardiac diseases (6 females and 21 males) mean age 55 ± 11 (range 31-70) years referred for cardiac catheterisation were underwent a simultaneous DTI to record IVCv at 3 levels across the RV free wall, basal, mid cavity and apical level.
Results: IVCv was correlated with RV end diastolic pressure at both basal (r=-0.41,p=0.032) and mid cavity levels (r=-0.48,p=0.014). Interestingly, a linear correlation was only seen between IVCv and dP/dt/P (r=0.41, p=0.035) at the mid cavity level. Heart rate was not related to these 3 measurements.



RV IVCv and RVEDP.

Conclusion: RV end diastolic pressure overload seems to have an import influence on the RV wall motion velocity during the phase of isovolumic contraction. IVCv is a non-invasive measurement that correlates well to invasive RV filling pressure and its contractile function. It could be of potential value to give insight about the contractile state of RV during acute changes. The exact role, and clincal implication of IVCv on terapeutic intervension and different types of RV involvement needs further investigation.

P1117 Automated classification of wall motion abnormalities by analysis of left-ventricular endocardial motion patterns

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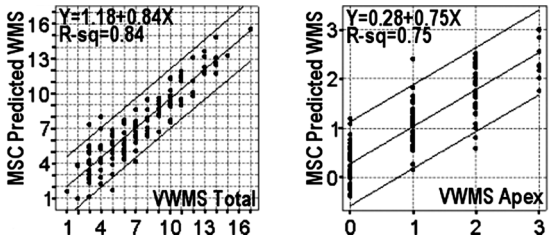
Objective: automated classification of wall motion abnormalities (WMA) is highly desired for objective stress echo analysis.
Methods: Principal Component Analysis of temporal sequences of endocardial contours over a large patient set renders eigenvariations of shape/motion, including typical normal/pathological contraction patterns. Individual patterns are closely approximated by a linear combination of these eigenvariations and thus completely expressed by their Modal Shape Coefficients (MSCs). We generated shape models and derived MSCs from expert-drawn endocardial borders and hypothesized these would allow classification of WMA.
Low-dose dobutamine (LDD) stress echo was performed in 129 infarct patients split randomly into training (TRN, n=65) and test set (TST, n=64). Visual Wall Motion Scoring (VWMS) was performed using a 13-segment model. Expert-verified left ventricular endocardial contours were available in 16-frame single-beat 4-chamber and 2-chamber sequences for baseline and LDD. Shape models were generated from TRN sets; MSCs for all sequences were extracted and statistically related to segmental and global VWMS and clinical infarct severity and volumetric parameters.
Results: Multivariate linear regression showed clear correlations between MSCs and both global (R^2=0.84) and segmental (average R^2=0.60) VWMS. Infarct severity measures correlated poorly to both MSCs and VWMS. Discriminant analysis showed good prediction from low #MSCs of both segmental (85±6% correctness) and global WMA (90% correctness). Volumetric parameters correlated well to global, but poorly to segmental VWMS, as expected.



Regression MSC/Visual for Total & Apex WMS.

Conclusion: 1) MSCs can be used with promising accuracy for automated classification of WMA. 2) VWMS and endocardial border motion are closely related.

P1118 Force-frequency relationship during exercise-echo predicts post-operative left-ventricular function in severe mitral regurgitation

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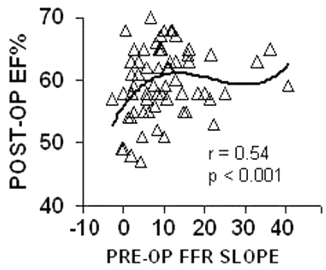
Background: Assessment of left ventricular contractility is difficult in mitral regurgitation, and latent dysfunction may be present despite conventional indices being in the "normal" range. Force- frequency relationship (FFR) can be noninvasively obtained in the echo lab.
Aims: To assess whether FFR during exercise echo can identify latent left ventricular dysfunction in severe MR.
Methods: We performed symptom limited exercise echocardiography in 63 patients (47 men, age = 54 ± 11 years) with severe MR, and no coronary artery disease, prior to mitral valve surgery (repair in 60, replacement in 3). To build a FFR, the force was determined at each step as the ratio of the systolic pressure (SP, cuff sphygmomanometer)/end-systolic volume index (ESV, biplane Simpson rule/body surface area). Left ventricular ejection fraction (EF) was also assessed post-operatively, before discharge.
Results: Non invasive SP/ESVindex ratio was obtained in all patients during exercise-echo and separated 2 groups: 52 patients with normal and upsloping FFR (group I, FFR slope >11 x 10-2) and 11 patients with abnormal flat or biphasic FFR (group II, FFR slope <11 x 10-2). The resting EF was similar at baseline (I= 68 ± 5 vs II= 66 ± 3, p = ns), but different 7 days post-op (I=60.1±5.2 vs II= 55.4±5.2%, one way ANOVA p =0.004). Postoperative EF was directly albeit weakly related to the FFR slope (r = 0.54, p = 0.000): see figure.
Conclusion: Despite normal resting preoperative EF, patients with severe MR show a variable spectrum of contractility response to exercise. A flat or biphasic FFR during exercise identifies patients with latent left ventricular dysfunction.



P1119 Early detection of cardiac involvement in patients with pulmonary sarcoidosis by the use of tissue Doppler image

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Pulmonary Sarcoidosis (PS) is a granulomatous disease of unknown aetiology that involves multiple organs among them the heart. Although cardiac involvement can lead to heart failure or sudden cardiac death, it may also remain clinical silent despite extensive involvement. Tissue Doppler Image (TDI) is a new ultrasound modality that records systolic and diastolic velocity and can detect LV and RV function. Aim of our study was the early detection of cardiac involvement in asymptomatic patients with PS by the use of TDI modalities.
Methods: 16 patients with established PS without clinical cardiac involvement (group 1, 9 men/7 females, 43±11 years old) were compared to 19 age-matched controls (group 2, 11 men/8 females, 39±14 yo). All the people underwent physical examination, electrocardiogram and transthoracic echocardiographic study including TDI velocities in order to exclude patients with cardiac involvement. Early and late transmitral (Em and Am) and transtricuspidal (Et and At) velocities, deceleration times of transmitral and transtricuspid velocities (DTm and DTt), isovolumic relaxation time (IVRT) and flow propagation (Fp) of left ventricle were measured whereas the TDI derived E,A and systolic velocities were measured at the mitral (TDIEm, TDIAm, TDISm) and the tricuspid valve (TDIEt, TDIAt, TDISt) annulus.
Results: Dimensions of left and right ventricle as well as left atrium were similar between the two groups. In addition, no significant differences were detected for the following parameters: Em, Am, Et, At, DTm, DTt, IVRT, Fp. We observed significant differences between the two groups in the TDIAm (14,6 vs 18,8, p=0.026), TDIAt (14,6 vs 18,8, p=0.006), TDIE/Am (1,56 vs 1,21, p=0.035) and TDIE/At (1,29 vs 0,91, p=0.004). Disease duration and SACE are not correlated with cardiac indices.
Conclusion: Tissue Doppler Image detected early cardiac involvement in patients with Pulmonary Sarcoidosis.

P1120 Validation of neural network-based approach to identification of intracardiac masses

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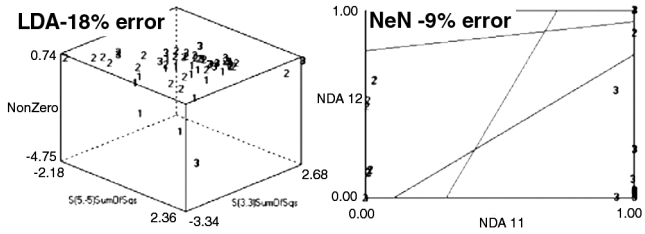
We have previously reported the feasibility of intracardiac masses recognition by neural network (NeN) according to their echocardiographic appearance. We aimed to prospectively validate the usefulness of neuronal network-based approach for the computer-based characterization of cardiac tumors.
Methods: 108 images (teaching set)from echocardiograms of patients with cardiac thrombi (62 images), benign (31) or malignant neoplasms (15) were digitized and analyzed with custom software. For each image, a region of interest covering a representative section of the image was defined and 291 image features were calculated (including 9 from pixel histogram, 6/gradient matrix, 20/Run length matrix and 256/2nd order histogram). The most efficient parameters were selected using Fisher's or probability of error minimalization (POE) approach. Linear (LDA) and non-linear (NeN) discriminative analysis was then used in prospective dataset of 44 samples of pediatric malignant and benign tumors and 55 adult samples: 29 thrombi, 13 myxomas, 13 malignant tumors.
Results: Simple analysis using on pixel feature histograms was insufficient for mass classification. Manually assisted POE was the most efficient feature selection procedure. In teaching set, LDA classified correctly only 55% of images but NeN - 91%. In the prospective dataset, the LDA using 5 best features correctly classified of 82% of tumors whereas NN - 91%, with similar results in pediatric samples.



LDA vs NeN in validation dataset.

Conclusions: Simple parameters of tissue texture derived from echocardiogram are insufficient for the classification of intracardiac masses. Our results confirm that neural network allows correct classification of intracardiac masses and might be optimized by validation in broader dataset to become a novel decision making tool.

DOPPLER MYOCARDIAL IMAGING: AN EMERGING CLINICAL TECHNIQUE

P1121 Afterload-induced diastolic dysfunction diagnosed by tissue Doppler echocardiography

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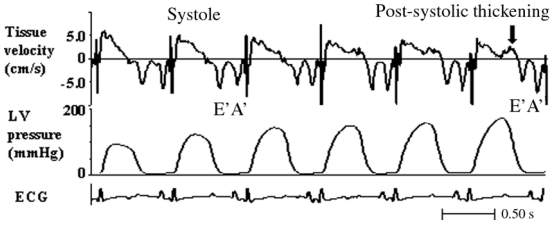
Background: Clinically relevant increase in left ventricular (LV) afterload is associated with impaired diastolic function. The aim of the study was to investigate if diastolic dysfunction can be detected by tissue Doppler echocardiography (TDE) during incremental increase in LV afterload.
Methods: Five anaesthetized open chest pigs were analyzed. LV pressure was measured by micromanometer and tissue velocities from the short axis view (inferolateral wall) by TDE. Simultaneous recordings were obtained at baseline and during incremental increase in LV pressure by briefly constricting the ascending aorta (5-10 sec). We calculated the time derivative of LV pressure (dP/dt) and defined end-systole at peak neg dP/dt. Tau was calculated as the rate of LV pressure fall (logarithmic method).
Results: LV peak systolic and end-diastolic pressures increased from 92 $\pm$ 4 ($\pm$ SEM) to 161 $\pm$ 5 mmHg ($p<0.05$) and 6.4 $\pm$ 0.5 to 8.3 $\pm$ 0.4 mmHg ($p<0.05$) at peak aortic constriction, respectively. Tau increased slightly from 39.8 $\pm$ 0.8 to 44.5 $\pm$ 3.6 ms (p=NS). Peak systolic velocities of the inferolateral wall decreased from 4.6 $\pm$ 0.6 to 2.6 $\pm$ 0.5 cm/s ($p<0.05$). The time from end-diastole to peak early diastolic tissue velocity (E') increased by 15 $\pm$ 2% (570 $\pm$ 9 ms to 656 $\pm$ 14 ms, $p<0.05$) when corrected for heart rate. E'/A' ratio did not change with aortic constriction (0.9 $\pm$ 0.1 and 0.8 $\pm$ 0.2), respectively. We observed post-systolic thickening by TDE (2.1 $\pm$ 0.3 cm/s) in all pigs during aortic constriction 79 $\pm$ 15 ms after end-systole (figure).
Conclusion: Our results suggest that TDE can detect impaired diastolic function during increased afterload by demonstrating post-systolic thickening combined with delayed onset of early diastolic peak velocity (E').



P1122 Estimating systolic contractile forces using myocardial Doppler imaging and mathematical modelling

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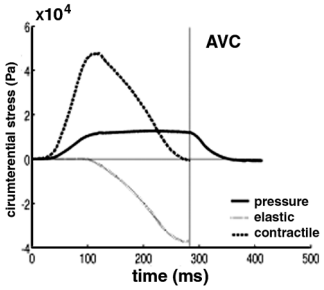
Ultrasound based deformation imaging has been proposed to quantify regional myocardial function. The deformation is a result of the combined force development within the ventricle. However, the contractile force component cannot be measured directly. In this study we investigated the feasibility of estimating the contractile force development based on velocity/deformation and pressure measurements and a simplified mathematical model.
Methods: A mid-wall, short axis slice, through the left ventricle is modeled as a circular array of nodes. The forces acting along the circumferential direction are the contractile force and an elastic force. Cavity pressure acts in the radial direction. In a pig, left-ventricular pressure was recorded using a micromanometer-tipped catheter. The elastic force was estimated by fitting a one dimensional simplification of Fung's law for soft tissue, to the deformation measured by CDMI velocity/deformation measurements, recorded concurrently with the pressure traces, during the A wave where no ventricular systolic contractile forces act. Knowing the elastic force and the pressure force it is possible to solve the balance of forces and estimate the systolic contractile force built up throughout systole.
Results: The systolic contractile force profile for a normal porcine heart is shown in the figure. It peaks at 120ms (1/3 of systole) after the onset of pressure rise after which it linearly decreases to zero during the rest of systole at aortic valve closure. The peak value is 47 KPa. In contrast the elastic stress peaks towards the end of systole.



Conclusions: The estimation of contractile force development is feasible. The results obtained match with experimental data of measuring contractile force in isolated muscle.

P1123 Serial evaluation of tissue Doppler velocities after percutaneous transluminal coronary angioplasty during acute myocardial infarction

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Background: The use of tissue Doppler echocardiography (TDE) to assess the recovery of wall motion has been less commonly studied. The aim of this study was to evaluate the recovery of ventricular wall motion in patients undergoing primary coronary angioplasty (PTCA) during acute myocardial infarction (AMI) with the use of TDE.
Methods: In the setting of first AMI, Eleven patients undergoing successful PTCA within 6 hours of presentation were studied by serial two-dimensional (2D) and TDE. 7 patients had anterior, 4 patients had inferior AMI. All patients underwent 2D and TDE before and at 1, 3, 7, and 21 days after PTCA. Coronary angiography was repeated at 21 days after AMI in order to determine the patency of the infarct related artery. For TDE velocity measurements, we used basal, mid and apical portion of anterior, inferior, septum and lateral walls of the left ventricle in the apical 4 and 2-chamber views. TDE velocities were recorded at a sweep speed of 50 mm/s. Friedman and Wilcoxon signed ranks test was used for repeated measurements.
Results: One hundred thirty three segments were studied. The peak systolic velocity values in the basal infarct segments increased significantly from 5.7±1 cm/s before PTCA to 7.5±1.2 cm/s at 1 day after PTCA ($p<0.007$). In mid portion of infarct segments, the peak systolic velocity values increased significantly at 3 days after PTCA compared with the values before PTCA (6.7±1.2 cm/s vs 4.9±1.8 cm/s, $p<0.007$), In apical portion of infart segments, the peak systolic velocity values did not changed significantly at day 1, 3, 7 days after PTCA. It increased significantly at 21 days after PTCA compared with the values before PTCA (4.3±1.7 cm/s vs 6.2±1.4 cm/s, $p<0.007$). There was no significant difference in the peak early and late diastolic velocities before and at 1, 3, 7 and 21 days after PTCA. In the noninfarct segments, no significant difference was found in the peak systolic, peak early diastolic and peak late diastolic values before and at 1, 3, 7 and 21 days after PTCA.
In conclusion, the peak early systolic velocities in the basal and mid portions of infarct segments recover earlier than the apical infarct segments after PTCA during AMI.

P1124 Regional ventricular function by Doppler tissue imaging in dilated cardiomyopathy; relationship with markers of inflammation and ongoing myocardial necrosis

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Introduction: In dilated cardiomyopathy (DCM) markers of inflammation and ongoing myocardial necrosis have been found. However there are no data concerning the relationship of these indices with the the longitudinal component of LV and RV function studied by DTI.
Methods: 22 pts with DCM were studied (age 53±14 years, ejection fraction (EF)33±10%). VO2max was 18±6 ml/kg/min. Mean time from DCM diagnosis was 6±4.4 years. The prolactin levels, troponin I, interleukin -6 soluble receptors and CRP were measured. DTI profile was interrogated in 9 (6 LV and 3RV) wall sites/pt: the annulus(site 1), in the middle of the segment (site 3) and in the middle between sites 1 and 3 (site 2) of septal (IVS), lateral wall (LAT) and right ventricular free wall (apical 4 chambers view). Systolic phase consisted of two waves an early-isovolumic (Siso) and a late one-ejection (Sez). Left ventricular enddiastolic/systolic volumes were estimated by echo (apical view, area-length method) as well as ejection fraction. Total annular displacement was measured in the posterior mitral annulus (LATann) and tricuspid annulus (Rvann).
Results: 1. Troponin I was related with: LAT1ez (r=0.43, p=0.05), LAT3ez (r=0.47, p=0.04), IVS3iso (r=0.49, p=0.04), IVS1ez (r=0.44, p=0.045), IVS2ez (r=0.75, p=0.001), IVS3ez (0.75, r=0.001) 2. CRP was related in lateral wall with: isovolumic systolic phase in sites 1(r=-0.43, p=0.05), site 2 (r=-0.51, p=0.04)and site 3 (r=-0.47 p=0.05)and ejection phase in sites 2 (r=-0.47,p=0.04)and 3 (r=-0.52, p=0.02). It was related in septum with: isovolumic phases in sites 2 (r=-0.60, p=0.01), and 3 (r=-0.64, p=0.02), and ejection phase in sites 1 (r=-0.50, p=0.02) and 2(r=-0.54, p=0.03) 3. There was no relationship of DTI indices with prolactin and s-interleukin 6 receptor. 4. EF was only related with troponin (r=0.55, p=0.02). No relationship was found for other conventional LV and RV overall systolic function indices.
Conclusions: Evidence of myocardial necrosis in DCM is related with regional increase of DTI ejection indices implying functional recruitment of less affected areas of myocardium. Increased levels of CRP are related with decreased systolic indices by DTI for both isovolumic and ejection phases in multiple myocardial sites.

P1125 Characterization of grades of diastolic dysfunction by diastolic strain rate patterns

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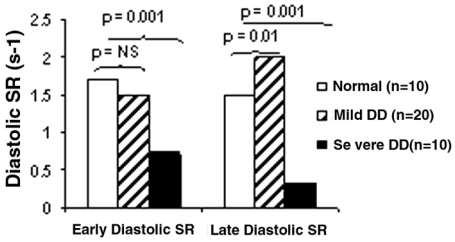
Background: Severity of global diastolic dysfunction (DD) may be related to changes that preferentially affect the early versus late phase of myocardial relaxation. Early myocardial relaxation is an energy-dependent active process while late relaxation is thought to be a passive process related to chamber compliance. Strain echocardiography (SE) can quantitatively depict regional mechanical activity and allows analysis of early and late myocardial relaxation.
Aim: We sought to correlate the severity of DD to changes in the early versus late phase of myocardial relaxation.
Methods: Conventional and SE were performed in 40 subjects-20 had grade 1 or 2 (mild DD), 10 had grade 3 or 4 (severe DD) and 10 were age-matched healthy volunteers (HV). Standard clinical criteria were used to classify grade of DD. For SE, single ventricular walls were imaged from apical views using high frame rates. Peak early and late diastolic strain rates (SR; 1/s) were measured and averaged to yield a mean value per subject.
Results: Peak early diastolic SR was similar in HV and mild DD (1.7±0.2 vs 1.5±0.17,p=NS) but significantly lower in severe DD(0.74±0.34, $p<0.001$). Late diastolic SR increases with mild DD when compared to HV (2±0.12 vs 1.5±0.17, $p<0.01$) but is substantially decreased, below HV and mild DD values in severe DD (0.32±0.15, $p<0.001$)(figure).



Conclusion: In mild DD, early diastolic SR appears unchanged while there is a significant increase in late diastolic SR. In contrast, severe DD is characterized by significant decreases in early and late myocardial relaxation probably reflecting abnormalities in both the compliance and energy dependent phases of relaxation.

P1126 The distinctive late systolic longitudinal and radial deformation in mitral valve prolapse detected by colour tissue Doppler-based strain rate and strain analysis

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In patients with mitral valve prolapse (MVP), distinctive late-systolic peaks in the longitudinal tissue Doppler velocity (TV), strain rate(SR),and natural strain analysis of the left ventricle (LV)and papillary muscles(PM) have been reported. We aimed to assess longitudinal and radial systolic TV and deformation of LV and PM in pts with MVP.Study population comprised of 29 pts with classical MVP with moderate to severe mitral regurgitation (F 18,M 11,age 40±12) and 25 healthy controls(F 12,M 13,age 42±10).Individual curves of TV,time-velocity integral(TVTI),SR and strain were extracted from selected segments. For longitudinal analysis of LV, 7 points from basal,mid and low septal (S) and lateral(L) segments, and base of the anterolateral PM were selected using the apical views. For radial assessment of LV, 3 points from basal, mid, and low segments along the posterior (P) wall on parasternal long axis, and 3 points from posterior, posteromedial (MP),and posterolateral (LP) segments of the mid-posterior LV wall on short axis were selected. Curves of the TV and TVTI from pts with MVP revealed late systolic spikes (up to 10 times compared with baseline) prominent in the PM, MP and LP segments which were not detected in controls.Similarly, SR and strain curves also showed significant late systolic peaks (up to 8-10 times compared with baseline) in PM, MP and LP segments. Late systolic peaks in the TV,TVTI, SR and strain curves tended to increase along the PM from its base to the chordal insertion points, and from midposterior wall to the MP and LP segments($p<0.05$), respectively. Late-systolic TV,TVTI,SR and strain values were higher in the radial direction compared with the longitudinal direction($p<0.05$).Late systolic TV,TVTI, SR and strain values were higher in PM ($p<0.0001$,$p<0.05$, $p<0.001$,$p=0.002$),MP and LP (<0.05) segments of the MVP pts compared with those of controls.
In conclusion, longitudinal and radial TV, SR and strain analysis suggest distinctive late systolic increases in motion and deformation related to specific LV segments and PM in pts with MVP. However,correlates and implications of this heterogeneity remain to be determined.

P1127 A new method for the evaluation of atrial function: transthoracic tissue Doppler echocardiography

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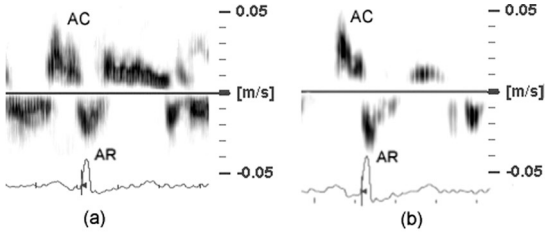
The assessment of left and right atrial function still remains a diagnostic challenge. Tissue Doppler echo (TDE) by measuring atrial velocities (VEL)could quantify atrial contractility.
Methods: To determine the potential clinical role of TDE in assessing atrial function pulsed TDE recordings of superior left and right atrial wall motion were recorded from 10 young normals.
Results: Atrial contraction (AC) and relaxation (AR) VEL were consistently identified (Fig.1: a)right atrium, b)left atrium). There was no statistical difference between peak left AC VEL (0,06±0,01 vs. 0,06±0,02 m/s, p=NS) and also between peak left AR VEL (0,04±0,01 vs. 0,05±0,01 m/s, p=NS) measured in apical 4-chamber and 2-chamber views. There was no significant difference between peak right AC and between peak right AR VEL (0,04±0,01 vs. 0,04±0,01 m/s, p=NS for AC VEL; 0,03±0,01 vs. 0,03±0,01 m/s, p=NS for AR VEL) measured in apical 4-chamber and parasternal short-axis views. The average values of peak left AC and AR VEL were significantly higher then their right atrial equivalents (0,06±0,02 vs. 0,04±0,01 m/s, $p<0,001$ for AC VEL; 0,05±0,01 vs. 0,03±0,01 m/s, $p<0,01$ for AR VEL). We have found strong correlations between peak left AC and AR VEL(r= 0,85) and also between peak right AC and AR VEL(r= 0,79).



Conclusions: In normal subjects, AC and AR VEL from both atria could be consistently and reproducibly recorded.Left AC and AR VEL were higher then their right atrial equivalents. The values of AR VEL were related to the values of AC VEL. TDE indices represent a promising new method to investigate atrial function (including atrial compliance).

P1128 Strain Doppler echocardiography: a moving sample volume improves the strain estimates

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Background: In conventional strain Doppler echocardiography, strain is calculated in the beam direction by integrating strain rates of a sample volume at a fixed location in space. If, in the case of longitudinal strain estimation, there is a misalignment between the beam and the myocardial wall, the technique will pick up wall thickening and thereby give erroneous strain estimates. Furthermore, the cardiac motion causes different portions of the myocardium to move in and out of the sample volume.
Aims: 1) To quantify the errors introduced by misalignment between beam and myocardial wall, and 2) to determine if the strain estimates can be improved by moving the sample volume.
Method: LV diameter, wall thickness and long axis were measured in 12 healthy individuals (age 23-39), and used as input to an ellipsoidal model of the LV. By the formalism of continuum mechanics, we could calculate three-dimensional strain and velocity gradient tensors for any material point within the wall. From the strain tensor we obtained strain in the wall direction (true strain). In analogy with strain Doppler echocardiography, we obtained strain in the beam direction from the velocity gradient tensors (estimated strain). We simulated myocardial deformations as imaged from an apical view.
Results: Table 1 compares estimated strains measured with fixed and moving sample volumes with true strains. alpha = angle between the myocardial wall and the ultrasound beam. Measurements from 3 different myocardial segments are included.

Table 1: Systolic strains

Segment	True strain	Estimated strain: fixed SV	Estimated strain: moving SV	alpha
Basal	-16.6 ± 1.6	-13.0 ± 1.4 (r=.75)	-14.2 ± 1.4* (r=.89)	13.2 ± 1.0
Mid	-16.5 ± 1.5	-14.1 ± 1.5 (r=.91)	-15.0 ± 1.5* (r=.94)	10.3 ± 0.9
Apical	-16.4 ± 1.7	-15.4 ± 1.6 (r=.96)	-16.2 ± 1.6* (r=.99)	1.8 ± 1.4

Mean ± 1SD. Pearson's r: estimated versus true strains. *p<.001 versus fixed SV.

Conclusion: Strain Doppler echocardiography was confounded by misalignment between the ultrasound beam and the myocardial wall. Therefore, the strains in the beam direction were consistently lower than the strains in the wall direction. This measurement error was markedly reduced by moving the sample volume during the cardiac cycle according to the motion of the material point. These results indicate that strain Doppler echocardiography should be done with a moving sample volume.

P1129 Evidence of ischaemic regional left atrial dysfunction. A tissue Doppler analysis

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Background: Assessment of atrial ischemia is difficult using conventional imaging. Left atrial (LA) blood supply is upon the left circumflex coronary artery (LCx) with no contribution from the left anterior descending coronary artery (LAD).
Objectives: The aim of this study was to evaluate the ability of tissue Doppler imaging (TDI) to objective ischemia-related regional atrial dysfunction by comparing LA lateral wall velocity and strain in patients with chronic anterior myocardial infarction (LAD occlusion, n=8) and chronic lateral myocardial infarction (LCx occlusion, n=7).
Methods: LA lateral wall was scanned from an apical 4-chamber view (Vivid 5). Atrial contraction peak velocity and systolic strain of the mid portion of the LA lateral wall were measured using tissue Doppler imaging modality. Additionally, LA surface area was planimetered from the apical 4-chamber view and left ventricular ejection fraction (LVEF) was calculated using the Simpson's rule. Data were compared to 10 age-matched normal subjects.
Results: For a similar degree of LV dysfunction (LVEF = 42±7% in LAD group vs. 46±5% in LCx group, p=ns) and LA enlargement (LA area = 19.3±3.6 cm^2 in LAD group vs. 19.8±2.3 cm^2 in LCx group, p=ns), LA contraction peak velocity as well as LA systolic strain were significantly higher in LAD group than in LCx group (4.9±2.1cm/s vs. 2.9±2.9 cm/s, $p<0.05$ and 11.8±5.0% vs. 4.5±3%, respectively). In LAD group, results were similar to those found in normal subjects(peak velocity: 5.2±2.4cm/s and strain: 12.3±4.9%, p = ns vs LAD group)
Conclusions: Therefore, regional LA function is specifically affected by ischemia and may be accurately diagnosed by TDI.

P1130 Familial amyloidotic polyneuropathy. Doppler myocardial imaging findings as a sensitive marker of cardiac involvement

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Familial amyloidotic polyneuropathy (FAP) is a hereditary disease, with amyloid deposition in several organs, including the heart. Cardiac involvement has prognostic implications. The aim of this study was to assess if Doppler myocardial imaging (DMI) could detect early abnormalities in patients (pts) with FAP before other echo-Doppler changes.
Methods: We studied 29 pts with FAP, 18 female, 45±8 years-old (23-55). Exclusion criteria: nonsinusal rhythm, hypertension, ischemic or valvular heart disease. All were submitted to conventional echo-Doppler and DMI and were analysed: 1. Left ventricle (LV): dimensions, wall thickness, echogenicity, fractional shortening; 2. Mitral flow - E and A velocity (cm/s)and Desaceleration time (ms)after Valsalva (Des); 3. DMI - Velocity of Em (early diastolic), Am (atrial systole), Sm (systolic), in basal and mid segments of LV walls (16 segments model), from the three apical views. DMI patterns were classified in three types: a) "Normal": $Em > 8$ cm/s and $Em/Am \geq 1$; b) Relaxation abnormality: $Em \leq 8$ cm/s and $Em/Am < 1$; c) Restrictive abnormality: Em, Am, Sm < 4 cm/seg. Mitral flow patterns: a) "Normal" (E/A - 1 a 1.9 and Des - 140 to 239); b) Relaxation abnormality ($E/A<1$ and $Des > 240$); c) restrictive abnormality ($E/A > 2$ and $Des <140$).
Results: All pts had normal LV dimensions and fractional shortening. Thirteen had increased echogenicity and/or septum hypertrophy (Group A) and 16 no structural changes (Group B). Mitral Doppler was normal in 16 pts, had a relaxation abnormality in 9 and restrictive in 4. From 348 analysed segments by DMI, 87 (from 18 pts) had relaxation or restrictive type abnormality. A normal DMI pattern in all segments was found in 11 pts; 8 pts had a relaxation abnormality pattern in one or more segments (mean 7.4 ± 1.7) (from these, 3 had a normal mitral pattern); there was a restrictive pattern in one or more segments of 10 pts (mean 5.3 ± 1.1) (3 from these had a normal mitral pattern). In Group A all pts had abnormal DMI pattern in one or more segments, with the exception of one pt. Eight pts from Group B showed a DMI pattern of relaxation change in one or more segments. There was a significant difference between Em and Sm of all segments in Group A and B (5.6 ± 1.7 vs 9.8 ± 3.5, p=0.004 for Em; 6.5 ± 4.4 vs 9.2 ± 3.8, p=0.005 for Sm)
Conclusions: Pts with FAP had a high incidence of abnormalities of LV longitudinal function as assessed by DMI, which occurred in pts with normal LV radial function and mitral flow Doppler. DMI may be a more sensitive method for early detection of heart involvement in FAP.

P1131 Mitral annular systolic velocity: does it reflect global or regional left-ventricular systolic function? Study of systolic annular velocities at 4 mitral annular sites

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Purpose: Mitral annulus (M ann) motion represents changes in LV long axis dimensions associated with LV volume and contractility changes during cardiac cycle. Our purpose is to determine whether systolic velocities of the M ann obtained at 4 annular sites, reflect global or regional LV systolic function.
Methods: This study included 35 subjects (25 with myocardial infarction "MI" and 10 normal persons). All cases were subjected to conventional echo Doppler evaluation of global LV systolic function, with measurement of 2D echo ejection fraction (EF), Aortic velocity (Ao-V) and integral (Ao-Int). Tissue Doppler imaging of the M ann was done with measurement of systolic annular velocity (Sa) at 4 different annular sites including lateral (Lat ann Sa), medial (Med ann Sa), anterior (Ant ann Sa) and inferior (Inf ann Sa) sites. Mean values of regional myocardial velocities (Sm) were calculated for the lateral, septal, anterior and inferior walls. Coronary angiography was done for pts with MI. Sa at each annular site was correlated with regional Sm at each wall and also with EF, Ao-V & Ao-Int. Sa at each of the 4 sites was compared in pts with versus those without LAD, LCX or RCA lesions.
Results: Sa at each annular site was significantly lower in patients with impaired EF compared to those with normal EF. No correlation was found between Sa at any annular site & Ao-V or Ao-Int. Sa in each annular site correlates better with Sm of the related wall than with other walls or EF. Lat ann Sa was significantly lower in pts with, versus those without LCX lesion (3.7 ± 1.6 vs 6.3 ± 1.6, $p=0.01$) and LAD lesion (5.1 ± 1.7 vs 6.6 ± 1.6, $p<0.05$) but was not significantly different in pts with from those without RCA lesion. Med ann Sa was significantly lower in pts with, versus those without LAD lesion (4.3 ± 1.2 vs 6.1 ± 1.1, $p<0.005$) and RCA lesion (4.5 ± 1.6 vs 5.6 ± 1.7, $p<0.05$) but was not significantly different in pts with from those without LCX lesion. Ant ann Sa was significantly lower in pts with, versus those without LAD lesion (4.4 ± 1.1 vs 6.3 ± 1.6, $p<0.01$) but was not significantly different in pts with from those without LCX or RCA lesions. Inf ann Sa was significantly lower in pts with, versus those without LAD lesion (4.8 ± 1.3 vs 6.2 ± 1.7, $p=0.01$) and RCA lesion (3.9 ± 1.3 vs 5.8 ± 1.6, $p=0.01$) but was not significantly different in pts with from those without LCX lesion.
Conclusion: Mitral annular systolic velocity in each annular site reflects more regional than global LV systolic function and is affected more by the presence of lesion in the related coronary artery.

P1132 Tissue Doppler imaging tools in the acute evaluation of the "region at risk after treatment by primary coronary angioplasty. About 25 patients mono-troncular patients

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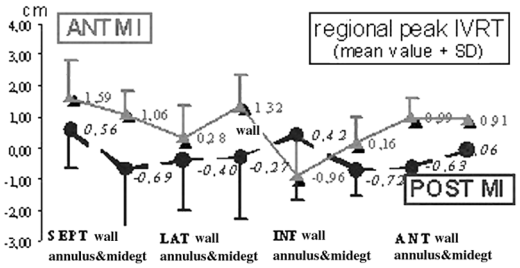
Multiples indices have recently been described using tissue Doppler imaging (DTI)technology for diagnosing myocardial ischemia. The relevance of these indices in the management of patient with an acute myocardial infarction (AMI) remains poorly evaluated in the routine practice. We sought to analyze systematically patients treated by primary angioplasty (PTCA) for AMI by transthoracic echocardiography and regional DTI analysis.
Methods: 25 consecutive patients (66.7±14.6 years old) were imaged in the 24 hours following the PTCA. Global and regional left ventricular function were measured. High frame rate color DTI cineloop were recorded in apical 4 and 2 chambers for subsequent analyses of regional myocardial velocities and gradients. At the level of the mitral annulus,the basal, mid and apical segments of each of the 4 studied walls, peak velocity during isovolumic contraction time, ejection time, isovolumic relaxation time (IVRT), filling time were measured.
Results: 14 patients were treated for anterior AMI (%rac 24±6%) and 11 for a posterobasal one (%rac 28±5%). The IVRT peak velocity was significantly different in the "region at risk" than in the control segments. This peak was negative in control segments (segments related to no coronary artery stenosis, -0.70±0.99 cm/s for the mean anterior wall) and became positive and delayed in ischemic segments (0.64±0.65 cm/s for the mean anterior wall, $p<0.001$). this parameter appeared to be the most discriminative one.
Conclusion: DTI is a powerful tool of assessing patients with ischemic heart disease. In the study of the "region at risk" 24 hours after a revascularized AMI, differences of the regional IVRT peak velocity between normal or not myocardial segments were striking,also quick and easy to observe.



Variation of IVRT peak velocity.

ECHO-DOPPLER, MISCELLANEOUS I

P1133 Factorial parametric imaging of the left-ventricular contraction: validation of a new tool for assessing segmental wall motion abnomalities

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Factor Parametric Imaging of left ventricular (LV) B&W images analyzes the time curve of each pixel of an image sequence, it extracts the most significant curves and the corresponding factorial images. The present study has tested its ability to automatically detect segmental wall motion abnormalities on 48 patients (including 12 pts with LBBB or pace maker). After alignment by correlation of each sequence, two factors were extracted (one flat curve and one curve describing the contraction-relaxation sequence). A synthetic factorial parametric image (FPI) was built for each sequence with the combination of the constant in green, the positive values of the second factor in red and the negative in blue. The FPI were read as follows: wide red = normal, narrow red = hypokinetic, mosaic or green = akinetic, blue = dyskinetic. The evaluation was carried out on 398 segments (38 apical four-chamber views and 35 apical two-chamber views). The segments were graded independently (normal, hypokinetic, akinetic, or dyskinetic) visually and by FPI by three experienced echocardiographers.

FPI vs Visual wall motion score

Visual/FPI	- 1	0	1	2
-1	7	3		
0	12	20	12	
1	3	11	53	39
2	1	1	43	193

On the entire population, an absolute concordance was obtained for 68.6% of the segments and a relative concordance (within one grade) for 98.7. The 5 discordant segments were found on the often confusing basal portion of the septum or the inferior wall. Wall motion indices derived from this scoring correlated strongly both with the biplane Simpson EF and with the visual score index.
In conclusion. the Factorial Parametric Imaging is a promising tool to study the regional wall motion of the left ventricle.

P1134 Tissue Doppler imaging of left atrial wall for detection of pseudonormalization of mitral inflow pattern

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Doppler echocardiographic study is the method of choice to evaluate the left ventricular diastolic dysfunction. But pseudonormalization pattern (PN) of mitral inflow often presents a major diagnostic problem in clinical practice. This investigation was designed to explore the feasibility and the diagnostic value of Tissue Doppler imaging (TDI) parameters of left atrial wall motion for assessment of PN and to validate these parameters against invasive measurements.
We performed echocardiography in 46 consecutive patients (52±12 years, 32 males/20 females) who underwent left-sided cardiac catheterization because of recently diagnosed coronary artery disease or suspected coronary artery disease. Pulsed wave TDI of posterior aortic (LA) wall was performed from the parasternal long-axis view. After a 8 mm sample volume was placed at the posterior aortic root at the level of walve opening, early (Ela) and late (Ala) diastolic velocities, Ela/Ala were derived. An average value was obtained from the recordings of 5 to 8 consecutive cardiac cycles with simultaneous electrocardiography. Patients with LVEDP of >17 mmHg and E/A>1 were supposed to be pseudonormal, and was found in 11 patients. There was no differences between normal (N) and pseudonormal group in respect to E/A(1,39±0,22 vs 1,32±0,24, p= NS), deceleration time(200±36 vs 196±27 ms, p= NS), and isovolumic relaxation time(90±6 vs 94±20 ms, p= NS). In the PN group Ela velocity (5,6±0,6 vs 8,4±2,0 cm/s, p< 0.001) was lower, and Ala velocity (8,2±2,0 vs 6,3±1,3 cm/s, p>0.001) was higher than normal group. Ela/Ala ratio revealed significant differences between groups (PN 0,70±0,12, N 1,27±0,18, p< 0.0001). Thus, simple application of a cut point of Ela/Ala ratio less than 1,0 was %100 sensitive and % 100 specific for the diagnosis of pseudonormal pattern in symptomatic patients with pseudonormal mitral inflow and elevated filling pressures.

P1135 Left atrial electrical and mechanical function during dobutamine stress in coronary artery disease

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Background: Long standing coronary artery disease (CAD) is frequently complicated by atrial fibrillation, the exact mechanism of which remains to be determined.
Aim: To study left atrial (LA) electrical and mechanical function at rest and during dobutamine stress echocardiography (DSE) in patients with CAD.
Methods: We studied 33 patients with 3-vessel CAD during DSE (aged 59±10 years, 30 males). LA diameter was measured from the aortic root-LA M-mode echogram. Mean LA longitudinal amplitude and shortening velocity were measured from M-mode and tissue Doppler recordings of the mitral ring motion at the left, septum (central fibrous body) and posterior sites. LA ejection velocity (mitral A wave) was measured from the transmitral pulsed wave Doppler. The P wave duration and amplitude were measured from V1-V2 on the 12-lead ECG recorded concurrently during stress. Results were compared with 15 controls (mean age 58±10 years, 10 males).
Results: At rest: LA diameter 4.3±0.6 vs. 3.4±0.3cm, amplitude 7.1±+2.0 vs. 5.9±1.2mm, and shortening velocity 12.6±2.8 vs. 7.7±1.8 cm/s were increased in patients compared to controls, all $p<0.001$, but LA ejection velocity was not different from controls. P wave duration was longer in patients 122±16 vs. 105±12 ms, $p<0.001$, but its amplitude was not different from controls 1.6±0.5 vs. 1.8±0.5mm, NS. At peak stress: LA amplitude failed to increase in patients 6.6±1.4cm, (NS) but increased in controls to 6.9±1.7, $p<0.005$. LA shortening velocity and ejection velocity increased by 28%, $p<0.001$, and by 37%, $p<0.01$ respectively, in both patients and controls. P wave duration fell by only 15±2ms in patients compared to 32±3ms in controls,$p<0.001$. P wave amplitude increased to 2.4±0.7mm, $p<0.001$ only in patients but not in controls.
Conclusion: Patients with CAD have abnormal LA electrical and mechanical function at rest. Further deterioration occurs with stress, manifested by failure of LA amplitude of motion to increase and its depolarisation to shorten. The maintained LA ejection velocities seem to be preserved at the expense of a possible rise in LA pressure as demonstrated by the voltage increase of P wave on the surface ECG.

P1136 Should exercise treadmill test be replaced by stress echocardiography in the risk stratification of medically stabilized unstable angina?

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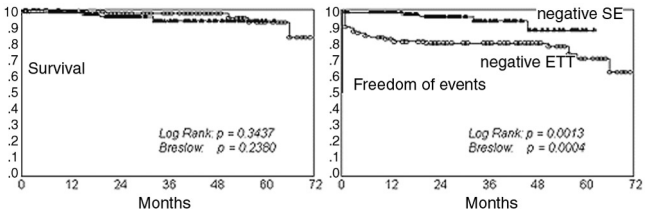
Background: Management of patients with medically stabilized unstable angina (MSUA) still deals with many controversies. The objective of this study was to compare the prognostic significance of a negative exercise treadmill test (ETT) and a negative stress echocardiography (SE) in these patients.
Patients and Methods: We identified and followed-up 326 patients hospitalized due to unstable angina that were medically stabilized and showed no ischemia at dypiridamole SE (n=128) or ETT with >85% of maximum heart rate reached (n=198). Long-term outcome was compared between both groups using Kaplan-Meier cumulative survival curves, and Log-Rank and Breslow tests.
Results: no significant differences were observed between both groups in long-term mortality rate: 98.2±1.3% vs. 99.5±0.2% at 1 year, 95.7±2.2% vs. 98.6±1.0% at 2 years 93.2±3.2% vs. 92.2±3.0% at 5 years in SE and ETT groups, respectively (Log Rank: p = 0.3437, Breslow: p=0.2380). However, probability of being free of events (death, myocardial infarction or coronary revascularization) was higher in SE: 98.2±1.3% vs. 82.5±3.0% at 1 year, 95.7±2.2% vs. 80.0±3.2% at 2 years, and 87.6±6.1% vs. 70.5±5.3% at 5 years in SE and ETT groups, respectively (Log Rank: p=0.0013; Breslow: p=0.0004).



Outcome in ETT versus SE groups.

Conclusion: both a negative ETT and SE are associated with very low mortality rates in patients with MSUA. However, a negative SE predicts a significantly lower rate of overall events rates.

P1137 Relation between the extent of coronary artery disease and arrhythmic disorders during dobutamine stress echocardiography after acute myocardial infarction

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Despite data regarding the safety of dobutamine stress testing, possible induction of arrhythmias during the test, especially after acute myocardial infarction, may interfere with diagnostic accuracy and prognostic implications of this procedure.
Aims: The aim of this study was the evaluation of the echocardiographic, angiographic and clinical predictors of arrhythmias during dobutamine stress testing after acute myocardial infarction.
Patients and Methods: The investigation comprised 91 patients hospitalized due to the acute myocardial infarction, all with uncomplicated AMI. The location of AMI was: anterior in 53 patients (58.2%), and inferoposterior in 38 patients (41.8%). 62 patients were treated with thrombolytic therapy (68.13%). After 10-12 days all of them underwent dobutamine stress echocardiography examination (DSE) and during the next 3-6 months they also underwent coronary angiography. Average follow-up period was 60 ± 8 months.
Results: During the DSE tests there were no fatal events. Ventricular and supraventricular tachycardia occurred in 5 (5.5%) and in 12 (13.2%) patients, respectively, and were non-sustained. In 4 (4.4%) patients junction rhythm was developed, and in 3 (3.3%) patients AV block II-III. Systolic blood pressure decrease of ≥40mmHg occurred in 7 (7.7%) patients. Coronary angiography showed that there was significant coronary artery disease in 36 (39.6%) patients, and they underwent PTCA and coronary artery bypass grafting. Two of them died immediately after surgical revascularisation. In 55 (60.4%) patients there was no significant artery stenosis (because of successful thrombolysis), and they were treated only with medicaments. There was no significant difference between patients with and without arrhythmias, regarding the prevalence of CAD or the mean number of diseased coronary arteries (1.62 ± 0.7 vs. 1.57 ± 0.6). Independent predictors of arrhythmias by multivariate analysis of clinical, angiographic, and echocardiographic characteristics were a higher resting wall motion score index ($p<0.01$), and male gender ($p<0.1$). Independent predictors of systolic blood pressure decrease ≥40mmHg were a higher baseline systolic pressure ($p<0.0001$), hypertrophic left ventricle with diastolic disfunction and a higher resting wall motion score index with systolic disfunction.
Conclusion: Arrhythmic disorders during DSE are predicted by the extent of systolic or diastolic left ventricular disfunction, but not by the presence or the extent of CAD.

P1138 Evolution of ischaemic heart failure: prognostic implications of brain natriuretic peptide and cytocine changes induced by dobutamine stress echo

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Introduction: Interleukin 6 (IL6) mediates the ischemia-reperfusion myocardial injury and is elevated in acute coronary syndromes. BNP is produced by the ventricles due to increased wall stress and is a marker of left ventricular dysfunction.
Aim: Aim of the study was to assess changes of these parameters during Dobutamine Stress Echo (DSE) and their prognostic implications for the evolution of ischemic heart failure.
Methods: We studied 55 consecutive patients (pts) with stable coronary artery disease (6 women, age 60±9, ejection fraction 40±12, 22 with previous myocardial infarction). The IL6 was measured at rest (R), peak (P) and during recovery (Rec), 15min post DSE. BNP was estimated at R and Rec. A 16 segments model was used for DSE analysis. During follow up (f-up) of 67±12 (range 22-78) months, 19 pts had cardiac events (CE) (8 deaths, 11 decompensation to NYHA class III-IV).
Results: Pts who died had greater BNP (R) (3553±25 vs 1981±30, $p<0.05$) but similar IL6 (P) compared with pts having uneventful f-up (N). Group CE compared with N had differences on EF (32±11 vs 44±10, $p<0.0001$), score (R) (30±8 vs 21±6, $p<0.001$), IL6 (P) (4.2±4.3 vs 2±1.4, p=0.02) and a trend in BNP (R) (291±242 vs 198±130, p=0.08). For prediction of CE, ROC analysis showed the following cut off points and respective sensitivity/specificity: EF=32%: 0.63/0.90, Score (R)=27: 0.58/0.87, BNP (R)=230: 0.42/0.77, IL6 (P)= 2.75: 0.50/0.86. In stepwise logistic regression analysis (SLRA) for prediction of CE including EF, score(R), IL6(P)>2.75, BNP>230 parameters and DSE ourcome, then only IL6 (P) >2.75 had independent contribution (exp(b)=0.0754, p=0.045). In SLRA for prediction of CE including DSE outcome, BNP>230 and IL6 >2.75, then DSE outcome was not selected in the model(exp(b)=3.5 and 0.11 for BNP and IL6(P)respectively, $p<0.01$). Pts with a positive DSE could be further stratified for CE by IL6 (P) >2.75 (Kaplan-Meier log rank p=0.052) Pts with a negative DSE and EF> 30% could also be further stratified for CE by IL6 (P) >2.75 (Kaplan-Meier log rank p=0.03). Among pts interrogated for viability, those with presence of viability had a worse prognosis in the presence of a BNP baseline value > 230 (Kaplan-Meier log rank p=0.027).
Conclusions: Markers of inflammation (IL-6)or LV dysfunction (BNP)contribute to stratification incrementaly to functional changes by DSE.

P1139 Does dobutamine stress echocardiography induce changes in brain natriuretic peptide levels?

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Background: Plasma brain natriuretic peptide (BNP) levels have been considered as a prognostic marker in patients (pts) with heart failure and acute coronary syndromes. There is limited evidence that exercise-induced ischemia causes early and transient rise in plasma BNP levels. However, the effect of dobutamine stress induced-ischemia on BNP levels has not been fully elucidated.
The aim of this study was to evaluate BNP levels pre- and post dobutamine stress echocardiography (DSE) in an unselected population.
Methods: We performed DSE for detection of inducible ischemia in consecutive pts. We measured plasma N-terminal proBNP (fragment of the BNP prohormone) levels before and 1 hour after DSE. N-terminal proBNP levels were measured by an electrochemiluminescence immunoassay (ECLIA) on a Roche Elecsys 1010 instrument.
Results: Seventy-one pts (mean age 55±10.4, 52 male) underwent DSE. Thirty-five (49.3%) pts had a history of known coronary artery disease, 11(15.5%) pts were diabetic, 35(49.3%) pts were hypertensive, and 7(9.8%) pts had ejection fraction <40%. Normal baseline BNP levels (cut off point 80 pg/ml) were detected in 23 (32%) pts. Inducible-ischemia during DSE was detected in 17 (24%) pts. Diabetic pts were found to have significantly higher baseline BNP levels compared with non-diabetics (298.75±245.76 vs. 149.88±173.78 pg/ml respectively, p=0.05). Baseline BNP levels were not significantly different in pts with or without history of hypertension (p=NS). BNP levels were not significantly changed after dobutamine infusion both in pts with (187.43±182.50 vs. 194.59±184.13 pg/ml, t=-0.98, p=0.33) and without inducible ischemia (155.30±198.52 vs. 161.58±208.83 pg/ml, t=-1.87, p=0.07). Moreover, baseline and post DSE BNP levels were not found significantly different both in pts with increased and normal baseline BNP levels (p=NS). There was no correlation between BNP levels and left ventricular hypertrophy (wall thickness>12mm), left ventricular end-diastolic diameter and diastolic dysfunction (p=NS).
Conclusions: BNP levels do not significantly increase shortly after DSE regardless of the presence of inducible ischemia.

P1140 Prognostic implications of cTnI elevation after elective percutaneous interventions on global and reginal left-ventricular function in one year, prospective follow-up study

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Background: cardiac troponins are sensitive markers of minor myocardial injury, its predictive role after elective PCI procedures is still uncertain.
Aim of the Study: was to assess the incidence of cTnI elevation after elective PCI, with and without stent insertion,it's impact on clinical and echocardiographic data in prospective,one-year study.
Methods: 90 pts,who underwent elective PCI, were included into the study. Serum levels of cTnI were measured before,12 and 24 h after procedure, by the use of immunoassay(OPUS,Dade-Behring),cut-off 0,1ug/L. CK-MB was measured 12 and 24 hours after the procedure,(enzyme activity method,cut-off<24IU/L).Global left ventricle systolic function (LVEF)as well as wall motion score index(WMSI)were assesed. One-year follow-up comprised clinical and echocardiographic data.
Results: No patient had abnormal marker value before the procedure. Baseline LVEF ranged from 25to60%(mean 50%), calculated WMSI was 1,2±0,2. Postproceduraly,we noticed a few fold rise of cTnI serum levels in 66 pts(73%)-cTnI positive (cTnI+) group, being the most prominent in PCI with stent. 24 pts (27%) presented with normal values of cTnI after PCI- cTnI negative(cTnI-)group. Only 8 of 66 cTnI(+)pts, had significant(>1,0ug/l) postprocedural cTnI concentration, coexisting with the rise of CKMB value. One year follow-up comprised 62 pts of cTnI (+) group and all (24) pts of cTnI (-)group. 4pts from cTnI(+) group died of AMI. Results of LVEF and WMSI 1-year analyzis and are given in table 1.Evaluation of post-procedural cTnI rise on the incidence of MACE, revealed a positive correlation (7 MACE versus no MACE in cTnI + and cTnI-group, respectively).No statistical significance was calculated(p=0.0967)

	rise in EF & fall in WMSI	fall in EF & rise in WMSI	no change in EF & WMSI
cTnI(+) 62pts	9 pts (15%)	22 pts (35%)	31 pts (50%)
TnI(-) 24pts	5 pts (21%)	0 pts	19 pts (79%)
p	ns	p<0.001	p<0.02

Conclusions: a small rise in serum cTnI level is a common finding after elective PCI; in our study it does not significantly correlate with adverse outcome, but it has some negative impact on global and regional left ventricle systolic function. Stenting procedures seem to be associated with higher degree of minor myocardial injury.

P1141 Early to late colour M-mode flow propagation velocity ratio is related with natriuretic peptides levels in patients with dilated cardiomyopathy

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Purpose: The ratio of early transmitral (E) wave velocity to colour M-Mode Doppler E flow propagation (Ep) in patients (pts) with heart failure, has been used to evaluate left ventricular (LV) filling pressure non-invasively. However, late LV filling velocity propagation (Ap) has not been studied. Atrial (ANP) and Brain (BNP) natriuretic peptides are secreted from cardiomyocytes in response to increased atrial stretch or elevated LV filling pressures. We assess the relationship between the Ap and Ep/Ap ratio with natriuretic peptide levels in patients (pts) with non-ischemic dilated cardiomyopathy (NIDC).
Methods: We studied 37 pts with angiographically proven NIDC, aged 58.1±11.3y, functional NYHA class II-III and LV ejection fraction (EF) 31.2±10.4%. A complete echocardiography study with colour M-Mode Doppler was performed, and Ep and Ap measured. Pro-ANP and pro-BNP levels were also calculated in all patients.
Results: The study population was divided into 2 groups. Group I [delayed relaxation pattern if E/A<1, isovolumetric relaxation time (IVRT) >100msec, Deceleration E time >220 msec and atrial component (AR) of the pulmonary venous (PV) flow <35 cm/sec (24 pts)] and Group II [pseudonormal pattern if E/A=1-2, IVRT=60-100 msec, DTE=150-200msec and AR>35 cm/sec].
There were no significant differences in age, NYHA functional class, LV dimensions, LVEF, left atrial size and Ap (0.69±0.29 vs 0.54±0.3, p=NS) between the two groups. Group II patients showed decreased peak systolic PV wave velocity (SPV)(0.44±0.31 vs 0.52±0.05 m/sec, p=0.02), Velocity time integral of SPV (11.3±3.8 vs14.8±5.5 sec, p=0.001), contribution of SPV to total atrial filling (0.51±0.06 vs 0.57±0.11, p=0.01) and increased Ep (0.44±0.21 vs 0.31±0.14 m/sec, p=0.01) and Ep/Ap ratio (1.19±1 vs 0.56±0.41, p=0.01) compared to Group I pts.
Group II pts also had increased ANP (6.2±4.2 vs 2.9±1.4 pmol/ml, p=0.03) and BNP (1.2±0.81 vs 0.57±0.33, p=0.03) levels compared to Group I. Ep/Ap ratio correlated with E/A ratio (r=0.73, p<0.001), AR(r=0.44,p=0.04), ANP (r=0.49,p=0.04)and BNP (r=0.82, p<0.001)levels. Multivariate linear regression analysis showed that the Ep/Ap ratio was the most powerful predictor of BNP levels (p<0.001).
Conclusions: In patients with NIDC, the Ep/Ap ratio, in addition to other markers of LV diastolic dysfunction, was found to be associated with BNP levels. This index may prove valuable in clinical practice in the assessment of LV diastolic dysfunction, especially in those who have a pseudonormal pattern.

P1142 Left atrial size by planimetry is closer associated with natriuretic peptides than M-mode diameter

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Left atrial (LA) size is routinely assessed by M-Mode (LA-diameter) upon echocardiography. Alternatively, the assessment via planimetry has been suggested. To determine which parameter reflects LA loading conditions best, we calculated correlations with ANP and BNP, the two cardiac natriuretic peptides. A total of 576 middle-aged subjects (50-67 years) from a population-based sample (MONICA Augsburg, Germany) were characterized with respect to LA area and volume from the apical two and four chamber views (2C and 4C, respectively) by planimetry and uniplane volumetry in addition to M-Mode echocardiography. ANP and BNP plasma concentrations were determined by sensitive and specific radioimmunoassay (Amersham, Shionogy, respectively). A significant univariate correlation with ANP and BNP was present with all atrial parameters. Other correlates were age, heart rate, LV mass-index (all p<0.05) and LV systolic function (only BNP significant, p<0.03). Among the atrial parameters, the univariate correlation coefficients were greatest with 2C-volume (r=0.205 with ANP and 0.285 with BNP, both p<0.01) and exceeded those with 2C-area (r=0.192 with ANP and 0.249 with BNP, both p<0.01), 4C-volume (r=0.143 with ANP and 0.228 with BNP, both p<0.01), and 4C-area (r=0.112 with ANP and 0.211 with BNP, both p<0.02). Most remarkably, the correlation was lowest with LA-diameter (r=0.113 with ANP and 0.093 with BNP, both p<0.04). Furthermore, when 2C-volume was entered into a multivariate model, it displaced LA-diameter and heart rate as statistically significant predictors of ANP (p<0.001) and LV systolic function and mass index as statistically significant predictors of BNP (p<0.001).
The current population-based echocardiographic study allows new insight into the value of different measures of LA size. The closer association between parameters derived from planimetry and uniplane volumetry (particularly 2C-volume) with natriuretic peptide concentrations suggests a superiority of these parameters over LA-diameter, possibly also reflecting diastolic function. 2C-volume should be included into routine echocardiography for optimized assessment of LA size.

ECHO-DOPPLER, MISCELLANEOUS II

P1143 Response of brain-type natriuretic peptide to exercise in diastolic heart failure: correlation with cardiac function, haemodynamics and workload

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Background: Diastolic heart failure (DHF) is characterized by dyspnea due to increased LV filling pressures during stress. B-type natriuretic peptide (BNP) is associated with elevated filling pressures, so we sought the relationship of increased BNP to exercise and whether this could be a useful marker of DHF.
Methods: Twenty-six treated hypertensive pts (18 women, age 62±6y) with DHF (symptoms of HF, no angina, LV ejection fraction>50%, E/A<1 and E deceleration time>250msec) underwent maximal exercise echocardiography. BNP (Triage, Biosite), transmitral Doppler, and tissue Doppler for systolic (Sa) and early (Ea) and late (Aa) diastolic velocities at septal and lateral mitral annulus were obtained at rest and peak stress. LV filling pressures were estimated with E/Ea ratios.
Results: Maximal exercise performance (4.6±2.5min) was limited by dyspnea. BP increased with exercise (from 143±19/88±8 to 191±22/90±10mmHg). Resting BNP correlated with resting pulse pressure (r=0.45, p=0.02). Peak exercise BNP correlated with peak transmitral E velocity (r=0.41, p<0.05) and peak heart rate (r=-0.40, p<0.05). BNP increased with exercise (from 48±57 to 74±97pg/ml, p=0.007), and increment of BNP with exercise was associated with maximum workload and peak exercise mitral annular velocities (Table); multiple linear regression revealed an independent relationship with peak lateral Ea (p<0.001).Filling pressures, approximated by lateral E/Ea ratio increased with exercise (7.7±2.0 to 10.0±4.8, p<0.01). BNP was higher in pts with possibly elevated filling pressures at peak exercise (E/Ea>10), compared to those with normal pressures (123±124 vs 45±71 pg/ml, p=0.027).

	r	p
Maximum workload	0.53	0.006
Peak Sa septal	0.41	0.046
Peak Sa lateral	0.54	0.005
Peak Ea lateral	0.84	<0.001
Peak Aa septal	0.54	0.007

Conclusions: Augmentation of BNP with exercise in DHF pts is associated with better exercise capacity, left atrial function, and LV systolic and diastolic function. Peak exercise BNP levels may identify exercise-induced elevation of filling pressures in DHF.

P1144 Validation of criteria for non-compacted myocardium in dilated cardiomyoapthy, valvular and hypertensive heart disease

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Background: The echocardiographic criteria described in isolated ventricular noncompaction (IVNC) have been described to rarely occur in patients (pts) with valvular or hypertensive heart disease (HTN) or idiopathic dilated cardiomyopathy (IDC). The definition of noncompaction (NC) includes thickened myocardium with a 2-layer structure consisting of compacted (C) and noncompacted (NC) myocardium (endsystolic ratio N/C >2), perfused deep intertrabecular recesses, and hypokinesis.
Methods/Results: Retrospectively, echocardiographic and clinical findings of 19 pts (43±16 years=yrs) with IVNC were compared to 31 pts with IDC(47±14 yrs), 20 pts with aortic regurgitation AR (44±10 yrs), 44 pts with aortic stenosis AS (59±17 yrs; bicuspid valve in 25 pts), 22 pts (59±10 yrs) with mitral regurgitation MR, 22 pts (58±14 yrs) with hypertensive cardiomyopathy (HTN) and 20 controls (48±17 yrs) to analyze frequency and specificity of NC. For analysis, the left ventricle was divided in 9 segments (apex, 4 middle and 4 basal segments). The number of coarse trabeculations was counted in the apical 4 chamber view; hypertrabeculation was defined as >3. Results see table.

	LVEDD cm	EF %	Hypertrabeculation % of pts	2layers N/C>2	Recesses % of pts	No. of NC segments	NC % of pts
Controls	4.6(0.4)	65(6)	0	0	0	0	0
IVNC	6.1(1.0)	39(13)	11	100	95	3.4(1.9)	100
IDC	7.6(1.2)	27(16)	0	26	48	0.2(0.7)	3
HTN	5.5(0.8)	49(18)	0	5	9	0.4(0.1)	5#
AS	5.2(0.7)	59(16)	2	7	5	1.5(0.2)	5*
AR	6.8(0.9)	48(13)	0	10	5	2.0(0.5)	0
MR	6.4(0.5)	60(7)	0	10	9	0.4(0.1)	0

LVEDD = left ventricular enddiastolic diameter; EF = ejection fraction; no = number. # retrospectively also NC and not HTN. *in both patients with IDC, criteria were met for NC, however there was no wall thickening.

Conclusion: Hypertrabeculation is not very useful. Perfused recesses or LV wall segments with a two-layered structure may be observed especially in dilated cardiomyopathy IDC - however without wall thickening which must be used as a criterion for IVNC. All criteria for noncompaction are rarely met in heart disease other than IVNC but may be rarely found in pts with bicuspid aortic valves.

P1145 The late consequences of anthracycline treatment on the left-ventricular function in patients treated for childhood cancer

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Introduction: The purpose of this study was to determine the incidence of changes in the left ventricular function as well as the presence of "late cardiotoxicity" of the heart in patients in long-term remission after a treatment with anthracyclines for a malignity in childhood.
Patients and Methods: The authors examined 155 patients who underwent a treatment comprising anthracyclines in childhood. The group comprised of 90 males and 65 females in the age range of 15+4.9 years (5-29, median 15 years). The age at the time of diagnosis and beginning of the treatment was 8.6+4.9 years (1-18, median 8 years). The average time of follow-up was 7.3+4 years (1-21, median 6,3 years). All the patients were in the long-term remission of the disease. The patients were given the cumulative dose of doxorubicin, possibly even daunorubicin 250+131 mg/m^2 (50-1200, median 240 mg/m^2). The patients were examined by means of echocardiography. The values of ejection fraction below 55% and of fractional shortening bellow 30% were considered as pathological. The control group comprised 40 healthy people.
Results: 12 patients (8%) showed pathological values of fractional shortening. Only one patient (0,64%) showed the development of heart failure on the basis of cardiomyopathy. The group of the patients after chemotherapy showed significantly worse values of left ventricular endsystolic wall stress ($p<0.001$), mean velocity of circumferential fibre shortening ($p<0.001$), Tei index ($p<0.001$), and isovolumic relaxation period ($p<0.05$) in comparison with the control group. We found good correlation between the given cumulative dose of anthracyclines and the indicators of the systolic function of left ventricle. We have not found a relation to the time indicators (age at the diagnosis, time of follow-up).
Conclusion: In the period of the first decade after the completion of chemotherapy the authors found subclinical cardiotoxicity in 11 patients (7%) and cardiomyopathy with the symptoms of heart failure only in 1 patient. Further indicators of subclinical damage are elevation of afterload (endsystolic stress), impaired relaxation and increased value of the Tei index. The presented findings entitle the authors to further monitoring of the patients and evaluating the relevant subclinical abnormalities with a longer lapse of time.

P1146 Handheld echocardiography at bedside: which patients can benefit most?

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Purpose: Handheld echocardiography (HE) has shown different degrees of correlation with standard echocardiography (SE) according with the environment where it is performed and the different variables tested. It is, however, important to define in which clinical settings it may proof to be more useful and accurate. The constant improvement of ultrasound technology may also overcome some of the current limitations. In the present study the authors tested the agreement between HE obtained at bedside in the adverse conditions of a busy hospital environment – using a recent device - and SE findings.
Methods: A handheld ultrasound device (SonoHeart Plus®) with M-mode, 2-D, pulse and color Doppler was used as a screening tool at bedside in hospitalized patients with a request for SE. The group included patients from medical and surgical wards and intensive care units. The studies were all performed by level III echocardiologists (ACC). According with the information needed, the findings and the quality of the obtained images, the echocardiologist classified each study as satisfactory or unsatisfactory. Ninety six studies were performed (42 men; 54 women; mean age 69.9±14.6 years; mean study time 6±3 minutes). An unsatisfactory result was obtained in 31 patients (32%). SE was performed in this subgroup by a different operator with no access to the previous study. An agreement analysis (weighted Kappa) was performed considering a categorical scale for left ventricular (LV) global systolic function, LV segmental contractility, LV and atrium dimensions, pericardial effusion, valvular disease (VD) and cardiac masses. Each valve was classified as normal, significant stenosis, significant regurgitation and prosthesis.
Results: The degree of agreement between HE and SE was very good for cardiac masses (Kw=1.00); good for LV global systolic function (Kw=0.80) and pericardial effusion (Kw=0.67); moderate for LV (Kw=0.59) and atrium (Kw=0.56) dimensions; fair for LV segmental contractility (Kw=0.39), aortic VD (Kw=0.25) and mitral VD (Kw=0.28) and poor for tricuspid VD (Kw=0.17).
Conclusions: HE has shown to be very accurate at bedside in assessing some variables (such as LV global function, cardiac masses and pericardial effusion), while it showed to be limited in obtaining others (such as valvular parameters or segmental LV wall analysis). Therefore, handheld echocardiography may represent a very important and accurate screening tool in some clinical settings, which should be continuously tested considering the fast development of the new ultrasound technologies.

P1147 Community screening for left-ventricular hypertrophy in hypertensive patients using hand-held ultrasonography

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Background: Left ventricular hypertrophy(LVH) confers increased cardiovascular risk in patients with hypertension. Echocardiography using hand-held devices might allow community-based cost-effective screening for LVH in a targeted hypertensive population. Thus, the aim of the study was to test the validity of hand-held ultrasound device to screen for LVH in the community.
Methods: Accordingly 189 hypertensive subjects attending a community-based heart failure screening programme underwent echocardiography by both hand-held and standard devices by an experienced echocardiographer. LV posterior wall thickness, interventricular septal thickness and end-diastolic diameter were measured in the parasternal short-axis view at the level of the papillary muscles. LVH was defined as LV mass index(LVMI)>134gm/sq.m for men and >110g/sq.m for women using the Devereux-modified ASE-cube equation.
Results: In the 179 subjects, who were assessed successfully by both echocardiography devices, no significant differences were noted between the 2 devices in the measurements of LV posterior wall thickness, interventricular wall thickness, end-diastolic diameter or LVMI. Overall agreement for estimation of LVH between the 2 devices was 86%(kappa=0.63). The sensitivity, specificity, positive and negative predictive values of hand-held device for predicting LVH were 72%, 91%, 73% and 90% respectively.
Conclusion: Hand -held echocardiography devices accurately assessed LVH and may be used for community-based screening for LVH in targeted hypertensive subjects.

P1148 Left-ventricular diastolic dysfunction and other complications in asymptomatic non-insulin-dependent diabetes mellitus patients

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Objective: The aim of this study was to evaluate diastolic function in patients with non-insulin-dependent diabetes mellitus (NIDDM), the presence of its pseudonormalization and the prevalence of the complications of NIDDM in these patients.
Methods: We studied 103 patients with NIDDM (with age 57±8.2 years, 34 men) and no clinical evidence for ischemic heart disease (Group 1) and 103 subjects without diabetes as a control group (Group 2) matched by age and sex. Two-dimensional, M-mode and pulsed-Doppler echocardiography were performed to assess LV systolic and diastolic function. Color M-mode echocardiography was performed in patients with normal pulsed-Doppler findings. To exclude the presence of coronary artery disease, exercise test with treadmill was performed.
Results: The E/A ratio of mitral inflow registered by pulsed-Doppler indices had significant differences between Group 1 and Group 2 patients (0.83±0.3 vs 1.16±0.38, $p<0.01$) and it was found in 71 (68.9%) patients of Gruop 1 and in 36 (34.9%) subjects of Group 2 ($p<0.01$). There was also significant difference of deceleration time of E wave (173±20.7ms vs 163.5±31.4ms, $p<0.01$) between groups.
Seven patients from group 1 and 3 subjects from group 2 with E/A > 1 resulted with velocity propagation (Vp) <55cm/s. This was a significant difference between groups ($p<0.01$).
The age of NIDDM patients had good correlation with E/A ratio (r=-0.38, $p<0.01$), whereas had non-significant correlation with EF (r=0.09, p=0.4). There was good correlation between the duration of diabetes in these patients with both systolic (EF) and diastolic (E/A ratio) function of left ventricle (r=-0.26, $p<0.01$, and r=-0.295, $p<0.01$, respectively).
Valsalva Ratio was abnormal in 8.7%, while deep breathing test was abnormal in 13.6% and standing-up test in 17.5% of NIDDM patients. Diabetic retinopathy was found in 26.2% in these patients.
Conclusions: Left ventricular diastolic function is reduced in NIDDM patients with no symptoms of cardiovascular disease and with negative exercise test.
The prevalence of pseudonormalization was significantly higher in NIDDM patients than in control subjects. The duration of diabetes had good correlation with both systolic and diastolic function of LV in NIDDM patients, whereas, the age of patients with NIDDM had good correlation with diastolic dysfunction of LV, but has not-significant correlation with its systolic function. The autonom neuropathy and diabetic retinopathy were frequent in patients with NIDDM.

P1149 Radiofrequency catheter ablation of ventricular tachycardia guided by intracardiac echocardiography

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Background: Ventricular tachycardia (VT) can originate from an anatomical substrate. Reentry involving border zone areas of infarcted regions causes VT in patients (pts) with ischemic heart disease. VT can also occur in the presence of other cardiomyopathies. Radiofrequency catheter ablation (RFCA) is a treatment option in a selected population of drugrefractory VT pts, but is associated with a risk of complications. Identification of anatomic abnormalities to predict the expected area of arrhythmogenicity and methods to monitor the occurrence of intra-procedural complications, are mandatory.
Purpose: To assess the value of intracardiac echocardiography (ICE) in guiding RFCA of VT (identifying VT substrate), guiding catheters and monitoring potential complications.
Methods: Sixteen pts (age 55 ± 18, 13 male) with drug refractory hemodynamic stable VT were studied. VT was post-ichemic in 7 pts, secondary to arrhythmogenic right ventricular dysplasia (ARVD)/hypertrophic cardiomyopathy in 4 pts and idiopathic in 5 pts. ICE was performed using a 10 F multifrequency (5-10 Mhz) phased array transducer (Acunav) positioned in the right ventricle. On initiation of all procedures, ventricular function and anatomy was investigated with ICE. VT mapping and ablation was performed using standard techniques including pace and entrainment mapping.
Results: One pt did no undergo RFCA because of intracardiac thrombus, detected with ICE (not detected by transthoracic echocardiography). Twenty-nine VT's were treated (CL 365 ± 115, 1.8 VT/pt). Localized ventricular aneurysms were identified in 6 post-infarct pts and in all pts with ARVD. At these sites early-activated endocardial areas were identified during VT mapping. Catheter position and tip-tissue contact was monitored with ICE. Procedural success (non-inducibility of hemodynamically stable VT after RFCA) was achieved in 14 pts (88%). Mean procedure time was 197 ± 53 min and fluoroscopy time 30 ± 15 min. Procedure related complications did not occur.
Conclusion: ICE is safe and feasible in guiding VT ablation procedures. ICE can be used to identify VT-substrate, to ensure adequate tissue tip contact and to safely manoeuvre catheters within the ventricles.

P1150 Left-ventricular hypertrophy in amateur and professional cyclists

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Purpose: Endurance cycling is associated with an increase in left ventricular (LV) mass. The differences between amateur and professional cyclists were not yet extensively investigated. The objective of our study was to compare the degree and type of LV hypertrophy in amateur and professional cyclists to sedentary control population.
Methods: LV mass was assessed using echocardiography by applying ASE cube formula in 149 professional cyclists of 1995 Tour de France race (group P), 51 amateur cyclists (group A) and 94 sedentary healthy controls (group C). LV mass was indexed for body surface area (BSA). Upper limit of normal values was derived as mean + 2 standard deviations of the control group. Concentric hypertrophy was considered for relative wall thickness above 0.42.
Results: The three groups did not differ in BSA significantly (1.89±0.12 vs. 1.91±0.13 vs. 1.92±0.15 in groups P, A and C, respectively, p=0.15). Interventricular septum thickness above 12 mm was present in 52 professionals (34.9%) but only in one amateur cyclist and not noted in group C. There were significant differences in LV mass among the three groups (144.1±22.0 g/m^2 vs. 108.7±23.0 g/m^2 vs. 80.4±13.7 g/m^2 in groups P, A and C, respectively, $p<0.001$). LV hypertrophy was present in 94,6%, 49.0% and in 2.1% of subjects in groups P, A and C, respectively ($p<0.001$). In all amateurs and controls the hypertrophy was eccentric. In contrast 17% of professionals had concentric type of LV hypertrophy.
Conclusions: In amateur cyclists we noted a high frequency of LV hypertrophy. However, the prevalence and extent of hypertrophy was incomparably lower than in professional athletes. Of note is the virtual absence of concentric hypertrophy and parietal thickness exceeding 12 mm in amateurs.

P1151 Is valve area always measured in patients with aortic stenosis?

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The measurement of aortic valve area (AVA) is the main criteria for assessing the severity of aortic stenosis (AS) in the current recommendations on the management of patients (pts) with valvular heart disease. We analysed the current practices in the evaluation of the severity of AS using the data from the Euro Heart Survey (EHS).
Methods: The EHS on valvular heart disease was performed between April and July 2001 and included 5001 pts from 92 centres in 25 countries. Of them, 1197 pts had isolated AS, as defined by a maximal Doppler jet velocity ≥2.5 m/s. Etiology was degenerative in 82%. Mean age was 69±12 years; 156 pts (13%) were asymptomatic; 484 (40%) had a mean aortic gradient < 50 mmHg.
Results: Of the 1197 pts with AS, transthoracic echocardiographic (TTE) measurement of AVA was available in 849 pts (71%). The availability of AVA did not differ either according to symptoms (71% in symptomatic pts vs. 69% in asymptomatic pts, p=0.70), or to mean gradient (81% for mean gradient <50 mmHg vs. 78% for mean gradient ≥50 mmHg, p=0.16). Of the 348 (29%) pts in whom AVA was not assessed by TTE, transesoephageal echocardiography (TEE) was performed in 23 pts (6.6%) and catheterisation in 117 pts (34%), among whom left and right catheterisation was performed in only 32 pts (9.2%). When considering the 512 pts who underwent surgery for AS during the study period, TTE measurement of AVA was available in 375 pts (73%). The availability of AVA did not differ according to symptoms (62% in symptomatic pts vs. 76% in symptomatic pts, p=0.07) but was more frequent in pts with low gradient (87% for mean gradient <50 mmHg vs. 78% for gradient ≥50 mmHg, p=0.05). Of the 137 pts (27%) in whom AVA was not assessed by TTE, TEE was performed in 10 pts (7.3%) and catheterisation in 70 pts (51%), among whom left and right catheterisation was performed in only 20 pts (14.6%).
Conclusion: 1) In current practice, the measurement of AVA using TTE is not performed in 29% of cases and in 27% of operated pts. 2) The availability of the measurement of AVA is not significantly higher in asymptomatic pts, in whom the evaluation of AVA is of particular importance. 3) In the absence of TTE evaluation of AVA, there is an infrequent use of alternative methods for assessing AVA, including TEE or left and right catheterisation.

P1152 Evaluation of pulmonary flow by Doppler echocardiography and scintigraphy after percutaneous closure of patent ductus arteriosus

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Background: Most patients (pts) submitted to percutaneous closure of a patent ductus arteriosus (PCPDA), show some degree of protrusion of the occlusive device into the left pulmonary artery (LPA). The purpose of this study is to assess the prevalence of coil protrusion, and if it causes significant obstruction.
Methods: A study group (SG) of 70 pts were submitted to PCPDA with Gianturco coils (mean age: 8.6 years). Doppler Echocardiographic studies were performed with a mean time follow-up of 55 months. The coil and LPA assessment were done by suprasternal, short-axis and high left parasternal views. LPA diameter was indexed to body surface area. A Doppler Index was calculated by the differences of the ratios of the velocities from each pulmonary artery in relation to the pulmonary trunk, expressed in percentage (VD Index). Pulmonary scintigraphy was performed using intravenous injection of 99Tcm labeled macroaggregated albumin to evaluate lung perfusion. The diameters and disturbances in flow velocities by Doppler Echocardiography of the pulmonary arteries were compared with lung perfusion by pulmonary scintigraphy. The same measurements were performed in a control group (CG) of 22 pts (normal or with minimal heart defects). VD Index values of the SG were compared with pulmonary scintigraphy values of the CG to establish normal and abnormal values. Mean time interval between the two studies was 81 days.
Results: In 66 pts (95%), the coil protruded into the LPA. The mean LPA diameter was 13mm (SG and CG). The mean VD Index was 22% in the SG and 1,7% in the CG. A cut off value of 50% for the VD Index was determined (ROC curve),with 100% of sensibility and 98% of specificity. In 8 pts (11%) the VD Index was $\geq$ 50%, with abnormal left pulmonary perfusion (LPP) in 7. A significant correlation between the VD Index and LPP was demonstrated (R^2 =65.19). To estimate the LPP by Doppler a formula was obtained from a regression line: LPP= 47,8 - 0,09 x (VD Index). The LPA diameter was compared between pts with VD Index $\geq$ 50%, < 50% and CG, with no statistically significant difference (p=0,6).
Conclusion: Protrusion of the coil to LPA was frequently found. LPA diameters did not correlate with flow disturbances and reduced LPP. Patients showing blood flow acceleration $\geq$50% at the left pulmonary artery by Doppler have significantly lower values of lung perfusion.

OXIDATIVE STRESS, NITRIC OXIDE AND ENDOTHELIAL FUNCTION

P1153 Vascular oxidative stress in patients with essential hypertension: role of superoxide dismutase, catalase and glutathione peroxidase

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Introduction: Endothelial vascular dysfunction is relatively well documented phenomena in essential hypertension (EH). Impairment of endothelium-dependent vasodilation in patients with EH is, at least in part, due to accelerated degradation of nitric oxide by oxygen radicals. Therefore we determined activities of major extracellular antioxidant enzyme systems (extracellular superoxide dismutase, ecSOD; glutathione peroxidase, GPX and catalase) as well as plasma markers of free radical activity (malondialdehyde, MDA; reactive carbonyl derivatives, RCD) and their relation to the severity of hypertension in EH patients.
Methods: Forty eight patients with different degrees of essential hypertension and 24 healthy persons matched for age were included in the study. Activities of ecSOD, GPX and catalase were analyzed using spectrophotometric assays. Plasma levels of MDA were determined by HPLC method. Plasma RCD were estimated after protein precipitation using 2,4-dinitrophenylhydrazine as carbonyl reagent.
Results: In patients with EH ecSOD activity was significantly reduced (26.1$\pm$2.7 vs. 33.3$\pm$3.6 U/L; $p<0.01$) and correlated negatively with systolic (r= -0.37) and diastolic blood pressure (r= -0.40). Catalase activity was also decreased (62.1$\pm$5.8 vs. 86.1$\pm$4.9 U/L; $p<0.01$) and inversely related to systolic (r= -0.33) and diastolic blood pressure (r= -0.38). At the same time, concentrations of MDA and RCD, well established markers of oxidative lipid and protein damage, were increased (0.78$\pm$0.06 vs. 0.40$\pm$0.05 μmol/L, $p<0.001$ and 0.82$\pm$0.09 vs. 0.61$\pm$0.06 μmol/g prot., $p<0.01$; respectively). Increases in MDA and RCD levels in EH patients were positively related to systolic (r=0.54 and r=0.48, respectively) and diastolic pressure (r=0.49 and r=0.51, respectively). EH patients exhibited an increase in the activity of extracellular GPX. Namely, GPX activity was increased by more than 100% (601$\pm$25 vs. 298$\pm$56 U/L; $p<0.001$) and positively related to systolic blood pressure (r=0.32).
Conclusions: These results suggest that both reduced ecSOD and catalase activities contribute to increased vascular oxidant stress in patients with EH. Increased GPX activity probably represents an adaptive phenomenon in such conditions, although production of free radicals overwhelms antioxidant potential. This loss of "vascular oxidative balance" likely represents an important mechanism contributing to endothelial dysfunction in patients with EH.

P1154 Inhibition of p38 mitogen-activated protein kinase prevents endothelial dysfunction in chronic heart failure: role of vascular superoxide anion production

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Endothelial dysfunction contributes to increased peripheral vascular resistance in chronic heart failure. The mitogen activated protein (MAP) kinase system, especially the p38 MAP kinase, is activated in heart failure. The aim of this study was to investigate the influence of p38 MAP kinase inhibition on vascular reactivity in rats suffering from heart failure. Coronary ligation (MI) or sham-operation (sham) was performed in male wistar rats. Animals were treated for 10 weeks with the p38 MAP kinase inhibitor SB239063 (800 ppm in standard rat chow) or placebo. Only animals suffering from heart failure were included (LVEDP>15 mmHg) in the vascular reactivity study. Acetylcholine-induced endothelium-dependent vasorelaxation was blunted in isolated thoracic aortae from placebo-treated MI rats compared with sham animals (Rmax 54$\pm$5% vs. 77$\pm$5%, $p<0.01$). Endothelium-independent relaxation induced by sodium nitroprusside was similar among the groups. Superoxide anion production was significantly elevated in rats suffering from heart failure (343$\pm$30 cpm/mg [lucigenin 5 μmol/l]) compared to sham animals (163$\pm$29 cpm/mg). Treatment with the p38 MAP kinase inhibitor SB239063 did neither influence vasoreactivity nor superoxide anion production in aortae from sham rats. However, in MI rats treated with SB239063, acetylcholine-induced relaxation was normalized (Rmax 80$\pm$4%, $p<0.01$ vs. MI placebo). Furthermore, the elevated vascular superoxide anion production was corrected by treatment with SB239063 (179$\pm$45 cpm/mg, $p<0.05$ vs. MI placebo). Chronic treatment with the p38 MAP kinase inhibitor SB239063 prevents endothelial dysfunction in rats with heart failure after myocardial infarction. SB239063 appears to elevate NO bioavailability through reduction of superoxide anion production.

P1155 Effects of pravastatin on endothelial function and oxidative stress in patients with unstable angina

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Purpose: Oxidative stress and local vascular inflammation is thought to be associated with endothelial dysfunction, which plays a pivotal role in pathogenesis of atherosclerosis and acute coronary syndromes. Latest studies provide evidence about the pleiotropic properties of HMG Co-A reductase inhibitors (statins). The aim of this study was to examine the effects of statins in oxidative stress and endothelial function independently from their lipid lowering properties in patients with unstable angina (UA).
Methods: 58 patients (males), 63.57+ 9.3 years, suffering from UA enrolled the study. 38 of them were not on statin medication before hospitalization, and they were randomized to receive either 40mg pravastatin daily (n=21)(group A), or placebo (n=17)(group B), in addition with their medication for UA, for 10 days. These two groups where matched for age, BMI, risk factors, severity of disease previous and current medication, and also with a third (n=20) group (C) comprised of patients who where already on statins medication for the last 6 months and also took 40mg of pravastatin daily. Malondialdehyde (MDA), a marker of lipid peroxidation, endothelium dependent flow mediated dilatation (FMD) and also endothelium (nitrate mediated) independent vasodilation (NMD) where obtained during the first 24 hours of admission, as well as 10 days later.
Results: Serum lipids were unaltered. FMD in group A increased (from 3.07+3.1% to 5.67+3% p=0.003), whereas in group B (from 3.01+3.6% to 2.25+2.3% p=ns) and C (from 2.69+2.1% to 2.71+2.3% p=ns) did not change (paired t-test). MDA in all groups decreased significantly (A, from 4.18+2.2μl to 2.80+1.3μl p=0,004), (B, from 3.21+1.4μl to 1.94+1.3μl p=0.003) and (C, from 3.32+1.2μl to 2.35+1.2μl p=0.006)(paired t-test). FMD value and also FMD alteration of the second examination in group A was higher than in the other groups (p=0.002 and p=0.009 respectively) (one-way ANOVA). Baseline and final values of MDA, and baseline of FMD didn't differ between groups. NMD showed no change during the 10 days and no difference between groups. Group C had lower initial LDL (p=0.026 one-way ANOVA) due to previous statin therapy.
Conclusions: Oxidative stress in unstable angina reduced within 10 days of hospitalization. Pravastatin therapy didn't influence additionally this phenomenon, but improved FMD before any changes in blood lipids, providing evidence about its pleiotropic effects during the early phase of an acute coronary syndrome.

P1156 Cytomegalovirus impairs the nitric oxide pathway. Role of ADMA in transplant arteriosclerosis

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Atherosclerosis is an inflammatory disease initiated by endothelial injury. Causes of endothelial injury may include pathogens such as cytomegalovirus (CMV). We hypothesized that a major mechanism by which CMV could initiate and/or accelerate arteriosclerosis is by dysregulation of the endothelial nitric oxide synthase pathway.

Methods and Results: Human microvascular endothelial cells infected with the clinical CMV isolates VHL/E and TP40/E elaborated more ADMA (the endogenous NO-synthase inhibitor) in a manner that was dependent upon time and the multiplicity of infection. The increased elaboration of ADMA, was due to reduced activity of dimethylarginine dimethylaminohydrolase (DDAH), the enzyme that metabolizes ADMA (DDAH activity index in TP40/E infected cells versus controls, $p<0.01$). Infected cultures showed high levels of oxidative stress with enhanced endothelial production of superoxide anion (+93±11%; $p<0.001$). Heart transplant recipients manifested elevated ADMA levels compared to non-transplant controls (+216%; $p<0.001$). Transplant patients with CMV positive leukocytes (RT-PCR) had higher ADMA plasma concentrations (2.27±0.8 uM compared to 1.96±0.7 uM; $p<0.05$) and more extensive coronary artery disease than transplant patients without detectable CMV ($p<0.05$).

Conclusion: CMV infection in endothelial cells increases oxidative stress, impairs DDAH-activity, and increases ADMA elaboration. CMV infection in human heart transplant recipients is associated with greater ADMA elevation and more severe transplant atherosclerosis. CMV infection may contribute to endothelial dysfunction and atherosclerosis by dysregulation of the NOS-pathway.

P1157 Long-term L-arginine therapy improves endothelial function assessed by a brachial artery vasoreactivity testing in patients with normal coronary arteries

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Purpose: About 10-15% of patients referred to coronary angiography because of recurrent chest pain have normal coronary arteries. Thus, the present study was designed to test the hypothesis that long-term oral L-arginine supplementation for 6 months improves endothelium-dependent flow-mediated dilation (FMD) of peripheral vessels assessed by a non-invasive brachial artery vasoreactivity testing (BRT) in symptomatic patients with normal coronary arteries.

Methods: We prospectively assessed endothelial function in 58 consecutive patients with stable angina pectoris [Canadian Cardiovascular Society (CCS) class II-III] who were referred to our laboratory 30±10 days after normal coronary arteries were found on coronary angiography. After an overnight fast and the discontinuation for ≥12 hours of all cardiovascular medications, endothelium-dependent brachial artery FMD and endothelium-independent nitroglycerin-mediated vasodilation (NTG) were assessed using high resolution (15 MHz) linear array ultrasound. Severe endothelial dysfunction (<6% FMD) was observed in 26% (15/58) of the patients. These 15 patients (10 men, mean age 66±11 years, mean left ventricular ejection fraction 52±9%, mean body mass index 28±3 kg/m^2) were recruited into the study. Oral L-arginine (Carginine®, Coraltis Ltd., Isarel) was given at a dose of 5 g daily for 6 months to all study participants. Patients were instructed to avoid taking other medications, over-the-counter vitamins, or amino acids. After 6 months a repeat endothelial function assessment was performed.

Results: See Table.

	%FMD	%NTG	No. SL NTG/day	CCS class
Baseline	4.5 ± 1.2	8.5 ± 1.4	2.7 ± 1.9	2.4 ± 0.4
6-month follow-up	9.8 ± 1.5	9.7 ± 1.6	0.4 ± 0.5	1.0 ± 0.4
p-value	0.03	0.55	0.01	0.01

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

Conclusion: Long-term oral L-arginine therapy for 6 months improves peripheral endothelial function assessed by BRT, and is associated with significant improvement of symptoms in patients with anginal syndrome and normal coronary arteries. Thus, L-arginine is a therapeutic option in symptomatic patients with endothelial dysfunction.

P1158 Synergistic stimulation of nitric oxide release from human endothelial cells with amlodipine and atorvastatin

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Epidemiology studies indicate that systolic hypertension and hyperlipidemia contribute to increased rates of cardiovascular disease (CVD). These risk factors are also causally related to basic mechanisms of atherogenesis, including endothelial dysfunction. Endothelial dysfunction, in turn, is associated with reduced nitric oxide (NO) bioavailability and increased vessel wall permeability to lipids and inflammatory cells. Agents that directly improve endothelial function and NO synthesis have a therapeutic advantage in CVD. The objective of this study was to compare the separate and combined effects of the HMG-CoA reductase inhibitor, atorvastatin, and the calcium channel blocker, amlodipine, on acute NO release from human vein endothelial cells (HUVEC).

Methods and Results: Amperograms (current vs. time) of NO release from HUVEC were measured using a porphyrinic nanosensor placed in close proximity 3 ± 1 μm to the endothelial cell surface. Treatment with amlodipine and atorvastatin produced a synergistic and dose-dependent increase in NO release. At 3.0 μM, the drug combination stimulated peak NO release (219 ± 6 nM) that was significantly greater ($p<0.05$) than either amlodipine (151 ± 18 nM) or atorvastatin (16 ± 2 nM) alone. The synergistic activity of the combination was even more apparent at lower concentrations; treatment with amlodipine and atorvastatin together resulted in greater NO release than that achieved by the sum of their individual effects. At the lowest level tested (1.0 μM), peak NO release of 126 ± 18 nM was observed for the combination, significantly greater ($p<0.01$) than amlodipine (53 ± 0.4 nM) or atorvastatin (2 ± 0.5 nM) alone. The basis for this highly synergistic activity may be due to coordinated interactions of these drugs with signaling proteins in the membrane, resulting in enhanced calcium-calmodulin formation, a co-factor for NO synthase. In support of this model, small-angle x-ray diffraction analyses demonstrated that these agents share a similar molecular location in the membrane lipid bilayer. Additionally, direct intermolecular interactions for these drugs were predicted from electrostatic potential maps.

Conclusion: These findings indicate that amlodipine and atorvastatin stimulate NO release from human endothelial cells in a synergistic and potent fashion, independently of effects on LDL levels or blood pressure. The highly synergistic effect of this drug combination on nitric oxide release from human endothelium represents a novel mechanism of action in the treatment of CVD.

P1159 Reduced level of tetrahydrobiopterin is responsible for the lack of nitric oxide mediation of flow-dependent arteriolar dilation in diabetes mellitus

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Diabetes mellitus (DM) favors the development of myocardial ischemia, hypertension and stroke, in part by altering the function and eventually the structure of blood vessels. Although the mechanisms leading to microangiopathy in DM are still not clearly elucidated the impairement of protective role of endothelium seems to be well established. We hypothesized that DM affects the function of the endothelium, thereby altering flow-dependent dilation of arterioles. Flow dependent dilation is an important local mechanism that regulates tissue blood flow and mediated by the release of endothelial factors. Thus, we isolated and pressurized gracilis muscle arterioles (~150 μm at 80 mmHg) from normal rats (control) and rats with streptozotocin-induced DM. Arterioles from DM rats exhibited reduced dilations to increases in intraluminal flow compared to vessels of control rats (plasma glucose: 25.7±0.7 vs. 6.4 ±0.5 mmol/L; increase in diameter at max.: 15±4 vs 31± 3 μm, $p<0.05$). In arterioles from control rats both nitric oxide (NO) and dilator prostaglandins mediated the flow-dependent dilation. In contrast, the reduced flow-induced dilation in arterioles from DM rats was unaffected by the NO synthase inhibitor L-NAME and was abolished by indomethacin an inhibitor of prostaglandin synthesis. Intraluminal administration of sepiapterin - precursor of the NO synthase (eNOS) cofactor tetrahydrobiopterin - restored the L-NAME sensitive portion of flow-dependent dilation of DM arterioles. Furthermore, depletion of tetrahydrobiopterin by 2,4-diamino-6-hydroxypyrimidine (DAHP) in arterioles from control rats also resulted in a reduced, L-NAME insensitive flow-dependent dilation. The reduced dilation was significantly augmented by sepiapterin, which then could be inhibited by L-NAME. Thus these responses mimicked the vasomotor dysfunction of endothelium observed in arterioles of DM rats. Collectively, these findings suggest that in diabetes mellitus, due to the reduced bioavailability of tetrahydrobiopterin, the endothelial synthesis of NO by eNOS is limited, resulting in a reduced flow-induced arteriolar dilation, a pathomechanism that may importantly contribute to the development of diabetic microangiopathy and exacerbation of other vascular diseases.

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P1160 Mammary artery and saphenous vein, but not radial artery release nitric oxide in response to histamine: role of H2 receptor

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The radial artery (RA) is increasingly used as coronary artery bypass graft because its long-term patency rates are expected to be superior to those of the saphenous vein (SV). Similar to SV, however, the RA can develop vasospasm. As histamine may play a role in the pathogenesis of vasospasm, we investigated the effect of histamine on vascular tone of human RA in comparison with mammary artery (MA) and SV. Vessels from patients undergoing coronary artery bypass graft operation were cut into 3 mm rings and placed in organ chambers for isometric tension recording. When added on baseline, histamine induced a concentration-dependent contraction. The sensivity of MA to histamine was lower as compared to RA and SV (ED50: MA 4.43x10-5 M; RA 4.58x10-6 M; SV: 6.23x10-6 M; n=6; $p<0.001$ for MA vs. RA and MA vs. SV; p=n.s for RA vs. SV). The contraction reached a similar maximal level in all three vessels (p=n.s.). In the presence of L-NAME (3x10-4 M), the concentration-response curve to histamine was shifted to the left for MA (ED50: 1.49x10-5 M; p=0.0005), but not RA (2.88x10-6 M; p=n.s.) and SV (3.17x10-6M; p=n.s.). After precontraction with norepinephrine, histamine induced a relaxation at low concentrations in MA and to a lesser extent in SV (maximal relaxation: MA -31.19%; SV -12.99%; p=0.0001 for MA vs. SV), but not in RA (-1.35%; p=0.0002 for RA vs. MA; p=n.s. for RA vs. SV). At higher concentrations, histamine caused a contraction, which reached a similar maximal level in all three vessels (p=n.s.). In the presence of L-NAME, the histamine-induced relaxation of MA and SV, but not RA, was blunted (MA: +4.78%, $p<0.0001$ vs. control; SV: +24.30%, $p<0.05$; RA: -4.27%, p=n.s.). Moreover, in the presence of L-NAME, the maximal contraction to histamine was increased in MA and SV, but not RA (MA: $p<0.005$ vs. control; SV: $p<0.005$; RA: p=n.s.). In the presence of cimetidine (10-5 M), the pattern of histamine-induced vasomotion was identical to that observed with L-NAME in all three vessels. Real time PCR could demonstrate significant endothelial expression of histamine H2 receptor in MA and SV, but not RA. Thus, histamine releases NO in MA and SV, but not RA, rendering the latter more sensitive to contraction. Production of NO is related to activation of histamine H2 receptor on the endothelium of MA and SV, while this receptor is not expressed on the endothelium of RA. These differences provide an explanation for the occurrence of vasospasm in the RA.

P1161 3-hydroxy-3-methylglutaryl coenzyme A reductase and angiotensin-converting enzyme inhibitors in cardiac syndrome X. Role of superoxide dismutase activity

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Purpose: Impairment of vasodilator capacity of coronary microcirculation due to abnormal production of vascular superoxide anions and consequent endothelial dysfunction have been suggested to be a mechanism cardiac syndrome X (SX, chest pain, myocardial reversible perfusion abnormalities during single photon emission computed tomography, and normal coronary angiograms). This study sought to establish whether treatment with ACE-inhibitors (ramipril) and statins (atorvastatin) reduces oxidative stress and improves quality of life of patients with of Sx.
Methods: Forty-five SX patients were prospectively studied in a single blind, placebo-control fashion. They were randomized to receive combination of ramipril (10 mg/day) and atorvastatin (40 mg/day) or placebo for 6 months. We determined the activity of extracellular (SOD), one of the major antioxidant enzyme system, and its relation to flow-dependent endothelium-mediated dilation (FMD). The quality of life was assessed by exercise capacity and by Seattle Angina Questionnaire (SAQ). Evaluation was performed before and after treatment. SOD activity on baseline was also tested in 20 healthy volunteers.
Results: On baseline, SOD activity (U/ml) was higher in SX, as compared with healthy controls. (268.4 ± 53.7 versus 170.01 ± 9.8; $p<0.001$). After 6 months, SX receiving atorvastatin and ramipril reduced significantly their SOD levels (188.1 ± 29.6, $p<0.001$). No significant changes were seen on placebo (262.9 ± 48.8). Reduction of SOD after therapy was negatively correlated with FMD (r=0.35, $P<0.02$) and positively with total cholesterol, and LDL cholesterol (r=-0.6, $P<0.001$). At six months follow up, SAQ (scores) and time of peak exercise (seconds) of patients with atorvastatin and ramipril (84.2 ± 9.8 and 555.6 ± 84.6, respectively) differ significantly ($p<0.001$) from those of placebo group (63.3 ± 8.6 and 488.4 ± 79.2, respectively).
Conclusions: Six months therapy with atorvastatin and ramipril improves endothelial function and quality of life of SX patients. Reduced SOD activity may reflect low superoxide anion production. Benefits of these drugs may be related to reduction of oxidative stress within the arterial wall.

P1162 Comparative effects of statin and fibrate on nitric oxide bioactivity and markers of inflammation in hyperlipidaemia

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Purpose: We investigated whether statins and fibrate improve nitric oxide (NO) bioactivity and reduce serological markers of inflammation.
Methods: We administered simvastatin 20 mg daily to 27 patients with hypercholesterolemia and coronary artery disease or fenofibrate 200 mg daily to 27 patients with pure hypertriglyceridemia in a random selection during 8 weeks. Data= mean±SEM and median (25%-75%).
Results: As expected, simvastatin significantly lowered TC and LDL-C more and fenofibrate decreased TG and increased HDL-C more than either therapy. Simvastatin and fenofibrate significantly improved the percent flow-mediated dilator response to hyperemia (FMD) from 3.36 ± 0.45 to 6.06 ± 0.47 and from 5.20 ± 0.35 to 6.38 ± 0.33, respectively (each $P<0.001$) and simvastatin significantly reduced plasma levels of malondialdehyde (MDA), a marker of free radical from 1.95 ± 0.13 to 1.60 ± 0.15 uM ($P<0.01$). Simvastatin and fenofibrate significantly lowered plasma levels of TNF-alfa from 3.31 ± 0.35 to 2.67 ± 0.27 pg/ml and from 1.61 ± 0.10 to 1.43 ± 0.10 pg/ml (each $P<0.01$), respectively and serum levels of CRP from 0.59 to 0.16 ($P<0.001$) and from 0.17 to 0.11 (P=0.280), respectively. However, simvastatin significantly changed FMD, MDA, and CRP levels to greater extent than fenofibrate. There were significant inverse correlations between LDL-C and flow-mediated dilation percent (r=-0.342, P=0.009) and between flow-mediated dilation percent and TNF-alfa levels (r=-0.293, P=0.035).
Conclusions; Simvastatin and fenofibrate significantly improved NO bioactivity through different biological mechanisms on lipoproteins and markers of free radical and inflammation.

VASCULAR FUNCTION AND MEDIATORS: EFFECTS OF LIVING HABITS AND TREATMENT

P1163 Inhibition of vascular xanthin oxidase improves endothelial dysfunction in patients with coronary artery disease

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Introduction: Impaired flow dependent endothelium-mediated vasodilation (FDD) has prognostic implications in patients with coronary artery disease (CAD). Increased vascular superoxide (O2.-) formation contributes to endothelial dysfunction in patients with CAD. Xanthine oxidase (XO) has been identified as one of the major superoxide forming enzyme systems within the human arterial vessel wall. In the present study we examined whether oxypurinol, a specific inhibitor of XO, improves endothelial dysfunction in patients with established CAD.
Methods: Flow-dependent, endothelium-mediated vasodilation of the radial artery was determined in 10 patients with CAD before and after infusion of oxypurinol (600μg x min-1, i.a.), the antioxidant vitamin C (25 mg x min-1, i.a.) and an intra-arterial coinfusion of both. Furthermore the endothelium-bound XO activity that is released into plasma after heparin bolus injection was determined by electron spin resonance spectroscopy (ESR) and related to the effect of oxypurinol on FDD.
Results: Intraarterial infusion of oxypurinol improves flow dependent endothelium-mediated vasodilation in patients with CAD ($54.7\pm4.8\%$;$p<0.05$ vs. control). Vitamin C improved FDD by more than 80% ($88.2\pm8.2\%$;$p<0.05$ vs. control), the coinfusion of both had no additive beneficial effect on endothelium-dependent vasodilatation. The activity of endothelium-bound xanthine oxidase in vivo as determined by ESR was positively related with the effect of oxypurinol on FDD (r=0.71; $p<0.05$).
Conclusions: The results of the present study suggest, that inhibition of vascular xanthine oxidase significantly improves endothelial dysfunction in patients with CAD. The close relationship between the endothelium bound XO activity in vivo and the effect of oxypurinol on FDD supports the concept that increased activity of vascular XO contributes to endothelial dysfunction and thereby may promote the atherosclerotic process in patients with coronary disease.

P1164 Brachial artery endothelial function is reversible impaired at moderate altitude

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Background: Hypoxia at moderate altitude leads to an improvement in cardiac work which might have a positive effect on the cardiovascular system in patients with metabolic syndrome. The aim of this AMAS (Austrian Moderate Altitude Study)-2000 substudy was to assess the effect of a 3 week stay at moderate altitude (1700m) on endothelial function.
Methods: Flow-mediated vasodilation (FMD) and nitroglycerin-mediated vasodilation (NMD) were assessed in 18 patients with coronary risk factors at 5 visits: visit 1 at location A (576m), visit 2 on the first day at moderate altitude (location B, 1700m), visit 3 after 3 weeks at moderate altitude, visit 4 und 5 again at location A (6 and 16 weeks after the stay at moderate altitude, respectively). In addition, serum endothelin was measured. All subjects performed moderate sports activities between 1500 and 2000m.
Results: FMD on the first day at moderate altitude was similar compared to FMD at location A (7.0±3.3 vs. 7.4±4.6%, NS). A 3 week stay at moderate altitude was associated with a significant reduction in FMD (3.8±2.5 vs. 7.0±3.3%, $p<0.05$) despite a decrease in baseline diameter (4.3±0.4 vs. 4.5±0.3mm; $p<0.05$). Six weeks after returning to location A, FMD was still reduced compared to the 1. visit (4.3±2.8 vs. 7.4±4.6%; $p<0.05$) and after further 16 weeks, FMD tended to increase again (5.5±3.5%). During the stay at moderate altitude body mass index, systolic und diastolic blood pressure, heart rate and total cholesterol tended to improve. In contrast, NMD and endothelin levels remained unchanged during the whole study period.
Conclusion: In patients with coronary risk factors, a stay of 3 weeks duration leads to a long lasting, but reversible impairment of endothelial dysfunction. The discrepancy to improvement of other physiologic and metabolic parameters requires further investigation.

P1165 Brachial artery vasoreactivity is a predictor of major cardiovascular events in patients with coronary artery disease

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Coronary endothelial vasodilator dysfunction is associated with increased cardiac events; an association between coronary vasomotor dysfunction and brachial artery vasoreactivity has been previously described, but the prognostic value of brachial artery vasoreactivity is not clear.
Methods: To assess the relation of brachial artery vasomotor function to cardiac events in patients with coronary artery disease (CAD), we examined 151 patients (pts) with CAD confirmed by angiography; age was 61±10.7 years. Flow-mediated, endothelium-dependent dilatation (FMD) and nitrate-mediated, endothelium-independent dilatation(NMD) of the brachial artery were examined in all patients using a high-resolution Echo Doppler ultrasound. Pts were followed for 20.9±4.3 months (12-30 months). Cardiac death, myocardial infarction and unstable angina were determined as cardiac events (CE).
Results: FMD correlated significantly to number of coronary vessels diseased (r=-0.188, p=0.02), Gensini score (r=-0.156, p=0.05), NMD (R=0.475, $P<0.001$) and intima-media thickness of the carotid artery (r=-0.250, p=0.001).NMD correlated significantly to FMD and the intima-media thickness of the carotid artery(r=-0.297, p=0.003) FMD did not differ in patients suffering CE from those without CE (3.3±2.9% vs 2.9±3.1%, ns) while NMD was significantly higher in patients free of CE) (10±5.5% vs 7.3±3.9%, p=0.034). CE were correlated to NMD (r=0.312, p=0.01) but not to FMD (r=0.047, ns). Patients with NMD< 10% had 46,7% CE while pts with NMD >10% 12.2% CE (p=0.01). Patients with FMD>2.5% had 19% CE while pts with FMD<2.5% 31% CE (p=0.1, ns). Multivariate analysis using Cox regression techniques showed that NMD was a prognosticator independent of FMD and carotid intima-media thickness (p=0.018).
In conclusion, endothelium-independent dilatation of the brachial artery, a marker of the function of the arterial smooth muscle cells, is a strong, independent prognosticator of CE in pts with CAD.

P1166 Indices of systemic inflammation and evidence for infection from helicobacter pylori and Chlamydia pneumoniae in patients with cardiac syndrome X

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Purpose: Inflammation has been shown to play a relevant role in the pathogenesis of coronary artery disease (CAD). In particular, it has also been reported to cause endothelial dysfunction. This latter is believed to be involved in causing microvascular coronary abnormalities in patients with cardiac syndrome X (SX). In this study we investigated whether there is evidence of systemic inflammation in SX patients and whether this might be related to an increased prevalence of infection with Helicobacter pylori (HP) and Chlamydia pneumoniae (CP).
Methods: We studied 55 consecutive SX patients (57.5±8 years, 27 women), 49 patients with stable angina and documented CAD (56.3±8 years, 24 women) and 60 apparently healthy controls (56.6±11 years, 24 women). Plasma high-sensitivity C-reactive protein (CRP) and interleukin-1 receptor antagonist (IL-1Ra) were measured in all patients. Seropositivity for HP (and for the specific virulence-associated HP antigen Cag-A) and for CP was assessed in 43 SX patients, 37 CAD patients and 39 healthy controls. HP infection was also assessed by 13C-urea breath test.
Results: CRP values were significantly higher in CAD patients (5.99±7.8 mg/L) than in SX patients (4.06±6.8 mg/L; p=0.01) and healthy controls (1.75±1.98 mg/L; p=0.01). However, CRP was also significantly higher in SX patients than in healthy controls (p=0.01). Similarly, IL-Ra values were higher in CAD patients (570±738 pg/mL), compared to SX patients (494±677 pg/mL; p=0.01) and healthy subjects (254±174, pg/mL; p=0.01), but they were also significantly higher in SX patients than in healthy subjects (p=0.01). Evidence of HP infection was found in 70% of SX patients, in 67.5% of CAD patients, and in 68% of healthy controls (p=0.97), with no differences among groups also in serum anti-HP-CagA antibody positivity (SX 53%, CAD 59%, healthy controls 64%; p=0.72). Furthermore, no differences among groups were found for CP infection (SX 35%, CAD 50%, healthy controls 40.5%, p=0.37).
Conclusions: While showing the highest indices of systemic inflammation in stable CAD patients, our data also show increased evidence of systemic inflammation in patients with cardiac SX compared to matched healthy controls, thus suggesting a possible role in the pathogenesis of the syndrome. There was no evidence of increased HP or CP infection, possibly explaining this increased evidence of inflammation, in SX patients.

P1167 Abnormal cardioesophageal reflexes in variant angina

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Purpose: The pathways of neural reflex arcs, connecting esophagus and heart, may have a pathogenetic role in vasospastic angina. We tasted this hypothesis in patients admitted to CCU for episodes of nocturnal angina.
Methods: ECG recording, and esophageal manometry (>4 hrs, mean 5.3 hrs) were monitored during bed stay in CCU. Patients underwent coronary angiography within 4 days from admission. Esophageal provocation with ice water and hydrochloric acid was performed throughout cardiac catheterization. Patients were grouped as variant angina (VA, angiographic evidence of no or minimal atherosclerosis and coronary artery spasm during ergonovine test) and coronary artery disease (CAD, lumen stenosis >50%).
Results Twenty-nine patients were asked to participate in the protocol. Twelve patients were able to complete the study. Seven patients were affected by VA and 5 by CAD. Manometric analysis in CCU showed a total of 143 esophageal spasms (ES, broad, high pressure, non-peristaltic contractions). ES resulted remarkably more frequent in VA than in CAD (16.4±1.4.3 vs 4.0±3.6, $p < 0.005$). ECG recording showed 28 spontaneous episodes of ST shift in VA and 16 in CAD. In VA, 85% of ST shifts were concurrent with or preceded (1 to 5 min before) by clusters of ES (>3 episodes in 5 min). The few ES episodes recorded in CAD were sporadic (< 1 in 30 min) and not related to ECG ischemia. During catheterization, 5 patients with VA developed coronary artery spasm on esophageal provocation. In the remaining 2 patients with VA esophageal maneuvers precipitated diffuse coronary artery constriction, but not focal segmental spasm. No significant changes were seen in patients with CAD.
Conclusion: In VA: (1) The occurrence of cluster of ES is common and time related with the development of ischemia. (2) Esophageal manipulation can induce abnormalities of coronary motility and spasm. (3) An impaired regulation of neural reflex arcs connecting esophagus and heart may play a role in the pathogenesis of VA.

P1168 Acute effects of growth hormone on vascular function

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Growth hormone (GH) is involved in the long-term regulation of peripheral vascular resistance (PVR) and vascular reactivity. Recently, it has been demonstrated that chronic GH administration might be able to improve endothelium mediated vascular reactivity in several diseases associated with endothelium dysfunction, such as GH deficiency or heart failure. We sought to determine whether GH plays a role in the acute regulation of vascular function in humans. We studied the acute vascular effects of GH in 8 healthy subjects, according to a double-blind, placebo-controlled design. Forearm blood flow (FBF), vascular resistance (FVR), and nitric oxide (NO) production were monitored during a 4-hour infusion of GH into the brachial artery, at a rate chosen to raise local GH to stress levels (40 ng/ml). During GH infusion, FBF rose 75% ($p<0.05$), whereas FVR decreased comparably ($p<0.05$). These changes were paralleled by augmented forearm release of NO ($p<0.02$). GH heightened the response of FBF to the endothelium-dependent vasodilator acetylcholine (Ach) ($p<0.02$). With the highest Ach dose, FBF reached 30.4±4.2 and 16.9±3.1 ml/dL/min in the GH and placebo study, respectively ($p<0.005$). The slopes of the dose-response curves also differed markedly (0.45±0.07 and 0.25±0.05 ml/dL/min/μg in the GH and placebo study, respectively; $p<0.01$). GH also potentiated the FBF response to the endothelium-independent vasodilator sodium nitroprusside ($p<0.01$). However, the entire dose-response curve was shifted upwards and the slope remained unchanged. GH infusion did not cause any appreciable increment in the venous insulin-like growth factor-I (IGF-I) concentration in the test arm. In conclusion, GH acutely lowers PVR and stimulates endothelial function. These effects are mediated by activation of the NO pathway and do not involve IGF-I.

P1169 Rapid bedside plethysmography detects statin responsive endothelial dysfunction in ischaemic heart disease and statin resistant endothelial dysfuction in syndrome X

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Introduction Endothelial dysfunction occurs in ischaemic heart disease (IHD), but current assays are not practical for clinical use. We assess a bedside test utilising the properties of the reflected wave in the digital volume pulse plethysmogram (DVP).

Methods Consecutive patients attending a Chest Pain Clinic (52 noncardiac controls and 44 IHD) and 22 with Syndrome X had DVPs before and after 400 μg inhaled salbutamol. The reflection index (RI) from the first derivative of the waveform and its change from baseline (dRI) were calculated. The DVP response is dependent on endothelial nitric oxide synthase is inhibited by L-NMMA. dRI was remeasured 3 months later in statin treated and untreated patients (table).

Multiple regression was used to control for age, mean blood pressure and smoking status. dRI reported as mean ± SEM.

HYPOTHESES DVP dRI is lower in IHD and Syndrome X than in controls. Statins improve endothelial function as assessed by an increase in dRI.

Results dRI is lower in patients with IHD (5% ± 2, p = 0.009) and Syndrome X (5% ± 3, p = 0.004) than those with noncardiac chest pain (18% ± 3). This is independent of age, smoking status and mean BP. Three month statin treatment was associated with increased dRI in treated IHD patients, but not in Syndrome X (table).

	Treated IHD	Control IHD	Treated Syndrome X	Control Syndrome X
Number	12	7	12	10
Cholesterol (mM, SD)	7.0 (1.1)	5.7 (1.4)	5.9 (1.2)	4.9 (0.4)
dRI change (%, SD)	13 (4.8)	-4.7 (4.8)	4.3 (4.3)	6.1 (3.1)
Within group/vs control	p = 0.01/0.02	p = 0.4	p = 0.3/0.7	p = 0.08

Effect of Statins on Reflection Index in Angina Pectoris and Syndrome X

Conclusion This rapid measure of endothelial function found similar degrees of dysfunction in classical angina pectoris and Syndrome X. Endothelial dysfunction improved with statins in classical angina pectoris. This supports the early use of statins in IHD. Syndrome X patients did not respond to statins. This may be due to their lower initial cholesterol levels or the pathogenesis of their endothelial dysfunction may be different to IHD.

P1170 Cerivastatin improves endothelial function in patients with type 2 diabetes and moderate lipid levels

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Purpose: To investigate the effect of cerivastatin on flow-mediated dilatation (FMD) in type 2 diabetic patients with moderate lipid levels and without ischemic heart disease.

Methods: Twenty-four patients (10 females) age 57 years (47-68) were investigated at 3 visits 3 months apart in a randomised, crossover study. FMD of the brachial artery was examined using a high-resolution ultrasound device along with 5 min ischemia and nitro-glycerine as control. A matched control group of 10 non-diabetic individuals (5 females) age 54 years (41-61) was investigated at one visit.

Results: Baseline total cholesterol was 5,0+0,8 mmol/l in the diabetic patients and 5,1+0,7 mmol/l in controls. FMD was reduced in type 2 diabetic patients at baseline compared to controls (3.7+0.7% vs. 13.5+1,2%, $p<0.0001$). FMD increased to 6.7+1.2% after treatment with cerivastatin compared to 2.1+0.6% after standard treatment ($p<0.001$). The response to nitro-glycerine was unchanged by cerivastatin. Total cholesterol was 4.0+0.14 mmol/l after treatment with cerivastatin and 4.8+0.17 mmol/l after standard treatment ($p<0.0001$).

Conclusions: Type 2 diabetic patients display endothelial dysfunction measured by FMD despite moderate lipid levels and in the absence of ischemic heart disease. This indicates additional mechanisms involved in the angiopathy attributed to the diabetic state per se. Cerivastatin improves endothelial function in these patients suggesting benefit of treatment regardless of lipid measurements.

P1171 Cigarette smoking-induced acute endothelial dysfunction is attenuated by red wines polyphenols

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Although chronic smoking causes endothelial dysfunction by inducing oxidative stress, there has not been described a mechanism through which acute smoking impairs vasodilatation. Considering the fact that red wine and its constituents have powerful antioxidant effect both in chronic and acute consumption, the present study was designed in order to investigate whether red wine and its constituents attenuate impaired endothelial function caused by acute cigarette smoking and if this dysfunction is caused through induced oxidative stress.

Methods: Sixteen healthy volunteers (8 males and 8 females) participated in a single – blind, cross - over study, comprised of three study days. In the first visit, each subject smoked one cigarette, in the second visit the volunteers smoked and drank 250 ml of red wine and in the third visit they smoked and drank 250 ml of dealcoholized red wine (containing the same type and similar concentration of regular red wine's antioxidants). Endothelium dependent, flow mediated dilatation (FMD) was measured with a B-Mode ultrasound device at fasting and 15, 30, 60 and 90 minutes after each trial (smoke or smoke and drink either beverage). Also, endothelium independent vasodilatation (nitrate mediated – NMD) was determined.

Results: Baseline FMD was not different in the two study days. Acute smoking of one cigarette caused a reduction in FMD ($p<0.001$), from 6.52+2.4% at baseline, to 1.91+2% ($p<0.001$), to 2.27+2% ($p<0.001$), to 4.1+2.6% (p=0.043) and to 5.22+2.5 (p=ns), at 15, 30, 60 and 90 minutes respectively, following the inhalation of smoke. However, simultaneous ingestion of red wine with smoking did not lead to a change in FMD (5.79+2.1% at baseline, to 4.12+2%, 4.05+1.8%, 4.87+2.4% and 5.05+2.3%, at 15, 30, 60 and 90 minutes) (ANOVA for repeated measures). The same results in FMD were observed with concurrent consumption of dealcoholized red wine with smoking (from 5.8+2.1%, to 4.65+3.6%, 6.08+3.6%, 5.66+2.5% and to 5.11+1.3%, at the study's time points respectively). Incremental areas under the response curves revealed a difference between smoking and smoking with concurrent consumption of regular red wine (p=0.016), as well as between smoking and smoking with concurrent ingestion of dealcoholized red wine ($p<0.001$). NMD didn't differ in the trials.

Conclusions: Acute smoking caused a significant endothelial dysfunction and concurrent ingestion of red wine or dealcoholized red wine, with smoking counteracted smoke's harmful effect on FMD, suggesting that this beneficial effect could be attributed to red wine's antioxidant substances.

P1172 Vascular mediators in the flow-or pressure-overloaded pulmonary circulation

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Background: Endothelial activation and alterations in vasoactive mediators like endothelin (ET) and nitric oxide (NO) have been implicated in the regulation of pulmonary vascular tone and the development of pulmonary hypertension (PH). Therefore, soluble markers of endothelial damage and vasoactive compounds were compared in patients with increased pulmonary flow (atrial septal defect, ASD) as well as in patients with pressure overload due to increased pulmonary resistance (Rp).
Patients: This study included 20 patients (median: age 6.1 years [range 3.5-17.1], median Qp/Qs 2.1, Rp/Rs<0.12) before (1) and after interventional closure of an ASD II (2), and 20 patients with PH (median: age 8.1 years [1.2-13.5], median Rp/Rs 1.1 (0.36-1.79) (3).
Methods: Plasma NO2, NO3 (GC-MS) and the endogenous inhibitor of NO production asymmetric dimethyl-L-arginine (ADMA) (HPLC) were analyzed in the pulmonary (PA) and femoral artery (SA). Transpulmonary ratio was calculated as [PA]/[SA]. Big-ET, ICAM, VCAM and P-selectin were measured in PA samples (ELISA).
Results: 1) ASD patients showed increased Big-ET (1.45 fmol/ml, 0.51-5.69, control: 0.95±0.68, p<0.001) and a significant transpulmonary ratio of 1.34 for NO2 (median, p<0.01 vs 1.0), but not for ADMA (1.05) or NO3 (1.01). 2) ASD closure resulted in a decrease of Big-ET (1.22, 0.42-4.92) and the NO2 transpulmonary ratio (0.89, p<0.05), indicating a switch from NO2 production to consumption. ADMA (1.00) and NO3 (0.99) remained unchanged. 3) In PH, significant transpulmonary ratios were observed for ADMA (1.11, p<0.05) and NO3 (1.03), but not for NO2 (0.84) reflecting inappropriate NO2 production. Median levels of big-ET (2.08fmol/ml, 0.97-23.90) and VCAM (967 pg/ml, 348-2617 vs 770, 407-1412 in ASD patients, p<0.05) were increased.
Conclusions: Different loading conditions of the pulmonary circulation are reflected by load-dependent changes in the intravascular hemeostasis of the ET and NO pathways and activation of the pulmonary endothelium.

P1173 Associations between urinary kallikrein, renin-angiotensin-aldosterone system components, electrolyte homeostasis and hypertension in Hong Kong Chinese

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Introduction: Kallikrein influences kidney function and regulates blood pressure through the production of kinin, a vasodepressor hormone and potent natriuretic. Aldosterone is a major regulator of kallikrein. Imbalance of the renin-angiotensin aldosterone system (RAAS) and the kallikrein-kinin system may be important in the development of hypertension. In this study we examined the relationship between blood pressure, RAAS components, urinary kallikrein, and other biochemical parameters in normoglycaemic Chinese subjects with and without primary hypertension.
Methods: Normoglycaemic Chinese subjects were studied including 106 normotensive controls and 75 hypertensive patients who had any antihypertensive medication stopped for at least 2 weeks before the study. The relationships between 24-hour urinary kallikrein excretion, electrolyte homeostasis and the RAAS components, plasma renin activity (PRA), angiotensin-converting enzyme (ACE) activity and aldosterone were analysed.
Results: The hypertensive subjects were older (46.5±9.0 vs 41.0±9.3 years, p<0.01) and more obese (BMI: 25.5±4.5 vs 23.9±3.3 kg/m^2, p<0.01) than the normotensive subjects. The urinary kallikrein level of the hypertensives was lower than that of the normotensive subjects, (geometric mean [95% CI], 4.5 [3.3-6.2] vs 6.7 [5.7-7.7] KU/24hr, p=0.016). Plasma sodium was significantly higher in the hypertensive subjects compared to controls (141.5±1.7 vs 140.7±1.5 mmol/24hr, p=0.001). PRA was not significantly different between hypertensive and control groups, and direct relationships between PRA and aldosterone (r=0.33, p=0.002) and plasma sodium (r=-0.19, p=0.051) were found only within the normotensive group. There was a positive correlation between PRA and kallikrein (r=0.24, p<0.05) in the whole group. Urinary kallikrein also had a negative relationship with plasma sodium (r=-0.27, p=0.01) and was weakly related with urinary potassium (r=0.18, p=0.09), but not with other plasma or urinary electrolytes in the whole group. It also correlated with systolic blood pressure (r=-0.31, p<0.005) in the whole group. There was no significant relationship between aldosterone and kallikrein in this subject group.
Conclusion: Reduced urinary kallikrein was associated with sodium retention and elevated blood pressure in these Hong Kong Chinese subjects. These relationships suggest that the kallikrein-kinin system may be responding inappropriately in these subjects and decreased kallikrein excretion may play a role in the development of hypertension.

ATRIAL AND VENTRICULAR REMODELLING: SIGNALLING PATHWAYS AND MYOCYTES PHENOTYPE

P1174 Cardiac hypertrophy and failure, abnormal calcium handling, and various arrhythmias in the transgenic mice overexpressing cardiac junctate-1

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Junctate is a newly identified and high capacity calcium binding protein existing in the integral ER/SR membrane and is an alternative splicing form of the same gene generating aspartyl beta-hydroxylase or junctin. Three complete mouse heart cDNAs homologous to the human junctate were cloned and these proteins consisted of 270, 259 and 215 amino acids were named as junctate-1, 2 and 3, respectively. Junctate-1 was expressed in heart, brain, spleen, lung, liver, kidney and stomach, but not in skeletal muscles. To elucidate the functional role of junctate in heart, junctate-1 transgenic (TG) mice under the control of mouse alpha-MHC promoter were generated. TG mice showed severe generalized cardiac hypertrophy (2-fold increase in mass compared with their wild-type (WT) littermates), slow heart rate and fluid retention. Perivascular or interstitial fibrosis was demonstrated in the TG hearts and intraatrial thrombi were observed. As assessed by echocardiography, LV end-systolic and end-diastolic dimension was increased and LV systolic function was moderately depressed (fractional shortening; TG 34.7±9.2% vs WT 48.3±7.5%) (p<0.005). In addition to bradycardia, various forms of cardiac arrhythmias such as ventricular premature beats, atrial fibrillation or sinus pause were observed in the young TG mice. In TG hearts, the expression levels of calreticulin and SERCA2a were significantly decreased without any changes in other E-C coupling proteins such as DHPR, calsequestrin, triadin, junctin and phospholamban. Bmax of ryanodine binding decreased without changes in Kd. Those morphological, physiological and electrical alterations could be caused by the perturbations of the intracellular calcium homeostasis due to the overexpression of junctate-1.This model may be helpful to investigate the molecular framework involved in the development of cardiac hypertrophy and failure and to elucidate the relationship between altered expression of junctional SR proteins and the pathogenesis of cardiac remodeling and arrhythmia generation.

P1175 Mitochondrial cardiomyopathy in mice overexpressing fra-1 and lacking junD

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The AP-1 transcription factor family consists of several bZIP (basic region leucine zipper) domain proteins, the Jun, the Fos, and the ATF subfamilies, which all have to dimerize before they can bind to their DNA target sites. AP-1 converts extracellular signals into changes in the expression of specific target genes which harbour AP-1 binding sites in their promoter or enhancer regions. AP-1 has been implicated in a large variety of biological processes including cell differentiation, proliferation, apoptosis and oncogenic transformation. In particular, it has been demonstrated that AP-1 is involved in muscle cell differentiation, transformation and apoptosis and is expressed upon hypertrophic stimuli in the heart.
In our study, we show that double mutant mice overexpressing fra-1 and lacking junD died predominantly within the first two weeks after birth and displayed marked cardiac ventricular and atrial dilation, myocard hypertrophy and reexpression of the fetal cardiac gene beta-myosin heavy chain (beta-MyHC) in the heart. Mitochondrial content was markedly increased in the cardiomyocytes of the double mutant newborn hearts and mitochondrial coupled respiration was stimulated, since the beta?subunit of the F1-F0 ATP synthetase (beta-ATPase), cytochrome C (CytC) and cytochrome oxidase II (COXII) were upregulated and the uncoupling protein 2 (UCP-2) was downregulated. These findings were associated with a junD dependend increased DNA binding activity of MEF2.
The few surviving mice developed a congestive heart failure with enlargement and disarray of myocytes and increased myocardial fibrosis. Interestingly, fra-1 transgenic hearts normally expressing junD were more susceptible to mechanical pressure overload and Isoproterenol. These data provide first genetic evidence in vivo, that appropriate expression of the two AP-1 members fra-1 and junD is required for mitochondrial function in heart and is important to maintain cardiac integrity.

P1176 Downregulation of sodium/calcium-exchanger expression by alpha-adrenergic stimulation in rabbit myocardium

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Introduction: Upregulation of Sodium/Calcium-exchanger (NCX) in end-stage heart failure was suggested to underlay contractile dysfunction and arrhythmogenesis. It may therefore be of major interest to identify factors which influence NCX expression to develop new therapeutic strategies. We tested the influence of sympathetic activation on NCX expression.
Methods and Results: Electrically stimulated (1 Hz, 1.75 mmol/l Calcium, 37°C, pH 7.4), isometrically contracting, dissected right ventricular trabeculae from adult rabbit hearts underwent continuous alpha-adrenergic stimulation by phenylephrine (PE) (100 μmol/l) for different time courses (3, 6, 10h). These trabeculae showed a downregulation of NCX-mRNA levels (normalized to GaPDH) when compared to control muscles (same conditions, no PE), as determined by quantitative real-time PCR to 149.28% ± 48.19 at 3h, 87.55% ± 6.95 at 6h, and 77.53% ± 3.22 at 10h ($p<0.05$) in per cent of control. This downregulation was completely abolished in the presence of the selective alpha-adrenoceptor blocker prazosine (130 μmol/l), as well as the protein kinase C (PKC) inhibitor GF 109203X (10 μmol/l). In contrast, no regulation of NCX expression was found in electrically stimulated unstretched trabeculae.
Furthermore, since the effect of alpha-adrenergic stimulation could be mediated by increase in intracellular Calcium, we tested the effect of increased extracellular Calcium (3 mmol/l) in the presence of prazosine. Under these conditions we observed a downregulation of NCX to 77.4% ± 7.82 $p<0.02$ as compared to control (1.75 mmol/l Calcium). In addition, we investigated the PE effects on isolated cultured (24h) rabbit myocytes, and determined NCX and BNP mRNA-levels. Similar to the unloaded trabeculae, we found no significant changes of NCX mRNA, while there was a significant increase in BNP mRNA (258.41% of control ± 54.36, $p<0.03$).
Conclusions: alpha-adrenergic stimulation decreases NCX mRNA expression in isometrically contracting multicellular rabbit muscle strips at optimum preload via activation of PKC. NCX downregulation may be calcium-mediated and critically depends on load. Interpretations of previous findings on NCX expression in isolated unloaded myocytes may be reconsidered.

P1177 Integrin signalling is activated and required after myocardial infarction and aortic banding in mice for early compensation

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Hypertrophic growth and cardiac remodeling is characterized by reorganization of the extracellular matrix (ECM) as well as growth and cytoskeletal reorganization of the cardiomyocytes. Integrin receptors are mediating extracellular changes to the cell through activation of non-receptor tyrosine kinases and cytoskeletal reorganization. Here we tested the hypothesis, whether integrin-mediated signalling plays a role in the cardiac remodelling after myocardial infarction (MI) or aortic banding (AB) in mice.
Methods: Adult C57/black 6 mice, weighing 22-25 g, were analyzed by western blot, echocardiographic and invasive hemodynamic analysis 1 wk and 8 wks after MI or 1 and 4 wks after AB.
Results: Hypertrophic growth was observed within 1 wk after AB and for the remote myocardium after MI, which was confirmed by echocardiography. The LV enddiastolic pressure was significantly elevated 4 wks after AB and 8 wks after MI. For western blot analysis detergent soluble and insoluble (membrane and cytoskeletal) fractions were prepared. Within 1 wk of MI and AB a strong tyrosine phosphorylation was observed in the cytoskeletal fraction with the strongest signal for proteins at 25, 60, 75, 116, and 160 kD. The proteins at 60 and 116 kD could be identified as tyrosine phosphorylated c-Src and focal adhesion kinase (Fak), respectively. Further analysis with phospho-specific antibodies revealed full kinase activation of c-Src and Fak in the cytoskeletal fraction. To understand the function of c-Src activation during hypertrophic growth c-Src knockout mice were used for AB. While no c-Src was detectable in these mice the tyrosine kinase Fyn was strongly upregulated and phosphorylated. Also LV hypertrophy was significantly increased 1 wk after AB in c-Src knockout mice.
Additionally, conditional beta.1-integrin KO mice and a specific integrin alpha.v/beta.3 inhibitor was used in the AB model. Echocardiography 1 wk after AB revealed for both groups revealed a severe reduction of LV function and contractility as well as LV dilatation. The mortality rate was significantly increased after AB compared to WT mice, while no changes in mortality and LV function were seen in beta.1-integrin KO mice or mice with an alpha.v/beta.3 inhibitor without pressure overload.
Summary: In summary, the data suggest that integrin-mediated signalling with tyrosine kinase activation is strongly activated after AB and MI. Further, integrin beta.1 and 3 are required for early compensation after AB and MI, while c-Src kinase can be replaced by Fyn for early hypertrophic signalling.

P1178 Nuclear factor-kappaB role at end stage heart failure in the hypertrophied myocardium

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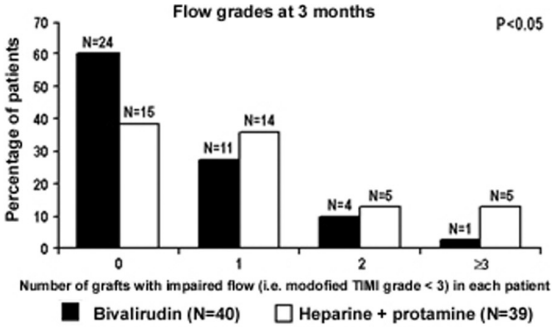
Recently we showed increased levels of apoptosis (A) and upregulated caspase-3 (C-3) activation in end stage heart failure (HF)left ventricles of 100 weeks of age and older spontaneously hypertensive rats (SHR).
Tumor necrosis factor alpha (TNF-alpha) is known to promote apoptosis and to activate Nuclear Factor-kappaB (NF-kB).
To further elucidate NF-kB's role in myocardial protection we investigated apoptosis, necrosis and the expression of: heat shock protein 72 (HSP72), TNF-alpha, and NF-kB in the SHR model of essential hypertension between 10 and 100 weeks of age.
Methods: Western Blotting: Left ventricles were removed, lysed, and proteins separated by SDS-PAGE and electroblotted onto nitrocellulose. Monoclonal antibodies specific for NF-kB (p65), TNF-alpha, and HSP72 were detected by chemiluminescent autoradiography (Fempto, Pierce).
Left ventricular apoptotic index was evaluated by DNA laddering.
Necrotic rate(percent change in necrotic areas) was detected immunohistochemically using the haematoxylin-eosin stain.
Image analysis was performed for autoradiography using Diversity Database imaging software and for optical microscopy determination of necrotic areas with Image Pro Plus software.
Results: are presented graphically in arbitrary units.



Apotosis-Necrosis-HSP72-TNFa in SHR.

These results suggest that in end-stage HF due to hypertrophy: 1. TNF-alpha and A levels are highly elevated 2. NF-kB and HSP72 expression is attenuated
Conclusions: 1. Although TNF-alpha is known to strongly activate NF-kB, there is evidence that TNF-alpha may predominantly trigger apoptosis in myocardial cells that are either deficient or defective for NF-kB activation. 2. In end stage heart failure, apoptosis and necrosis appear to be the outcome of probably different pathways.

P1179 Beta-1-adrenoceptor antibodies induce apoptosis in adult isolated cardiomyocytes

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Beta-1-adrenoceptor autoantibodies are present in about 30% of patients suffering from dilated cardiomyopathy. The apoptotic effects mediated by beta-1-adrenoceptor antibodies remain to be studied. Monoclonal antibodies were raised against a synthetic peptide corresponding to the second extracellular loop of the human beta-1-adrenoceptor in BALB/C mouse, and were characterized by enzyme immunoassay. Purified immunoglobulin G from non-immunized animals (controls) did not influence the rate of apoptosis. beta-1-adrenoceptor antibodies caused a dose-related increase in apoptotic cells: Annexin test (dilution 1:2: 21±1.1% apoptotic cells vs. 4±0.4% apoptotic cells in controls; $p<0.01$); TUNEL test (dilution 1:2: 26±2% apoptotic cells vs. 10±2% apoptotic cells in controls; $p<0.01$). The effect of the beta-1-adrenoceptor antibodies was blocked by the antigenic peptide and by the antagonist metoprolol (10μmol/l). The apoptotic effect induced by isoproterenol was attenuated by the beta-1-adrenoceptor antibody. After pre-incubation of cardiomyocytes with the protein-kinase-A-inhibitor RpcAMPS, beta-1-adrenoceptor antibody was not capable of inducing an increase of the rate of apoptosis. Beta-1-adrenoceptor antibodies induce apoptosis in adult rat cardiomyocytes via the protein-kinase-A-cascade.

P1180 Angiotensin converting enzyme and endothelial nitric oxide synthase polymorphisms in patients with atrial fibrillation

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Experimental studies show a significant increase in angiotensin-converting enzyme (ACE) expression in atrial tissue of patients with atrial fibrillation (AF). ACE regulates the synthesis of endothelial nitric oxide (NO), which modulates autonomic nervous activity involved in the development of AF. The aim of our study was to evaluate the prevalence of ACE insertion/deletion and endothelial nitric oxide synthase (eNOS) T-786C, G894T and 4a/4b polymorphisms in 239 patients with persistent AF, compared to 210 control subjects. ACE I/D polymorphism genotype distribution and allele frequency were significantly different between patients and controls ($P < 0.0001$ and $P < 0.0001$, respectively). ACE DD genotype was significantly associated with the risk of AF (OR DD/ID+II=2.31, $p<0.0001$). Analysis of eNOS polymorphisms showed no significant difference in genotype distribution and allele frequency between patients and controls. As far as idiopathic and secondary AF are considered, no significant difference in genotype distribution and allele frequency in ACE and eNOS polymorphisms was observed. Our results suggest a possible role of ACE DD genotype as a predisposing factor to AF and a pathophysiologic mechanism through which ACE inhibition could reduce the incidence of AF in patients with LV dysfunction.

P1181 The selective aldosterone receptor antagonist eplerenone ameliorates angiotensin II-induced endorgan damage

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The RALES study suggests that aldosterone (Ald) acts independently from angiotensin (Ang) II as a pathogenic factor in cardiovascular disease. The action of Ald on cardiovascular endorgans is poorly understood. We treated rats harboring the human renin and human angiotensinogen gene (dTGR) with the Ald antagonist eplerenone (Epl). This selective Ald blocker ameliorated Ang II -induced renal and cardiac damage with only a small effect on blood pressure. Untreated dTGR showed significantly increased systolic blood pressure, compared to Epl-treated dTGR and non-transgenic rats (204±5 vs. 180±5 vs. 119±6 mm Hg, $p<0.05$ respectively). Urinary albumin excretion was markedly higher in untreated, than in Epl treated dTGR and SD rats (17.8±2.1 mg/d; 9.2±1.3 mg/d; $p<0.05$; 0.2±0,02 mg/d). Epl also reduced collagen IV matrix deposition in the kidney and heart. Epl reduced the cardiac hypertrophy index (4.5±0.1 vs. 5.4±0.2 mg/g; $p<0.05$) and improved left ventricular diastolic function (normalized E/A ratio) compared to untreated dTGR. These data document marked amelioration of renal and cardiac damage by selective Ald blockade via Epl in this Ang II-dependent model of end organ damage. To further explore how MR blockade might act, we next investigated the effects of Ang II (10-7 M) and Ald (10-7 M) on extracellular regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling in vascular smooth muscle cells (VSMC) with western blotting and confocal microscopy. Ang II induced ERK 1/2 and JNK phosphorylation at 2 min. Ald achieved the same by 10 min. Ang II + Ald had an additive effect at 2 min. The oxygen radical scavenger gluthatione, as well as the specific epidermal growth factor receptor antagonist AG1478, markedly reduced the Ang II, Ald, and combination-induced ERK1/2 phosphorylation. Similar results were obtained for JNK activation. Preincubating the cells with the nonselective Ald blocker, spironolactone (10-6 M), abolished Ang II-induced ERK1/2 phosphorylation. Our data show that, not only Ang II, but also Ald participates in both JNK and ERK signaling. These in vitro data may help explain the effects of Ald blockade on Ang II-induced end organ damage in vivo and suggest that blockade of both receptors may be necessary to accrue maximal effects in terms of vascular protection.

ANGIOGENESIS AND COLLATERAL FORMATION

P1182 Intracoronary angiogenic gene therapy is well tolerated in patients with coronary artery disease

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Background: Theoretical risks from angiogenic therapy include angiogenesis at non-targeted sites or viral vector related inflammation. A review of safety data from the earliest trials is encouraging. We add our experience with Ad5FGF-4, a replication deficient adenovirus, serotype 5, encoding the angiogenic growth factor FGF-4 gene.
Method: Two double-blind studies, AGENT and AGENT 2, enrolled patients with stable angina (CCS class II-III), LVEF ≥30% and NYHA heart failure ≤class III, who did not require immediate CABG or PTCA (AGENT) or were not optimal candidates (AGENT 2). Patients were randomized to one-time intracoronary administration of Ad5FGF-4 or placebo (AGENT: placebo n=19, Ad5FGF-4 dose 3.2×10^8-3.2×10^{10} viral particles (vp) n=60; and AGENT 2: placebo n=17, Ad5FGF-4 10^{10} vp n=35) and were followed for 12 months. Antiischaemic effects were evaluated by exercise testing AGENT) and perfusion radionuclide imaging AGENT 2).
Results: Adenoviral vector uptake and distribution following administration was examined in AGENT. First-pass cardiac vector uptake was high (median 87%). For dose ≥3.2×10^9 vp there was vector measured in venous blood at 1 hour (36% of patients at highest dose). No vector was shed in urine over 6 hours and no Ad5FGF-4 DNA was detected in semen (n=12) at 2 months. Neutralizing Ad5 antibody titre increased ≥4 x baseline in 56/60 patients. In the combined trials (active n=95) the safety response to Ad5FGF-4 was favourable. There were no procedural complications. Dose-related transient fever was present (n=8). There was no myocarditis or significant arrhythmia. Mild inflammatory response to Ad5FGF-4 included transient increase in liver enzymes (n=3, including 1 unrelated hepatitis C), increase in uric acid (n=18) and decrease (<100,000/μl) in platelet count (n=1). There was no evidence of remote angiogenesis including retinal neovascularization. Two patients were diagnosed with cancer (judged present prior to treatment and tumour negative for Ad5FGF-4 DNA) and 1 death occurred due to unrelated cardiac arrest. Ad5FGF-4 was associated with a trend toward less worsening/unstable angina (13% vs 22%) and revascularization (8% vs 17%) versus placebo. An additional 190 patients have since received Ad5FGF-4 10^{10} or 10^9 vp, or placebo, and have been followed for up to 14 months. Blinded review has revealed no cancers and 1 unrelated death. The safety profile appears similar to that seen in AGENT and AGENT 2.
Conclusion: Intracoronary Ad5FGF-4 is well tolerated in patients with stable angina and evaluation in a larger population is warranted.

P1183 Significant improvement of local wall motion assessed by NOGA after intramyocardial injection of genes into chronic ischaemic myocardium. Preliminary results from NOGA Core Lab of EUROINJECT-ONE study

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Purpose: The task of the NOGA Core Lab of EUROINJECT-ONE, a multicenter double-blind placebo controlled study, was to assess myocardial voltage and local linear shortening (LLS) values by NOGA endocardial mapping before and 3 months after percutaneous intramyocardial injection of plasmid (either VEGF A-165 encoding or inactive plasmid) in patients with chronic myocardial ischemia not amenable for conventional revascularization.
Methods: Eighty patients (82% male, 61±8.5 years) with stress-induced myocardial ischemia underwent diagnostic endocardial mapping before NOGA-guided plasmid injections. According to double-blind study principles, 40 patients were treated with active (encoding VEGF A-165), and 40 patients with placebo plasmid. Three months after plasmid injection, control coronary catheterization was performed, NOGA endocardial mapping was repeated in 75 patients. The mapping images were analysed in two NOGA Core Labs (delineation of the region of interest, ROI in Copenhagen, analysis of ROI in Vienna) in a blinded fashion.
Results: Eighty baseline and 75 voltage and 74 LLS follow-up (FUP) NOGA (1 FUP LLS map was not interpretable) images were analysed. The ROI was the anterior wall in 31, lateral wall in 15, posterior wall in 10, posterolateral wall in 9, and mixed regions in 15 patients. The distribution of mapping points in ROI was sufficient in all patients, 19.4±18.9 points at baseline and 20.5±7.7 points at FUP. According to qualitative analysis, normal, dominantly decreased and dominantly non-viable voltage values of the ROI were observed in 45, 32 and 3 patients at baseline, and 48, 21 and 6 patients at FUP. Normal, decreased LLS, akinesia and dyskinesia of ROI were found in 18, 26, 24 and 12 patients at baseline, 36, 27, 4 and 7 patients at FUP. The average voltage values of the treated zone did not differ between baseline and FUP (13.2±4.4 vs 12.5±3.8 mV). However, the LLS of the ROI increased significantly, from 7.2±6.7 to 11.3±5.8%, $p<0.001$. The average voltage and LLS values of the non-treated myocardial area did not change significantly during the FUP (voltage: from 11.5±3.7 to 11.5±3.6 mV, LLS: from 9.6±4.54to 10.3±3.5%).
Conclusions: A significant improvement of local wall motion, assessed by NOGA endocardial mapping was found in patients enrolled in the EUROINJECT-ONE Study. After completion of the FUP, the randomization code will be broken in the near future and the final (non-blinded) results of the effect of intramyocardial injection of plasmid encoding VEGF A-165 on chronic myocardial ischemia will be presented.

P1184 Growth factor generation in the collateral system of chronically occluded coronary arteries and its relation to invasively determined collateral function

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Background: Basic Fibroblast Growth Factor (bFGF) and monocyte chemotactic protein 1 (MCP-1) promote arteriogenesis. Their interaction play a central role in the collateral development of ischemic myocardium. In this study by direct sampling of blood from human collaterals in vivo we aimed to assess to what degree growth factor production is related to collateral function in chronic coronary occlusions (TCOs) of more than 2 weeks duration. **Methods:** Fifty consecutive patients were studied during successful recanalization of a TCO. After crossing the occlusion with a guide wire, an over-the-wire probing catheter was advanced distal to the occlusion, and blood samples were drawn from this collateral receiving site, and at the same time from the guiding catheter proximal to the occlusion. The concentrations of proximal and distal bFGF and MCP-1 were measured with a standard immunoassay (Quantikine®). Then a pressure wire were advanced distal to the occlusion and distal coronary pressure (Pd), and aortic pressure (PAo) were recorded. From these parameters a collateral pressure index CPI=Pd/PAo as parameter of collateral function was calculated. The duration of the occlusion was defined by the time of a previous myocardial infarction or angina onset. Data are given as x±SEM.
Results: We observed a significantly higher concentration of bFGF in the collateralized vascular bed as compared to the aortic root (distal: 43±2 vs proximal: 34±4 pg/ml; p=0.03). A similar concentration gradient was observed for MCP-1 (distal: 78±20 vs proximal: 45±8 pg/ml; p=0.02). The duration of the TCO had a significant influence on the gradient of bFGF (p=0.02). In TCOs of <1 month duration a higher systemic concentration of bFGF as compared with TCOs>1 month duration was measured (41±3 vs 28±4 pg/ml; p<0.05), whereas concentrations in the collateralized bed were equally high (46±4 vs 45±6 pg/ml). For MCP-1 such a time-dependent influence was not observed. A higher bFGF concentrations was detected in collaterals with a low CPI, i.e. collaterals with insufficient function (CPI<0.25: 58±7 vs CP>0.25: 40±3 pg/ml; p=0.03).
Conclusion: In patients with TCOs a gradient for bFGF and MCP-1 between the collateralized vascular bed and the aortic root is observed as evidence for an ongoing local growth factor release. While MCP-1 showed no time-dependent relation with collateral function, the systemic bFGF concentration was higher in recent than in TCOs of longer duration, and bFGF was generated more in collaterals of insufficient functional capacity.

P1185 In vitro angiogenesis: identification, growth and function of endothelial progenitors cells from peripheral blood

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Purpose: To identify best growth conditions of mononuclear cells isolated from human peripheral blood (PBMNCs) for the in vitro differentiation into endothelial progenitor cells (EPCs) involved in adult vasculogenesis.
Methods: 8x106/ml PBMNCs harvested from healthy volunteers were cultured on fibronectin with the following experimental settings: 1) M199; 2) M199 with VEGF, bFGF, and IGF-I; 3) M199 with bovine retina-derived growth supplement (RDGS); 4) M199 with RDGS, VEGF, bFGF and IGF-I; 5) endothelial basal medium (EBM) and 6) EBM supplemented with SingleQuots (EGM). 20% FCS was added. For FACS analysis of EPCs, the adherent cells were detached by trypsin/EDTA and incubated with mAbs for endothelial markers. Single color flow cytometric analysis was performed using FACScan flow cytometer. EPCs migration was determined using a modified Boyden chamber using VEGF as chemoattractant. For in vitro angiogenesis, EPCs were collected at day 20, labeled with CM-DiI and plated alone or with unlabeled HUVECs (ratio 1:4) in 24-well plates precoated with 100 μl of matrigel. After 24 h of incubation the three-dimensional network was examined under an inverted confocal laser scanning microscope.
Results: With media 1-3, cell clusters appeared within 1 week. Spindle-shaped and attached cells sprouted from them, differentiating in endothelial cell-like cells (EC-like cells) within 2 weeks and eventually forming cobblestone-like monolayers within 3 weeks. With medium 4, numerous large cell clusters appeared within 1 week. Spindle shaped and attached cells sprouted also from these clusters, but the number of differentiated cells with the morphology of mature endothelial cells decreased during culture. Interestingly, the use of media without specific growth factors (setting 1) allowed the differentiation in EC-like cells but only when a consistent number of PBMNCs was plated. With media 5-6, although few clusters were observed, an earlier differentiation of many EC-like cells was obtained. FACS analysis confirmed the endothelial phenotype. All cultured EPCs were able to migrate in response to VEGF in Boyden chambers. EPCs were be incorporated in capillary-like structures formed by HUVECs on Matrigel; moreover, growth factors-induced EPCs developed angionesis networks also when plated on matrigel alone.
Conclusions: EPCs with the capability to participate into angiogenesis processes can be obtained under appropriate culture conditions. This may be helpful for in vivo EPCs application in ischaemic patients.

P1186 Abnormal angiopoietin-2 levels as an index of angiogenesis in congestive heart failure; relationship to disease severity

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Recent studies have suggested abnormal angiogenesis (as indicated by increased levels of vascular endothelial growth factor (VEGF)) in congestive heart failure (CHF). Angiopoietin-2 (Ang-2) is a new index of angiogenesis, being highly abnormal in cancer biology but limited data are available in cardiovascular disease. We hypothesised that Ang-2 may be abnormal in CHF and related to ejection fraction.
We studied 39 patients with acute CHF (defined by European Society of Cardiology criteria) who were compared with 40 patients with chronic CHF and 18 normal healthy controls. Plasma Ang-2 was measured by ELISA, and the ejection fraction ascertained by echocardiography.
Results: Ang-2 levels were highest in acute CHF, intermediate in chronic CHF and lowest in healthy controls. A significant difference was noted between acute and chronic CHF (Tukey's post hoc test, p<0.05). There was a modest relationship between Ang-2 levels and ejection fraction (p=0.02).

Variables according to groups

	acute CHF	chronic CHF	controls	p
Age	67(10)	63(10)	66(8)	p=0.295
Ejection fraction (%)	29(10)	33(9)	—	p=0.072
Ang-2 (ng/ml)	16.0(10.0-20.0)	7,6(6.0-11.0)	5.0(4.0-6.0)	p<0.001

Age and ejection fraction expressed as mean (SD); Ang-2 expressed as median (IQR). One way ANOVA with Tukey's post hoc analysis for age and Ang-2 after log transformation; t test for ejection fraction

Conclusion: Abnormal angiogenesis in CHF extends to abnormality of the angiopoietin system, with a modest relationship to the severity of CHF. Further studies are required to ascertain the association with treatment and prognosis in CHF.

P1187 High-resolution magnetic resonance angiography demonstrates arteriogenesis in response to sustained release murine vascular endothelial growth factor in a mouse model of peripheral arterial disease

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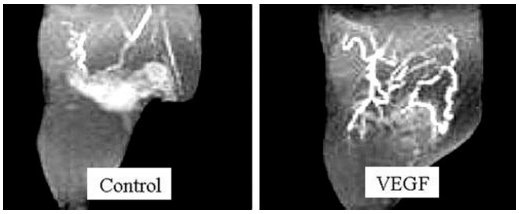
Introduction: Preclinical studies have been unable to serially visualise arteriogenesis due to limitations of existing techniques. We therefore refined high-resolution magnetic resonance angiography (MRA) to assess the effect of sustained-release murine VEGF165 (mVEGF) in a murine model of peripheral arterial disease.
Methods and Results: Hindlimb ischemia was induced in male C57 mice by left femoral artery ligation. Serial time-of-flight MRA was able to detect spontaneous arteriogenesis by five days post-ligation. Twenty-one days after ligation, 50μg sustained-release mVEGF or vehicle was injected into the left calf. MRA demonstrated a dramatic enhancement of collateral vessels by mVEGF treatment, increasing over time from treatment. Figure 1 shows representative angiograms from animals five days after injection with vehicle or VEGF. Further, mVEGF induced a marked angiogenic reaction in the injected area as assessed by an anti-PECAM1 radioimmunoassay (relative endothelial cell density: 1.5±0.07 VEGF versus 0.68±0.02μg mAb/g Vehicle, p<0.01). In association with this vascular expansion, resting left gastrocnemius perfusion measured by radiolabelled microsphere deposition was significantly higher in mVEGF treated animals (57±11 VEGF versus 7±1 ml/min/100g Vehicle, p<0.01).
Conclusion: High resolution MRA can be used to serially visualise arteriogenesis in an experimental setting. We have established that in addition to induction of angiogenesis, controlled intramuscular delivery of mVEGF promotes growth of collateral vessels that enhance tissue perfusion.



P1188 Inhibition of nitric oxide synthase impairs ischaemia-induced angiogenesis in the rat heart in vivo: a magnetic resonance imaging study

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Background: In vivo studies revealed that NO synthase blockade or knockout reduces angiogenesis in the hindlimb of rodents. We hypothesized that inhibition of NO synthase impairs ischemia-induced angiogenesis in the myocardium. Therefore, functional myocardial microcirculation was determined by Magnetic Resonance Imaging (MRI) in the ischemic rat heart in vivo during antagonism of NO synthase by L-NAME (NG-nitro-L-arginine methyl ester).
Methods: In twenty female Wistar rats coronary stenosis was induced by a probe of 300 μm which was quickly removed after artery ligation. Ten animals received L-NAME (67 mg/100ml) and hydralazine (8 mg/100 ml) in drinking water. Ten animals were not treated (controls). Two weeks later, myocardial perfusion (in ml/g/min) and intracapillary blood volume (RBV, in %) were quantitatively measured at rest and during adenosine (2mg/kg/min) by MRI (Bruker 7 Tesla Spectrometer). Formalin-fixed tissue sections were double-stained for lectin BS-1 (1:200, Sigma) and Ki67 (1:30, Santa Cruz). For the analysis of angiogenic tissue response, colocalization of endothelial cells and Ki67 staining as a marker for endothelial cell proliferation were counted on a x400 field (/mm^2). All results (mean $\pm$ SEM) were determined in the poststenotic (sten.) and the remote (rem.) left myocardium (table).

Group	Scar tissue (%)	Perfusion sten. rest	Perfusion sten. adenosine	Perfusion rem. rest	Perfusion rem. adenosine
L-NAME	6.1 $\pm$ 0.8	1.14 $\pm$ 0.19*+	2.45 $\pm$ 0.38#	1.98 $\pm$ 0.19*+	4.22 $\pm$ 0.29*
Controls	6.8 $\pm$ 0.7	1.79 $\pm$ 0.11+	3.12 $\pm$ 0.20#	3.34 $\pm$ 0.12+	5.24 $\pm$ 0.24

Group	Cell proliferation sten.	Cell proliferation rem.	RBV sten. rest	RBV sten. adenosine	RBV rem. rest	RBV rem. adenosine
L-NAME	15.6 $\pm$ 1.0*	13.5 $\pm$ 1.3	11.31 $\pm$ 0.60+	20.51 $\pm$ 0.61	12.32 $\pm$ 0.62+	22.91 $\pm$ 0.99
Controls	9.6 $\pm$ 5.3*#	29.9 $\pm$ 2.0	12.63 $\pm$ 0.42+	22.42 $\pm$ 0.81	12.92 $\pm$ 0.33+	23.32 $\pm$ 0.52

*p$<$0.05 L-NAME vs. controls, #p$<$0.01 sten. vs. rem., +p$<$0.01 rest vs. adenosine

Conclusion: Inhibition of NO synthase in the ischemic rat heart impaired the angiogenic response of the endothelium and resulted in a reduction of myocardial perfusion and RBV. The results indicate that MRI allows to detect functional changes in the microcirculation during impaired angiogenesis in the heart induced by compromised NO production.

P1189 Tumour necrosis factor-alpha antagonism by Infliximab inhibits collateral artery growth

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TNF-alpha plays a decisive role during inflammatory diseases, such as rheumatoid arthritis. Recent studies also showed a pathophysiological role of TNF-alpha for cardiovascular diseases, e.g. chronic heart failure. Therefore, the successful clinical use of the TNF-alpha antagonist Infliximab against rheumatoid diseases promised comparable benefits for patients suffering from chronic heart failure. Unexpectedly, clinical trials however showed an increased mortality in the verum group as compared to placebo. In previous studies, we could show that TNF-alpha is essential for proliferation and growth of pre-existing arteriolar connections towards functional collateral arteries (arteriogenesis). The current study therefore aims to examine the effect of Infliximab on collateral artery growth in the rabbit hind limb after femoral artery ligation.
Methods: 24 White New Zealand rabbits were divided into two groups, n=12 each. Group 1 received a single dose Infliximab intravenously after ligation of the right femoral artery, whereas group 2 served as control and received PBS after the surgical procedure. Seven days later, collateral conductance was measured in-vivo via fluorescent microspheres, injected at different pressure levels (n=6 per group). Post-mortem high-resolution angiograms were used to quantify the number of detectable collateral arteries (n=6 per group).
Results: Consistent to our previous results that TNF-alpha deficient mice show a reduced arteriogenic response, mediated by the TNF p55 receptor, the single application of Infliximab significantly inhibits arteriogenesis as compared to untreated controls (PBS: 52.39 $\pm$ 8.14 ml/min/100mmHg; Infliximab: 33.35 $\pm$ 6.15 ml/min/100mmHg; p$<$0.01). Immunohistochemistry revealed a strong accumulation of TNF-alpha in the adventitia of the proliferating vessels and double-staining verified Infliximab binding to TNF-alpha.
Conclusion: TNF-alpha is one of the key factors during arteriogenesis. The negative results for the treatment of patients with chronic heart failure might be partially explained by the inhibition of the collateral circulation.

P1190 Pancreatic islet transplantation reverses impaired angiogenesis in diabetic mice after limb ischaemia

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Introduction: Diabetes is a major risk factor for peripheral artery disease and impairs endogenous neovascularization of ischemic tissues. Insulin induces Akt phosphorylation and activity, increasing endothelial survival and proliferation.
Aim: Here, we tested the hypothesis that hyperinsulinemia after pancreatic islet transplantation in diabetic mice has a major beneficial impact on neoangiogenesis after peripheral ischemia through Akt activation.
Methods: Diabetes was induced by streptozotocin (Stz) administration. The animals were randomized in three groups: 1) Stz-induced diabetic mice; 2) Diabetic mice in which 250 pancreatic islets taken from syngenic mice were transplanted under the kidney capsule; 3) Diabetic mice in which 400 pancreatic islets were transplanted. Non-diabetic mice were our control group. Unilateral hindlimb ischemia was created by ligation of the femoral artery. Hindlimb perfusion was evaluated by serial laser Doppler studies at 7, 14, 21 and 28 days after surgery. At 28 days, mice were sacrified, the ischemic muscles exised and capillary density was measured by immunostaining for CD31 (specific marker for endothelial cells). Additional mice were sacrificed 7 days after hindlimb ischemia to assess Akt phosphorylation and activity by western blotting.
Results: 7 days after surgery, in diabetic mice Doppler flow ratio between the ischemic and the normal limb was already significantly reduced compared to the control mice. This impairment in blood flow recovery persisted throughout the duration of the study. Trasplantation of 200-islet rescused the impaired flow in diabetic mice whereas an absolute improved flow ratio was observed with 400-islet trasplant compared both to diabetic and control mice. At 28 days after hindlimb ischemia, capillary density was reduced in diabetic mice compared to controls. 200- and 400-islet trasplant in diabetic mice significantly increased capillary density compared to controls and non-trasplanted diabetic mice. Finally, ischemic muscles isolated from diabetic mice compared to controls revealed a strongly reduced Akt phosphorilation and activity, which were restored and increased after 200 and 400 pancreatic islet trasplant, respectively.
Conclusions: Hyperinsulinemia produced by islet transplantation increases Akt activity in ishemic muscle and improves neovascularization after limb ischemia in diabetic mice.

P1191 Recombinant adeno-associated virus vector-mediated human VEGF165 gene transfer stimulates angiogenesis and wound healing in the genetically diabetic mice

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It has been widely demonstrated that diabetes is a pathological condition associated with a high incidence of atherosclerosis. Moreover,inefficient angiogenesis is one of the main mechanisms underlying the wound healing disorders related to diabetes.
Experimental evidences indicate that in such conditions an altered expression pattern of Vascular Endothelial Growth Factor (VEGF) plays a pivotal role in the decrease of neovascularization observed in chronic diabetic ulcers.
Purpose: Here we explore the efficacy of gene therapy of diabetes-associated skin repair disorders with a recombinant Adeno-Associated Virus (AAV) vector expressing the 165 amino acid isoform of VEGF-A (rAAV-VEGF 165).
Methods: Diabetic C57BL/KsJ db+/+ mice and their normal littermates (db+/+m) were randomized to receive intradermally into the edges of full-thickness incisional skin wounds, either recombinant AAV-Lac-Z (rAAV-LacZ) or rAAV-VEGF165.
Wounded skin specimens collected at different time points after delivery of the vectors were used for gene marker studies, histological and immunohistochemical evaluation and wound breaking strength analysis.
Results: By beta-galactosidase activity assay, we found that AAV vectors are highly efficient for gene transfer to the mouse skin. Moreover, injection of rAAV-VEGF165 into the wounds resulted in a remarkable increase of the tissue content of the mature protein. This phenomenon was associated with a significant induction of new vessel formation, with consequent reduction of the healing time. Histological examination of rAAV-VEGF165 treated wounds revealed an improvement in reepithelization, granulation tissue formation, synthesis and organization of extracellular matrix and wound breaking strength.
Conclusions: Our study suggests that VEGF gene transfer might represent a novel therapeutic approach to treat wound healing disorders associated with diabetes.

STEM CELL THERAPY

P1192 Improvement of coronary flow reserve following inctracoronary stem cell

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Experimental studies indicate that transplantation of adult progenitor cells from circulating blood (endothelial progenitor cells, EPC) or bone marrow-derived cells (BMC) improves neovascularization and myocardial function after acute myocardial infarction (AMI).
Methods: We investigated in 56 patients 4.7±1.3 days after successful revascularization (stent implantation) of the infarct vessel the effect of intracoronary progenitor cell therapy with either EPC (n=28) or BMC (n=28) on coronary flow reserve (CFR) as a measure of coronary vascularization. EPC (isolated from peripheral blood and subsequently expanded) and BMC (derived from bone marrow aspiration) were reinfused in the infarct artery during low pressure balloon inflation. CFR (adenosine 2.4 mg/min i.c.) was measured in the infarct and a reference vessel prior to cell therapy and at 4 months follow up in patients without restenosis (n= 32, out of 44 patients with follow up available up to date).
Results: Prior to cell therapy, CFR was significantly reduced in the infarct compared to the reference vessel (2.5±0.69 vs. 3.4±0.88, $p<0.001$). After 4 months, CFR was normalized in the infarct vessel (3.6±1.0, $p<0.001$), whereas CFR in the reference vessel only slightly increased to 3.8±0.95 (p=0.045). After 4 months, there was no longer a significant difference between CFR in infarct and reference vessel (p=0.21). Furthermore, relative CFR (infarct vessel CFR normalized to reference vessel) significantly increased from 0.79±0.29 prior to progenitor cell therapy to 0.96±0.26 after 4 months (p=0.017). In addition, diastolic deceleration time improved significantly in the infarct artery from 907±207 ms to 1012±207 ms (p=0.023), whereas, there was no relevant change in the reference vessel (867±157ms vs. 900±315ms, p=0.52). For all parameters, no significant difference was observed between EPC and BMC therapy.
Conclusions: The nearly complete normalization of coronary flow reserve in the infarct vessel following progenitor cell therapy after acute myocardial infarction suggests that intracoronary transplantation of progenitor cells contributes to improved neovascularization.

P1193 Autologous bone marrow cells for the regeneration of infarcted myocardium in patients

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Mononuclear BMC are thought to have the potential to improve myocardial function after myocardial infarction. The effect of autologous BMC on myocardial function and myocardial blood flow was investigated over a 12 months period in patients with an acute myocardial infarct (MI) and in patients with a chronic MI.
Methods: In 6 patients (3 male, mean age 59 ± 11) with an acute anteroseptal MI (max CK 2240 ± 432 U/l) and single vessel disease, the occluded artery was recanalized by PTCA and stent implantation within 12 hours after symptom-onset. On day 5 - 6 post MI 5.0 ± 1.3 x 107 autologous monocytic BMC in a volume of 8 – 12 ml were injected with an over the wire PTCA-balloon catheter expanded to 4 bar over 10 min. into the open and stented infarct artery. The same methodological approach was performed in 5 patients with a chronic MI, and an open infarct related artery. Global and regional ejection fraction, myocardial perfusion by contrast echo, coronary flow reserve (CFR) and average peak velocity (APV) were determined at this time and at 3 months follow up. LVEF with determined at 3 months intervals within the first year.
Results: Within 12 months there were no major adverse cardiac events. All stented arteries remained open within the first 3 months. The table summarizes the results of BMC transplantation on myocardial function and myocardial blood flow in pts with an acute MI. In pts with a chronic MI LVEF was virtually unchanged over time. Echo contrast imaging demonstrated an unchanged area of malperfusion.
Conclusion: Autologous transplantation of monocytic BMC in patients with an acute and chronic MI has no significant effect on myocardial function or coronary flow capacity. The higher CFR after 3 months is related to a reduced basal flow, and cannot be interpretated as neoangiogenesis.

	Global LVEF %	CFR	APV basal (cm/s)	APV maximal (cm/s)
day 5-6 post MI	41 ± 14	1.75 ± 6.4	21.2 ± 6.4	37.5 ± 14
3 months post MI	41 ± 10	2.75 ± 0.69	14.2 ± 1.9	38.8 ± 12
12 months past MI	41 ± 9			
p <	ns	< 0.05	< 0.05	ns

Global LVEF, coronary flow rate (CFR) and average peak flow (APV) in the coronary circulation in response to autologous bone marrow cells after myocardial infarction.

P1194 Autologous marrow stromal cell transplantation improves cardiac function after myocardial infartion in rats

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Objective: Marrow stromal cell(MSC) transplantation is promising for the treatment of end-stage heart failure. This study investigated the value of autologous MSC transplantation into infracted myocardium through intramyocardial injection and intracoronary infusion. Methods: Myocardial infarction was created in 46 rats by left coronary artery ligation. All the rats were divided into two groups: intracoronary implatation group(IC) and intramyocardial implantation group(IM). Each group was consisted of three subgroups: injection of induced MSC cells, MSC cells or culture medium alone(control rats) 7 days after infarction. Left ventricular size and function were assessed by echocardiography (Philips Sonos 5500) before and 1 week after infartion, 2 weeks, 4 weeks and 8 weeks after implantation. The thickness of left ventricular wall, the diastolic diameter of left ventricular(LVDd) and EF were measured. Results: LVDd of implantation group was smaller and EF was increased compared with that in the control group 2 weeks, 4 weeks and 8 weeks after MSC implantation ($p<0.01$). The improvement in EF was similar in the MSC group and the induced MSC group. The improvement in EF was greater in the IC than in the IM($p<0.01$). Conclusions: Autologous MSC transplantation improves contractibility of infracted heart. This technique may lead to a novel therapy to treat congestive heart failure caused by ischemic heart disease.

P1195 Magnetic resonance imaging of targeted catheter-based implantation of myogenic precursor cells into infarcted left-ventricular myocardium

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Background: In vivo imaging of targeted catheter-based implantation of myogenic precursor cells (MPC) into infarcted left ventricular (LV) myocardium is unavailable.
Methods and Results: The study was conducted in 7 farm pigs (4 with anterior myocardial infarction), in which autologous MPC were injected through a percutaneous catheter allowing for LV electromechanical mapping and guided transendocardial micro-injections into normal and infarcted myocardium. Cardiac magnetic resonance imaging (MRI) was used to detect implanted MPC previously loaded with iron oxide nanoparticles. MRI data were compared with LV electromechanical mapping and cross-registered pathology. All 9 injections into normal and 12 injections into locally damaged myocardium were detected on T2-weighted spin echo and inversion-recovery true-fisp MRI (low signal areas) with good anatomical concordance with sites of implantation on electromechanical maps. All sites of injection were confirmed on pathology that showed in all infarct animals iron-loaded MPC at the center and periphery of the infarct as expected from MRI.
Conclusions: Targeted catheter-based implantation of iron-loaded myogenic precursor cells into locally infarcted LV myocardium is accurate and can be reliably demonstrated in vivo by cardiac MRI. The ability to identify noninvasively intramyocardial cell implantation may be determinant for future experimental studies designed to analyze subsequent effects of such therapy on detailed segmental LV function.

P1196 Statin therapy reverses the impaired endothelial progenitor cell differentiation into cardiomyocytes in patients with coronary artery disease

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Further to promoting angiogenesis, cell therapy with stem or progenitor cells may be an approach for cardiac regeneration in ischemic heart disease. We have previously shown that human endothelial progenitor cells (EPCs) can differentiate into cardiomyocytes in vitro. Here, we tested the effects of statin therapy on the differentiation of EPCs from patients with coronary artery disease (CAD) who may benefit from autologous cell therapy.
EPCs from 3 age-matched groups were tested: No CAD (n=13), CAD patients with (n=10) or without (n=16) statin therapy. From 4 CAD patients, EPCs were tested before and after 4 weeks of therapy with 20 mg atorvastatin. EPCs were obtained from peripheral blood mononuclear cells by cultivating with endothelial cell medium and growth factors. After 3 days, >95% of adherent cells were functionally and phaenotypically EPCs. EPCs were co-cultured in vitro with rat neonatal cardiomyocytes to induce cardiomyocyte differentiation. EPC differentiation was quantified by alpha-sarcomeric actinin staining (cardiomyocyte marker) followed by flow cytometry.
After 6 days of co-culture, the percentage of alpha-sarcomeric actinin–positive human EPCs was significantly (p=0.014) higher in EPCs of adults without CAD (8.07%±1.48% of EPCs) compared to EPCs of CAD patients without statin (3.56%±0.72%). Importantly, patients with statin therapy revealed significantly higher numbers of alpha-sarcomeric actinin-positive EPCs (6.36%±0.69%, p=0.01) when compared to CAD patients without statin. EPCs from CAD patients with statin were no longer different from control (No CAD) EPCs. In addition, statin therapy resulted in a significant (p=0.017) increase of EPC differentiation in all 4 CAD patients prospectively investigated before and 4 weeks after statin therapy. The survival of EPC assessed after 6 days of co-culture did not differ between the different groups indicating that the regulation of EPC differentiation is not secondary to modulation of EPC survival. Finally, we tested whether statin treatment of EPCs in vitro enhances the EPC differentiation into cardiomyocytes. However, EPC treatment with 0.1 μM atorvastatin did not affect EPC differentiation (116.15%±49.11% alpha-sarcomeric actinin–positive EPCs of control).
EPCs from CAD patients display an impaired in vitro differentiation capacity into cardiomyocytes. This defect can be reversed by in vivo, but not in vitro statin therapy. The therapeutic use of autologous EPCs may aid cardiomyocyte regeneration in patients with ischemic heart disease.

P1197 Transplantation of bone marrow cell overexpressing FrzA reduces infarct size and improves cardiac function after myocardial infarction

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Background: We have recently shown that ubiquitary overexpression of a secreted frizzled related protein, FrzA, in transgenic (Tg) mice (CMV promoter) reduced infarct size and modified infarct healing. However, myocardial infarct size was not reduced in two others transgenic mice line overexpressing FrzA in the vascular hood (tie-2 promoter) and in the cardiomyocytes (alpha-MHC promoter). During characterization, we have shown by RT-PCR that FrzA transgene was expressed in Bone Marrow Cells (BMC) and in circulatory mononuclear cells only in Tg mice overexpressing FrzA under CMV promoter. As these inflammatory cells play keys role in myocardial healing process after myocardial infarction, we would like, in this study, to explore if secretion of FrzA by inflammatory cells during the first days after myocardial infarction could play a role in reparation process.
Methods: Our strategy is based on BMC transplantation. BMC of giver mice (Tg mice and Control C57Bl/6J mice) were extracted from femur and purified in ficoll paque®. Receiver mice (RM)were lethaly irradiated (9 grays). 24 hours after irradiation, these mice were transplanted with 500 000 Tg-BMC mice or Control-BMC (Cont- BMC mice) by sub-claviar veinous injection. RM were then kept in sterile cage with oral antibiotic during 1 month and were subjected to myocardial infarction by ligation or by cryolesion two months after irradiation. 15 days after surgery, hemodynamics study (HS) (Millar's probe) and infarct size (morphometric analysis) were determined.
Results: 32 mice were transplanted. 2 mice suffered of gaseous embolism during transplantation. 6 mice died after transplantation (20%). 22 mice were used for surgery (11 Tg- BMC mice and 11 Cont- BMC mice). 2 Cont- BMC mice died by cardiac rupture. During HS, dp/dt max and dp/dt min were improved in Tg-BMC mice (+3864 mmHg/s, -3406 mmHg/s, n=5) as compared to Cont- BMC mice (+2519 mmHg/s, -1808 mmHg/s, n=3), p<0.001. Infarct size is decreased in Tg- BMC mice after ligattion or cryolesion (30.5% Left Ventricle Necrosis for ligation, n=5 and 20% Left Ventricle Necrosis for cryolesion, n=4) as compared to Cont- BMC mice (45% Left Ventricle Necrosis for ligation, n=3 and 26% Left Ventricle Necrosis for cryolesion, n=5), p<0.01.
Conclusion: Overexpression of FrzA in BMC can reduce infarct size and improve cardiac function after myocardial infarction.

P1198 Transplanted mesenchymal progenitor cells differentiate to an endothelial phenotype and improve heart function in infarcted rat myocardium

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Purpose: Cellular cardiomyoplasty is promising for improving postinfarcted cardiac function. Over the past decade, a variety of cell types have been proposed including mononuclear bone marrow cells. The latter contains different lineages including mesenchymal stem cells (MSCs). The aim of this study was to analyse the differentiation pathways of engrafted syngenic mesenchymal progenitor cells (MPCs) obtained in culture from bone marrow MSCs and their effects on the left ventricular function in a rat model of myocardial infarction.
Methods: Bone marrow was obtained from Lewis inbred rats and then cultured. MPCs were isolated by bone marrow cell adherence. In vitro differentiation was assessed by immunohistochemical analysis using anti-alpha SM actin, anti-vimentin, anti-beta actin, anti-CD31, anti-myosin heavy chain (MHC) and anti-desmin. A ligation model of left coronary artery was used. Seven days after ligation, MPCs labeled with 4,6-diamidino-2-phenylindole (DAPI) were injected into the infarcted myocardium (n=8). For control, culture medium was injected (n=8). Transthoracic echocardiography was performed 6 days after myocardial infarction (baseline measurements) and 30 days after cell implantation. For assessment of the cell grafting and vascular density, rats were sacrified 30 days after implantation. Histological and immunohistochemical analysis were performed using the same antibodies as above.
Results: In vitro, all the cells express vimentin showing their mesenchymal origin. Moreover, they expressed alpha SM actin and beta actin filaments which are respectively specific of smooth muscle and non-muscle cells, but they did not express skeletal MHC and desmin. DAPI-labeled cells were observed in the luminal face of endothelium vessels expressing the endothelial marker CD31 and not alpha SM actin or desmin. Many loci positively stained for alpha SM actin were observed which were discrete positively stained for desmin. Furthermore, vessel density was augmented in the MPC group in comparison with the control group (8.4±0.9/0.2 mm^2 vs 5.4±0.9/0.2 mm^2; p=0.001). After 30 days, echocardiography showed an improvement on left ventricle ejection fraction (42±2.7% vs 28±1.5%; p=0.002) and fractional shortening (16.7±1.3% vs 10.4±0.7%; p=0.003) in the MPCs compared to the control group.
Conclusion: The implantation of syngenic MPCs into a rat model of myocardial infarction was safety demonstrated. Some engrafted cells appeared to differentiate into endothelial cells. MPC engraftment seemed to contribute to the improvement on the cardiac function.

P1199 Bone marrow derived human mesenchymal stem cells have the potential for myogenic differentiation both in vivo and in vitro

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It has been proposed that stem cell-like cells might provide a valuable source to restore function of injured heart tissue. Although numerous basic biological properties of stem cell-like cells still remain unresolved its seems clear that operationally defined stem cell-like cells have the potential to express numerous markers characteristic for differentiated cell types. The aim of our investigation was to analyse the potential of bone marrow derived human mesenchymal stem cells (HMSC) to differentiate into cardiomyocytes both in vitro and in vivo. Methods: Human mesenchymal stem cells were isolated from bone marrow aspirates and enriched in cell culture in DMEM/10% FCS. In co-culture experiments, HMSC were first labelled with DiI (fluorochrome) and after 24h were added to cultured ventricular cardiomyocytes from adult mice. Differentiation of HMSC was analysed by antibody staining. The DiI labelled HMSC were also injected into both the heart and skeletal muscle of SCID (severe combined immunodeficiency) mice, and the fate of DiI-labelled HMSC was analysed 14d after transplantation. Results: In cell culture, HMSC were positive for vimentin but showed no expression of muscle specific markers MF20, Troponin I, Troponin T, and F-Aktin. After 14d of co-culture of DiI-labelled HMSC and adult murine cardiomyocytes, approximately 30% of cultured HMSC showed immunoreactivity against MF20, cardiac Troponin T, and F-Aktin. In vivo, 14d after injection of labelled HMSC into the heart of SCID mice, a rather low percentage of the transplanted stem cells expressed MHC and cardiac Troponin T. Additionally, DiI-positive myotubes were found after transplantation of labelled HMSC into skeletal muscle. Conclusions: In our experiments we demonstrate that human bone marrow derived HMSC have the capacity to express marker molecules that are indicative for the myogenic lineage both in vitro and in vivo. The number of HMSC expressing myogenic markers was by far higher in cell culture experiments than in vivo. We propose that the close interaction of HMSC and cardiomyocytes achieved in cell culture favours the differentiation process as every cultured HMSC gets into close contact with several cardiomyocytes. After in vivo transplantation, only few of the injected HMSC's get into direct contact with the host's cardiomyocytes or myotubes, while the majority of the injected cells forms an isolated cluster. Therefore, in future experiments either an optimized way of HMSC delivery or transplantation of pre-differentiated HMSC should result in a higher extent of new muscle formation.

P1200 Vascular endothelial growth factor modulates skeletal myoblast function

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Vascular Endothelial Growth Factor (VEGF) expression is enhanced in ischemic skeletal muscle and is though to play a key role in the angiogenic response to ischemia. However, it is not known whether VEGF modulates skeletal muscle cell function. The objective of the present study was to examine the expression and function of VEGF receptors (Flk-1 and Flt-1) in skeletal myoblasts in vivo and in vitro.

Methods and Results: Unilateral hindlimb ischemia was induced in mice by left femoral artery ligation (FAL) at its proximal origin as a branch of the external iliac artery. Immunoistochemical analysis showed that, in normoperfused hindlimbs, Flk-1 and Flt-1 receptors were expressed in quiescent satellite cells. At day 3 and day 7 after FAL, Flk-1 and Flt-1 expression was observed in newformed myotubes. In order to characterize the role of VEGF receptors on skeletal myoblasts, experiments were performed with C2C12 cells, a murine myoblasts cell line. C2C12 cells were grown in DMEM supplemented either with 20% or 2% fetal calf serum for proliferation and differentiation studies, respectively. Western blot analysis showed that Flk-1 and Flt-1 expression was downregulated during C2C12 myogenic differentiation. In a modified Boyden Chamber assay, VEGF enhanced C2C12 myoblasts migration 5 fold (n=5; $p<0.01$). Moreover, VEGF administration to differentiating C2C12 myoblasts prevented apoptosis by activating the serine-threonine protein kinase AKT, while inhibition of VEGF signaling either with selective VEGF receptor inhibitors (SU1498 and CB676475) or a neutralizing Flk-1 antibody, enhanced C2C12 cell death approximately 3.5 fold as evaluated by TUNEL labeling.

Conclusions: These results support a role for VEGF in myoblast migration and survival, and suggest a novel autocrine role of VEGF in skeletal muscle repair during ischemia.

P1201 Infusion of human umbilical cord blood-derived AC 133+ stem cells to treat myocardial infarction

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Background: We designed a study to test the hypothesis that human umbilical cord blood may be an alternative and novel source for stem cells that may participate in post MI healing and neovascularization.

Methods and Results: Cord blood cells were isolated from human umbilical cord bloods. AC 133 (+) cells were separated by a Miltenyi Biotec's magnetic cell separation technology (MACS) and stored for transplantation. Athymic nude rats (n=17) were used for cell transplantation study and the left anterior descending coronary artery was permanently ligated to create MI. AC 133 (+) cord blood stem/progenitor cells (~2x106) or saline (control) were infused IV at 24 h after MI. By 3 weeks after transfusion, the hearts, lungs, spleen, liver, kidneys and bones were harvested and representative sections were either fixed or frozen sectioned. The presence of human- donor cells in recipient heart was confirmed by fluorescent in situ hybridization (FISH) using deoxyribonucleic acid probes specific for human X and Y chromosomes or immunostaining for HLA-DR. HLA immunostaining revealed that the infused donor cells homed and colonize the bone marrow and infarcted myocardium. Positive HLA staining was observed in vessel walls suggesting differentiation of the donor cells into vasculature cells. Examination of representative slides from control hearts was negative for HLA or human sex chromosomes. Blinded computerized image analysis of representative slides stained for smooth-muscle alfa-actin detected a higher density (vessels/mm^2) of capillaries and arterioles (mean"bSE) (260"b18 vs. 187"b57;p=0.38) and vessel area (vessel area/slide) (12"b1% vs. 9"b1%; p=0.01) in the cell-treated vs. control hearts.

Conclusion: Our preliminary findings suggest that infused human umbilical cord blood derived AC 133+ stem/progenitor cells can migrate to and colonize the infarcted myocardium. The donor cells might give rise to a new vessel formation. Our ongoing research evaluates whether these encouraging preliminary results would be translated to improved myocardial remodeling and function.

CONVENTIONAL AND EMERGING RISK FACTORS IN CORONARY HEART DISEASE

P1202 Folic acid and B12 supplementation correct abnormal endothelial function in asymptomatic population with dual abnormality in homocysteine metabolism

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Background and Aims: In a previous study we have shown that 34% of asymptomatic individuals with MTHFR C677T mutation have abnormally low B12 levels and that these individuals have endothelial dysfunction (ECD). The present study was designed to test the hypothesis that B12 and folic acid can correct ECD in subjects with homozygosity for the C677T mutation and concomitant B12 deficiency.

Methods: Endothelial function using high-resolution ultrasound images of the brachial artery was measured in three groups of subjects: Group A (n=19) consisted of homozygotes for the C677T mutation and concomitant B12 deficiency (<150 pmol/L), Group B (n=15) consisted of C677T homozygotes with normal B12 levels, and Group C (n=15) consisted of subjects with no mutation and normal B12 levels (control). Group A was treated with B12 for 12 weeks and with folic acid for additional 12 weeks. Group B was treated with folic acid for 12 weeks. Endothelial function and blood tests for B12, folic acid and homocysteine were measured prior to, and after treatment.

Results: Abnormal flow mediated dilation (FMD), the major measurable parameter of endothelial function, was observed in groups A and B. Baseline FMD in Group A was 3.6±1.2%, FMD increased to 8.1±1.2% after correction of B12 deficiency but was normalized only when folic acid was supplemented (11.5±3.1%). In group, B baseline FMD was 6.7±2.6% and with folic acid supplementation reached 13.3±3.6%. In group C (controls) FMD was 15.1±3.0.%. Conclusion: 1) Individuals with abnormal homocysteine metabolism have endothelial dysfunction. 2) Folic acid alone can correct endothelial function in individuals with the C677T mutation, while B12 and folic acid are neccecary to correct endothelial dysfunction in individuals with concomitant homozygosity for the mutation and B12 deficiency.

P1203 Homocysteine-induced endothelin-1 release is dependent on hyperglycaemia and mitochondrial reactive oxygen species production in endothelial cells

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Background: Hyperhomocysteinemia is a risk factor for cardiovascular disease and causes endothelial dysfunction. This is thought to involve reactive oxygen species (ROS) production although the mechanism for this is not clear. Raised glucose levels in cell culture and diabetics are also associated with increased ROS production. As endothelin-1 (ET-1) is strongly implicated in atherogenic processes, we investigated whether homocysteine (Hcy) either alone or with high glucose induces endothelin-1 synthesis mediated by ROS.
Methods and Results: Bovine aortic endothelial cells were grown in high (25mM) and low (5mM) glucose medium. In high glucose, Hcy caused a concentration and time dependent increase in ET-1 release, which was greatest with 50μM Hcy ($p<0.01$) and at 24h was 40$\pm$8% above basal levels ($p<0.01$). This effect was not seen in low glucose conditions. ET-1 mRNA levels were maximal at 1h ($p<0.05$) and remained elevated for 4h ($p<0.05$). Tissue factor mRNA levels were raised at 4h ($p<0.05$) and functional activity was raised at 6h ($p<0.05$). Intracellular ROS production was increased by Hcy 50μM at 24h (44$\pm$14% v. basal, $p<0.05$) but only in high glucose conditions. To investigate the role of mitochondrial metabolism in ROS production, cells were incubated with thenoyltrifluoroacetone (inhibitor of complex II) or carbonyl cyanide m-chlorophenylhydrazone (uncoupler of oxidative phosphorylation). Both compounds abolished the Hcy-induced increase in ROS production and ET-1 release. Phospholipase A (DEDA) and C (U-73122) inhibitors also abolished the Hcy-induced increase in ET-1 release.
Conclusion: The combined metabolic burden of Hcy and high glucose stimulates ET-1 synthesis from endothelial cells and involves the production of mitochondrial ROS.

P1204 The effect of lowering plasma homocysteine level on vasomotor function and exercise-induced myocardial ischaemia in coronary patients with no traditional risk factors

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Background: Risk factor modification has shown to improve vasomotor function and exercise performance in patients with traditional risk factors (diabetes, hypertension, smoking, dyslipidemia). This study was performed to determine whether modification of high homocysteine level, as a novel risk factor, improves vasomotor function and whether this results in a reduction in exercise-induced ischemia in coronary patients with no traditional risk factors.
Methods: Thirty-four male patients (homocysteine levels >15 μmol/L) on a waiting list for percutan coronary intervention (PCI) of a focal stenosis in the LAD artery were studied. Twenty patients were received homocysteine lowering therapy-HLT (folic acid, vitamin B6 and B12) and 14 patients did placebo until the time of PCI (mean 3.2 weeks). At baseline and follow-up brachial artery ultrasonography and exercise SPECT were performed in each patient. All patients had follow-up angiogram at the time of PCI.
Results: All patients had no traditional risk factors. Also, HLT and placebo groups were comparable according to plasma total cholesterol, LDL, HDL, triglyceride, CRP, fibrinogen levels and blood pressures. Plasma homocysteine levels were significantly reduced by HLT compared with baseline (12.3$\pm$4 vs. 21.4$\pm$6 μmol/L; $p<0.001$) whereas placebo had no effect (20.9$\pm$5 vs. 22.2$\pm$8 μmol/L; p=NS). HLT produced a marked improvement in flow-mediated, endothelium dependent vasodilatation from 3.7$\pm$1.5% to 8.9$\pm$3.2% ($p<0.001$), and a significant reduction in exercise-induced ST depression (1.4$\pm$0.7 vs. 0.9$\pm$0.5 mm; p=0.01) and redistribution gradient on the polar map display of SPECT imaging (26$\pm$14% vs. 17$\pm$8%; $p<0.001$). There were no significant changes on all these parameters by placebo. The severity of LAD stenosis was not different between the baseline and follow-up angiograms in both HLT (82$\pm$11% vs. 80$\pm$9%; p=NS) and placebo (79$\pm$8% vs. 80$\pm$10; p=NS) groups.
Conclusion: Lowering plasma homocysteine levels may improve vasomotor function with no change in angiographic stenosis and this may result in a reduction in exercise-induced myocardial ischemia in coronary patients with hyperhomocysteinemia.

P1205 Elevated levels of oxidized low-density lipoprotein are associated with an increased risk of reperfusion injury in patients with acute myocardial infarction

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Background: There is accumulating data that increased blood levels of oxidized low density lipoprotein (ox-LDL) could play a role in acute myocardial infarction, but few data are available on their role in the reperfusion injury. The aim of the study is to assess the relative risk of malondialdehyde-modified LDL (MDA-LDL) on the reperfusion injury during acute myocardial infarction.
Methods: 33 patients of a first acute anterior myocardial infarction with primary angioplasty were studied prospectively. Lipid parameters including MDA-LDL were assayed at presentation, as were creatine kinase (CK) and high sensitive C-reactive protein (CRP). All patients underwent stress sestamibi myocardial perfusion gated SPECT imaging after 2 weeks. SPECT images were quantified by severity index using a polar map. Gated SPECT measurement for left ventricular end-diastolic volume (LVEDV) index and ejection fraction (EF) was obtained according to QGS methods.
Results: MDA-LDL levels at presentation were increased by 135 $\pm$ 47 U/L. A significant relationship was seen between CK and MDA-LDL ($r=0.66$; $p<0.0001$) and between severity index of sestamibi defect and MDA-LDL ($r=0.62$; $p<0.0001$). There was also a significant relationship between post stress left ventricular enlargement (stress LVEDV - rest LVEDV) and MDA-LDL ($r=0.70$; $p<0.0001$). By contrast, MDA-LDL was not correlated with EF, CRP and other lipid parameters. Multivariate regression analysis revealed that the most significant risk factor for the larger severity index was the high level of serum MDA-LDL.
Conclusion: This study demonstrated that ox-LDL levels showed a significant positive collation with the severity of myocardial damage in reperfused acute myocardial infarction patients. The observations suggested that increased levels of ox-LDL might play an important role of reperfusion injury in these circumstances.

P1206 C-reactive protein is related to heart rate variability – a predictor of sudden cardiac death

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C-reactive protein (CRP) is an independent predictor of cardiovascular events. Recently, it has been suggested that CRP testing should be used in coronary risk assessment, with CRP levels <1 mg/l, 1-3 mg/l and >3 mg/l indicating low, intermediate and high risk, respectively. CRP has also been related to the risk of sudden cardiac death (SCD) in apparently healthy men.
Purpose: To investigate a possible relation between CRP and HRV, which is a strong predictor of SCD.
Methods: Subjects were recruited among patients referred for elective coronary angiography at the Department of Cardiology, Aalborg Hospital, Aarhus Universityhospitals, Denmark, due to suspected coronary artery disease (CAD). Before the angiogram, a 24-hour Holter recording was obtained from each patient and time-domain HRV variables were analysed. CRP was measured using a highly sensitive assay.
Results: A total of 269 patients (171 men and 98 women; mean age 60 $\pm$ 8 yrs) were included. Thirty-six % had previously had a myocardial infarction and 70% had a positive angiogram. Patients were divided into 3 groups according to CRP levels (<1 mg/l, 1-3 mg/l, and 3-10 mg/l). Patients with intermediate and high CRP levels both had significantly lower SDNN, SDNNindex, and SDANNindex than patients with low CRP levels (table). There was no statistically significant differences in RR, PNN50 and RMSSD between groups.

	C-reactive protein		
	<1 mg/l (n=63)	1-3 mg/l (n=91)	3-10 mg/l (n=115)
RR (ms)	935	913	901
SDNN (ms)	142	124*	116*
SDNNindex (ms)	55	48*	46*
SDANNindex (ms)	127	113*	104*
PNN50 (%)	8.2	7.6	8.1
MSSD (ms)	27	29	29

Mean values of HRV indices in the three groups. *$p<0.01$ vs. CRP <1 mg/l

Conclusion: We report a strong relation between CRP and several HRV indices in patients with angiographically documented CAD. This is a novel finding supporting a possible link between CRP and SCD. Thus, risk assessment of CAD by CRP testing might also be applicable to the risk of suffering SCD.

P1207 White blood cell count and microalbuminuria are both independent predictors of late ventricular tachycardia/fibrillation in non-diabetic patients with acute myocardial infarction

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Aim: The role of inflammation and endothelial dysfunction in arrythmiogenesis has not been elucidated. The aim of this study was to examine if microalbuminuria (ML), an index of endothelial dysfunction and white blood cell count (WBC), an index of inflammation, are related to the development of malignant arrythmias in patients (pts) with acute myocardial infarction (AMI).
Methods: We studied 201 nondiabetic patients, 157 men and 44 women, 61.3±12 years old, admitted with AMI. Cardiac enzyme measurements were done every 8 hours for the first 3 days of hospitalization to assess the peak CK-MB (MB isoenzyme of creatine kinase) value. WBC was measured on the first day of admission. Patients enrolled in the study underwent a complete echocardiography examination prior discharge to assess left ventricular ejection fraction (EF). Signal averaging of the surface QRS complex was done at the third day in order to record late potentials (LP). A 8-hour urine sample was collected on the third day and urinary albumin concentration was measured by a radioimmunologic method. ML was defined as an albumin excretion rate of 20-200 μg/min. Symptomatic ventricular tachycardia/fibrillation (VT/VF), which occurred after the first 48 hours, were defined as malignant arrythmias.
Results: Twenty six out of 201 pts (12.9%) developed VT/VF after the first 48 hours of hospitalization. Univariate logistic regression analysis revealed that the presence of VT/VF was predicted by WBC (Exp(b)=1.179, p=0.002), CK-MB (Exp(b)=1.005, p=0.006) and the presence of ML (Exp(b)=2.968, p=0.016). Multiple logistic regression analysis which included the above variables, showed that only WBC and ML were independent predictors of VT/VF (Exp(b)=1.12, p=0.046 and Exp(b)=3.02, p=0.029, respectively). It is worth to note that the presence of LP and EF, did not correlate with the development of VT/VF.
Conclusions: WBC and ML, but not LP and EF are independent predictors of late VT/VF, in non-diabetic patients with AMI. Thus, the development of late ventricular arrhythmias in AMI is possibly more closely related to the coexisting inflammatory process and increased endothelial permeability, rather than to the heterogeneity of impulse propagation around the infarct size.

P1208 Recombinant human C-reactive protein inhibits platelet function independent of Fcγ RIIa-R-H131 genotype

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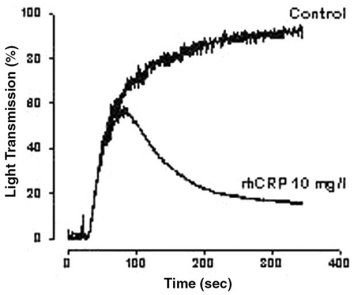
Background: Elevated levels of C-reactive protein (CRP) are associated with cardiovascular events. CRP is an acute-phase reactant reported to modify platelet function depending on its physiochemical state and purity. Recently, it has been proposed that the immunoglobulin receptor FcgammaRIIa that is also expressed on the platelet membrane surface binds CRP in an allele-specific manner. We studied the effect of recombinant human CRP (rhCRP) on platelet function and the potential involvement of FcgammaRIIa-R-H131 polymorphism.
Methods and Results: Agonist-induced platelet aggregation (5μM ADP and 4μg/ml collagen) was studied in 19 healthy subjects with known FcgammaRIIa-R-H131 genotype (5 HH, 7 RH, and 7 RR, determined with fluorogenic probes) after 10 minutes incubation with either rhCRP or PBS as a control. Incubation with rhCRP resulted in a pronounced reduction of maximal aggregation (ADP: from 99.6 ± 12.2% to 43.6 ± 14.8%, P < 0.001), decrease of ATP release (ADP: from 1.23 ± 1.37 to 0.01 ± 0.05 nmol, P < 0.001) and increase of deaggregation (ADP: from 5.1 ± 15.4% to 72.6 ± 22.8%, P < 0.001). Original traces of a typical experiment are shown in the figure. The inhibitory effect of rhCRP on ADP-induced aggregation was dose-dependent (EC50 = 0.05). The inhibitory effect of rhCRP was independent of FcgammaRIIa-R-H131 genotype [reduction of max. ADP-induced aggregation: 58.1 ± 9.9% (HH), 52.7 ± 17.2% (RH) and 58.7 ± 12.4% (RR), P = 0.69].
Conclusions: rhCRP is a potent inhibitor of agonist-induced platelet aggregation. The data does not suggest allele-specific binding of rhCRP to platelet FcgammaRIIa as the underlying mechanism.



rhCRP inhibits platelet aggregation.

P1209 Serum levels of interleukin-10 are inversely related to future events in patients with acute myocardial infarction

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Background: Inflammation is generally accepted to play a major role in the development of atherosclerosis. Increased attention has therefore been paid to markers of inflammatory activity, and several studies have shown pro-inflammatory markers to be related to clinical events in patients with coronary heart disease. Little is known about the role of anti-inflammatory cytokines in atherosclerosis. In the present study we have investigated the levels of IL-10 in patients after an acute myocardial infarction (AMI) and related them to future clinical events during 4-years follow-up.
Methods: The present investigation is a sub-study of the WARIS-II trial in which patients with an AMI had been randomly assigned to treatment with aspirin alone, aspirin and warfarin or warfarin alone and followed for 4 years. The clinical end-points were pre-defined as a composite of death, myocardial reinfarction and stroke. The present population consisted of 239 patients randomly recruited. Fasting blood samples were collected 3 months after the AMI for determination of serum IL-10. Commercial ELISA method (R&D Systems Europe) was used.
Results: No differences in IL-10 levels were observed between the treatment groups. During the 4-years follow-up, 27 patients suffered a primary endpoint. In those patients the levels of IL-10 were significantly lower compared to those without: (medians) 1.79 vs 3.00 pg/mL, p<0.0001. When separating the levels of IL-10 into quartiles there was a highly significant trend for increased event rate with lower levels of IL-10 (p for trend <0.0001) with an odds ratio of 6.69 (95% CI 2.09-23.7) when dicotomizing the levels (p=0.0001).
Conclusion: The results show prospectively that an anti-inflammatory cytokine may be protective for future clinical events in patients who have suffered an AMI. These findings contribute to the understanding that anti-inflammatory activity is implicated in the progression of atherothrombosis.

P1210 Early interleukin-1 receptor antagonist elevation in patients with acute myocardial infarction

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Background: Inflammatory markers are elevated in patients (pts) with unstable coronary syndromes, but interleukin-1 receptor antagonist (IL-1Ra) levels during the early phases of acute myocardial infarction (MI) were not previously investigated. Goal of the study was to evaluate IL-1Ra levels in pts with ST-segment elevation MI upon Emergency Department (ED) admission and to assess sensitivity of such determination in comparison with common markers of myocardial necrosis.
Methods: IL-1Ra levels were measured in 44 consecutive pts with MI and compared with creatin-kinase (CK), CK-MB, Troponin I, Myoglobin and C-reactive protein (CRP).
Results: On admission, 82% of pts had elevated (>230 pg/ml) IL-1Ra levels vs 41% of pts with raised CK (P=0.001), CK-MB (45%, P=0.002), Troponin I (57%, P=0.027), Myoglobin (48%, P=0.004) and CRP (57%, P=0.019) levels. IL-1Ra values were significantly higher in pts with heralded MI vs those without pre-infarction angina [671 vs 320 pg/ml, P=0.013]. Sensitivity of IL-1Ra determination increased to 86% if pre-coronary time was ≤3 hours and to 91% if heralded infarction occurred.
Conclusions: Our study indicates that, unlike markers of necrosis, elevation of IL-1Ra levels occurs early in pts with MI, is more significant in those with heralded infarction and with pre-coronary time ≤3 hours, and it precedes the release of markers of necrosis. Thus, IL-1Ra determination may be an important early adjuvant to diagnosis of MI in the Emergency Department.

P1211 Early C-reactive protein levels in acute myocardial infarction predicts short- and long-term prognosis

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C-reactive protein (CRP) reflects the intensity of the inflammatory process associated with atherosclerosis and may be more predictive than low density lipoprotein levels in predicting coronary events. Assuming that very early CRP levels are reflective of the intensity of the inflammation preceding and precipitating acute myocardial infarction (AMI), this study was prospectively performed to evaluate its predictive power in assessing short and long term prognosis in AMI. Methods: 118 patients with AMI, 88 men, age 63.3±8 yrs, were evaluated, and CRP was assessed within the first 6 hours after the onset of chest pains. Results: Average CRP was 15.7±14.1 mg/l. CRP levels increased with higher killip class, 11.2±5 in class 1, and 62±7 mg/d in class 4, $p<0.01$. A negative correlation was found between CRP and left ventricular ejection fraction, 32.3±10 (EF<30%) and 9±4 mg/l(EF>40%), $p<0.01$. Higher CRP values were found in patients with 3 vessel coronary artery disease 20.7±8, vs 8.7±4 in 2 and 1 vessel disease, $p< 0.05$. Patients with in-hospital events had higher CRP, 33.7±10 vs 12.1±5 mg/l,$p<0.001$. At 1 year follow up 8 patients died, with CRP 45.2±17 higher than the average 15.7±14.1 mg/l, $p<0.01$. Admission CRP was similar to the average in those re-admitted with unstable angina and re-infarction 11.6±9 and those who had coronary bypass surgery 13.3±16 mg/dl. Conclusions: Very early CRP levels in patients with AMI predicts functional capacity, ventricular function, extent of coronary disease, early and short term complications and 1 year mortality but not late recurrent myocardial ischemic events.

CARDIOVASCULAR DISEASE IN WOMEN: VARIA

P1212 Oral 17β-oestradiol treatment increases serum C-reactive protein levels but not necessarily global inflammatory activity in postmenopausal women

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Recent secondary and primary prevention trials have failed to demonstrate beneficial effects of oral hormone replacement therapy in the prevention of CHD in postmenopausal women. An explanation for these unexpected findings has been suggested by the observation that oral oestrogen increases the levels of C-reactive protein (CRP) which is an independent risk factor for CHD in healthy men and women. CRP is and acute phase protein and the most potent and broadly effective stimulant of its production by human hepatocytes appears to be interleukin-6 (IL-6). Therefore, we studied the effects of oral and transdermal 17beta-oestradiol (E2) administration on serum CRP and bioactive IL-6 levels as well as the spontaneous production of bioactive IL-6 by peripheral blood mononuclear cells (PBMC) of postmenopausal women.

Methods: Forty five healthy postmenopausal women were randomized to receive either oral micronized E2 (2mg/day, n=20) or transdermal E2 (50μg/day, n=25) for 12 months. Preparations used in the study also contained sequential norethisterone acetate for the 10 days in a 28 day cycle at 1mg/day in the oral group (Trisequens, Novo Nordisk) and for the 14 days at 250μg/day in the transdermal group (Estalis Sequi, Novartis Pharma) to induce endometrial shredding. Blood samples were drawn at baseline and after 6 and 12 months of E2 treatment during "oestrogen only" phase to adjust for the progestin effect. Serum CRP levels were measured using highly sensitive latex-enhanced immunoturbidimetric assay and an automated clinical chemistry analyzer (CRP High sensitivity assay, RANDOX Laboratories Ltd., UK). Bioactive IL-6 levels in the sera and supernatants from PBMC cultures were measured using a hybrydoma B9 bioassay.

Results: Compared to baseline values, serum CRP levels in women treated with oral E2 increased significantly after 6 and 12 months of the therapy by 178±57% and 210±45% respectively ($p<0.05$). In contrast, transdermal administration of E2 did not elevate serum CRP levels after 6 and 12 months of treatment. Serum bioactive IL-6 levels did not change significantly during the study in both groups. However, the spontaneous production of bioactive IL-6 by the non-stimulated PBMC of postmenopausal women into the culture supernatants was significantly lower after 12 months of E2 therapy in both groups ($p<0.05$).

Conclusions: Our results strongly suggest that the increase in serum CRP levels during oral oestrogen treatment is not mediated by the enhancement of IL-6 production by the immune cells but is rather caused by the hepatic first-pass metabolism effect.

P1213 Endothelial-dependent vasodilatation and the incidence of atrial fibrillation in hypertensive postmenopausal women. A long-term follow-up study

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Background: Hypertensive postmenopausal women (PW) have been shown to have abnormal endothelial-dependent vasodilatation (EDVD). However, the prognostic role of an impaired EDVD has been not investigated in terms of incidence of atrial fibrillation (AF) that require hospitalization. AF is a common complication of hypertensive cardiomyopathy, that is associated with often recurrent hospitalization and therefore significant increase in hospital costs. This study was designated to investigate the relationship between abnormal EDVD and long-term incidence of AF. It also allowed the assessment of the incidence of AF in a less studied specific population.

Method: 213 PW (mean age: 63±10 years) with newly diagnosed mild to moderate hypertension and sinus rhythm at the baseline electrocardiogram were enrolled. All patients (pts) underwent an ultrasonographic study of the brachial artery and were then followed-up for a mean period of 80 months (range: 65-92). Pts were seen in our outpatients clinic at regular intervals (every 6 months). In the interim, pts received an "optimal" antihypertensive treatment, in order to maintain a systolic blood pressure (BP) < 140 and a diastolic BP < 90 mmHg. Women were excluded from the study in case of BP $> 140/90$ mmHg in two or more consecutive controls. Women with previous cardio and cerebrovascular diseases were also excluded. All cases were validated by a review of hospital records. EDVD was evaluated by measuring the diameter of the brachial artery before and during reactive hyperaemia (induced after deflation of a blood pressure cuff inflated to suprasystolic pressure for 5 minutes) and was calculated from the diameters as: (reactive hyperaemia - baseline)/baseline %.

Results: The population was divided into tertiles according to the distribution of EDVD. During the follow-up we noticed 27 episodes of AF that required hospitalization: 17 (62.9%) in the lowest tertile, 6 (22.2%) in the intermediate tertile, and 4 (14.9%) episodes in the highest tertile of EDVD. The relative risk (RR) of future episodes of AF for women in the lowest vs highest tertile was 4.3 (95% confidence interval [CI]: from 2.7 to 5.6; $p < 0.001$). A significant association persisted after adjustment for multiple factors: age, body mass index, mean BP values at admission, use of beta-blockers and use of ACE-inhibitor during follow-up. Multivariate RR for the lowest vs highest tertile was 1.5 (95% CI: 1.1-2.2; $p < 0.05$).

Conclusions: Our data support a possible role for endothelial dysfunction in the genesis of AF in PW.

P1214 Short term treatment with edaravone, a free radical scavenger, reduced vascular injury response in rat carotid artery and the vasoprotection was more favorable in ovariectomized females than males

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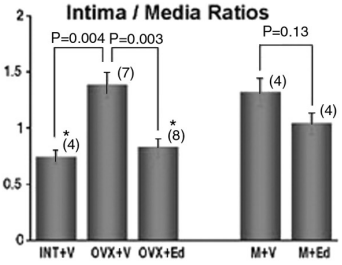
Background: Increased free radicals found in estrogen depletion may be involved in the pathogenesis of atherosclerosis in postmenopausal women. In this study, we examined the effect of edaravone (free radical scavenger) on the vascular injury response.

Methods: Treatment groups; (a) intact ovary female (INT)+vehicle(V), (b) ovariectomized female (OVX)+V, (c) OVX+edaravone 30mg/kg/day (Ed), (e) male (M)+V, and (f) M+Ed. Each treatment was initiated soon after the balloon injury of the right common carotid artery and continued for 4 days. Two weeks later, the intima to media ratios of injured arteries were evaluated.



Results and Conclusion: the observation that edaravone effectively prevented the injury response in OVX but could not in male, suggests the potential use of free radical scavenger for the vasoprotection in postmenopausal women.

P1215 Short-term transdermal oestradiol enhances nitric oxide synthase III and oestrogen receptor mRNA expression in arteries of women with coronary artery disease

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Objective: The knowledge of the mechanisms by which estradiol E2 exerts its vascular effects may facilitate the design of newer drugs with reduced side effects that might be effective in the primary and secondary prevention of coronary heart disease. Our aim was to analyze the short-term effects of (E2) on the expression of nitric oxide synthase (NOS III) and estrogen receptors (ER) a and b.
Methods: We studied 20 post-menopausal women with coronary artery disease (CAD) undergoing CABG surgery with left internal mammary artery (LIMA) grafting. Ten women received treatment with transdermal E2 prior to surgery (48-72 hours) and 10 did not. The distal segment of the LIMA was excised and processed to determine mRNA expression of NOS III and ER a and b (reverse transcription reaction and amplification with polymerase chain reaction). Semiquantitative expression of NOS III and ER a and b was measured in arbitrary densitometric units (ADUs) relative to GPdH expression, constitutively expressed in human vessels. Plasma levels of E2 were also determined.
Results: E2 plasma levels were similar in both groups of women at baseline, but increased after E2 treatment (from 11.9 $\pm$ 4.2 to 37.0 $\pm$ 9.4 pg/dl, $p < 0.01$). NOS III and ER a and b mRNA expression was enhanced in women treated with E2 as compared to the control group (NOS III: 1.7 $\pm$ 0.6 vs 1.3 $\pm$ 0.3 ADUs, p = 0.04; ER a: 6.5 $\pm$ 6.8 vs 1.8 $\pm$ 1.2 ADUs, p = 0.04; ER b: 4.2 $\pm$ 3.4 vs 1.5 $\pm$ 0.6 ADUs, p = 0.03). ER a, but not ER b expression, correlated with NOS III expression (r = 0.70, $p< 0.001$).
Conclusions: After short-term treatment with E2, NOS III, ER a, and especially ER b mRNA expression was enhanced in arterial vessels of postmenopausal women with CAD. NOS III mRNA expression was only correlated to ER a expression. Both ER may have a role in the vascular effects of E2, although NOS III activation could be more mediated by ER a.

P1216 Preeclampsia is a risk factor for coronary artery diasease in women

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Purpose: Endothelial dysfunction is known to be one of the pathophysiological mechanisms in coronary artery disease (CAD) and preeclampsia. CAD and preeclampsia share also common risk factors. History of preeclampsia could indicate increased risk for CAD.
Methods: The patients were 141 parous women under 65 years of age with angiographically documented CAD.There were two age matched control groups, one unselected (outpatient) and one selected (hospital), altogether 211 women without diagnosed CAD. Obsteric history and CAD risk factors were asked with questionnaires and checked from hospital records.
Results: The history of preeclampsia in the first and in any pregnancy were observed more often in CAD patients (17-21%) than in controls (1.8-3.0%, $P<0.005$). In logistic regression analysis age of >55 years (OR= 2,7, 95% CI 1.4-5.4), BMI >28 kg/m^2 (OR=2.3, 95% CI 1.2-4.7), current smoking (OR= 4.2, 95% CI 1.8-9.8), hypertension (OR= 6.5, 95% CI 3.2-13.4), preeclampsia in any pregnancy (OR=4.6, 95% CI 1.2-18) and multiparity (OR= 3.3, 95% CI 1.6-6.9) were independent risk factors for CAD whereas current hormone replacement therapy and time length from menarche to menopause were not.
Conclusions: This study suggests that preeclampsia is an independent risk factor for developing CAD in relatively young women.

P1217 Coronary heart disease risk profile: comparison between Arab and Jewish women in Israel

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Background: Little is known on CHD and risk factor distributions among Arabs in Israel. We showed that CHD mortality and all-cause mortality rates were significantly higher among Arab residents of Jerusalem (males and females) than among Jewish residents at ages between 35-74 years.The risk factor profile of CHD among Arab women in Israel is unknown, but there are clear dietary differences between Arab and Jewish women in Israel (consumption of oils), socioeconomic inequalities and differences in medical care.
Aim: to establish and compare the risk profile of CHD between Arab and Jewish women who underwent coronary angiography at the Hadassah University Hospital and were found to have CAD.
Methods: Multiple risk factors were compared between 800 women residents of Jerusalem (512 Jewish women, 288 Arab) according to a pre-determined protocol.
Results: We found a number of statistically significant differences between the two groups with respect to the life style, e.g., physical activity, alcohol and olive oil consumption as well as socio-economic status.

Demographics

	Arab (n=228)	Jewish (n=512)	p value
Age	64 $\pm$ 9	69 $\pm$ 9	<0.001
Family History	34.7%	55.5%	0.05
Smoking	19.4%	24.2%	0.484
Diabetes Melitus	63.9%	42.2%	0.05
Hypertension	66.7%	74.8%	0.252
Hyperlipidemia	72.2%	79.4%	0.295
Physical activity	11.1%	44.5%	<0.001
Olive oil	92.2%	67.5%	<0.001
Alcohol	2.8%	28.6%	<0.001
Socio-economic status	Low: 84.7%	Low: 7.5%	<0.001
Socio-economic status	Average: 15.3%	Average: 56.3%	<0.001

Conclusions: In addition to a higher incidence of diabetes, the life style of Arab women in Jerusalem, compared with that of Jewish women, seems to increase the risk factors leading to CAD. The results may help to invest more effort in reducing the incidence of CAD by early detection, modification and prevention of the appropriate risk factors among this ethnic group.

P1218 Effect of high-density lipoprotein cholesterol levels on carotid artery geometry and oxidation markers in a Mediterranean female population

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Background and Purpose: Women generally have higher plasma HDL-C concentration than men and this difference is believed to account in part for their lower risk of coronary heart disease. In the present analysis, we evaluated the effect of HDL-C concentrations on carotid artery geometry and oxidation markers in a large sample of asymptomatic middle-aged women.
Methods: Over 5000 women (n = 5062, aged 30-69 years) living in the area of Naples, Southern Italy, were recruited for a prospective, currently ongoing, study on the etiology of cardiovascular disease and cancer in the female population (the Progetto ATENA study). A sample of 310 participants (those potentially at higher atherosclerotic risk) underwent high resolution B-mode ultrasound examination and the intima-media thickness and diameters of common carotid artery were measured using a semiautomated computerized program. In addition to routine biochemical tests, these women had the determination of serum IgG antibody titer against oxidized-low-density-lipoproteins and measurement of thiobarbituric acid reactive substances and total radical-trapping activity potential of plasma. The study population was classified into quartiles according to HDL-C concentrations.
Results: Women in the upper quartile (HDL-C $\geq$ 73 mg/dL) had significantly lower body mass index and waist to hip ratio values, and triglycerides concentrations when compared with women in the first 3 quartiles. A linear negative association was found between HDL-C and carotid intima-media thickness (1.07 $\pm$ 0.16 mm for the IV quartile vs 1.10 $\pm$ 0.20 mm for the III quartile, 1.15 $\pm$ 0.26 mm for the II quartile and 1.19 $\pm$ 0.23 mm for the I quartile; $p < 0.01$ by ANOVA). No difference was found between groups with regard to carotid diameters and oxidation markers. After adjustment for other cardiovascular risk factors, women in the highest versus the lowest quartile of HDL-C had a decreased risk of carotid intima-media thickening (OR 0.30, 95% CI 0.12-0.74).
Conclusions: In asymptomatic middle-aged women, HDL-C levels were independently and negatively associated with preclinical atherosclerotic changes of the carotid artery wall. High HDL-C concentrations were not related to a decreased oxidative stress.

P1219 Normalization of elevated plasma levels of aminoterminal pro-brain natriuretic peptide after surgically induced massive weight-loss in morbid obese females

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Obesity is a risk factor for heart failure in both sexes but the population attributable risk of obesity is higher in women than in men.
Purpose: The aim of our study was to investigate NT-proBNP levels in female patients with morbid obesity before and after a gastric banding procedure.
Methods: 50 female patients with morbid obesity (body mass index (BMI) 40,1-68,4) lacking physical and radiological signs of heart failure were investigated before and 12 months after a gastric banding procedure and compared to an age and sex matched normal-weight control group. NT-proBNP were analyzed in triplicate with a competitive enzyme immuno assay test kit (NT-proBNP/BIOMEDICA) in diluted plasma on an automated system (MINI BOS-BIOMEDICA, Vienna). Samples <250fmol/ml were considered normal, 251-350 borderline and >350 as abnormal.
Results: NT-pro BNP levels were highly abnormal in females with morbid obesity (mean 352,8fmol/ml, 53,1% within pathological range) before surgery. One year after gastric banding procedure BMI decreased from 45,5 to 38,0, but was still above 30 in 94% of patients. NT-proBNP was now markedly lower (mean 203fml/ml), only three patients were now in the pathological range but was still significantly elevated when compared to normal-weight subjects. (Table). There was no correlation of NT-proBNP with weight decrease but a significant correlation with baseline levels of NT-proBNP and age.

	Pts before gastric banding	Pts 1 year after gastric banding	Normal-weight controls	p (col B vs C)
N	50	50	52	
BMI (kg/m^2)	45,5	38,0	20,9	<0,0001
Weight (kg)	123,8	110,2	58,5	<0,0001
NT-proBNP	352,8	203,4	160,2	<0,0001

Conclusion: NT-proBNP levels are elevated in the majority of females with morbid obesity but normalize after weight reduction despite persisting obesity. As left ventricular hypertrophy and dysfunction are typical consequences of morbid obesity the measurement of NT-proBNP could be seen as an inexpensive screening method in a highly endangered population.

P1220 Phytoestrogens do not abolish the protective effect of preconditioning in vivo

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Aim: Phytoestrogens are present in high concentrations in the diet of East Asian subjects and may contribute to the strikingly low incidence of atherosclerosis and coronary heart disease seen in this population. We have previously shown that conjugated estrogens protect ischemic myocardium in ovariectomized female rabbits. We now investigated the effect of genistein, a phytoestrogen derived from soy diet, on myocardial infarct size.
Methods: We studied 3 groups of sexually mature New Zealand white female rabbits. Group A (n=8) were normal controls, group B (n=14) were ovariectomized (OVX) 4 weeks prior to the experiment and group C (n=10) 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, with (subgroup 1) or without (subgroup 2) preconditioning (PC) with two cycles of 5 minutes ischemia - 10 minutes reperfusion prior to sustained ischemia. 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%).
Results; We analyzed our results with one way analysis of variance (ANOVA) and used the Least Square Differences test for post hoc analysis. There were significant differences between the groups (p=0.0003). The groups with preconditioning had significantly smaller infarcts compared to those without (A1 vs A2, B1 vs B2 and C1 vs C2, p<0.01). Genistein did not protect ischemic myocardium (B2 vs C2, p=NS). Estrogen deprivation for 4 weeks was not associated with larger myocardial infarction (A2 vs B2, p=NS) (table).

	A1 (n=4)	A2 (n=4)	B1 (n=6)	B2 (n=8)	C1 (n=5)	C2 (n=5)
I/R%	11.34±2.07*	43.79±2.96	18.53±2.36*	43.05±8.37	10.61±1.63*	44.5±5.47

*: p<0.01 vs non PC groups

Conclusions: Phytoestrogens do not abolish the protective effect of preconditioning in OVX rabbits. Protection remains in animals with intact gonads as well as estrogen deprived. Estrogen deprivation is not associated with larger myocardial infarction whereas treatment with phytoestrogens does not reduce it.

P1221 N terminal pro-brain natriuretic peptide in healthy elderly men and women: influence of age, gender

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Background: In previous studies on healthy adults plasma levels of Brain Naturetic Peptide (BNP) have been shown to increase with age and differ according to gender with higher basal levels found in women than in men. No such data is available for the N-terminal part of BNP's prohormone, NT-proBNP.
Study Population: 407 apparently healthy men and women (between 40-75 years old, median age 65) recruited as control subjects in a case-control study on cardiovascular risk factors in an elderly population during 2000-2001. Subjects were screened by history and clinical examination. Exclusion criteria were established cardiovascular disease, diabetes mellitus or other chronic disease, or cardiovascular medication.
Methods: NT-proBNP was determined using Elecsys proBNP sandwich immunoassay on an Elecsys 2010(Roche Diagnostics).

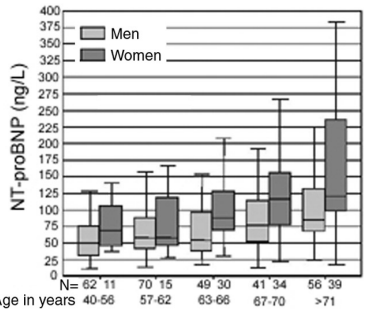

Figure 1. Boxplots depicting 10th, 25th, 50th, 75th and 90th percentiles of NT-proBNP according to age and gender.

Conclusion: This study corroborates previous findings of the impact of gender and age on natriuretic peptides and contributes with novel information concerning levels of NT-proBNP in healthy elderly men and women.

CARDIOVASCULAR DISEASE IN WOMEN: THE GENDER DEBATE IS STILL ALIVE

P1222 Differences in utilization of diagnostic tools between men and women accessing the emergency department for chest pain: is the gender gap closing?

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Gender-specific differences in intensity of cardiovascular care are well-recognized. Recent data, however, have suggested that utilisation rates of cardiac services are not significantly dependent upon sex.
Purpose: Aim of this study was to verify whether differences in use of diagnostic tools occur between men and women accessing the emergency department (ED) for chest pain.
Methods: During 2001, 4,843 consecutive patients were admitted to the ED of a large urban tertiary referral hospital because of chest pain and a possible myocardial infarction (MI). They were 3,095 men (age: 63±21 years) and 1,748 women (age: 57±19 years). At entry, all patients were risk-stratified on the basis of AHCPR's classification and were then managed according to recently developed ED critical pathways. Pathways include a protocol for ruling out MI (i.e. q3 hour ECGs and serum markers of myocardial necrosis for 9 hours) as well as pre-specified indications for Doppler echocardiography, continuous 12-lead ST-segment monitoring, and exercise stress testing.
Results: During a mean stay of 12±10 hours at the ED, no significant differences between men and women were seen in the use of Doppler echocardiography (32% vs 38%, NS), continuous 12-lead ST-segment monitoring (15% vs 10%, NS), or exercise stress testing (18% vs 11%, NS). At the end of the observation period at ED, a similar proportion of men and women was admitted to the hospital (39% vs 33%, NS). A MI could be diagnosed at ED in 191 men and 88 women (6% vs 5%, NS), while it was subsequently detected during hospital stay in additional 111 men and other 62 women (4% vs 4%, NS). Diagnostic accuracy at ED for MI was similar for men and women (63% vs 59%, NS). In-hospital mortality was not significantly different between men and women (2.8% vs 1.9%, NS).
Conclusions: In patients accessing the ED because of chest pain, men and women are similarly likely to undergo diagnostic tests and a MI is usually diagnosed irrespective of sex. The finding that, in the era of critical pathways, sex-specific differences in cardiovascular care are no more evident supports the concept that gender gap for acute chest pain is eventually closing.

P1223 Women are treated less aggressively than men after a high-risk myocardial infarction

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Background: Previous reports have indicated that gender-related differences exist in the way patients with coronary artery disease are managed. The OPTIMAAL trial included 5477 patients with acute myocardial infarction (AMI) and clinical evidence of heart failure or left ventricular dysfunction, within 10 days after AMI, at 329 centres in seven western European countries. Patients were, in addition to conventional management, randomized to treatment with either losartan or captopril. The aim of this analysis was to evaluate non-randomized management patterns in women as compared to men.
Results: There were 1575 (28.8%) women and 3902 (71.2%) men who were followed for an average of 2.7 ($\pm$0.9) years. The table presents data on the management of the AMI during the initial phase and during follow-up. Significantly fewer women were revascularized during follow-up. Women were older than men, 70.9($\pm$9.4) versus 66.0($\pm$9.7) years respectively; $p<0.0001$, at the time of AMI. However, even after adjusting for age, women were less likely to be revascularized (risk ratio 0.82; p=0.001), mainly due to a lower rate of bypass surgery (risk ratio 0.71; $p<0.001$).

Treatment	Women	Men	p value
Thrombolytics	784 (49.8%)	2196 (56.3%)	<0.0001
Beta-blockers	1208 (76.7%)	3098 (79.4%)	0.029
Aspirin	1495 (94.9%)	3739 (95.8%)	0.15
Statins	484 (30.7%)	1198 (30.7%)	0.99
Revascularization (CABG and/or PCI)	373 (23.7%)	1299 (33.3%)	<0.001
CABG	162 (10.3%)	617 (15.8%)	<0.001
PCI	222 (14.1%)	736 (18.9%)	0.001

CABG = Coronary artery bypass grafting, PCI = Percutaneous coronary intervention

Conclusion: Our data demonstrates that women are less likely to receive thrombolytic treatment than men, and are less likely to be revascularized after a high-risk AMI. Some, but not all of this difference is explained by a higher age in women. However, the age difference put women at a higher risk of adverse events, which should not result in less aggressive management.

P1224 Equal survival with equally aggressive primary percutaneous intervention in women and men with acute myocardial infarction – insights from a single centre 2001–2002 registry

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Background: Prior studies have indicated that women have worse prognosis in acute myocardial infarction (AMI) than men and there are conflicting data whether this is attributable to gender per se, higher baseline risk profile or less intensive treatment. Most such studies were performed before the era of widespread use of stents and glycoprotein receptor inhibitors in primary percutaneous intervention (pPCI).
Methods: Baseline clinical characteristics, procedural data and in-hospital outcomes were evaluated by means of a prospective registry of 882 consecutive unselected patients treated in years 2001-2002 with pPCI within 12 hours of AMI. The setting was a single tertiary center dedicated to providing round-the-clock cathlab service to the region.
Results: Women (n=243) were older than men (n=639), had more often diabetes or hypertension and were less often current/past smokers. Rate of stenting (70% of women vs. 78% of men, p=0.02) and abciximab use (46% and 48%, NS) was high in both sexes. Unadjusted mortality was higher in women (7% vs. 3%, p=0.01) but after controlling for baseline clinical variables and stent and abciximab use female gender was not an independent predictor of death. In patients <65 years there was no difference between men and women in stenting rate, abciximab use and early mortality (3% vs. 2%, NS). In patients >65 years women and men had similar rate of abciximab use but women received a stent less often than men did and demonstrated a trend towards higher mortality (11% vs 6%, p=0.10).
Conclusion: If treated equally aggressively with pPCI with stents and glycoprotein receptor inhibitors women and men with AMI have similar in-hospital outcome. Female gender is not an independent adverse prognostic factor.

P1225 Does admission ST depression and troponin impact the use of angiography and revascularization differently in men and women with acute coronary syndromes (ACS)? Insights from the GUSTO-IV ACS trial

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Background: Although ECGs are used qualitatively for risk stratification, quantification of ST depression (STdep) along with troponin (tpn) may offer additional insight into the triage to angiography (angio) and revascularisation (revasc(PCI/CABG))in men vs women with ACS.
Methods: GUSTO-IV ACS patients with either elevated tpn or STdep had baseline ECGs read in a central core laboratory by blinded observers. Angio was not recommended $\leq$12 hours of study-drug (abciximab/placebo) infusion.
Results: Of 7227 patients in this analysis, 36.9% underwent angio within 30 days (40.8% (1826men), 30.5% (891women), $p<0.001$). Angio rates did not vary significantly in men according to STdep or tpn (table). In women, angio rate tended to decrease as STdep increased (p=0.08); however, angio rate increased with rising tpn (p=0.01). After baseline adjustment, women were still less likely than men to undergo angio as STdep rose (no STdep: OR 0.66 95%CI (0.29,0.79); 1mm: 0.51 (0.39,0.66); $\geq$2mm: 0.48 (0.29,0.79), p-interaction=0.04). In contrast, angio was more likely to occur in women than men as tpn increased ($\leq$0.01μg/L: 0.66 (0.52,0.85); >0.01μg/L: 0.97 (0.75,1.25), p-interaction<0.001). Of those with angio, more men underwent revasc within 30 days than women (52.1% vs 42.6%, $p<0.001$). Increasing STdep was not significantly associated with revasc rates in men, but unlike angio, was positively so in women ($p<0.001$, table). After adjustment, women were more likely than men to undergo revasc within 30 days as STdep increased (no STdep: 0.58 (0.44,0.78); 1mm: 0.95 (0.67,1.35); $\geq$2mm: 0.58 (0.21,1.62) p-interaction<0.02). Elevated tpn was associated with higher rates of revasc in both men and women ($p<0.001$); however, the interaction was not significant.

	F, angio % (N)	M, angio % (N)	F, revasc % (N)	M, revasc % (N)
no STdep (2573)	33.2 (303)	40.2 (667)	34.0 (103)	50.1 (334)
1mm (4222)	29.0(490)	41.1 (1042)	48.6 (238)	53.4 (556)
>=2mm (432)	29.6 (45)	41.8 (117)	42.2 (19)	57.3 (67)
Tpn $\leq$0.01 (1904)	25.2 (251)	40.4 (367)	29.9 (75)	43.1 (158)
Tpn >0.01 (4701)	31.8 (489)	40.4 (1276)	49.1 (240)	55.0 (702)

Conclusion: STdep and tpn are differentially associated with angio and subsequent revasc in men and women. Further investigation into the multifactorial content vs process of care issues modulating this paradox is warranted.

P1226 Gender-related differences in outcome after myocardial infarction: possible role of survival hormones

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Purpose: Reasons for the worse age-adjusted prognosis of women with ST-elevation acute myocardial infarction (STEMI) vs men are unclear. Insulin-like growth factor-1 (IGF-1) and dehydroepiandrosterone sulphate (DHEAS) are increasingly recognised survival hormones, lower values signalling worse outcomes. We investigated possible gender-differences in circulating IGF-1 and DHEAS in the acute and chronic phases of MI.
Methods: Venous blood was collected soon after admission (146±74 min. from symptom onset), at discharge, and after 18 months in 44 consecutive patients, 50 to 80 yrs (66±10) with STEMI (8 women, 75±4 yrs; 36 men, 63±10 yrs). Matched controls (n=29, 60±10 yrs) were also investigated. Serum total (ng/ml) and free IGF-1 (pg/ml) were measured by RIA, and DHEAS (ng/dl) by electrochemiluminescence. Values are age-adjusted; comparisons with controls are sex-matched.
Results (Table): Total IGF-1 was lower in female vs male patients at all 3 times (p=0.02, p=0.004 and p=0.036). Women, but not men, had lower total IGF-1 at discharge vs controls (p=0.017). Patients' free IGF-1 did not differ significantly by gender; values increased at follow-up vs admission in both genders ($p<0.040$); in females, but not males, admission values were lower vs controls (p=0.003). As expected, DHEAS was significantly higher on admission vs subsequent times;levels, however, were lower in females vs males on admission (p=0.006) and at follow-up (p=0.047). At follow-up, DHEAS was lower in women (p=0.03), but higher in men (p=0.01), vs controls. At follow-up, women experienced more hard end-points (death, recurrent infarction) vs men, even after age-adjustment (p=0.005).

Total and free IGF-1 and DHEAS

	Adm W	Adm M	Disc W	Disc M	F/U W	F/U M	Cont W	Cont M
T IGF-1	1.1><0.6	2.1><1.2	0.6><0.7	2.0><1.3	1.0><1.3	2.7><1.9	1.8><1.4	2><1.3
F IGF-1	5><1	7><6	5><1	6><3	8><3	10><3	15><8	12><9
DHEAS	1.0><0.5	3.0><2.0	0.9><0.5	2.2><1.6	0.6><0.2	2.1><1.6	1.5><0.9	1><0.6

Adm=admission, W=women, M=men, Disc=discharge, F/U=follow-up, Cont=controls, T=total, F=free

Conclusions: In both genders, IGF-1 levels were lowest, and DHEAS levels highest, in the early phases of MI. However, compared to men, female patients exhibited persistently lower total IGF-1 and DHEAS concentrations. These gender-related differences may contribute to explain the worse outcome of women admitted with acute MI.

P1227 Sex differences in rate of thrombolysis in acute ST-elevation myocardial infarction is caused by longer delay times in women

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Background: Previous studies have suggested that women with acute myocardial infarction receive acute thrombolysis to a lesser degree than their male counterparts. The aim of this study was to evaluate if there is a sex-difference in the use of acute thrombolysis in patients with ST-elevation myocardial infarction (STEMI) and, if so, to evaluate if that is due to longer delay times in women, either symptom-to-door-time, door-to-needle-time, or both.
Methods: RIKS-HIA, the Register of Information and Knowledge about Swedish Heart Intensive care Admissions, contains data including 100 variables for each patient admitted to parcipitating ICCU's in Sweden. Data for this study was collected between 1995 and 2000. The study population consists of 29651 patients with STEMI, defined as ST-elevation upon arrival-ECG and the diagnosis of myocardial infarction. Study objectives were delay times and the rate of thrombolysis, the former divided into symptom-to-door-time and door-to-needle time. Rate of thrombolysis was adjusted for age, delay-time and other co-variates using logistic regression analysis.
Results: The study population consisted of 19187 men (65%) and 10464 women (35%). The women were in average 6 years older than the men (73 vs. 67 years, $p<0.001$). Female patients more often had diabetes or hypertension. They more seldom had a previous AMI, were smokers or had undergone CABG or PCI. Women had 36 min longer delay-time from symptom to thrombolysis compared to men (5:09h vs. 4:33h, $p<0.001$). This was due to 40 min longer symptom-to-door-time, (5:46h vs. 5:06h, $p<0.001$) while there was no difference in door-to-needle-time (1:25 vs. 1:20, p=ns). Men had 26% higher odds for receiving acute thrombolysis than women (OR 1.26, CI 1.20-1.32). After age-adjustment they still had 9% higher odds for receiving this treatment (OR 1.09, CI 1.04-1.20), but after adjustment for symptom-to-door-time the difference between the sexes was no longer significant (OR 1.03, CI 0.97-1.10). Further adjustment for other co-variates such as higher co-morbidity did not change this result.
Conclusion: Woman with STEMI more seldom get acute thrombolysis compared to men, even after correcting for age. This is due to longer delay times for women, as they wait longer than men before seeking medical care.

P1228 Outcome differences in women and men after early percutaneous coronary intervention in "high-risk patients with acute coronary syndromes

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Previous studies of acute coronary syndromes (ACS) have suggested gender differences in outcomes and response to conservative and invasive strategies.
Objectives: To determine sex differences in outcomes after early percutaneous intervention (PCI) in high risk patients (pts) with ACS.
Methods and Results: A total of 694 consecutive pts [151 women/233 treated lesions and 543 men/850 treated lesions] were included. Inclusion was limited to ACS pts judged to be at high risk [unstable angina (UA)/non-ST elevation myocardial infarction (MI) with recurrent ischemia/dynamic ST changes (53.6% vs 52.4%) or post infarction UA (46.4% vs 47.6%)] who underwent PCI within 24h of admission if coronary anatomy was deemed suitable. Both groups were well matched as regard clinical and lesions characteristics except that women were older (67.9±11.3 vs 62.3±12.3, with higher prevalence of hypertension and with lower prevalence of thrombus containing lesions (6.9% vs 15.2%). All the lesions were treated with stenting and GPIIb/IIIa inhibitors were used equally (27.1% vs 30.5%). Acute procedural success rates were similar (94% and 93.7%) with similar incidence of in-hospital MACE rates (4% vs 3.8% p=0.56). After a mean follow-up of 564±294 days there were similar mortality rates (2% vs 3.2%), MI (6.7% vs 7.1%) and TLR (7.2% vs 8.3%). The event-free survival was 88±0.3% vs 83±0.3% at 1 yr and 87±0.1% vs 78±0.2% at 2 yrs (p=0.58) for women and men respectively.

Procedural and outcomes data

	Women	Men	p value
QCA: Reference diameter (mm)	3.18 ± 0.63	3.31 ± 0.92	NS
Final MLD (mm)	3.11 ± 0.49	3.35 ± 0.71	NS
Mean stent length (mm)	11.37 ± 7.92	11.93 ± 9.4	NS
In-hospital death/TLR (%)	0	1	NS
In-hospital MI (%)	4	2.8	NS
Follow-up death (%)	2	3.2	NS
Follow-up MI (%)	6.7	7.1	NS
Follow-up TLR (%)	7.1	8.3	NS
MACE (%)	15.74	15.4	NS

Conclusion: High risk women with ACS treated with early coronary stenting of culprit lesion derive the same treatment benefit as men with satisfactory in-hospital and mid-term outcomes.

P1229 Management of acute ST-elevation myocardial infarction differs between the sexes, which may impair the outcome for the female patient

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Background: Previous studies have suggested that women with acute myocardial infarction (AMI) receive less aggressive treatment than men and that they have a poorer prognosis. The aim of this study was to assess sex-differences in acute reperfusion therapy in patients with ST-elevation myocardial infarction (STEMI) and to assess the short- and long-term mortality and evaluate if there is an association between treatment and outcome.
Methods: RIKS-HIA, the Register of Information and Knowledge about Swedish Heart Intensive care Admissions, contains data including 100 variables for each patient admitted to 73 ICCU's in Sweden. Data for this study was collected between 1995 and 2000. The study population consisted of 29651 patients with STEMI. Primary endpoints were reperfusion therapy (acute PCI or thrombolysis), 30-days-mortality and 1-year-mortality, merging the RIKS-HIA database with The National Cause of Death Register. Adjustment for age and other co-variates was done with logistic regression analysis.
Results: The study population consisted of 19187 men (65%) and 10464 women (35%) with mean ages of 67 years (men) and 73 years (women) respectively, $p<0.001$. Women had more often diabetes and/or hypertension but were more seldom smokers, had less previous AMI and/or had undergone less CABG or PCI ($p<0.001$). Men had 42% higher odds of receiving acute reperfusion therapy than women (OR 1.42, CI 1.35-1.49). Correcting for age decreased the OR to 1.14 (CI 1.08- 1.20), but further adjustment for co-morbidity and longer symptom-to-door-time did hardly decrease the OR any further; OR1.13 (CI 1.05-1.21).
30-day-mortality was 66% higher for women (OR 1.66, CI 1.56-1.79) but after adjustment for age the difference in mortality decreased to 9% (OR 1.09, CI 1.02-1.17). Further adjustment for co-morbidity did not change the odds ratio (OR 1.09, CI 1.02-1.17). However, after adjustment for acute reperfusion therapy and/or CABG or PCI during the in-hospital-time, the difference in mortality was no longer significant (OR 1.09, CI 0.99-1.19). 1-year-mortality was 63% higher for women (OR 1.63, CI 1.54-1.73), but after correcting for age, no more difference in mortality between the sexes could be seen(OR 1.06, CI 0.99-1.13).
Conclusion: Woman with STEMI more seldom get acute reperfusion therapy than men, even after correcting for age, co-morbidity and symptom-to-door-time. This may contribute to the higher short-term mortality in women.

P1230 Lower persistence with antihypertensive drugs among women compared to men

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Purpose: The aim of the study was to investigate gender differences in persistence with antihypertensive drugs (AHT).
Methods: Data for this study were obtained from the PHARMO system including pharmacy records and hospitalisations in the Netherlands (n=950,000). Patients between 1997-2001 who newly received monotherapy of AHTs were selected. One-year persistence was defined as the percentage of patients using AHTs at least 270 days and receiving AHT in 3 months after the one-year follow-up period. Persistence was presented as one-year persistence (95%CI). Odds ratios (OR) were calculated with logistic regression and adjusted for age, use of antidiabetics and lipid lowering drugs, and prior cardiovascular hospitalizations.
Results: In the period 1997-2001, 17,113 patients newly received at least one AHT prescription with a follow-up >15 months. Of these patients, random samples of 500 patients per drug class were drawn. Persistence was highest in angiotensin II receptor blockers (ARBs) (62.1%), progressively lower in ACE-inhibitors (60.2%), betablockers (35.5%), calciumchannelblockers (34.7%), and diuretics (33.0%), resulting in the highest OR of 3.3 [95%CI: 2.5-4.4] for ARBs compared to diuretics. The persistence of AHT use in women is substantially lower than in men (40.4% versus 50.3%, OR 0.7 [95%CI: 0.6-0.8]). Results of gender differences are further presented in Table 1.
Conclusions: These results demonstrate marked differences in persistence between AHT classes, with the highest persistence for ARBs and lowest for diuretics. Women were less persistent with their AHT compared to men. This low persistence leads to suboptimal treatment with substantial consequences. Especially in women, more improvement can be gained to improve their cardiovascular outcome.

Table 1. Persistence of AHT users by gender

Type of AHT drug	Men		Women	
	% persistent	OR adjusted	% persistent	OR adjusted
Diuretics	37.9	1.0 [ref.]	30.1	1.0 [ref.]
Beta-blockers	41.6	1.3 [0.8-2.1]	31.1	1.3 [0.9-1.8]
Calcium-channel-blockers	42.7	1.2 [0.8-1.9]	28.5	0.9 [0.7-1.8]
ACE-inhibitors	63.1	3.0 [1.9-4.7]	57.1	2.8 [2.2-4.6]
ARBs	61.0	3.0 [1.9-4.7]	63.0	3.9 [2.8-5.8]

Adjusted for age, use of antidiabetics, use of lipid lowering drugs, prior cardiovascular hospitalisations.

P1231 Differential effects of combined and uncombined replacement therapy on large artery elasticity in hypertensive postmenopausal women

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Purpose: To assess the hypothesis whether progesterone attenuates the beneficial effects of hormonal replacement therapy (HRT) on large artery stiffness in hypertensive postmenopausal women.
Methods: Towards this end, we studied aortic compliance in 56 postmenopausal women (aged 52 years, 3.4 years after menopause) with untreated, mild essential hypertension randomized to either conjugated estrogen alone (n=20), estrogen plus medroxyprogesterone (n=20) or placebo (n=16). Aortic elasticity was evaluated non-invasively on the basis of pulse wave velocity (PWV) measurements at baseline and at 12 weeks after treatment.
Results: In our women BMI was 27.2 kgr/m^2, office BP 146/93 mmHg, left ventricular mass index (LVMI) 104±26 gr/m^2, and mean plasma levels of total cholesterol 230 mg/d. The three groups were matched regarding age, time since menopause, smoking status, office blood pressure, BMI, LVMI and PWV values at baseline. At 12 weeks of treatment, in the women receiving estrogen alone, aortic PWV was significantly reduced (231 vs 209 cm/sec, $p<0.005$), while in the women receiving combined HRT or placebo, PWV did not change (232 vs 228 and 233 vs 230 cm/sec, respectively, p=NS for both cases). In all three groups, blood pressure and heart rate values did not change significantly after treatment. At baseline, aortic PWV had a positive correlation with the age of women ($r=0.32$, $p<0.05$) and LVMI ($r=0.29$, $p<0.05$).
Conclusions: Long-term combined HRT is without beneficial effects on large artery function in hypertensive postmenopausal women. These findings supports the view that progesterone may attenuate the beneficial effects of unopposed HRT.

GENETIC AND OTHER RISK MARKERS FOR CARDIOVASCULAR DISEASE

P1232 Unexpected identification of two new KCNQ1 mutations in the general population

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Background: Long QT syndrome (LQTS) is an arrhythmogenic disorder characterized by a prolonged QT interval, syncopes and sudden death. Mutations in KCNQ1 are responsible for dominant (Romano-Ward) and recessive forms (Jervell and Lange-Nielsen), with severe or milder phenotypes. We aimed to evaluate the frequency of such mild mutations in the general population.
Materials and Methods: We selected 2008 unrelated and untreated healthy individuals from the D.E.S.I.R. cohort (Data from an Epidemiological Study on the Insulin Resistance Syndrome). KCNQ1 was screened on 50 males and 50 females presenting the longest QTc intervals (398 ms to 442 ms) by dHPLC.
Results: We identify two new mutations consisting of a heterozygous nonsense mutation in exon 1, Y148X, and an in-frame heterozygous 3-bp deletion in exon 5, 828-830delCTC, leading to serine 276 deletion (DelS276) in S5 transmembrane domain. DelS276 KvLQT1 channel isoforms and MinK expressed in COS-7 cells failed to conduct any K^+ current in contrast to homomeric WT KvLQT1 channels. When DelS276 KvLQT1 were coexpressed with WT KvLQT1 and MinK, no significant reduction in channel activity was observed. Immunohistochemical methods and confocal microscopy were performed on transfected COS-7 cells. Immunofluorescence pattern was localized in the endoplasmic reticulum when cells were transfected with DelS276 KvLQT1, whereas WT KvLQT1 labelling was localized to the cell membrane.
Conclusions: Two subjects issued from a cohort of healthy individuals were carriers of KCNQ1 mutations (Y148X, DelS276) inducing a borderline QTc prolongation (QTc = 438 and 442 ms). Deletion of serine 276 disrupts the cell surface localization of the mutant. These results demonstrate a new mechanism that accounts for loss of functional KvLQT1 channels causing mild phenotype at heterozygous state.

P1233 Relationship between the angiotensinogen (AGT) M235T gene polymorphism and blood pressure in a large, homogenous study population

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Background: The aim of this study was to assess the association of the angiotensinogen M235T polymorphism with arterial blood pressure at rest and under physical stress in a homogenous large-scale study population.
Method: 1903 men who passed routine medical examination for military flying duty were recruited. Blood pressure and heart rate was measured at rest, during, and after bicycle ergometry. Low physical activity was defined as regular sports activity of three or less hours per week. Genotyping for the AGT M235T polymorphism was done by PCR and RFLP-technique.
Results: The AGT T235 allele was associated with a non-significant lower systolic and a significantly higher diastolic blood pressure (p=0.003). Pulse pressure at rest differed significantly between AGT genotypes (n=1903; MM 51 $\pm$ 10 mmHg, MT 49 $\pm$ 10 mmHg, TT 49 $\pm$ 10 mmHg; p = 0.001). This effect was pronounced in men with low physical activity (n = 916; MM 51 $\pm$ 10 mmHg, MT 48 $\pm$ 10 mmHg, TT47 $\pm$ 9 mmHg; p = 0.002). During physical activity, blood pressure values showed no significant difference between genotypes.
Conclusion: In healthy young men the AGT T235 allele is significantly associated with elevated diastolic blood pressure but also reduced pulse pressure at rest. Hence reduced pulse pressure is inversely associated with cardiovascular mortality, the AGT T235 allele is likely not to have a harmful effect. During physical activity, the AGT polymorphism had no impact on blood pressure, indicating the existence of other counteracting mechanisms, which might balance the influence of this gene.

P1234 Chemokine receptor (CCR2) genotype is associated with myocardial infarction and heart failure in patients under 65 years of age

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Background: Inflammation is associated with atherosclerosis of coronary arteries. Chemokines have an important role for inflammation. The CCR2 chemokine receptor mediates leukocyte chemoattraction, which is involved in the pathogenesis of coronary heart disease.
Methods: In this study we prospectively recruited 1960 consecutive patients at an age of less than 65 years referred for their first-time left heart catheter. Left heart catheter were analyzed by two independent cardiologist for presence of myocardial infarction (regional wall motion abnormality) and moderate or severely reduced left ventricular function on cineventriculography and presence of coronary atherosclerosis on angiograms. Genotyping for CCR2 V64I polymorphism was performed.
Results: The presence of the rare allele of the CCR2 gene was significantly associated with a higher prevalence of myocardial infarction on cinventriculography (32.0 versus 24.2%; p=0.002; OR 1.47; 95%CI 1.16-1.87), moderately or severely reduced left ventricular function (14.0 versus 9.5%; p=0.009; OR 1.56; 95%CI 1.12-2.16) and NYHA class III or IV (16.7 versus 12.2%;p=0.017; OR 1.45; 95%CI 1.07-1.96). There was no association of the CCR2 genotype with coronary atherosclerosis.
Conclusion: The CCR2 genotype seems to predispose patients for premature myocardial infarction with consecutive higher prevalence of heart failure.

P1235 Screening for youth obesity: links to premature parental coronary artery disease

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Purpose: The pathology of coronary artery disease (CAD) is a long-term process originating in childhood and adolescent years. To date, body mass index (BMI) is recognized as an acceptable measure of body composition due to its practical use in large community epidemiology research. Typically, a BMI score $>$25 positively correlate with disease. Furthermore, a BMI $>$30 is considered to be an unfavorable body composition and is indicative of obesity in adults. Despite the acceptance and accuracy of BMI in determining the health status of an individual's body composition, it is less accurate in peri-adolescent populations due to variability in physical maturation among youth. Preliminary research by Faught and de Ruiter (2002) suggested obesity in youth is more accurately identified using BMI cut-off scores $>$23 and $>$25 in female and males, respectively. The primary purpose of the study was to further validate these findings in screening for youth obesity.
Methods: A 3-year cross sectional investigation of 10401 grade 9 students (males=5165, females=5236) was conducted from grade 9 students. Body mass index was calculated from standing weight and height evaluated on a medical scale. Percent body fat (%BF) was measured using the Bio-electrical Impedance Analysis (BIA). Clinical obesity was considered $>$25% and $>$30% for males and females, respectively. Finally, subjects completed a standardized questionnaire on family history of CAD.
Results: Prevalence of obesity was 14$\pm$2% in males and 36$\pm$2% in females. ROC curve analysis identified the most appropriate BMI cut-off score for males and females at $>$25 and $>$23, respectively. Calculated sensitivity (M=71%; F=87%), specificity (M=84%; F=83%), and likelihood ratio (M=4.5; F=5.2) were markedly elevated. Chi-square analysis indicated no significant difference ($p>0.05$) between BMI cut-off scores and BIA measures in identifying obesity. Finally, 23% of obese youth had a parent with premature CAD. Percent body fat correlated with parental CAD in female youth ($r=0.20$, $p<0.01$), but not in male youth ($r=0.01$, $p>0.05$).
Conclusions: This study further validates the gender specific BMI cut-off scores previously identified in screening for youth obesity. The BMI cut-off for identifying obesity was lower in youth compared to the customary adult cut-off (ie. $>$30). This could be attributed to variability in maturation levels found in youth. Finally, the positive correlation between female %BF and parental CAD suggests that BMI may be useful in screening for early detection of familial premature CAD.

P1236 Peak oxygen pulse and the risk of cardiovascular diseases and overall mortality in men

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Background: We investigated the prognostic value of peak oxygen pulse (POP), which indicates the amount of oxygen consumption during exercise.
Methods: During an average follow-up of 13 years, there were 393 overall and 134 coronary deaths in 2225 men from Finland. The POP was calculated by dividing peak oxygen uptake with maximal heart rate and was expressed in mL per beat during exercise.
Results: Among men with either no history of coronary disease or the use of beta-blockers at baseline, the relative risk was 2.9 (95% confidence interval 1.1 to 7.1) times higher for coronary death and 2.3 (95% confidence interval 1.4 to 3.3) times higher for overall death in men with low POP ($<$13.5 mL per beat, lowest quartile) than in those with high POP ($>$17.8 mL per beat, highest quartile), after adjustment for age, smoking, body mass index, blood pressure, serum lipids, diabetes, family history of coronary heart disease, regular use of aspirin, anti-hypertensive or lipid lowering drugs and ischemic ST changes during exercise. In men with coronary disease, POP increase of 3.9 mL (a standard deviation) per beat was related to decreased risk of coronary death (RR=0.53, 95% confidence interval 0.38 to 0.72) and overall mortality (RR=0.53, 95% confidence interval 0.42 to 0.67).
Conclusions: This study provides new prospective evidence that oxygen pulse can be used as a prognostic measure in the exercise test for identifying men at increased risk of cardiac disease.

P1237 Pulse pressure and coronary risk in dyslipidemic men

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Coronary risk associated to pulse pressure (PP), the pulsatile element of blood pressure (BP), was studied in a prospective, nested case-control study among dyslipidemic middle-aged men using logistic regression analyses. The cases consisted of 241 men who suffered either coronary death or nonfatal myocardial infarction during the 8.5 year follow-up in the Helsinki Heart Study, a coronary primary prevention trial. The 241 controls consisted of men without coronary events, matched for study drug (gemfibrozil/placebo) and the area of residence. BP levels at study baseline were measured by study nurses in sitting position. There was a close correlation between PP and systolic BP (r=0.75), but no correlations were found between PP and diastolic BP (r=-0.05), or between PP and heart rate (r=0.09). Coronary risk (Odds Ratios) in the middle (46-55mmHg) and highest ($>$55mmHg) PP tertiles were 1.14 and 1.58. The product of heart rate and PP (HRPP) represents the frequency of pressure generations during one minute. The risks in the middle and highest HRPP tertiles were 1.64 and 1.93, respectively. When diastolic BP was $<$90 mmHg (lowest tertile), the ORs in the highest tertiles were 2.34 for PP and 4.43 for HRPP, while when diastolic BP was $>$90 mmHg, the corresponding ORs were 1.35 and 1.37. When systolic BP was below the median (140 mmHg), the ORs in the highest PP and HRPP tertiles were 3.86 and 3.85, but when systolic BP was elevated, the ORs for PP and HRPP were 0.77 and 0.75, respectively.
Our results suggest that among middle-aged men, the product of pulse pressure and heart rate can be used in coronary risk estimation, especially when blood pressure is not high.

P1238 Relation of daily alcohol consumption with the prevalence of metabolic syndrome: the ATTICA study

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Objective: The aim of this study was to examine the association between the clinical and biochemical features of the metabolic syndrome and quantity of alcohol intake in cardiovascular disease free people.
Methods: During 2001 – 2002, 1128 men (18-87 years old) and 1154 women (18-89 years old) from Athens greater area were randomly selected, according to the age-gender distribution provided by the National Statistical Services. Among others, we studied data regarding waist circumference, as well as high lipoprotein cholesterol, triglycerides, fasting glucose, and blood pressure levels. Data on alcohol consumption was collected by serial clinical interviews and a questionnaire. The metabolic syndrome was defined according to the NCEP ATP III criteria.
Results: Of the 2282 participants, 284 (25.2%) males and 169 (14.6%) females ($P < 0.001$) met the ATP III criteria. 570 (25%) of the participants reported that they consume at least one wineglass per day. Multiple logistic regression analysis revealed that alcohol consumption is associated with higher prevalence of the metabolic syndrome (odds ratio = 1.53, $P < 0.02$). Also, alcohol consumers showed a marked reduction in the adjusted odds ratio of type-2 diabetes (odds ratio = 1.45, $P < 0.05$) compared with rare or nonconsumers. However, when quantities of alcohol were taken into account there was a U-shaped relationship between the amount and frequency of alcohol consumption and the prevalence of the metabolic syndrome (odds ratio for 1-2 wineglasses consumption/day: 0.84, odds ratio for 3 – 4 w/d: 1.81, and odds ratio for +5 w/d: 2.28, $P < 0.001$). The effect was attenuated when diabetics were excluded from the analysis. Timing of alcohol consumption did not influence outcome measures.
Conclusion: Light-to-moderate alcohol consumption is associated with a lower prevalence of metabolic syndrome. On the contrary, larger quantities of alcohol consumed were associated with higher likelihood of having the metabolic syndrome.

P1239 Interleukin 18 and the risk of coronary artery disease in apparently healthy European men

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Background: Interleukin (IL)-18 facilitates atherosclerotic plaque growth and/or vulnerability. Elevated systemic levels have been linked to fatal cardiovascular events in patients with coronary artery disease. However, information about the prognostic value of IL-18 in a population-based healthy cohort is lacking.
Methods: We evaluated the relationship between baseline levels of IL-18 and the subsequent development of incident coronary event during a 5 yr follow-up in the PRIME study including healthy French and Northern Irish men aged 50-59 at entry. Analysis was performed in a nested case-control study comparing 335 cases with a coronary event to 670 age-matched controls.
Results: Baseline levels of IL-18 were significantly higher in men who developed a coronary event compared to controls (225.1 vs 203.9 pg/ml, P=0.005). After adjustment for most potential confounders, including C-reactive protein, IL-6, and fibrinogen, the relative risk of future coronary event comparing the highest versus the lowest tertile of IL-18 was 2.43 (95% CI 1.14 to 5.16, P=0.02) in Northern Ireland, 1.90 (95% CI 1.05 to 3.45, P=0.02) in France, and 2.06 (95% CI 1.32 to 3.23, P=0.002) in both countries pooled (P=0.59 for the test of homogeneity between populations). In all models, IL-18 had an independent contribution to prediction of risk in addition to lipids or other inflammatory markers such as CRP, IL-6 or fibrinogen.
Conclusions: Plasma IL-18 level was identified as a strong and independent predictor of coronary events among healthy European middle-aged men. This result strengthens the hypothesis of a pathophysiological role of IL-18 related to plaque growth and/or vulnerability. Determination of circulating IL-18 might provide an improved method of identifying men at risk for coronary events.

P1240 Evaluation of cardiovascular risk factor at the acute phase of a coronary syndrome does not allow a valuable estimation: the hidden cause of failure of reducing the risk of recurrent disease

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The aim of this study was to evaluate the evolution and the distribution of the main cardiovascular risk factors (CRF) between the acute(first week) and the chronic phase (3 months) of an acute coronary syndrome (ACS)
We included 205 consecutive patients admitted to our institution for an ACS; we studied systematically and extensively their CRF during the first week (M0) (from day 4 to day 10) of the hospitalization and then at three months(M3)
Patients were 60 $\pm$ 13 year-old (83% men). 36% of the smokers at MO still smoked at M3. At MO, 17% of the subjects with a normal BMI were overweight at M3. At M3, 19% of patients had always high blood pressure although receiving at least one drug in 98% and at least two in 56%; 15% of the patients with proved high blood pressure at M3 were considered as non hypertensive at M0. At M3 35% of the patients still had high LDL-cholesterol level (>1.3 g/l) although 87% of them had statins since M0; 15% of the patients with a normal LDL-cholesterol at MO had high level (>1.3 g/l) at M3. HDL-cholesterol significantly increased (1.14 $\pm$ 0.27 g/l vs 1.29 $\pm$ 0.33 [p<0.0001]) 41% had high level of triglycerides at M3; a quarter of them had normal level at MO. At MO 12% had glucose intolerance, 13% were diabetics; 15% of patient with normal glucose level at MO were at least glucose intolerant at M3 and 4% were really diabetics. hsCRP remained over 1.5mg/l in 72% of patients at M3 although 100%of them were taken at least one antiaggregant. Between MO and M3 the absolute and the relative risk according to Framimgham score were significantly but poorly reduced (18.6 vs 16.30 and 1.92 vs 1.67, p<0,0001)
In conclusion, the evaluation of CRF at the acute phase of a ACS underestimated lipids and thrombotics profile but also blood pressure and glycemic profile. Although an optimized treatment following the acute phase and a better correction of CRF than in Euroaspire population, the risk remains high in this study population. Because of biais CRF estimation at the acute phase, we conclude to the need of a systematic reevaluation of CRF far from the initial event.

P1241 Major cardiovascular events are associated with increased incidence of resistance to activated protein C and factor V Leiden mutation in well controlled hypertensives

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Background: Reduced response to activated protein C (APC-R), an inherited hemostatic defect and heterozygosity of factor V (FV Q506) Leiden mutation have been identified as risk factors not only for venous but also for arterial thrombosis as well. This, study was designed in order to examine both APC-R and FV Q506 mutation incidence in a cohort of Greek hypertensives (Hs) and to test the possible effect of the above mentioned defects on the incidence of cardiovascular events (CVE) in this group of patients (pts) during a five year follow-up period under treatment.
Methods: FV Q506 mutation was estimated by a DNA analysis (Bertina method) and APC-R was determined using the Coatest APC Resistance kit of Chromogenix, Sweden, in 160 untreated Hs. The prevalence of APC-R was 36,25% (58/160). Twenty-two out of 160 had heterozygosity for FV Q506 mutation (13,75%, Group A), while the remained 138 were negatives (Group B) APC-R value expressed as mean$\pm$SD was 1,8$\pm$0,1 in group A vs. 2,04$\pm$0,2 in group B (p<.0001). The two groups are matched for age, sex, BMI, systolic and diastolic blood pressure levels, smoking habits and lipid profile.
Results: During the 5-year follow-up period, under treatment and well controlled (BP<140/90 mmHg), 7/22 (31,8%) pts of group A vs. 8/138 (5,8%) of group B had been suffered a major cardiovascular event (p<.001).
Conclusions: These findings suggest that 1) there is an extremely high prevalence of APC-R in hypertensives (in general population 3-5%), 2) there is also an increased incidence of heterozygosity of FV Q506 mutation in the same population (in general population in Greece 8%), 3) it seems that the above hemostatic defects may be additional risk factors for major CVE in treated well controlled hypertensive patients.