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Vienna-Mayo Contemporary Clinical Cardiology 2006

September 14–16, 2006, Vienna

Abstracts

B-Type Natriuretic Peptide in Low-Flow Aortic Stenosis: Relationship to Hemodynamics and Clinical Outcome. Results from the Multicenter TOPAS Study

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Background B-type natriuretic peptide (BNP) has been studied in aortic stenosis (AS), but no data have been reported for patients with low-flow/low-gradient AS. Therefore, we studied the relationship of BNP and Nt-BNP with rest and stress hemodynamics as well as clinical outcome in this group.

Methods Plasma BNP and Nt-BNP were measured in 72 pts with AS undergoing dobutamine stress echocardiography (DSE). 63 pts had low-flow AS with indexed effective orifice area [EOA] < 0.6 cm²/m², mean gradient [MG] < 40 mmHg and LV ejection fraction [EF] ≤ 0.40 biplane Simpson technique. Nine pts with AS and normal EF served as controls. Pts were classified as truly severe [TS] or pseudo-severe AS [PS] based on their projected EOA at a normal flow rate of 250 mL/s ≤ or > 1.0 cm² in DSE, as previously proposed in the TOPAS study.

Results BNP and Nt-BNP were markedly elevated in low-flow AS (BNP 991 ± 1115 vs. controls 190 ± 183 pg/mL, *p* = 0.025; Nt-BNP 7330 ± 16,261 vs. 193 ± 199 pg/mL), but varied widely. Log BNP was inversely related to EF at rest (*r* = 0.60; *p* < 0.0001) and peak stress (*r* = 0.51; *p* < 0.0001), as well as to EOA at rest (*r* = 0.48, *p* < 0.0001) and peak stress (*r* = 0.47, *p* < 0.0001), stroke volume (BNP, *r* = 0.32, *p* = 0.012), mean transvalvular flow rate (*r* = 0.26, *p* = 0.04) and wall motion score index (*r* = 0.40, *p* = 0.001). Similar findings were observed for Nt-BNP. BNP was significantly higher in 25 TS compared to 38 PS pts (1162 ± 1229 vs. 680 ± 866 pg/mL, *p* = 0.008). Similarly, BNP was higher in 23 vs. 40 pts with a peak stress EOA ≤ or > 1.0 cm² (1466 ± 1448 vs. 530 ± 467 pg/mL, *p* < 0.001). In the subgroup of 24 patients who underwent aortic valve replacement, BNP was higher in 6 pts who died postoperatively compared to 18 pts surviving valve replacement (1975 ± 2261 vs. 815 ± 492 pg/mL, *p* < 0.05). In the total cohort, cumulative 1-year survival of pts with BNP ≥ 550 pg/mL was significantly lower than of pts with BNP < 550 (51 ± 11 % vs. 92 ± 5 %, *p* = 0.04).

Conclusion In pts with low-flow AS, BNP and Nt-BNP are markedly elevated and related to EF and EOA at rest and peak DSE. BNP is significantly higher in truly severe compared to pseudo-severe AS. BNP predicts poor postoperative outcome in the subset of patients undergoing valve replacement. Overall one-year survival is poor in pts with BNP ≥ 550, but reasonable in pts with BNP < 550 pg/mL.

Exercise-Induced Pulmonary Hypertension in Patients after Successful Pulmonary Endarterectomy

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Background Pulmonary endarterectomy (PEA) provides potential cure for patients with chronic thromboembolic pulmonary hypertension (CTEPH). Successfully operated patients have been shown to normalize exercise capacity and hemodynamic parameters in long-term studies.

Methods To investigate whether pulmonary hypertension can be provoked by exercise, we studied patients at least one year after successful PEA with documented (near) normalization of exercise capacity and hemodynamics. Patients (*n* = 13) and age-matched non-pulmonary hypertensive controls (*n* = 14) underwent echocardiography at submaximal treadmill exercise.

Results Resting mean pulmonary arterial pressure was 25 ± 9 mmHg, mean pulmonary vascular resistance was 291 ± 148 dynes × s × cm⁻⁵, mixed venous saturation was 71 ± 5 % and mean cardiac output was 5.2 ± 1.1 l/min at 63 ± 31 (range 16–120) months after PEA. There was no difference in age (61 ± 10 vs. 57 ± 13 years, *p* = 0.5) or 6-minute walking distance (489 ± 114 vs. 456 ± 45 meters, *p* = 0.32) between patients and controls. While the difference in resting systolic pulmonary arterial pressures (sPAP) reached only borderline significance (41 ± 18 vs. 30 ± 6 mmHg, *p* = 0.05), there was a significant difference in exercise-sPAP (71 ± 23 vs. 46 ± 11 mmHg, *p* = 0.001), resting pulmonic valve acceleration time (102 ± 24 vs. 132 ± 17 ms, *p* = 0.0008) and serum BNP levels (207 ± 134 vs. 70 ± 77 pg/mL, *p* = 0.007).

Conclusions Patients with normal exercise capacity and resting hemodynamics after PEA demonstrate significant pulmonary hypertension at exercise. There is a need for studies investigating whether this patient population does additionally benefit from vasodilator therapies.

Bacterial Infection is a Mechanism Underlying a Failure of Thrombus Resolution in Chronic Thromboembolic Pulmonary Hypertension

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Background Chronic thromboembolic pulmonary hypertension (CTEPH) results from single or recurrent pulmonary thromboemboli arising from sites of venous thrombosis. In patients with CTEPH, thromboemboli do not resolve but form endothelialized, fibrotic obstructions of the pulmonary vascular bed. Mechanisms underlying thrombus organisation are poorly understood. Because of the observation that infected intravenous leads enhance the likelihood of CTEPH, we tested the hypothesis that bacterial infection causes a failure of thrombus resolution.

Methods Human thromboendarterectomy specimens were sterily collected during surgery and analyzed with a bacterial 16S ribosomal DNA screening protocol. In a next step, a mouse model of venous thrombus formation was employed to investigate thrombus resolution in the absence and presence of low doses of *Staphylococcus aureus* (0.15 ml of 10⁵/ml injected as a single bolus into the tail vein). On days 1, 3, 7, 14 and 28 after thrombus induction, animals were sacrificed, thrombi were harvested, fixed and embedded in paraffin.

Results 520 bp PCR products were obtained in 16 of 25 CTEPH thrombi, but in only 4 specimens derived from patients with acute pulmonary embolism. Cross-sectional area analysis demonstrated that thrombi from infected animals were larger than control thrombi (day 7: median cross-sectional area (CSA) 0.431 vs. 0.279 mm²; day 28: median CSA 0.128 vs. 0.018 mm², *n* = 8, *p* < 0.05). Volumetry confirmed significantly larger thrombus volumes on days 3 and 28 (day 3: median thrombus volume 1.798 vs. 1.441 mm³; day 28 median thrombus volume 0.427 vs. 0.056 mm³, *n* = 8, *p* < 0.05). Real-time PCR demonstrated increasing expression of connective tissue growth factor (CTGF) in the thrombi over the observation period, contrasting the decline of CTGF expression in controls.

Abstracts in alphabetical order based on first authors' last names.

Discussion The data demonstrate that infection with *staphylococcus aureus* enhances thrombus formation and persistence. CTGF expression analysis suggests that abnormal thrombus organization occurs after bacterial infection.

Bosentan for the Treatment of Chronic Thromboembolic Pulmonary Hypertension – One-Year Experience

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Background Bosentan, an oral endothelin ET_A/ET_B-receptor antagonist, is effective in the short-term treatment of inoperable chronic thromboembolic pulmonary arterial hypertension (CTEPH). We investigated hemodynamics, safety and efficacy of bosentan therapy at one year of therapy in 21 patients (13 ♀/8 ♂, mean age 71 ± 12 years) who were treated off-label over 16 ± 6 months.

Results After one year of treatment, NYHA functional class had improved by one class in 14 patients. Mean six-minute walking distances increased from 299 ± 131 m at baseline to 387 ± 121 m ($p = 0.04$). In parallel, proBNP decreased from 3365 ± 2923 pg/ml to 1579 ± 2103 pg/ml ($p = 0.02$). Overall, mean pulmonary arterial pressure (mPAP) decreased from 48 ± 10 to 43 ± 12 mmHg ($p = 0.17$), pulmonary vascular resistance (PVR) changed from 653 ± 247 to 468 ± 205 dynes × s × cm⁻⁵ ($p = 0.04$). If hemodynamic non-responders to therapy were excluded ($n = 5$), mPAP decreased from 50 ± 10 to 42 ± 11 mmHg ($p = 0.17$), and PVR changed from 757 ± 232 to 420 ± 137 dynes × s × cm⁻⁵ ($p = 0.015$). Neither AST (25 ± 2 vs. 25 ± 2 U/l, $p = 0.25$) nor ALT (23 ± 12 vs. 24 ± 9 U/l, $p = 0.57$) changed significantly. Two deaths occurred from causes unrelated to pulmonary hypertension.

Conclusions Our study suggests a beneficial long-term effect of the oral dual endothelin receptor antagonist, bosentan, in patients with inoperable CTEPH. Non-responders to bosentan therapy must be further characterized.

Decreased Cardiac Remodeling after Combined (Intramyocardial and Intracoronary) Autologous Stem Cell Treatment in Chronic Heart Failure

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Background The aim of our prospective study was to assess the effect of combined (intramyocardial and intracoronary) autologous bone-marrow stem cell (BM-SC) therapy on cardiac remodeling in patients with severe coronary artery disease and chronic heart failure.

Methods Thirty-two no-option patients (94 % men, 55 ± 12 y) with congestive heart failure and left ventricular (LV) ejection fraction (EF) < 40 %, not amenable for conventional revascularization, underwent combined, NOGA-guided intramyocardial (3.8 ± 0.3 ml) and intracoronary (29 ± 14 ml) autologous BM-SC therapy. Baseline and 6-month follow-up (FUP) clinical symptoms (NYHA, CCS), LV systolic and diastolic functions (measured by contrast ventriculography), myocardial viability and segmental wall motion (NOGA endocardial mapping) and stress-induced as well as resting perfusion defect sizes (99m-Tc-Sestamibi SPECT myocardial perfusion scintigraphy) were compared.

Results At FUP, a marked increase in LV EF (from 36.5 ± 8.0 % to 43.0 ± 10.4 %, $p < 0.001$) along with a significant ($p < 0.05$) decrease in LV end-diastolic volume (from 240 ± 57 to 223 ± 60 ml), end-diastolic pressure (from 24.1 ± 7.9 to 20.8 ± 8.0 mmHg), LV end-diastolic diameter (from 57.9 ± 5.2 to 54.9 ± 4.6 mm) and diameter of the left atrium (from 46.6 ± 6.9 to 44.0 ± 8.1 mm) was found. This improvement was accompanied by a decrease ($p < 0.01$) in heart rate (from 72.3 ± 13.4 to 67.7 ± 12.6), CCS (from 2.4 ± 1.1 to 1.3 ± 0.6) and NYHA (from 2.5 ± 0.8 to 1.5 ± 0.7). Combined stem cell therapy induced a reduction of stress-induced perfusion defect size (from 26.9 ± 8.7 to 22.2 ± 10.1 % of the total myocardium, $p < 0.05$), while a trend to smaller resting defect at FUP was measured. Myocardial viability (measured by NOGA mapping, from 7.7 ± 2.8 to 8.6 ± 2.3 mV) and the local linear shortening (from 5.6 ± 1.4 to 7.3 ± 1.5 %) of the treated area improved significantly.

Conclusions Combined application of stem cell therapy decreases cardiac remodeling in patients with chronic heart failure, improving the systolic and diastolic functions of the heart.

Rheumatoid Arthritis is Associated with Systemic Arterial Stiffness

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Background Rheumatoid arthritis (RA) is associated with premature atherosclerosis. Chronic inflammation may impair arterial function and lead to the increase of their stiffness.

Aim of the Study was to assess whether RA, disease duration and increase of high-sensitivity C-reactive protein (hsCRP) can influence arterial stiffness in RA patients.

Methods This study included 53 RA patients (40.1 ± 9.8 years) with moderate and high disease activities (DAS28 3.21–7.05) and 55 controls (39.7 ± 8.1 years). Blood tests included serum lipid profile, glucose and hsCRP measurements. The augmentation index (AIx), a measure of systemic arterial stiffness, was assessed non-invasively by applanation tonometry (Sphygmocor v. 7.01, AtCor Medical).

Results In RA patients, the AIx values adjusted for heart rate and level of CRP were significantly higher compared to controls (AIx 21.3 ± 13.3 % vs. 12.7 ± 13.2, $p = 0.001$; CRP 31.32 ± 40.29 mg/l vs. 1.58 ± 3.36 mg/l, $p < 0.001$, respectively). Significant influence of disease duration on AIx was observed by multiple regression analysis (adjusted $r^2 = 0.559$; $p = 0.002$). Correlation between hsCRP and AIx was not significant in RA patients (Pearson's $r = -0.044$; $p = 0.752$) as well as in controls (Pearson's $r = 0.215$; $p = 0.121$).

Conclusion Duration of rheumatoid arthritis but not elevation of serum hsCRP is related to the premature increase of systemic arterial stiffness.

Lp(a) Predicts Early Onset of Atherosclerosis

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Background A family history of premature coronary artery disease (CAD) is one of the main risk factors in middle-aged patients.

Aim The aim of our study was to assess the relationship between intima-media thickness (IMT), measured by B-mode ultrasound, and conventional risk factors in families with premature CAD.

Methods The study population consisted of 32 families with premature CAD. In total, 50 subjects were studied. Each family in the cohort has at least one affected sibling with premature CAD. Data about sex and other risk factors were obtained. Plasma levels of homocysteine, IL-6, CRP, ox-LDL and lipids were measured. Carotid and femoral IMTs were assessed by high-resolution B-mode carotid ultrasound (GE, 13 MHz).

Results Patients with premature CAD were more likely to have diabetes mellitus (5.3 % vs. 0 %, $p = 0.001$), arterial hypertension (69 % vs. 25 %, $p = 0.017$), dyslipidemia (96.9 % vs. 71.5 %, $p = 0.006$) and were male (97 % vs. 50 %, $p = 0.001$) with a higher Body Mass Index (31.7 ± 6.1 vs. 28.19 ± 3.2, $p = 0.03$). Advanced sub-clinical atherosclerosis was present in 69 % of family members, but prevalence of elevated IMT was higher in CAD patients ($p = 0.001$). Patients with premature CAD had major values of Lp(a) and lower values of total cholesterol, HDL-C, ApoA1, IL-6 and Ox-LDL-C. In a stepwise regression model, only gender ($p < 0.036$) independently predicted the mean IMT. After controlling for gender, the independent predictor of mean IMT was Lp(a) ($p < 0.015$) (Table 1).

Conclusion Lp(a) and gender showed a significant association with subclinical atherosclerosis. The present study demonstrates that Lp(a) is a strong predictor for early onset of atherosclerosis.

Table 1. V. Dzenkeviciute et al.

Variable	Beta	95 % CI	P	β	SE
Gender	0.351	0.01–0.037	0.036	0.019	0.009
After adjustment of gender Lp(a)	0.398	0.0078–0.86	0.021	0.337	0.015

Assessment Of Plaque Composition in Cardiac Allograft Vasculopathy by Virtual Histology™

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Background Previous pathological studies of coronary plaque in heart transplant patients showed a predominance of fibrous plaque components. In this prospective study, we aimed to assess coronary plaque composition in cardiac allograft vasculopathy by intravascular ultrasound with Virtual Histology™ (Volcano Therapeutics Inc.).

Methods Intravascular ultrasound runs with automatic pullback (0.5 mm/s) were available for 20 heart transplant patients (transplantation was performed 8.6 ± 3.2 years ago). In each patient, one lesion of interest was defined at the site of maximal coronary plaque burden. Analysis of plaque composition was performed with the Virtual Histology™ software.

Results Mean lesion length was 11.7 ± 4.8 mm. Three patients showed hemodynamically significant stenoses. Mean plaque burden was 33.7 ± 8.4 % (minimal lumen diameter: 3.0 ± 0.7 mm; minimal lumen area: 9.4 ± 3.3 mm). Plaque composition as assessed by Virtual Histology™ was predominantly fibrotic (66 %), whereas fibrofatty, calcified and necrotic plaque fractions were present in 21 %, 5 % and 8 %, respectively.

Conclusions Intravascular ultrasound with Virtual Histology™ allows for differentiation of coronary plaque components in cardiac allograft vasculopathy. Comparable to previous *ex vivo* studies, plaque composition in heart transplant patients was predominantly fibrotic.

Stenting of Coronary Bifurcations: One- vs. Two-Stent Strategy in a Bench Model

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Background Bench-testing provides insights into complex stenting strategies of bifurcations. A two-stent strategy to completely cover the carina results in a higher sidebranch (SB) restenosis rate when compared to a single-stent strategy of covering only the mainbranch (MB). This might be due to a smaller SB ostial lumen when using crushing techniques.

Methods We compared a kissing-balloon (KB) only strategy to external-crush (EC) and internal-crush stenting (IC) in a bifurcational silicon model. Minimal lumen diameter (MLD) of the SB ostium as well as the proximal carina (PC) and distal carina (DC) of the mainbranch stent were measured by a nozzle gauge. Testing was performed using Cypher Select (Cordis, NY) and Taxus Express (Boston Scientific, MA) stents in a 45-degree-angled 3.00 mm MB and 3.00 mm SB bifurcational model ($n = 8$ for all techniques). Cypher stents were implanted with 16 atm, Taxus Express stents were implanted with 13 atm and postdilated with a Cypher balloon with 16 atm. Stents overlapped for > 5 mm in EC and IC. Final kissing was performed with two Cypher balloons with 8 atm (Table 2).

Results MLD of SB ostium was significantly larger in KB vs. EC and IC.

Conclusions KB leads to a significantly larger MLD of the SB ostium compared to EC and IC. This might explain in part the higher SB restenosis rate after a two-stent strategy.

Table 2. B. Frey et al.

	KB	EC	IC
SB	$2.69 \pm 0.21^*$	$2.47 \pm 0.07^*$	$2.42 \pm 0.11^*$
PC	2.94 ± 0.24	2.95 ± 0.08	2.94 ± 0.08
DC	2.65 ± 0.14	2.57 ± 0.17	2.54 ± 0.15

All values in mm, * $p < 0.001$

Detection of Coronary Artery Fistulas in Asymptomatic Patients. The Role of Two-Dimensional Doppler Echocardiography

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Background Coronary artery fistulas are occasionally found in patients who undergo coronary angiography and they may involve any epicardial coronary artery. The natural history in asymptomatic adult patients is unknown.

Aim The aim of the study was to assess the role of two-dimensional echocardiography (TTE) complemented by pulsed Doppler ultrasound and color flow imaging in the diagnosis of coronary artery fistulas (CAF) in asymptomatic patients, usually diagnosed by coronary angiography and cardiac catheterization.

Material and Methods In a retrospective study covering the years 1985–2005, 19 patients (pts.) with silent CAF were identified. The patients, aged 8–60 years, 12 of them men (63 %), were studied by two-dimensional TTE with pulsed Doppler and color flow imaging and by other noninvasive methods (ECG, chest X-ray, phonocardiogram, first pass radionuclide). In all pts, the final diagnosis of CAF was made by selective coronary angiography.

Results The clinical, echocardiographic, ECG and angiographic findings of clinically silent CAF were analyzed. Indications for echocardiography were: continuous murmur in 15 pts (79 %) and ECG changes in 4 pts (21 %). CAF was detected with two-dimensional TTE (Doppler and color flow) in 13 pts (70 %). The CAF originated from the left coronary artery in 5 pts, the right coronary artery in 7 pts and bilaterally in 1 patient. The drainage sites were the right ventricle in 6 pts, the left ventricle in 4 pts, the right atrium in 1 patient and the pulmonary artery in 3 pts. In all patients, the final diagnosis of CAF was made by selective coronary angiography. In one case, TTE showed the enlarged origin of a single left coronary artery with CAF communicating with the right ventricle.

Conclusions Our study confirmed that two-dimensional TTE (with PW Doppler and color flow) is a useful non-invasive technique in identifying asymptomatic pts with CAF.

Multiple Interatrial Septal Defects – Assessment of Morphology and Pathological Associations

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Background Multiple interatrial septal defects (ASDs) are a morphological variant of ASDs about which there is little data in the literature, but they have gained more importance in recent years.

Objective To determine the frequency of multiple ASDs, their association with other cardiac anomalies and morphological features.

Methods We carried out a retrospective study on 389 consecutive patients with ASD admitted in the cardiology department from 2000–2005. Patients with multiple ASDs were selected upon their transthoracic and/or transesophageal echocardiography. In patients who have undergone surgical repair of the defect, the echocardiographic findings were compared with surgical data.

Results 16 patients of 312 (for whom an echo examination was available) had multiple ASDs (5.12 %). Most of them (10 of 16) were diagnosed with multiple ASD by a transthoracic 2D color Doppler examination. In the majority of cases (12 of 16 patients), the multiple ASDs were of ostium secundum type, with 7 patients with a double defect and the others with a multiperforated interatrial septum. The most frequent anomalies associated with multiple ASDs were the septal aneurysm (Figure 1) (6 of 16 pts) and the anomalous pulmonary venous drainage (4 pts). Six patients associated different valvular lesions: 2 cases of pulmonary stenosis, 2 cases of tricuspid valve anomalies, and we found Ebstein disease, bicuspid aortic valve and mitral stenosis, each in one patient.

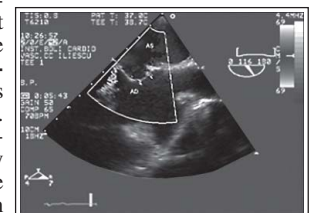


Figure 1: C. Ghingina, et al.

Conclusions Multiple interatrial septal defects are relatively rare (5.3 % of ASD) with an increasing frequency due to better echocardiographic techniques. In most cases, they are associated with other cardiac anomalies including various valvular lesions, interatrial septal aneurysms and anomalous pulmonary venous connections.

FDG Gamma Camera PET Equipped with a 1-inch Crystal In Detection of Viable Myocardium: Comparison with Dedicated PET and Tc-Tetrofosmin

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Background The purpose of this study was to compare FDG gamma camera PET (GCPET) equipped with one-inch NaI crystals and Tc-99m-Tetrofosmin- (Tc) SPECT with and without attenuation correction with FDG-dedicated PET (dPET) as validated reference method for detection of myocardial viability.

Material and Methods GCPET, Tc and dPET were performed in 11 patients (10 males, 1 female, age 63 ± 10 years) with coronary artery disease and reduced left ventricular ejection fraction. Tc imaging was assessed with a dual-headed gamma camera (Siemens ECAM). For GCPET imaging, a dual-headed gamma camera (GEMS Millennium VG with Hawkeye) equipped with 1-inch thick NaI crystals was used. PET studies were performed with a dedicated PET camera (GE-Advance). For all three methods, polar maps were generated using the "Munich Heart" image analysis tool. For quantitative analysis of polar maps, each polar map was divided into 16 myocardial segments (4 apical, 6 midventricular and 6 basal segments). Segmental tracer uptake was normalized to the maximal uptake and expressed as percentage of the maximal segmental tracer uptake.

Results Regression analysis of averaged segmental activity of all myocardial segments ($n = 176$) showed significant correlation between GCPET-ac and dPET ($R = 0.82$), GCPET-nc and dPET ($R = 0.63$), Tc-ac and dPET ($R = 0.75$), Tc-nc and dPET ($R = 0.75$). Cross-table analysis between different techniques and dPET for identification of viable segments showed an agreement of 89 % ($\kappa = 0.63$) for GCPET-ac, 63 % ($\kappa = 0.26$) for GCPET-nc, 93 % ($\kappa = 0.71$) for Tc-ac and 89 % ($\kappa = 0.64$) for Tc-nc and dPET.

Conclusion GCPET-ac, Tc-ac and Tc-nc show similar agreement with dPET for identification of viable myocardium and comparable correlation with dPET. However, GCPET-nc is qualitatively inferior compared to dPET.

Reduced Coronary Flow Reserve in Patients with Angina and Normal Angiogram: Mechanism and Influencing Parameters

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Objectives Typical angina in patients with normal angiogram can be caused by a reduction of coronary flow reserve (CFR), reflecting the presence of microvascular disease. CFR is defined as the ratio of hyperemic to resting blood flow. Consequently, a reduced CFR can result from an increase of resting blood flow as well as from an impairment of vasodilator capacity. Accordingly, the present study was undertaken to determine whether the altered CFR is due to increased resting or to reduced stress flow. In addition, the possible influence of clinical parameters (age, sex, blood pressure, heart rate and left ventricular wall thickness using echocardiography) was investigated.

Methods In 65 patients (45 ♀/20 ♂, age 58 ± 10 years) with angina, normal angiogram and a positive stress test, myocardial blood flow was measured at rest and after administration of intravenous dipyridamole (0.6 mg/kg/5 min.). After injection of 800–900 MBq ¹³N-ammonia (800–900 MBq), dynamic images were performed using positron emission tomography (PET). According to previous studies, a CFR below 2.0 was considered abnormal.

Results 34/65 patients had a normal CFR (3.4 ± 1.0), 31/65 patients had a reduced CFR (1.6 ± 0.3 , $p < 0.0001$). Patients with abnormal CFR had both, higher resting (1.35 ± 0.4 vs. 1.0 ± 0.3 , $p < 0.0001$) and lower hyperemic blood flow (2.1 ± 0.6 vs. 3.15 ± 1.0 , $p < 0.0001$). Patients with left ventricular hypertrophy (interventricular septal thickness above 11 mm) had a significantly lower mean CFR value compared to patients with normal ventricles (2.1 ± 0.9 vs. 2.9 ± 1.2 , $p < 0.01$). Patients with reduced CFR were older (60 ± 11 vs. 55 ± 9 , $p < 0.03$) and had higher systolic blood pressure (146 ± 25 vs. 129 ± 16 , $p < 0.002$).

Conclusions A reduced CFR in patients with angina and normal angiogram is due to an impairment of coronary vasodilator capacity as well as to an increase of resting blood flow. Age and arterial hypertension are the main factors influencing the CFR.

Gender Differences in Patients with Acute STEMI Treated with Primary PCI or Thrombolytic Therapy and Impact On In-Hospital Mortality

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Background and Aim Several studies have shown that among patients (pts) with acute STEMI treated either with thrombolytic therapy (TT) or with primary PCI (PPCI), female gender is associated with worse outcome. The aim of this analysis was to evaluate gender differences in both reperfusion strategies and impact on in-hospital mortality.

Patients and Methods In a period of 20 months, 912 pts (female [♀] $n = 247$, 27.1 %) with acute STEMI of ≤ 12 hours duration were treated with reperfusion therapy according to recent guidelines. 631 (69.2 %; ♀: $n = 171$, 27.1 %) pts underwent PPCI and 281 (30.8 %; ♀: $n = 76$, 27 %) received TT, and gender differences were calculated.

Results As shown in table 3, female gender was associated with more advanced age and higher in-hospital mortality in both treatment groups. In the TT group, female gender was additionally associated with prolonged time to reperfusion. No significant difference was observed in terms of infarct location, incidence of shock at presentation and times from onset of pain to hospital and to reperfusion, respectively, in both groups.

In a logistic regression analysis for prediction of in-hospital mortality, female gender was no predictor of death in both treatment groups (PPCI: $p = 0.558$; OR 0.758 and TT: $p = 0.430$; OR 1.712). In the PPCI group, predictors for mortality were age ($p < 0.001$; OR 1.115), incidence of shock ($p < 0.001$; OR 62.5), time from onset of pain to reperfusion ($p = 0.003$; OR 1.248) and infarct location ($p = 0.059$; OR 0.444), in the TT group predictors were age ($p = 0.001$; OR 1.092) and shock ($p < 0.001$; OR 53.71), respectively.

Predictors for mortality in men in the PPCI group were age ($p < 0.001$; OR 1.131), shock ($p < 0.001$; OR 133.328), time from onset of pain to arrival at hospital ($p = 0.019$; OR 0.531) and from onset of pain to reperfusion ($p = 0.001$; OR 2.137) and in the TT group, age ($p = 0.056$; OR 1.062) and shock ($p < 0.001$; OR 33.507). Predictors for mortality in women in the PPCI group were age ($p = 0.004$; OR 1.1), shock ($p < 0.001$; OR 33.678) and time from onset of pain to arrival at hospital ($p = 0.011$; OR 1.342); and in the TT group age ($p = 0.033$; OR 1.136) and shock ($p < 0.001$; OR 176.598).

Conclusion In pts with STEMI, women are associated with higher mortality rates compared to men, either treated with PPCI or TT, mainly because of their more advanced age, but female gender did not emerge as an independent predictor of death.

Table 3: M. Gulesserian et al.

Gender differences	PPCI			TT		
	♂	♀	p-value	♂	♀	p-value
In-hospital mortality (%)	6.5	12.3	0.018	5.4	15.8	0.005
anterior wall infarction (%)	50.3	49.4	0.954	49.3	47.9	0.846
shock (%)	11.2	13.5	0.419	11.4	16.4	0.267
age (y; mean $\pm$ SD)	59 $\pm$ 12	66 $\pm$ 14	< 0.001	59 $\pm$ 13	67 $\pm$ 14	< 0.001
pain to hospital (h; mean $\pm$ SD)	2.9 $\pm$ 2.4	3.0 $\pm$ 2.6	0.58	2.7 $\pm$ 2.3	2.8 $\pm$ 2.3	0.653
pain to reperfusion (h; mean $\pm$ SD)	4.2 $\pm$ 2.8	4.4 $\pm$ 2.8	0.553	2.4 $\pm$ 1.7	3 $\pm$ 2.1	0.039

Taxus Stents for Treatment of Multivessel Disease: 6-Month Clinical and Angiographic Results of the Multicenter Austrian Taxus Multivessel Registry

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Background Randomized trials reported similar or worse long-term outcome of PCI as compared with CABG in multivessel disease. The aim of the multicenter Austrian Taxus Multivessel Registry was to investigate the long-term clinical and angiographic outcomes of patients with multivessel disease after implantations of Taxus drug-eluting stents, in a real-world setting.

Methods Between June 2004 and January 2005, 285 consecutive patients (65 ± 12 y, 64 % male) with symptomatic multivessel coronary artery disease (CAD) were prospectively included in the Registry in 8 Austrian high-volume PCI centres. Six-month clinical control was performed in 230 patients, while 202 patients underwent control coronary angiography (71 % control angiography rate). The primary clinical endpoint of the study was freedom from composite of major adverse cardiac events (MACE, defined as non-fatal MI, death and target vessel revascularization [TVR]). Baseline and follow-up (FUP) quantitative angiographic parameters of in-stent and in-lesion (defined as lesion within 5 mm proximal or distal from stent edge) were measured. Acute lumen gain (ALG) as well as in-stent and in-lesion late lumen loss (LLL) were calculated.

Results Three-vessel disease was documented in 159 patients, 2-vessel disease in 285 patients. The stent/patient ratio was 3.6 ± 1.8. An acute lumen gain of 1.52 ± 0.43 mm was achieved, with a procedural success rate of 99 %. Two patients suffered from subacute stent thrombosis and were repeatedly revascularized. During the long-term FUP, the incidence of AMI was 0.35 %, repeat TVR was necessary in 13 % of all patients, death occurred in 0.7 %. The 6-month overall freedom from MACE was 86.3 %. The binary in-stent restenosis of the angiographically controlled lesions was 20.7 %; an in-stent LLL of 0.33 ± 0.63 mm was measured. No significant edge effect was demonstrated, as the proximal and distal in-lesion LLLs were 0.25 ± 0.26 and 0.38 ± 0.29 mm.

Conclusions. Multivessel Taxus stent implantation can be safely performed on patients with complex coronary artery disease. The need for TVR increases because of the cumulative effect of target lesion re-intervention on patients with multiple lesions.

Inhibition of IL-1-Beta Convertase and Caspase-1 Reduces the Neointimal Development after Balloon Injury and Stenting of the Porcine Coronary Arteries

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Purpose Intravenous application of interleukin1 (IL-1) receptor antagonists has been shown to be associated with a sustained, significant reduction of neointimal proliferation after vessel wall injury. The aim of our study was to investigate the effect of the irreversible IL-1-beta convertase and caspase-1 inhibitor acetyl-tyrosinyl-valyl-alanyl-aspartylchloromethyl-ketone (Ac-YVAD-cmk) on the development of neointima after oversized balloon injury and stenting of the porcine coronary arteries.

Methods Sixteen pigs received intracoronary infusion of 50 mg Ac-YVAD-cmk into the left coronary arteries before stenting (group 1, n = 8) or oversizing balloon injury (group 2, n = 8), while 16 animals served as controls (group 3 with stenting, n = 7; and group 4 with balloon injury, n = 9). After 4 weeks, control coronary angiography was performed. The degree of neointimal hyperplasia was assessed by histomorphometry. Terminal transferase-mediated dUTP nick end labeling (TUNEL) was carried out to calculate the percentage of the number of apoptotic cells in relation to the total number of intimal cells. The tissue IL-1-beta concentration was measured by porcine-specific ELISA.

Results Histomorphometry revealed significantly ($p < 0.05$) smaller neointima in the Ac-YVAD-cmk treated groups compared with the controls: neointimal area in stent groups: 0.7 ± 0.2 vs. 1.73 ± 0.76 mm² in groups 1 vs. 3; and in balloon-groups: 0.5 ± 0.58 vs. 0.93 ± 0.7 mm² in groups 2 vs. 4. Similarly, the maximal % area stenosis was significantly ($p < 0.05$) smaller in treated groups: 31.2 ± 11 % vs. 53.8 ± 12.6 % in groups 1 vs. 3 (stent groups); and $21.8 \pm$

21.3 % vs. 42.0 ± 22.8 % in groups 2 vs. 4 (balloon groups). Lower apoptotic indices of the neointimal cells were observed in the treated animals as compared with the controls: stent groups (group 1 vs. 3): 3.5 ± 3.8 % vs. 13.4 ± 8 %, and balloon groups (group 2 vs. 4): 4.7 ± 5.8 % vs. 13.8 ± 8.6 % of total intimal cells. The coronary arterial tissue IL-1-beta level was significantly ($p < 0.05$) decreased in the animals treated with Ac-YVAD-cmk, as compared with the controls: stent groups (groups 1 vs. 3): 0.29 ± 0.13 vs. 0.6 ± 0.21 pg/mg protein, and balloon groups (groups 2 vs. 4): 0.27 ± 0.15 vs. 0.54 ± 0.18 , 21 pg/mg protein. The tissue IL-1-beta level exhibited a positive linear correlation ($r = 0.68$, $p < 0.001$) with the degree of neointimal hyperplasia.

Conclusions Pre-procedural intracoronary administration of IL-1-beta convertase and apoptosis inhibitor results in significantly decreased neointimal hyperplasia in the animal model of coronary stenting or oversizing balloon injury.

Clinical Presentation and Abnormalities of the ECG in Patients with Acute Central and Peripheral Pulmonary Embolism

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Background and Aim As patients with acute pulmonary embolism (PE) present a high variability in clinical symptoms and ECG abnormalities, we tried to correlate clinical parameters and changes in the ECG at time of admission with the severity of disease (central or peripheral PE).

Methods 426 consecutive patients with acute pulmonary embolism (central/peripheral) in 3 specialized centers (1, 3, 5) were retrospectively analyzed with respect to clinical symptoms at presentation (dyspnoe on effort, dyspnoe at rest, tachypnoe, pleuritic pain, haemoptysis), abnormalities in the first documented 12-lead-ECG (P-pulmonale, S1Q3T3- and S1S2S3-types, clockwise rotation, incomplete or complete right BBB, ST-depression in all leads, ST-elevation in leads V₁ and aVR) and by therapeutic strategy (heparin or thrombolytic therapy), respectively. Data were compared between patients with central (cPE) and peripheral PE (pPE). Statistic calculations (χ -square tests and multivariate analyses) were performed by use of version 11.04 of SPSS software.

Results Compared to pPE (n = 275) patients with cPE (n = 151) suffered significantly more frequently ($p < 0.001$) from dyspnoe at rest (46.4 % vs. 25.8 %) and tachypnoe (29.1 % vs. 10.9 %), whereas pleuritic pain (33.1 % vs. 54.2 %) as well as haemoptysis (0.7 % vs. 9.1 %) were more frequently observed in pPE ($p = 0.001$). Patients with cPE also exhibited more abnormalities in the ECG (Fig. 2) among which especially an isolated ST-segment-elevation in aVR was a significant predictor for cPE. In a multivariate analysis, ST-elevation in V₁ lost its significance, while tachypnoe, dyspnoe at rest, P-pulmonale and isolated ST-elevation in aVR were independent significant predictors for cPE (Tab. 4). Moreover, of the 65 patients receiving thrombolytic therapy (15 %) ST-elevation in aVR was present in 67 %.

Discussion Patients with cPE had more clinical symptoms and ECG abnormalities compared to patients with pPE. The independent ECG parameter "isolated ST-elevation in aVR" seems to predict more severe cases and possibly might indicate the need for thrombolytic therapy in PE patients.

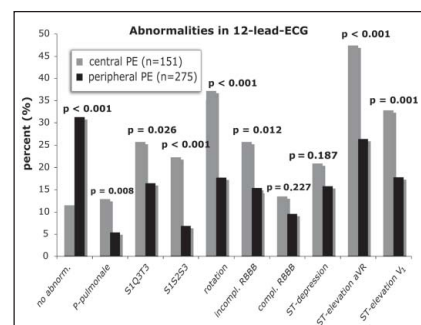


Figure 2: T. Höchtel et al.

Table 4: T. Höchtel et al.

Multivariate analysis (p-value < 0.1 significant)		
Clinic parameter	p-value	Odds ratio (OR)
ST-elevation aVR	0.02	2.1
tachypnoe	0.03	2.1
P-pulmonale	0.07	2.1
dyspnoe at rest	0.07	1.6

Higher Risk of Myocardial Infarction in Young Patients (≤ 40 Years) from Former Yugoslavia

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Background Myocardial infarction is the major killer in the Western society. Around ten percent of myocardial infarction patients are below 45 years of age. A high proportion of young myocardial infarction cases cannot be explained by established risk factors. It came to our attention that a high proportion of young infarction patients treated at our institutions were born in former Yugoslavia. It was our aim to scientifically assess if „Yugoslavian descent“ was an independent risk factor for developing myocardial infarction at a young age.

Methods We performed a hospital-based case control study recruiting myocardial infarction patients 40 years of age or younger. Patients were recruited from two Viennese centers in the immediate post-infarction period. We also recruited a random sample of hospital controls matched on age, gender, time, and center. Logistic regression was used to assess associations between risk factors and myocardial infarction.

Results We recruited 57 myocardial infarction patients and 195 controls. The mean age of infarction patients was 34.6 years. Ninety-one percent of them were male. Eleven infarction patients (19 %) but only eight control patients (4 %) were born in former Yugoslavia. The univariate odds ratio of the association between Yugoslavian descent and myocardial infarction was 5.6 (95 % CI 2.13–14.7, $p < 0.001$). When we adjusted for other risk factors (elevated blood pressure, BMI, smoking, physical activity, family history, HbA_{1c}, total cholesterol, Lp(a), and triglycerides) this association remained unchanged (odds ratio 5.78, 95 % CI 1.25–26.8, p -value 0.025).

Conclusions We found that, in our collective, Yugoslavian descent was associated with the risk of developing myocardial infarction at a young age. This association was independent of other established risk factors. Considering the fact that sixty percent of non-EU immigrants to Austria were born in former Yugoslavia, this is a considerable public health problem.

PCI-Outcome General Hospital of Vienna vs. Europe

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Background The Euro Heart Survey (EHS) on percutaneous coronary interventions (PCI) is part of the European Society of Cardiology (ESC) quality assurance programme to improve cardiac care in Europe.

Methods The registry included procedural and in-hospital outcome data of patients treated with PCI in the General Hospital, Vienna (AKH Wien). During 10 months, 976 consecutive PCI patients were registered. Recorded data included the percentage of acute STEMI, left main stenosis ≥ 50 %, three-vessel disease ≥ 50 %, previous CABG, previous PCI, diabetes, HLP, hypertension. Interventional data such as the rates of left main PCI, multiple-vessel PCI and PCI in bypass were also evaluated as well as the complication rate (mortality, re-infarction, stent thrombosis, percutaneous arterial complications). Our center results are compared to the European outcome (53 centers in 18 countries; 17,022 patients).

Results Acute STEMI (29.51 % AKH Wien vs. 18.75 % ESC); left main stenosis ≥ 50 % (5.43 % vs. 4.64 %); three-vessel disease ≥ 50 % (33.81 % vs. 23.25 %); previous CABG (9.12 % vs. 6.59 %); previous PCI (40.16 % vs. 21.97 %); diabetes (27.46 % vs. 25.34 %), HLP (74.39 % vs. 58.40 %); hypertension (78.28 % vs. 64.52 %); left main PCI (1.64 % vs. 2.49 %); multiple-vessel PCI (18.85 % vs. 17.15 %); PCI in bypass (3.79 % vs. 1.96 %); mortality (3.89 % vs. 1.50 %); re-infarction (2.97 % vs. 1.66 %); stent thrombosis (1.74 % vs. 0.65 %); percutaneous arterial complications (2.46 % vs. 1.78 %).

Conclusion In comparison to the other European centers, the General Hospital of Vienna has a higher mortality rate (3.89 % vs. 1.50 %) and complication rate after PCI. The reasons for this outcome might be the worse health condition of our patients and the fact that we evaluated all patients during a period of time. Therefore, not only a few of the „best“ were selected.

Plasma Interleukin-6 and Nt-proBNP Levels are Strong and Independent Predictors of Outcome in Patients With Cardiogenic Shock

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Introduction High plasma levels of interleukin-6 (IL-6) have been shown to be associated with multiple organ failure in cardiogenic shock (CS) but its relation to outcome has not yet been investigated. Recent studies reported massively elevated levels of N-terminal pro-B-type natriuretic peptide (Nt-proBNP) in critically ill patients admitted to an intensive care unit. At present, however, little is known about prognostic significance of Nt-proBNP in patients with CS.

Methods Plasma levels of IL-6 (R & D Systems, Germany) and Nt-proBNP (Roche Diagnostics, Austria) were determined in blood samples of 48 patients collected at admission to the coronary care unit.

Results Both IL-6 and Nt-proBNP levels were significant predictors of mortality both in univariate ($p = 0.005$ for IL-6 and $p = 0.009$ for Nt-proBNP) as well as in multivariate Cox-regression analyses ($p = 0.01$ and 0.009 , respectively). According to ROC analyses, IL-6 of 200 pg/ml and Nt-proBNP of 12,782 pg/ml had the highest predictive value of 30-day mortality. None of the patients with both markers above these respective cut-offs survived more than 15 days, while patients with lower levels of Nt-proBNP and/or IL-6 had significantly better survival ($p < 0.001$; **Figure 3**).

Conclusion Nt-proBNP and IL-6 levels are strong and independent predictors of outcome in patients with CS. Simultaneous measurements of these markers in the intensive care unit could help develop early risk stratification of CS.

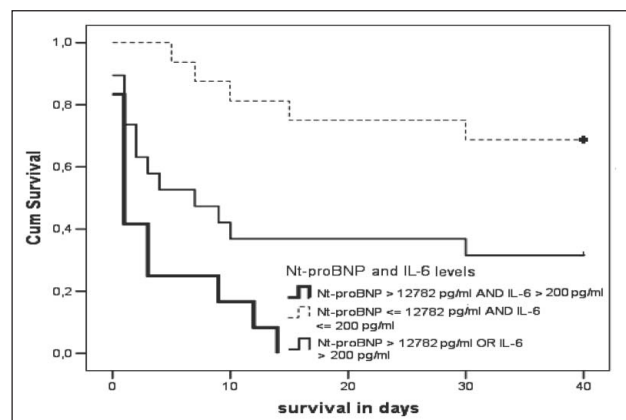


Figure 3: R. Jarai et al.

Influence of Pre-Hospital Delay on Door-to-Balloon Time and Impact on In-hospital Mortality in Patients With Acute STEMI Treated With Primary PCI

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Background and Aim The purpose of this analysis was to evaluate if prolonged pre-hospital delay (PHD) influences door-to-balloon (DTB) times and in-hospital mortality in the Vienna STEMI registry.

Patients and Methods In this registry, 631 consecutive patients (pts) with acute STEMI of < 12 hours (h) duration underwent primary PCI (PPCI). PHD was calculated as the time from symptom onset to arrival at hospital and DTB time was calculated as the time from arrival at hospital to 1st balloon inflation. According to the median PHD of 2 hours (h), pts were divided into 2 different groups, with PHD of ≤ 2 h and > 2 h, respectively.

Results Pts with PHD of ≤ 2 h had significantly shorter DTB times than patients with PHD of > 2 h ($p = 0.021$). In a univariate logistic regression for prediction of in-hospital mortality, DTB time was a significant predictor of death in the PHD ≤ 2 h group ($p = 0.001$) but not in the PHD > 2 h group ($p = 0.256$). In a multivariate analysis including age, shock at presentation, gender, infarct location and DTB time, predictors of mortality in the PHD ≤ 2 h were age ($p = 0.001$; OR 1.078), shock ($p < 0.001$; OR 37.123) and DTB time ($p = 0.088$; OR 1.007), while in the PHD > 2 h group predictors were age ($p < 0.001$; OR 1.304) shock ($p < 0.001$; OR 1068.072) and infarct location ($p = 0.068$; OR 0.198) but not DTB time ($p = 0.951$; OR 1).

Conclusion In this registry, pts with shorter PHD had a significant benefit of short DTB in terms of in-hospital mortality. On the other hand, in pts with prolonged PHD additional loss of time for PPCI did not further influence in-hospital mortality. Accordingly, in pts with short PHD (≤ 2 h) time from 1st medical contact to PPCI is crucial and should be kept as short as possible.

Table 5. K. Kalla et al.

	PHD ≤ 2 h	PHD > 2 h	p-value
in-hospital mortality (%)	7.9	7.6	0.91
shock (%)	13	10.2	0.285
anterior wall infarction (%)	49.1	50.7	0.691
female (%)	26	28.4	0.504
age (y; mean $\pm$ SD)	60 $\pm$ 13	61 $\pm$ 13	0.547
PHD (h; mean $\pm$ SD)	1.3 $\pm$ 0.5	4.8 $\pm$ 2.5	< 0.001
PHD (h; median $\pm$ SD)	1.3 $\pm$ 0.5	4 $\pm$ 2.5	< 0.001
DTB (min; mean $\pm$ SD)	77 $\pm$ 46	86 $\pm$ 55	0.021
DTB (min; median)	65	72	0.021

Dynamic N-13 Ammonia-PET Myocardial Blood Flow Quantification: Comparison of Two Tracer Kinetic Models

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Aim The aim of the study was the comparison of two tracer-kinetic models (two- [2CM] and three- [3CM] compartment models) for quantification of myocardial blood flow (MBF) under resting (MBFR) and stress conditions (MBFS) and coronary flow reserve (CFR) from dynamic N13-ammonia (NH3) PET images.

Methods 26 patients (19♂, 7♀; age: 55 $\pm$ 13 yrs) with coronary artery disease (n = 19) or typical angina and coronary risk factors underwent NH3-PET imaging during resting conditions and after pharmacological stress with adenosine (140 μ g/kg/min for 5 min.). Dynamic PET acquisition protocol consisted of 21 frames for a total of 23 min. The 2CM used the first 12 frames (120 s) to determine MBF, while the 3CM used all 21 frames. Time-activity curves for 12 sectional regions of 4 short-axis planes were calculated and model-fitting was applied to generate estimates of myocardial blood flow. For both methods, an identical set of short-axis slices was used.

Results The calculated MBF (ml/g/min) by 2CM and 3CM were 0.9 $\pm$ 0.33 and 1 $\pm$ 0.36 under resting ($p < 0.05$), and 2.05 $\pm$ 0.98 and 2 $\pm$ 0.84 under stress ($p = n. s.$) conditions, respectively. CFR was 2.29 $\pm$ 0.72 for 2CM and 2.1 $\pm$ 0.9 for 3CM ($p = n. s.$, paired t-test). The two methods correlated significantly for calculation of MBFR ($r = 0.8$, SEE = 0.22, $p < 0.0001$) and MBFS ($r = 0.7$, SEE = 0.61, $p < 0.0001$).

Conclusion MBFR calculated by 2CM were found to be slightly lower than MBFR performed by 3CM, while MBFS and CFR did not significantly differ between the two models. This difference needs to be considered for patient follow-up and in clinical trials.

Comparison of Model-Based Analysis of Gated ¹¹C-Acetate-PET and Echocardiography for Determination of Left Ventricular Ejection Fraction

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Aim The purpose of this study was to compare model-based analysis of gated ¹¹C-acetate positron emission tomography (PET) and echo-

cardiography (ECHO) for determination of left ventricular ejection fraction (EF).

Material and Methods 9 patients (8♂, 1♀; age: 61 $\pm$ 9 years) with coronary artery disease underwent ECG-gated cardiac ¹¹C-acetate PET imaging for evaluation of myocardial oxygen consumption and perfusion. After injection of 500 MBq ¹¹C-acetate, a 15-minute ECG-gated acquisition with 8 phases per heart cycle was performed. For PET images, endocardial and epicardial borders of the LV were generated on a set of short axis images with a model-based analysis tool. Endsystolic and enddiastolic volumes and EF were measured using Simpson's method. EF was then compared to the echocardiographic measurements, obtained by Simpson's method applied on the 4- and 2-apical chamber views.

Results EF (mean $\pm$ SD) measured by PET and ECHO were 29.5 $\pm$ 6.4 % and 32 $\pm$ 10.4 %, respectively. PET measured slightly lower EFs than ECHO, however the difference was not significant (paired t-test). A significant correlation was observed between PET and ECHO for calculation of EF ($r = 0.86$, SEE = 5.5; $p < 0.01$).

Conclusion Measurements of contractile function by ECG-gated cardiac ¹¹C-acetate PET imaging using a model-based method showed close agreement with results from ECHO. However, ¹¹C-acetate PET measures slightly lower EFs than ECHO.

Neurohormones Predict Outcome in Asymptomatic Severe Mitral Regurgitation

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Background The management of asymptomatic severe mitral regurgitation (MR) remains controversial. This study sought to evaluate whether plasma levels of neurohormones can predict short-term development of symptoms or left ventricular (LV) dysfunction and, therefore, improve timing of surgery.

Methods 78 asymptomatic pts (age 57 $\pm$ 15 yrs; female n = 27) with severe MR, normal LV function (LVEF > 60 % [64 $\pm$ 5 %], LVESD < 45 mm [33 $\pm$ 5 mm]) and no severe pulmonary hypertension (systolic pulmonary artery pressure [PAP] 36 $\pm$ 9 mmHg) were followed for 465 $\pm$ 221 days (range, 41–811). Clinical and echocardiographic evaluation as well as determination of plasma levels of B-type natriuretic peptide (BNP) and N-terminal BNP (NtBNP) were repeated every 6 months. Endpoints were defined as development of symptoms or of LV dysfunction (LVEF ≤ 60 %, LVESD ≥ 45 mm).

Results 18 of 78 pts became symptomatic during FU whereas no pt developed LV dysfunction. Pts who developed symptoms within the following 6 months had higher BNP and NtBNP levels and higher PAP at their previous visits than those who remained asymptomatic. By univariate analysis, BNP, NtBNP and PAP were significant predictors of symptom development whereas LV size and EF were not. ROC-analysis yielded c-values of 0.874, 0.839 and 0.824 for BNP, NtBNP and PAP, respectively. By multivariate analysis, neither BNP nor NtBNP nor PAP reached statistical significance as an independent predictor of symptom development. A BNP value ≥ 65 pg/ml had a sensitivity of 84 % and specificity of 77 % for symptom development within 6 months. Sensitivity/specificity were 82 %/76 % for NtBNP ≥ 234 pg/ml and 80 %/60 % for PAP ≥ 37 mmHg. Pts with BNP < 47 pg/ml, NtBNP < 182 pg/ml or PAP < 33 mmHg had a very low likelihood to become symptomatic (sensitivity for values beyond these cut-offs 95 %) whereas those with BNP > 93 pg/ml, NtBNP > 510 pg/ml or PAP > 44 mmHg were very likely to develop symptoms during the following 6 months (specificity for values beyond these cut-offs 90 %).

Conclusion BNP and NtBNP together with PAP are predictors of outcome in asymptomatic severe MR. Their serial measurement (every 6 months) appears to allow stratification of these pts into a group likely to benefit from elective surgery, a group that may safely be followed conservatively and an intermediate group that requires further evaluation.

Flow-Mediated Dilatation is Associated With the Carotid Intima-Media Thickness and Presence of Carotid Plaques in Patients Without Cardiovascular Disease

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Background Brachial artery flow-mediated dilatation (FMD), carotid intima-media thickness (IMT) and presence of carotid plaques are used as surrogate markers of advanced subclinical atherosclerosis. The relationship between carotid IMT, presence of carotid plaques and brachial FMD has not been well-established. The purpose of the study was to determine the relationship of brachial artery FMD with carotid IMT and ultrasound-detected carotid plaques (CP) in individuals without cardiovascular (CV) disease.

Methods We assessed traditional risk factors, carotid IMT and brachial artery FMD in 160 individuals (69 males, aged 49.91 ± 7.16 years) without clinical evidence of atherosclerotic disease and analysed relationship of brachial artery FMD with carotid IMT and presence of carotid plaques.

Results Carotid IMT correlated with Body Mass Index (BMI) ($p = 0.001$), systolic blood pressure (SBP) ($p < 0.001$), diastolic blood pressure (DBP) ($p < 0.001$), total cholesterol (TC) ($p = 0.001$), high-density lipoprotein (HDL) cholesterol ($p = 0.003$), low-density lipoprotein (LDL) cholesterol ($p < 0.001$), glucose ($p < 0.001$) and with ten-year total fatal CV risk, estimated by SCORE ($p < 0.001$). Presence of CP was associated with SBP ($p < 0.001$), DBP ($p < 0.001$), BMI ($p = 0.019$), TC ($p = 0.002$), HDL cholesterol ($p = 0.006$), LDL cholesterol ($p < 0.001$) but not with the SCORE risk ($p = 0.869$). Brachial artery FMD inversely correlated with DBP ($p < 0.001$), carotid IMT ($p < 0.001$) and with SCORE risk ($p = 0.005$). Multivariate analysis revealed that after adjustment for brachial artery diameter and patients' age carotid IMT and presence of carotid plaques remain significant predictors of FMD ($p = 0.009$ and $p = 0.006$, respectively).

Conclusion Carotid IMT and brachial FMD correlated with ten-year total fatal CV risk, estimated by SCORE. Flow-mediated dilatation was associated with the carotid intima-media thickness and presence of carotid plaques in patients without cardiovascular disease.

Stenting of Aortic Coarctation: a Ten-Year Follow-Up

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Background Stent implantation for the treatment of aortic coarctation is a field of increasing importance in adolescent and adult congenital heart disease. While balloon coarctation angioplasty has been considered an alternative to surgery, stent implantation is evolving now as the treatment of choice for coarctation in the adolescent and adult patient. Moreover, the availability of covered stents offers new interventional perspectives, extending the technique to long and extreme subaortic forms of coarctation. We report our 10-year experience with stenting of aortic coarctation.

Patients and Methods In our institution, 16 patients (13 male [81 %]; mean age 29 ± 16 years, age range 13–64 years) underwent stent implantation for the treatment of aortic coarctation between July 1996 and December 2005. Six patients (37.5 %) underwent the procedure for native coarctation of the aorta, another six patients presented with recurrent coarctation after surgical repair, three patients (19 %) had developed re-coarctation after previous balloon angioplasty, and one patient (6 %) had a history of surgical repair and balloon angioplasty. From 1996 until 2003, ten Palmaz stents (lengths 40–50 mm) were implanted in nine patients. Since 2004, the coarctations of seven patients were treated with Cheatham platinum (CP) stents (lengths 28–39 mm; two covered stents). A bicuspid aortic valve was the most frequent anomaly associated with aortic coarctation.

Results Stent implantation was successful in all cases. The minimal narrowing of the stenosis before stent implantation was 7 ± 2 mm (range 3–10 mm). Prestenotic aortic diameter was 15 ± 5 mm (range 8–27 mm), poststenotic diameter was 21 ± 7 mm (range 13–37 mm). Stents could be dilated to a diameter of 15 ± 4 mm (range 9–20 mm). Systolic aortic pressure gradients dropped from 35 ± 15 mmHg (range 10–65 mmHg) to 6 ± 6 mmHg (range 0–19 mmHg), while mean pressure gradients dropped from 13 ± 8 mmHg (range

0–32 mmHg) to 2 ± 3 mmHg (range 0–9 mmHg). The postinterventional course of one patient was complicated by a spurious aneurysm of the femoral artery requiring surgical repair. All other patients had an uneventful course. Antihypertensive drug treatment could be reduced in most patients after stent implantation. No reintervention has been necessary in any patient so far.

Conclusions Transcatheter therapy of aortic coarctation with stent implantation is safe and effective. Thus, the procedure can be considered the treatment of choice for patients with coarctation from adolescence to adulthood. With the advent of covered stents, even long and extreme subaortic coarctations can be treated. Whether these promising mid-term results can be maintained needs to be determined.

Echocardiographic Phenotyping in a Transgenic Mouse Model

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Background With the advent of transgenic technology, genetically altered mice with remarkable cardiovascular phenotypes have become available. To benefit from the full potential of these genetically engineered mice, it is crucial to have approaches to an accurate and reproducible assessment of cardiac anatomy and performance. Cardiac ultrasound is a proved and well-established technique for non-invasive evaluation of left ventricular (LV) morphology and function in different species. In this particular study, we used transthoracic echocardiography (TTE) for cardiac phenotyping in mice lacking adipose triglyceride lipase (ATGL). ATGL-deficient mice are supposed to die from lethal cardiomyopathy due to defective lipolysis.

Materials and Methods TTE was performed in non-anesthetized mice (12 knock-out, 11 wild-type, age range 59–136 days) using an Acuson Sequoia 512 equipped with a 15 MHz linear transducer (15L8). The heart was first imaged in the two-dimensional (2-D) mode in the parasternal long- and short-axis view. From short-axis view at the tip of the papillary muscle, motion-mode (M-mode) images were obtained for measurement of LV enddiastolic and end-systolic diameter as well as interventricular septum (IVS) and left ventricular posterior wall (LVPW) thickness during diastole and systole. From these M-mode dimensions, LV fractional shortening (FS), LV ejection fraction (EF), IVS and LVPW thickening, IVS/LVPW ratio, and LV myocardial mass (LVMM) were calculated.

Results 2D-echocardiography revealed marked concentric LV hypertrophy with an abnormal myocardial texture in ATGL-deficient animals. LV hypertrophy, abnormal myocardial texture, and impaired LV systolic function with asynchronous contraction patterns developed progressively with age. Additionally, in one older animal a large circumferential pericardial effusion could be clearly detected. M-mode tracings confirmed pronounced LV hypertrophy in ATGL-deficient mice as indicated by increased diastolic wall thickness and LVMM, while systolic wall thickness as well as chamber dimensions were not significantly different between the two groups. Systolic thickening of the IVS and LVPW was markedly reduced in ATGL-deficient mice, indicating a significantly reduced LV systolic function. This was also reflected by a significant reduction in LV FS and LV EF in ATGL-deficient mice compared to controls.

Conclusions Echocardiography provides a powerful tool for studying cardiac morphology and function in mice. In this particular mouse model, TTE clearly allowed to discriminate knock-out animals from controls and to follow the development of heart failure in ATGL-deficient mice.

The Prognostic Value of Exercise Echocardiography for Long-Term Mortality is Greater in Patients without Left Atrial Enlargement

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Background Exercise echocardiography (EE) is useful to detect coronary artery disease (CAD) and a negative test result is associated with an excellent prognosis. Left atrial (LA) enlargement is an indicator of longstanding diastolic dysfunction, associated with heart failure and other cardiovascular events including death. It is unknown if the predictive value of EE is independent of LA size.

Methods

- 1133 patients (mean age 60 ± 14 years, 49 % men) who underwent exercise echocardiography (EE) following the Bruce protocol between 1995 and 2001 were identified.
- Exclusion criteria were hx of MI/CABG/PCI, valvular disease/prosthetic valve, inadequate images, pacemaker, pericardial effusion.
- Exercise wall motion score index (WMSI) was calculated using a 5-point scoring system and 16-segment model by dividing the score sum by the number of segments visualized. Double product was calculated from peak blood pressure and heart rate.
- LA anteroposterior dimension at rest was measured using 2D-guided M-mode transthoracic echocardiography and indexed to BSA.
- An exercise WMSI > 1 and LA size > 40 mm were considered abnormal.
- Clinical risk factors were obtained at the time of the EE. Follow-up was complete. Death was ascertained from the Accurant® tracking system and medical record.

Results

- 123 patients (11 %) died after a median FU of 4.9 years.
- 42 deaths (8 %) occurred in the group of 542 patients with LA size ≤ 40 mm compared to
- 81 deaths (14 %) in 591 patients with LA size > 40 mm.
- The hazard ratio of an abnormal EE to predict death was 1.5 ($p = 0.1$, 95 % CI 0.9–2.2) in patients with LA size > 40 mm and 3.0 ($p < 0.0001$, 95 % CI 1.6–5.5) in patients with normal LA size. (Figure 4).
- In a multivariable analysis of all patients, every increase in LA size of 1 mm/m^2 independently increased the risk of death by 8 % ($p = 0.002$) (Table 7).

Conclusion Patients with enlarged LA uniformly share a poor prognosis. EE is more useful to risk stratify patients without LA enlargement.

Table 6. M. Osranek et al.

	Percent (%)
• Male	49
• Angina	
None	50
Atypical	40
Typical	10
• Hypertension	53
• Diabetes mellitus	7
• Smoker	44
• Family history of CAD	37
• Hypercholesterolemia	56
• Medications	
Beta blockers	21
Calcium channel blockers	16
Digoxin	8

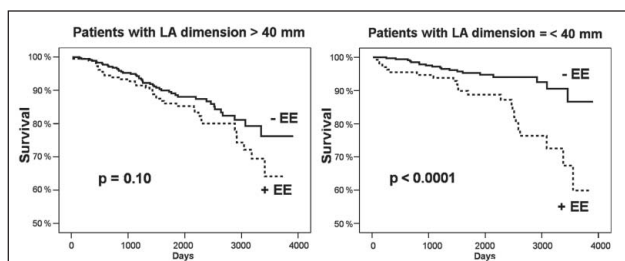


Figure 4. M. Osranek et al.

Table 7. M. Osranek et al.

	p-value	Hazard ratio	95 % lower CI	95 % upper CI
Age	< 0.0001	1.04	1.02	1.06
Double Product ($\text{mmHg} \times \text{s}^{-1}$)	0.001	0.95	0.92	0.98
LA size (mm/m^2)	0.002	1.08	1.03	1.13
Exercise WMSI	0.02	1.60	1.01	2.33
Male gender	0.02	1.57	1.08	2.29
Diabetes mellitus	0.03	1.88	1.07	3.28
Hypercholesterolemia	0.10	0.74	0.52	1.06
Smoking	0.17	1.29	0.90	1.86
Hypertension	0.53	0.89	0.62	1.28

VE-Cadherin Real-Time PCR Assay for Vessel Quantification

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Background Vascular endothelial cadherin (VE-cadherin) is stably expressed and localized at adherens junctions exclusively in vascular endothelial cells. VE-cadherin is required for cell survival, vasculogenesis and angiogenesis. Quantitation of vessel formation is important for the understanding of tissue remodeling. Human VE-cadherin was employed to quantify the number of human endothelial cells *in vitro* and *in vivo*, with the ultimate goal to quantitate vessels.

Methods A standard curve of the pDR2 plasmid containing the VE-cadherin DNA was prepared. The number of plasmids per μl isolate was calculated by dividing the measured DNA concentration by the calculated molecular weight of a single plasmid (0.0136 fg). RNA isolated from a pellet of control cells not containing VE-cadherin was used to spike the pDR2 plasmid standard with 18S RNA. VE-cadherin copy numbers in 10 ng cDNA of 3 different HUVEC cell cultures were determined and divided by the input number of cells yielding the number of VE-cadherin copies per cell. Using the same techniques, fresh endothelial cells were scrape-isolated from pieces of human aorta removed during cardiopulmonary surgeries, separated, and employed in the RT-PCR assay.

Results The number of VE-cadherin copies per cell were 45 (median, range 30–60) depending on the use of various culture systems. By contrast, VE-cadherin copy numbers per cell were 15 (median, range 11–29) in freshly isolated aortic endothelial cells.

Discussion Cultured endothelial cells contain higher copy numbers of VE-cadherin than cells *in vivo*. The VE-cadherin real time PCR assay allows to calculate the number of vascular endothelial cells in different tissue samples and is sufficiently accurate to determine low cell numbers. Ongoing studies clarify VE-cadherin copy numbers in different tissues, and attempt to correlate the molecular data with endothelial cell counts derived from 3D-microscopy.

Implantable Loop Recorder in Unexplained Syncope: Mechanisms and Predictors of Recurrence in Patients with and without Structural Heart Disease

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Aim To stratify mechanisms and predictors of unexplained syncope documented by an implantable loop recorder (ILR) with IS-SUE-study-based electrocardiographic classification in patients with and without structural heart disease (SHD).

Patients and Methods An ILR was implanted in 70 patients where syncope remained unexplained after conventional testing (34 male/36 female, aged 55 ± 17 years). SHD was present in 33 patients (ischemic cardiomyopathy = 16, dilated cardiomyopathy = 9, and hypertrophic cardiomyopathy = 8) and absent in 37 patients (LV-ejection fraction 46 ± 3.6 % vs. 61.4 ± 6.9 %).

Results During a mean implantation time of 16 ± 8.1 months, recurrences occurred in 30/33 patients with SHD (91 %) and in 30/37 patients without SHD (81 %). Fifteen patients (46 %) vs. 19 patients (51 %) had an ILR-documented arrhythmia at the time of recurrence which led to specific therapy: beta-blocker therapy, amiodarone/catheter ablation and pacemaker therapy in 4, 5 and 6 patients with SHD and in 8, 1 and 10 patients without SHD, respectively. The remaining 15 patients (46 %) with SHD and 11 patients (30 %) without SHD had normofrequent sinus rhythm during the syncopal recurrence. Recurrences were stratified according to the ISSUE-study-proposed electrocardiographic classification and the two groups differed significantly in "Type 3 arrhythmia" (no or slight rhythm disturbances) (SHD: 57 %, no SHD: 33 %, $p = 0.0356$) only. Brady-arrhythmias leading to pacemaker implantation were detected in 18 % of patients with SHD and 27 % of patients without SHD ($p = \text{n.s.}$). On stepwise multivariate analysis, major depression was the only variable predictive for early recurrence during ILR implantation ($p = 0.0123$, HR 3.353), but with sinus rhythm during recurrence in 88 % of cases.

Conclusions Using the proposed electrocardiographic classification, the presence of SHD has no predictive value in the occurrence of asystole, critical bradycardia or tachycardia in patients with unexplained syncope. Major depression is predictive for early syncopal recurrence but without arrhythmogenic substrate in most cases. The ILR leads to specific therapy in half of the patients irrespective of an underlying heart disease.

Multislice Computed Tomography in Detection of Coronary Artery Disease in Heart Transplant Patients

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Objectives We sought to assess whether multislice computed tomography (MSCT) permits the exclusion of coronary artery disease in asymptomatic heart transplant patients.

Background Post-transplant follow-up of heart transplant patients consists of regular angiography (1, 3, 5, 7, 10 and 15 years) after transplantation and goes along with a significant amount of costs, discomfort and risk.

Methods MSCT scans (Philips "CT MX 8000 IDT") and invasive coronary angiography were performed in 66 consecutive heart transplant patients in sinus-rhythm scheduled for routine invasive coronary angiography. 100 ml non-ionic iodinated contrast medium were applied for CT-angiography. All scans were performed during one breath-hold. In axial MSCT images and multiplanar reconstructions, all coronary arteries and side branches were assessed for the presence of stenoses exceeding a 70 % diameter reduction. Coronary segment analyses were performed according to a modified American College of Cardiology/American Heart Association (ACC/AHA) classification in vessels with a diameter exceeding 1.5 mm. Results were compared with quantitative coronary angiography analysis.

Results MSCT was successfully performed in 60 patients enrolled in our analysis; fourteen patients (21 %) had at least one significant stenosis, 9 (14 %) suffered from coronary artery disease without significance and the remaining 43 (65 %) were totally free from graft sclerosis. Forty-one out of 43 patients (95 %) who were estimated to be fully evaluable in MSCT were correctly classified. On a per-segment-basis, 10 out of 19 high-grade stenoses were assessed correctly, 4 were unevaluable and 5 were incorrectly classified as non-significant (sensitivity: 53 %, specificity: 94 %). After exclusion of 45 out of 764 coronary segments (6 %) due to motion artifacts or severe calcification, sensitivity, specificity, positive and negative predictive values were 67 %, 100 %, 91 % and 99 %, respectively.

Conclusion Despite a low sensitivity, the high negative predictive value allows the exclusion of significant CAD with a high certainty in a large number of patients. From the clinical point of view, this might spare this patient cohort an additional invasive coronary angiography.

Accuracy of Non-Invasive 16-Slice CT Angiography in Patients with Stable Angina Pectoris Compared with Invasive Coronary Angiography

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Objectives To assess whether 16-slice computed tomography (CT) permits detection or exclusion of coronary artery disease in patients with stable angina.

Background Non-invasive coronary CT angiography is a promising coronary imaging technique.

Methods 30 consecutive patients with stable angina pectoris underwent routine invasive and CT coronary angiography. Retrospective ECG-gated CT coronary angiography was performed with a 16-slice CT-scanner (Philips MX 8000 IDT) after bolus-triggered i. v. administration of 100 ml non-ionic iodinated contrast medium. Beta blockers were not administered routinely before the examination. In axial MSCT images and multiplanar reconstructions, all coronary arteries and side branches exceeding 1.5 mm in diameter were assessed for the presence of stenoses using a 15-segment classification according to the American College of Cardiology/American Heart Association (ACC/AHA). The consensus results of two blinded readers were compared with quantitative coronary angiography analysis.

Results MSCT was performed successfully in all patients enrolled in our analysis. According to invasive coronary angiography, 11 (37 %) patients had no significant coronary artery disease and 1VD, 2VD and 3VD were found in 7 (23 %), 9 (30 %) and 3 (10 %) patients, respectively. After exclusion of all unevaluable segments, the sensitivity of coronary CT-angiography for detection of significant lesions was as high as 47 % (20 of 43 significant stenoses), specificity

was 95 % (204 of 214), positive predictive value (PPV) was 67 % (20 of 30) and negative predictive value (NPV) was 90 % (204 of 227).

Conclusion Coronary MSCT is a sufficient method to exclude coronary artery disease. However, in the detection and quantification of significant coronary artery stenoses 16-slice CT cannot be regarded as a reliable diagnostic tool.

Gender Differences in Severe Aortic Stenosis Referred to Aortic Valve Surgery

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Background Aortic stenosis has become the most frequent valve disease in developed countries and has been extensively studied in recent years. Although gender differences have drawn increasing attention in cardiology, little is known so far about gender differences in aortic stenosis.

Methods The clinical and echocardiographic characteristics of 439 consecutive patients (age 70 ± 11 yrs) who were seen in our outpatient clinic and referred to surgery because of severe symptomatic aortic stenosis were analysed with regard to potential gender differences.

Results Patients were almost equally distributed between men ($n = 205$) and women ($n = 234$). Female pts were, however, significantly older at presentation with a mean age of 73 ± 10 yrs compared to 66 ± 11 yrs ($p < 0.0001$). They were more symptomatic than males with a New York Heart Association class 2.5 ± 0.7 vs. 2.1 ± 0.7 , respectively ($p < 0.0001$). Females had smaller valve areas. However, when adjusting for body surface area (BSA), this difference disappeared (0.33 ± 0.1 vs. 0.34 ± 0.08 cm²/m²; $p = 0.21$). Nevertheless, mean aortic valve gradients were significantly higher in females with 66.6 ± 19.1 vs. 62.1 ± 20.2 mmHg ($p = 0.017$). LV size did not differ when adjusting for BSA but females presented with significantly less LV hypertrophy. Notably, 74 % of women presented with hypertension compared to 58 % of men ($p < 0.0005$). However, coronary artery disease was significantly more frequent in male patients (39 % vs. 27 %; $p = 0.01$).

Conclusion Female patients with aortic stenosis referred to aortic valve replacement are older and more symptomatic compared to male patients. Further research must address whether this is due to differences in disease onset and progression or whether female patients get delayed medical attention for some reasons.

Left Atrial Size Independently Predicts Outcome in Asymptomatic Severe Mitral Regurgitation

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Background Left atrial (LA) size is affected by left ventricular (LV) diastolic pressure, the degree of ventricular remodeling, the occurrence of atrial fibrillation and the presence of mitral regurgitation (MR) itself. LA size has been proposed to be a predictor of outcome after mitral valve replacement with preserved LV function. However, the predictive value of LA size for development of symptoms or LV dysfunction among pts with severe MR has not been studied.

Methods 132 consecutive asymptomatic pts (age 55 ± 15 yrs, 49 female) with severe degenerative MR and normal LV function were prospectively followed for a median of 69 months. Pts underwent serial clinical and echocardiographic exams. The following potential predictors of outcome were studied: LA size, endsystolic and enddiastolic LV diameter, pulmonary artery pressure and clinical risk factors.

Results Kaplan-Meier event-free survival for the entire pt group, with endpoints defined as development of symptoms or LV dysfunction ($n = 38$) and death related to MR ($n = 0$) was 92 ± 2 % at 2 yrs, 78 ± 4 % at 4 yrs, 65 ± 5 % at 6 yrs and 55 ± 6 % at 8 yrs. LA size was the strongest independent predictor of outcome: no events were

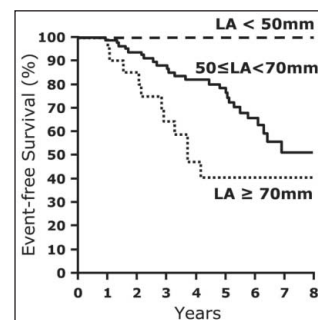


Figure 5. R. Rosenhek et al.

observed in the group with a LA < 50 mm. Event-free survival for patients with LA 50 to 69 mm was $94 \pm 3\%$ at 2 yrs, $82 \pm 5\%$ at 4 and $51 \pm 8\%$ at 8 yrs vs. $85 \pm 8\%$ at 2 yrs, $47 \pm 12\%$ at 4 yrs and $40 \pm 12\%$ at 8 yrs for patients with a LA ≥ 70 mm ($p = 0.0001$). None of the other studied parameters reached significance as predictors of outcome in multivariate analysis (Figure 5).

Conclusion LA size is a strong and independent predictor of outcome in patients with asymptomatic severe MR. Patients can be stratified by LA size in groups at low, intermediate and high risk for subsequent symptom or LV dysfunction development requiring surgery.

Core and Concomitant Components of the Metabolic Syndrome

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Aim of the Study We sought to analyze what the core components of the metabolic syndrome are and which cardiovascular risk factors are concomitant according to their relation to the insulin resistance indexes.

Methods or Patients We studied 127 subjects (64 % men and 36 % women, aged 49.8 ± 9.4 years) suspected of having metabolic syndrome (MS). All patients underwent detailed assessment of cardiovascular risk factors, including a serum lipid profile measurement and an oral glucose tolerance test (OGTT). Serum insulin was measured at baseline and 120 minutes after glucose load.

Results The metabolic syndrome according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III was diagnosed in 55 patients (43 %), according to the IDF classification in 83 patients (65 %). Newly diagnosed diabetes, impaired glucose tolerance or fasting hyperglycaemia was present in 84 patients (66 %). Normal fasting glucose (< 5.6 mmol/l) had 39 % of patients with impaired glucose tolerance ($n = 9/23$). Dyslipidemia, typical of the metabolic syndrome according to the IDF criteria, was found in 70 patients (55 %). Any type of dyslipidemia was present in 91 patients (72 %). Insulin resistance indexes (HOMA_{IR} and ISI) were correlated with Body Mass Index ($r = 0.36$, $p < 0.0001$ and $r = -0.321$, $p = 0.003$, respectively) and waist circumference ($r = 0.40$, $p < 0.0001$ for HOMA_{IR}; $r = -0.31$, $p = 0.004$ for ISI), as well as with fasting and OGTT glycaemia. No relationship was found between insulin resistance indexes and the presence of arterial hypertension (logistic regression coefficient $\beta = 0.17$, $p = 0.52$ for HOMA_{IR} and $\beta = -1.23$, $p = 0.34$ for ISI). Correlation between insulin resistance indexes (HOMA_{IR}, ISI) and serum lipid profile was not found, either.

Conclusions Abdominal obesity and any type of glycaemic disorder seem to be the core components of the metabolic syndrome. An oral glucose tolerance test gives additional value for discrimination of subjects with glycaemic disorder.

Single-Center Analysis of a Randomized Trial Comparing PCI and CABG in Patients with Significant Three-Vessel and/or Left Main Disease

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Background BARI and ARTS showed significant clinical improvement in patients with three-vessel disease after coronary artery bypass graft (CABG) when compared to balloon angioplasty and stenting, respectively. Thus, the aim of the SYNTAX trial is to compare the clinical outcome of the percutaneous coronary intervention (PCI) with drug-eluting stents and CABG in patients with three-vessel disease and/or left main artery disease.

Methods If patients accepted randomization, they were allocated either to PCI or to CABG. During PCI, they received Taxus-Express² drug-eluting stents. Follow-up visits comprised a clinical examination, a specialized questionnaire and ECG. An angiographic six-month follow-up was also planned.

Results From November 2005 on, twenty patients have been randomized, of whom twelve were allocated to PCI and eight to CABG. One PCI patient with perforated LAD and following emergency CABG died one week after the procedure due to multiorgan dis-

eases. One patient suffered from subacute stent thrombosis four days after PCI, which was successfully revascularized. On average, patients indicated dyspnea NYHA I-II or angina CCS I-II at the one-month follow-up visit. One patient was hospitalized due to an increase of enzymes. Angiography revealed an occlusion of a diagonal branch in a completely stented LAD. Between first and second follow-up, one patient died due to a septic shock. At the six-month visit, the observed patients felt quite as well as after first follow-up.

Conclusion At short-term follow-up, there was no significant difference between PCI with drug-eluting stent and CABG concerning the clinical outcome, although PCI showed more post-procedural events.

L-arginine and Asymmetrical Dimethylarginine (ADMA) in Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

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Background Nitric oxide (NO) is synthesized from L-arginine by NO synthase, which can be inhibited by asymmetrical dimethylarginine (ADMA). ADMA is increased in idiopathic pulmonary hypertension (iPAH) and associated with unfavorable outcome. Chronic thromboembolic pulmonary hypertension (CTEPH) shows vascular hypertensive changes similar to iPAH. Therefore, we hypothesized that plasma levels of ADMA may be increased in patients with CTEPH.

Methods We collected data from 10 patients with iPAH and 28 patients with CTEPH (13 proximal and 15 distal). L-arginine and ADMA plasma levels were measured by high-performance liquid chromatography. All patients underwent right heart catheterization. In addition, levels of ADMA were measured in 14 age- and sex-matched controls.

Results All patients had severe pulmonary hypertension (iPAH: MPAP 56 ± 11 mmHg, CI 2.2 ± 0.5 L $\times$ min⁻¹ $\times$ m⁻²; CTEPH: MPAP 51 ± 6 mmHg, CI 2.3 ± 0.6 L $\times$ min⁻¹ $\times$ m⁻²). There was no difference in haemodynamics between proximal and distal CTEPH. L-arginine plasma levels were significantly decreased in all patients with pulmonary hypertension. L-arginine plasma levels correlated significantly with mixed-venous saturation ($r = 0.48$, $p < 0.01$) and cardiac index ($r = 0.39$, $p < 0.05$). ADMA plasma levels were significantly elevated in distal CTEPH and iPAH patients (0.81 ± 0.22 μ mol/l and 0.69 ± 0.13 μ mol/l) compared with controls (0.52 ± 0.14 μ mol/l; $p < 0.05$, respectively). ADMA was significantly higher in distal CTEPH than in proximal CTEPH ($p < 0.01$).

Conclusions ADMA plasma levels are increased in CTEPH patients. The data confirm similar pathophysiologic mechanisms of vascular remodeling in iPAH and CTEPH.

Survival in Patients with Inoperable CTEPH Treated with Subcutaneous Treprostinil

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Background Treprostinil improves exercise capacity, hemodynamics and signs and symptoms of pulmonary arterial hypertension (PAH). Inoperable CTEPH may be a target for vasodilator therapy.

Aim In an open-label uncontrolled study, we investigated efficacy and survival in patients with severe inoperable CTEPH treated with subcutaneous treprostinil.

Methods Between September 1999 and 2005, 25 consecutive inoperable CTEPH patients were treated with s. c. treprostinil. Inclusion criteria were New York Heart Association (NYHA) functional class III or IV and six-minute walking distance (6-MWD) ≤ 380 m. NYHA functional class, 6-MWD and B-type brain natriuretic peptide (BNP) served as primary efficacy endpoints. Right heart catheterization was performed at baseline and after at least 12 months of treatment. A historical group of 31 untreated patients with inoperable CTEPH matched for NYHA functional class was used for comparative survival analysis.

Results Under treatment, patients demonstrated improvements in 6-MWD, NYHA functional class, and decreased BNP levels. 12 patients (age 55.4 ± 10 years) were catheterized after 25.4 ± 10 months

at a final mean treprostnil dose of 37.7 ± 9.6 ng/kg/min demonstrating significant improvements of cardiac output $+0.7 \pm 1.0$ L $\times$ min⁻¹ ($p = 0.03$) and pulmonary vascular resistance -193 ± 287 dynes $\times$ s $\times$ cm⁻⁵ ($p = 0.02$). Overall survival rates of treprostnil-treated patients at one, two, three, and five years were 80 %, 80 %, 80 % and 53 %, respectively, compared with the untreated group (67 %, 43 %, 37 % and 16 %, $p = 0.02$). Treprostnil was an independent predictor of improved survival ($p = 0.02$).

Conclusions Subcutaneous treprostnil improves exercise capacity, hemodynamics and survival in patients with severe inoperable CTEPH.

Microcirculation Changes after ACAT-Inhibitor, VULM 1457, in Diabetic and Non-Diabetic Hyperlipidemic Hamsters

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Aim of the Study The effect of the new ACAT-inhibitor, VULM 1457, on velocity of red blood cells in hypercholesterolemic and hypercholesterolemic/streptozotocine-diabetic hamsters was studied by videocapillaroscopy. It is a non-invasive examination of microcirculation recently used in cardiologic and diabetic patients.

Methods Experimental studies were performed in 6 groups of hamsters: a) fed on cholesterol lipid diet (CHL); b) streptozotocine-induced diabetes (D); c) streptozotocine-induced diabetes fed on cholesterol lipid diet (D CHL); d) fed on cholesterol-lipid diet receiving VULM 1457 (CHL VULM 1457); e) streptozotocine-induced diabetes fed on cholesterol-lipid diet receiving VULM 1457 (D CHL VULM 1457); f) control group. ACAT-inhibitor VULM 1457 was given orally 50 mg/kg. The effect of treatment on hamster's paw microcirculation was assessed using capillary microscopy by measuring red blood cell velocity after 3 months of treatment.

Results The high cholesterol-level diet decreased significantly the red blood cell velocity (6.2 %, $p < 0.05$) and this effect was even higher in diabetic animals (10.1 %, $p < 0.01$). Treatment of animals with the new ACAT-inhibitor, VULM 1457, most significantly improved the velocity rate in all groups, most significantly in D CHL VULM 1457 in comparison to untreated groups of animals.

Conclusion VULM 1457 positively improved red blood cell velocity reduced in diabetic and hypercholesterolemic hamsters. Significant effect was seen when VULM 1457 was given to diabetic hamsters fed on cholesterol-lipid diet.

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Percutaneous Coronary Intervention of Unprotected Left Main Stenosis: Safety and Long-Term Efficacy in Stable Patients

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Background Percutaneous coronary intervention (PCI) of unprotected left main (LM) stenosis is still controversial. This retrospective analysis evaluated the clinical and angiographic outcome of this patient cohort in a single high-volume PCI center.

Methods 42 consecutive patients with LM stenosis and acute coronary syndrome (ACS) not eligible for acute coronary artery bypass surgery and 50 selected patients with stable coronary artery disease (CAD) were treated by PCI with either bare metal stent (BMS, 44 %) or drug-eluting stent (DES, 56 %) implantation between August 2001 and July 2006.

Results The cumulative survival rate up to one year (median 81 days, range 0–365) of selected elective patients with LM stenosis was 94 %, compared to 65.2 % in hemodynamically stable ACS patients with LM stenosis and 36.8 % in ACS patients with cardiogenic shock and LM stenosis ($p < 0.00001$). Angiographic follow-up (median 194 days, range 1–1310 days) was performed in 39 % of all patients, with a restenosis rate of 2.8 % after DES compared to 11.1 % after BMS implantation ($p = n. s.$).

Conclusion Whereas ACS patients with LM stenosis are still a highest-risk patient cohort, especially in hemodynamically unstable conditions, LM PCI can be safely and efficaciously performed in selected stable patients preferably with DES implantation in an experienced center.

"Oldest-Old" Patients In Intensive Care: Prognosis and Therapeutic Activity

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Objective The present investigation aims at giving a descriptive overview on the prognosis and therapeutic activity for "oldest-old" patients, admitted to an intensive care unit (ICU) in comparison to younger patients.

Patients and Methods 3069 patients, admitted to the ICU during a seven-year study period, were assigned to one of 4 age categories: younger than 65 years (48 %), aged 65 to 74 years (26 %), aged 75 to 85 years (22 %) and aged 85 years or older (5 %). Type and reason for ICU admission, length of ICU stay, severity of illness as measured by the Simplified Acute Physiology Score (SAPS) -II, level of provided care as measured by the Simplified Therapeutic Intervention Scoring System (TISS) -28, vital status at and date of ICU discharge were recorded.

Main Results The mortality rate of patients aged 85 years and older was significantly higher than in patients younger than 65 years (OR for survival: 2.8, $p < 0.001$). Non-survivors had higher SAPS-II levels (even when age points were excluded) and daily average TISS points. Daily average TISS score was negatively correlated to age ($r = -0.03$; $p < 0.001$) and was significantly lower in the "oldest old" when compared to all younger patient groups ($p < 0.001$). "Oldest-old" patients showed significantly shorter length of stay (median: 2; 1st–3rd quartiles: 1 to 3, $p < 0.001$) compared to the younger patient groups.

Conclusions Within the very elderly population, age is an important and independent predictor of mortality, but acute severity of illness is even stronger associated with mortality. Consequently, age alone may be an inappropriate criterion for allocation of ICU resources.

Restenosis Caused by Stent Fracture of Overlapping Zotarolimus-Eluting Stents

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Abstract The introduction of drug-eluting stents (DES) revolutionized the field of interventional cardiology by dramatically reducing the development of late in-stent restenosis (ISR). Stent fracture, however, has recently been suggested as one possible mechanism of restenosis after DES implantation. We report the first case of ISR caused by fracture of overlapping zotarolimus-eluting stents.

Introduction Restenosis after intracoronary DES implantation most commonly occurs in a localized pattern associated with either injury outside the stent (edge restenosis) or discontinuity of stent coverage (under expansion, gap or fracture) [1]. To date, various cases of fractures of sirolimus-eluting stents (Cypher®, Cordis) [1–4] and one case of a paclitaxel-eluting stent (Taxus®, Boston Scientific) [5] have been described.

To our knowledge, this is the first report on a case of delayed fracture of overlapping zotarolimus-eluting stents (Endeavor®, Medtronic).

Case report A 66-year-old male with a history of hypertension and non-insulin-dependent diabetes mellitus was admitted to another hospital without cardiac catheterization facilities due to acute inferior ST elevation myocardial infarction (STEMI). Despite immediate thrombolytic therapy with tenecteplase (Metalyse®, Boehringer Ingelheim) his clinical condition deteriorated with development of pulmonary edema and cardiogenic shock. After intubation he was transferred on high-dose catecholamine for rescue percutaneous coronary intervention (PCI) to our institution.

Coronary angiography showed a severe three-vessel disease with a proximally occluded right coronary artery (RCA, **Figure 6a**), two significant stenoses in the proximal left anterior descending artery (LAD, not shown) with diffuse disease in the mid and distal portion, as well as a high-grade stenosis in the mid-left circumflex artery (LCx, not shown) supplying the distal RCA via collaterals.

Due to the severe hemodynamic instability of this critically ill patient we intended to perform a complete percutaneous revascularization. Starting with the culprit vessel, two Endeavor® stents (3.5/24 mm and 3.0/18 mm, 16 atm) were implanted after balloon predilatation in the mid proximal RCA with a very generous over-

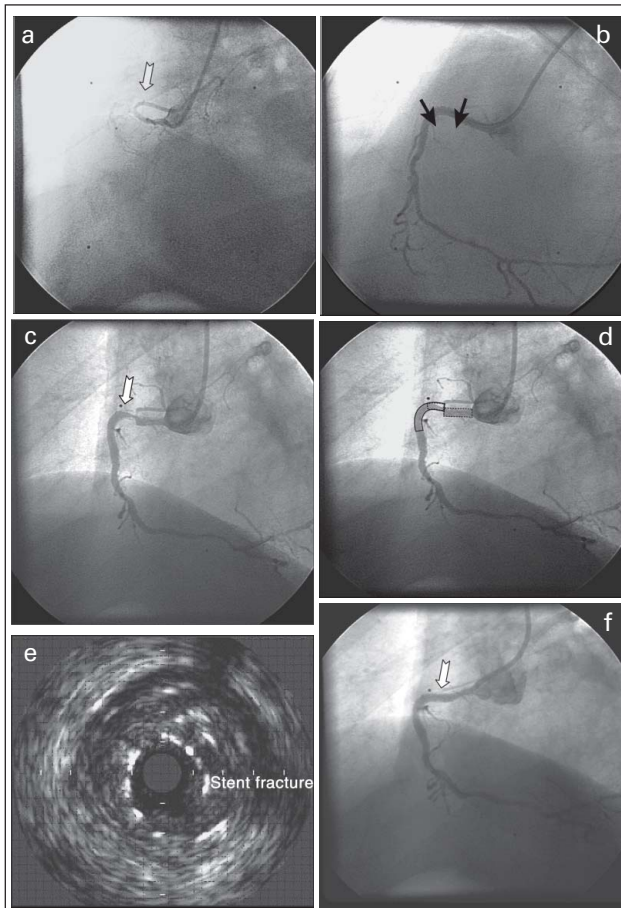


Figure 6. R. Badr Eslam et al. Angiograms of the right coronary artery (RCA). **a)** Initial pre-interventional proximally occluded RCA (arrow); **b)** Result of sequential implantation of two Endeavor stents (3.0/18 mm and 3.5/24 mm) with a wide overlapping zone (two black arrows); **c)** Restenosis after 6 months at the proximal edge of the overlapping zone (arrow); **d)** Schematic drawing of the fractured stent position (red: distal stent, white: proximal stent); **e)** IVUS image of the fracture site; **f)** Result after Cypher stent implantation (3.5/13 mm).

lapping zone of 8–10 mm (due to a temporarily narrow choice of stent sizes on the shelf) (**Figure 6b**). The LCx received a 3.5/15 mm Endeavor® stent with 16 atm after predilatation. The proximal and mid-LAD were reconstructed with two more overlapping Endeavor® stents (3.0/24 mm and 3.0/30 mm, 12 and 16 atm). The patient survived and could be discharged for cardiac rehabilitation.

An elective control angiography was scheduled after 6 months. Apart from low-grade atypical angina pectoris symptoms (CCS II)

and two episodes of pulmonary congestions, the patient was in good clinical condition. On angiogram, LAD and LCx stents showed an excellent long-term result with no significant intimal hyperplasia. The proximal RCA, however, showed a highly significant ISR due to complete fracture of the proximal Endeavor® stent on the proximal edge of the overlapping segment (**Figures 6c, 6d**) confirmed by intravascular ultrasound (**Figure 6e**). After predilatation, an additional 3.5/13 mm Cypher® stent was successfully implanted with 16 atm (**Figure 6f**).

Discussion ISR in the era of DES experiences a quantitative and qualitative change. The overall amount of reduction of newly developing intimal hyperplasia – best characterized by late lumen loss (LL) – of DES compared to bare metal stents (BMS) seems to primarily depend on the eluted drug [6]. In case a hemodynamically significant ISR still develops in DES, it usually exhibits rather a localized than a diffuse pattern, suggesting anatomical and/or mechanical difficulties to be responsible by decreasing local drug availability [1]. Beside incomplete lesion coverage and inadequate wall apposition due to undersizing or heavy calcification, stent fracture seems to become increasingly important. One could speculate that the reduction of LL by DES unmasks a rare but, due to excess intimal hyperplasia in BMS, so far clinically not significant problem of coronary stents per se.

In our case of fracture of overlapping Endeavor® stents, we believe that the unintentional fact of creating a rather wide double-layer stent zone added substantially to an unfavorable new vessel geometry with higher shear forces on the proximal end of this tortuous RCA segment. This finding supports the idea that predisposing risk factors for stent fracture are 1) overlapping of stents, 2) higher local shear stress primarily in often vigorously moving proximal segments of RCA or LCx, 3) very tortuous vessel segments especially in 4) heavily calcified lesions [2, 4]. Three out of these four risk factors applied to our case.

We suggest that during complex percutaneous revascularizations, overlapping of DES in briskly moving, tortuous segments – especially in the proximal RCA and LCx – should be restricted to a very short segment to minimize the risk of stent fracture.

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