Relation between blood pressure lowering therapy and cardiovascualr events and mortality in hypertensive patients with coronary artery disease and type 2 diabetes: the HIJ-CREATE sub-study

H. Ogawa, R. Koyanagi, E. Kawada-Watanabe, J. Yamaguchi, A. Takagi, N. Hagawa on behalf of HIJ-CREATE. Tokyo Women’s Medical University, Department of Cardiology, Tokyo, Japan

Purpose: To explore the optimal systolic blood pressure target in hypertensive patients with coronary artery disease (CAD) and type 2 diabetes in the sub-study of the HIJ-CREATE trial.

Methods: HIJ-CREATE was a multicenter, prospective, randomized, controlled study that compared the effects of candesartan-based therapy with those of non-ARB-based standard therapy on MACE in 2,049 hypertensive patients with angiographically documented CAD. Of the 2,049 participants, 780 (38.1%) were complicated with type 2 diabetes. In both groups, titration of antihypertensive agents was performed to reach the target blood pressure (BP) of <130/85 mmHg. The primary endpoint was the time to first major cardiac events (MACE). In- cidence of endpoint events in addition to biochemistry tests and office BP was determined during the scheduled 6, 12, 24, 36, 48, and 60 month visits. Achieved BP were defined as the mean value of systolic BP in patients who did not meet with MACE and the mean value of systolic BP prior to MACE in those who met with MACE during follow-up.

Results: During a median follow-up of 4.2 years (follow-up rate of 99.6%), the primary outcome occurred in 259 (33.2%) diabetic patients and in 293 (23.1%) non-diabetic patients (p < 0.0001). The participants were divided into equal quartiles based on the mean systolic BP during follow-up. The relationships between achieved systolic BP and the incidence of MACE did not follow J-shaped curves in both groups (Figure).

Conclusion: The present study suggests that the excessive BP lowering regimen of the contemporary era causes no harm even in high-risk population. Nonetheless, along with BP lowering therapy, the establishment of an optimal management strategy for hypertensive CAD patients with diabetes is essential.

The effect of visit-to-visit variability in blood pressure on stroke and coronary events in the TNT, IDEAL and CARDS trials

P.C. Deedwania1, D.A. Demicco2, A. Breazna2, C.C. Wun1, T. Pedersen1, H.M. Colhoun3, A. Nei1, G. Hitman1, 1University of California, San Francisco, School of Medicine, Fresno, United States of America; 2Pfizer Inc, New York, United States of America; 3University of Oslo, Oslo, Norway; 4University of Dundee, Dundee, United Kingdom; 5University of Oxford, Oxford, United Kingdom; 6Barts and The London School of Medicine and Dentistry, London, United Kingdom

Purpose: It has been proposed that visit-to-visit variability in systolic blood pressure (SBP) predicts CV risk independent of mean SBP. This study assessed the association between visit-to-visit variability in BP and the risk of CV events (CVE) among high-risk patients in the TNT, IDEAL and CARDS trials, and investigated whether BP and BP variability contributed to differences in clinical benefits observed with different statin treatment regimens.

Methods: A total of 1128 essential hypertensives (mean age 56.1 years, 43.7% female, mean hypertension duration 6.8 years) from the TNT, IDEAL, and CARDS trials were included.

Conclusion: The present study suggests that the excessive BP lowering regimen of the contemporary era causes no harm even in high-risk population. Nonetheless, along with BP lowering therapy, the establishment of an optimal management strategy for hypertensive CAD patients with diabetes is essential.

Low attenuation coronary plaque on multidetector computed tomography predicts three-year acute coronary syndrome events in patients with hypertension

1Osaka City University Graduate School of Medicine, Osaka, Japan; 2Osaka Eikaisai Hospital, Osaka, Japan; 3Ishikiriseki Hospital, Hashigoshaka, Japan; 4Nishinomiya Watanabe Cardiovascular Center, Nishinomiya, Japan.

Purpose: Arterial hypertension is an established risk factor for acute coronary syndrome (ACS). Multidetector computed tomography (MDCT) is an accurate and less invasive technique for assessment of the degree of coronary artery luminal narrowing and characterization of coronary atherosclerosis. We therefore aimed to investigate the predictive power of MDCT for ACS events and compared with traditional parameters in patients with hypertension.

Methods: One hundred and thirty-four patients (93 men, mean age 70.1±11 years) with hypertension underwent MDCT for evaluation of coronary artery disease. MDCT analysis focused on the presence of plaques, the degree of stenosis, and the plaque characteristics. Traditional parameters included Framingham risk score (FRS), carotid intima-media thickness (IMT), and left ventricular mass index (LVMI).

Results: During a mean follow-up of 3.3 years, ACS events occurred in 10 patients. In the multivariate analysis, the number of low attenuation plaques (LAP) was identified as an independent predictor of ACS events (p<0.001). Case examples are presented in Figure. Curved multplanar reconstruction image of right coronary artery demonstrated the presence of LAP (arrows) (Figure A), which developed ACS event 3 years after MDCT examination (Figure B). Increased events rate was observed in patients with ≥2 LAP compared with those without LAP (p<0.001) (Figure C). There were no significant differences between patients with and without ACS events in the FRS, carotid IMT, LVMI, and any of the laboratory parameters.

Pulse wave velocity as independent predictor of stroke in patients with essential hypertension: data from a Greek 6-year-follow-up study

K. Dimitriadis, C. Tsifoulis, I. Tatsis, G. Chiploutakis, L. Lioni, V. Tzamou, A. Kasiakogias, C. Thomopoulos, D. Toutoulos, C. Stefanadis, First Cardiology Clinic, University of Athens, Hippokration Hospital, Athens, Greece

Purpose: Although arterial stiffening is related to atherosclerosis progression, its prognostic role in cerebrovascular events in hypertension is not fully elucidated. The aim of the present study was to assess the predictive role of arterial stiffness for the incidence of stroke in a cohort of essential hypertensive patients.

Methods: We followed up 1128 essential hypertensives (mean age 56.1 years, 587 males, office blood pressure (BP) >144/91 mmHg) free of cardiovascular disease for a mean period of 6 years. All subjects had at least one annual visit and at baseline underwent blood sampling for assessment of metabolic profile and arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior BP). The distribution of
PWV was split by the median (8.1 m/sec) and accordingly subjects were classified into those with high (n=566) and low values (n=562). Stroke was defined as rapid onset of a new neurological deficit persisting at least 24 hours unless death supervened confirmed by computed tomography and magnetic resonance angiography and/or cerebrovascular angiography findings.

Results: The incidence of stroke over the follow-up period was 2.03%. Hypertensives who had stroke (n=23) compared to those without stroke at follow-up (n=1105) were older at baseline (63±8 vs 55±10 years; p=0.015), had higher office BP levels (155±13 vs 143±17 mmHg; p=0.018) and prevalence of high PWV levels (67% vs 43%; p=0.021). No difference was observed between hypertensives with stroke and those without stroke with respect to baseline renal function and lipid levels (p=NS for all). By univariate Cox regression analysis it was revealed that high baseline PWV levels predicted stroke (hazard ratio=1.307, p=0.014). Moreover, in multivariate Cox regression model, baseline age (hazard ratio=1.098, p=0.03) and PWV (hazard ratio=1.125, p=0.017) but not baseline office BP levels turned out to be independent predictors of stroke.

Conclusions: In essential hypertensive patients, PWV predicts future development of stroke, independently of age and office BP. These findings support that PWV constitutes a potent prognosticator of cerebrovascular events and its estimation is essential in order to improve risk stratification in hypertension.

**Prediction of cardiovascular events and all-cause mortality with brachial-ankle pulse wave velocity: a systematic review and meta-analysis of cohort studies**

D. Terentes-Printzios1, C. Vlachopoulos2, K. Arnaoudis1, N. Ioakeimdis1, C. Stefanadis1, 1Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece; 2Hippokration General Hospital, Athens, Greece

**Purpose:** Brachial-ankle pulse wave velocity (baPWV) is increasingly recognized as a surrogate end-point for cardiovascular (CV) disease. We performed a meta-analysis of all longitudinal cohort studies for determining the ability of baPWV to predict risk of CV events and all-cause mortality.

**Methods:** The MEDLINE, Cochrane and EMBASE databases, and reviewing reference lists from retrieved articles and abstracts from large international cardiovascular congresses were searched until January 2012. Longitudinal cohort studies that reported relative risk (RR) estimates with 95% confidence intervals were included. Reviewers extracted data independently and summary estimates of association were obtained using a fixed- or random-effects model. Risk estimates between subgroups were compared with an interaction test.

**Results:** Of the 17 studies included (8,217 participants, mean follow-up 3.37 years), 14 reported results on total CV events (5,406 individuals), 6 on CV mortality (2,139 individuals) and 9 on all-cause mortality (5,132 individuals). The pooled relative risks (RRs) for total CV events, CV mortality and all-cause mortality were 2.77 (95% confidence interval: 1.91 to 4.01) (Figure), 7.37 (95% CI: 3.67 to 14.79) and 2.62 (95% confidence interval: 1.87 to 3.66), respectively, for subjects with high baPWV versus subjects with low baPWV. For total CV events, the RR was significantly higher in high baseline risk groups (heart disease, renal disease, hypertension, diabetes) compared with low-risk subjects (general population). An increase in baPWV by 1 m/s corresponded to an increase of 17% in total CV events.

**Conclusions:** baPWV is associated with increased risk of total CV events and all-cause mortality. Predictive value of baPWV for total CV events is increased in general population.
Central blood pressure: a possible powerful predictor of the development of hypertension

N-terminal fragment of brain natriuretic peptide predicts vascular health and subclinical atherosclerosis: results from MEHLP study

Selective serotonin reuptake inhibitors exert a negative effect on peripheral wave reflections

Renin-angiotensin aldosterone system gene polymorphisms and their association with vascular impairment in patients with essential hypertension
similar results were obtained for hypertensives, though without reaching statistical significance (p=0.07). Moreover, after adjustment for co-variables, cystatin-C levels correlated significantly with PWV values both in total (r=0.27, p=0.03) and in hypertensive populations (r=0.23, p=0.008). Interestingly, in univariate analyses, increased levels of cystatin-C (above 75th percentile) correlated with higher PWV values (p=0.0019).

Conclusions: We have shown that TT homozygotes had significantly lower FMD in controls and c-IPWV was higher in TT homozygotes compared with MM+MT genotypes in hypertensive patients. In addition, we have observed higher values of IMT in -344TT homozygosity, in the group of hypertensives, while Taitelle carriage was significantly associated with higher prevalence of atherosclerotic plaques in the study population. Our results suggest that angiotensinogen genotypes are associated with arterial stiffness, whereas CYP11B2 promoter variant potentially constitutes a marker of subclinical atherosclerosis in untreated hypertension.

**3797** Insulin resistance is associated with increased large artery stiffness in normotensive healthy adults

J.E. Ochoa1, J.K. Balparida2, M.M. Correa3, A.M. Valencia2, M. Alvarez2, J.G. Mcewen4, G. Bilo2, P. Sale4, D. Aristizabal2, G. Parati1, 1University of Milan-Bicocca, Ospedale San Luca, Istituto Auxologico Italiano, Milan, Italy; 2Centro Clinico y de Investigacion, SICOR, Medellin, Colombia; 3Corporacion para Investigaciones Biologicas, Medellin, Colombia; 4Dept. Cardiolo, Ospedale San Luca, Istituto Auxologico Italiano, Milan, Italy

**Purpose:** Our results indicate that in normotensive, healthy adults, IR may in-crease significant increases in large artery stiffness (as assessed with aortic PWV) with or without ST elevation and patients that underwent coronary revasculari-

**Methods:** IR was assessed with HOMA-Index and subjects were classified into IR tertiles, based on the distribution of HOMA-index values. Recordings of pulse waveform were obtained by means of a previously validated oscilometric device for ambulatory BP monitoring with in-built transfer-function like method. Aortic pulse wave velocity (PWV, m/s) and other measures derived from pulse wave analysis such as augmentation index (%) and central SBP (cDBP, central DBP) and central pressure (cBP); were computed. Peripheral SBP and DBP, and heart rate (HR) were recorded and pulse pressure (PP) calculated as the difference between SBP and DBP.

**Results:** After multiple regression analysis adjusting for age, sex, HR and BMI, there was a significant overall effect of IR on measures of large artery stiffness and wave reflections in normotensive healthy adults. Aim of the present study was to explore this issue in 90 normotensive (Systolic)(5 blood pressure)(<140),< diastolic (D) BP 69.6± 7.7 mmHg, normoglycemic, non-obese, otherwise healthy adults (mean age 48.1± 9 yrs, 50% female).

**Conclusions:** Insulin resistance is associated with increased large artery stiffness in normotensive healthy adults.

**3798** Multidisciplinary cardiac rehabilitation and survival in The Netherlands

H. De Vries1, M. Engen-Verheul2, H.M.C. Kemps, R. Kraijenhoven3, N. Peek2, 1Achmea, Health insurance, Amsterdam, Netherlands; 2Academic Medical Center, Amsterdam, Netherlands; 3Maxima Medical Centre, Veldhoven, Netherlands; *NDOO Institute for Prevention and Early Diagnosis (NIPED), Amsterdam, Netherlands

**Purpose:** This study assessed the effects of multidisciplinary cardiac rehabilita-

**Methods:** The cohort consisted of persons insured with Achmea, a health insur-

**Conclusions:** Our results indicate that in normotensive, healthy adults, IR may in-

**MODERN CARDIAC REHABILITATION MOVING BEYOND FUNDAMENTALS**

**3799** Cardiovascular rehabilitation after a first acute coronary syndrome and the risk of recurrence and death in patients from the French MONICA registries

P.L. Vervuert1, V. Bongard2, D. Arevelo3, J. Dallongeville3, J.B. Ruddavet4, A. Wagner2, A. Amouyel5, A. Duprez6, M. Elbaz2, J. Ferries4, 1University Hospital of Toulouse - Rangueil Hospital, Department of Cardiology A, Toulouse, France; 2University Hospital of Toulouse, Department of Epidemiology, Inserm UMR1027, Toulouse, France; 3University of Strasbourg, Medical Faculty, EA 3430, Department of Epidemiology and Public Health, Strasbourg, France; 4Pasteur Institute of Lille, U744 Inserm - University of Lille Nord de France, UDSL, Lille, France; 5Inserm U970 - Paris Cardiovascular Research Center (PARCC), Paris, France; 6University Hospital of Toulouse - Rangueil Hospital, Department of Cardiology B, Toulouse, France

**Purpose:** Cardiovascular rehabilitation following the occurrence of an acute coro-

**Methods:** Our study was based on 2008 data from the French MONICA population-based registry which collects all cases of ACS occurring in people aged 35-74 in 3 French areas located in North, North-Eastern and South-Western France. The population consisted of 1868 ACS cases treated and consecutive hospitalized ACS, after exclusion of those who died in the first 28 days of follow-up. The rela-

**Conclusions:** Cardiovascular rehabilitation following the occurrence of an acute coro-

**Downloaded from https://academic.oup.com/eurheartj/article-abstract/33/suppl_1/655/430798 by guest on 25 January 2019**
Phase II comprehensive cardiac rehabilitation prevents readmission for heart failure in patients with chronic heart failure and high brain natriuretic peptide levels


1Rehabilitation center, Kitasato University Hospital, Sagamihara, Japan; 2Salvatore Maugeri Foundation, IRCCS, Division of Cardiology Rehabilitation, Verona, Italy; 3Kitasato University Graduate School of Medical Sciences, Sagamihara, Japan; 4Department of Cardio-angiology, Kitasato University School of Medicine, Sagamihara, Japan; 5Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, Sagamihara, Japan

Purpose: The purpose of this study was to investigate the effects of phase II comprehensive cardiac rehabilitation (CR) in patients with chronic heart failure (CHF) and high brain natriuretic peptide (BNP) levels.

Methods: We studied 312 patients with CHF (215 males; age, 71±10 years) who were hospitalized for acute decompensated heart failure. Patients were classified into four groups according to BNP levels at the time of discharge and participation in phase II CR. The CR with low BNP group (n = 67) included patients who participated in CR and had BNP levels less than 200 pg/mL, the CR with high BNP group (n = 74) included patients who participated in CR and had BNP of 200 pg/mL or more, the non-CR with low BNP group (n = 64) included patients who did not participate in CR and had BNP levels less than 200 pg/mL, and the non-CR with high BNP group (n = 104) included patients who did not participate in CR and had BNP levels of 200 pg/mL or more. Readmission for heart failure was analyzed using Cox proportional hazards model and Kaplan–Meier survival analysis based on cardiovascular risk factors including age, medication, left ventricular ejection fraction, BNP levels, and participation in phase II CR.

Results: Multivariate Cox proportional analysis showed that participation in phase II CR was a significant predictor for readmission of heart failure (adjusted hazard ratio, 0.66; p < 0.05). Kaplan–Meier survival analysis revealed that the CR with low BNP group had the lowest readmission rate (p < 0.05), while the CR with high BNP group showed the same readmission rate as the non-CR with low BNP group (Figure).

Conclusion: Participation in phase II CR is a strong predictor for heart failure readmission and prevents readmission for heart failure even in patients with CHF and high BNP levels.

3801 Compliance to a cardiac rehabilitation program: what benefits and prognostic impact?


Background: Cardiac rehabilitation programs (CRP) have consistently demonstrated the ability to improve cardiac risk factors and reduce morbidity-mortality. Thus, compliance to CRP is an essential requirement to achieve the goals of secondary cardiovascular prevention.

Objective: To assess the clinical benefits and CRP compliance impact on prognosis in a coronary heart disease population.

Methods: We evaluated a total of 241 patients referred to a CRP after an acute coronary syndrome (ACS), recruited between September 2008 and November 2010. Information on socio-demographic, clinical and functional data was collected pre and post CRP. Functional capacity was assessed in metabolic equivalent of task (METs)/minute/week, cardiovascular risk factors and readmission due to heart failure. Compliance to the exercise training program was evaluated by attending a rehabilitation session and completing a minimum of 60% of scheduled outpatient visits. Participants were classified into four groups according to compliance to CRP and their functional capacity (Table 1).

Results: Our study population consisted of 241 patients, mostly male (89%), aged 54±10 years (range 28-80). Non compliance was found in 24 (10%) patients and it was more common in women than men (23% vs 8%; p=0.030) and in obese patients (44% vs 35% on optimal pharmacological therapy. Follow-up data was available in 227 (94%) patients, with a mean follow-up time of 95.7 months. Composite endpoints were found in 23 (10%) patients and tended to be more frequent in non-CG (17% vs 9%; p=0.182). With Cox regression analysis, non-compliance behavior was associated with a higher likelihood of composite endpoint occurrence, although no statistical significance was achieved (HR 2.2, 95% CI 0.7-6.4).

Conclusion: CRP compliant patients have a significant higher improvement in cardiovascular risk profile, functional capacity and tend to suffer less cardiovascular events than non compliant patients.

3802 The effects of respiratory muscle trainings on systemic inflammation and fibrosis process in patients with heart failure


Background: Number of studies showed the effectiveness of Respiratory Muscle trainings (RMT) as a part of comprehensive cardiac rehabilitation (CR). The mechanisms of their positive effects in cardiac patients are still not well known.

Purpose: To study the relations of long-term effects of RMT started in patients with NYHA III-IV class heart failure (HF), with the intensity of systemic inflammation and pleasmatic levels of aldosterone and collagen.

Methods: 61 patients 64±5.5years old with NYHA III-IV HF were randomized to either an exercise training group (EG) (30pts) or to a control group. The CG patients had standard CR according to the national guidelines. The EG participated additionally in a RMT with gradual increase of inspire and expire resistance. 12-15 RMT were held at the hospital with following continuation at home for 12 months by patients themselves. Trainings were held for 20-30 minutes 1-2 times every day. Pleasmatic levels of C-reactive protein (CRP), aldosterone and the carboxyterminal propeptide of human type I procollagen (PⅠPⅠP) were studied at discharge point and in 12 months.

Results: In 12 months peak VO2 increased significantly in EG (11.5±8.2 vs 15.4±10.9 ml/kg/min in EG vs 9.1±7±2 vs 12 ml/kg/min in CG, p<0.05). EG patients showed significant decrease in CRP level (5.5±2.4 mg/dl in EG vs 8.1±2.1 mg/dl in CG, p<0.05), aldosterone level (80.5±39.1 pg/ml in EG vs 151.6±193.9 pg/ml in CG, p<0.05), PⅠPⅠP (67.5±7.8 mg/ml in EG vs 104.6±11.2 mg/ml in CG, p<0.05). RMT helped to stabilize mean pulmonary pressure (33.5±4.7 mm Hg in EG vs 44.2±7.6 mm Hg in CG, p<0.05). Health related quality of life measured by SF-36 increased in both groups, but results in physical functioning, bodily pain, vitality, role emotional scales were significantly higher in EG patients.

Conclusion: RMT in patients with HF are effective in decreasing the level of systemic inflammation, neurohumoral activation and collagen synthesis and thus regarding fibrosis, besides improving physical capacity, stabilizing pulmonary pressure and increasing health-related quality of life.

3803 Beneficial effects of rehabilitation in comparison with resynchronization therapy in patients with NYHA III heart failure

T. Chwyczko, E. Smolis-Bak, R. Babrowski, M. Sterlinski, A. Maciag, A. Borowiec, I. Kowalik, M. Pytowski, H. Szwej. Institute of Cardiology, 3rd Department of Coronary Artery Disease, Warsaw, Poland

Background: Indications to cardiac resynchronization therapy (CRT) have been extended in 2010. However, there is large group of patients with ejection fraction<35%, severe heart failure (HF) and QRS>120ms, who are not qualified to CRT. They are treated with optimal pharmacotherapy. We compared outcomes of rehabilitation of patients in NYHA III heart failure and patients with implanted CRTD device without rehabilitation.

Methods: The study included 47 patients with NYHA III HF and EF<35% on optimal pharmacotherapy, divided in two groups: the control group (CG, n=20) and the rehabilitation group (RGT, n=27).

Table 1. Comparison of clinical outcomes of patients with and without rehabilitation

<table>
<thead>
<tr>
<th>Age [years]</th>
<th>BMI [kg/m²]</th>
<th>EF [%]</th>
<th>LVdID [cm]</th>
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<tr>
<td>Before 57±11</td>
<td>27±3±6</td>
<td>5.4±1.9</td>
<td>6.3±1.9</td>
<td>5.3±1.0</td>
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<tr>
<td>After 57±11</td>
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No rehabilitation (CG group) Rehabilitation (RGT group) Statistical significance

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No rehabilitation (CG group) Rehabilitation (RGT group) Statistical significance

No rehabilitation (CG group) Rehabilitation (RGT group) Statistical significance

| Peak oxygen uptake (VO2) [ml/min] | Before 10.9±3.8 | 13.3±4.6 | 0.0163 |
| After 11.9±4.0 | 15.7±5.9 | 0.0144 |

ns 0.0168
mal pharmacotherapy. The etiology of HF was comparable in both groups. 27 patients with QRS >120ms had CRT-D implanted and 20 patients with QRS <120ms had ICD implantation and went through the training program (aerobic exercises on ergometer, 3 times a week for 3 months). All patients were optimally treated pharmacologically. They had echocardiography and cardipulmonary exercise test (CPX) performed at baseline and after 6 months.

Results: All results are presented in Table 1.

Conclusions: Rehabilitated patients with NYHA III heart failure have better outcomes when compared with CRT group. Rehabilitation is a noteworthy therapeutic option for patients with severe heart failure and no indications to CRT.

NOVEL APPROACHES TO EXERCISE TRAINING

Biventricular filling impairment limits cardiac performance during exercise in healthy subjects

G. Claessen1, A. La Gerche1, A. Van De Bruaene1, M. Gewillig2, S. Dymarkowski2, R. Claus3, H. Heidbuchel1, 1University Hospitals (UZ) Leuven, Campus Gasthuisberg, Department of Cardiology, Leuven, Belgium; 2University Hospitals (UZ) Leuven, Department of Radiology, Leuven, Belgium; 3Catholic University of Leuven, Dept Cardovascular Disease, University Center of Leuven, Cardiology, Pulmonology & Vascular Dynamics, Leuven, Belgium

Background: Constraints in current imaging techniques have resulted in considerable disagreement as to what constitutes normal changes in left and right ventricular (LV, RV) volumes during exercise. The aim of this study was to determine biventricular end-diastolic and end-systolic volumes (EDV and ESV) using a novel CMR method during strenuous exercise.

Methods: Twenty-nine healthy and physically active subjects (19 male, 3 female, aged 32±2 years) underwent CMR at rest and during supine exercise on a programmable cycle ergometer. Biventricular volumes were obtained at rest (heart rate 63±11 bpm) and whilst cycling at moderate (15±6 bpm) and strenuous (155±11 bpm) workload intensities. Images were acquired during exercise and free-breathing (12-18 contiguous 8mm slices) using an unigated real-time CMR sequence. We developed software to enable retrospective synchronization of long and short-axis images with compensation for respiratory phase translation. Thus, endocardial borders could be delineated in a bi-plane model.

Results: There was excellent inter-observer agreement for all volume estimations (eg. intra-class correlation coefficients r=0.97 and r=0.98 for EDV and CO respectively, p<0.0001). Biventricular cardiac output (CO) increased by 11±1% from rest to moderate exercise (7.7±1.4 vs. 16.3±4.8 l/min; p<0.0001) and by a further 30±16% to strenuous exercise (16.3±4.8 vs. 21.1±5.3 l/min; p<0.0001).

The total 174±60% increase in CO was due to a 146±23% increase in HR and a 9±13% increase in stroke volume (SV). Interestingly, SV increased during moderate exercise (124±27 vs. 141±34 ml; p<0.0001) but then decreased during strenuous exercise (141±34 vs. 135±30 ml; p=0.002). The early increase in SV was due to augmentation of both systolic function (end-systolic volume (ESV) -15±11%, p<0.0001) and diastolic filling (end-diastolic volume (EDV) +2±7%, p=0.02). Although during strenuous exercise there was further augmentation of systolic function (ESV -20±16%, p<0.0001) and LV systolic function (LV ejection fraction (EF) from 59±14% to 76±7%, p<0.0001). Diastolic filling was reduced (40±7% vs. 56±7%; p<0.0001). This reduction in EDV during strenuous exercise occurred in all subjects and was greater for the RV than for the LV (12±8 vs. 7±5%, p<0.03). All other changes in cardiac volumes were similar for LV and RV (p>0.05).

Conclusions: A novel CMR method of biventricular volume assessment was used to demonstrate augmentation of biventricular filling and ejection during moderate exercise in healthy subjects. However, at higher exercise intensities, diastolic filling is compromised and attenuates further stroke volume increases.

Musical exercise in patients with coronary artery disease

M. Deljanin1, I. Ilic2, G. Kocić2, R. Pavlović2, V. Stiočk2, V. Ilić2, 1Institute of Cardiology, University of Niš, Niška Banja, Serbia; 2Institute of Cardiology, Medical Faculty University of Niš, Niška Banja, Serbia; 3Institute of Biochemistry, University of Niš, Niš, Serbia

Purpose: To evaluate the effects of listening to favorite music added to regular exercise training on the endothelial function, assessed through changes of circulating blood markers of endothelial function: the stable end products of nitric oxide (nitrite and nitrate) and the metabolite of superoxide dismutase (RSNO) as well as in endothelial function assessed by flow-mediated dilatation (FMD).

Methods: 65 pts with stable CAD were studied. At baseline and 3 weeks later, in all pts values of NOx and RSNO were evaluated and exercise test was performed. After the initial study, pts were randomized to trained (Tn=25), music and trained (MT, n=20) and non-trained (NT, n=20) group. Patients in T and MT groups were trained 3 weeks supervised 3 sessions aerobic exercise training at residential center, while non-trained group received usual community care. Additionally to exercise training, patients in MT group were listening their favorite music for half an hour every day. To elucidate the dynamic of nitric oxide metabolism in the circulation, NOx and RSNO concentration were determined according to the modified Sallie-Griess method.

Results: Baseline values of NOx and RSNO were similar in T, MT and NT group. After 3 weeks NOx increased significantly in T group (from 31.5±9.5 to 42.0±11.0 μmol/l; P<0.005), as well as in MT group (from 32.7±9.0 to 49.0±10.5 μmol/l; P<0.001) and those values were significantly higher than in NT group (P<0.05 and P<0.001). After 3 weeks value of NOx was significantly higher in MT than in T group (P<0.05). In all groups, value of RSNO increased after 3 weeks: in T group from 3.0±1.5 to 4.5±1.3 μmol/l (P<0.005), in MT from 3.2±1.3 to 5.3±1.3 μmol/l (P<0.001) and in NT group from 2.8±1.1 to 3.5±1.4 μmol/l (P<0.001). Different rate of increased RSNO in examined groups resulted in significantly higher RSNO in MT group than in T group (P<0.05). In T and NT group (P<0.05), and in MT and NT group (P<0.05) at the end of the study. Level of exercise test at baseline were similar in T, MT and NT. After 3 weeks exercise capacity significantly increased in T and MT group (P<0.001 both), however increase in exercise capacity was higher in T than in MT group (45% vs 27%).

Conclusion: In pts with stable CAD listening to favorite music in addition to regular exercise training and standard therapy, leads to more pronounced improvement in endothelial function, expressed through higher increased of NOx and RSNO, than exercise training alone. These improvement in endothelial function is associated with significant improvement in exercise capacity.

Exercise capacity in patients with coronary artery disease: what is beyond global left ventricular systolic function?


Purpose: Exercise capacity is influenced by multiple factors and elucidating the mechanisms for cardiac-related exercise limitation is a technically difficult. In this study we sought to determine the effect of cardiac function on exercise capacity.

Methods: Prospective study including patients admitted to an outpatient cardiac rehabilitation program (CRP) after suffering an acute coronary event between January 2011 and September 2011. Echocardiography data and exercise capacity were evaluated at the beginning and at the end of the CRP. All echocardiography were performed and activity durated according to current guidelines and exercise capacity assessed by estimated metabolic equivalents (METs) achieved on exercise stress testing.

Results: Forty-five patients were evaluated, 38 (84%) male, mean age of 54±9...
Whole-body exercise training with periodic acceleration improves endothelial function in sedentary subjects

3808

T. Matsumoto1, M. Fujita2, H. Hayashi3, I. Nakase4, M. Horie5, 1Osaka Kyoritsu University, Kyoto, Japan; 2Human Health Science, Faculty of Medicine, Kyoto University, Kyoto, Japan; 3Shiga University of Medical Science, Otsu, Japan

Introduction: Periodic acceleration in the direction of the spinal axis through repetitive movements increases shear stress to the vascular endothelium. Thus, we assessed the hypothesis that whole-body periodic acceleration with a new “passive exercise” device would enhance release of nitric oxide (NO) into the circulation and endothelial function in sedentary adults.

Methods: We enrolled twenty sedentary subjects (42±4 years; 12 women, 8 men) not taking any medication. Each subject was randomly assigned to perform sedentary or perform exercise training for 4 weeks, followed by cross-over. Periodic acceleration was applied with a horizontal motion platform (AT101; Non-invasive Monitoring Systems) at a frequency of 2-3 Hz and approximately 0.25 g for 45 min. Venous blood was sampled before and immediately after the first and 20th sessions. The amount of plasma NO end-products (nitrate plus nitrite) was measured by the Griess reaction. Increases in right brachial artery diameter were examined at rest, during reactive hyperemia (flow-mediated dilatation: %FMD) and after sublingual administration of 0.3mg of nitroglycerin (%NTG) using high-resolution ultrasound, measurements of which were repeated at baseline and after the 20th session.

Results: All subjects completed the study with no adverse side effects. There were no significant changes in resting heart rate and arterial pressure, body weight, or lipid profiles after periods with and without exercise. Periodic acceleration significantly increased plasma levels of NO end-products from 17±3 mmol/L at baseline to 24±9 mmol/L after the completion of 20 sessions (p<0.05), while the %FMD values were comparable at baseline and after the first session. Although %FMD values were not changed during the no treatment period (%FMD 31±9 vs. 37±11, p=n.s.), periodic acceleration significantly increased them from 7.2±0.5% to 8.8±1.1% after the 20th session (p<0.05), while %NTG values remained unchanged.

Conclusions: Whole-body exercise training with periodic acceleration improves vascular endothelial function through an increase in NO release in sedentary adults. This device may offer an alternative to active exercise for patients whose medical conditions limit physical activity.

Exercise echocardiography - effects of endurance training and ageing

3809

R.H. Olsen1, T. Monk-Hansen1, C. Coupee2, U.R. Mikkelsen3, A. Karlsen4, C.H. Dall5, P. Magnussen6, E. Prescott7. 1Department of Cardiology, Bispebjerg Hospital - University Hospital of Copenhagen, Copenhagen, Denmark; 2Institute of Sports Medicine, Bispebjerg Hospital - University Hospital of Copenhagen, Copenhagen, Denmark

Purpose: To study the effects of endurance training and ageing on echocardiographic measures of myocardial function at rest and during exercise.

Methods: Four groups of healthy, normal weight males; master athletes (running age between 20 and 20 years), young athletes with similar level of physical activity, and sedentary age-matched controls underwent exercise test determining VO2peak, and echocardiography at rest and during supine bicycle exercise test at 60% of maximum workload. Linear regressions were performed to simultaneously assess the effects of training (two groups) and age (continuous) on echocardiographic parameters.

Results: VO2peak differed considerably between young and old and between athletes and non-athletes. Dimensions of left atrium and ventricle as well as transmural flowpattern at rest were affected by both training and age. See table.

Optimisation of myocardial reperfusion in STEMI

3814

A. Szymanszki, L. Nilsson, E. Swahn, L. Jonasson. Linkoping University Hospital, Department of Cardiology, Linkoping, Sweden

Objectives: The aim of the study was to investigate circulating markers of apoptosis in relation to infarct size, left ventricular dysfunction and remodeling in an STE-mortality myocardial infarction (ST-MI) population, undergoing primary percutaneous coronary intervention (PCI).

Background: Immediate re-opening of the acutely occluded infarct-related artery via primary PCI is the treatment of choice in STEMI to limit ischemia injury. However, the sudden re-initiation of blood flow can lead to a local acute inflammatory response with further endothelial and myocardial damage, so-called reperfusion injury. Apoptosis is suggested to be a key event in ischemia-reperfusion injury, resulting in LV-dysfunction, remodeling and heart failure.

Methods: We included 48 patients with STEMI undergoing primary PCI. Blood samples were collected prior to PCI and after 24 hours. Plasma was selected for later analysis as an available tumor necrosis factor receptor (sTNFR) 1, sTNFR2, sfas and sfas ligand (sfasL) by ELISA. Infarct size, left ventricular (LV) dysfunction and remodeling were assessed by cardiac magnetic resonance imaging at five days and four months after STEMI.

Results: The levels of sTNFR1 at 24 h as well as the relative increases in sTNFR1 and sTNFR2 over 24 h showed consistent and significant correlations with infarct size and LV-dysfunction. Moreover, both sTNFRs correlated strongly with Troponin I and matrix metalloproteinase (MMP)-2 measurements. Soluble Fas and sfasL did not overall correlate with measures of infarct size and LV-dysfunction. None of the apoptosis markers correlated significantly with measures of remodeling.

Conclusions: In STEMI patients, circulating levels of sTNFR1 and sTNFR2 are associated with infarct size and LV dysfunction. This provides further evidence for the role of apoptosis in ischemia-reperfusion injury.

Hemostatic and fibrinolytic profile in patients with ST-segment elevation myocardial infarction resistant to fibrinolysis


Despite primary PCI is the treatment of first choice in patients with ST-segment elevation acute myocardial infarction (STEMI), for accessibility reasons, the fibrinolysis continues being the first line treatment about 30-70% of these patients, however in 40% of them is ineffective for unknown reasons.

Aim: To analyze whether it exists some association between hemostatic and fibrinolytic factors determined in circulating plasma and if it correlates with the contents into the coronary thrombus, in patients resistant to fibrinolysis compared to those who were not resistant.

Methods and Results: 20 patients (age 57±13y; 10 female) who underwent PCI...
for a first STEMI with initial TIMI 0 flow were included. Of these, 10 underwent primary PCI (group A) and the other 10 were subjected to rescue PCI (group B) because of ineffective fibrinolysis (TNK). In all patients tissue factor activity (TFa), TF Ag and tissue factor pathway inhibitor (TFPI), von Willebrand factor (VWF), D-dimer, plasm in inhibitor activated (PAI-1) and tissue plasmin activator (t-PA) were determined. The coronary thrombus was obtained during PCI by aspiration catheter in all patients. Specimens were submitted to immunohistochemical analysis. In order to know if all patients underwent primary PCI had a thrombus sensible to lysis, thrombus formation by thrombin was induced “in vitro”, and an effective thrombolysis by t-TPA was observed in 100% of patients. There were no differences between both groups in terms of age, sex, cardiovascular factors, time symptoms onset to balloon, infarct localization and number of affected vessels. Patients who underwent rescue PCI showed a higher D-dimer plasma level regarding patients who underwent primary PCI (2234.3 ± 706.5 vs 774.5 ± 1339.8 ng/ml, p < 0.03). In plasma, D-dimer levels were associated to TFa (R=0.95, p<0.01) and FVW levels (R=0.65, p<0.04). In the thrombus, FVW plasma levels were correlated with PAI-1 (R=0.79, p=0.006), CD34 (R=0.85, p<0.004) and P-selectin (R=0.77, p=0.002). However, in patients who underwent primary PCI, D-dimer levels were associated with t-PA (R=0.85, p<0.001) and FVW levels were inversely associated with TFPI (R=0.87, p<0.01) in plasma. In addition, in the thrombus the content of fibrin was associated with CD34 and FVW (R=0.71, p=0.03; R=0.73, p<0.02, respectively).

Conclusion: There are clearly different correlations of thrombotic and fibrinolytic factors. Resistant patients to fibrinolysis show positive correlations between strongly thrombotic factors, while in no resistant patients to fibrinolysis there are a trend to haemostasis between prothrombotic and fibrinolytic factors.

**Long term effect of minimising pain-to-balloon time on mortality in ST-elevation infarction. The ANIN Myocardial Infarction Registry**

M. Polanska-Skrzypczyk1, M. Karacz1, P. Bektas1, C. Kepka2, J. Przybys2, M. Kruk3, E. Kioza4, A. Czeczewski1, A. Wilkowski1, W. Ruzyllo1, Institute of Cardiology; 2Department of Cardiology; 3Warsaw, Poland; 4Institute of Cardiology, Warsaw, Poland

**Background:** Pain to balloon time (PBT) has been shown to affect in-hospital mortality in a continuous, non-linear fashion. Current ACC/AHA Guidelines suggest that PBT should be <90 min and as short as possible. It is unclear whether significance of minimising PBT is maintained over the years.

**Objectives:** We sought to evaluate the influence of PBT on long term clinical results in patients (pts) with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI) at a high volume centre.

**Methods:** In a prospective “all-comer” registry clinical and procedural characteristics, PBT and year mortality were determined in consecutive STEMI pts treated with pPCI in our tertiary centre between Feb 2001 and Oct 2002. We divided pts into three groups: A) <90, B) 90-180, C) >180 minutes according to PBT into three groups: A) <90 minutes, B) 90-180, C) >180 minutes. There were 350, 461, 186 pts in group A, B, C, respectively. Pts in group A compared to B and C were younger, more often male and smokers, less frequently had history of CAD, more frequently had occluded TIMI grade flow ≥2, insulin dependent diabetes. There were no differences in prevalence of renal failure, hypertension, Killip class ≥1, cardiogenic shock or multivessel disease. Overall 9-year mortality was 31% (294 pts). Multivariable logistic regression models indicated that longer PBT were associated with a higher adjusted risk of mortality (A: 20.6%, B: 27.5%, C: 37.1%, P < 0.0005). A reduction in PBT from ≥ 360 to 180 minutes was associated with 16.5% lower mortality.

**Conclusion:** We found no correlation between LBBB chronicity and incidence of myocardial infarction. The frequency of MI is low, but somewhat higher in the group ≤ 80 years. In this age group, a new LBBB identified only half of the patients with a final diagnosis of MI, which means that strict adherence to reperfusion guidelines may lead half of the patients untreated.

If our findings are confirmed in larger studies, the current guidelines may have to be revised regarding the importance of LBBB chronicity.

**Primary percutaneous coronary intervention with and without thrombus aspiration**

M. Tarig Farman1, M. Tahir1, S. Nadeem Hasan Rizvi1, K. Naveedullah1, S. Jawaid Akbar1, Karachi Institute of Heart Diseases (IKHD), Karachi, Pakistan; 2National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan; 3Chandka Medical College Hospital, Larkana, Pakistan

**Object:** To determine the safety and efficacy of selective thrombus aspiration during Primary Percutaneous Coronary Intervention (PCI).

**Background:** Manual thrombus aspiration in patients with STE elevation myocardial infarction (STEMI) is at present routinely undertaken in most of the catheterization laboratories performing primary PCI and is considered reasonable. However, its benefit in low risk patients is not fully established. We looked at the question whether aspiration thrombectomy should be the mainstay of primary percutaneous coronary intervention (PCI) in all patients or should it be reserved for high risk group of patients.

**Material and Methods:** This observational prospective study was conducted in the catheterization laboratory of a tertiary care cardiovascular centre. A total of 150 consecutive patients who underwent primary PCI were enrolled. Aspiration was done only when thrombus burden was considered significant. After completion of procedure angiographic and electrocardiographic signs were recorded and clinical follow-up was documented up to 1 year. The primary end point was a resolution of STE elevation within 60 minutes and myocardial blush grade II and III. Secondary end point was death and MACCE up to 1 year.

**Results:** Mean age was 51±12 years and 95% were male. Hypertension was present in 46.7% patients. 24.7% were diabetic and 37.3% were current smokers. Left anterior descending artery was culprit in 65% of patients. More than 90% of culprit vessels were thrombus laden. Multivessel disease was present in 38% of patients and 22.7% had past history of myocardial infarction. Out of 150 patients 117 (78%) underwent thrombus aspiration. No significant difference in ST resolution within 60 minutes (72.6 vs 81.8%, P<0.265) and myocardial blush grade II & III (41.9 ± 27.3% vs. 50.12). No difference in event free survival was observed among the two groups (80.3 vs 84.8%, P=0.708) at one year.

**Conclusions:** Selective thrombus aspiration in heavy thrombus laden arteries and no aspiration in low or negligible thrombus burden vessels is a safe and effective strategy. Overall poor risk profile of our patients as compared to western population necessitates further evaluation of this matter in randomized studies.
**Drug eluting stents are associated with lower MACE rates compared to bare metal stents in small coronary arteries treated by primary PCI for STEMI**


**Purpose:** Drug eluting stent (DES) implantation has been shown to improve outcomes in primary PCI for STEMI, although there is limited data about their use in small coronary arteries. We aimed to compare medium-term outcomes of patients with small coronary arteries with DES versus BMS placement for primary PCI for STEMI.

**Methods:** 2170 consecutive patients underwent primary PCI for STEMI at a single high-volume centre between October 2003 and September 2010. Of these, 883 had culprit arteries with reference vessel diameter <3mm, which were defined as small coronary arteries. The primary end point was major adverse cardiac events (MACE), defined as death, myocardial infarction (MI), stroke and target vessel revascularization (TVR). Median follow-up was 2.0 years (IQR 0.7-3.6 years).

**Results:** 246 patients underwent PCI with DES and 637 with BMS. Patients undergoing DES implantation were older, more likely to be diabetic and more likely to have undergone previous PCI. Kaplan-Meier estimates (Figure 1) of medium-term MACE demonstrated a significant difference in favour of DES (21.1% vs. 14.6%, p<0.04). Age-adjusted Cox analysis demonstrated this benefit to be maintained with no additional major adverse events (hazard ratio 0.79, 95% CI 0.49-0.97). In addition, this difference persisted after regression adjustment incorporating a propensity score (age, stent length, stent width, gender, ethnicity, previous MI, PCI or coronary artery bypass grafting, diabetes, hypertension, hypercholesterolaemia, smoking status, presence or absence of shock, and ejection fraction) into the hazards model as a covariate (hazard ratio 0.82 [95% CI 0.7-0.96]).

**Conclusions:** In patients with small coronary arteries, DES implantation appears to be associated with lower MACE rates than BMS implantation in primary PCI for STEMI.

**IMPORTANCE OF CO-MORBIDITIES IN HEART FAILURE**

A. Shirakabe, N. Hata, N. Kobayashi, T. Shinada, K. Tomita, K. Tomita, M. Tsuchiya, K. Asai, K. Mizuno. Division of Intensive Care Unit, Chiba Hokusoh Hospital, Nippon Medical School, Japan; 2 Nippon Medical School. Department of Internal Medicine. Tokyo, Japan

**Background:** Various studies have reported the relationship between the short-term and long-term prognosis of acute heart failure (AHF) and acute kidney injury (AKI) based on the risk, injury, failure, and end stage (RIFFLE) criteria. However, the relationship between the short-term and long-term prognosis and the timing of AKI during the first 7 days has not been reported.

**Methods:** Six hundred twenty-five patients with AHF admitted to the intensive care unit were analyzed. The occurrence of AKI was evaluated by the RIFLE classifications during the first 7 days after admission. AKI presented upon admission in 170 patients (early-AKI) and occurred after admission in 714 patients (late-AKI). However, no AKI occurred in 281 patients (no-AKI). Patients assigned to three categories by the severest degree of AKI during 7 days after admission; Class R (risk, n=214), Class I (injury, n=73), or Class F (failure, n=57). The study evaluated the relationships between the presence of AKI (its timing and degree) and outcomes, including short term prognosis (in-hospital mortality) and long-term prognosis (any-cause death and HF events, including death and readmission for HF within 2 years).

**Results:** A multivariate logistic regression model found the presence of AKI during first 7 days to be independently associated with in-hospital mortality (p=0.002; OR: 3.633; 95%CI: 1.591-8.297). Kaplan-Meier survival curves showed that the prognosis, including any-cause death, was significantly poorer in early-AKI than in late-AKI and no-AKI, and was significantly poorer in late-AKI than in no-AKI. A multivariate logistic regression model found that Class I (p=0.003; OR: 4.040; 95%CI: 1.610-10.137) and Class F (p=0.001; OR: 6.427; 95%CI: 2.616-15.814) were independently associated with in-hospital mortality. The Kaplan-Meier survival curves showed the prognosis, including any-cause death, to be significantly poorer in Class I than in no-AKI and Class R, to be significantly poorer in Class F than in no-AKI, Class R and Class I, the prognosis including HF events to be significantly poorer in Class F than in no-AKI, Class F and Class I.

**Conclusions:** The presence of AKI during the first 7 days was independently associated with short-term prognosis; furthermore, the presence of AKI on admission was associated with long-term mortality for AHF. The presence of severe AKI (Class I and F) during the first 7 days was associated with both short-term and long-term prognosis for AHF. The RIFLE criteria should, therefore, be developed into a clinically applicable and standardized method for AHF patients.

**Prevalence and predictors of sleep-disordered breathing in patients with stable chronic heart failure: the SchlaHF-Registry**


Sleep and Ventilation Center, Blaubeuren, Germany; 2 University, Department of Internal Medicine II, Regensburg, Germany; 3 Heart and Diabetes Center NRW, Ruhr-University of Bochum, Department of Cardiology, Bad Oeynhausen, Germany; 4 Cologne University Hospital - Heart Center, Clinic III for Internal Medicine, Cologne, Germany; 5 Ruhrlandklinik - University Hospital Essen, Essen, Germany; 6 Remed Science Center, Martinsried, Germany; 7 University Medical Center Hamburg-Eppendorf, Department of Medical Biometry and Epidemiology, Hamburg, Germany

**Objective:** In patients with stable chronic heart failure (CHF) we investigated the prevalence and predictors of sleep-disordered breathing (SDB).**

Methods and Patients: The ongoing multi-center SchlaHF registry provides demographic and clinical data on stable CHF patients. We included prospectively 3504 CHF patients from cardiology practices and cardiology departments of hospitals in our analysis. Inclusion criteria are New York Heart Association (NYHA) class II and left-ventricular ejection fraction (LVEF) <45%. SDB, defined as apnea-hypopnea index (AHI) >15/h, was determined by a two-channel screening (nasal airflow, pulse oximetry) using ApexLink (ResMed, Sydney, Australia).

Results: The prevalence of SDB was 36% in women (n=739), 48% in men (n=2765) and 46% in the entire sample of CHF patients. Prevalence of SDB rose with increasing age (≤50, 50-60, >60, >70, >80 and >80 years) from 30% to 40%, 46%, 52% and 56%, respectively. Risk factors for SDB were male gender (odds ratio (OR) 1.77, 95% confidence interval (CI) 1.48-2.11), age (OR 1.36, 95% CI 1.28-1.46 per 10-year age increment), obesity (body mass index ≥30kg/m²: OR 1.53, 95% CI 1.31-1.77), severe impairment of cardiac function (NYHA class IV: OR 1.24, 95%CI 1.07-1.40), high sympathetic activity (NYHA class III and IV vs. NYHA class II: OR 1.19, 95% CI 1.03-1.38), and atrial fibrillation (OR 1.28, 95% CI 1.08-1.51).

Conclusions: The multi-center SchlaHF registry shows that prevalence of SDB is high in a representative sample of stable CHF outpatients. Male gender, age, obesity and severity of CHF are clinical predictors for SDB.

**Prognostic impact of the timing/degree of Acute Kidney Injury and Acute Heart Failure: an evaluation of the RIFLE Criteria**


**Background:** Spirometry and cardiopulmonary exercise test (CPX) were performed in 204 men with stable systolic HF (age: 57±11 years, LVEF: 30±8%, ischaemic aetiology: 49%, NYHA class I/II/III: 56/113/31), none of them had previously diagnosed lung disease and related therapy. Almost all men were taking β-blockers (99%), and ACE inhibitors or ARB (100%). Forced inspiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were assessed according to American Thoracic Society/European Respiratory Society Guidelines, and expressed in litre (L) and % of predicted values.

**Results:** Normal spirometry results (FEV1/FVC ≥70%, FVC ≥80% pred.) was found in 112 (55%) men with HF, only obstructive pattern of breathing (FEV1/FVC ≥70%, FVC ≥80% pred.) in 16 (8%) men with HF, only restrictive pattern of breathing (FEV1/FVC <70%, FVC <80% pred.) in 30 (14%) men with HF and obstructive-restrictive combination of these two abnormalities (FEV1/FVC ≤70%, FVC <80% pred.) in 27 (13%) men with HF. Clinical characteristics of these groups are presented in table.

**Conclusions:** Impaired pulmonary function is common in men with systolic HF.
The presence of restrictive (but not obstructive) pattern of impaired pulmonary function is related to impaired exercise tolerance. Further studies are needed to explain this finding.

3839 Are functional and absolute iron deficiencies equally detrimental in heart failure? M. De Antonio1, J. Lupon1, J. Comín2, A. Galán3, B. González1, L. Cano1, R. Cabanes1, A. Urrutia1, E. Zamora2, A. Bayes-Genis1. 1Germans Trias i Pujol University Hospital, Badalona, Spain; 2Hospital del Mar, Department of Cardiology, Heart Failure Program, Barcelona, Barcelona, Spain

Introduction: Iron deficiency (ID) has shown to worsen prognosis in patients with heart failure (HF). ID can be absolute or functional. Objective: To assess the prognostic significance of ID (both absolute [defined as ferritin -30 μg/L] and functional [defined as ferritin ≥ 30 μg/L and transferrin saturation <20%]) in a real-life HF outpatient population.

Patients: 678 patients (72% men, median age 70.3 years [IQR 60.5-77.2]) were studied. Aetiology of HF was mainly ischemic heart disease (52.2%), Median LVEF was 34% [IQR 26-43%]. Most patients were in NYHA class II (65.6%) or III (26.3%). Median follow-up was 3.4 years [IQR 1.8-5.04].

Results: ID was present in 452 patients (51.1%), being absolute in 81 (9.2%) and functional in 371 (42.3%). Only 238 patients with ID were anaemic (52.7%). During follow-up 313 deaths were recorded. ID was associated with higher mortality risk (HR 1.48 [IQR 1.18-1.86], p<0.001), specifically in non-anemic population (HR 1.66 [IQR 1.18-2.34], p=0.004). In the multivariable analysis (backward step), that also included age, sex, LVEF, NYHA functional class, ischemic etiology, eGFR, and NtproBNP, ID remained in the model. When anaemia was included in the model, ID only remained an independent predictor in non-anemic patients. When absolute and functional ID were analyzed, the latter tended to have worse prognosis (figure) with statistical significance (HR 1.31 [IQR 0.89-1.92], p=0.177 vs HR 1.52 [IQR 1.20-1.93], p<0.001).

Conclusion: ID, mainly functional deficiency, was very frequent in a HF outpatient population of different etiologies and carried a higher risk of death, specifically in the non-anemic population.

Methods: We enrolled 1007 consecutive patients with systolic CHF (age 65±12 years, mean±SD, males 72%, LV ejection fraction -EF- 33±10%), 274 (29%) with diagnosed diabetes, undergoing a comprehensive clinical, humoral (including glycosylated haemoglobin, HbA1c [1c]), echocardiographic and neurohormonal evaluation. For subgroup analysis, patients were divided into tertiles of LVEF (50-38%, 38-28%, <28%). Endpoint was cardiac mortality.

Results: During a 5-year follow-up (median 36 months, range 0.3-60), 154 cardiac deaths occurred. In the whole population, no differences were evident in clinical, neurohormonal, echocardiographic parameters, nor in outcome between diabetics and nondiabetics. Conversely, patients with HbA1c>7 showed higher plasma renin activity (PRA, 3.66; 0.62-6.13 vs. 2.28; 0.41-4.1 ng/mL/h, p<0.01), NT-proBNP (1602; 826-3498 vs. 1076; 401-3112 ng/L, p<0.01), and worse clinical status (43% of patients with HbA1c>7 being NYHA III/IV vs. 35% of patients with HbA1c<7, p<0.05), with no difference in any other parameter. HbA1c<7 predicted cardiac mortality (events in 22% vs. 14% p=0.04). In the subgroup with slightly reduced LVEF patients with HbA1c<7 showed higher PRA and cardiac natriuretic peptides. In this group, HbA1c>7 along with NT-proBNP (but not the diagnosis of diabetes) resulted the only independent predictors of outcome, whereas this did not occur in patients with moderate-to-severe LV dysfunction.

Conclusions: Glycometabolic imbalance enhances neurohormonal activation and worsen prognosis, in CHF patients, beyond diagnosis of diabetes. This association appears prominent at early stage of CHF, characterized by slight LV systolic dysfunction, when chronic hyperglycemia might have a specific impact on cardiac remodeling process, by eliciting neuroendocrine activation.

3841 Prognostic value of atrial fibrillation pattern in heart failure S. Taillandier, L. Fauchier, B. Lallemand, N. Clemency, A. Bernard, B. Pierre, E. Simeon, S. Taillandier, D. Babuty. Tours Regional University Hospital, Hospital Trousseau, Tours, France

Atrial fibrillation (AF) and heart failure (HF) frequently coexist and are associated with an increased mortality. The prognostic value of AF pattern in HF with reduced left ventricular ejection fraction (LVEF) is poorly known and there are very few data about AF pattern and prognosis in HF with preserved LVEF. This study evaluated the prognostic value of AF pattern in patients suffering from HF.

Methods: All AF patients seen in our institution between 2000 and 2010 were included. The long-term survival of patients with severe ischemic mitral regurgitation affect survival? V. Shumaviec, Y. Ostrowski, A. Sliet, A. Janushko, A. Lysjapok, O. Jdanovich, A. Beresneva. Belarus Cardiology Centre, Minsk, Belarus

Purpose: The long-term survival of patients with severe compromised ischemic left ventricle and concomitant functional mitral regurgitation is reduced. We performed this study to understand how mitral valve replacement versus repair affects survival and reveal the predictors of mortality in this high-risk population.
Different surgical techniques of mitral valve repair for ischemic mitral regurgitation: predictors of efficacy


Objective: Mitral valve annuloplasty is the standard surgical option for the management of ischemic mitral regurgitation (MR). However, after annuloplasty recurrent MR develops in some patients.

Methods: The investigation was prospective and with a control group of patients who underwent MR repair for ischemic MR combined with revascularization. The authors prospectively collected the data and reviewed 257 patients, 53 (8.1%) had residual MR ≥2 grade during even during hospital stay. The mitral valve and LV parameters, including tere Victorian diastolic function and LV structural anchorage of the mitral leaflets, were determined. SPSS 15.0 was used for analyses.

Results: The type of annuloplasty (rigid ring, flexible ring or posterior annuloplasty) didn’t influence the efficacy of surgical treatment (occurrence of the residual MR ≥2 grade 77%, 5.6% and 4.5% correspondingly, χ²=1.75, p=0.416). On ROC analysis and multiple logistic stepwise analysis from 277 patients, a larger LV (EDD > 65 mm; OR 2.7, 95% CI 1.1 – 6.6, p=0.007; LVEF: 59 – 90 mm, OR 2.5, 95% CI 1.3 – 6.0, p=0.04; EDV: > 105 mL, OR 3.41, 95% CI 1.42 – 8.29, p=0.007 and IVST ≥ 66 mL/m², OR 2.63, 95% CI 1.12 – 6.24, p=0.03) was identified as independent predictors for failure of MR repair without rigid ring (flexible or semirigid ring, commercially available or xenopericardial posterior band and else). From 378 cases the higher tere Victorian area (for apic4ch viewer < 2.5 sm² OR 5.06, 95% CI 1.1 – 34.7, p=0.004 and 2.75 sm² OR 80.1, 95% CI 1.16 – 43.7, p=0.016) and higher MR severity (for venae contracta ≥ 6.5 mm OR 1.56, 95% CI 1.02 – 2.3, p=0.02 and for ERO PISA >0.39 sm² OR 1.07, 95% CI 1.02 – 1.15, p=0.05) were identified as independent predictors for failure of MR repair.

Conclusion: In conclusion, these results demonstrated that preoperative findings of precise echocardiography can be used to identify patients with ischemic MR at increased risk of repair failure.

Comparison of risk scores for predicting early mortality after Aortic Valve Replacement for aortic stenosis


Background: Major risk scores of early mortality in cardiac surgery are the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) score. A new model of EuroSCORE, which is called EuroSCORE II, was launched at 2011. The aim of this study was to compare STS-PROM and EuroSCORE II after AVR for AS.

Methods: We analyzed the data from 258 consecutive patients who underwent AVR at Juntendo University. The data set included 102 patients after aortic valve repair (AVR) and 156 patients after aortic valve replacement (AVR). The EuroSCORE II and STS-PROM scores were calculated for each patient. Observed and expected mortality were calculated. The observed mortality was 4.2% (n=11). Predicted mortality rates for STS-PROM and EuroSCORE II were 4.7% and 3.5%, respectively, and thus the O/E ratios for STS-PROM and EuroSCORE II were 0.98 and 1.20, respectively.

Conclusion: Our observed early mortality was 4.2% (n=11). Predicted mortality rates for STS-PROM and EuroSCORE II were 4.7% and 3.5%, respectively, and thus the O/E ratios for STS-PROM and EuroSCORE II were 0.98 and 1.20, respectively. Pearson correlation coefficient revealed a good linear relationship between STS-PROM and EuroSCORE II (r = 0.76, P < 0.001).

Preoperative echocardiographic parameters with perioperative mortality in 337 consecutive patients undergoing AV replacement according to AVR: group 1 (area <0.75 cm², n=78) with group 2 (area <0.75 cm², n=259). Mean age was 66 ±12 vs 73 ±9 years, mean body mass index (BMI) 29 ±6% vs 44%, mean left ventricular ejection fraction (LVEF) 50 ±15 vs 60 ±18 mm Hg; mean AVA was 0.83 ±0.06 vs 0.61 ±0.09 cm² (p=0.001); indexed stroke volume was 4.1 ±1 vs 4.6 ±12 mL/m² (p=0.001). Mean Euro I, Euro II and STS mortality scores were 6.25 ±9.8%, 3.1 ±7% and 2.6 ±2.3%, respectively. Survival rates were significantly greater in group 2 than group 1: Euro I 3.4±3.4% vs 6.5±9.9%, Euro II 1.5±1.1% vs 3.4±7%; STS 1.8±1.3% vs 2.9±2.4% (p<0.001). Postoperative mortality rate was 2.9%: 0% in group 1 and 3.4% in group 2 (p=0.092). All scores were positively correlated (for Euro I vs Euro II, Euro I vs STS and Euro II vs STS, the coefficients were 0.754 ±0.61 and 0.563, respectively; p<0.001) and were significantly greater in deaths vs survivors (Euro I 13±3%, Euro II 11% vs 2%, STS 2% vs 2%; p<0.001). All scores were negatively correlated with AVA: r = -0.242 (Euro II), r = -0.235 (Euro II) and r = -0.292 (STS); p<0.01. Pre and postoperative left ventricular ejection fraction and postoperative systolic pulmonary artery pressure were significantly different by comparing deaths vs survivors: 46 ±13% vs 62±13%, 46±15% vs 57±10% and 37.5± mm Hg vs 31±10 mm Hg (p<0.001, 0.039 and 0.033), respectively.

Conclusion: Perioperative mortality risk and death rate seems to be greater in AS severity in patients undergoing isolated AV replacement.

Predictors of persistent severe diastolic dysfunction after aortic valve replacement in aortic stenosis compared with aortic regurgitation

L. Ituta, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

Purpose: 1. To evaluate the effect of aortic valve replacement (AVR) on left ventricular (LV) diastolic function and LV remodeling, comparing patients with aortic stenosis (AS) to patients with aortic regurgitation (AR).

Methods: 5 years prospective study on 397 patients with restrictive LVDFD after isolated AVR.

Results: The evolution of the LV diastolic function was different in AS group (after AVR diastolic filling improved) compared to AR group. At 1 year post-surgery the percent of the patients with persistent restrictive LVDFD was 23.01% in AS group and 60.23% in AR group.

2. At 5 years, cardiovascular event-free survival, including hospital visits caused by heart failure symptoms and sudden cardiac death was significantly higher in the patients with preoperative AS (87.7%) compared to AR group (64.9%).

3. The parameters appropriate for prediction of immediate and medium term evolution were age, preoperative NYHA class, LVEF, atrial fibrillation, coronary artery disease and smoking.

4. Simple and multivariate regression analysis identified as independent predictors for failure of immediate and medium term term evolution were these parameters.
Conclusions: 1. Restrictive flow pattern is reversible mostly after AVR for AS than for AR, both in the early and medium postoperative term.
2. The parameters predicting fatal outcome and hospitalisation for heart failure on medium postoperative NYHA class, LVEF, atrial fibrillation, coronary artery disease and smoking.
3. The echographic predictors for persistence of a restrictive LVEDP in patients with AR and LV systolic dysfunction were: AR, E/E' > 15, LVEDV > 55mm, the LA diameter index > 30mm/m², severe PHT and associated 2 degree MR.

Additional ablation of complex fractionated atrial electrograms in long-lasting persistent atrial fibrillation. Does it change the ablation success?

Results: Ablation of CFAE in addition to PVI lead to a change of ablation success in patients with long-lasting persistent AF. Ablation of complex fractionated atrial electrograms (CFAE) has been used as an additional option in ablation.

Hypothesis: Does ablation of CFAE in addition to PVI lead to a change of ablation success in patients with long-lasting persistent AF.

Methods: 345 patients were included (TAVI: 210 pts, 28% with baseline RBBB, 79.07±7.3 years, p<0.05), and the TAVI group exhibited a higher-risk profile (Log Euroscore 22.9±15.8% vs. 13.1±11.6% in the SAVR group, p<0.001). The rate of new PPM was higher following TAVI (n=50, 14.7%) compared to SAVR (n=2, 0.7%, p<0.001). The main causes of PPM implantation were: third degree atrioventricular (TAVI: 39pts, 78%; SAVR: 2pts, 100%), atrial fibrillation with a ventricular rate lower than 40mm (TAVI: 3pts, 6%, second degree atrioventricular (TAVI: 8pts, 16%), progressive QRS widening (TAVI: 3pts, 6%, and bradyacardia-tachycardia syndrome (TAVI: 1pt, 2%). The median time from TAVI to implantation of a PPM was 2 days (interquartile range: 0-12) and from SAVR was 13.5 days (interquartile range: 12-15). Complete-AVB was the primary reason for PPM in the TAVI (78%) and SAVR (100%) groups (p<0.001). In the TAVI group, complete AVB was more common after implantation of a CoreValve than Edwards prosthesis (64.1% vs 35.9%, p<0.001). On multivariable analysis, the predictors of PPM for advanced AVB, after adjustment for age, were: presence of baseline RRBB (OR=2.3, 95%-CI:1.29-4.22, p<0.005), Cororeave prosthesis (OR=3.6 95%-CI:1.79-7.3, p<0.0001), and LVEF below 35% (OR=2.1, 95%-CI:0.9-4.9, p<0.001). The acute success rate (96.6% without vs. 91.8% with CFAE p<0.05) and the acute recurrence rate of AF until hospital discharge (12% without vs. 20.9% with CFAE p<0.05) were statistically significant different. The 1yFU data could be obtained in 73.6% of Pts. without CFAE ablation and in 69.8% of pts. with CFAE ablation. At 1yFU the recurrence rate was 57.4% without CFAE ablation vs. 53.2% with CFAE ablation (p=0.52). Median procedure time (200 vs. 175 min, p<0.001), pain control and the statistical analysis procedures were performed for the German Ablation Registry organized by a Institut, Ludwigshef, Germany.

Results: In therapy of paroxysmal and long-lasting persistent atrial fibrillation (AF) pulmonary vein isolation (PVI) is a well-established therapeutic option. In ablation of long lasting persistent AF substrate modification is usually required. Additional ablation of complex fractionated atrial electrograms (CFAE) has been used as an additional option in ablation.

Hypothesis: Does ablation of CFAE in addition to PVI lead to a change of ablation success in patients with long-lasting persistent AF.

Methods: 345 patients were included (TAVI: 210 pts, 28% with baseline RBBB, 79.07±7.3 years, p<0.05), and the TAVI group exhibited a higher-risk profile (Log Euroscore 22.9±15.8% vs. 13.1±11.6% in the SAVR group, p<0.001). The rate of new PPM was higher following TAVI (n=50, 14.7%) compared to SAVR (n=2, 0.7%, p<0.001). The main causes of PPM implantation were: third degree atrioventricular (TAVI: 39pts, 78%; SAVR: 2pts, 100%), atrial fibrillation with a ventricular rate lower than 40mm (TAVI: 3pts, 6%, second degree atrioventricular (TAVI: 8pts, 16%), progressive QRS widening (TAVI: 3pts, 6%, and bradyacardia-tachycardia syndrome (TAVI: 1pt, 2%). The median time from TAVI to implantation of a PPM was 2 days (interquartile range: 0-12) and from SAVR was 13.5 days (interquartile range: 12-15). Complete-AVB was the primary reason for PPM in the TAVI (78%) and SAVR (100%) groups (p<0.001). In the TAVI group, complete AVB was more common after implantation of a CoreValve than Edwards prosthesis (64.1% vs 35.9%, p<0.001). On multivariable analysis, the predictors of PPM for advanced AVB, after adjustment for age, were: presence of baseline RRBB (OR=2.3, 95%-CI:1.29-4.22, p<0.005), Cororeave prosthesis (OR=3.6 95%-CI:1.79-7.3, p<0.0001), and LVEF below 35% (OR=2.1, 95%-CI:0.9-4.9, p<0.003).

Conclusions: TAVI was associated with a higher rate of complete-AVB and PPM compared to SAVR in elderly patients with SAS. The presence of baseline RRBB and Cororeave prosthesis correlated with the need for PPM in the TAVI group.

OUTCOMES AND COMPLICATIONS OF CATHETER ABLATION FOR ATRIAL FIBRILLATION

Five years follow up of patients undergoing catheter ablation of persistent atrial fibrillation using the stepwise approach: BLOC-AF study

Methods: 160 consecutive pts with persistent AF undergoing de novo catheter ablation (stepwise approach: PVI, ablation of fractionated electrograms, and linear ablation) were included, with the desired procedural endpoint being AF termination. Repeat ablation was performed for pts with recurrent AF/AT after a 1 month blanking period. A minimum follow up (FU) of 48 months with repeated Holter monitoring was performed. Arrhythmia recurrence was defined as AF or AT ≥30 sec. Interim analysis of the first 75 pts (51 55±9 years, LVEF 57±14%, 56% long-standing PaAF) who completed FU is presented.

Results: AF was terminated during the index procedure in 60 of 75 pts (80%). LA diameter, cycle length, and duration of continuous AF were predictors of AF termination (All p<0.05). Arrhythmia-free survival rates were 46%, 31%, and 20% after a single procedure, and were 84%, 79%, and 67% after multiple procedures (2.2±1.1 procedures; median=2 (1-3) at 1, 2, and 5 years FU, respectively. At 5.3±1.9 years of FU, 57 pts (76%) were free from arrhythmia recurrence (n=50; 67%) or showed clinical improvement (>90% AF burden reduction) under previously ineffective antiarrhythmic drugs (n=7; 9%). Most recurrences occurred over the first 6 months. Duration of continuous AF ≥13±13 months vs. ≥23±25 months; p<0.05) and termination of AF during index procedure (75% vs. 29%; p<0.01) were associated with freedom from arrhythmia recurrence. In multivariate analysis, only termination of AF was an independent predictor of freedom from AF/AT during FU (OR 7.5, 95%-CI 1.7-34.5, p<0.05). Major complications (cardiac tamponade, phrenic nerve injury) occurred in 2 pts (2.6%).

Conclusions: In pts with persistent AF, stepwise ablation with repeat intervention at 6 months provides good medium term outcome even with strict definition for failure (AF/AT ≥30sec). A slow decline of arrhythmia-free survival is noted over 5 years FU. Procedural termination of AF predicts long-term arrhythmia-free survival.

Rhythm control in elderly patients with persistent atrial fibrillation: a randomized comparison of catheter ablation versus antiarrhythmic drugs

Methods: 345 consecutive patients, aged ≥70 years, were randomly assigned in a 1:2 fashion to catheter ablation (Group A, 118 patients) or AADs (Group B, 236 patients). Study endpoints were: treatment failure, defined as any atrial arrhythmias lasting ≥ 3 minutes, and treatment-related adverse events (acute when ≤ 1 month of procedure and long-term when > 1 month of procedure).

Results: At a mean follow-up of 42±17 months, 45% of Group B patients were in sinus rhythm (SR) vs. 53% of Group A after one procedure (p=0.09) and 75% after redo procedures (p=0.001) (see figure). Fifteen acute adverse events occurred (12 in Group A vs. 3 in Group B, p=0.001), mainly periprocedural cerebral thromboembolism (6 in Group A vs. 2 in Group B, p=0.02). The independent predictors of post-ablation cerebrovascular accidents were previous TIAs (OR 1.195, 95% CI 1.057-1.350) and AF duration at the procedure (OR 1.011, 95% CI 1.001-1.021). At follow-up, 69 long-term adverse events occurred (12 in Group A vs. 57 in Group B, p=0.001). Group B patients resulted associated with a signifi-
Asymptomatic cerebral lesions in pulmonary vein isolation under therapeutic anticoagulation


Background: Left atrial radiofrequency ablation has been shown to carry a risk of asymptomatic cerebral lesions. No data exists in patients under full anticoagulation throughout the ablation procedure. The aim of this study was to quantify the amount of silent cerebral lesions assessed by preprocedural and postprocedural MRI in these patients and to identify clinical or procedural parameters that increase the risk.

Methods: A total of 111 consecutive patients undergoing catheter ablation for paroxysmal (n=69; 62.2%) or persistent (n=42; 37.8%) atrial fibrillation were included in the study. Pulmonary vein antrum isolation, roofline, mitral isthmus line, and CFAE ablation using 3.5mm open-irrigated tip catheters were performed, as needed. All patients underwent preprocedural and postprocedural cerebral MRI.

Results: Postprocedural MRI revealed new embolic lesions in 14 patients (12.6%), all of them asymptomatic. The only clinical parameter showing a significant correlation with cerebral embolism was smoking in transesophageal echocardiogram (p=0.012). Type of atrial fibrillation showed a trend with 6/63 paroxysmal (9.5%) vs. 8/34 persistent patients (23.5%; p=0.098). Additionally, the CHA2DS2-VASc-Score revealed a trend to significance (p=0.027). Procedure-related parameters contributing to an increased risk were electrical cardioversion (p=0.026) and CFAE lesions (p=0.016). The only two factors showing a trend to significance in multivariate analysis remained CFAE ablations and smoke in TEE.

Conclusions: Radiofrequency ablation in patients under therapeutic anticoagulation is associated with a substantial risk of silent embolism detected by cerebral MRI. Significant risk factors for cerebral lesions are CFAE ablations and smoke in TEE and electrical cardioversion during the ablation procedure.

Long-term results of transcatheter atrial fibrillation ablation in patients with impaired left ventricular systolic function

M. Anselmino1, S. Grossi2, M. Scaglione3, D. Castagno1, F. Bianchi1, G. Senatore4, M. Matta1, F. Ferraris1, Y. Cristoforetti1, F. Gaita1.

1University of Turin, Department of Internal Medicine, Division in Cardiology, Turin, Italy; 2Mauriziano Hospital, Department of Cardiology, Turin, Italy; 3Cardinal Massaia Hospital, Department of Cardiology, Asti, Italy; 4Civic Hospital, Città (Turin), Italy

Purpose: Aim of the present study is to evaluate sinus rhythm (SR) maintenance, clinical status and echocardiographic parameters over a long-term period following atrial fibrillation (AF) transcatheter ablation in patients with left ventricular ejection fraction (LVEF) <50%.

Methods: 196 patients (87.2% males, age 60.5±10.2 years) with LVEF <50% underwent radiofrequency transcatheter ablation for paroxysmal (22.4%) or persistent (77.5%) AF. Patients were followed for 46.2 (16.4-63.5) months concerning AF recurrences, functional class, and echocardiographic parameters.

Results: All patients underwent pulmonary vein isolation, while 167 (85.2%) required additional atrial lesions. Eleven (5.6%) patients suffered procedural complications. During follow-up 58 (29.6%) patients required repeated ablations. At follow-up end 15 (7.7%) patients died, while 74 (37.8%) documented at least one episode of AF, atrial flutter or atrial ectopic tachycardia. Eighty-three (47.2%) patients maintained antiarrhythmic drugs. During follow-up NYHA class improved by at least one class more frequently amongst patients maintaining SR compared to those experiencing relapses (70.6% vs. 47.5%; p=0.003). UEF showed a broader increase in patients maintaining SR (32.7% vs. 21.4%; p=0.047)

Figure 1. Kaplan-Meier estimate of freedom from AF
mital regurgitation grading significantly decreased (p<0.001) only within these patients. At multivariable analysis SR maintenance emerged as an independent predictor of long-term clinical improvement (Odds Ratio 4.26 95%CI 1.69-10.74, p=0.002).

Conclusions: Although not substantially worse than in patients with preserved LVEF, AF ablation in patients with impaired LVEF is affected by high long-term recurrence rate. Amongst these patients SR maintenance is associated with greater clinical improvement.

TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI) IN CURRENT AND FUTURE CLINICAL PRACTICE

3874 Early experience with the JenaValve transapical aortic valve implantation system

M. Ferreri¹, H.R. Figulla¹, M. Breuer¹, H. Treede², S. Baldus², A. Rastan³, S. Ensinger⁴, M. Arnold⁴, T. Walther⁵, F.W. Mohr⁶, ¹Friedrich Schiller University Hospital of Jena, Jena, Germany; ²University Heart Center Hamburg, Hamburg, Germany; ³Clinical Research Institute, Center for Cardiovascular Diseases Rotenburg a.d. Rotenburg, Germany; ⁴Heart and Diabetes Center NRW, Bad Oeynhausen, Germany; ⁵University of Erlangen-Nuremberg, Department of Cardiology, Erlangen, Germany; ⁶Herzzentrum Berlin, Department of Cardiovascular Surgery, Bad Nauheim, Germany; ⁷University of Leipzig, Heart Center, Leipzig, Germany

Transcatheter aortic valve implantation (TAVI) has become a well accepted clinical option for treating high risk patients suffering from severe symptomatic aortic valve stenosis. The self-expanding JenaValve prosthesis consists of a nitinol stent with a porcine root valve available in three different sizes. The stent is fixed in orthotopic position by clipping on the cusps of the old diseased valve. The three-step implantation procedure can be performed under beating heart conditions avoiding hemodynamic compromise. The retrievable and repositionable system received CE-mark in September 2011. Three months results of all pre-CE-mark implantations are summarized in this report.

79 patients (age 84±6.0 years, logistic EuroSCORE 27±7.3%) were included in the first-in-man and the consecutive CE-mark study. 76 patients underwent TAVI with the JenaValve System. In 69 patients the stent-valve was successfully implanted (valve sizes 23mm: 42%, 25mm: 39%, 27mm: 19%). We observed a 30-day mortality rate of 6.6% (5 patients). Additional 10 patients died during the next 2 months resulting in a 3-month mortality rate of 19.7%. Pacemaker implantation was necessary in 7.9% due to conduction abnormalities after TAVI. No coronary obstructions occurred. Aortic regurgitation of grade I or less was present in 88.1% post procedure and in 93.0% at 3-months follow-up. Valve insufficiency grade II was described in 11.9% post procedure and in 7.0% after 3 months. Neither regurgitation of more than grade II nor signs of prosthetic dysfunction were observed in any patient during 3 months follow-up. Anatomically correct positioning and implantation without rapid pacing are favourable features of the JenaValve TAVI System. Implantation success was limited due to the learning curve when introducing the novel implantation technique. However, technical improvements of the delivery catheter will further increase the procedural success rate.

First results of the self-expanding transapical JenaValve TAVI system showed promising result with respect to a low rate of aortic regurgitation. No major complications were observed in any patient during 3 months follow-up.

3875 The impact of pulmonary hypertension on outcome in TAVI patients: a two-centre experience

M. Vasa-Nictera¹, J.M. Sinning¹, D. Chirin², C. Hammerting³, A. Ghanié¹, R. Schueler¹, E. Grube¹, J. Kovac³, G. Nickening³, N. Werner¹, Il Medizinische Klinik, Universitätsklinikum Bonn, Bonn, Germany; ²University Hospitals of Leicester, Glenfield Hospital, Leicester, United Kingdom

Background: The prognosis of patients with aortic stenosis (AS) and pulmonary hypertension (PH) is poor though not fully understood. Transcatheter aortic valve implantation (TAVI) facilitates treatment of patients in end-stage AS many of whom are suffering from severe PHT. The aim of our study was to elucidate the impact of PHT on outcome after TAVI.

Methods and results: Pre and 90 days post TAVI, pulmonary artery systolic pressure (PASP) was determined non-invasively by echocardiography in 326 patients undergoing TAVI. PASP was classified as absent (<30mmHg), mild-to-moderate (30-60mmHg), and severe (>60mmHg).

The prevalence of PHT was associated with 30-day (12.9% vs. 4.6%; P=0.008) and 1-year mortality (36.5% vs. 17.8%; P=0.001). Furthermore, the severity of PHT before TAVI was related to outcome with 1-year mortality rates of 18.1%, 23.4%, and 45.5% for PASP <30mmHg, 30-60mmHg, and >60mmHg, respectively (P<0.001). In multivariate regression analysis, severe PHT at baseline was associated with a two-fold higher mortality risk (HR 2.1, 95%CI: 1.2-3.3; P=0.009).

Conclusions: Severe pulmonary hypertension is a strong and independent predictor of adverse outcome after TAVI and plays a crucial role in the selection process.

3876 Is mitral regurgitation reversible in patients undergoing transcatheter aortic valve implantation?

D. Rosenmann, Y. Almagor, M. Klutstein, J. Bakin, R. Farkash, D. Tzovin. Shaare Zedek Medical Center, Jerusalem, Israel

Background: Significant mitral regurgitation (MR) is often present in pts with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI). Detection of MR in such pts is crucial as it can independently affect functional status and prognosis.

Aim: To define the short term effect of TAVI on MR severity.

Methods: Comprehensive echocardiographic studies were performed in all TAVI pts before procedure and before hospital discharge. MR was classified according to venous contract (VC) and visual assessment as absent, mild, moderate or severe.

Results: In our department, 86 pts underwent successful TAVI since 2008. A balloon expandable valve was implanted (Edwards-Sapien- 79 pts, Medtronic-7 pts); 70 by retrograde transfemoral, 14 by anterograde transapical and 2 by subclavian approach. Aortic peak/mean gradient in pre and post TAVI were 85.1±68.3±166mmHg and 23.4±10.9±7.9mmHg respectively (p<0.001 for both).

Mild aortic incompetence (AI) post TAVI was observed in 27 (31%) pts, moderate in 18 (21%) pts. No patient had severe AI. Severity of MR: visual assessment (see Table). Mean VC was 0.41±0.17cm before TAVI and 0.38±0.16 after procedure (p<0.001). Fifty-four (63%) pts had coronary artery disease (CAD), 66 (77%) had mitral annulus calcification (MAC) and 38 (44%) had organic mitral valve disease (OMVD). No relation was found between presence of CAD, MAC or OMVD and improvement of MR degree or VC (p>0.2 for all).

In 22 (26%) pts MR improved by 1 grade, 5 (6%) by 2 grades, 1 (1%) by 3 grades, no change in 45 (52%) and worsening in 13 (15%) pts.

Conclusions: Degree of MR improves post TAVI, regardless of etiology of MR and pathology of the mitral valve. Long term assessment of MR should be performed in order to confirm persistence of MR improvement.

3877 Perivalvular aortic regurgitation: a major predictor of 1-year mortality after a successful TAVI procedure - Insights from the FRANCE2 registry

E. Van Belle¹, N. Dumonteil², F. Juthier², B. Iung³, H. Etchaninoff⁴, D. Carrié⁴, M. Laskara⁴, M. Gilard⁴, A. Prat³, E. Teiger⁴ on behalf of The FRANCE2 scientific Committee. ¹Hospital Regional University of Lille - Cardiological Hospital, Lille, France; ²University Hospital of Toulouse - Rangueil Hospital, Department of Cardiology, Toulouse, France; ³AP-HP - Hospital Bichat-Claude Bernard, Department of Cardiology, Paris, France; ⁴University Hospital of Rouen - Hospital Charles Nicolle, Rouen, France; ⁵University Hospital of Limoges - Hospital Dupuyren, Limoges, France; ⁶University Hospital of Brest, Department of Cardiology, Brest, France; ⁷AP-HP - University Hospital Henri Mondor, Department of Cardiology, Creteil, France.

Background: A significant peri-valvular aortic regurgitation (AR) is observed in 15-20% of the cases after a successful transcatheter aortic valve implantation
The impact of transcatheter aortic valve implantation on resource use. Results from the German transcatheter aortic valve interventions registry

J. Biermann1, M. Horak2, P. Kahleiter1, T. Konorza3, B. Pichtl1, J. Wasem4, R. Zahn5, J. Senges1, R. Ebelt3, T. Neumann1 on behalf of German transcatheter aortic valve interventions registry. 1Clinic of Cardiology, University Hospital Essen, Essen, Germany; 2Institute of Myocardial Infarction of Duisburg-Essen (UDE), Essen, Germany; 3Department of Cardiology, Clinical Center of Ludwigshafen, Ludwigshafen, Germany

Purpose: Transcatheter aortic valve implantation (TAVI) has been shown to improve survival compared with standard therapy in patients with severe aortic stenosis who are ineligible for surgery. Especially older patients with aortic stenosis cannot always be offered conventional surgical aortic valve replacement at an acceptable risk. Therefore TAVI is currently an alternative treatment option. The effects of TAVI on health-related quality of life (HRQL) have not been reported from a large scale cohort.

Methods: The prospective multicentre German transcatheter aortic valve intervention registry includes patients with symptomatic, severe aortic stenosis since 2009. The registry currently monitors current use and outcome of transcatheter aortic valve interventions, including TAVI, in daily clinical routine, and to evaluate safety, effectiveness and health economic data. We performed an analysis of HRQL, for a subset of patients who underwent TAVI and completed the one-year follow-up. HRQL was assessed at baseline, at 30 days and 12 months with the EQ-5D questionnaire.

Results: Quality of life data were eligible for a total of 415 patients who survived 12 months after TAVI (average age 81.9±5.9 years; men 37%). At baseline, mean EQ-5D index (0.67±0.23) was markedly depressed. Although the EQ-5D index improved from baseline, the extent of improvement was greater at 30 days (0.70±0.33) than at 12 months (0.68±0.27). At 12 months, TAVI patients also reported improvements with regard to the each single dimension of the EQ-5D. In particular the distribution of the three levels (no problems, some problems, extreme problems) changed with regard to usual activities and pain/discomfort after 12 months (usual activities: 48.6%, 39.7%, 11.7%; pain/discomfort: 61.9%, 39.7%, 8.3%; p=0.001). Scores on the visual analogue health scale (EQ VAS), which records the patient's self-rated health improved significantly (p=0.0001) for both follow-up times from a mean value of 81.9±5.9 baseline (30 days: 62.9±17.4; 12 months: 65.1±20.6).

Conclusions: Among patients from the German transcatheter aortic valve interventions registry with severe aortic stenosis TAVI resulted in meaningful improvements in HRQL that were maintained for at least 1 year.

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NEW INSIGHTS IN MYOCARDIAL INFARCTION BY MULTIMODALITY IMAGING

Effect of manual thrombus aspiration during primary percutaneous coronary intervention on infarct size: a delayed enhancement MDCT study


Objectives: We sought to assess whether manual thrombus aspiration could reduce infarct size in patients with acute STElevation myocardial infarction (MI) undergoing primary percutaneous coronary intervention (PCI).

Background: The efficacy of manual thrombus aspiration during primary PCI for acute MI remains controversial.

Results: Between April 2009 and March 2011, 86 consecutive patients presenting with first acute STEMI (Killip-I/II) within 12 hours after the symptom onset were randomized to standard routine manual thrombus aspiration (group I, N=44) or conventional PCI without thrombus aspiration (group II, N=42). The use of glycoprotein IIb/IIIa inhibitor ( GPI) was left to the discretion of the operator. All patients received aspirin 300 mg and clopidogrel 600 mg before PCI and underwent delayed enhancement (DE) multi-detector computed tomography (MDCT) immediately after PCI without injection of an additional contrast media for assessment of infarct size, defined as the total volume of myocardium showing DE. DE MDCT was repeated at 2 months after PCI. The primary endpoint was infarct size reduction at 2 months. Baseline clinical characteristics and angiographic findings were similar between the 2 groups. There were no differences between group I and II in symptom-to-door time (204±205 min vs. 217±168 min), door-to-balloon time (70±4.2 min vs. 69±25 min), PCI-to-MDCT time (17±15 min vs. 13±6 min), Pre-PCI TIMI 0, post-PCI TIMI 3, or the use of GPI. Markers of myocardial reperfusion showed better reperfusion in group I but with no statistical difference: ST-Resolution rate >70% (74% vs. 65%), myocardial blush grade 3 (88% vs. 68%), and corrected TIMI frame count –28 (31% vs. 24%). Initial infarct size determined by DE MDCT and left ventricular ejection fraction (LVEF)
by 2-dimensional echocardiography were similar between group I and II (17.1±18 mL vs. 22±23 mL and 58±11% vs. 55±10%, respectively). At 2 months, there was no difference in infarct size and left ventricular ejection fraction between the groups: 14±10 mL vs. 17±12 mL and 62±12% vs. 60±12%, respectively. No adverse cardiac events occurred in either group during the 2-month clinical follow-up.

Conclusions: Manual thrombus aspiration was not associated with reduction in infarct size in patients with acute ST-elevation MI receiving timely reperfusion therapy.

In vivo non invasive quantitative assessment of passive diastolic stiffness of infarcted myocardium using shear wave imaging

M. Perrot1, W.N. Lee1, M. Couade1, P. Mateo2, B. Crozatier3, A. Bel3, M. Tanter1, E. Messas2. 1 Institut Langevin, ESPCI ParisTech, Inserm, Paris, France. 2 AP-HP-Hôpital Européen Georges Pompidou, Pôle Cardiovasculaire, Inserm U633, Univ. Paris Descartes, Paris, France

Background: Quantitative imaging of myocardial stiffness is important for the evaluation of systolic (active) and diastolic (passive) LV function. No tool is available to quantify non-invasively myocardial stiffness, which is determinant in case of diastolic heart failure. Shear Wave Imaging (SWI) is a new non invasive ultrasound technique which is able to quantify the time-varying myocardial stiffness in vivo. In this study, we investigate the potential of this new technique to quantify the change of passive diastolic myocardial stiffness in ovine model of ischemic heart failure.

Methods: SWI was performed in vivo on five open-chest sheep. A linear conventional ultrasonic transducer (8 MHz) was positioned on the LV anterior wall. Shear waves were generated remotely in the myocardium using the acoustic radiation force induced by the ultrasonic probe. The shear wave propagation was imaged in real-time using an ultrafast scanner prototype (12 000 frames/s, Supersonic imagine, France). The local myocardial stiffness was derived from the shear wave speed. SWI were performed every 60 s to measure the stiffness variation within one cardiac cycle. Myocardial stiffness was also assessed invasively in the same region using the pressure-segment length relationship obtained by sonomicrometers (Sonometrics, Canada). The ligation of one diagonal of the left anterior descending coronary artery was achieved to induce ischemia during 2 hours, and reperfusion was performed during 30 minutes. Measurements were made at baseline, during ischemia and after reperfusion.

Results: Diastolic stiffness of the ischemic myocardium was found to increase after 45 minutes of ischemia. The shear wave speed increased from 0.8±0.16 m/s to 1.5±0.4 m/s (p <0.01). After reperfusion, diastolic stiffness increased even more strongly and diastolic shear wave speed reached 2.8±1.1 m/s (p<0.002). The slope of the end-diastolic pressure-segment relationship, which increased from 10.3±4.2 to 31.6±16.2 kPa, confirmed the stiffening. The peak diastolic strain rate decreased from 2.43±0.35 s-1 to 0.82±0.13 s-1 demonstrating impaired relaxation of the ischemic segment. Finally, TTC stained imaging performed on the explanted myocardium confirmed the presence of a large infarct zone.

Conclusion: SWI was able to quantify non-invasively the increase of passive diastolic myocardial stiffness after myocardial infarction and reperfusion. We believe that this new non invasive real time ultrasound evaluation of passive myocardial stiffness opens the door to an improvement of early detection and treatment of patient with diastolic heart failure.

Myocardial fibrosis and fat may be substrates of critical ventricular arrhythmia. comparison of 320 slice CT images in subjects who had ventricular fibrillation with sustained ventricular tachycardia

K. Ozawa, N. Funabashi, H. Takaoka, A. Katoaka, M. Uehara, Y. Kobayashi. Chiba University Graduate School of Medicine, Chiba, Japan

Purpose: If specific organized substrates of ventricular fibrillation (VF) are identified, they may provide important information for prevention of sudden cardiac death. 320 slice CT can acquire heart images in one heart beat and even if arrhythmia occurs during acquisition, clear heart images can be obtained. We compared 320 slice CT heart images in subjects who had VF with those who had sustained and non sustained ventricular tachycardia (VT).

Methods: A total of 94 subjects who had VF (18 subjects; age, 57±16 yrs), sustained VT (18 subjects; 60±20 yrs) or non sustained VT (58 subjects; 59±15 yrs, mean age 55 years old). If there was a contrast defect in myocardium in early phase, late phase acquisition was added, and if abnormal late enhancement was observed in the corresponding site, we diagnosed myocardial fibrosis (MF). If the contrast defect continued in late phase with CT values < -9 HU, we diagnosed myocardial fatty change (MFC).

Results: There were no significant differences of several factors except ratio of complete right bundle branch block as represented in the table. On CT, there were no significant differences in percentage of coronary arteries with >50% stenosis among the 3 groups, but MF was significantly more common in VF group (67%, all MF was in left ventricle) than in non sustained VT group (28%, p <0.05). MFC was significantly more common in sustained VT group (56%, half of MFC was in right ventricle) than in VF group (22%, p <0.05) and in non sustained VT group (29%, p <0.05).

Conclusion: MF and MFC may be substrates of VF or sustained VT. 320 slice CT can evaluate coronary arteries and myocardium in subjects with arrhythmia and even with implantable cardioverter defibrillators which cannot be acquired on magnetic resonance imaging.

Association between left ventricular longitudinal function and neurohumoral activation after acute myocardial infarction. A two dimensional speckle tracking study

M.K. Erbsoll1, N. Valeur2, U.M. Mogensen1, M.J. Andersen1, R.G. Greibe1, J.E. Møller1, C. Hassager1, P. Sogaard2, L. Kober3, 1Rigshospitalet - Copenhagen University Hospital, Heart Centre, Department of Cardiology, Copenhagen, Denmark; 2Gentofte University Hospital, Department of Cardiology, Copenhagen, Denmark

Background: N-terminal pro-B type natriuretic peptide (NT-proBNP) is released in response to increased myocardial wall stress and is associated with adverse outcome in acute myocardial infarction. However, little is known about the relation between longitudinal deformation indices and NT-proBNP.

Methods and results: We consecutively included 611 patients with acute myocardial infarction admitted to a tertiary centre and performed echocardiography within 48 hours of admission. Global longitudinal myocardial function was assessed by two-dimensional speckle tracking (DSTe) simultaneously with measurement of plasma NT-proBNP. A significant linear relation between NT-proBNP and global longitudinal strain (GLS) was found (r =-0.0001, r =-0.44). GLS emerged on multivariable analysis including age, sex, estimated glomerular filtration rate, Killip class, diabetes, hypertension, presence of ST segment elevation, anterior infarction, Troponin level, Left atrial volume index, mitral valve deceleration time and E/e' as the strongest predictor of log(NT-proBNP) (p <0.0001). In patients with preserved systolic function (LVEF ≥ 45%), GLS remained strongly correlated with NT-proBNP (p<0.0001, r=0.50). The C statistic associated with prediction of upper versus lower quartiles of NT-proBNP was significantly higher for GLS compared to LVEF (0.76 vs. 0.56; p <0.0001).

Conclusion: Left ventricular longitudinal function assessed by GLS exhibits a stronger association with NT-proBNP levels in acute myocardial infarction compared to LVEF. In patients with apparently preserved systolic function GLS is superior to LVEF in identifying increased neurohumoral activation.

Two-dimensional longitudinal strain is more accurate than three-dimensional longitudinal strain to identify infarcted LV segments in STEMI patients


Purpose: To compare 2D vs 3D longitudinal strain (LS) in normal hearts and in patients with recent STEMI.
Methods: In 123 healthy subjects (aged 44±14 years, range 18-75) and 46 patients (58±13 years) with recent STEMI, three apical LV views for measuring 2D-LS (70±9 fps) and 4-beat LV full-volume data sets (31±4 vps) for measuring 3D-LS were acquired 8.6±3 days after primary PCI using Vivid E9 scanner and analyzed with dedicated software (BT11, GE Healthcare, Horten, N). All subjects were selected for good image quality, sinus rhythm and adequate 2D/3D speckle-tracking in at least 14 of all 17 segments. In pts, 2D-LS and 3D-LS were compared against 3D wall motion score (WMS) and delayed-enhancement at magnetic resonance (DE-MRI) performed >24h apart from echo study, both at segmental and global levels.

Results: In healthy subjects, global 2D-LS values were significantly lower than 3D-LS (21.5±1.9% vs -19.1±2.1%, bias 1.3±2.2%, p<0.001), with whom were also weakly correlated (r=0.37, p<0.001). In pts, global 2D-LS had closer correlations with infant size index at DE-MRI, 3D WMS index and EF (r=0.65, 0.70, -0.68) than global 3D-LS (r=0.36, 0.48, -0.56, respectively, p<0.01 for all). Segmental 2D-LS values showed a higher discriminative power (F ANOVA = 144 vs 50 for 2D-LS vs 3D-LS, p<0.0001) to separate normal segments from those with non-transmural and transmural necrosis (DE 0-50% and >50%, respectively). At ROC curve analysis, segmental 2D-LS had a greater predictive power than 3D-LS to identify segments with a(dys)kinesia (AUC 0.81 vs 0.70) or transmural necrosis (AUC 0.83 vs 0.73, p<0.0001 for all).

Conclusions: Significant differences were identified between 2D-LS and 3D-LS in both normals and STEMI patients. Between the two tested vendor-specific algorithms, 2D-LS was more accurate than 3D-LS to identify infarcted LV segments and to reflect global LV dysfunction in STEMI patients.
these patients. In addition, among patients on dual antiplatelet therapy, there was a 7-fold (95% CI: 1.7-29.3) crude and a 4.9-fold (1.1-20.8) adjusted increase in the risk of non-fatal HS in patients with vs. without prior stroke/TIA. The excess risk of HS was greatest in the 1st year following a stroke/TIA (adjusted HR: 3.62, 95% CI: 1.67-7.85, p= 0.0003), whereas beyond 1 year, risk was not increased (adjusted HR = 1.11, 95% CI: 0.47 – 2.61).

Crude and adjusted 4-year outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prior history of stroke/TIA</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>11.2 (2072)</td>
<td>1.67 (1.53-1.82)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MI</td>
<td>6.0 (1097)</td>
<td>1.48 (1.31-1.68)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.1 (739)</td>
<td>3.43 (3.06-3.85)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total serious bleed</td>
<td>2.5 (460)</td>
<td>1.39 (1.14-1.69)</td>
<td>0.001 0.06 (0.4-1.30)</td>
</tr>
<tr>
<td>Non-fatal haemorrhagic stroke</td>
<td>0.3 (49)</td>
<td>0.6 (0.3)</td>
<td>0.003 0.052</td>
</tr>
</tbody>
</table>

Adjustment included all baseline characteristics found to be independent correlates of prior stroke/TIA.

Conclusions: In CAD, a history of stroke/TIA is associated with an increased risk of death, MI, or stroke. However, it is also associated with a disproportionate increase in HS, particularly when patients receive dual antiplatelet therapy and in the first year following stroke/TIA. This suggests that while these patients are at high risk of cardiovascular events, increasing antithrombotic therapy carries a specific risk of HS.

P3910 Triple anticoagulant therapy following an acute coronary syndrome: prevalence, bleeding rate and utility of the HAS-BLED score

J. Van Der Pals1, J.G. Smith1, M. Wieloch1, S. Kouil1, J. Lumsden1, E. Rydell1, J. Ohman2, F. Schersten1, P. Svensson1

1Lund University, Skane University Hospital, Department of Cardiology, Lund, Sweden; 2Lund University, Skane University Hospital, Department of Coagulation, Malmö, Sweden

Purpose: The aim of this study was to evaluate the prevalence of triple anticoagulant therapy (TT; warfarin, aspirin and clopidogrel) and associated bleeding risk, compared to double anticoagulant therapy (DAPT; aspirin and clopidogrel) in patients discharged from a Coronary Care Unit (CCU) following an acute coronary syndrome. Furthermore, we investigated the accuracy of the HAS-BLED risk score in predicting bleeding events in TT patients.

Methods: We retrospectively identified all patients from the Lund municipality on TT upon discharge from the CCU at Skane University Hospital in Lund between 2005 and 2010. TT patients were compared with age- and sex-matched controls discharged with DAPT. Major bleeding was defined in accordance with the HAS-BLED derivation study. Any bleeding requiring hospital care or causing a decrease in haemoglobin level of more than 20 mg/L or requiring blood transfusion.

Results: A total of 2423 patients were screened, of whom 159 (6.6%) were on TT. The mean age was 67.2 (±6.9) years. The most common indication for TT was atrial fibrillation (n=63). 36.9% followed by apical akinisia (n=60, 37.8%), and the mean duration of TT was 3.7 (±0.3) months. A cumulative incidence of spontaneous bleeding events was significantly higher in the TT group at one year (10.2% vs 3.2%, p<0.01). The HAS-BLED score significantly predicted spontaneous bleeding events in TT patients (area under the ROC curve 0.67, 95% CI = 0.54 – 0.79, p=0.004).

Conclusions: TT was relatively common following an acute coronary syndrome and associated with a significant increase in major bleeding at one year compared to DAPT. The HAS-BLED risk score predicted bleeding events with moderate accuracy. Careful patient selection and clinical follow-up for TT appears warranted.

P3912 Prognosis of unrecognized myocardial infarction in elderly men and women: the Rotterdam Study

A. Delhagårn1, M.J.G. Leeming1, E. Boersma1, J.W. Dekkers1, J. Heeringa1, J.A. Kors1, A. Holman1, O.H. Franco1, A. Ikrar1, J.C.M. Wiltman1 on behalf of The Rotterdam Study. 1Erasmus Medical Center, Department of Epidemiology, Rotterdam, Netherlands

Background: Unrecognized myocardial infarction (MI) is frequent in the general elderly population. Its prognosis is reportedly at least as unpropitious as that of recognized MI, particularly in men. However, contemporary data with long follow-up are lacking.

Objective: To investigate the long-term prognosis of unrecognized MI with respect to all-cause and cause-specific mortality, and to investigate any sex differences in prognosis.

Methods: In the population-based Rotterdam Study (2672 men and 3862 women), we determined the presence of unrecognized MI and recognized MI at the baseline (1990-1993). The cohort was followed for nearly two decades for all-cause and cause-specific mortality.

Results: During 82,268 person-years of follow-up (median 15.6 years) 3,412 persons died (1300 due to a cardiovascular cause). Both men and women with unrecognized MI had an increased risk of all-cause mortality (Hazard ratio [95% confidence interval] = 1.72 [1.43 – 2.07] and 1.36 [1.14 – 1.61] respectively). Having an unrecognized MI increased the risk of cardiovascular mortality by two-fold among men (2.19 [1.86 – 2.91]) and by approximately 30% among women (1.36 [1.03 – 1.81]), and by approximately 40-45% the risk of non-cardiovascular mortality (1.46 [1.14 – 1.89]; 1.39 [1.10 – 1.75]) in men and women respectively. Recognized MI was associated with an increased risk of all-cause mortality in men and women (1.67 [1.45 – 1.94]; 1.87 [1.54 – 2.30]).

Conclusions: The long-term prognosis of persons with unrecognized MI is worse than that of persons without any type of MI. In men the prognosis is as unfavorable as that of persons with recognized MI. This adverse prognosis applies to both cardiovascular mortality and non-cardiovascular mortality.

P3913 Impact of positive airway pressure therapy for cardiovascular outcomes in patients with coronary artery disease and sleep-disordered breathing


Tokyo Medical University, Tokyo, Japan

Background: The aim of this observational study is to determine whether positive airway pressure (PAP) therapy affects the long-term outcomes of patients with coronary artery disease (CAD) and sleep-disordered breathing (SDB).

Methods: We studied 1693 consecutive patients who underwent polysomnography from November 2004 to July 2011, and enrolled 150 patients with SDB (apnea-hypopnea index [AHI] ≥ 15), who had been admitted to hospital because of CAD before polysomnography. They were divided into two groups; a PAP-treated group (AHI ≥ 15/hour and treated with continuous positive airway pressure or adaptive servo ventilation) and an untreated SDB group (AHI ≥ 15/hour and untreated with PAP devices).

Results: The mean follow-up period was 35.2±23.8 months and 26% of the patients died or were re-admitted to hospital due to CVD. Kaplan-Meier survival curve indicated that event-free survival was significantly higher in the PAP-treated group than in the untreated SDB group (Figure 1). Multivariate analysis showed that the risk for death and hospitalization was significantly higher in the untreated SDB group (hazard ratio [HR], 2.62; 95% confidence interval [CI], 1.09 to 6.64; p < 0.05) than the PAP-treated group.

Conclusion: In patients with CAD and SDB, the use of PAP therapy improves long-term cardiovascular outcomes.
Prasugrel 5mg in the very elderly is non-inferior to prasugrel 10mg in non-elderly patients: the generations trial, a pharmacodynamic (PD) study in stable CAD patients


1. Lund University Hospital, Department of Cardiology, Lund, Sweden; 2. Saint Center for Thrombosis Research, Baltimore, United States of America; 3. Uppsala Clinical Research Center, Department of Medical Sciences, Uppsala, Sweden; 4. Linkoping University Hospital, Department of Cardiology, Linkoping, Sweden; 5. Lund University, Dept Coagulation Medicine, Malmo, Sweden; 6. Eli Lilly and Company, Indianapolis, United States of America; 7. St Antonius Hospital, Department of Cardiology, Nieuwegein, Netherlands; 8. University of Florida College of Medicine, Center for Thrombosis Research, Jacksonville, United States of America.

Purpose: In the TRITON trial, prasugrel (pras) 10mg reduced ischemic events vs. clopidogrel (clop) 75mg but increased bleeding, notably in very elderly patients (VE, ≥75y). Pras 5mg is suggested in VE patients to reduce the risk of bleeding, but PD data are limited. We examined PD with pras and clop in a three-period, blinded, cross-over study involving VE or non-VE (NE, 45-65y) stable CAD patients. Assuming that VE patients on pras 5mg would show lower platelet inhibition, the primary hypothesis was that the median of pras 5mg in VE would be non-inferior to the 75th percentile of pras 10mg in the NE.

Methods: After a run-in on low dose aspirin, VE patients (n=73) and NE patients (n=62) were randomized to pras (5 or 10mg) or clop (75mg) during three 12-day periods. PD was measured by turbidimetric aggregometry (MPA) to 20 μM ADP, VerifyNow P2Y12 (VN), and VASP-PRI at pre-dose and the end of each period.

Results: Median MPA during pras 5mg in VE was non-inferior to the 75th percentile of pras 10mg in the NE.

Conclusions: In patients with CAD, pras 5mg in the VE achieved pre-defined non-inferiority for PD by MPA compared to pras 10mg in NE while still providing significantly better PD and fewer poor responders than clop 75mg in VE.

Two-dimensional strain measures of left ventricular systolic function are new independent predictors of ventricular arrhythmic events in chronic heart failure patients


The aim of this study was to evaluate the role of Two-dimensional (2-D) speckle tracking measures of left ventricular systolic function in predicting the occurrence of ventricular arrhythmic events in chronic heart failure (CHF) patients. We enrolled 230 outpatients (75% males, 64±13 years, NYHA class 2.1±0.6, left ventricular ejection fraction 34±5% with CHF due to left ventricular systolic dysfunction, in conventional therapy (80% ACE-inhibitors and/or ARBs, 93% betablockers, 78% with implantable cardioverter defibrillator). At echocardiogram, by standard apical views left ventricular global strain (GS) and global strain rate (GSr) were measured by using 2-D speckle tracking analysis (Echo-PAC, GE). NT-proBNP and presence of non-sustained ventricular tachycardia (NSVT) at ECG Holter were also evaluated. None of the enrolled patients had previously experienced major ventricular arrhythmias.

During follow-up (22±10 months), in 27 patients at least an episode of ventricular tachycardia and/or ventricular fibrillation requiring cardioverter defibrillator intervention (anti-tachycardia pacing and/or DC-shock) occurred. At Cox univariate analysis GS (HR=1.23; CI: 1.12-1.36; p=0.001) and GSr (HR=1.18; CI: 1.15-1.91; p=0.011) were significantly associated to arrhythmic events. At multivariate analysis, after correction for NSVT, NYHA class and logNT-proBNP GS (HR=1.16; CI:1.01-1.33; p=0.035), but not GSr (HR=1.18; CI:0.88-1.59; p=0.270) remained significantly associated to the events. Figure shows Kaplan-Meier curves for arrhythmic events according to GS and GSr median values.

In conclusion, the results of this study support the possible clinical usefulness of the left ventricular systolic function 2-D strain measures in detecting CHF outpatients prone to experience major arrhythmic events.

Quantitative left ventricular flow vortex analysis is superior to conventional echo-doppler to predict exercise capacity in patients with systolic heart failure


1. Yonsei University College of Medicine, Cardiology Division, Seoul, Korea; Republic of; 2. Yonsei University, Daegu, Korea; Republic of; 3. Busan National University Hospital, Busan, Korea; Republic of; 4. Siemens Medical Solution, Mountain View, United States of America.

Background: Conventional echo-Doppler parameters could not predict exercise capacity and symptoms in patients with compensated chronic systolic heart failure (CHF). We have previously shown that left ventricular (LV) vortex flow is closely correlated with hemodynamic changes in the LV. The aim of this study was to evaluate whether quantitative LV flow vortex analysis by contrast echocardiography (CE) was superior to conventional echo-Doppler parameters to predict exercise capacity in patients with systolic heart failure.

Methods: 35 patients who had chronic systolic dysfunction (EF < 40%) underwent 2-dimensional CE with intravenous infusion of Definity® and imaged at a mechanical index of 0.4-0.6 in the A4C and APAX views. The morphologic and pulsatility parameters of LV vortex flow were measured using Omega Flow® (Siemens Medical Solution, Mountain View, CA). After CE, 6 minute walk test and cardiopulmonary stress test were performed in all patients.

Results: There were no significant correlation between conventional echo-Doppler parameters and exercise capacity. However, vortex pulsatility parameters RS and VRS showed significant correlation with 6 minute walking distance (r= -0.645, p<0.01, r= -0.586, p<0.05, respectively) and VO2 (r=0.577, p<0.01, r=0.503, p=0.03, respectively). Vortex morphology and location parameters did not show significant correlation with exercise capacity. Figure represents patients who have higher vortex pulsatility (A) show longer 6MWD than lower pulsatility (B) with comparable conventional echo-Doppler parameters.
The incremental prognostic value of inotropic contractile reserve combined with advanced mitral regurgitation in identifying responders to cardiac resynchronization therapy

C. Aggelii, E. Poulidakis1, I. Felekos1, S. Sideris2, P. Dilaveris1, K. Gatzoulis1, A. Katsaros1, E. Stendoukri1, G. Roussakis1, C. Stefanadis1, 1Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece; 2Hippokration Hospital, Department of Cardiology, Athens, Greece

Purpose: Inotropic contractile reserve (ICR) during dobutamine stress echo (DSE) differentiates the viable myocardium from scar tissue according to inotropic response. Furthermore, low dose DSE provides information for the global left ventricular response. The aim of this study was to identify the role of inotropic contractile reserve, in combination with the presence of functional mitral regurgitation in patient selection for cardiac resynchronization therapy (CRT) and to compare it with other echocardiographic indices used in predicting CRT response.

Methods: 42 pts referred for clinically indicated CRT were evaluated. All patients underwent low-dose dobutamine stress echocardiography to assess inotropic contractile reserve, defined as an improvement of ejection fraction (EF) >5%. Mitral regurgitation (MR) severity was divided in four grades and advanced MR was defined as the presence of grade III or IV regurgitation. The interventricular mechanical delay index (by PW Doppler) and Opposing Wall Delay Index (by TDI) were used to assess interventricular and intraventricular dyssynchrony respectively. Responders were defined by >15% reduction in left ventricular end systolic volume after CRT.

Results: 42 pts (mean age 68±7 years old, 28 men, NYHA III-IV) were included. The mean QRS duration was 154±9ms. During a 12-month follow-up, 29 pts (69%) had responded. The ejection fraction before CRT was 24±5% and increased to 31±4% after CRT (p<0.05). The presence of ICR was the strongest predictor of response to CRT (area under the curve, 0.84; p<0.01) compared with interventricular dysynchrony index (area under the curve, 0.66; p=0.05) and intraventricular dysynchrony index (area under the curve, 0.74; p<0.05). The combination of ICR with the presence of advanced MR offered even greater predictive value (area under the curve, 0.89; p<0.001).

Conclusions: Inotropic contractile reserve was a stronger predictor of CRT response than conventional and TDI indices, and its diagnostic value can be further enhanced when combined with the presence of advanced functional MR. Dobutamine stress echocardiography may play a pivotal role in identifying responders to CRT, thus avoiding ineffective interventions and reducing the cost of desynchrony management.

Improved differential diagnosis between left ventricular non-compaction and dilated cardiomyopathy

B.E. Staelhi, C. Gebhard, M. Greutmann, R. Jenni, F.C. Tanner, University Hospital Zurich, Cardiovascular Center, Department of Cardiology, Zurich, Switzerland

Introduction: Left ventricular non compaction (LVNC) is characterized by a two-layered myocardium consisting of a non-compacted inner and a compacted outer layer. Since left ventricles of many LVNC patients are dilated and exhibit poor systolic function, LVNC can be misinterpreted as dilated cardiomyopathy (DCM). This study assesses whether novel echocardiographic criteria may facilitate differential diagnosis between DCM and LVNC.

Methods: Transthoracic echocardiography was performed in 30 LVNC patients (mean age 36±3 years, 17 men, 40 age-matched patients with DCM, and 42 age-matched controls. Maximal systolic thickness of ‘non-compacta’ and ‘compacta’ was measured in standard short axis views (2-D) at the apical or midventricular level in the segment with most prominent recesses (LVNC) or most prominent trabeculations (DCM and controls). The thickness of the basal septum was measured in parasternal long axis view (M-mode).

Results: LV ejection fraction was 37% (range: 10-59) in LVNC, 29% (16-51) in DCM, and 63% (range: 55-74) in controls. Maximal systolic thickness of “non-compacta” was 1.8±0.01 cm in LVNC compared to 0.4±0.02 cm in DCM (p<0.0001), and 0.2±0.01 cm in controls (p<0.0001). Maximal systolic thickness of “compacta” was lower in LVNC (0.5±0.02 cm) compared to DCM (1.0±0.02 cm; p<0.0001) and controls (1.1±0.03 cm; p<0.0001). Maximal systolic thickness of “compacta” was 8.2 mm (range: 3.5-8.2) in LVNC versus >8.5 mm (range: 8.5-14.0; p<0.0001) in DCM and >8.6 mm (range: 8.6-15.0; p<0.0001) in controls. The ratio of maximal systolic thickness of the indexed basal septum to that of the “compacta” was ≥0.64/m² (range 0.64-1.90) in LVNC versus <0.61/m² (range 0.29-0.61) in DCM and ≥0.57/m² (range 0.28-0.57) in controls.

Conclusion: Maximal systolic “compacta” thickness >8.2 mm and a ratio of indexed septal wall thickness to “compacta” thickness ≥0.64/m² is specific for LVNC. This observation may be particularly useful in patients with dilated ventricles and facilitate the differential diagnosis between LVNC and DCM.

Visual assessment of apical rocking predicts response and long-term survival following cardiac resynchronization therapy

I. Stankovic1, M. Aarons1, A. Clark1, C. Prins1, M. Szulik1, T. Kukulski1, R. Willems1, L. Faber1, S. Aakhus2, J.-U. Vogl1, 1Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece; 2Hippokration Hospital, Department of Cardiology, Athens, Greece

Purpose: Apical rocking was a stronger predictor of CRT response and long-term survival following cardiac resynchronization therapy (CRT) candidates.

Methods: A total of 201 patients eligible for CRT (63±11 years, ejection fraction 26±6%) underwent standard echocardiographic examination before and 12±2 months after device implantation. Three blinded physicians were asked to predict response to CRT (yes/no) by visually assessing the presence of apical rocking and extend and localization of infarct scar. Response was defined as LV end-systolic volume decrease >15%. Patients were followed for an average period of 37±19 months for the occurrence of cardiac death.

Results: Visually assessed apical rocking predicted reverse remodeling with a sensitivity, specificity and accuracy of 95, 85, and 90%, respectively. Physicians’ prediction of CRT response integrating apical rocking and scar burden resulted in a sensitivity, specificity and accuracy of 95, 85, and 90%, respectively. When corrected by CRT, visually detected apical rocking was the only parameter associated with favorable outcome, whereas worse functional class, a high scar burden (>6 segments) and atrial fibrillation were associated with poorer survival (Figure). Baseline LV ejection fraction and QRS duration did not predict outcome.

Conclusions: Simple visual assessment of apical rocking is a robust predictor of response and long-term survival after CRT. In patients with heart failure of ischemic origin, visual assessment of scar burden further enhances predictive power of visible LV dysynchrony.

Diagnostic and prognostic role of global longitudinal strain in patients with heart failure and normal ejection fraction

P. Pellicori, A. Bennett, O. Khaleva, S. Hurren, V. Carubelli, N. Sherwi, K. Wong, A.L. Clark, J.G.F. Cleland1, University of Hull, Department of Academic Cardiology, Hull, United Kingdom

Introduction: Many patients have clinical and bio-marker evidence of heart failure but normal left ventricular (LV) ejection fraction (EF; HfEF). More subtle abnormalities of systolic function may explain the syndrome. We measured global longitudinal strain (GLS) to identify LV systolic dysfunction in patients with HfEF. Methods: 313 patients referred to our clinic with symptoms and signs suggesting heart failure (median age 74 years, 42% women, 40% in atrial fibrillation (AF)) with an LVEF >50% were recruited. Three different subgroups were identified: 161 patients with no substantial cardiac disease (n=40; mean proBNP <400ng/L); 99 “gray cases” (n=40 mm or NTproBNP >400ng/L) and 138 with definite HfEF (LA >40 mm and NTproBNP >400ng/L). All underwent detailed echocardiography. Peak systolic strain was defined as the peak negative
value on the strain curve during the entire cardiac cycle. Values obtained from each of 18 LV segments were averaged.

Results: Median plasma NTproBNP levels (IQ range) were 164 ng/l (59-268) in patients with no evidence of cardiac dysfunction, 414 ng/l (143-847) for grey cases and 1627 ng/l (868-2837) for definitive HfEF. Mean LVEF was 58% in each subgroup. Patients with HfEF were older (78 years), more often had AF (73%) had more symptoms and signs of fluid retention, were treated with higher doses of diuretics. They also had more right ventricular dysfunction and more mitral and tricuspid regurgitation. Mean GLS (SD) was higher (worse function) in patients with HfEF (−15.9 (2.4) % vs −15.2 (31) % vs −13.6 (3.0) % p < 0.001). During a median follow-up of 647 days in survivors, 30 patients had an unplanned hospitalisation due to HF and 32 patients died from cardiovascular (CV) causes. In univariable Cox regression analysis, GLS but not LVEF predicted events. In multivariable analysis, urea, inferior vena cava (IVC) diameter. NTproBNP and atrial fibrillation (AF) were the only independent predictors of adverse outcome.

Conclusions: GLS is impaired in patients with HfEF conditioned to those with no evidence of heart failure, but does not add independent prognostic information to other simpler variables.

P9393
Comparison of left ventricular discoordination and dysynchrony assessment by radial strain imaging in cardiac resynchronization therapy

Y.H. Chan, L.S. Wu, Y.H. Yeh, C.L. Wang, Y.J. Ho, L.A. Hsu, C.T. Kuo on behalf of First Division of Cardiovascular Department, Chang Gung Memorial Hospital, Linkou. Chang Gung Memorial Hospital, Taoyuan, Taiwan

Background: Patients with nonischemic etiology, left bundle-branch block (LBBB) and QRS duration ≥150 ms are more likely to derive benefit from cardiac resynchronization therapy (CRT) than those without. This study aimed to compare mechanical discoordination and dysynchrony in CRT candidates.

Methods: Speckle-tracking strain imaging was performed in 120 CRT candidates and 60 patients with LVEF ≤35% and QRS duration ≤120 ms. CRT candidates were divided into subgroups according to the etiology of heart failure (ischemic vs nonischemic). QRS morphology (LBBB vs non-LBBB) and QRS duration (<150 ms vs <150 ms), respectively. Dysynchrony indices based on time-to-peak radial strain of anteroseptal and posterior walls (AS-P delay) and standard deviation of time-to-peak radial strain (RS-SD) were measured. Discoordination was indexed using the mid-ventricular radial strain index (RDI-M).

Results: RDI-M could distinguish between patients in the narrow and wide QRS groups and between subgroups with and without favorable characteristics. Compared to ischemic candidates, nonischemic candidates had greater myocardial thinning (P<0.003), smaller myocardial thickening (P<0.003) and a greater RDI-M (P=0.001). In contrast, AS-P delay and RS-SD failed to demonstrate significant differences between ischemic and nonischemic subgroups. CRT candidates with ischemic etiology were more likely to show dysynchrony without significant discoordination than nonischemic candidates.

Conclusions: Mechanical discoordination performed better than dysynchrony in differentiating CRT candidates with and without favorable characteristics.

THE ENDOTHELIIUM: KEY PLAYER IN VASCULAR CONTROL

3957 Reduced leukocyte telomere length are associated with increased levels of vascular oxidative stress in patients with acute myocardial infarction

J. Lorin1, S. Saliques1, J.C. Guillett1, S. Ragot2, A. Donze2, J.R. Teysyrier2, Y. Cottin1, L. Rochette1, C. Vergely1, M. Zeller1
1University of Burgundy, Faculty of Medicine, LPPCE (IFR100), Dijon, France; 2University Hospital Center, Laboratory of molecular genetics, Dijon, France; 3University Hospital Center, Department of Cardiology, Dijon, France

Purpose: Asymmetric dimethylarginine (ADMA) competes with L-arginine to inhibit NO synthase (NOS), leading to a decreased NO bioavailability, increasing vascular oxidative stress and endothelial dysfunction. Recent data suggest that reduced leukocyte telomere length (LTL) could be associated with increased risk for acute myocardial infarction (MI). The aim of our study was to analyse the relationship between LTL and ADMA, as a biomarker of oxidative stress, in patients with acute MI.

Methods: Blood samples from 33 consecutive patients hospitalized ≥24 hours after symptom onset for acute MI were taken on admission. Serum levels of ADMA, SDMA (its biologically inactive stereoisomer and L-arginine) were determined using high-performance liquid chromatography. LTL was assessed by extraction of leukocyte DNA from venous blood samples and performing real-time PCR. The L-arginine/ADMA ratio was used as a biomarker of vascular oxidative stress and endothelial dysfunction. Patients from the lowest L-arginine/ADMA tertile were compared with patients from the higher L-arginine/ADMA tertiles.

Results: Demographic data, chronic treatments, cardiovascular risk factors and history were similar for the 2 groups. Strikingly, in patients with the lower L-arginine/ADMA tertile, LTL was markedly reduced when compared with the higher L-arginine/ADMA levels (1.15 vs 1.27 ratio T5-T1, p=0.005). LTL was negatively correlated with age (r=-0.356, p=0.0042). Moreover, a trend for a positive correlation between LTL and L-arginine/ADMA ratio was noted (r=0.339, p=0.053) but not with SDMA, (r=0.069, p=0.686).

Conclusion: Our study showed that, in MI patients, reduced LTL was associated with increased levels of vascular oxidative stress, as assessed by serum L-arginine/ADMA ratio levels. Further experimental studies are now needed to explore the relationship between L-arginine metabolism pathways, endothelial dysfunction and mechanisms of leukocyte telomere shortening.

3958 Circulating plasma free heme levels correlate with endothelial injury and atherosclerotic lesions extent in patients with stable coronary artery disease

N. Amabile1, C. Guerin1, C. Cassuın1, O. Blanc-Brude2, C.M. Boulanger1, Marie Lannelongue Hospital, Department of Cardiology, Le Plessis-Robinson, France; 1INSERM U970, Paris Cardiovascular Research Center (PARCC), Paris, France

Purpose: Spontaneous hemolysis is associated with plasma free heme release in that could increase oxidative stress phenomenon and enhance vascular cell damages, leading to endothelial dysfunction and ultimately atherosclerosis. We investigated if free heme release could be related to endothelial injury and atherosclerotic lesion extent in patients with cardiovascular risk factors (CFR).

Methods: Patients with cardiovascular risk factors who underwent coronary angiography for suspected stable coronary artery disease were eligible for inclusion. Levels of endothelial (CD144+ EMPs), erythrocytes (CD235+ RBCMPs), platelets (CD41+ PMPs) and leukocytes-derived microparticles (CD11c+ LMPs) were measured by flow cytometry methods on free platelets plasma samples. Levels of circulating free heme (CFH) were analyzed by absorption spectro-photometry methods. Significant CAD was angiographically defined as presence of at least 1 stenosis with ≥50% luminal diameter narrowing. The atherosclerotic lesions extent was evaluated by the Gensini score calculation.

Results: A total of n= 97 subjects (63.6±1.1 years; 78% male gender;32% diabetes) fulfilled the inclusion criteria. These patients had significantly higher levels of CFH compared to healthy subjects without CFR. We observed higher levels of CFH in diabetic patients compared to non-diabetic subjects (10.21±3.9 vs 8.2±0.5 AU, p=0.03), whereas no significant influence of other risk factor (hypertension, dyslipidemia, active smoking) was noted. Moreover, CFH levels were correlated with CD144+ EMPs (r=0.26, p=0.01), suggesting a potential link between hemolysis and endothelial dysfunction. Significant CAD was diagnosed in n=71 patients in whom the Gensini score was significantly correlated with CFH levels (r=0.44, p=0.001), as well as LMPs (r=0.31, p=0.01) and fasting glycemia (r=0.49, p=0.001). Multivariate regression analysis revealed that CFH levels were independently related to atherosclerotic lesions extent (p=0.017) after adjustment for other confounding factors.

Conclusions: Increases in circulating free heme levels are associated with endothelial injury in patients with cardiovascular risk factors and atherosclerotic lesions severity in stable CAD subjects. These results suggest that CFH might influence coronary artery disease development.

3959 Changes in blood flow determine endothelial vasomotor responses: insight into the meaning of flow-mediated constriction and dilation

F. Fasola1, A. Beule1, S. Muen1, S. Schaefer1, A. Damask1, A. Vosseler1, J.D. Parker2, T. Munzel2, T. Gori1, 1University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; 2Mount Sinai Hospital at the University Health Network, Toronto, Canada

Introduction: Flow-mediated dilation (FMD) is an accepted parameter of endo-
Epigenetic regulation of cell adhesion and communication by enhancer of zeste homolog 2 in human endothelial cells

H. Dreger1, A. Ludwig1, A. Weller1, V. Stangl1, G. Baumann1, G. Peter1, K. Stadler1, 1University Medicine Berlin, Campus Mitte, Department of Cardiology and Angiology, Berlin, Germany; 2Comprehensive Pneumology Center (CPC), Helmholtz-Zentrum, Munich, Germany.

Objective: Epigenetic modifications such as DNA and histone methylation have long-term effects on gene expression. The histone methyltransferase Enhancer of zeste homolog 2 (Ezh2) mediates trimethylation of lysine 27 in histone 3 (H3K27me3) which acts as a repressive epigenetic mark. Previous studies described an essential role for Ezh2 in different histologies of human stem cells. In differentiated endothelial cells, however, information about the function of Ezh2 is missing. Therefore, the aim of our present study was to identify Ezh2 target genes in endothelial cells.

Methods and Results: Whole genome mRNA expression arrays identified 964 genes that were regulated by more than twofold within 4.5 minutes of distal ischemia, the release of the pneumatic cuff caused a reac-

4.5 minutes following cuff deflation (FMD). Providing support to the concept that L-FMD (like FMD), is systematically related to changes in blood flow, there was a strong correlation between L-FMD and the reduction in blood flow caused by the inflation of the pneumatic cuff (r=0.26, P<0.0001). After 4.5 minutes of distal ischemia, the release of the pneumatic cuff caused a reactive hyperemia (302±238% compared to baseline flow) and a subsequent FMD (r=0.19, P<0.0001) for the correlation between increase in arterial diameter and the increase in arterial blood flow.

Conclusions: Arterial blood flow and shear stress are important determinants of endothelial tone in resting conditions as well as during reactive hyperemia. By measuring the change in arterial diameter in the setting of reduced shear stress, L-FMD quantifies "resting" endothelial function. In contrast, FMD reflects the (endothelial) reactivity to supranormal increases in shear stress (endothelial reactivity, or recruitability). From this perspective, a lower FMD in subjects with (endothelial) reactivity to supranormal increases in shear stress (endothelial stress, L-FMC) quantifies "resting" endothelial function. In contrast, FMD reflects the reactivity of the endothelium. We hypothesized that baseline conduit arterial diameter is inversely related to endothelial function. We assessed endothelial function in the radial artery of 647 patients (age ± 20 years) with and without untreated hypertension, and we calculated an FMD index using the equation:

FMD index = [Dmax - Drest] / Drest × 100

where Dmax is the diameter at maximum response and Drest is the baseline diameter.

Results: The baseline conduit arterial diameter was significantly lower in patients with untreated hypertension compared to patients without untreated hypertension (4.3 ± 0.6 mm vs. 4.5 ± 0.6 mm, P<0.001). The FMD index was also significantly lower in patients with untreated hypertension compared to patients without untreated hypertension (11.2 ± 6.4% vs. 14.3 ± 5.4%, P<0.001). The FMD index was inversely related to baseline conduit arterial diameter (r=0.26, P<0.001) and directly related to age (r=0.26, P<0.001). The FMD index was also inversely related to the prevalence of hypertension (r=-0.26, P<0.001) and directly related to the prevalence of untreated hypertension (r=0.26, P<0.001). The FMD index was inversely related to the prevalence of diabetes (r=-0.26, P<0.001) and directly related to the prevalence of untreated diabetes (r=0.26, P<0.001). The FMD index was inversely related to the prevalence of smoking (r=-0.26, P<0.001) and directly related to the prevalence of never-smokers (r=0.26, P<0.001). The FMD index was inversely related to the prevalence of dyslipidemia (r=-0.26, P<0.001) and directly related to the prevalence of normolipidemia (r=0.26, P<0.001). The FMD index was inversely related to the prevalence of atrial fibrillation (r=-0.26, P<0.001) and directly related to the prevalence of no history of atrial fibrillation (r=0.26, P<0.001).

Conclusions: Our findings indicate that baseline conduit arterial diameter is inversely related to endothelial function and that changes in endothelial function are associated with changes in baseline conduit arterial diameter.
Drug treatment and compliance in hypertension

Antihypertensive and laxative effects by inhibition of NHE3-mediated sodium absorption in the gut

D. Linz1,2, K. Wirth1, W. Linz1, P. Arndt1, U. Schweinhuth1, M. Boethm1, H. Ruetten2,1. 1Saarland University Hospital, Department of Internal Medicine III, Cardiology, Homburg, Germany; 2Sanofi-Aventis, Frankfurt/Main, Germany

Purpose: High intestinal sodium absorption is one important mechanism of hypertension and constipation. The sodium-proton-exchanger (NHE3) is an important mediator of sodium absorption in the gut. Inulin stimulates the NHE3-exchanger. We used senescent lean hypertensive rats (SHR-lean) and a hypertensive, obese and hyperinsulinemic rat strain (crosstbreeding leptin receptor deficient hypertensive rats, SHR-ob), and treated them orally with a non-absorbable specific NHE3-inhibitor.

Methods: Twenty-eight 78 weeks old senescent SHR-lean were randomized in 2 groups (n=14/group): placebo (PLAC) and NHE3-inhibitor SAR (1mg/kg/d in chow), treated for 14 weeks. Eight weeks old SHR-ob were randomized in two groups: PLAC (n=7) and SAR (n=8), treated for 6 weeks. Water and sodium consumption were measured via osmid, sodium via flame spectrometry. Blood was analyzed via flame spectrometry. Cardiac, systolic blood pressure via tail cuff, gene expression of NHE3 in the gut and plasma renin activity and aldosterone were studied.

Results: SAR treatment resulted in a dose dependent increase of feces sodium and water content in normotensive Sprague Dawley rats. In senescent SHR-lean, inhibition of intestinal NHE3 increased sodium (33.5±3.4 mmol/L vs. 20.2±2.1 mmol/L, p<0.01), fluid content (AC, p<0.01), and water content (58% vs. 42% in PLAC, p<0.001) in the feces and reduced systolic blood pressure from 222±7 mmHg to 184±2 mmHg (p<0.01). Aldosterone plasma concentration or renin- and ACE plasma activity was not modified in SAR. Gene expression of NHE3 was up-regulated in the ileum and colon but not in the jejunum of SAR treated rats. Treatment did not cause hypokalemia or impairment of kidney function. In hyperinsulinemic SHR-ob, SAR treatment resulted in a more pronounced reduction of systolic blood pressure (275±8 mmHg to 193±10 mmHg, p<0.01) and diastolic blood pressure (152±7 mmHg to 118±11 mmHg, p<0.01) in the group treated for 6 weeks. In the group treated for 14 weeks, the reduction of systolic blood pressure was 259±6 mmHg to 170±10 mmHg, p<0.01)

Conclusion: Reduction of intestinal sodium absorption by selective NHE3-inhibition in the gut reduces high blood pressure and increases feces water excretion. Intestinal NHE3-blockade could be a new treatment strategy for elderly patients suffering from high blood pressure and constipation.

Predictive factors of adherence in uncontrolled hypertensive patients in France: results of the observational real life survey HBP-ADHERENCE

J.-J. Mourad1, C. Mounier-Vehier2, F. Liard3, F. Beaussais4. 1Unité Médecine Interne – HTA et CHU Avicenne, Paris, France; 2Hospital Regional University of Lille - Cardiological Hospital, Department of Hypertension, Lille, France; 3General Practitioners office in France; 4AP-H - Hospital Lariboisiere, Department of Cardiology, Paris, France

Purpose: Despite antihypertensive treatment, the proportion of uncontrolled hypertensive patients remains high and the non adherence to treatment is a major issue. One of the aims of this study was to determine the predictive factors of antihypertensive medication adherence in uncontrolled hypertensive patients treated by general practitioners in France.

Methods: HBP-ADHERENCE observational study was conducted in France from March to September 2011. A population of 3560 hypertensive patients was included by 1049 French general practitioners. Hypertensive patients whose blood pressure was not controlled with at least two antihypertensive drugs were included. Adherence was determined according to a validated questionnaire. Comparative analyses were performed on two subgroups of patients: “adherent or minor non-adherent” versus “major non-adherent”.

Results: Mean systolic and diastolic blood pressure (SBP/DBP) were 157±11/91±8 mmHg. The majority of patients (60%) were over 60 years and nearly 40% were women. Patients were classified as “major non-adherent” in 28% of cases. Age and sex were not predictive factors of adherence. Major non-adherent patients had a significantly higher number of drugs prescribed (5.4±2.6 versus 4.6±2.4 p<0.0001), larger number of daily medication intakes (3.6±2.9 versus 3.0±2.3, p<0.0001) and less knowledge about their treatments (73.7% versus 88%, p<0.0001) than adherent or minor non-adherent patients. Multivariate analysis, independent factors strongly associated with risk of major non-adherence were: OR (95% CI); fear of adverse effects (2.7, 1.23-5.34), presence of at least one other symptom (1.93, 1.39-2.65), sedentariness (1.15, 1.02, 1.28), excess alcohol intake (1.65, 1.24-2.20). The regular practice of home blood pressure measurement was the only factor inversely correlated to the risk of major non-adherence (0.64, 0.48-0.86).

Conclusion: In this real life study, we identified several modifiable factors to predict risk of non-adherence in uncontrolled hypertensive patients. Therapeutic education focusing on the expected benefits of antihypertensive drugs, their mechanisms of action and their adverse effects, as well as a wider use of long acting fixed-dose combinations would improve long-term effective care of hypertensive patients.

Valsartan suppresses cardiovascular events in hypertensive subjects with diabetes mellitus (DM) comparable to those with impaired glucose tolerance (IGT)

T. Kondo, K. Yamashita, T. Muramatsu, K. Matsuhashi, T. Nagahiro, K. Nakamura, S. Shintani, T. Murohara on behalf of NAGOYA HEART Study Group. Nagoya University Graduate School of Medicine, Department of Cardiology, Nagoya, Japan

Purpose: The randomized Nagoya Heart Study has demonstrated that compared cardiovascular outcomes were comparable between the valsartan- and amlopidine-based treatments in Japanese hypertensive patients with glucose intolerance. The present subanalysis aims to clarify whether or not the effects of those two drugs differ depending on the pattern of glucose intolerance (diabetes mellitus: DM vs. impaired glucose tolerance: IGT).

Methods: Treatment effects were evaluated among 942 hypertensive subjects with DM (valsartan, N=471; amlopidine, N=472) and 208 hypertensive subjects with IGT (valsartan, N=105; amlopidine, N=103). The primary outcome was a composite of acute myocardial infarction, stroke, coronary revascularization, admission attributed to heart failure, or sudden cardiac death. The median follow-up was 12 years.

Results: Among hypertensive subjects with DM, 101 events occurred, against only 9 among those with IGT (hazard ratio: 2.48 [95% CI: 1.27-4.82]; P=0.007). When subjects who remained IGT was used as a reference group, the hazard ratio was 1.39 (P=0.6156) in the new onset DM group and 2.83 (P=0.020) in the DM group. In the amlopidine-based treatment, the event rate was higher among DM subjects compared to IGT subjects (hazard ratio: 3.06 [95% CI: 1.22-12.10]; P=0.020). Similar trend was observed in the valsartan-based treatment, but it was not statistically significant (hazard ratio: 1.79 [95% CI: 0.79-4.07]; P=0.166). The cumulative number of new onset from IGT was lower in the valsartan-based treatment (N=33) than in the amlopidine-based treatment (N=43), although it was not statistically significant (hazard ratio: 0.79 [95% CI: 0.52-1.08]; P=0.125).

Conclusion: Comparative cardiovascular events increased in the order of IGT, new onset DM from IGT, new compared to senescent DM in Japanese hypertensive subjects. In the amlopidine-based treatment, more cardiovascular events occurred in DM compared to IGT, but not in the valsartan-based treatment. Moreover, the number of new onset DM from IGT was less in the valsartan-based treatment than in the
Impact of intensive blood pressure lowering therapy on costs of cardiovascular screening with ECG in young athletes in Switzerland using basically the 2010 recommendations of the European Society of Cardiology (ESC) for interpretation of ECG in athletes.

Conclusions: DAPA is associated with modest mean reductions in sBP and dBP in patients with T2DM, with no increased risk of orthostatic hypotension and without any clinically relevant changes in heart rate. These post-hoc observations are intriguing and further studies will be needed to evaluate potential clinical benefit in hypertensive patients.

**SPORT CARDIOLOGY – PRE-PARTICIPATION SCREENING: CONSEQUENCES AND PITFALLS**

**3977 Exercise related out-of-hospital cardiac arrest: incidence, prognosis, and prevention of sudden death**

Purpose: Although regular physical activity has beneficial cardiovascular effects, exercise can triggers an acute cardiac event. We aimed to determine the incidence of exercise-related out-of-hospital cardiac arrest (OHCA) and the association of specific exercise-related OHCAs among patients aged 13 to 35 years. Methods: We analyzed all OHCA cases prospectively collected from January 2006 to January 2009. The relation between exercise during or within 1 hour before OHCA and outcome was analyzed using multivariable logistic regression, adjusting for age, gender, public location, bystander witness, bystander cardiopulmonary resuscitation (CPR), automated external defibrillator (AED) use and shockable initial rhythm. Incidence is shown per 100,000 person-years. Results: Of 2517 OHCA's, 145 (5.8%) were exercise-related, of whom 7 were ≤35 years. Most patients were men (93.1% and 85.7%, respectively). The incidence of exercise-related OHCA was 2.0 in all ages and 0.2 in those ≤35 years. Survival after exercise-related OHCA was distinctly better than after non-exercise-related OHCA (44.8% vs. 15.4%) (unadjusted odds ratio 4.13; 95%CI 2.93-5.62;P<0.001), even after adjustment for other prognostic factors (odds ratio 1.57; 95%CI 1.04-2.37;P=0.03). Patients ≤35 years did not benefit from exercise; survival was 33.3% versus 34.5%, respectively (adjusted odds ratio 0.47; 95%CI 0.04-3.57;P=0.54). In-hospital treatment did not differ between groups. Conclusions: Exercise-related OHCA has a low incidence, particularly among young and predominant affected men. Cardiac arrests occurring during or shortly after exercise carry a markedly better prognosis than cardiac arrests that are not exercise-related in persons older than 35 years.**

**3978 Costs of cardiovascular screening with ECG in young athletes in Switzerland**

Purpose: Adding ECG to cardiovascular screening in young athletes remains controversial. One of the reasons refers to costs of the screening program and the subsequent cardiac examinations generated mainly by the false positive ECG. The aim of this study was to assess the total costs of a program of cardiovascular screening with ECG in young athletes in Switzerland using basically the 2010 recommendations of the European Society of Cardiology (ESC) for interpretation of ECG in athletes.

Methods: In this observational prospective study, competitive athletes from 14 to 35 years were examined following the 2005 ESC proposal. ECG was interpreted based on the ESC 2010 recommendations (adapted). Further examinations were proposed in cases of positive findings. The costs of the screening and of all subsequent examinations was calculated for each athlete according to the Swiss medical rates. We present the intermediate results of this study.

Results: From 2002/11 to 2002/12, 920 athletes were examined. Mean age was 19.9±6.5 years, 75% were men. Football (35%) and ice hockey (12%) were the sports most often represented. Mean weekly training's hours were 7.9±4.8 for a
Concentric remodelling of the right ventricle in African football players

G.F. Gjerde1, J. Hisdal1, E.E. Solberg3, T.E. Andersen3, Z. Rudanovic4, K. Steine5, 1Oslo University Hospital, Aker and Boknikes College, Oslo, Norway; 2Dakotahjemmet Hospital, Oslo, Norway; 3Oslo Sports Trauma Research Center, Norwegian Football Association, Oslo, Norway; 4Oslo University Hospital, Aker, Oslo, Norway; 5Akershus University Hospital, Oslo, Norway.

Purpose: We have previously shown that male Caucasian athletes have a larger increase of both LV and RV size than Africans. African athletes, however, had similar LV mass but markedly more concentric remodelling LV than the Caucasian athletes. Thus, the aim of this study was to investigate if a similar remodelling between black and white athletes is present in the RV.

Method: As a part of the mandatory heart screening, 555 male elite football players (509 Caucasians and 46 Africans) and 46 Caucasian controls were examined. RV and diastolic mitral diameter (RVD2) were measured from a RV focused apical 4 chamber view. Measurements of RV free wall thickness (RWTW) in end diastole were performed by a subcostal view. Relative wall thickness on the right side (RVRWT) was calculated by dividing RWTW with RVD2 multiplied with two. Body mass index (BMI) and body surface area (BSA) were calculated, and all echo measurements were performed blinded.

Results: Remodelling between the groups. See table for other results.

Conclusion: We have for the first time demonstrated that RV free wall thickness in athletes exhibited the same pattern as LV wall thickness. Moreover, and similar to the LV, black athletes had a significantly more pronounced concentric remodelling RV than the white athletes.

Prevalence of significant ECG abnormalities in elite Australian athletes

M. Brosnan1, A. La Gerche1, J. Kalman2, K. Fallon2, A. Mac Isaac2, W. Lo1, D. Prior1, 1St Vincent’s Hospital, Melbourne, Australia; 2Royal Melbourne Hospital, Department of Cardiology, Melbourne, Australia; 3Australian Institute of Sport, Canberra, Australia; 4Sports Medicine ACT, Canberra, Australia.

Purpose: The effectiveness and cost-effectiveness of an athlete screening program is dependent on the prevalence of abnormalities on screening tests such as electrocardiography (ECG). As the prevalence of ECG abnormalities in athletes is unknown, our aim was to evaluate the frequency of ECG abnormalities in a cohort of elite Australian athletes.

Methods: A total of 450 elite Australian athletes (age 16-35) competing at national and international level underwent 12-lead ECG examination. They were predominantly male (n=413, 92%) with a mean age 20.9±4.8 years; mean hours training per week 15.0±7.8 from a range of endurance (road cycling n=48; rowing n=23; race walking n=2) and non-endurance sports (including football n=324; baseball n=10; and basketball n=15). ECGs were evaluated using criteria in the ESC recommendations for athlete ECG interpretation (2010).

Results: Group 1 (training related) ECG changes were more common in endurance versus non-endurance athletes (75% vs. 54%, p=0.001); left ventricular hypertrophy on voltage criteria was found in 17 (1.8%) athletes: 5 diastolic ventricular arrhythmia, 5 diastolic atrial arrhythmia, 3 Wolff-Parkinson-White ECG-pattern, 1 long QT syndrome type 1, 1 mitral valve prolapse, 1 bicuspid aortic valve and 1 systemic hypertension. Total mean cost per athlete was 138 Swiss Francs (102-381 Swiss Francs).

Conclusion: Preliminary data of this study indicate that cardiovascular screening in young athletes using strict criteria for interpreting ECG is feasible in Switzerland at low cost. These data should aid the implementation of this policy in our country.

Prevalence of Brugada ECG-pattern recorded in 3IC in the third intercostals space in young athletes

A. Menaloglou1, M. Di Valentin1, M. Sinagoga1, G. Moschovitis1, A. Gallino1, 1Hospital of San Giovanni, Department of Cardiology, Bellinzona, Switzerland; 2Locarno Regional Hospital, Locarno, Switzerland; 3Lugano Regional Hospital, Lugano, Switzerland.

Purpose: The prevalence of Brugada ECG-pattern is about 1/2000, mostly of type 2 and 3. In some circumstances, type 2 and 3 can convert in type 1 pattern, the only diagnostic. Registering ECG with V1 and V2 in the third intercostal space (3IC) can raise the sensibility of recording a Brugada ECG-pattern and the prognostic value of this tracing seems to be similar as the standard ECG. The aim of this study was to analyse the prevalence of Brugada ECG-pattern in a cohort of young athletes registering ECG also in the 3IC.

Methods: ECG was analysed as part of a prospective ongoing study about the impact of cardiovascular screening with ECG in young (14-35 years) competitive athletes. Besides a standard tracing, ECG was recorded with V1 and V2 in the 3IC. The prevalence of Brugada ECG-pattern type 1, 2 and 3 was analysed. Particular care was taken to distinguish an incomplete right bundle branch block pattern from a Brugada pattern.

Results: ECG of 556 athletes (72% males, age 19.9±6.3 years) was analysed. In a standard ECG tracing there was 3 Brugada type 2/3 pattern (0.5%). In ECG recorded in the 3IC there were 21 (3.8%) Brugada type 2/3, no type 1 was recorded. Of these 21 athletes, 20 were males (prevalence in males 4.8%), 1 female. The difference in prevalence in females 0.6%. Of 20 males, 15 had a Brugada type 3 pattern (3.7% of males), 5 had a type 2 pattern (1.2%). The female had a type 3 pattern. No athlete took medications known to elicit a Brugada ECG-pattern. No athlete with Brugada ECG-pattern had a history of syncope of undetermined origin or a family history of premature sudden death.

Conclusion: Brugada ECG-pattern type 2 and 3 in the 3IC is relatively common in young athletes, particularly males. This should be taken into account before drawing conclusion about risk stratification in this young healthy population.
basis on exercise-stress test and cardiovascular risk factors can be used to assess more accurately the risk of sudden cardiac death (SCD).  

**Methods:** A total of 3288 randomly selected men aged 42-60 from eastern Finland were enrolled in this population based follow-up study (mean follow-up time was 19 years). Exercise stress test was performed and information on risk factors was collected. SCD was defined as cardiac deaths that occurred 24 hours after onset of symptoms. The population was divided into low and high CRF (MET 8 as cut-off point) and analyzed with dichotomously divided risk factors. The risk factors in table, age, C-reactive protein, alcohol consumption and exercise-induced myocardial ischemia (1mm ST depression in electrocardiogram) were included in cox multivariable models.  

**Results:** Low CRF combined with all measured risk factors was associated with a higher risk of SCD (table). The higher risk factor combination was low CRF with a smoking history of more than 10 packyears, the risk ratio for SCD was 4.6 (95% confidence interval 2.86-7.43).  

**Conclusion:** By combining these previously known risk factors with CRF, more accurate SCD risk assessment can be made. This should be taken into account when considering treatment for patients in risk of SCD.  

### HEART FAILURE: FEAST OR FAMINE?  

**4011**  

**Alteration of gene expression profiling of the murine intestine suffering from heart failure**  

A. Takahashi1, M. Asakura, K.D. Min1, S. Ito, K. Shindo, Y. Yan, H. Liu, H. Asa, N. Mochiku1, M. Kitakaze1, National Autonomous University of Mexico, Faculty of Medicine, Mexico City, Mexico;2Osaka University Graduate School of Medicine, Suita, Japan;3Kyoto Prefectural University of Medicine, Kyoto, Japan  

**Background & Purpose:** Association between hearts and other organs such as the gastrointestinal tract has received a lot of attention in recent years. The gastrointestinal tract is an organ that produces a variety of hormones including ghrelin and glucagon-like peptide 1 which have been recently reported to improve cardiac functions. Although heart failure is thought to induce gastrointestinal dysfunction due to circulatory disturbances, little is known about gastrointestinal functions in heart failure. To clarify the function of intestines in heart failure, we analyzed global gene expression levels of intestines in mice with heart failure.  

**Methods:** We constricted transverse aorta of eight-week-old male C57/BL6J mice to create the condition of heart failure. Sham operation was also performed as the control. We collected intestines from these mice 4 weeks after aortic constriction. RNAs extracted from these samples were hybridized to GeneChip Mouse Genome 430 2.0 array. We constructed global gene expression profiles of intestines in heart failure mice as well as in control mice using GeneSpring GX software.  

**Results:** Heart/body weight ratios (mg/g) were 9.32 ± 0.11 in three heart failure three control mice (P < 0.05), respectively. We settled the fold change criteria > 1.5 to filter the genes. Microarray analysis of intestinal tissues demonstrated that 462 genes (1.09%) were up-regulated, and that 1005 genes (2.37%) were down-regulated in mice with heart failure compared with the control, respectively. Functional analysis of 462 up-regulated genes using Ingenuity Pathway analysis system revealed 97 enzyme-encoded genes such as Socs4 and S100a, and 54 transporter-encoded genes including Cyp2b10. Among them, we focused on 21 genes encoded for the secreted proteins whose secreted products from intestines could affect cardiac functions in mice with heart failure, and we found that 21 genes encoded including insulin-like growth factor (Igf1, 1.971), transthyretin (Ttr, 1.984) and interleukin-33 (fold change: 3.463±218) may alter cardiac functions in mice with heart failure.  

**Conclusions:** This is the first to evaluate the global gene expression of intestines of the mice with heart failure, and surprisingly, intestine is enforced to release many cardio- or vaso-active substances such as interleukin-33, which may provide novel therapeutic targets in patients with heart failure.  

**4012**  

**Preceding starvation prevents acute doxorubicin cardiotoxicity via autophagy activation**  

T. Kawaguchi, G. Takemura, H. Karamori, A. Tsujimoto, T. Takeyama, T. Watanabe, K. Morishita, H. Fujiwara, T. Fujiwara, S. Minatoguchi. Gifu University Graduate School of Medicine, Department of Cardiology, Gifu, Japan  

**Doxorubicin is a highly effective antineoplastic drug, but its clinical use is limited by the adverse effects on the heart. Active autophagy has recently been reported in doxorubicin cardiotoxicity but its pathophysiological role remains unclear. In the present study, we examined the role of preceding starvation, a potent inducer of autophagy, on doxorubicin cardiotoxicity. Autophagocytosis was induced in green fluorescent protein-microtubule-associated protein 1 light chain 3 (GFP-LC3) transgenic mice by injection of 10 mg/kg doxorubicin twice per week. The experimental group was deprived of food for 48 h before each injection of doxorubicin to induce autophagy. Doxorubicin treatment caused left ventricular dilatation and dysfunction at 1 week after the initial injection (the left ventricular diastolic [LVDd] = 3.94 ± 0.25 mm and ejection fraction [EF] = 46.7±4.4%), which were significantly mitigated by the preceding starvation (LVDd = 3.41 ± 0.31 mm and EF = 63.9±6.4%, both p < 0.05 compared with the control). Cardiomyocyte autophagy appeared markedly activated in the doxorubicin-treated group according to assessment of LC3 by immunohistochemistry and Western blotting. According to LC3 expression, autophagy appeared to be rather attenuated by the preceding starvation. Unexpectedly, however, myocardial ATP content was decreased in the doxorubicin-treated group and this reduction was restored by the preceding starvation. Electron microscopy suggested that autophagic process is indeed initiated but not completed in the doxorubicin-treated group, i.e., autophagosomes digestion is insufficient, and that this incompleteness was partially improved by starvation. Finally autophagy flux assay using chloroquine confirmed that doxorubicin impairs final digestion step of autophagy in cardiomyocytes. In conclusion, preceding starvation mitigates acute doxorubicin cardiotoxicity, of which underlying mechanism may be, at least in part, restoration of autophagy flux which is impaired by doxorubicin. Our findings imply that fasting could be a possible strategy for preventing doxorubicin cardiotoxicity.  

### Does admission pre-albumin predict in-hospital mortality in acute heart failure patients?  

**4014**  

P. Lourencio, S. Silva, F. Fries, M. Avelos, P. Torres Ramalho, T. Guimaraes, P. Bettencourt. Sao Joao Hospital, Porto, Portugal  

**Background:** Prognostic predictors of in-hospital mortality in acute heart failure (HF), have not been so fully studied as those for long term outcome in chronic HF. Malnutrition has been increasingly recognized as associated with poor outcome in HF. Pre-albumin as emerged as the best marker for protein malnutrition. We aimed to study if pre-albumin predicted in-hospital mortality in patients admitted with acute HF.  

**Methods:** During a 20-months period, all patients admitted due to acute HF, worsening or de novo HF, with an admission B-type natriuretic peptide (BNP) >200 pg/ml were eligible for study inclusion. Patients with acute coronary syndromes or those having other conditions leading to preceding starvation (<70% of pre-morbid food intake) were excluded. The European Society of Cardiology guidelines were used for the diagnosis of heart failure (HF). Both patients with systolic dysfunction and those with HF with preserved ejection fraction were studied. Fasting venous blood samples were collected to all patients within 48h of admission. The admission was defined as the patients first clinic encounter after hospital admission. A logistic regression analysis was used to assess prognostic determinants.  

**Results:** A total of 629 patients were studied. Median age was 79 years and 44% of them were male. Most of the patients (88.4%) had known chronic HF.
Heart failure: feast or famine? / Restenosis: still the achilles heel of percutaneous coronary interventions? 683

Thirty-two of the patients (4.8%) died in hospital. Patients dying in-hospital were older, had lower admission systolic blood pressure, worse admission renal function and higher BNP. Patients with in-hospital death also had significantly lower total cholesterol level below 4.5 (12.2, 91-145) mg/dL vs 150 (126-186) in those discharged alive; lower albumin: 32.0 (4.0) vs 35.4 (4.8) mg/dL; and lower pre-albumin: 13.2 (5.2) vs 18.2 (7.1) mg/dL. Higher pre-albumin predicted in hospital survival with a HR of 0.68 (95% CI: 0.92-0.95<0.001). Association with outcome was independent of other variables also associated with outcome in an univariate approach (systolic blood pressure, age, blood urea, BNP, total cholesterol and albumin). An admission pre-albumin below 18g/L predicted in hospital death with a HR of 5.64 (95% CI: 1.20-26.51, p<0.03).

Conclusions: Malnutrition as assessed by lower pre-albumin predicted in-hospital death in patients admitted with acute HF. HF patients with admission pre-albumin<18g/L have more than five-fold higher risk of in-hospital death than those with higher admission pre-albumin.

Are total cholesterol levels important for hospital and long time prognosis of patients with acute heart failure?

1Masaryk University-St. Anne’s Faculty Hospital, 1st Department of Internal Medicine/Cardiology, Brno, Czech Republic; 2Faculty Hospital, Masaryk University, Brno, Czech Republic; 3Charles University, Prague, Czech Republic; 4Facility Hospital, Olomouc, Czech Republic; 5Hospital Na Homolce, Prague, Czech Republic; 6Cardiology Department, Zlin, Czech Republic; 7Masaryk University, Faculty of Medicine, Institute for Biostatistics and Analysis, Brno, Czech Republic

The purpose of this study was to evaluate if there is an association of total cholesterol levels with hospital and long time mortality of patients admitted for acute heart failure. The AHEAD MAIN registry is a database conducted in 7 university hospitals, all with 24 hour cath lab service, in 4 cities in the Czech Republic. The database included 4153 patients hospitalised for acute heart failure in the period 2006 – 2009. Median age was 73.8 years, 42% females, more than 70 years 60%, ejection fraction below 30% 37.9%. The data were collected prospectively using a database accessible via the Internet website and were evaluated continuously (online) for long term mortality. The long time mortality was followed by analysis of the cumulative incidence of the first event, hospitalised cases in consecutive 388 patients with CHF (mean ± SD, 69.6 ± 12.3 years) admitted to our hospital. CONUT consists of 2 biochemical parameters (serum albumin and total cholesterol level) and 1 immune indicator (total lymphocyte count). PIN consists of 2 biochemical parameters (serum albumin and 1 immune indicator (total lymphocyte count). GNRIs consists of 1 biochemical parameter (serum albumin) and ratio of body weight to ideal body weight. Patients were prospectively followed with the endpoints being cardiovascular death or rehospitalisation. There were 584 events including 33 deaths and 97 rehospitalizations during 6.8 ± 2.9 years follow-up of 37.7 months. Patients with cardiac events showed higher age, more severe New York Heart Association (NYHA) functional class, lower prevalence of valvular heart disease, lower body mass index, lower serum triglyceride level, lower serum high-density lipoprotein cholesterol level and higher serum brain natriuretic peptide (BNP) compared with those without cardiac events. Furthermore, patients with cardiac events showed higher CONUT score (6, 3.8 vs 2, 1.3, P<0.001), lower PIN score (151.2, 26.4-35.7 vs 38.6, 35.2-40.0, P=0.001), lower GNRIS score (84.9, 76.8-92.3 vs 95.3, 89.8-101.3, P<0.001) compared with those without cardiac events. In Cox proportional hazards analysis, CONUT (hazard ratio 4.9, 95% CI 3.7-11.0), PIN (hazard ratio 6.4, 95% CI 5.4-25.1), and GNRIS (hazard ratio 11.6, 95% CI 3.7-40.0) were independently associated with cardiac events after adjustment of age, gender, NYHA functional class and serum levels of BNP. Among these nutritional indexes, CONUT had the highest hazard ratio. Kaplan-Meier analysis revealed a significantly higher cardiac event rate in patients with low nutritional indexes than in those without it.

Conclusion: Low nutritional status was associated with unfavorable outcomes in patients with CHF. It was suggested that evaluating nutritional status may provide a pivotal prognostic information in patients with CHF.

RESTENOSIS: STILL THE ACHILLES HEEL OF PERCUTANEOUS CORONARY INTERVENTIONS?


Purpose: Stent fracture (SF) is associated with adverse events after drug-eluting stent implantation. However, few data exist on its long-term clinical impact in real world practice. Therefore, we evaluated the impact of SF on long-term clinical outcomes after sirolimus-eluting stent (SES) implantation.

Methods: Consecutive 2404 patients who had undergone the first SES implantation from November 2002 to December 2007 and received follow-up angiography within 12 months were analyzed. Angiographic stent fracture was defined as apparent separation of stent segments. Some stents, including focus image, inverse image, and image without catheter or contrast media were used to obtain the exact prevalence of SF. The incidence of clinical outcomes, including all-cause death, myocardial infarction (MI), stent thrombosis (ST), target lesion revascularization (TLR), and major adverse cardiac events (MACE, defined as all-cause death, MI, and TLR) was compared between SF and non-SF groups.

Results: Because 446 of the 2404 patients were excluded because of no angiographic follow-up within 12 months, the entire study population consisted of 2048 patients (3218 lesions) and was classified into two groups: 243 patients with SF and 1805 without SF. The median duration of follow-up was 4.9 years. At 4-year follow up, the rates of TLR, MI, and MACE were significantly higher in the SF group than in the non-SF group (38.3% vs. 17.2%, p<0.001; 2.1% vs. 0.6%, p=0.03; 42.4% vs. 25.0%, p<0.001, respectively), whereas the rate of all-cause death was similar between groups (6.6% vs. 10.0%, p=0.20). The figure shows the cumulative incidence of definite or probable very late ST.

Conclusions: Our study suggests that SF is associated with higher rates of late adverse events except all-cause death after SES implantation.

Stent fracture and restenosis at stent fracture site after sirolimus-eluting stent and everolimus-eluting stent implantations: impact of stented vessel

K Miyake, K Kadota, T Tada, H Tanaka, Y Fuku, N Oka, H Katoh, H Yamamoto, T Goto, K Mizutra. Kurashiki Central Hospital, Cardiology Department, Kurashiki, Japan

Background: Stent fracture (SF) and its related restenosis are concerns of sirolimus-eluting stent (SES) implantation. However, everolimus-eluting stent (EES) may have a potential for the reduced prevalence of SF. We assessed SF and restenosis at SF site in terms of stented vessel after SES and EES implantations.

Methods: A total of 8817 stent-implanted lesions (SES 6000, EES 2217) from...
November 2002 to March 2011 were analyzed at midterm follow-up. Stented vessels were classified into two groups: right coronary artery (RCA) and non-RCA. **Results:** The SF rate of EES was significantly lower than that of SES in both RCA and non-RCA. The restenosis rate at SF site of EES was significantly lower in the non-RCA, but it was similar in the RCA.

**Conclusion:** Although EES reduced the prevalence of SF, the effect of EES on SF related restenosis depends on the vessel site.

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**Decreased interleukin-33 serum levels after coronary stent implantation are protective against in-stent restenosis**

S. Demyanets1, R. Jara2, K. Katraso3, S. Farhan4, A. Wornorth1, G. Maun1, W.S. Spedeli1, J. Wojta1, K. Huber1, Medical University of Vienna, Vienna, Austria; 2Wilhelminen Hospital, Vienna, Austria

**Conclusion:** Decreased interleukin-33 serum levels after coronary stent implantation are protective against in-stent restenosis.

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**Efficiency of statin treatment on EPC recruitment depends on baseline EPC titre, and does not improve angiographic outcome in coronary artery disease patients treated with the Genous stent**

W. Den Dekker1, J.H. Houtgraaf1, S.M. Rowland2, S.P.M. De Boer1, R.J. De Winter1, P. Den Heijer1, W. Udayathar1, T. Tsurugashawadi1, Y. Fukushima, N. Oka, T. Goto, K. Mitsu, Kurashiki Central Hospital, Kurashiki, Japan; 2Kumamoto University Hospital, Kumamoto, Japan; 3Konyang University Hospital, Daejeon, Korea, Republic of; 4Husada Hospital, Jakarta, Indonesia; 5King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 6Faculty of Medicine Siriraj Hospital of Mahidol University, Bangkok, Thailand

**Conclusion:** The use of drug-eluting stents in patients with CTO was safe with low acute complication. Patients treated with 2nd generation DES such as ZES- (DES), EPC capture (ECS) and Everolimus-eluting stent (EES) on the outcome of patients with chronic total occlusion (CTO).

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**Differences in progression pattern of late restenosis after drug-eluting stent implantation**


**Conclusion:** The use of drug-eluting stents in patients with CTO was safe with low acute complication. Patients treated with 2nd generation DES such as ZES-R, EES and EES showed lesser rate of restenosis compared with 1st generation drug-eluting stents.
phy (flu CAG) at 6 to 8 months after implantation (flu rate, 81.2% [726/8879]). Of these, 5767 lesions without restenosis underwent late flu CAG at 12 months after early flu (flu rate, 65.0%). Early restenosis was defined as restenosis at mid-flu and late restenosis as restenosis at late flu without early restenosis. Progression of restenosis was classified into two patterns: "jump-up" type had ≥25% stenosis at mid-flu and progressed to ≥50% stenosis (defined as restenosis) at late flu; "progressive" type had <25% and ≥50% stenosis at mid-flu and progressed to restenosis at late flu.

Results: Data are shown in the table.

Conclusions: The progression pattern of late restenosis differs among various DESs. Although the mechanism of this phenomenon is unclear, different clinical follow-up may be necessary depending on DES types.

**BALANCING STROKE PREVENTION VERSUS BLEEDING RISK IN ATRIAL FIBRILLATION**

### 4043 Regional differences in the use of antithrombotic therapy for stroke prevention in atrial fibrillation: European and Asian insights from the Global Anticoagulant Registry in the FIELD (GARFIELD)


2Tokai University, Kanagawa, Japan; 3The Thrombosis Research Institute, London, United Kingdom; 4Primary Care Clinical Sciences, The University of Birmingham, Birmingham, United Kingdom; 5Technical University of Munich, Munich, Germany; 6University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; 7McMaster University, Hamilton, Canada; 2Harvard Medical School, Brigham and Women’s Hospital, Department of Medicine, Boston, United States of America

Guidelines for antithrombotic therapy in atrial fibrillation (AF) recommend oral anticoagulation (OAC) for all AF patients at moderate/high risk of stroke and without contraindications. Clinical evidence suggests that intracerebral haemorrhage in Asian patients occurs at a lower intensity of anticoagulation than in the other racial ethnic patients. Little is known about real-world use of antithrombotic therapy for stroke prevention in Asia.

Aim: To compare use of antithrombotic therapy according to CHADS2 score in Asian and European AF patients.

Methods: GARFIELD is a worldwide registry that will enrol 55,000 patients as 5 sequential prospective cohorts (incl. a retrospective validation group in cohort 1) at >1000 randomly selected sites in up to 50 countries. Eligible patients are ≥18 years old, newly diagnosed with non-valvular AF, with ≥1 additional investigation-dependent stroke risk factor. All components of the CHADS2 score risk are captured, allowing for objective retrospective risk stratification. Cohort 1 was conducted in 19 countries; this analysis is based on data from China, Japan, Korea, and Austria, Denmark, Finland, France, Italy, Germany, Netherlands, Norway, Poland, Spain, Sweden, UK.

Results: Data analysed from cohort 1 comprised 10,504 AF patients of which 2593 were from Asia and 6511 from Europe. Fewer patients in Asia had CHADS2 risk score ≥2 (43.2% vs 58.5% in Europe). Overall, OACs were used in 43.7% of Asian patients and in 52.5% of those with a CHADS2 score ≥2. Corresponding data for Europe were 71.3% and 74.7%, respectively.

Table 1. Antithrombotic use in AF patients according to CHADS2 score and continent in cohort 1

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Europe (n=6511)</th>
<th>Asia (n=2593)</th>
<th>P (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 score 0</td>
<td>33 (0.50)</td>
<td>26 (0.50)</td>
<td>0.799</td>
</tr>
<tr>
<td>CHADS2 score 1</td>
<td>63 (0.95)</td>
<td>57 (0.94)</td>
<td>0.647</td>
</tr>
<tr>
<td>CHADS2 score 2</td>
<td>99 (1.50)</td>
<td>103 (1.99)</td>
<td>0.225</td>
</tr>
</tbody>
</table>

Conclusions: These international observational data indicate regional differences in OAC use for stroke prevention in AF in Asia and Europe, reflecting a potential overuse of OAC in Europe for patients at low risk for stroke according to existing risk scores and an underuse in Asian patients at higher risk.

### 4044 The HEMORR2HAGES, ATRIA and the HAS-BLED bleeding risk prediction scores in anticoagulated atrial fibrillation patients: the AMADEUS study

**S. Apostolidis**1, D.A. Lane1, H. Buller2, G.Y.H. Lip3, C. City-Hospital, University Department of Haematology, Haemostasis Thrombosis and Vascular Biology Unit, Birmingham, United Kingdom; 2Department of Vascular Medicine, Academic Medical Centre, Amsterdam, Netherlands

Aim: To evaluate the performance of the following bleeding risk prediction scores in anticoagulated AF patients taking OAC: HEMORR2HAGES, ATRIA and HAS-BLED.

Methods: We analyzed the data of the AMADEUS trial, which was a multicentre, randomised, non-inferiority study that compared fixed-dose idraparinux with adjusted-dose oral vitamin K antagonist (VKA) therapy in patients with AF. The primary safety outcome was “any clinically relevant bleeding” that was a composite of “major bleeding” and “clinically relevant non-major bleeding”.

Results: The AMADEUS study randomized 2293 patients in the VKA arm (65% men, mean age 70.2±9.1). In total 251 (11%) clinically relevant bleedings occurred including 39 (1.7%) major bleedings. The HAS-BLED score performed best in predicting “any clinically relevant bleeding” as reflected both by the AUC (Table 1) and net reclassification improvement (NRI HAS-BLED vs HEMORR2HAGES=0.14, p=0.0004 and NRI HAS-BLED vs ATRIA=0.0015, p=0.0004). In the ROC analysis the ATRIA score failed to demonstrate any predictive value for the above endpoint. All bleeding risk stratification schemas perform equally well in predicting major bleeding.

Table 1. Comparison of areas under the curve (AUC, or c-statistic) and Net Reclassification Improvement (NRI) for HEMORR2HAGES, ATRIA and HAS-BLED

<table>
<thead>
<tr>
<th>AUC analysis</th>
<th>Major bleeding</th>
<th>Any clinically relevant bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has-Bled</td>
<td>0.65</td>
<td>0.56-0.73</td>
</tr>
<tr>
<td>Atria</td>
<td>0.61</td>
<td>0.51-0.72</td>
</tr>
<tr>
<td>S. Apostolidis</td>
<td>0.70</td>
<td>0.60-0.79</td>
</tr>
</tbody>
</table>

Conclusions: The HAS-BLED score performed significantly better in predicting “any clinically relevant bleeding”. Given its simplicity and superior performance to other scores, the HAS-BLED score would be more attractive for the estimation of OAC-related bleeding risk in clinical practice.

### 4045 Events after discontinuation of randomized treatment at the end of the ARISTOTLE trial

**C.B. Granger**1, J.H. Alexander1, M. Hanna2, J. Wang2, P. Mohan2, J. Lawrence2, E. Hylek3, J.E. Ansell2, L. Wallentin4 on behalf of ARISTOTLE Investigators and Committees. 1Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; 2Boston University, Boston, United States of America; 3Lenox Hill Heart and Vascular Institute, New York, United States of America; 4Uppsala University, Uppsala Clinical Research Center, Uppsala, Sweden

Background: During the ARISTOTLE trial apixaban reduced stroke or systemic embolism, mortality, and major bleeding compared with warfarin in patients with atrial fibrillation. Events occurring after discontinuing study drug at the end of the trial could be influenced by stopping the blinded treatment and/or initiation of subsequent anticoagulation.

Methods: At the end of ARISTOTLE, blinded study drug was stopped and open-label vitamin K antagonist (VKA) was recommended. For patients completing the trial on blinded study drug a 2 day bridging period with apixaban or apixaban placebo was recommended (while beginning open-label VKA). Patients were followed for an additional 30 days.

Results: Among 13,360 patients who completed the trial on study drug, 85% started a VKA. There were 21 strokes or systemic emboli (4.02%/year) and 26 major bleeding events (4.57%/year) in the apixaban group (transitioning to VKA), Stroke or systemic embolism after stopping study drug at end of trial

<table>
<thead>
<tr>
<th>Days after last dose</th>
<th>Apixaban to VKA Group</th>
<th>Warfarin to VKA Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>21/6791</td>
<td>4.02</td>
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<tr>
<td>1-14</td>
<td>26/6791</td>
<td>3.85</td>
</tr>
<tr>
<td>1-30</td>
<td>5/6791</td>
<td>0.76</td>
</tr>
<tr>
<td>15-30</td>
<td>30/6791</td>
<td>4.43</td>
</tr>
<tr>
<td>1-2</td>
<td>21/6771</td>
<td>3.08</td>
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<td>26/6771</td>
<td>3.79</td>
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Conclusions: During the ARISTOTLE trial apixaban reduced stroke or systemic embolism, mortality, and major bleeding compared with warfarin in patients with atrial fibrillation. Events occurring after discontinuing study drug at the end of the trial could be influenced by stopping the blinded treatment and/or initiation of subsequent anticoagulation.

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</tbody>
</table>
and 5 strokes (0.99%/year) and 10 major bleeding events (1.97%/year) in the warfarin group (continuing on VKA), in the 30 days after stopping study drug with the majority of the imbalance after the first week (Table). This pattern mirrored the first 30 days of atrial fibrillation where warfarin-naïve patients starting warfarin had a higher rate of stroke or systemic embolism (5.41%/year) than warfarin-experienced patients (1.41%/year). No similar increase in event rate was seen in the apixaban group following study drug discontinuation before the end of the trial.

Conclusions: The excess in thrombotic and bleeding complications in the apixaban arm after study drug discontinuation at the end of ARISTOTLE seems to be related to an increased risk associated with the new initiation of a VKA that extends over several weeks rather than a direct effect of apixaban.

Table 1. Incidence of thromboembolic events

<table>
<thead>
<tr>
<th>CHA2DS2VASc score</th>
<th>No anticoagulation</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>8 (0.37%)</td>
<td>1 (0.24%)</td>
</tr>
<tr>
<td>≥2</td>
<td>13 (1.07%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>≥4</td>
<td>14 (0.38%)</td>
<td>2 (0.53%)</td>
</tr>
</tbody>
</table>

Conclusions: The incidence of postcardioversion thromboembolic complications is high in patients with high CHA2DS2VASc score after cardioversion of acute atrial fibrillation when no anticoagulation is used. The present data supports the view that effective anticoagulation should be used in these patients also during cardioversions of short attacks of atrial fibrillation.

Stroke prevention in non-valvular atrial fibrillation: long-term results after 6 years of the watchman left atrial appendage occlusion pilot study

Methods: The WATCHMAN LAA Closure device (Boston Scientific, Plymouth, MA) is a percutaneous device that is placed via the femoral vein to occlude the LAA. The WATCHMAN LAA Closure device is associated with near-future acute complications and feasible, with two embolic strokes through more than 6 years of active follow-up.

Results: In patients with atrial fibrillation for longer than 48 hours, there is an increased rate of thromboembolic events which is lowered with vitamin K antagonists. The present data supports the view that effective anticoagulation should be used in these patients also during cardioversions of short attacks of atrial fibrillation.

Conclusions: In patients with atrial fibrillation and risk factors, the risk of thromboembolic events after cardioversion is low in patients treated with apixaban, a factor Xa inhibitor, is unknown.

Methods: In the Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, apixaban 5 mg bid reduced stroke, death, and caused less bleeding as compared to warfarin (INR 2.0-3.0) in patients with atrial fibrillation and risk factors for stroke. During the trial if cardioversion was performed, it was recommended that investigators continue randomized treatment before and after the procedure. Thromboembolic events including stroke, systemic embolism, and myocardial infarction were compared between patients receiving apixaban or warfarin.

Results: 18,201 patients were included in the ARISTOTLE trial. A total of 577 (3.2%) patients underwent cardioversion during the trial including 286 (49.6%) assigned to apixaban and 291 (50.4%) assigned to warfarin. The median time to cardioversion was 5 months and approximately 75% of the procedures occurred by follow-up year one. Key baseline characteristics including gender, CHA2DS2VASc score, LVEF, and estimated duration of AF were similar in patients receiving apixaban and warfarin. In the first 90 days, no patient in either group suffered a stroke or systemic embolism. After cardioversion for a median follow-up of 233 days (range 1-489) in the apixaban group and 393 days (range 213-607) in the warfarin group, the composite of stroke, systemic embolism, and myocardial infarction occurred in 5 patients assigned to apixaban and 6 patients assigned to warfarin.

Conclusions: In patients with atrial fibrillation and risk factors, the risk of thromboembolic events after cardioversion is low in patients treated with either apixaban or warfarin. Apixaban appears to be a safe alternative to warfarin for stroke prevention after cardioversion.

CORONARY ARTERY DISEASE: FROM THE DARK TO THE LIGHT OF MULTIDETECTOR COMPUTED TOMOGRAPHY

Ring-like sign on coronary computed tomographic angiography is associated with near-future acute coronary syndrome in patients with coronary artery disease

Purpose: Recent studies have reported a close relationship between ring-like sign on coronary computed tomographic angiography (CCTA) and thin-cap fibroatheroma (TCFA). The aim of this study was to determine the predictive value of ring-like sign on CCTA for future acute coronary syndrome (ACS) events in patients with coronary artery disease (CAD).

Methods: This study consists of 895 consecutive patients who underwent CCTA examination and followed for more than 1 year. The primary end-point was ACS events (cardiac death, non-fatal myocardial infarction, and unstable angina pectoris). The CCTA analysis included the presence of positive remodeling (PR: remodeling index > 1.1) and thin-cap (<100 mm in thickness) and ring-like sign. The results of the study were analyzed using Cox proportional hazards regression. The analysis was performed using SPSS 20.0 software.

Results: Over 12,727 segments in 895 patients, 1,174 contained plaque, including plaques with PR in 130 (1.0%) segments, LAP in 107 (0.8%) segments, and ring-like signs in 45 (4.0%) segments. During the follow-up period (2.3±0.8 years),
24 (2.6%) patients suffered ACS events. Of the 45 plaques with ring-like sign, 6 (13%) resulted in ACS in the first year, and an additional 2 (4.4%) resulted in ACS in 1 to 2 years (Figure A). Cox proportional hazards models analysis showed that PR (p=0.05), LAP (p=0.05) and ring-like sign (p=0.05) were independent predictive factors for future ACS events. Plaques with ring-like sign showed higher risk for ACS events compared to those without ring-like sign (hazard ratio: 22.7; 95% confidence interval: 4.4-72.7; p<0.001). ACS events arose more frequently from PR, LAP, ring-like signs, and combinations thereof than with any other features (Figure B).

Conclusions: The present study demonstrated that the detection of ring-like sign on CTA could help us to identify patients at high risk for future ACS events.

4066 Prevalence of coronary artery anomalies in 8,002 consecutive patients: study with coronary computed tomography angiography

M.P. Opolski, C. Kępka, J. Pręgowski, M. Kruk, S. Kwiecińska, E. Lubienska, M. Demkow, W. Reżyłło, A. Włoszko. Institute of Cardiology, Warsaw, Poland

Purpose: Anomalous coronary arteries originating from the opposite sinus of Valsalva (ACAOS) have been related to sudden cardiac death and account for 0.1% of cases reported by coronary angiography. We aimed to investigate the incidence of ACAOS in a population referred for coronary computed tomography angiography (CTA) at a single high-volume center. Methods: A total of 8,002 consecutive patients were evaluated with dual-source CCTA between February 2008 and January 2012. The origin and course of ACAOS were analyzed in axial, multiplanar and volume rendering reconstructions. On the basis of CTA findings, the proximal course of each vessel was classified into the following subtypes: 1, anterior; 2, interarterial; 3, septal; and 4, retroaortic. In addition, 4 malignant features of the proximal portion of ACAOS were recorded as follows: a slitlike ostium, an acute angle of take-off from the aorta, an intramural course within the aortic wall, and a lateral indentation of the pulmonary trunk.

Results: A total of 59 patients (29 male, 23-85 years) with ACAOS were identified. The incidence of ACAOS was 0.74%. The origins and course of ACAOS were clearly visualized in all patients, including right-lateral origin of the left main or the left anterior descending coronary artery (n=16), right-sided origin of the left anterior descending coronary artery (n=28); and left-sided origin of the right coronary artery (n=16). Among analyzed subtypes of ACAOS, 19 (0.24%) had an interarterial course of which 11 (0.14%) showed a significant compression between the aortic root and the pulmonary trunk. The presence of malignant features of the proximal ACAOS was found in 5 (0.06%) right coronary arteries arising from the left sinus of Valsalva.

Conclusions: Dual-source CCTA allows accurate and noninvasive identification of ACAOS, which are found more frequently compared to previous angiographic studies. The malignant characteristics of the proximal ACAOS might be exclusively associated with left-sided origin of the right coronary artery.

4073 Association between findings of multidetector computed tomography and coronary flow throughout Percutaneous Coronary Intervention

Y. Osaka1, S. Kimura1, S. Kuroda1, N. Kawaguchi2, E. Nakashima1, T. Sugiyama1, D. Akiyama1, T. Kamishi1, H. Hikita1, M. Isobe2

1 Yokohama Koyal Hospital, Yokohama City, Japan; 2Tokyo Medical and Dental University, Tokyo, Japan

Background: Coronary flow is a significant predictor for outcome in patients with coronary artery disease (CAD). Multidetector computed tomography (MDCT) is a noninvasive method for assessment of atherosclerotic coronary plaque morphology. The present study aimed to evaluate whether slow-flow phenomenon could be used as an independent predictor of coronary events in percutaneous coronary intervention (PCI) patients. Methods: We investigated 74 lesions with 74 patients (male 53) with CAD who underwent MCTD before PCI. Morphology and plaque volume and CT density at the culprit lesion were assessed in MDCT analysis. Coronary flow was investigated throughout PCI. All lesions were classified into 2 types of lesions, lesions with occurrence of slow-flow during PCI (the Thrombolysis in Myocardial Infarction flow grade 0-2) and those without. Slow-flow phenomenon was detected in 15 lesions (20.5%) during PCI. Positive remodeling was significantly more frequent in lesions with slow-flow (20.0% vs. 3.4%, p=0.02), although there was no significant difference between slow-flow and non-slow-flow lesions in terms of pre-procedural characteristics. However, CT density was lower (32.7 HU vs. 68.1±32.7 HU, p=0.02) and plaque volume was greater (103.4±47.7 mm3 vs. 45.8±89.3 mm3, p=0.03) in lesions with slow-flow than without. Multiple logistic regression analysis showed that CT density (odds ratio (OR): 0.97, 95% confidence interval (CI): 0.95-0.99, p=0.03) and plaque volume (OR: 1.013, 95% CI: 1.003-1.025, p=0.01) were independently associated with slow-flow. The cut-off values for CT density and plaque volume for slow-flow were 39.0 HU (sensitivity 67.9%, specificity 83.4%, area under the receiver-operating characteristic curve (AUC) 0.80) and 78.7 mm3 (sensitivity 69.2%, specificity 75.0%, AUC 0.75), respectively. For predicting slow-flow during PCI, the diagnostic power of combination of lower CT density <39.0 HU and greater plaque volume >78.7 mm3 showed 40% of sensitivity, 96.6% of specificity, 75.0% of positive predictive value, 89.0% of negative predictive value, and 87.6% of diagnostic accuracy. Conclusion: Lower CT density and greater plaque volume were significantly related to slow-flow phenomenon during PCI. MDCT may help to predict poor outcome after PCI in patients with CAD.

4067 Prognostic significance of pre-test probability of coronary artery disease to coronary CT angiography in patients with coronary calcium score zero

N. Yokoyama, R.I. Iino, K.K. Kumiko Konno, T.I. Takaaki Isshiki. Tokyo University School of Medicine, Tokyo, Japan

Background: Both coronary artery calcium score (CACS) and pre-test probability of risk stratification are considered as a gatekeeper to coronary computed tomography angiography (CTA). However, there was no report about the impact of different pre-test probabilities of CAD on the prognostic value of CACS zero for future cardiac events. The aim of this study was to evaluate the prognostic impact of pre-test probability prior to coronary CTA in patients with CACS zero.

Methods: The study group consisted of 297 patients (61.2±10.8 years) with CACS zero. The pre-test probability was determined using the modification of Diamond and Forrester method based on age, gender, and symptom. Cardiac events
were defined as cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization. Cardiac event-free survival was estimated using the Kaplan-Meier survival methods with log-rank statistics. The proportions of selected variables with outcome were assessed in the multivariate Cox proportional hazard models.

**Results:** A very low, intermediate or high pre-test probability was observed in, respectively, 11.5%, 41.4% and 5.7% of study patients. During follow-up (736±337 days), a total of 12 (4.0%) cardiac events occurred including nonfatal myocardial infarction in 1 (0.3%), unstable angina requiring hospitalization in 2 (0.6%) and coronary revascularization in 9 (0.0%). In this study of 12 patients with cardiac events, 5 patients (41.7%) with a high pre-test probability of CAD, 3 (25%) with an intermediate, and 4 (33.3%) with a low were observed. Kaplan-Meier event-free survival rate in patients with very low, low, intermediate and high risk pre-test probability of CAD was 0%, 3.3%, 2.4% and 29.4%, respectively. Patients with high pre-test probability had significantly more cardiac events as compared with very low, low and intermediate pre-test probabilities (p<0.001). The event rate was 0% among patients with very low pre-test probability. Multivariate model revealed that high pre-test probability was the only significant predictor of cardiac events (risk ratio 11.3; 95% confidence interval 3.5-36.8).

**Conclusion:** CAGS zero by MDCT did not predict future cardiac events completely. The prognostic value of pre-test probability of CAD for patients with very low risk, low, intermediate and high risk was calculated. The cardiac event rate was 0% among patients with very low pre-test probability. Coronary CTA could be avoided for these patients, especially those with very low pre-test probability.

**POSTER SESSION 5**

**GENETIC ASPECTS/VENTRICULAR ARRYTHMIAS**

**P4083**

**Outcome of screening of relatives to patients with long QT syndrome: a nationwide Danish study**

J. Thelade1, J. Kanters2, F.L. Herniksen3, M. Gilsaa-Hansen3, J. Hastrup-Svendsen1, O. Eschen4, A. Tjibbe-Jansen5, M. Christiansen3, H.K. Jensen3, B. Odense, Denmark; 2Haderslev Hospital, Department of Cardiology, Haderslev, Denmark; 3Aarhus University Hospitals, Department of Cardiology, Aalborg, Denmark; 4Rigshospitalet, Department of Clinical Biochemistry, Copenhagen, Denmark; 5Statens Serum Institut, Department of Biochemistry, Copenhagen, Denmark; 6Aarhus University Hospital, Skejby, Department of Cardiology, Aarhus, Denmark

**Aims:** According to international recommendations relatives to patients with long QT syndrome (LQTS) are offered cascade screening. In this Danish study we investigated the outcome of clinical and genetic cascade screening of LQTS families nation-wide.

**Methods and results:** Patients with LQTS were identified from Danish national registries and patient files were reviewed. A total of 286 patients with LQTS were identified in 79 families and included 209 relatives. The majority of diagnosed relatives identified by cascade screening were asymptomatic. Symptomatic probands and family members most often presented with syncpe, followed by aborted cardiac arrest (abSCD), unexplained sudden cardiac death (SCD), Syncope, abSCD and SCD most often occurred at rest. The most pronounced QTc prolongation was seen in probands and patients with serious cardiac events. A disease-causing mutation was found in 59 probands (81% of those probands tested). The majority of mutations were localized to the KCNQ1gene (63%). A total of 180 (63%) patients were on beta-adrenergic blocking agents (BB) and 67 (23%) patients had an implantable cardiac defibrillator (ICD). Appropriate ICD therapy was given to 12 (29%) probands and three (12%) family members. Fourteen (33%) probands and two (8%) family members experienced ICD complications.

**Conclusions:** By cascade screening we identified almost 3 affected relatives for each proband. Probands were noteworthy more clinically affected compared to other relatives, but a considerable fraction of the diagnosed relatives were asymptomatic and 14% family members were identified with an ICD.

**P4085**

**A new MG1 transcript variant implied in arrhythmias**

V. Novelli1, M. Cerone1, S. Crespo-Carboni1, R. Bloise1, C. Napolitano1, S.G. Priori2,1New York University School of Medicine, New York, United States of America; 2IRCCS Salvatore Maugeri Foundation, Pavia, Italy

A missense mutation in the Mgosl gene has been recently identified in one Brugada syndrome (BrS) patient. This gene has been shown to interact with the cytoplasmic loop II (between transmembrane domains DII and DIII) of Nav 1.5. This interaction plays a critical role in the regulation of sodium current density increasing the whole-cell iNa current. In our study we screened a cohort of 181 BrS and 79 IVF (idiopathic ventricular fibrillation) patients by direct sequencing on all the alternative transcript variants of the Mgol gene. All patients were informative for mutations on the SCNSA, ACNAC1g and GPI6, associated with BrS.
Two different variations, L18F and D133N, have been identified in three unrelated patients. L18F located in a region common to all the three transcript variants of M01g1, has been identified in a BrS patient and in a LVF patient. Variation D133N, identified in a LVF patient, is positioned in the alternative exon 3 of the transcript variant M01g1. Bioinformatic searches have been performed in the single-nucleotide polymorphism database (build 135) and in the National Heart, Lung, and Blood Institute Grand Opportunity Exome Sequencing Project (ESP) for both variations. Mutation L18F has been reported with a very low minor allele frequency (MAF <0.0712%) and mutation D133N has never been reported as variation.

To explore the expression of the alternative transcript variants c, not yet characterized, we performed a RT-PCR using primers specifically designed to amplify the alternative region that allow to distinguish the variant M01g1 from the other two variants M01g1a and M01g1b. Results show the expression of M01g1c in all the 16 tissues, including heart.

Our screening discovered two novel, unreported amino acid variants on M01g1 gene in patients with a BrS or IVF phenotype. These findings also strengthen the role of the novel M01g1c transcript in the human heart and reinforce the hypothesis that M01g1 could play a role in the pathophysiology of BrS and IVF.

A novel mutation affecting the transmembrane domain of the KCNJ2 protein is associated with high prevalence of life-threatening ventricular arrhythmias in a family with Andersen-Tawil syndrome

E. Ferrant1, C. Lundin2, E. Hertesvig2, O. Kongstad3, M. Alders1, P.G. Plataniotis1,1, Lund University Hospital, Lund, Sweden; 2Lund University, Lund, Sweden; 3Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background: Andersen-Tawil syndrome is a rare inherited multisystem disorder associated with mutations in KCNJ2 and relatively low prevalence of ventricular arrhythmias. Our aim was to describe the clinical course of a family, in which the proband survived aborted cardiac arrest (ACA) and genetic screening revealed a previously unknown mutation (c.271_282del12[p.Ala91_Leu94del]) resulting in the loss of four amino acids in the first transmembrane domain of the KCNJ2 protein.

Methods: A cascade family screening was performed in a 5-generation family upon identification of the KCNJ2 mutation in the proband. Subsequently, 10 of 21 screened individuals appeared to be mutation carriers (median age 38 [range 10-75] years, 3 female). Mutation carriers underwent clinical examination including biochemistry panel, cardiac ultrasound, Holter ECG and exercise stress test. Genotype-positive family members were followed-up for a median of 36 months (range 26-48 months).

Results: 1) At baseline, 2 patients survived ACA, 3 had syncope or presyncope attacks and 2 reported palpitations. Exercise-induced non-sustained bidirectional ventricular tachycardia was documented in 4 patients, 2 of whom received implantable cardioverter-defibrillators (ICD) for primary prevention and 2 for secondary prevention. 2) During follow-up, 1 primary prevention and 1 secondary prevention patient received in total 4 adequate ICD shocks. In total, life-threatening ventricular arrhythmias were documented during childhood between 7 and 17 years of age in 5 of 10 mutation carriers. 3) All mutation carriers presented with characteristic mild dysmorphic features. Only 1 patient suffered from periodic paralysis, and 1 had renal dysplasia requiring extirpation at the age of 3. All carriers of the novel variant demonstrated normal serum potassium level at repeated assessments and none had any other extracardiac disease manifestation.

Conclusion: Our findings suggest that the novel KCNJ2 mutation is associated with a predominantly cardiac phenotype of Andersen-Tawil syndrome with high propensity to life-threatening ventricular arrhythmias.

Inherited cardiovascular diseases (ICVDs) in the every day clinical practice: diagnostic yield and genetic family screening

A. Anastassakis1, X. Kotsakia1, N. Protonotarios2, A. Voutilias1, A. Antonakopoulo1, C. Ritalis1, D. Kotsas1, C.H. Stefanadis1, 1Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece; 2University Medical Center of Naxos, Naxos, Greece

Purpose: ICVDs have variable clinical expression and incomplete penetrance. The aim of this study is to identify the diagnostic yield of genetic testing on each disease in every day clinical practice and the response of family members to genetic screening.

Methods: 109 probands were clinically diagnosed with Hypertrophic Cardiomyopathy (HCM), Long QT syndrome (LQTS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), Dilated Cardiomyopathy (DCM-LMNA), Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Brugada syndrome (BrS) and Marfan syndrome (MFS) according to the latest diagnostic criteria for each disease and molecular genetic analysis was performed. Family members (n=210 out of 352 that were invited) of mutation positive probands (n=58) were clinically and genetically evaluated. Available data were used to evaluate the impact of sudden death (SD) on the number of relatives that accepted to be tested.

Results: A pathogenic mutation was identified in 58 out of 109 (52.3%) index cases suffering from the above mentioned ICVDs. In most common ICVDs (HCM, LQTS, ARVC, BrS), the Mut(+) Phen(–) relatives reached an average of 30.2% (Table). We categorized the families on SD-families and non-SD-families regarding the presence or not of SD on their pedigrees. On SD-families, we suggested on 198 relatives to be tested while 130 of them proceeded on genetic screening. Similarly, 80 out of 154 relatives were tested on non-SD-families. Relatives response on genetic screening is strongly stimulated by the presence of a SD case in the family [OR: 1.91 (CI: 1.24-2.96, p:0.003)].

Conclusion: The diagnostic yield coming from ICVD clinic is satisfactory in most of the cases. The experience of a family motivates relatives to accept better the usefulness and the economic burden of genetic family screening. The importance of genetic testing as a prophylactic health approach should be further highlighted.

Long QT3 mice have disrupted sympathovagal balance and in vivo ventricular stimulation does not determine risk of sudden cardiac death, suggesting that a second perturbation may be required

A. Opel1, C. L-H Huang2, A. Grace3, A. Tinker1, 1University College London, The Rayne Institute, London, United Kingdom; 2Physiology Laboratory, University of Cambridge, Cambridge, United Kingdom; 3Cardiovascular biology group, Department of Biochemistry, University of Cambridge, Cambridge, United Kingdom

Purpose: Long QT 3 (LQT 3) is a cause of sudden cardiac death (SCD) by Torsades des points (TdP). SCD often occurs during sleep, rest and bradycardia, suggesting that heightened parasympathetic tone provokes TdP in LQT 3. It is challenging to ascertain the risk of SCD in these patients. We performed in vivo electrophysiological studies (EPS), ventricular tachycardia (VT) stimulation and telemetry in LQT 3 (LKPQ) and wild type (WT) mice, without and with provocation with the muscarnic agonist, carbachol.

Methods: EPS were performed in young (8-week) and old (≥6 months of age) anaesthetised mice with a 1.1F catheter inserted into the right ventricle via the
The effect of corticosteroid, antiarrhythmic agents, and radiofrequency catheter ablation on ventricular tachycardia associated with cardiac sarcoidosis

Y. Naruse1, Y. Sekiguchi1, H. Tada1, T. Machino1, K. Kuroki1, H. Yamasaki1, M. Igashira2, H. Okada2, Y. Yamashita1, A. Konuma1.
1University of Tsukuba, Graduate School of Comprehensive Human Sciences, Division of Cardiovascular, Tsukuba, Japan; 2Musashino Red Cross Hospital, Department of Cardiology, Tokyo, Japan

Purpose: Ventricular tachycardia (VT) and sudden death are commonly observed in cardiac sarcoidosis, however, the clinical impact of a multimodality therapy is still uncertain.

Methods: We enrolled 35 patients (55±12 years, 11 male) who had a diagnosis of sustained VT associated with cardiac sarcoidosis. All patients were initially treated with corticosteroids and antiarrhythmic agents unless they refused to take them. Steroid therapies were started with an initial dose of 30 mg/d day, and the doses were gradually decreased over a period of 6 to 12 months to 5-10 mg/day as a maintenance dose. If the VTs recurred even on the antiarrhythmic and steroid therapy, radiofrequency catheter ablation (RF-CA) was performed. Patients who underwent RF-CA before being medicated, including with corticosteroids and antiarrhythmic agents, were excluded from this study. The clinical impact of both a steroid and antiarrhythmic therapy associated with RF-CA was evaluated.

Results: All patients received antiarrhythmic drugs and 32 patients received steroid therapy. During a 51.37 month follow-up, 22 (65%) patients were free from any VT episodes. The ejection fraction and prevalence of a Gallium-67 uptake were lower in those with VT recurrence than in those without (40.1±12% vs. 54±3%, p=0.005, 22% vs. 9%, p<0.001, respectively). The multivariate Cox regression analysis demonstrated that the absence of a Gallium-67 uptake in the heart was an independent predictor for a VT recurrence under the drug therapy (Hazard ratio, 8.89; 95% confidence interval, 1.86 to 42.43; p=0.01). Thirteen patients who experienced VT recurrences underwent RF-CA. An electrophysiologic study revealed that the mechanism of VT could be classified into 2 subgroups that were Purkinje related VT and scar related VT. The VT-QRS duration was higher in patients who experienced VT recurrences than in those without (6.2±1.4 vs. 5.6±1.0 ms; p<0.001). After a mean follow up of 24±11 months, 6 of 13 patients experienced VT recurrences. The number of induced and sustained VTs was higher in the patients with VT recurrences than in those without (6.2±2.5 vs. 2.7±0.8; p<0.05, 4.0±1.4 vs. 2.0±0.8; p<0.001, respectively). An ROC curve revealed that the number of induced VTs of more than 4 identified VT recurrences after RF-CA for ventricular tachycardia is equal to 63% and specificity of 86%. The mortality data were obtained in the 3 groups: patients with no VT/VF, early (<48h) VT/VF and late (>48h) VT/VF. Of the 7669 patients with ACS, 7369 (96%) had no VT/VF, 166 (2.1%) had early VT/VF and 194 (1.7%) had late VT/VF. Baseline characteristics were significantly different among the 3 groups; with higher number of coronary risk factors and comorbid conditions in the VT/VF groups and notably younger age (mean 60±12 years) in the early VT/VF group.

After adjustment for multiple confounders early VT/VF was shown to be associated with increased risk of in-hospital death (OR=2.8; CI 95% 1.3-5.9), but not with increased post discharge 30-day mortality (OR=0.94; CI 95% 0.12-7.1) or 1-year mortality risk (HR=1.3; CI 95% 0.5-3.2), in contrast, late VT/VF was associated with increased 30-day mortality risk (HR=6.7; CI 95% 1.7-19.15) and a trend for increased 1-year mortality risk (HR=1.9 CI 95% 0.85-4.35).

Conclusions: In this study early VT/VF was associated with increased risk of in-hospital death but not with increased post discharge, whereas late VT/VF was associated with increased risk of 30-day death and a trend for increased 1-year mortality risk.

Changes in NT-proBNP level after successful PVC ablation in patients without structural heart disease: evidence for PVC-induced chronic wall stress

C.F.B. Van Huls Van Taxis, D. Leong, S.R.D. Piers, A.P. Wijmaa, K. Dyrd, V. Delgado, A. Van Der Laar, D.A. Pijnappels, M.J. Schalij, K. Zeppenfeld. Leiden University Medical Center, Department of Cardiology, Leiden, Netherlands

Purpose: NT-proBNP is synthesized in ventricular myocardium in response to increased wall stress. A high, chronic PVC burden has been associated with a reversible cardiomyopathy. However, the majority of patients with symptomatic PVCs presents with only slightly impaired or normal LV function. We evaluated NT-proBNP levels before and after ablation to determine the potential wall stress caused by PVCs in symptomatic patients with slightly impaired or normal LV function.

Methods: Eighty patients (42 male, 481±6y with a LVEF≥50%, referred for ablation (11%); 6% were refractory (2/1 drugs) PVCs, underwent clinical assessment including standardized echocardiography, 24H Holter monitoring and assessment of NT-proBNP before and 3 months after ablation. Symptoms increased in dependence on patients’ fatigue and impaired exercise tolerance. Success ablation was defined as PVC burden reduction of ≥80% on Holter monitoring. Patients were divided into 2 groups according to LVEF prior to ablation: Group 1, slightly impaired LVEF (50-60%); Group 2, normal LVEF (>60%).

Results: Group 1 consisted of 33 patients (41%) and Group 2 of 47 patients (59%). Age (47±17 vs 48±15 y, p=ns), symptom duration (49±64 vs 44±47 months, p=ns), PVC burden (28±14 vs 23±13%, p=ns) and baseline NT-proBNP levels (90±90 vs 124±99 ng/L, p<0.05) did not differ between groups. Ablation was successful in 28 patients in Group 1 (85%) and 41 patients in Group 2 (87%). All patients with PVC burden reduction ≥80% were asymptomatic after ablation. NT-proBNP levels decreased significantly during follow-up (±61ng/L [90±125ng/L], p<0.001 in Group 1 and ±52ng/L [90±76ng/L], p<0.001 in Group 2). In contrast, NT-proBNP levels did not decrease in patients with a PVC burden reduction of <80% in either group.

Conclusions: NT-proBNP levels decreased significantly after successful PVC ablation suggesting that frequent PVCs cause chronic increased wall stress even in the absence of marked LV dysfunction. Increased wall stress may explain symptoms of fatigue and exercise intolerance despite a slightly impaired or normal LV function, and development of a cardiomyopathy in the long term in some patients.
The characteristics of malignant premature extrasystoles originating from right ventricular outflow tract

Department of Cardiology, Ise Red Cross Hospital, Ise, Japan

Premature extrasystoles (PES) originating from right ventricular outflow tract (RVOT) are often observed in patients without structural heart diseases and are generally considered as benign ventricular arrhythmias. However, ventricular fibillation (VF), and/or polymorphic ventricular tachycardia (PVT) are occasionally initiated by the PES. The aim of this study was to clarify how to differentiate malignant (M) PES from benign (B).

Methods: Consecutive 30 patients, in whom radiofrequency catheter ablation was conducted for PES originating from RVOT, were enrolled. Spontaneous VF and/or PVT initiated by the PES were showed in 9 patients (M-gr). Coupling interval, QRS duration, QRS morphology and optimal ablation site of the PES in M-gr were compared with them in the other 21 patients group (B-gr).

Results: There were no differences between M-gr and B-gr in coupling interval (419±0.5ms vs. 448±1.0ms, P>0.05) and QRS duration (165±1.1ms vs. 153±0.15ms, P>0.05). The prevalence of onset on QRS in inferior leads of PES was significantly higher in M-gr than in B-gr (9/9 vs. 3/21, P<0.01). Broad R wave (>150ms in I) was significantly more frequently observed in M-gr than in B-gr (7/9 vs. 1/21, P<0.01). The prevalence of aVR/aVL (the ratio of negative amplitude of aVR to aVL) >1 was not significantly higher in M-gr than in B-gr (7/9 vs. 4/21). PES originated from posterior, left wall in 7 out of 9 patients in M-gr, and 1 out of 21 patients in B-gr (P<0.01).

Conclusion: In conclusion, PES originating from posterior side of free wall in RVOT, with notch in inferior leads and broad R wave in I, frequently initiate VF and/or PVT. Malignant form of PES in RVOT could partially depend on the localization of its origin.

Effect of vagal nerve on the monophasic action potential of ventricular outflow tract

D. Chang, L.J. Gao, S.L. Zhang, Y.L. Xia, Y.Z. Yang. First Affiliated Hospital of Dalian Medical University, Department of Cardiology, Dalian, China, People’s Republic of China

Objective: Vagal nerve may be related with idiopathic ventricular tachycardia (IVT). The present study was aimed to investigate the effect of vagal nerve on the monophasic action potential (MAP) of ventricular outflow tract.

Methods: Eight adult mongrel dogs were involved. Bilateral vagosympathetic trunks were decentralized for stimulation. Metoprolol was given to block sympathetic nervous system. MAP was recorded at the LVOT, RVOT, RVA with or without vagal stimulation (VS) respectively.

Results: MAPD90 (IVT) under VS was shorter than base line (P<0.05). With or without VS, the MAP at RVA were significantly shorter than that at RVOT and LVOT (P<0.05), while MAP of MAPD90 at LVOT was 26ms vs. 438ms (P<0.05), while there was no difference of MAPD90 between LVOT and RVOT (P=0.05).

Conclusions: MAPD90 were significantly shorter under VS than under B, the present study might be related to vagal modulation, which may be related to the occurrence of IVT.

Electromechanical coupling interval: a new marker of PVC in LV dysfunction

Arrhythmia Section, Cardiology Dep. Thorax Institute. Hospital Universitar de Barcelona, Barcelona, Spain

Introduction: Mechanisms responsible of PVC-induced left ventricular (LV) dysfunction are not fully understood. We studied whether the electromechanical coupling interval (EMCI) is a marker of reversible cardiomyopathy. This suggest an association between early irruption of PVC in the preceding mechanical cardiac cycle and the development of LV dysfunction.

Methods: Total, 1744 consecutive STEMI patients were admitted to a Swedish tertiary care hospital for primary PCI during 2007-2009. Clinical characteristics and information about presence of VF were obtained from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions. Medical records were reviewed to determine VF timing in relation to the infarct-related artery (IRA) opening. Clinical and angiographic characteristics were tested for association with reperfusion VF using logistic regression analysis.

Results: Acute IRA occlusion was present in 1127 patients (age 66±12 years, 72% male) at admission, of whom 26 (2.3%) developed VF at IRA opening. Increased risk of VF during reperfusion was observed for aspirin, beta-blockers or digoxin at admission, VF before reperfusion, inferior location of infarct and multivessel disease. In multivariate analyses, only multivessel disease and the use of digoxin remained independently associated with reperfusion VF (Table). Reperfusion VF was not associated with either age, gender, body mass index, history of hypertension, heart failure, diabetes, stroke, PCI, CABG, myocardial infarction, IRA or the presence of left main artery stenosis.

Clinical factors associated with VF during reperfusion in PCI-treated acute STEMI

Conclusions: Multivessel disease and digitalis use at admission independently predict VF at IRA opening in patients with acute STEMI. Our data further support a prosarhythmogenic effect of digitalis in the setting of acute coronary syndrome.

Electroanatomical substrate mapping guidance for left ventricle aneurysmectomy in patients after myocardial infarction

P. Neuzil1, J. Petru1, S. Cerny1, P. Pavel1, J. Skoda1, S. Kralovec1, L. Plevkova1, F. Holý1, L. Sedivá1, V.Y. Reddy2. 1Na Homolce Hospital, Prague, Czech Republic; 2Mount Sinai Medical Center, New York, United States of America

Introduction: Left ventricle aneurysmectomy (LVAR) with peri-infarction cryoablation...
is an effective approach for the treatment of post-MI patients who present with VF.

The purpose of this prospective study was to evaluate the efficacy of catheter-based electroanatomical mapping (EAM) prior to aneurysmectomy to identify the arrhythmogenic substrates as a guide for surgical resection and intervention.

**Method:** We included 35 pts (M/F: 28/7), average age 64 years (38 – 79). Mean LVEF prior the surgery was 23.5% (20-50%) and post MI aneurysms were documented by echocardiography or LV angiography. VT inducibility was confirmed prior to surgery and EAM was performed (CARTO, Biosense-Webster) to identify border zones and late fractionated potentials. The surgeon used the EAM image during surgery; arrhythmogenic zones were eliminated by aneurysmectomy, endocardial resection and cryotherapy. An EP study and EA mapping were repeated – at 3 mo after surgery.

**Results:** In 27 pts we performed LVAR + CAGB, in 5 pts LVAR + mitral valvuloplasty and in 3 pts LVAR + cryoablation. The EF improved significantly to 48%.

The end-systolic volume decreased from 142ml to 93ml. Pre-surgery, VT was inducible in 24 pts (68.5%), but after LVAR only in 4 pts (11%). Post-surgical EAM revealed reduction of late and fractionated potentials. When present, MRI revealed significant scar tissue reduction in all pts.

**Conclusion:** EA mapping prior to LVAR can facilitate arrhythmogenic substrate elimination with significant reduction of VT induction – this minimizes the risk of life threatening arrhythmias.

**Circulating biomarkers of extracellular matrix remodeling are associated with arrhythmic ventricular hypertrophy in heart failure patients**

K. Kelemen1, J.L. Bermejo2, P. Elinghaus3, T. Krahm4, P. Lugenbiel1, R. Becker1, C. Zugck1, A. Bauer4, H.A. Katus1, D. Thomas1, 1University Hospital of Heidelberg, Department of Cardiology, Heidelberg, Germany; 2Institute of Medical Biometry and Informatics, Heidelberg, Germany; 3Bayer Schering Pharma AG, Wuppertal, Germany

**Background:** Ventricular hypertrophy is a major contributor to cardiovascular mortality and morbidity in heart failure (HF) patients. At the molecular level, ventricular remodeling is associated with extracellular matrix (ECM) remodeling. The aim of this study was to assess the correlation between circulating biomarkers of ECM and ventricular tachycardia (VT) or ventricular fibrillation (VF) in heart failure patients who presented with sudden cardiac death after an episode of resuscitated sudden cardiac death. A control group consisted of heart failure patients without ventricular tachycardia/VF.

**Methods and Results:** Blood samples were obtained from 90 HF patients (left ventricular ejection fraction (LVEF) < 30%) with an ICD and 32 healthy volunteers for ECM proteins and CRP as control. Healthy volunteers (LVEF ≥ 60±2%; n = 10) served as control group. C-reactive protein (CRP) did not differ between groups, excluding acute inflammatory response being a potential proarrhythmic trigger. Vascular tachycardia/VF (VT/VF) were assessed using stored ICD electrograms. Increased levels of osteopontin, matrix metallopeptidase (MMP)-2, MMP-7, MMP-9, and N-terminal brain natriuretic peptide (NT-proBNP) were detected in all heart failure patients, whereas circulating tenascin C was reduced compared to healthy controls. With respect to the biomarker levels, ventricular tachycardia (VT) or fibrillation (VF) among heart failure patients were associated with elevated MMP-7 and NT-proBNP levels compared to the heart failure patients without ventricular tachycardia. Considering the best performance of biomarker predicting VT/VF in heart failure patients, logistic regression analysis identified osteopontin and MMP-9 as strongest predictors of HF-associated ventricular arrhythmia after adjustment for gender and β-blocker treatment.

**Conclusions:** Heart failure correlates with elevated circulating biomarkers of extracellular matrix remodeling. Monitoring of plasma osteopontin and MMP-9 may contribute to ventricular arrhythmia risk stratification in HF patients.

**Efficacy of ICD therapy in high-risk children with Long QT syndrome**

R. Ildarova, M. Shkolnikova, V. Bereznitskaya, S. Teremosov. Moscow Institute for Paediatrics & Surgery, Moscow, Russian Federation

Long QT syndrome (LQTS) is an inherited disorder caused by mutations of the genes encoding cardiac ion channels. Affected patients are characterized by increased risk for polymorphic ventricular arrhythmias (PVA), aborted cardiac arrest, and sudden cardiac death (SCD). Beta-blocker therapy is considered the most effective therapy for patients, however it does not protect all patients. An ICD implantation is recommended for patients at high risk for cardiac events, including those who have recurrent syncope despite beta-blocker therapy. The study aimed to describe a single-centre experience in management of patients with severe forms of LQTS treated with ICDs.

**Methods and Results:** The study population consisted of 30 LQTS pts from 29 unrelated families aged from 7 to 32 (mean age 16±5 years; 15 boys) from a broader group of 340 LQTS pts. Genotype was known in 16 pts (53%): 2 had combined mutations, 1 boy had compound mutation in KCNQ1 and 9 pts had single mutations in KCNH2. Mean QTc on resting ECG was 509±36 ms. All pts except one had multiple syncpe before ICD implantation. Mean age at implantation was 12±4 years (from 4 to 18 years). Mean ICD follow-up length after the implantation was 50±18 months. Inefficient beta-blocker therapy was the major or the only indication for ICD in 24 cases (80%). Among the other indications were: high concentration of SCD cases in patients' families (2 cases), severe bradycardia with transient AV block during 24-hours Holter monitoring (3 cases) and aborted cardiac arrest (1 case). During the follow-up, 16 pts (53%) experienced PVA during ICD follow-up; 15 pts. experienced sustained VT treated with ICD shocks; episodes of spontaneously terminated asymptomatic VF were registered in 7 pts., and sustained ventricular tachycardia - in 4 pts. Inappropriate shock (T oversensing) was registered in 1 patient. Among genotypy the greater number of patients were treated with combination of ICDs and beta-blockers (14 pts compared with 11 pts with ICDs alone). In 8 of these 14 pts withHeaderView=""""/>
Takotsubo cardiomyopathy and arrhythmic risk

F. Rotondi, F. Manganelli, F. Candelmo, T. Lanzillo, G. Stancio, F. Allano. Department of Cardiology and Cardiovascular Surgery, Avellino, Italy

Purpose: "Takotsubo" cardiomyopathy (TTC) is a recently described cardiac syndrome, usually triggered by intense emotional and/or physical stress, characterized by transient severe localized left ventricular dyskinesia and changes of ST segment that can mimic acute myocardial infarction, without significant coronary artery stenoses. Although the prognosis is considered good, TTC is associated with significant alterations of the QT interval that could trigger life-threatening cardiac arrhythmias. The aim of our study was to assess the extent of the alterations of the QT interval and the arrhythmic risk associated with this disease.

Methods: From August 2006 to December 2011 we prospectively enrolled all patients with TTC. In order to observe the patient on the first day of hospitalization, the period of TTC was defined as the time between the onset of chest pain or cardiac symptoms and the first 24 hours of hospitalization. The QT interval was calculated using the Bazett formula. The QTc interval was calculated using the Fridericia formula. A T-wave inversion (J waves) was defined as a notched or slurred terminal part of the T-wave ≥ 1.0 mm in > 1 leads. A T-wave inversion of ≥ 2.0 mm was defined as a T-wave inversion ≥ 0.05 mm in > 1 leads. In all patients, ECGs recorded at the time of hospitalization were analyzed for the presence of these clinical characteristics. The incidence of the J-wave potential was compared between groups with and without TTC. Statistical analysis was performed using Student’s t for unpaired data. Results: The QTc interval was significantly shorter (< 0.05) in patients with TTC (543 ± 109 ms) compared to the control group (554 ± 102 ms). Moreover, J waves were present in 60.5% (92/152) of patients who was higher than 16.4% that observed in the age and sex comparable subjects. The mean amplitude of the J wave in the inferior region in 56.5% of patients, followed by the high lateral (33.7%), the left precardial (16.3%) and the right precardial (2.2%) regions. J waves were more frequent in inferior than anterior MI (67.7% versus 55.2%, respectively, P=0.0142).

Conclusions: J waves in the early recovery phase of acute myocardial infarction and its clinical implication

M. Nakayama1, H. Kitazawa2, M. Sato3, M. Okabe1, A. Yamashina1, Y. Aizawa4. Tachikawa general hospital, Cardiovascular Center, nagaoka, Japan. 1Tokyo Medical University, Tokyo. Japan

Purpose: J waves can be arrhythmogenic and to be studied in ischemic heart disease. We studied the prevalence and clinical significance of J waves in the early recovery phase of myocardial infarction (MI).

Methods: In 152 consecutive patients with acute MI, electrocardiogram (ECG) was monitored for one week after coronary intervention for revascularization. The mean age was 68.6±13.5 years, and 78.3% were males. J waves were diagnosed when the amplitude was ≥ 1.0 mm as either notch or slur at the terminal part of the QRS complexes in contiguous 2 or more leads on 12-lead ECG recorded at the end of monitoring for one week. The relationship between the location of J waves and the location of MI and the culprit lesion were determined. Then the ECG parameters and the incidence of arrhythmias were compared between groups with and without J waves. Finally, the rate dependency of J waves was evaluated in the conducted beats of atrial premature beats.

Results: J waves were present in 60.5% (92/152) of patients which was higher than 16.4% that observed in the age and sex comparable subjects. The mean amplitude of the J wave was 0.18±0.09 mm. J waves of the patients in the early recovery phase of MI had a higher incidence of VT/VF, premature ventricular contractions (PVCs) and atrial fibrillation (AF) compared to patients without J waves. The presence of J waves was associated with a higher incidence of VT/VF. Moreover, the presence of J waves was associated with a higher incidence of PVCs and AF.

Conclusions: J waves have a significant impact on the arrhythmic risk of patients after myocardial infarction.
How do female electrophysiologists deal with radiation exposure during pregnancy: Results from the EPIC global survey


Royal Brompton Hospital, London, United Kingdom; 1Cleveland Clinic Foundation, Cleveland, United States of America; 2University Cardiology Group, Cherry Hill, United States of America; 3Municipal Hospital Munich-Bogenhausen, Heart Center, Munich, Germany; 4Arrhythmia Specialist Inc, Walnut Creek, United States of America; 5University of California, San Diego, San Diego, United States of America; 6Uppsala University Hospital, Uppsala, Sweden; 7University of Washington, Seattle, United States of America

Background: Awareness of radiation exposure is variable among different set-
tings of practice in invasive electrophysiology (EP) laboratories around the world.

Methods: As part of a web-based questionnaire on individual practices focusing on radiation exposure during invasive EP procedures, a total of 8 questions were asked specifically at female cardiologists.

Results: A total of 165 physician (50% female) responses were received with the majority of them located in the US (38%), Canada (8%), Italy (7%) and Germany (6%). Nearly 80% of the participants were qualified cardiologists for more than 3 years (45% for more than 10 years). Of the 50 female participants, 18 were pregnant at some time during their time in the catheterization laboratory (5 in the first trimester, 9 between the 2nd and 3rd trimester and 4 in the 3rd trimester). Two thirds of the catheters were continued to work as first-hand operator, or supervised junior colleagues without being directly exposed. Personal protection was used in 6, 9 did wear double layers of lead aprons and 2 used a pro-
tection cabin. Of note is that fetal badges were included in all cases, but only in 2 cases showed higher readings. Female colleagues continue to work up till 6 (4), 4 (3), 2 (3) and less 2 (8) weeks before delivery. The majority of pregnancies went successfully to full-term, but 3 pre-term deliveries at 34, 36, and 36 weeks happened (1 miscarriage at 11 weeks).

Conclusions: This is the first global survey on radiation exposure and protection measures during EP procedure and specifically focused on female cardiologists. While information about specific recommendations for radiation exposure during pregnancy was scarce, all but one pregnancy were successful with the majority of colleagues continuing their clinical work taking some personal precautions such as double leading.

Determinants of immediate intracardiac intervals prolongation after percutaneous aortic valve implantation

J. Segura1, J. Suarez De Lezo1, F. Mazuelos1, P. Martín2, E. Caballero2, M. Paní3, M. Romero1, S. Cjedal4, J. Lopez Aguilera5, A. Medina6.
1University Hospital Reina Sofia, Cordoba, Spain; 2Doctor Negrin University Hospital, Las Palmas, Spain

Percutaneous aortic valve implantation (PAVI) in patients (pts) with aortic stenosis may induce changes in atrioventricular conduction, as assessed by intracardiac electrograms. However, there is little information on factors influencing changes in intracardiac electrograms in pts immediately after CoreValve implantation. The aim of this study was to analyze determinants of immediate increases in surface and intracardiac intervals after PAVI.

Methods: From a total of 160 pts with aortic stenosis undergoing PAVI, we an-
alysed the last 70 consecutive cases who had intracardiac electrograms prior to and 30 minutes after valve implantation. The changes observed were com-
pared with intervals obtained from the surface electrocardiogram (ECG) both before and after 6 years. The mean age was 78.6±8.4 years; 43 (61%) were male. The increases in PR, QRS, AH and HV intervals were defined as the differences be-
tween measurements taken 30 minutes post implantation and at baseline. Also, the increments of AH and HV and HV were correlated with the depth of valve implantation (r=0.53; p<0.001).

Results: There was a significant inverse correlation between the increase in PR interval and the annulus/prosthesis size ratio (r=-0.34; p<0.05). Also, increases in PR, QRS, AH and HV intervals were defined as the differences be-
tween measurements taken 30 minutes post implantation and at baseline. Moreover, transseptal puncture in patients with hypermo-
 bile/aureus interstitial septal myocardial infarction may be challenging with the classical Brockenbrough needle approach. We sought to assess safety and efficiency of a novel device which delivers needle system for transseptal puncture in patients with dif-
cult/risks transseptal access.

Methods: From January 2011, we performed 485 transseptal ablation proce-
dures for atrial arrhythmias. The classical ‘Brockenbrough’ needle approach (71 cm BRK-1, SJM) for transseptal access was applied in all patients under TEE guidance. When the transseptal puncture was met with difficulties, the novel RF-
nneedle (NRG, Baxil, Canada) was used. In pts with right bundle branch block (RBBB) the increment of corrected-HV was signif-
ically higher (p<0.001). Similarly the prolongation of HV was higher in pts with baseline RBBB and left anterior hemiblock (LAHB).

Conclusions: The baseline presence of RBBB and LAHB was a determining fac-
tor influencing the prolongation of HV electrograms immediately after CoreValve implantation. In addition, annulus size, the sinus of Valsalva diameter and annu-
lus/prosthesis size ratio may all influence the increments in intracardiac electro-
grams and PR intervals. These changes do not seem to influence the need for pacemaker implantation.
Epicardial electrophysiologic mapping of ganglionic plexi for concomitant atrial fibrillation

Y. Kobayashi1, M. Ueda1, M. Watanabe2, T. Ichikawa3, G. Matsumiy4, Y. Kobayashi1
1Chiba University Graduate School of Medicine, Department of Cardiovascular Science and Medicine, Chiba, Japan; 2Chiba University Graduate School of Medicine, Department of Cardiovascular Surgery, Chiba, Japan.

Purpose: Ganglionic plexi (GP) are hopeful optional targets for MAZE procedure. This study was aimed to reveal and identify activity of GP by epicardial location.

Methods: Fifteen patients with concomitant atrial fibrillation underwent intraoperative epicardial electrophysiologic mapping in our institution. Autonomic GP were identified by rapid atrial pacing via a temporary pacemaker after removal of fatty epicardial tissues on the surface. A 24-point high-frequency stimulation (1000/min, 18V) was achieved by placing tweezers directly on the left atrial epicardium. Diagram of epicardial mapping locations is shown below. (Picture) Locations where the stimulation resulted in ventricular slowing with doubling of the electrocardiographic R-R interval were identified as active GP.

Results: Active GP were found in 13 out of 15 patients. The incidence of activity by epicardial location is shown below. (Table)

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Figure 1. Diagram of epicardial mapping locations

Conclusion: Active GP could be identified dominantly in the inferior right area in left atrium.

Distribution of delayed potentials on the right ventricular endocardium in patients with late potentials on signal-averaged electrocardiograms due to arrhythmogenic right ventricular cardiomyopathy

T. Kobayashi, S. Kamakura, K. Satomi, T. Noda, K. Miyamoto, Y. Yamada, H. Okamura, T. Alba, S. Yasuda, W. Shimizu. National Cerebral and Cardiovascular Center Hospital, Department of Cardiovascular Medicine, Suita, Osaka, Japan.

Purpose: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive inherited disease characterized by life-threatening ventricular arrhythmias, which is associated with left ventricular dysfunction, and is often linked to desmin protein abnormality. The purpose of this study is to clarify the distribution of delayed potentials (DPs) on the right ventricular endocardium in ARVC patients with ventricular tachycardias (VT) and late potentials (LPs) after QRS segment on the signal-averaged electrocardiograms (SAECG).

Methods: A total of 46 ARVC patients (mean age 50.2 ± 15.8 years, 30 males and 16 females) with sustained or non-sustained VT underwent programmed electrophysiological study. The SAECGs were recorded during sinus rhythm. LPs were defined positive when two of three parameters (total filtered QRS > 120 ms, root mean square voltage of the last 40 ms < 18 micro V and duration of the low amplitude signals in the terminal portion of QRS > 38 ms) were fulfilled and low amplitude signals were noted on SAECG during period consistent with ST segment in simultaneously recorded orthogonal XYZ ECGs. The distribution of DPs, fractionated electrograms, and double-potentials in the right ventricle (RV) evaluated by detailed endocardial mapping (3D electroanatomical voltage mapping and conventional mapping) during sinus rhythm was compared with the outcome of catheter ablation.

Results: Active GP were positive for successful ablation in 37 of 46 patients (80%). DPs were not obtainable in the remaining 12 patients (20%). DPs were located in the RV basal area (100%), particularly in inferobasal wall in 30 patients (81%), RV posterobasal wall in 17 patients (46%), RV lateralbasal wall in 20 patients (54%), anterobasal wall and/or RV outflow tract (RVOT) in 7 patients (19%) and RV basal septum in 8 patients (22%). They were distributed in the RV mid to apical area in only 2 patients (5%, P < 0.01). VT was eliminated by endocardial catheter ablation in 24 (83%) of 29 patients with inducible VT by programmed electrical stimulation. DPs were mainly located in the inferobasal area in 20 (63%) of 24 successful patients. Distribution of fractionated electrograms or double-potentials was not predictable for successful ablation site.

Conclusions: In ARVC patients, DPs were mainly located in the basal RV wall especially in the inferior region around tricuspid valvular annulus. We conclude that catheter ablation following endocardial mapping should be applied first in the RV inferobasal wall in patients with LPs on SAECG.
Mortality and morbidity after cavotricuspid isthmus radiofrequency catheter ablation for atrial flutter: outcomes from a controlled nonrandomized long-term study

L. Fauchier, L. Desprets, N. Clementy, B. Pierre, B. Lallemand, I. Lagренад, S. Taillandier, A. Bernard, D. Babuty. Tours Regional University Hospital, Hospital Trousseau, Tours, France

Cavotricuspid isthmus radiofrequency catheter ablation (CTI RFA) is recommended for typical atrial flutter since it is safe and effective to maintain sinus rhythm, but the long-term outcomes have not been compared with those in patients with other types of atrial arrhythmia and/or other management. This study investigated the outcomes after CTI RFA for atrial flutter, expected to maintain sinus rhythm and possibly to reduce mortality and morbidity.

Methods: We examined the clinical course of 8,962 consecutive patients with atrial fibrillation and/or atrial flutter. The outcomes in 875 patients with CTI RFA for typical atrial flutter (in whom 32% had a pre-ablation history of atrial fibrillation) were compared with those in other patients.

Results: Complete cavotricuspid isthmus block was successfully obtained in 97% of the patients. Median follow-up was 93.4±113.3 days. Death (n=1,125), stroke/thromboembolic events (n=715) or bleeding events (n=791) were recorded in 2,025 of 9,962 patients. Kaplan-Meier analysis showed that patients who underwent CTI RFA had longer survival than other patients (p<0.0001) and higher net clinical benefit (freedom from combined death, stroke, thromboembolic and bleeding events, p<0.0001). Using cox proportional-hazards model, results remained significant after adjustment for age, CHADS2 and HAS-BLED scores, use of cardiovascular medications and other confounders. Patients in the ablation group revealed lower risk of all-cause mortality (hazard ratios [HR] = 0.60, 95% CI, 0.41-0.89; p=0.01) and of bleeding events (HR=0.71, 95% CI, 0.40-0.78; p=0.0007), of stroke/thromboembolic events (n=715) or bleeding events (n=791) were recorded in 7.3 patients (n=1,125), stroke/thromboembolic events (n=715) or bleeding events (n=791) were recorded in 7.3 patients. CTI RFA had longer survival than other patients (p<0.0001). One patient experienced a sinus arrest and recovered spontaneously. Two others were treated with an advanced cardiac life support and were successfully treated by the WCD with single 150 joule shocks. Both patients were unconscious during the episodes, survived acutely, and had ICD re-implanted afterwards.

Conclusion: Atrial flutter with CTI RFA is independently associated with a lower mortality and morbidity as compared with other sustained atrial arrhythmias such as atrial fibrillation.

Predictive value of programmed ventricular stimulation in ischemic cardiomyopathy and dilated cardiomyopathy patients with preserved systolic function

D. Tsitarchis, K.A. Gatzoulis, A. Vouliotis, P. Dilaveris, S. Sideris, P. Assimakopoulos, I. Skidas, I. Kallikazaros, C. Stefanidis. Hippokration General Hospital, Athens, Greece

Purpose: To date, programmed ventricular stimulation (PVS) is not considered as a reliable risk stratifier for primary prevention of sudden cardiac death in patients with structural heart disease and preserved systolic function. The objective of the present study is to investigate the prognostic value of PVS in ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM) patients with left ventricular ejection fraction (LVEF) >40%.

Methods: We followed up for a mean period of 52.4± months 76 patients with ICM and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in the previous month. Stimulation protocol consisted of up to triple extrastimuli and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia.

Results: Sustained nonmonomorphic VT or VF was triggered in 40 cases (30.76% of ICM patients and 10.39% of DCM patients) and subsequently implantable cardioverter-defibrillators (ICD) was implanted in 36/40 of these patients. During the follow-up period, 7 patients died; 2 experienced sudden cardiac death and 5 non cardiac death. Although no difference was observed between patients with VT/VF induction and those without in the incidence of total mortality (10% vs. 4%, log rank p=0.20), the incidence of sudden cardiac death was higher in the former group (13.8%) than in the latter (1.8%; log rank p=0.05), indicating an absolute negative prognostic value of PVS in patients without VT/VF induction.

Conclusion: During long-term follow-up, CTI and ICM patients with preserved systolic function and VT/VF inducibility experienced a significant incidence of appropriate ICD therapy. Additionally, SCD was absent in non inducible patients with structural heart disease. PVS may be considered as a reliable risk stratifier for primary prevention of sudden cardiac death in high risk patients with structural heart disease and preserved systolic function.
Long-term follow-up and predictors of arrhythmic events in the brugada registry of the piedmont region of Italy


1University of Turin, San Giovanni Battista Hospital, Department of Cardiology, Turin, Italy; 2University Hospital San Luigi Gonzaga, Genetics Department, Orbassano, Turin, Italy; 3Saint Andrea Hospital, Department of Cardiology, Veneto, Italy; 4Mauriziano Hospital, Department of Cardiology, Turin, Italy; 5University Hospital San Luigi Gonzaga, Department of Cardiology, Orbassano, Italy; 6University of Turin, San Giovanni Battista Hospital, Medical Statistics Department, Turin, Italy.

Introduction: Brugada syndrome is an arrhythmogenic disease characterized by increased risk of sudden death (SD) and so far the only proven therapy is the implantable cardioverter defibrillator (ICD), although there are some evidence in favor of hydroquinidine. The question of risk stratification in patients with Brugada ECG pattern, especially if asymptomatic, remains still very controversial. The aim of our study is to analyze the long-term prognosis and the role of clinical and electrophysiological risk factors in the Brugada Registry of Piedmont Region in Italy.

Methods and results: Four hundred and eighteen patients with spontaneous or drug-induced type 1 Brugada ECG were enrolled consecutively. 24-h well defined area of Northern Italy. Mean age was 45±14 years; 42% had spontaneous diagnostic ECG; 72% were asymptomatic; 26% had syncope; 1% aborted SD. Prolonged QT interval (QTc) ≤ 480 ms (PES) was performed in 251 patients (60%) and ventricular fibrillation (VF) was induced in 99 (39%). In 158 subjects (63%) PES was performed with up to 2 extrastimuli (protocol A), in 93 (37%) up to 3 extrastimuli (protocol B) and the rate of VF induction was 41% and 37% respectively (p=NS). Ventricular refractory period (VRP) was available in 135 patients and it was > 200 ms in 89, < 200 ms in 46. During a mean follow-up of 48 months the incidence of SD/VF was 3% (0.75% per year) in the whole population, 50% (0.9% per year) in patients with PES, 7% (1.84% per year) in those with sponta neous ECG pattern and 1% (0.25% per year) in the asymptomatic. Predictors of arrhythmic events in the whole population were aS0 (p=0.0001); RR>7; C100%≥75); syncope (p=0.0001; RR=7; C100%≥27) and induction of VF at PES (p=0.0005; RR=17; C195%≥129). When induction at PES with 2 and 3 extrastimuli was considered independently, only induction with protocol A was predictive of events at follow-up (p=0.007). No spontaneous type 1 ECG, nor a VRP > 200 ms were predictive of events. In the asymptomatic no independent risk factors were identified.

Conclusions: In the whole population of Brugada patients of the Piedmont region, syncope and positive PES with up to 2 extrastimuli were the only predictors of arrhythmic events. No predictors of SD were identified in the asymptomatic, mainly due to the low number of events at follow-up.

Electrophysiologic studies/sudden cardiac death

C.M. Malta Hansen1, M. Wissenberg1, P. Weeke1, M.H. Ruwald1, F. Lipper1, G.H. Gislaslon1, S.L. Nielsen1, L. Koeber1, C. Torp-Pedersen1, F. Folke1.

1Copenhagen University Hospital Gentofte, department of cardiology, Gentofte, Copenhagen, Denmark; 2Emergency Medicine and EMS Office, Capital Region of Denmark, Copenhagen, Denmark; 3Mobile Emergency Care Unit, Capital Region of Denmark, Copenhagen, Denmark; 4HighHospital - Capital Region University Hospital, Heart Centre, Copenhagen, Denmark.

Purpose: Increased focus on automated external defibrillators (AED) to be used by lay persons has led to a boost of publicly available AEDs. Nevertheless, little is known about how increased AED dissemination affects AED availability in case of a nearby out-of-hospital cardiac arrest (OHCA).

Methods: All OHCA s in public from 1994 through 2010 and all publicly available AEDs in Copenhagen, Denmark, were geographically located. High-incidence areas of OHCA were defined as those with ≥1 arrest every 2 years, within a 100-m radius. All OHCA s occurring within a 100x100 area were counted as well as the number of AEDs in these areas. A registry of publicly available AEDs, available for the emergency dispatch centers, was established in Copenhagen in 2007.

Results: We identified 114 high-incidence areas of OHCA, accounting for 18.3% (n=376) of the arrests in public. In 2005, 104 publicly available automated external defibrillators were located in the high-incidence arrest sites (however, these were not linked to the emergency dispatch center). By the end of 2010, 399 AEDs available to lay persons and the emergency dispatch center covered 35.1% of all high-incidence arrest sites (Table 1). Consequently, the potential number of patients who could be treated with an AED had grown more than 6 times, from 11 (0.7%) to 91 (4.4%), in the same period.

Conclusion: Initiative for strategic placement of publicly available AEDs has increased coverage of OHCA high-incidence areas substantially, hereby raising the potential number of patients who could be treated with an AED and save additional lives.

Electrocardiogram fails to identify high-risk individuals: analysis of a series of 50 sudden death cases

M. Salar Alcaraz1, P. Penafiel-Verdú1, C. Munoz-Esparza1, J.M. Lopez Ayala1, G. Gonzalez Canovas2, D. Lopez Cuenca3, F. Escudero1, F. Pastor Quirante4, J.R. Gimeno Blanes1, M. Valdes Chavarr1, C.M.H. Malta Hansen1, M. Wissenberg1, P. Weeke1, M.H. Ruwald1, F. Lipper1, G.H. Gislaslon1, S.L. Nielsen1, L. Koeber1, C. Torp-Pedersen1, F. Folke1.

1University of Granada, Department of Cardiology, Granada, Spain; 2University Hospital San Carlos, Cardiology Department, Madrid, Spain; 3University Hospital Reina Sofia, Department of Pathology, Murcia, Spain; 4University of Murcia, School of Medicine, Department of Cardiology, Murcia, Spain.

Purpose: Electrocardiogram (ECG) is an essential and easily available diagnostic test in the management of cardiomyopathies and channelopathies. We aim to explore the value of ECG for the diagnosis of SD.

Methods: ECGs from 50 consecutive cases (age 36±20 years, 36 men), 26 non-sustained ventricular tachycardia and 24 SD patients, were analyzed after the arrhythmia was documented by continuous Holter monitor recording until the clinical diagnosis was achieved. The ECG findings were compared with final diagnosis.

Results: Final diagnoses were hypertrophic cardiomyopathy in 13 patients, Brugada syndrome in 7, long QT syndrome in 4, 3 patients had other cardiomyopathies: catecholaminergic ventricular tachycardia, Chagas cardiomyopathy and dilated cardiomyopathy with coronary artery disease (n=2). After complete study, 13 patients remained with non-conclusive diagnosis. The results of ECG analysis and its relationship with the final clinical diagnosis are shown in Table 1. Of the 50 ECGs analyzed, 29 (58%) were classified as normal or nonspecific. Genetic diagnosis was achieved in 14 individuals, and familial disease was demonstrated in 16 cases.

Association between an invasive strategy involving electrophysiologic study with prophylactic pacing and survival outcomes among adults with myotonic dystrophy type 1 and conduction system disease

K. Wabbi1, C. Meune1, R. Porcher1, H.M. Becane2, A. Lazzeres1, P. Lafrel1, T. Stojkovic1, A. Behin1, B. Eymand1, D. Duboc1, 1AP-HP - Hospital Pitie-Salpetriere, Paris, France; 2AP-HP - Hospital Cochin, Paris, France; 3AP-HP Saint-Louis Hospital, Biostatistics and Medical Information Technology Department, Paris, France; 4InParsy clinical research group, France.

Purpose: Up to 1/3 of patients with myotonic dystrophy type 1 (DM1) die suddenly. No intervention has thus far, effectively prevented sudden death (SD) in DM1. Our objective was to determine whether an invasive strategy (IS) based on electrophysiologic study (EPS) and prophylactic pacemaker insertion if HV interval is >70 ms, prolongs the survival of patients with DM1.

Methods: Between January 2000 and December 2009, the DM1 Heart Registry included 914 patients suffering from DM1 in 1 hospital: Pitie-Salpetriere Hospital. Among 486 patients whose electrocardiogram showed a PR interval >200 ms, a QRS duration >100 ms, or both, we compared overall survival (primary outcome measure) and SD, respiratory death and other deaths (secondary measures) of 341
Cardiac conduction system involvement in patients with steinert's myotonic dystrophy

P-G. Golzo1, E. Pistone1, T. Mongini2, M. Morello1, W. Grosso Marra1, F. Gaia1, 1University of Turin, San Giovanni Battista “Molinette” Hospital, Cardiology Department 1, Turin, Italy; 2University of Turin, Department of Neurology, Turin, Italy

Introduction: Steinert’s myotonic dystrophy (DM1) is an autosomal dominant genetic disease: male/female ratio is 1:1 and an affected parent has a 50% risk of transmitting the disease in each pregnancy. In Europe and North America it is the most common muscular dystrophy (18000 population). Affected patients have a lower life expectancy with an average age of death of 53 years and there is a correlation between the age of onset of dystrophy and age of death: respiratory failure and cardiovascular arrest are the main causes. The cardiac involvement is quite common, especially in the conduction system, which can sometimes cause sudden death.

Patients and methods: From January 2010 to September 2011 at our Centre 39 patients were evaluated with Steinert muscular dystrophy. The inclusion criteria was the confirmation of Steinert’s dystrophy by genetic analysis and clinical examination. Muscle strength with MRS (muscular impairment rating scale).

Results: 39 patients were evaluated: 21 males and 18 females aged between 22 and 73 years. 23.1% (n = 9) presented family history of sudden death, while 17.8% (n = 7) reported idiopathy or syncope. PR: 0.20s was observed in 26% (n = 11) and > 0.24s in 10.3%. A PFR: 0.24s, was shown to be influenced by patients’ age (p = 0.028), disease duration longer than two years (p = 0.02) and five years (p = 0.027), by severe neuromuscular involvement (p = 0.027), assisted walking (p = 0.028), evidence of obstructive lung disease (p = 0.043), presence of Supraventricular Premature Contractions, single (0.040) and couples (0.06) at Holter monitoring. Complete Left Bundle Branch Block was observed in 2 patients, and left anterior fascicular block in four (10.3%). The retrospective analysis of ECGs, disclosed an increase of PR in 20.5% of cases, and widening of QRS in 5.1%. The progression of AV conduction delay was showed to be influenced by sex (p = 0.032) and neuromuscular involvement (0.046). The development of Atrial Fibrillation was recorded in three patients. No significant abnormalities were found at Echocardiography.

Conclusions: We observed that an important involvement of the conduction system in the observed patients trends up to deteriorate quickly. Therefore it is essential that they continue to be assessed periodically. In addition to the ECG abnormalities, also others parameters seems to be associated with an increased risk of sudden death: positive family history, pulmonary involvement and degree of neuromuscular involvement.

P4124

P4124

PCI during prolonged CPR: only patients with survival benefit

G. Simonis, J. Steglich, R.H. Strasser. Dresden University of Technology, Dresden, Germany

Background: Acute myocardial ischemia with consecutive malignant arrhythmias is one major contributor to sudden cardiac death. Urgent revascularization (PCI) is the mainstay of treating ischemia-induced arrhythmias. After a successful cardiopulmonary resuscitation (CPR), consensus exists that patients with myocardial ischemia should undergo urgent PCI. It is, however, not known if in patients with prolonged CPR, PCI during CPR can improve outcomes.

Purpose: In a retrospective analysis from a single center, all patients undergoing PCI during CPR were identified during a five-year period (02/2004-05/2009). The patient characteristics were analyzed and related to the survival of the patients.

Results: 32 patients were subjected to PCI during continued CPR (mean age, 64 ± 15 years). 10 patients died in the IS and 30 in the NIS group. The 9-year survival rate was higher in the IS than in the NIS group (76.7% vs. 70.4%, mean age 67.15 ± 12.3 years). Nearly one quarter (256 cases, 22%) were 55 years or younger and 42% were 65 or younger with a male predominance in the younger groups and a greater proportion of females among those ≥ 75 yrs. Cumulative rates (%) per gender and age-group are shown in Figure. Survival rates to hospital discharge were not significantly different between subjects ≥ 55 and ≥ 55 years (7.5 vs 7.0%, P= 0.7; Fisher’s exact test). The race/ethnicity distribution of the population was Caucasian (63%), African American (9%), Asian (3%), Hispanic (2%), and Other (3%).

Conclusions: The proportion of subjects under age 55 among cardiac arrest victims in the community is substantial and is likely to influence survival outcomes. Especially since younger age does not provide a survival advantage, a continued focus on improved and early risk prediction of SCA is warranted.

Figure 1. Cumulative burden of SCA per age-group

P4125

Circulating microRNAs after cardiac arrest

Y. Devaux1, E. Goretti1, M. Vuasori1, L. Zhang1, D.R. Wagner2, P. Stammel1. 1Centre de Recherche Public - Santé, Luxembourg; 2Hospital Centre, Luxembourg, Luxembourg

Purpose: Prediction of clinical outcome after cardiac arrest is clinically important. While the potential of circulating microRNAs (miRNAs) as biomarkers of acute coronary syndromes is an active field of investigation, it is unknown whether miRNAs are associated with outcome in cardiac arrest patients.

Methods: Twenty-eight patients with cardiac arrest treated by therapeutic hypothermia after cardiac resuscitation were enrolled in this prospective, single centre proof-of-concept study. Blood samples were obtained at 48 hours after cardiac arrest.
Impacts of rewarming speed differences on outcomes of therapeutic hypothermia in out-of-hospital cardiac arrest: is rapid rewarming efficient?

1Sapporo Medical University, 2nd Department of Internal Medicine, Sapporo, Japan; 2Sapporo Medical University, Sapporo, Japan; 3National Center of Neurology and Psychiatry, Tokyo, Japan; 4National Cerebral and Cardiovascular Center Hospital, Department of Cardiovascular Medicine, Suita, Osaka, Japan; 5Nihon University Surugadai Hospital, Tokyo, Japan; 6Shizuoka City Shizuoka Hospital, Shizuoka, Japan

**Background:** Although therapeutic hypothermia (TH) has been reported to improve neurological outcomes of patients with out-of-hospital cardiac arrest (OHCA), procedures of TH remain to be established. Particularly, rewarming speed that maximizes protection afforded by TH has not been identified.

**Methods:** We analyzed data from 408 patients submitted to the multicenter registry of OHCA patients treated with TH from 2005 to 2009 in Japan. The patients were retrospectively divided into three groups according to rewarming speed: 53 patients with rewarming speed 1.0-1.9°C/12 hours (Moderate group), 54 patients with rewarming speed 2.0°C/12 hours (Rapid group), and 301 patients with rewarming speed >2.0°C/12 hours (Slow group). We defined favorable neurological outcomes as cerebral performance category 1 or 2.

**Results:** There was no significant inter-group difference in gender, age, and percents of presence of bystanders, bystander cardiopulmonary resuscitation and ventilator fibrillation in initial ECG. Incidence of return of spontaneous circulation before admission and target temperature were also comparable between the three groups, but the duration of hypothermia at target temperature in the Rapid group was shorter than that in the other groups (28±11 hours for Rapid, 33±12 hours for Moderate, 33±13 hours for Slow, p<0.01). Both the mortality and the rate of favorable neurological outcomes in 30 days were not statistically different in all three groups (Figure 1A, 1B).

**Conclusion:** These results suggest that benefits of TH in terms of mortality and neurological outcomes are not affected by differences in rewarming speeds. TH with rapid rewarming (≥ 2.0 degrees C/12 hours) appears to be as efficient as the other rewarming protocols.

Circadian variation in shockable heart rhythm and survival in out-of-hospital cardiac arrests

F. Folke1, C.M. Hansen2, M.W. Joergensen3, F.K. Lipper1, S.L. Nielsen4, G.H. Gislason5, M.H. Ruwald1, L. Koebel6, J.M. Cruz7, J. Bayler1, J. Engell-Pedersen1, P. Weeke8. 1Copenhagen University Hospital Gentofte, Department of Cardiology, Copenhagen, Denmark; 2Emergency Medicine and EMS, Head Office, Copenhagen, Denmark; 3Mobile Emergency Care Unit, Capital Region of Denmark, Copenhagen, Denmark; 4Rigshospitalet - Copenhagen University Hospital, Heart Centre, Copenhagen, Denmark; 5Rigshospitalet - Copenhagen University Hospital, Cardiology, Copenhagen, Denmark

**Purpose:** Out-of-hospital cardiac arrest (OHCA) frequency is known to have circadian variation, but little is known about whether shockable heart rhythm (VF/pulseless VT) and survival among OHCA patients also show circadian variation. The purpose of our study is to evaluate the circadian variation in shockable heart rhythm and survival.

**Methods:** Data from all patients with OHCA in Copenhagen were collected from 1994-2010 including age, sex, initial heart rhythm and emergency medical system (EMS) response time. Occurrence of shockable heart rhythm and 30-day survival according to time of day were analyzed by logistic regression models, adjusted for sex, age and EMS response time.

**Results:** Of 6,766 patients included, 70.2% suffered OHCA at home. Median age among patients with and without initial shockable heart rhythm was 66 (IQR 55-76) and 73 (IQR 60-82) years, respectively. The median EMS response time was 5.0 minutes (IQR 4.7-7.6). The incidence of OHCA (7 AM to 7 PM) for 43.5% (n=2945), evening OHCA (3 PM to 11 pm) for 27.8% (n=1556) and nighttime OHCA (11 AM to 7 PM) for 16.7% (n=1265). Compared with nighttime, daytime and evening OHCA were positively associated with shockable heart rhythm (OR 1.90, CI 1.57-2.29; OR 1.76, CI 1.45-2.13) and increased 30-day survival (OR 1.62, CI 1.18-2.22; OR 2.06, CI 1.50-2.81), despite a constant EMS response time.

Cardiac screening of first-degree relatives after sudden cardiac death in young population

B. Munoz-Caleiro, A. Recio Mayoral, F. Trujillo, M. Chaparro, L. Gonzalez-Torres, M.J. Valle-Caballero, M.J. Iglesias, R. Hidalgo, J.M. Cruz. University Hospital of Virgen Macarena, Department of Cardiology, Seville, Spain

**Purpose:** Cardiac screening of first-degree relatives after sudden cardiac death could be the first and last manifestation. SCD in the young is a strong risk factor for the presence of inherited cardiac disease in surviving first-degree relatives. Therefore, screening and identification of high-risk subjects could reduce the incidence of SCD. We sought to evaluate the prevalence of disease and diagnostic effectiveness of a cardiac screening of first-degree relatives of patients with premature SCD or aborted cardiac arrest (ACA).

**Methods:** One hundred first-degree relatives of 11 referred families after SCD (n=9) or ACA (n=2) of a family member were analysed. A detailed family history of SCD, electrocardiogram (EGC), echocardiogram, treadmill test and 24 hours ECG-monitoring were performed in all cases. Additional tests were performed depending on the underlying disease, cardiac magnetic resonance imaging (CMRI=6) and electroanatomic voltage mapping (EAVM=6).

**Results:** Causes of SCD were arrhythmogenic right ventricular cardiomyopathy (ARVC=6 cases) and hypertrophic cardiomyopathy (3 cases), all of them confirmed with autopsy. Causes of ACA were Brugada syndrome (n=1) and long QT syndrome (n=1). The cardiac screening led to a diagnosis of 25 high-risk subjects. ECG anomalies were found in 14 subjects and echocardiogram scanned abnormalities in 9. During exercise test 7 subjects developed arrhythmias and 11 arrhythmias were recorded on 24 hours ECG-monitoring. CMRI confirmed or established the diagnosis in 15 relatives and EAVM identified myocardial scar in 4 of 6 patients with ARVC.

**Conclusion:** In our population, a cardiac screening of first-degree family of patients with SCD was found to have a high effectiveness identifying high-risk subjects. Systematic familial study of victims of SCD or ACA with inherited cardiac disease could identify a number of asymptomatic patients who could benefit from early treatment to prevent complications.
Risk factors for sudden cardiac death: Results from the Nordic arrhythmogenic right ventricular cardiomyopathy registry

A.G. Holm1, K.H. Haagaa2, P.G. Platonov3, T. Edvardsen4, L.드립니다5, T. Gills6, O. Eschen7, J. Hansen8, H. Bundergaa9, J.H. Svendsen10, 1Copenhagen University Hospital, Dept. of Cardiology, Laboratory of Molecular Cardiology, Copenhagen, Denmark; 2Oslo University Hospital, Dept. of Cardiology, Oslo, Norway; 3Lund University, Lund, Sweden; 4Sahlgrenska University Hospital, Dept. of Cardiology, Gothenburg, Sweden; 5Aalborg Hospital of the Aarhus University Hospital, Dept. of Cardiology, Aalborg, Denmark; 6Dept. of Cardiology, Gentofte University Hospital, Gentofte, Denmark; 7Righospitalet - Copenhagen University Hospital, Heart Centre, Dept. of Cardiology, Copenhagen, Denmark

Purpose: Risk factors for sudden cardiac death (SCD) in arrhythmogenic right ventricular cardiomyopathy (ARVC) are not clear. We aimed to study this in a registry study of ARVC patients.

Methods: The study was based on a newly started Nordic ARVC registry including patients from centers in Denmark, Sweden and Norway. It was performed as a retrospective cross sectional case control study. The outcome definition was a composite of SCD, aborted SCD, electrical storms or appropriate implantable cardioverter-defibrillator (ICD) shocks. The inclusion criterion was a diagnosis of definite or possible ARVC according to the 2010 task force criteria (TF2010).

The following factors were studied for their association with the outcome: age, gender, history (Hx) of syncope, Hx of atrial fibrillation, inverted T waves in ECG lead V1, right ventricular dilation (RV), right bundle branch block (RBBB), a pathogenic mutation, family Hx of sudden death, inducibility during electrophysiological study, > 500 ventricular premature complexes (VPC) in Holter monitoring during 24 h, ventricular tachycardia (VT), being an competitive athlete, right ventricular dilatation (TF2010), left ventricular ejection fraction (< 50%). All factors were primarily analyzed univariately using logistic regression, if they reached a univariate P-value < 0.05 they were subsequently studied in a multivariable logistic regression model.

Results: The population was comprised of 129 patients of which 57% were male and 71% probands. The median age was 49 (IQR 38-59) years and 73% had a positive family history. Median reactive follow-up was 7 (IQR 0-16) years and during follow up there were 2 patients suffering SCD, 12 suffering aborted SCD, 6 patients suffering an electric storm and 25 patients experiencing appropriate ICD shocks.

Of the tested factors, epsilon waves on the ECG and Hx of VT were found to be univariately associated with the outcome. The other factors were not significantly associated. The odds ratios (OR) from the multivariable model were 3.4 (95%CI 1.29-9.27) for epsilon waves on the ECG and 8.4 (95%CI 1.88-38.6) for Hx VT. They differed only insignificantly from the ones found univariately.

Conclusions: In this registry study risk factors for sudden cardiac death in ARVC we found that a presence of an epsilon wave on the ECG and a history of ventricular tachycardia were associated with the composite outcome of sudden cardiac death, aborted sudden cardiac death, electrical storms and appropriate ICD shocks.
P4134

Copeptin predicts neurological outcomes in out-of-hospital cardiac arrest survivors

P. Ostadal1, M. Frucha2, A. Kruger1, D. Vondrakova1, M. Janotka1, T. Sandvik2, D. Almgren1, J. Hjarne1, S. G. Hales3, J. S. Torp-Pedersen4
1Heart Center, Na Homolce Hospital, Prague, Czech Republic; 2Na Homolce Hospital, Prague, Czech Republic; 3Ares Medical AB, Karlskrona, Sweden; 4Department of Biochemistry, Karolinska Institutet, Stockholm, Sweden

Purpose: Copeptin is a stable endocytotic fragment of the pituitary hormone pro-opiocortin. It is elevated in myocardial injury and death. The aim of this study was to investigate whether copeptin levels could predict neurological outcomes in survivors of out-of-hospital cardiac arrest.

Methods: A total of 360 patients resuscitated from cardiac arrest were included in the study. Copeptin levels were measured in plasma samples obtained from the patients at 30 days. Cerebral Performance Categories (CPC) were used to assess neurological outcomes.

Results: Fifty patients had a CPC score of 1, 50 patients had a CPC score of 2, 30 patients had a CPC score of 3, and 120 patients had a CPC score of 4. Copeptin levels were significantly lower in patients with a CPC score of 2 compared to patients with a CPC score of 1 (P < 0.001).

Conclusion: Copeptin levels are significantly lower in patients with severe neurological dysfunction compared to patients with mild to moderate dysfunction. Copeptin may be a useful biomarker for predicting neurological outcomes in survivors of out-of-hospital cardiac arrest.

P4135

Survivors of sudden cardiac death with depression are not at significantly greater risk of recurrent arrhythmias and death

M. Turgam1, P. Velagapud2, A. Szabo3, A. Visoticky2, A. Koczenh2
1University of Wisconsin-Madison, Department of Medicine, Madison, United States of America; 2Medical College of Wisconsin, Milwaukee, United States of America; 3University of Wisconsin-Madison, Madison, United States of America

Introduction: Depression is a common comorbidity in patients with sudden cardiac death. The objective of this study was to investigate whether depression in patients with sudden cardiac death is associated with an increased risk of recurrent arrhythmias and death.

Methods: The study included patients with sudden cardiac death who were treated with ICD. Depression was assessed using the Beck Depression Inventory. Recurrence of arrhythmias and death were recorded during follow-up.

Results: Of the 257 patients included in the study, 50% had depression. There was no significant difference in the rate of recurrence of arrhythmias or death between patients with and without depression.

Conclusion: Depression in patients with sudden cardiac death is not associated with an increased risk of recurrent arrhythmias or death.

P4136

Detection of pulseless electrical activity by a public access defibrillator using ECG and ICG

1Heart Center, Na Homolce Hospital, Prague, Czech Republic; 2Na Homolce Hospital, Prague, Czech Republic; 3Ares Medical AB, Karlskrona, Sweden; 4Department of Biochemistry, Karolinska Institutet, Stockholm, Sweden; 5Department of Clinical Neurosciences, Uppsala University, Uppsala, Sweden

Purpose: The detection of pulseless electrical activity (PEA) is challenging in the out-of-hospital resuscitation setting. The aim of this study was to evaluate the performance of a public access defibrillator (PAD) in the detection of PEA.

Methods: A PAD with a built-in ECG and ICG was used to detect PEA. The performance of the PAD was evaluated in a simulated resuscitation setting.

Results: The PAD correctly detected PEA in 98% of cases. There was no false positive detection of PEA.

Conclusion: The PAD is a promising device for the detection of PEA in the out-of-hospital resuscitation setting.

P4137

Analysis of the relationship between T-wave alternans and myocardial ischemia diagnosed by gated-SPECT: results of the SPECTACLE study

1New Civil Hospital, Cardiovascular Medico-Surgical Activities, Strasbourg, France; 2New Civil Hospital, Department of Biophysics and Nuclear Medicine, Strasbourg, France; 3GE Healthcare Information Technologies, Freiburg, Germany; 4Insem U970 - Paris Cardiovascular Research Center (PARCC), Cardiovascular Epidemiology-Sudden death, Paris, France

Sudden cardiac death (SCD) occurs each year 50000 patients in France. Coronary artery disease should be responsible for 80% of SCD. There is a need for new predictive markers of the occurrence ventricular arrhythmia, and microvolt T wave alternans (mTWA) seems to be a promising one. The objective of our study was to analyze the relation between T-wave alternans and myocardial ischemia diagnosed by gated-SPECT.

Methods: We analyzed a group of twenty-four out-of-hospital cardiac arrest survivors. All patients were treated by endovascular hypothermia, patients with ST elevation myocardial infarction underwent direct percutaneous coronary intervention. Copeptin levels were measured in blood samples taken at admission using commercially available immunoassay. Neurological outcome was assessed at 30 days according to Cerebral Performance Category (CPC): CPC 1 - no neurological deficit, CPC 2 - mild to moderate dysfunction, CPC 3 - severe dysfunction, CPC 4 - coma, CPC 5 - death.

Results: Fifty patients had a CPC score of 1, 50 patients had a CPC score of 2, 30 patients had a CPC score of 3, and 120 patients had a CPC score of 4. Copeptin levels were significantly lower in patients with severe neurological dysfunction compared to patients with mild to moderate dysfunction. Copeptin may be a useful biomarker for predicting neurological outcomes in survivors of out-of-hospital cardiac arrest.
heart rate increasing during the exercise was correlated with mTWA in recovery phase (r=0.22; p<0.0001). The presence of necrosis zones has influenced mTWA in recovery phase.

To conclude, patients with ischemia in gated-SPECT seem to have a higher mTWA during recovery phase. However myocardial ischemia solely is not sufficient to induce an important mTWA.

**P4138** Improved prognosis after implementation of chest compression device in out-of-hospital cardiac arrest

S.N. Morozov1, S.N. Abdusalamov2, A.Y. Fedorov1, 1Moscow, State University of Medicine and Dentistry, Moscow, Russian Federation; 2Institute of Postgraduate Education of the Federal Medical-Biological Agency, Moscow, Russian Federation; 3M.K. Ammosov Yakkut State University, Yakutsk, Russian Federation

Out-of-hospital cardiac arrest (OHCA) is associated with a poor prognosis. Following European Resuscitation Council Guidelines for Resuscitation 2010, application of several cardio-pulmonary resuscitation (CPR) devices may improve prognosis when used by well-trained providers. The load-distributing band (LDB) device (AutoPulse) was used for chest compressions during CPR. The aim of this study was to assess if there changes improved the outcomes after OHCA before and after implementation of LDB.

**Methods:** The study was carried out in the Emergency Medical Services from 2009 to 2011 based on analyzing 188 emergency call-out reports. Patients were divided into two groups: 83 patients, when LDB device was used during CPR, were included in the first group (CPR-A); 95 patients were included in the second manual CPR group (CPR-M). The primary endpoint was Return of Spontaneous Circulation (ROSC) at scene, but we also recorded survival to hospital admission. Groups were compared using IBM SPSS Statistics 19 software for odds ratio (OR) and relative risk (RR).

**Results:** We found that ROSC increased significantly after implementation of LDB device: 44 (52.6%) out of 83 patients of CPR-A group and 24 (25.2%) out of 95 patients of CPR-M group (OR 2.32). On the other hand the probability of an adverse outcome in the group CPR-M was higher than in patients with CPR-A (RR 1.55). CPR duration median value made: 19.6 min for CPR-A group and 28 min for CPR-M group. Among patients who survived to hospital admission, 28 (33.7%) belonged to CPR-A group, and 17 (17.9%) to CPR-M group. No significant difference was found in age, gender and cause of out-of-hospital cardiac arrest.

**Conclusion:** The implementation of LDB device is associated with improved ROSC and survival to hospital admission after OHCA, therefore it is expedient to apply it in pre-hospital environment.

**P4139** Normal limits of the adult electrocardiogram for ages 16-90 years

P.R. Rijnbeek1, G. Van Herpen1, M.L. Bols2, C.A. Sweeney3, N. Verwey3, J.C.M. Wittersma1, J.A. Kons4, 1Erasmus Medical Center, Department of Medical Informatics, Rotterdam, Netherlands; 2University Medical Center Utrecht, Department of Epidemiology, Utrecht, Netherlands; 3Leiden University Medical Center, Department of Cardiology, Leiden, Netherlands; 4University Medical Center Groningen, Department of Epidemiology, Groningen, Netherlands; 5Erasmus Medical Center, Department of Epidemiology, Rotterdam, Netherlands

**Purpose:** Normal limits for the adult electrocardiogram (ECG) have been determined in many good studies, but they all carry their imperfections: study populations are often small, they do not cover the full range of ages or give data only for one sex, or they focus on only a limited set of parameters. In this study, we established an up-to-date and comprehensive set of clinically relevant normal limits for the adult ECG, covering all ages for both sexes.

**Methods:** The study population included 13,364 by all evidence healthy individuals (ages ranging from 16 to 90 years, 55% men), taken from four population-based studies in The Netherlands. Standard 12-lead ECGs were available for all volunteers. For each lead, we calculated mean derived parameters, absolute and relative RDIs (range of the ages, and the scope of parameters). Our results demonstrate that diagnostic ECG criteria should be age- and sex-specific.

**Results:** We determined age- and sex-dependent normal limits of the adult ECG, exceeding previous studies in various aspects like the size of the study population, the range of the ages, and the scope of parameters. Our results demonstrate that diagnostic ECG criteria should be age- and sex-specific.

**Conclusion:** Our study corroborates many findings of previous studies, but also establishes an up-to-date and comprehensive set of clinically relevant normal limits of the adult ECG, covering all ages for both sexes.
Frontal plane ST-segment and QRS complex abnormalities as predictors of extent of necrosis and left ventricular dysfunction assessed by 3 Tesla cardiac MRI.


Purpose: Some ECG changes are related to left ventricular dysfunction (LVD). Few studies have correlated the ECG findings with cardiac magnetic resonance (CMR). Our purpose was to explore the ability of the ST-segment patterns in the frontal plane compared to established data of the QRS complex to identify LVD and extent of necrosis assessed by 3 Tesla CMR.

Methods: Consecutive patients (pts) referred for 3 Tesla CMR evaluation constituted the study population. A 12-lead ECG was obtained in the same day of the CMR scan. QRS complex duration, abnormal Q waves, and ST-segment morphology (normal=up-slope ST-segment; or abnormal=ST-despersion or down-slope ST-segment) on leads DI or DII (the one with the largest R wave) and aVF leads were studied. These leads were selected due to the usual projection of the QRS complex and ST-segment, and to evaluate the usefulness of this simplified methodology. For detection of the presence and extent of infarcted myocardium, a breath-hold, T1-weighted, contrast-enhanced inversion-recovery segmented gradient echo sequence was used. Late gadolinium enhancement (LGE) images were acquired, 12 leads were selected due to the usual projection of the left bundle branch (LBB) and right bundle branch (RBB). These leads were selected due to the presence of a left-to-right frequency gradient.

Results: Seventy consecutive patients, 48 male, mean age 64±15 years, were included. The most common indication for CMR was coronary artery disease and chronic valvular disease. Thirty four pts had LVD and 44 pts had LGE. QRS duration was longer in pts with LVD as compared to patients with preserved LV function (114±27 ms vs. 97±19 ms, p<0.001). Overall, abnormal Q waves and ST-segment abnormalities had lower LV ejection fraction (43±18% vs. 56±12%, p<0.001) and larger segments of necrosis (5.4±3.5 vs. 1.5±2.2, p<0.001) than pts with normal II-II ST-segment. For LVD detection, QRS>110 ms odds ratio was 7.14 (95% CI 2.09-28.6), abnormal Q wave was 5.92 (95% CI 1.81-20.1) and abnormal ST-segment on DII was 6.82 (95% CI 2.08-23.3).

Conclusions: The current hypothesis generating study demonstrates for the first time that chronic ST-segment abnormalities on DII are strongly related to LVD and to the extent of myocardial necrosis as assessed by CMR.

A left-to-right interatrial frequency gradient during aﬁbrillation can be detected using standard 12-lead ECG

F. Holmqvist1, I. Nault1, J. Carlson2, M. Hocini3, M. Haassaguerre1, 2, F. G. Platzer4. 1 Lund University Hospital, Lund, Sweden; 2 University Hospital of Bordeaux - Hospital Haut Leveque, Department of Cardiology, Bordeaux-Pessac, France; 3 The Center for Integrative Electrophysiology at Lund University (CIEL), Lund, Sweden; 4 Lund University Hospital, Department of Arrhythmias, Lund, Sweden.

Introduction: The presence of an interatrial frequency gradient may be used to guide catheter ablation of atrial fibrillation (AF). In the 12-lead ECG, Lead V1 has a left-to-right frequency gradient.

Methods: Nineteen recordings from 13 patients (mean age 61±10 years, 11 male) undergoing catheter ablation of persistent AF were studied. Standard 12-lead ECG was recorded simultaneously with electrograms from the right and left atrial appendages. AF frequency spectra were calculated from all 12 leads using spatiotemporal QRS cancellation and Welch periodogram.

Results: Mean left and right atrial appendage fibrillatory frequency was 5.6±1.2 and 5.5±1.5 Hz respectfully (p<0.05 for all cases). Indeed, pts with chronic DI-DII ST-segment abnormalities had lower LV ejection fraction (43±18% vs. 56±12%, p<0.001) and larger segments of necrosis (5.4±3.5 vs. 1.5±2.2, p<0.001) than pts with normal DI-II ST-segment. For LVD detection, QRS>110 ms odds ratio was 7.14 (95% CI 2.09-28.6), abnormal Q wave was 5.92 (95% CI 1.81-20.1) and abnormal ST-segment on DII was 6.82 (95% CI 2.08-23.3).

Conclusions: The current hypothesis generating study demonstrates for the first time that chronic ST-segment abnormalities on DII are strongly related to LVD and to the extent of myocardial necrosis as assessed by CMR.

Epicardial cooling increases opportunity of spiral wave termination: a simulation study

S. Inada1, T. Ashihara2, R. Haraguchi2, T. Arafun2, I. Sakuma3, M. Yamazaki2, H. Horjo1, I. Kodama2, K. Nakazawa1. 1 National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan; 2Shiga University of Medical Science, Otsu, Japan; 3The University of Tokyo, Graduate School of Engineering, Tokyo, Japan; *Nagoya University, Research Institute of Environmental Medicine (RIEM), Nagoya, Japan

Purpose: Ventricular fibrillation (VF) is the major cause of cardiac death. There are many studies to investigate the mechanism to generate and maintain VF. However, the mechanism has not been clearly clear until yet. During VF, spiral wave rotate around a line of phase singularly called filament. Recently, increased opportunity for self-termination of VF under moderate hypothermia was demonstrated in this study, we investigated the possibility of VF termination in a cooling heart using computer simulation.

Methods: We performed computer simulations to observe the behavior of spiral wave propagation. The left and right ventricular slab models were designed to reflect part of the ventricular wall with a thickness of 10 mm and 5 mm, respectively. The ventricular walls were composed of discrete myocardial units: 10 million units for left ventricle and 5 million units for right ventricle. The membrane kinetics in the simulated myocardium was represented by modified Luo-Rudy equations, which can simulate the effects of myocardial cooling. Electrical heterogeneity and rotational anisotropy through the ventricular wall were also incorporated into the model. Spiral waves were generated using an S1-S2 cross-field stimulation. Then, we simulated spiral wave reentry using normothermia (37°C), moderate hypothermia (32°C), and severe hypothermia (27°C) heart model.

Results: The spiral wave filament, expressed as a continuum of phase singularities, within the ventricular wall were stable, and therefore the spiral wave reentry sustained. In the case of global myocardial cooling, prolongation of action potential duration (APD) and reduction of conduction velocity were mainly observed. In addition, fluctuations in the filament were increased with time, and finally the spiral wave reentries were terminated. This might be due to heterogeneous increase in the APD through ventricular wall.

Conclusion: To improve the possibility of terminating VF, we additionally simulated the effects of epicardial cooling on spiral wave behavior. When we set the linear gradient of myocardial temperature from epicardium (32°C) to endocardium (37°C), spiral wave reentry was terminated. This study demonstrated epicardial cooling due to disappearance of phase singularities on epicardial surface earlier.

Conclusion: Our simulation results suggest that heterogeneous myocardial cooling from the epicardial surface can increase the opportunity of self-termination of VF.

Role of new task force ECG criteria in the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomopathy


Introduction: Former ECG signs included in the Task Force Criteria 1994 (TF94) for diagnosis of arrhythmogenic right ventricular dysplasia/cardiomopathy (ARVD/C) were replaced by new criteria in 2010 (TF10) that excluded the age of the probands (12 to 14 years), the extension and distribution of repolarization abnormalities in the precordial leads and the presence of intraventricular conduction abnormalities. For example, epsilon waves were typical major criteria TF94 did not include major repolarization signs, and with the TF10, 38% of the patients, whereas TF10 major depolarization signs (epsilon waves) were present in 31% of the patients. Repolarization ECG signs were present in 20% of patients, whereas TF10 major repolarization signs (epsilon waves) were present in 31% of the patients.

Methods: We have analyzed the ECG TF10 in 47 patients with ARVD/C (66% male, 55±15 years) and compared them with the previous TF94. All of them had a complete 12-lead ECG at diagnosis, without previous antiarrhythmic drugs or ion disturbances. None of them were under pacemaker therapy. ECG findings were divided into major and minor repolarization and depolarization signs according to TF criteria.

Results: The ECG was abnormal in 86% of the patients. All of them were on systolic (mean PR interval 177±20 ms). Mean duration of the QRS complex was 107±27 ms (46% had a QRS width >110 ms, 7% an incomplete RBBB and 47% a complete RBBB). Epsilon waves were present in 23% and in a terminal S-wave >55 ms in 13% of the patients. Distribution of negative T waves in the precordial leads in the absence of RBBB was: V1-V3 (32%), V1-V3 and beyond (6%), V1-V2 (4%), and 47% had negative T waves in V1-V4 with RBBB. In 11% of the patients there were no repolarization abnormalities. TF94 major depolarization signs (epsilon waves or QRS>110 ms) were fulfilled by 51% of the patients, whereas TF10 major depolarization signs (epsilon waves) were present in 23% of them (p<0.05), and 6% had a left-to-right frequency gradient of 0.7 Hz and the one false negative had a left-to-right gradient of exactly 1.0 Hz.

Conclusion: Patients in AF with a clinically significant left-to-right atrial frequency gradient can be identified using spatiotemporal QRS cancellation and time frequency analysis of standard 12-lead ECG. This enables improved noninvasive patient characterization that, in future studies, may prove useful in selecting patients for catheter ablation of AF.
with the TF10. These results may improve the diagnosis of the disease, especially in minor or incipient forms and in relatives

**P4146 Role of home monitoring in effective device management of patients with implantable cardiovascular-defibrillators: a prospective randomized trial**

O. Osner1, A. Bulva2.
1 Regional Hospital, Department of Cardiology, Ceske Budejovice, Czech Republic; 2 Faculty of Health and Social Studies, University of South Bohemia, Ceske Budejovice, Czech Republic

**Introduction:** Telemedicine attracts the attention of health care providers and payers due to possibly increased safety and cost-effectiveness issues.

**Objective:** Comparison of the standard approach in the outpatient follow-up after implantation of cardiovascular-defibrillator (ICD) with the remote follow-up using the access to the Home Monitoring® (HM) service (BIOTRONIK) with respect to workload, efficiency and safety in ambulatory care.

**Methods:** 198 patients (67.12 years, 81% men) with newly implanted dual or single chamber ICD (165/35) were followed prospectively. One-third represented patients with primary prevention indications. Mean follow-up was 626±215 days. Patients were randomized to standard outpatient management (HM-) group and remotely monitored group (HM+). We evaluated regular outpatient visits, emergency visits, delivered shock therapy, and their adequacy and hospitalization associated with the ICD. Geographical data and availability of the access to the cardiology department were also analyzed.

**Results:** Both groups of patients were comparable with respect to the demographic data, clinical data and parameters of the ICD with significant difference only in the representation of single and dual chamber devices between the groups. Almost two-thirds of the total 621 outpatient controls were carried out in the HM- group. The number of planned inspections decreased by more than 40% in the HM+-group, but the number of extra controls with the physician assistance called upon the inspection of HM messages significantly increased. Mortality did not differ significantly in both groups as well as the number of hospitalized patients and patients with delivered shock therapy. The proportion of inadequate shocks, however, was significantly reduced in the HM+ group.

**Conclusion:** Home Monitoring system proved to be effective in reducing the number of planned visits and the proportion of inadequate shock therapy with no impact on the overall mortality in our patient group. Patients with poorer accessibility of the adequate medical management tend to prefer to be monitored remotely.

**IN-STENT-RESTENOSIS AND INVASIVE CORONARY IMAGING**

**P4147 Higher stroke rate in patients undergoing elective PCI for in-stent-restenosis in clinical practice in Europe: Results from the EHS PCI registry**

1 Herzcentrum Ludwigshafen, Institut f. Herzinfarktforschung Ludwigshafen an der Univ. Heidelberg, Ludwigshafen am Rhein, Germany; 2 Herzcentrum Ludwigshafen, Ludwigshafen, Germany; 3 Institut f. Herzinfarktforschung Ludwigshafen an der Universitat Heidelberg, Ludwigshafen, Germany; 4 Kerkhoff Clinic, Department of Cardiology, Bad Nauheim, Germany

**Background:** Although in-stent-restenosis (ISR) decreased due to better techniques, we expect significant numbers of patients suffering from ISR due to the increased overall number of PCIs. Little is known about the treatment details of ISR in elective PCI in clinical practice in Europe.

**Methods:** Between 2005 and 2008, 47 407 consecutive patients undergoing PCI were enrolled in the PCI-Registry of the Euro Heart Survey to document patient characteristics, PCI details and hospital complications. We examined the differences in treatment of ISR versus de novo lesions in elective PCI.

**Results:** A total of 22 917 patients underwent elective PCI, in 1 885 (8.0%) had ISR. Patients with ISR were younger, more often male, more often had prior MI or CABG and diabetes. They were more likely to receive unfractionated heparin rather than LMWH. No differences were found for the use of GP IIb/IIIa blockers, while bivalirudin was more frequently administered in patients with ISR. Patients with ISR got stents in 75%, of which 3/4 were DES. In patients with de-novo lesions, 95.4% received stents, with 48.3% DES. There were no differences in hospital mortality between both groups, however death/MI Stroke was significantly higher in patients undergoing PCI for ISR (1.4% vs 0.9%).

**Conclusions:** Patients undergoing elective PCI for ISR were younger and had more co-morbidities. They more often received DES. In hospital complications were low, however the rate of death/MI/stroke was higher in ISR mainly due to a higher rate of stroke.

**P4148 The optimal strategy for restenosis with stent fracture after drug-eluting stent implantation: 1st generation DES vs. 2nd generation DES**


**Background:** Stent fracture is related to restenosis after drug-eluting stent (DES) implantation. As percutaneous coronary intervention (PCI) advances for complex lesions increased, those for stent fracture-related restenosis also increased. However, the optimal PCI strategy for such restenosis remains unclear. We compared the results of PCI with 1st generation DES (sic) and paclitaxel eluting stent) and 2nd generation DES (zotarolimus-eluting stent, everolimus-eluting stent, biolimus-eluting stent) for restenosis with stent fracture after DES implantation.

**Method:** From November 2002 to December 2010, 8797 patients with 11467 lesions underwent DES implantation successfully. Of these, 9239 lesions were angiographically followed after 6 to 8 months (midterm f/u) and 6682 were followed at 12 months after midterm f.u. Stent fracture occurred at 471 lesions (4.7/329, 5.0%) and that with restenosis occurred at 212 lesions. Of these 212 lesions, target lesion revascularization (TLR) by PCI with 1st generation DES or 2nd generation DES was performed on 73 lesions.

**Results:** Data are shown in the table. At midterm f/u, the rates of restenosis and TLR were significantly lower after restenting with 2nd generation DES than with 1st generation DES.

**Conclusions:** Restenting with 2nd generation DES could be an acceptable treatment for restenosis with stent fracture after DES implantation.

**P4149 Coronary flow velocity and fluid shear stress predict late catch-up after sirolimus-eluting stent implantation**

H. Hikita1, S. Kuroda1, Y. Osakada1, N. Kawaguchi1, D. Akiyama2, T. Sugiyama1, T. Kamishii1, S. Kimura1, A. Takahashi1, M. Isobe1, 1 Yokosuka Kyosai Hospital, Cardiovascular Center, Yokosuka, Japan; 2Tokyo Medical and Dental University, Department of Cardiology, Tokyo, Japan

Recent studies have suggested the possibility of late catch-up after sirolimus-eluting stent (SES) implantation. This study sought to assess predictive values of coronary flow velocity and shear stress throughout the vessel for angiographic late catch-up after SES implantation.

**Methods and Results:** A total of 520 study patients (age 66±11, mean±SD, men n=345, women n=175) with stable angina underwent successful implantation of SES for de novo lesions located in native coronary vessels and underwent follow-up coronary angiography (CAG) 6–9 months later (midterm restenosis defined as more than 50% diameter stenosis) and 1–3 years later (late catch-up defined as more than 50% diameter stenosis). The patients were followed up for at least 3 years. The TIMI frame count method and quantitative digital angiographic analysis were performed based on the post-stenting angiogram. Coronary flow velocity (CFV; vessel length/TIMI frame count/15) and Reynolds number (an index of shear stress: velocity×diameter×density/viscosity) were measured. The study patients included the Midterm Restenosis group with 30 patients, the Late Catch-up group with 16 patients and the Non-Restenosis group with 474 patients. There were no significant differences between the 3 groups with respect to age, gender, location of target vessel. The Midterm Restenosis and Late Catch-up groups indicated significantly lower CFV and lower Reynolds number than did the Non-Restenosis, while CFV and Reynolds number were not different between the Midterm Restenosis group and the Late Catch-up group (CFV: 142.7±37.6a mm/sec (Midterm Restenosis) vs 156.0±42.6b (Late Catch-up) vs 253.4±82.4c (Non-Restenosis), ANOVA p<0.001, Reynolds: 109.0±38.4a (Midterm Restenosis)}
Virtual histology intravascular ultrasound comparison of neointimal morphology of in-stent restenosis with drug eluting stents versus bare metal stents

S. Fujita, S. Sakurai. Department of cardiology, Tokushima, Japan

Background: The process of in-stent neointimal hyperplasia (NIH) between drug-eluting stents (DES) and bare metal stents (BMS) might be different. We compared the composition of in-stent NIH between BMS and DES using Virtual Histology Intravascular Ultrasound (VH-IUS).

Methods and Result: VH-IUS was performed in 63 patients (BMS 40 and DES 23) who underwent coronary revascularization because of in-stent restenosis. The region of interest was placed between the luminal border and the inner border of the struts. NIH tissue composition was reported as percentages of NIH area: percent fibrous (%F), percent fibrofatty (%FF), percent necrotic core (%NC), percent dense calcium (%DC). Mean follow-up times between stent implantation and VH-IUS were 334 days for BMS treated lesions and 694±822 days for DES treated lesions (n.s.). At the sites of stent distal edge, stent proximal edge and in-stent minimum lumen area, %NC volume was higher in DES than in BMS (74±12% vs. 70±13%; p=0.016), whereas %DC volume was higher in DES than in BMS (11±5% vs. 8±6%; p=0.02).

Conclusion: VH-IUS analysis demonstrated that the composition of NIH was different between DES and BMS, suggesting that the process of in-stent NIH in DES and BMS is diverse.

In-stent-restenosis and invasive coronary imaging

P4150

Predictors of neointima hyperplasia in in-stent restenosis

M. Popovic, I. Popovic, S. Kostin, V. Cobet, V. Ivanov, N. Cibicaru, I. Cibicaru, Institute of Cardiology, Chisinau, Moldova, Republic of Moldova

Objective: The expression and quantity of microRNA/145, protein modifications of extracellular matrix in in-stent restenosis as well as of circulating levels of some principal inflammatory markers.

Material and methods: The expression and quantity of microRNA-145 (muscle cell phenotype marker), metalloproteinase 2 (MPT2) and its specific tissue inhibitor (TIMPT2), fibrillar collagen type I content were assessed in media and neointima of the arterial segment belonged to bare-metal restenosis taken from 111 patients using following methods: hybridization in situ, confocal microscopy, immunofluorescent microscopy with specific monoclonal antibodies, PCR in real-time. In the blood of 22 patients made ISR averages after 6 months since angioplasty were determined concentrations of TNF-alpha, IL-1, IL-6, C reactive protein (CRP) and lipoprotein associated phospholipase A2 (Lp-PLA2) using ELISA method and PLAC-test, outcomes being compared with indices obtained from 33 patients without ISR (control series).

Results: The in-stent restenosis evolution has been associated with microRNA/145 expression decrease by up 90% in coronary media, correlatively to ISR degree and to number of smooth muscle cell with secretory (synthetic) phenotype sentences migrated and accumulated in neointima. Extracellular matrix reorganization in ISR was basically due to fibrillar collagen I degradation, and the denaturated collagen progressively accumulated in media and neointima, a process accompanied by external elastic lamina perforation. To be noted a significant rise (until 4-times) of MPT2 quantity while TIMPT2 content respectively reduced leading to a marked MPT2/TIMPT2 ratio elevation. Development ISR after 6 months since angioplasty is underlined by a potentiated inflammation inasmuch blood proinflammatorycytokines and CRP levels were higher than control pattern by 28-52%. Endothelium inflammation marker, Lp-PLA2, rose above control value by 42%.

Conclusions: 1) The expression and quantity of smooth muscle cell phenotype marker, microRNA-145, are reduced in media of ISR artery, that correlated with neointimal hyperplasia level. 2) Extracellular matrix reorganization in ISR is triggered by fibrillar collagen I degradation, and the denaturated collagen progressively accumulated in media and neointima, which facilitates the cell migration and neointima hyperplasia. 3) Negative coronary remodeling associating ISR is link to inflammation activation exhibited by significant increments of TNF-alpha, IL-1, IL-6, CRP, and Lp-PLA2 in the blood, which can be estimated as predictors of risk of the stent re-occlusion.

P4151

Changes in early cardiac gene transcript levels in peripheral blood mononuclear cells after percutaneous coronary intervention and their relationship to restenosis

J.E. Kontaraki, G.E. Kiochadaki, M.E. Marketou, N.E. Igoumenidis, P.E. Vardas. University of Crete, Faculty of Medicine, Molecular Cardiology Laboratory, University Hospital of Heraklion, Department of Cardiology, Heraklion, Greece

Purpose: Early cardiac genes such as myocardin, GATA4 and Nkx2.5 play a role in both embryonic cardiovascular development and adult cardiovascular disease. In peripheral blood they are expressed in circulating bone marrow derived cardiac progenitor cells which are of the mesenchymal cell type. The impact of circulating cardiac progenitor cells expressing early cardiac genes on in-stent restenosis has not been investigated. We evaluated transcript levels of the early cardiac genes myocardin, GATA4 and Nkx2.5 in peripheral blood mononuclear cells (PBMCs) in relation to in-stent restenosis after percutaneous coronary intervention.

Methods: Thirty one patients (aged 65.9±8.9 years) with stable angina who underwent percutaneous coronary intervention (PCI) and were randomized to drug eluting stents (DES) or bare metal stents (BMS) were participated. Follow-up coronary angiography was performed 3-9 months later. Blood samples were taken before and 48h after stent implantation. Gene transcript levels were determined by quantitative real time reverse transcription PCR.

Results: Significant negative correlations were found between transcript level changes expressed as fold induction 48h after stent implantation of myocardin (r=-0.6 for BMS and r=-0.4 for DES; p=0.021), GATA4 (r=-0.4 for BMS and r=-0.5 for DES; p=0.045) and Nkx2.5 (r=-0.4 for BMS and r=-0.2 for DES; p=0.045) in PBMCs of patients with in-stent restenosis. In patients without significant restenosis, defined as luminal diameter stenosis of ≤50% on follow-up angiography (n=17), were found to be upregulated (r=0.4 for BMS and r=0.5 for DES; p=0.045). Although differences in mean transcript levels of myocardin, GATA4 and Nkx2.5 were found to be significant, they did not correlate with clinical outcomes.

Conclusions: Early cardiac gene transcript levels in PBMCs 48h after bare metal or drug eluting stent implantation do not correlate with the development of in-stent restenosis.
No harmful effect of stem cell mobilization by granulocyte-colony stimulating factor on restenosis or late luminal loss after sirolimus-eluting stent implantation.

**Purpose:** We evaluated the effects of stem cell mobilization by granulocyte-colony stimulating factor (G-CSF) on neointimal growth after sirolimus-eluting stent (SES) implantation.

**Methods:** The present double-blinded randomized placebo-control study that primarily evaluated the effect of stem cell mobilization by G-CSF on endothelial function after SES implantation assigned patients to the G-CSF group (n=50) or the placebo group (n=50). After successful SES implantation, patients received subcutaneous injection of G-CSF (300 mg daily) or saline for 5 days. Follow-up angiography was performed 9 months after SES implantation.

**Results:** Plasma CD34+ cell level did not differ between the 2 groups at baseline (0.94±0.55 vs. 0.93±0.68; p = 0.96). It significantly increased after G-CSF injection (0.94±0.55 vs. 1.89±1.35; p < 0.001) but did not in the placebo group (0.93±0.68) vs. 1.35±2.36; p = 0.22). Follow-up angiography was performed in 41 patients (82%) at 292.0±22.6 days in the G-CSF group and 46 patients (92%) at 287.0±10.3 days in the placebo group (p = 0.14 and p = 0.18 respectively). No death or myocardial infarction was observed in the study participants during follow-up. There was no significant difference in restenosis rate between the 2 groups (0.0% vs. 6.5%; p = 0.10). Late luminal loss was not significantly different (0.17±0.25 mm vs. 0.30±0.36 mm; p = 0.06). Regression analysis showed no significant correlation between plasma CD34+ cell level after study drug injection and late luminal loss at follow-up (r = -0.14, p = 0.21).

**Conclusion:** Stem cell mobilization by G-CSF does not increase restenosis or late luminal loss after SES implantation.

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**Table 1**

<table>
<thead>
<tr>
<th>Lesions</th>
<th>SES</th>
<th>PES</th>
<th>ZES</th>
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<tr>
<td>169</td>
<td>75</td>
<td>20</td>
<td>74</td>
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<tr>
<td>RVD (mm)</td>
<td>3.0±1.58</td>
<td>3.0±1.63</td>
<td>3.14±0.47</td>
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<td>MLD pre (mm)</td>
<td>0.91±0.58</td>
<td>0.85±0.60</td>
<td>0.72±0.72</td>
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<tr>
<td>MLD goal (mm)</td>
<td>2.67±0.65</td>
<td>2.71±0.59</td>
<td>2.79±0.47</td>
<td>2.82±0.46</td>
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<tr>
<td>MLD follow-up (mm)</td>
<td>1.98±0.87</td>
<td>1.98±0.77</td>
<td>1.92±0.60</td>
<td>2.15±0.81</td>
</tr>
<tr>
<td>% Stenosis pre</td>
<td>69.9±17.7</td>
<td>72.1±18.7</td>
<td>77.1±22.3</td>
<td>75.1±18.5</td>
</tr>
<tr>
<td>% Stenosis post</td>
<td>14.5±7.9</td>
<td>14.4±8.2</td>
<td>15.1±11.0</td>
<td>15.6±7.7</td>
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<tr>
<td>% Stenosis follow-up</td>
<td>36.7±24.7</td>
<td>36.8±22.9</td>
<td>41.1±22.0</td>
<td>30.9±22.9</td>
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<tr>
<td>Acute gain (mm)</td>
<td>1.76±0.61</td>
<td>1.86±0.69</td>
<td>2.06±0.46</td>
<td>1.86±0.58</td>
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<tr>
<td>Late loss (mm)</td>
<td>0.70±0.08</td>
<td>0.81±0.01</td>
<td>0.96±0.84</td>
<td>0.47±0.69</td>
</tr>
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</table>

RVD: reference vessel diameter; MLD: minimal lumen diameter. *p > 0.05 vs. SES, PES, ZES.

**Conclusion:** EES might be superior to other drug-eluting stents in angiographical results of hemodialysis patients.

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**Severe insulin resistance is a predictor of restenosis after drug-eluting stent implantation**

Y. Yufu, Dokkyo Medical University Koshigaya Hospital, Koshigaya-city, Japan.

**Introduction & Hypothesis:** Percutaneous coronary intervention (PCI) is an effective treatment for patients with ischemic heart disease; especially, restenosis is suppressed after drug-eluting stent (DES) implantation. The aim of this study was to clarify the factors associated with coronary restenosis after DES implantation. We evaluate the homestasis model assessment of insulin resistance (HOMA-IR) index as a predictor of restenosis. We researched the clinical records of 258 patients who had been subjected to elective PCI and DES implantation between May 2007 and December 2010. We evaluated these patients by the value of HOMA-IR, and examined the relationship between restenosis and HOMA-IR.

**Results:** The overall restenosis rate was 14% (37/258). HbA1c levels were no difference between positive and negative of restenosis. But positive of restenosis was significantly greater than negative of restenosis (7.17±6.32 vs 5.47±9.94, p=0.008) in HOMA-IR index. We distributed three groups by value of HOMA-IR (less than 2.5; n=115, 2.5 to 5.0; n=56, over 5.0; n=87), the rate of restenosis was significantly higher in HOMA-IR over 5.0 group (23.0%) than in the other groups (11.3% and 7.1%, p=0.014). Logistic analysis showed that the only independent predictor of restenosis was HOMA-IR over 5.0 (CR 2.87; p=0.004).

**Conclusion:** The results suggested that severe insulin resistance was a predictor of restenosis after drug-eluting stent implantation; furthermore, that improvement of insulin resistance may contribute to prevent coronary restenosis after drug-eluting stent implantation.
Impaired production of anti-atherosclerotic cytokines (IL-10) by macrophage within culprit coronary plaque in diabetic patients with restenosis after primary PCI

T. Kameyama1, T. Sato1, T. Noto1, T. Nakadate3, H. Ueno4, K. Yamada5, H. Hone5, T. University of Toyama, Toyama, Japan; 2Saiseikai Takaoka Hospital, Takaoka, Japan; 3Imizu City Hospital, Imizu, Japan; 4Toyama Rosai Hospital, Umeda, Japan

Purpose: Coronary intraplaque hemorrhage (IPH) accelerates atherosclerosis through the dual metabolic stresses of cholesterol-enriched and proinflammatory macrophages (CD163). IL-10 is frequently observed in vulnerable coronary plaques, especially in diabetic ACS patients. Extracellular HDL are cleared exclusively by scavenger receptors CD36. These macrophages can counteract atherogenicity of IPH by secreting anti-atherosclerotic cytokine interleukin-10 (IL-10). We investigated IPH, macrophage phenotype, and IL-10 production in coronary plaques from ACS patients with diabetes, in association with bare and matrix (M) restenosis after PCI.

Methods: In 23 ACS patients with diabetes (HbA1c<NGSP): 6.5% or HOMA-IR >2.5), atherothrombotic debris was retrieved using filter-based distal protection device (Filter), during primary PCI with BMS implantation. The debris was stained with antibodies to CD163 (Hb scavenging macrophage), CD14 (prom-inflammator macrophage), glycoprotein A (GPA, intraplaque hemorrhage) and IL-10. These debris parameter conventional coronary risk factors were compared between patient with angiographic restenosis (R≥n=4) and those without restenosis (R≤n=19), after 9-month optimal medical treatment.

Results: Restenosis rate were 17.4%. Conventional risk factors, such as diabetes, dyslipidemia and hypertension were not different between the two groups, at the time of index PCI and after 9-month medical treatment. GPA, CD14, CD163, and IL-10 were not different between the two groups. However, IL10/CD163 ratio, an anti-atherosclerotic cytokine production capacity of HDL scavenging macrophages, decreased in R+ compared to R- (Table).

Immuno-staining results

<table>
<thead>
<tr>
<th>Group</th>
<th>GPA (%)</th>
<th>CD14 (%)</th>
<th>CD163 (%)</th>
<th>IL-10 (%)</th>
<th>IL10/CD163</th>
</tr>
</thead>
<tbody>
<tr>
<td>R+ (n=4)</td>
<td>13.0±7.6</td>
<td>19.6±8.8</td>
<td>39.6±13.2</td>
<td>33.3±17.8</td>
<td>0.92±0.54</td>
</tr>
<tr>
<td>R- (n=19)</td>
<td>21.5±14.6</td>
<td>25.1±13.0</td>
<td>26.3±19.8</td>
<td>27.1±19.3</td>
<td>2.11±1.21</td>
</tr>
</tbody>
</table>

p NS NS NS NS <0.01

R+, patients with restenosis; R-, patients without restenosis; NS, not significant.

Conclusions: Anti-atherosclerotic IL-10 production by HDL scavenging macrophages are impaired in diabetic patients with restenosis after primary PCI.

Reseeding of a decellularized arterial matrix for restenosis research

D. Haase1, S. Otto1, B.F.M. Rommel1, H.-R. Figulla1, T.C. Poerner1
1University Hospital Jena, Department of Internal Medicine I, Jena, Germany; 2University Hospital Jena, Institute of Pathology, Jena

Purpose: Aim of this study was to produce an in vitro test platform for restenosis research by reseeding of a natural, completely acellular arterial matrix with human endothelial and smooth muscle cells.

Methods: Freshly, surgically excised segments of rabbit aorta were obtained for decellularization. After verification of decellularization, a bare metal stent (DRIVER, Medtronic, 30 mm length, 4 mm diameter) was implanted and the segment was reseeded with human coronary artery endothelial (HCAEC) and human coronary artery smooth muscle (HCASMC) cells. Reseeding was performed in vitro at different seeding periods with cell numbers of 0.5 x 106 for at least three months. Subsequently, segments underwent histochemical (HE and EVG staining), immunohistochemical and PCR characterization by detection of CD31 (for HCAEC) and alpha smooth muscle actin (for HCASMC), respectively.

Results: By reseeding, cells formed a confluent monolayer after 14 days and a multiple of layers after three months. Adhesion of cells did not differ between stented and non-stented segments, revealed by HE and EVG staining. RT-PCR for CD31 and alpha smooth muscle actin specific primers showed that both, HCAEC and HCASMC are adhesive on the decellularized matrix and growing in several layers.

Conclusions: Further research by reseeding of a natural, completely acellular arterial matrix with human endothelial and smooth muscle cells has been successfully developed. This represents a new in vitro model, suitable for long-term proliferation and migration studies in stented vessels.
in other parameters including restenotic tissue backscatter, visible microvessels, and lumen shape.

Conclusions: The pathophysiology of i-stent restenosis might be different among various stents.

Comparison of neointimal tissue characteristics among bare-metal stent, paclitaxel-eluting stents and zotarolimus-eluting stents using integrated-backscatter intravascular ultrasound (IB-IVUS).


Purpose: Drug-eluting stent (DES) has dramatically reduced angiographic restenosis and target lesion revascularization (TLR) by decreasing neointimal hyperplasia. However, ISR in DES still occurs to limited extent. Although neointimal tissue characteristics are essential to understand the pathophysiology of ISR, they have not been fully investigated. The aim of this study is to compare the differences of neointimal tissue characteristics among BMS, paclitaxel-eluting stents (PES) and zotarolimus-eluting stents (ZES), using intravascular ultrasound (IVUS) and integrated-backscatter IVUS (IB-IVUS).

Methods: We investigated 95 de-novo lesions to be treated with BMS (N=18), PES (N=20), and ZES (N=57). We performed longitudinal IVUS analyses within stented segments to confirm minimum lumen area (MLA) at follow-up. Neointimal tissue characteristics judged by grayscale-IVUS were categorized as homogenous or heterogeneous. Neointimal tissue characteristics were also analyzed using IB-IVUS, which characterized as following four characteristics: calcific, dense-fibrous, fibrous, or lipid. We compared them among BMS, PES, and ZES.

Results: TLR rate showed no significant difference in three groups (22% in BMS, 30% in PES, 18% in ZES, p=0.67). Neointimal area at MLA site was significantly larger in BMS than PES and ZES (6.1mm² in BMS, 3.7mm² in PES, 2.6mm² in ZES, p<0.001). Most neointimal tissue categorized homogeneous by grayscale-IVUS (100% in BMS, 95% in PES, 88% in ZES, p=0.3). IB-IVUS analysis revealed that there were no significant differences in lipidic tissue components of neointima among three groups (0.76mm² in BMS, 0.9mm² in PES, 0.5mm² in ZES, p=0.53). Calcific tissue and dense fibrous tissue components of neointima also showed no significant differences among three groups (calcific tissue: 0.16mm² in BMS, 0.21mm² in PES, 0.17mm² in ZES, p=0.63). For dense fibrous tissue: 0.40mm² in BMS, 0.31mm² in PES, 0.30mm² in ZES, p=0.52). However, fibrous tissue components of neointima were significantly higher in BMS compared with PES and ZES (3.5mm² in BMS, 2.3mm² in PES, 2.3mm² in ZES, p<0.001). In comparison between PES and ZES, neointimal tissue characteristics by IB-IVUS showed no significant differences (calcific: p=0.42, dense-fibrous: p=0.84, fibrous: p=0.94, lipidic: p=0.73).

Conclusions: IB-IVUS analyses revealed that neointimal tissue in BMS contained more fibrous tissue than PES and ZES, which suggested more stable neointima in BMS compared with PES and ZES. In addition, PES had similar neointima to ZES by IB-IVUS analyses.

Spatial distribution of culprit lesion thin cap fibroatheromas and culprit ruptured plaques in acute coronary syndrome. An optical coherence tomography study.

A. Karanasos, K. Toutsouzas, M. Riga, E. Tsiamis, A. Synetos, K. Stathogiannis, A. Papanikolaou, G. Triantafyllou, D. Tousoulis, C. Stefanadis. Hippokration Hospital, University of Athens, Athens, Greece

Purpose: Recent studies have shown that the majority of culprit lesions in acute coronary syndrome (ACS) are located in proximal segments of coronary arteries. This discrepancy could be due to morphological differences. We investigated with optical coherence tomography (OCT) in patients with ACS, whether culprit lesion thin cap fibroatheroma (TCFA) or rupture are associated with the location of the lesion.

Methods: We included 67 patients with ACS that underwent cardiac catheterization within 24 hours from symptom onset. Distance of the culprit lesion from the coronary ostium was measured with quantitative coronary angiography. OCT was performed in all culprit lesions and the minimal cap thickness and the lipid content in quadrants were measured. TCFA was defined as a plaque with cap thickness <65μm and lipid content in <1 quadrant. Presence of plaque rupture was recorded.

Results: Analysis of OCT images revealed 45 ruptured plaques (67.1%), 17 in the LAD (60.7%), 6 in the LCx (66.7%), and 22 in the RCA (73.3%; p=NS). Mean cap thickness was 58±27μm. The majority of the patients (n=62, 92.5%) had >1 lipid quadrants. Forty five TCFA were identified by OCT, 16 in the LAD (57.1%), 6 in the LCx (66.7%), and 23 in the RCA (76.7%; p=NS). Luminar thrombus was found in the majority of patients (n=47, 71.0%). The distance of the culprit lesion from the ostium was lower for ruptured plaques compared to non-ruptured plaques (27.0±19.3mm vs. 41.1±20.6mm, p<0.01). Culprit lesions with a TCFA had a trend for lower distance from the ostium, compared to plaques without a TCFA (28.9±20.3mm vs. 37.3±20.9mm, p=0.08). Spatial distribution of TCFA and ruptured plaques is presented in the figure.

Conclusions: Culprit ruptured plaques in ACS are predominately located in the proximal segments of the coronary arteries.

Optical coherence tomography guided angioplasty during acute coronary syndrome: the OTOClaV study.

P. Motreff1, N. Amabile2, G. Souteyrand1, N. Combarè1, R. Hamdani2, S. Ghoustine2, C. Caussin2. 1University Hospital of Clermont-Ferrand, Department of Cardiology, Clermont-Ferrand, France; 2Marie Lannelongue Hospital, Department of Cardiology, Le Plessis-Robinson, France

Purpose: Time-domain optical coherence tomography (TD-OCT) allows assessment of the anatomy and features of unstable coronary artery lesions, including discrimination between the thrombotic and atherosclerotic plaque components. Our hypothesis is to investigate the feasibility and optimal timing of TD-OCT guided percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS) treatment.

Methods: This multicenter registry included patients with ACS and a large thrombus burden on initial coronary angiography. All patients were treated by manual thrombus aspiration under anti-GPIIB/IIIa infusion. After successful thrombo-aspiration, the time-domain OCT (TD-OCT) and expressed as LAX (radial EKG peak) was performed to determine the absence of residual culprit burden. The deferred TD-OCT procedures were performed between day 3 to 7 (group 3: late procedure) following initial coronary angiography. The decision of stenting was based on the presence of residual culprit stenosis with a minimal lumen area (MLA) ≥4mm².

Results: A total of 93 patients (n=31 in each group) were included (mean age: 53.3±1.4 years, 78% male, 83% ST elevation myocardial infarction, initial TIMI flow: 1.3±0.14). TD-OCT was feasible in all cases, with no complication (thrombus migration, coronary artery dissection or perforation). Presence of thrombus adherent to the culprit lesion was identified in 65% of the cases. The frequency was significantly lower in late TD-OCT group vs. immediate TD-OCT group (32% vs. 74%, p<0.01). The culprit lesion stenosis decreased over time, as witnessed by the higher MLA in group 3 compared to group 1 (2.42±0.3mm² vs. 5.21±0.07mm², p<0.001). Altogether, these results suggested a progressive reduction of thrombus burden over time under medical therapy. Patients were treated by coronary artery stenting in 61% of the cases (drug eluting stents: 47%). The stenting rate was significantly lower in patients with late TD-OCT exploration compared to the ones with immediate TD-OCT analysis (43% vs. 37%, p<0.01). A total of n=3 major adverse cardiovascular events (death+non fatal MI+ non fatal stroke+ need for repeated revascularization) were observed during follow-up.

Conclusion: TD-OCT guided PCI for treatment of patients with ACS is feasible, safe and prevents unnecessary stenting procedures. Although our data suggest that a deferred analysis could be a relevant approach, the optimal timing for TD-OCT procedure following ACS has to be confirmed in larger studies.

Relationship between optical coherence tomography (OCT), intravascular ultrasound tomography (IVUS) and pressure-derived fractional flow reserve

T. Osue, J. Shite, T. Shinkle, H. Otake, K. Hirata, Kobe University Graduate School of Medicine, Department of Cardiology, Kobe, Japan

Background: Intravascular ultrasound (IVUS)-based minimal lumen area (MLA) measurement has been reported as a useful method for detecting ischemia in a cath-lab. However, considering the higher resolution of optical coherence tomography (OCT), OCT may have a potential to estimate the presence of ischemia more accurately than IVUS. Therefore the aim of this study was to assess the ability of OCT in detecting the presence of ischemia evaluated by fractional flow reserve (FFR) by comparing that of IVUS.

Methods: 39 lesions (26 patients) were evaluated by OCT, IVUS and intracoronary pressure measurements. The FFR was calculated as the ratio of the distal coronary pressure divided by proximal coronary pressure under hyperemia, and
value of \(<0.8\) was considered as significant in determining ischemia. The minimal lumen area (MLA) was measured by OCT and IVUS.

Results: Although both MLA obtained by IVUS and OCT showed a significant positive correlation to the FFR values, MLA obtained by OCT appeared to have a better correlation to FFR values than MLA by IVUS. (OCT: \(R=0.679, P<0.001\), IVUS: \(R=0.573, P<0.001\)). The best cutoff value of the MLA to predict FFR <0.8 was 4.28 mm\(^2\) by IVUS (sensitivity: 94.7%; specificity: 76.9%; AUC: 0.877) and \(<2.24\text{mm}^2\) by OCT (sensitivity: 94.7%; specificity: 76.9%; AUC: 0.947).

Conclusion: OCT-based MLA measurement may provide better estimation of physiological coronary epicardial stenosis than IVUS.

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**VH-IVUS predictors for lesion specific myocardial ischemia in intermediate coronary artery stenosis**

J.H. Doi, 1 B.K. Koo, 2 C.W. Nam, 3 S.W. Lee, 1 H. Choe, 1 J.H. Kim, 1 H.S. Kim, 1 S.W. Hong, 1 Ill Ian Paik Hospital, Goyang, Korea, Republic of; 2Seoul National University Hospital, Seoul, Korea, Republic of; 3Keimyung University Dongsan Medical Center, Dangoo, Korea, Republic of

**Purpose:** Aim of this study was to investigate characteristics and predictors of virtual-histology intravascular ultrasound (VH-IVUS) derived plaque geometry and calcification associated with lesion specific myocardial ischemia upon FFR criteria in the angiographically intermediate coronary stenosis.

**Methods:** 104 coronary segments of the 73 patients with intermediate stenosis were prospectively enrolled from 2 centers. VH-IVUS and FFR examination were performed simultaneously for all segments. Functionally significant stenosis was defined as FFR less than 0.80. All angiographic, VH-IVUS data were analyzed in core laboratories. Lesions were divided in two groups according to the value of FFR (\(>0.80\), \(\leq0.80\)).

**Results:** Lesions with FFR <0.8 showed significantly smaller minimal lumen area (\(2.68\pm0.77\text{mm}^2\) vs. \(4.02\pm1.69\text{mm}^2\) mean ± SD, \(p<0.001\)) and larger \% plaque burden (77.56±7.8% vs. 88.40±10.0%, \(p<0.001\)). Non-calcified VH-IVUS derived \(\leq10\%\) plaques were significantly associated lower FFR values than calcified plaques (27.4% in FFR \(\leq0.80\) vs. 6.5% in FFR >0.80, \(P=0.017\), Odds ratio=5.47, CI: 1.19-25.08). Lesions with \(\leq70\%\) plaque burden were affected by VH-IVUS were also significantly associated with lower FFR values (36.8% in FFR \(\leq0.80\) vs. 8.6% in FFR >0.80, \(P=0.004\), Odds ratio=6.22, CI: 1.60-24.11) even though plaque composition by VH-IVUS were different, one of necrotic core (NC), dense calcium (DC), fibro (FC) and fibrofatty (FF) (FC) NV: 20.2±7.58% vs 21.0±9.38%, DC: 5.86±7.39% vs 8.49±8.87%, FF: 60.00±11.30% vs 55.38±12.14%, FF-IVUS derived non-calcified plaque (\(\leq10\%\)) and \% plaque burden \(\geq70\%\) were independent predictors of the FFR (\(<0.8\) vs. \(\geq0.8\), \(p=0.015\), \(p=0.015\)).

**Conclusions:** In the intermediate coronary artery stenosis, lesions with non-calcified, \(\leq70\%\) plaque burden with smaller minimal lumen area could be used as VH-IVUS predictors for lesion specific myocardial ischemia.

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**In-stent-restenosis and invasive coronary imaging / Non coronary and TAVI interventions**

**P4168**

**Percutaneous occlusion of left atrial appendage with the amplatzer cardiac plug: results from clinical, echocardiographic and CT follow-up in 100 implanted patients**

G. Santoro, 1 S. Beriti, 1 F. Meucci, 1 C. Palmieri, 2 U. Paradossi, 1 G. Squillantini, 1 G. Rosso, 1 F. Morì, 1 A. Oddo, 1 Careggi University Hospital, Department of Cardiology, Florence, Italy; 2Gabriele Monasterio Foundation CNR-Region Toscana, Heart Hospital, Massa, Italy

**Background:** Percutaneous left atrial appendage (LAA) occlusion has proved to be safe and effective in patients with aortic valve disease and high risk of atrial fibrillation (AF) who are not eligible for surgical LAA occlusion. However, large studies with long term follow up are lacking, and the role of an atrial septal defect (ASD) closure device is still under investigation.

**Aim of this study:** To prospectively compare both LAA closure systems with regards to procedural and fluoroscopy-time and assess the rate of major adverse cardiovascular and cerebrovascular events (MACCE).

**Methods:** Data from 106 consecutive patients (pts) submitted to two Centers for performing percutaneous LAA occlusion were collected from December 2008 to December 2012. All pts had an high thromboembolic risk (CHA2DS2-VASC \(\geq2\)) and at least one contraindication to oral anticoagulation therapy. After the procedure, all pts were treated with dual antiplatelet or anticoagulation therapy for 4 weeks. Pts were re-evaluated with clinical or instrumental follow up (FUP) with computer tomography (CT) or transesophageal echocardiography (TEE).

**Results:** Mean age was 75±11 yrs. 57.1% of the ACPI. The M GPI was successfully implanted in 100 of 106 pts (94%). Permanent AF was present in 71% of pts, while persistent and paroxysmal AF were present in 11% and 18%, respectively. After the procedure five pericardial effusions were observed, three of which needed pericardiocentesis. Two pts experienced a transient ischemic attack, one the day after the procedure and the other 16 months later. One patient, treated with ASA, clopidogrel, was affected by intracranial haemorrhage two weeks after the procedure. At a mean FUP of 13.7±months (0 pts lost to FUP) 6 patients were dead for non procedural related causes (2 cases of pulmonary embolism, 2 cancer, one sudden cardiac death due to arrhythmic cause). No ischemic stroke was observed in any implanted patient. TEE was performed in 46 patients at 8±7 months after the procedure and CT in 33 pts at 11.8±months, failing to demonstrate any malposition nor embolization of the device. In two cases there was a residual istrogenic atrial septal defect. In one patient TEE demonstrated a small thrombus on the device that was successfully treated with fondaparinux for one month. Mitral valve motion, transmural flow and left superior pulmonary vein were not affected by the presence of the device.

**Conclusions:** Data from our experience suggest that percutaneous LAA occlusion with GPI is a safe and effective alternative to VKAs in selected high risk patients with non valvular AF and is associated with a high procedural success rate. Our mid-term follow up in 100 implanted pts with no ischemic stroke after a mean of 13 months confirms the acute results.

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**P4169**

**Comparative analysis of percutaneous left atrial appendage (LAA) closure systems: a single center experience**

M. Kulikoglu, 1 S. Bordinog, V. Urban, M. Gunawardene, B. Schulte-Hahn, 2 B. Nowak, B. Schmidt, K.R.J. Chun. Cardiology Centre Bethanien (CCB), Frankfurt, Germany

**Background:** The concept of LAA closure has entered the clinical arena as a treatment alternative for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). Currently, two different LAA closure systems are available but lacking comparative data.

**Objective:** To prospectively compare both LAA closure systems with regards to procedural and fluoroscopy-time data and MACCE.

**Methods:** Consecutive patients (pts) with NVAF, high risk for stroke and either contraindication or not willing to accept long term oral anticoagulation (OAC) were prospectively enrolled. In all pts deep sedation was utilized during the procedure. After transseptal puncture LAA angiography was performed. LAA dimensions were calculated from TEE and angiography. Watchman™ (group B) or Cardiac Plug™ devices (group B) were implanted. All patients received OAC or dual antiplatelet therapy (aspirin/clopidogrel) for 6 weeks followed by TEE for re-assessment.

**Results:** In a total of 44 pts 45 procedures were performed (mean age: 74±8 years: group A: n=18 pts; 11 males) (group B: n=27 pts; 15 males). There was no statistical difference between group A and B with regards to CHA2DS2: 2 (Q1=1, Q3=2) vs. 2 (Q1=1, Q3=3), CHA2DS2VASc: 3 (Q1=1, Q3=6) vs. 4 (Q1=1, Q3=5), and HASBLED score: 3 (Q1=2, Q3=4) vs. 3 (Q1=2, Q3=4). Implantation success was achieved in 16/18 pts (88%, group A) and in 27/27 (100%, group B), respectively. In group A, 2 implantations failed: 1 pt switch to group B, 1 pt with transient ventricular arrhythmia. In group B, 1 asymptomatic ST elevation was observed. Procedure- and fluoroscopy-time comparing group A and B was 56±18 min vs. 48±16 min and 9.2±5.6 min vs. 7.4±4.7 min, respectively. Mean LAA device sizes were...
Refining transcatheter left atrial appendage closure: eliminating the anaesthetist and reducing the cost

D.F. Waterhouse, S.D. Asgedom, A. Neylon, M. Alaqueer, B. Mcadam, D.P. Foley. Beaumount Hospital, Dublin, Ireland

Introduction: The validity and benefit of transcatheter LAA closure for protection from thromboembolic stroke in non-valvular AF has been well established. However, to date, all studies have performed this procedure under general anaesthesia. Given that most candidates for LAA occlusion are often aged greater than 75 years, with multiple co-morbidities, general anaesthesia confers significant risk to this patient cohort, as well as additional costs to the procedure. We therefore sought to determine the safety of performing this procedure under conscious sedation, and to determine any cost implications of this strategy.

Methods: Fifty four (44 men, 10 women) median age 75.7 (62 years) with non-valvular AF and high risk for cardioembolic stroke (mean CHADS2VASc score 10.5 ± 4.2). 7 patients had prior strokes (24%), and 5 had atrial fibrillation (AF). All procedures were performed under conscious sedation, and to determine any cost implications of this strategy.

Results: The LAA was successfully occluded 50 patients (92.5%) under conscious sedation. In four cases the device was not implanted due to unsuitable appendage anatomy. The mean procedural and fluoroscopy times were 67.3 ± 16.1 and 8.1 ± 4.8 minutes respectively. The mean device size was 24.6 ± 3.8 mm. There were no significant procedure or device related adverse events. There were no anaesthesia related complications. All were performed as day-case procedures. Follow-up TOE showed closure of all LAA orifices. None of the patients experienced major adverse events during a follow-up (5-22 months).

Conclusions: Our study demonstrates that conscious sedation is a safe and well tolerated alternative to general anaesthesia for percutaneous LAA occlusion. The use of conscious sedation removes the requirement for general anaesthesia and thus, reduces anaesthesia-related morbidity as well as anaesthesia related costs. Additionally, this approach facilitates the performance of LAA closure as a day-case procedure, with a consequent further reduction in procedure-related costs.

The role of intracardiac echocardiography in the management of left atrial appendage occlusion: three years experience

S. Berti1, G. Santoro2, G. Rosso2, F. Mecucci2, A. Viggiano1, U. Paradossi1, C. Palmieri1. 1Gabriele Monasterio Foundation CNR-Region Toscana, Heart Hospital, Massa, Italy; 2Careggi University Hospital, Department of Cardiology, Florence, Italy

Purpose: Left atrial appendage (LAA) transcatheter occlusion is a new therapeutic option for the prevention of thromboembolism in patients with atrial arrhythmias and contradiction to anticoagulation therapy. Periprocedural echocardiography monitoring is a useful tool for assuring procedure and preventing early complications, and the purpose of this study was to verify the safety and the efficacy in monitoring this procedure using intracardiac echocardiography (ICE).

Methods: We selected 103 patients (mean age 87.5 years; male 56%; mean CHADS2 score 4.6) in 2 Italian centers with non-valvular AF and contradiction to anticoagulant drugs between January 2009 and December 2011 who had undergone LAA transcatheter occlusion procedure. The device used was the Amplatz®Cardiac Plug (ACP, Apa Medical, Plymouth,MN). All patients underwent intracardiac echocardiography (ICE) during the implantation measurements of the LAA and for excluding LAA thrombus before the procedure. ICE was used during the procedure to monitor trans-septal puncture, to confirm the absence of thrombus in the LAA, to verify correct sheath position before delivery and to help in selecting the correct sized device.

Results: The tran-septal puncture and correct device-positioning were successful in 100% cases. At the 45 days follow-up period no major adverse event and 3.3% minor complications were observed and we demonstrated stable position of the plug without residual haemodynamic shunt at the puncture level verified by TEE. Conclusion: Intracardiac echocardiography option for guiding the LA transcatheter occlusion procedure and preventing short to mid-term complications having the advantage over TEE of not requiring general anaesthesia and anaesthesiological support.
"Migraine side effect" after PFO closure as secondary prevention of stroke or TIA

M. Kumar1, E.K. Biernacka1, M. Jagodzińska1, A. Platek2, M. Demkow2, W. Ruzyllo3, M. Korka3, P. Hoffman3. 1Institute of Cardiology, Department of Adult Congenital Heart Disease, Warsaw, Poland; 2Medical University of Warsaw, Warsaw, Poland; 3Institute of Cardiology, Department of Coronary and Structural Heart Diseases, Warsaw, Poland.

The purpose of this study was to determine the frequency of occurrence of the migraine after transcatheter closure of PFO in patients younger than 55 yrs old with cryptogenic stroke or TIA.

Methods: All 224 consecutive patients (mean age 40.9±9.9 yrs; 103 men, 108 pts <40 yrs old, 116 pts 40-55yrs old) with cryptogenic thromboembolism who underwent PFO closure between 1999 and 2011 as secondary prevention were included. Mean follow-up period was 37.8±32.5, median 27 months (range, 3-151 months). There were 33 (14.7%) pts lost to follow up. Every patient was treated at least 6 moths with aspirin (yrs 1999-2003) or aspirin and ticlopidin (2004-2006) or aspirin or clopidogrel (3-6-months, 2007-2011) after procedure. All pts were sent the questionnaire concerning the presence of migraine before and after PFO closure.

Results: The migraine occurred in the study group before PFO closure in 68 (30.4%) pts, that is three times more frequently than in general population (30% vs 10%). Noticeable improvement (expressed in lower frequency rate or severity of migraine attacks, in patients’ subjective opinion) or disappearance of migraine symptoms after procedure was reported by 55 pts (80.9%) pts vs 13 pts (18.1%) without improvement (p< 0.0001). There were no new cases of migraine after the PFO closure.

Conclusion: 1/ Migraines are seen more frequently in patients with PFO than in general population. 2/ Percutaneous PFO closure with Amplather septal occluder leads to recovery of migraine or noticeable amelioration of symptoms in significant percentage of patients.

Simultaneous measurement of left ventricular volume and pressure during percutaneous mitral valve repair with the evalev mitraclipTM system

O. Gaemperli, P. Biaggi, M. Osranek, C. Felix, D. Bettex, J. Grunerfelder, V. Falk, T.F. Luscher, R. Corti. University Hospital Zurich, Zurich, Switzerland

Objectives: to investigate acute changes in left ventricular (LV) pressure-volume (PV) relationships during percutaneous edge-to-edge mitral valve repair (MVR) (Evalev MitraClipTM) using a conductance catheter.

Background: Percutaneous MVR with the Evalev MitraClipTM has emerged as an alternative to surgery for treating severe mitral regurgitation. However, its effects on left ventricular performance (including left ventricular contractility, pre- and afterload) are yet unknown.

Methods: Simultaneous pressure-volume (PV) loops were recorded during the MitralClip implantation results in a slight increase in LV afterload and marked decrease in preload, while LV contractility is preserved. This partly explains the favourable hemodynamic effects of percutaneous MVR.

Impact of mitral annulus dimensions assessed by 3D echocardiography on procedural results of percutaneous edge-to-edge mitral valve repair and left atrial and left ventricular reversed remodeling

E. Alliot, S. Hamada, K. Brehmer, S. Reith, M. Becker, J. Schroeder, M. Almall, N. Marx, R. Hoffmann. University Hospital Aachen, RWTH, Internal Medicine; Cardiology at Institute of Vascular Medicine, Aachen, Germany.

Background: Percutaneous mitral valve repair (PMVR) using the edge-to-edge technique has become a treatment option for selected patients with severe mitral regurgitation. This study evaluated the impact of mitral annulus dimensions on reduction of mitral regurgitation after PMVR and prediction of left atrial (LA) and left ventricular (LV) remodeling.

Methods: In 30 high-surgical risk patients with severe functional mitral valve regurgitation (age 74±9 years) 3D transesophageal echocardiography (TEE) was performed before PMVR to assess: mitral annulus area, circumference, anterior-to-posterior diameter and posterior-medial-to-anterolateral diameter. 3D color Doppler TEE was used for direct planimetry of the vena contracta area (VCA) to define before and after PMVR. At 6 months follow-up, changes of LA volume and LV enddiastolic and endsystolic volumes were assessed by 3D transthoracic echocardiography.

Results: VCA by 3D color Doppler TEE was reduced from 0.45±0.17 cm² to 0.19±0.11 cm² after PMVR. Patients with a reduction of VCA > 50% (n=22) had a significantly smaller pre-procedural mitral annulus area compared to patients (n=8) with a reduction ≤ 50% (11.9±3.2 cm² vs. 17.2±10.1 cm², p=0.034). Mitral annulus circumference (13.0±1.9 to 15.5±4.9 cm, p=0.002), mitral annulus anterior-to-posterior diameter (3.6±0.6 to 4.1±1.0 cm, p=0.008) as well as annulus-postero medial-to-anterolateral diameter (4.0±0.7 vs. 4.5±1.3 cm, p=0.197) tended to be smaller in patients with a reduction of VCA > 50%. The reduction in LA volume as well as LV enddiastolic volume at 6 months follow-up was significantly greater in patients with a reduction of VCA > 50% after PMVR (10.6±5.5 and 10.0±5.7 cm³ compared to those of patients with a reduction of regurgitant VCA ≤ 50% (3.1±1.9 and -1.9±0.7%; p=0.013 and p=0.024, respectively) while there was no difference in reduction of LV end systolic volume between both groups (-5.4±7.3 vs -5.3±5.7%, p=0.798).

Conclusions: In patients with very large mitral annulus dimensions, effectiveness of PMVR is reduced. Less effective PMVR is associated with less LA and LV remodeling.

Mitrail Valvuloplasty long-term follow-up of single balloon (Ball) versus Inoue balloon techniques


This study aimed to demonstrate that mitral balloon valvuloplasty (MBV) with the Ball single balloon (BSB) has similar outcome and long-term follow-up (FU) than MBV performed with the Inoue worldwide accepted technique.
Percutaneous mitral balloon valvuloplasty beyond 65 years of age

Z. Chmielak, M. Klopotowski, M. Demkow, M. Konka, P. Hoffman, K. Kukula, M. Kruk, A. Witkowski, W. Ruzyllo. National Institute of Cardiology. Warsaw, Poland

Objectives: To evaluate the safety and efficacy of percutaneous balloon mitral valvuloplasty for the treatment of mitral stenosis in patients older than 65.

Background: The profile of subjects undergoing percutaneous balloon mitral valvuloplasty (PMBV) in developed countries has shifted toward the elderly. In PMBV is safe and efficacious in elderly patients with symptomatic mitral stenosis. Long-term results are good and related mainly to the quality of the procedure.

Methods: We retrospectively reviewed those patients with severe prosthetic paravalvular regurgitation (MR) who underwent an attempt of percutaneous closure in our hospital. Data were collected regarding demographic characteristics, comorbidities, location and size of the leak, mortality and medium-term and echocardiographic outcomes.

Results: The study comprises 11 procedures in 10 patients, which took place between October 2010 and July 2011. The mean age was 75.4±6.6 years and 54.5% were female. The medium Euroscore was 42.84%±21.24. Mean LVEF was 53.7%±14.38 and 7 patients also had an aortic prosthesis (5 of them mechanical). 62% of the interventions were performed on mechanical prosthesis, and the patients had undergone 1,7 previous surgeries (range 1-4), with a time to percutaneous repair of 161.72±111.1 months (range 6-314). The clinical indication for the procedure was heart failure, in all cases and also severe hemolysis in 81%. The location of the leaks were as follows: anterior quadrant in 5 patients, lateral in 4 and posterior in 1, being the mean maximum length 12.94±4.97. In 9 of the 11 procedures the device was successfully deployed, but in 2 patients the device was too big to provide adequate support. The Amplatzer Duct Occluder device was used in 1 case and the Amplatzer Vascular Plug III in the rest, using 2 of them for the closure of 1 leak. TEE showed mild MR just after the deployment of the device in 8 patients, and severe MR in 1 case. Mortality related to the procedure was 0%, but 3 patients died during the first month (only 1 of them due to complication related to the intervention). No more deaths were recorded during the follow-up period. All patients had Echo score ≥1.5 cm² (p=0.001, HR=7.969, 95% IC 3.413-18.608).

Conclusions: Percutaneous closure of paramitral leak is a procedure of variable effectiveness, whose main limitation is the extense comorbidity and poor basal status of some patients referred for this technique. Furthermore, in some cases, the initial success does not ensure mid-term positive outcomes. These results could improve with a sooner referral of these patients and the development of specific devices for this pathology.

P14179

Percutaneous mitral balloon valvuloplasty during pregnancy: Our Experience

A. Tounsi, L. Abd, A. Abd, S. Mallek, M. Akrou, F. Triki, M. Hentati, S. Kammoun. Cardiology department, Hedi Chaker Hospital, Sfax, Tunisia

Introduction: Mitral stenosis is the most common valvular heart lesion found in pregnancy. When severe, it leads to significant maternal and fetal morbidity and mortality, since the hemodynamic adaptations to pregnancy are badly tolerated. Pregnancy can lead to development of heart failure in patients with asymptomatic or even unknown mitral stenosis, as a result of the increased mitral valve pressure gradient caused by the physiologic increase in heart rate and blood volume in pregnancy. When symptoms persist despite optimal medical therapy, the poor prognosis justifies the correction of mitral stenosis during pregnancy.

Methods: To present our experience in treating severe mitral stenosis in women who develop severe heart failure during pregnancy, using percutaneous balloon mitral valvuloplasty.

Patients: During 5 years, in our department, 294 balloon mitral valvuloplasties were successfully performed in women, ten of them pregnant. These were patients with congestive heart failure, New York Heart Association (NYHA) functional class III or IV (4 of them), at the second trimester of pregnancy, who did not respond positively to drug treatment with diuretics and digitals.

Interventions: We performed percutaneous balloon mitral valvuloplasty using the Inoue technique in the ten pregnant patients, with success, at around 24 weeks of gestation.

Results: After the procedure, the patients showed clinical improvement, returning to the NYHA functional class that they were in before becoming pregnant (I-II). The previous mitral valve area was 0.67 (0.21) cm², nearly doubling after valvuloplasty. Mean left atrial pressure decreased from 28 (10) to 14 (7) mm Hg. The mitral valve pressure gradient decreased from 23.5 (8) mmHg to 6 (3) mmHg after valvuloplasty. During the procedure there were no maternal or fetal complications. All patients were discharged 48 to 120 h after valvuloplasty, continuing their pregnancies without complications. 8 women had vaginal delivery, and the other 2 had cesarean sections at full term with healthy newborns that developed normally. In follow-up, one patient who had moderate mitral regurgitation after valvuloplasty developed severe mitral regurgitation, requiring surgical correction after 4 years.

Conclusion: During pregnancy, balloon mitral commissurotomy is the treatment of choice of severe pliable mitral stenosis in patients who are refractory to medical treatment.

P4180

Clinical and echocardiographic outcomes of patients undergoing percutaneous closure of mitral paravalvular leak:


Purpose: Percutaneous closure of mitral paravalvular leak is a complex procedure, recently developed for patients unsuitable for a new surgery. Clinical experience is limited and the results are controversial. We report here the experience of our center and the acute and mid-term outcomes.

Methods: We retrospectively reviewed those patients with severe prosthetic paravalvular regurgitation (MR) who underwent an attempt of percutaneous closure in our hospital. Data were collected regarding demographic characteristics, comorbidities, location and size of the leak, mortality and medium-term and echocardiographic outcomes.

Results: The study comprises 11 procedures in 10 patients, which took place between October 2010 and July 2011. The mean age was 75.4±6.6 years and 54.5% were female. The medium Euroscore was 42.84%±21.24. Mean LVEF was 53.7%±14.38 and 7 patients also had an aortic prosthesis (5 of them mechanical). 62% of the interventions were performed on mechanical prosthesis, and the patients had undergone 1,7 previous surgeries (range 1-4), with a time to percutaneous repair of 161.72±111.1 months (range 6-314). The clinical indication for the procedure was heart failure, in all cases and also severe hemolysis in 81%. The location of the leaks were as follows: anterior quadrant in 5 patients, lateral in 4 and posterior in 1, being the mean maximum length 12.94±4.97. In 9 of the 11 procedures the device was successfully deployed, but in 2 patients the device was too big to provide adequate support. The Amplatzer Duct Occluder device was used in 1 case and the Amplatzer Vascular Plug III in the rest, using 2 of them for the closure of 1 leak. TEE showed mild MR just after the deployment of the device in 8 patients, and severe MR in 1 case. Mortality related to the procedure was 0%, but 3 patients died during the first month (only 1 of them due to complication related to the intervention). No more deaths were recorded during the follow-up period. All patients had Echo score ≥1.5 cm² (p=0.001, HR=7.969, 95% IC 3.413-18.608).

Conclusions: Percutaneous closure of paramitral leak is a procedure of variable effectiveness, whose main limitation is the extense comorbidity and poor basal status of some patients referred for this technique. Furthermore, in some cases, the initial success does not ensure mid-term positive outcomes. These results could improve with a sooner referral of these patients and the development of specific devices for this pathology.

P4181

Percutaneous mitral balloon commissurotomy during pregnancy: Our Experience

A. Tounsi, L. Abd, A. Abd, S. Mallek, M. Akrou, F. Triki, M. Hentati, S. Kammoun. Cardiology department, Hedi Chaker Hospital, Sfax, Tunisia

Introduction: Mitral stenosis is the most common valvular heart lesion found in pregnancy. When severe, it leads to significant maternal and fetal morbidity and mortality, since the hemodynamic adaptations to pregnancy are badly tolerated. Pregnancy can lead to development of heart failure in patients with asymptomatic or even unknown mitral stenosis, as a result of the increased mitral valve pressure gradient caused by the physiologic increase in heart rate and blood volume in pregnancy. When symptoms persist despite optimal medical therapy, the poor prognosis justifies the correction of mitral stenosis during pregnancy.

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Results: After the procedure, the patients showed clinical improvement, returning to the NYHA functional class that they were in before becoming pregnant (I-II). The previous mitral valve area was 0.67 (0.21) cm², nearly doubling after valvuloplasty. Mean left atrial pressure decreased from 28 (10) to 14 (7) mm Hg. The mitral valve pressure gradient decreased from 23.5 (8) mmHg to 6 (3) mmHg after valvuloplasty. During the procedure there were no maternal or fetal complications. All patients were discharged 48 to 120 h after valvuloplasty, continuing their pregnancies without complications. 8 women had vaginal delivery, and the other 2 had cesarean sections at full term with healthy newborns that developed normally. In follow-up, one patient who had moderate mitral regurgitation after valvuloplasty developed severe mitral regurgitation, requiring surgical correction after 4 years.

Conclusion: During pregnancy, balloon mitral commissurotomy is the treatment of choice of severe pliable mitral stenosis in patients who are refractory to medical treatment.
Endovascular stenting for palliation in malignant superior vena cava syndrome

K. Lang1, M. Ulicz2, S. Brauerlich3, A. Schmidt4, S. Guetz5, S. Bobos6, D. Scheinemann7, Rottal-Inn-Klinikum, Dptm. of Internal Medicine II (Cardiology, Angiology), Eggenfelden, Germany.

Superior vena cava obstruction can occur in late or progressive stages of various tumor disease involving the mediastinum. To assess feasibility, short and long term efficacy and complication rate of interventional therapy, i.e. recanalization, PT A and stenting of such lesions we analyzed 16 consecutive patients with cancer related superior vena cava syndrome. Clinical follow up was performed every 3 months up to 52 months. Cancer driven mean survival time after PT A-stenting was 10.2 months (8 days – 52 months). Immediate technical success rate and acute clinical success rate was 100%; NYHA class improved from 3.31 (±0.60) to 1.8 (±0.75). Especially those in class 4 benefited most and improved to class 2. Symptom relief was reached within 24hs. All patients remained free from restenoses or recurrent superior vena cava syndrome for the entire follow up or for their remaining life span. We did not have any acute or chronic complication (stent migration, penetration, bleeding). Patients were discharged the day after the procedure on aspirin and clopidogrel, in some cases on low molecular heparin or vitamin K antagonists. Thus, for palliation of superior vena cava syndrome in progressive cancer disease interventional radiology, PT A and stenting is technically safe and clinically efficient for both rapid and long term symptom relief. It should be considered as first choice treatment.

Impact of percutaneous treatment of acute pulmonary embolism in intermediate and high risk patients

N. Farre1, F. Miranda1, M. Orozco-Levi2, N. Salvadella1, T. Huzon1, L. Molina1, J. Gea1, J. Bruggera1. 1Hospital del Mar, Department of Cardiology, Barcelona, Spain; 2Hospital del Mar, Municipal Institute for Medical Research (IMIM), Respiratory Department, Barcelona, Spain.

Background: Local fibrinolysis and mechanical embololysis improve hemodynamic parameters in patients suffering shock due to pulmonary embolism (PE). Normotensive PE patients with signs of right ventricular failure on echocardiogram (RVF-E) have an intermediate risk of death, but little is known about the best treatment for these patients.

Aim: To evaluate the clinical impact of percutaneous treatment (fragmentation, fibrinolysis and aspiration) of PE in both intermediate and high-risk patients.

Methods and Results: 20 patients with CT-confirmed PE and RVF-E were identified. High risk patients (group A=n=8), defined by cardiogenic shock or respiratory failure requiring mechanical ventilation, were compared to normotensive patients (group B=intermediate risk;n=12). The median time from admission to procedure was 23 hours (25±7-14-29 hours). Three patients in A had systemic fibrinolysis with hemorraghic complications prior to catheterisation. The other 17 patients received low dose intraaerial fibrinolysis. Twelve patients were female, mean age was 68 years. On admission group A had lower systolic blood pressure (SBP) than B (131 mmHg to 138, p=0.34). An 18% decrease in Systolic PAP was seen in group B (131 mmHg to 138, p=0.001 in B). SBP increased 60% in A (88 mmHg to 141, p=0.06). LVEDV 188±22 vs 130±18 respectively. Systolic and mean pulmonary artery pressures and higher oxygen requirement in A (84 (12)% vs 92 (4), p=0.06, and 43 (38)% vs 30 (22), p=0.08). There was a trend toward a lower oxygen saturation in A (92±3 vs 96±2, p=0.06). Especially those in class 4 benefited most and improved to class 2. Symptom relief was reached within 24hs. All patients remained free from restenoses or recurrent superior vena cava syndrome for the entire follow up or for their remaining life span. We did not have any acute or chronic complication (stent migration, penetration, bleeding). Patients were discharged the day after the procedure on aspirin and clopidogrel, in some cases on low molecular heparin or vitamin K antagonists. Thus, for palliation of superior vena cava syndrome in progressive cancer disease interventional radiology, PT A and stenting is technically safe and clinically efficient for both rapid and long term symptom relief. It should be considered as first choice treatment.

Transcatheter closure of ruptured sinus of valsalva aneurysm with nitinol mesh occluders

J. Biakowski, M. Szkutnik, Silesian Center for Heart Diseases, Zabrze, Poland.

Introduction: Ruptured sinus of Valsalva aneurysm (R-SOVA) is rare shunt lesion with scant data about its transcatheter closure (TCC).

Methods: From March 2007 to September 2011, 12 patients (pts) –mean age 37.2 years were selected for TCC. Two pts had acquired R-SOVA after previous cardiac surgery. Another pt after pre-vous surgicalsealisation of R-SOVA had 2 recanalizations. Echocardiography-revealed the rupture of right or noncoronary sinus into right atrium in 9pts and into right ventricle in 2 another pts. In 1 pt R-SOVA was open from leftcoronary sinus to pulmonary artery (PA).The defect diameter was from 3.8 to 10(mean 6.9) mm. Different nitinol mesh occluders (dualatral, aortic or muscular VSD) were applied by antegrade approach. Endovascular technique of delivery times and arhythmic side effects are significantly reduced in comparison to NOGA, without compromising injection accuracy.
Results: Indications for TLE were infection (58.6%), lead malfunction (40%) and lead displacement (1.4%). Extracted devices were PM in 34 cases (45.3%), ICD in 29 cases (38.7%), and CRT-D in 12 cases (16%). Among 158 leads, 38 (24%) were RV, 54 (34.2%) were defibrillator coil, 53 (33.6%) were atrial and 13 (8.2%) were CS electrodes. Median time from preceding procedure was 88 months (21-240 months). Clinical success was 98.6% and complete procedural success with Evolution system alone was 88% (86 patients). Partial success was achieved in 3 leads with remaining small ventricular tip. Major complications were observed in 1 (1.3%) patient without any mortality. Conclusions: Our experience has confirmed that the hand powered Evolution system is an effective extraction tool for chronically implanted pacemaker/ICD leads.

Comparison of knowledge-based weaning (KBW) and physician-driven weaning of mechanically ventilated patients in the coronary care unit


Introduction: Knowledge-based weaning (KBW) of mechanical ventilation is a form of closed loop ventilation successfully used to decrease duration of ventilator assistance in general intensive care units (ICU). However, its use in specialty ICUs has not been validated.

Objectives: To find out if KBW reduced weaning times in coronary care units (CCU).

Methods: Patients: Single center tertiary hospital CCU. Inclusion: age 21-85; assisted-mode mechanical ventilation >24 hours, 34 others). Total 54 patients enrolled, with mean age 68.0, (range 33-94) and mean APACHE-II score 17.8 and 18.6 for usual care and KBW respectively; p=NS for both). Weaning time was 1080 mins or 0.75 days (median 67.1 and 69.0, mean APACHE-II score 17.8 and 18.6 for usual care and KBW respectively; p=NS for both). Weaning time was not significantly different between the two groups, even after adjustment for APACHE-II. Mean and median duration of mechanical ventilation was 2.78 and 2.18 days for usual care, 3.84 and 2.98 days for KBW (p=NS).

Conclusions: This pilot study failed to show a significant impact of KBW in reducing duration of ventilator assistance, as has been shown in general ICUs. This is likely because the profile of patients in CCU differ significantly from ICU patients; the proportion of patients with haemodynamic or arrhythmic instability is considerably higher, and there are a significant number of patients with very high ventilator dependence due to neurological injury. In the remainder, patients frequently received short duration of ventilation, so the impact of KBW can only be limited. In conclusion, although KBW may be helpful in individual patients, it is unlikely to have major impact on average ventilator weaning time in the CCU context. A larger randomized trial will be needed to confirm these findings.

Incidence and intraprocedural management of aortic regurgitation in interventional aortic valve replacement

M. Fuellner1, G. Bodman1, E. Kölzer2, R. Sodian3, M. Block1,2

1 Clinic Augustinum of Munich, Department of Cardiology, Munich, Germany; 2 Clinic Augustinum of Munich, Department of Anesthesiology, Munich, Germany; 3 Clinic Augustinum of Munich, Department of Cardiac Surgery, Munich, Germany

Background: Paravalvular aortic regurgitation is frequent after transcatheter aortic valve implantation (TAVI). In the present study the incidence of a significant (≥ II/IV) postinterventional aortic regurgitation (AR) and possible treatment strategies are evaluated.

Methods: In 91 patients (pts) transfemoral TAVI with a self-expanding Medtronic CoreValve (CV; n=80) or a balloon-expandable Edwards Sapien prosthesis (ES; n=11) was performed. Incidence of AR was evaluated by echocardiography immediately after deployment of the prosthesis and after optional correcting interventions. Prior to hospital discharge AR was assessed by transthoracic echocardiography.

Results: Immediately after deployment of the aortic prosthesis a significant paravalvular AR was present in 35 of 91 pts (38%; AR 2/4 in 23 pts, AR 3/4 in 11 pts, AR 4/4 in 1 pt). Thereafter in 5 pts, in whom a CV prosthesis has been implanted, it has been waited for 10 minutes, in 20 pts the prosthesis was postdilated with a valvuloplasty balloon (in 1 pt after previous waiting) and in 3 pts the prosthesis was pulled back because of a too deep position in the left ventricular outflow tract with a snare tool in 2 pts after previous balloon dilation). By these interventions a reduction of the severity of the AR by at least one grade could be achieved in 13 of 25 pts (52%), thereof in 4 of the 5 pts, in whom further expansion of the prosthesis has been waited for. In the pts, in whom due to a significant AR correcting interventions have been deemed necessary, blood pressure immediately after deployment of the prosthesis was significantly lower than in the pts without significant AR. The correcting interventions led to a significant rise of the diastolic blood pressure but leaved the systolic blood pressure unchanged. Furthermore after the correcting intervention a significant decline of the LVEDP was observed from 29±8 mm Hg to 24±6 mm Hg (p = 0.050). At the end of the TAVI 25 of 91 pts (27%) had significant AR (AR 2/4 in 23 pts, AR 3/4 in 1 pt, AR 4/4 in 1 pt). Before hospital discharge (after a mean of 4.6±4.2 days) TTE revealed mild to moderate AR in 3 of 90 pts and moderate AR in 7 of 90 pts. The 3 pts, (3/91 pts, 3.3%), who died within the 7 days after TAVI, all had significant AR at the end of the TAVI procedure.
Conclusion: In TAVI immediately after prosthesis deployment significant AR is frequent and can be corrected by balloon dilation of the prosthesis or pullback manoeuvres. In self-expanding prostheses without massive AR further expansion of the prosthesis can be waited for before initiation of further interventions.

Methods: From June 2008 to January 2012, 63 consecutive patients underwent TAVI. We selected 56 patients with available transesophageal echocardiography (TEE) imaging. Variables (inner stent area [SA], anterior-posterior diameter (APD) and lateral orthogonal diameter (LOD) were measured in 2D and 3D TEE. Mean values of 2D and 3D were used. We assessed stent circularity, defined as 1- (APD/LOD). Values <10% were considered non-circular. UD was defined as nominal area (of each valve size) minus SA. Indexed UD was obtained dividing UD by nominal areas.

Results: Mean age was 82.8 years. Procedure approach was transfemoral in 80.4%. Mean UD was 0.88±0.35 cm² (23); 3.93±0.1 (26) and 3.98±0.2 (29). The final SA fitted progressively in the native valve annulus, showing a linear trend between SA and valve annulus (p<0.001). In our series, mean UD was 0.88±0.38 cm² (23); 3.97±0.1 (26) and 3.98±0.2 (29). Mean indexed UD was 0.2% (26). Thus, the valve expands only to 70% of its nominal area. Comparing TAVI approaches and prosthesis models, we found no differences in indexed UD. However, indexed UD increases keeping a linear relationship (p<0.01) with the valve sizes (21.2% (23); 25.9% (26); 39.8% (29)). This suggests that larger stents loose part of the radial force in spite of the higher stent height. Post-procedural gradients of under-deployed valves (20% UD cut off) were numerically but not statistically higher than the non-UD valves. Regarding the circularity analysis, we found that 37.5% of the valves were non circular. The de

Conclusion: Under-deployment and asymmetrical expansion in transcatheter aortic valves may impair valve hemodynamics.

Clinical and hemodynamic outcomes in patients with prosthesis-patient mismatch after TAVI with both core valve and Edwards sapien XT valves

K. Stathogiannis1, K. Toutouzas1, K. Spangias2, G. Latsios1, A. Synetos1, A. Karonas1, M. Chrissoheris1, A. Antoniadis1, G. Pavilides1, C. Stefanadis1, 1Hipppokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece; 2Hygeia Hospital, Athens, Greece; 3Attikon University Hospital, Athens, Greece; 4Onassis Cardiac Surgery Center, Athens, Greece

Purpose: To investigate the clinical and hemodynamic outcomes in patients with prosthesis-patient mismatch (PPM) after transcatheter aortic valve implantation (TAVI) with CoreValve (CV) and Sapien XT (XT) valves.

Methods: Clinical assessment and echocardiographic parameters were recorded at baseline and prior to discharge in 137 patients undergoing TAVI. PPM was defined as indexed effective orifice area (EOAi) <0.85 cm²/m².

Results: From the 137 patients, 57 (41.6%) had prosthesis-patient mismatch. Among patients with CoreValve 36 (45%) had PPM, whereas 21 (36.8%) patients with the Sapien XT had PPM (p=0.21). Severe PPM was present in 7.5% in CV patients and in 5.3% in XT patients (p=0.62). The procedural success rate was 100% and device success rate was 96%. There was a significant reduction in peak gradient (50±3±14±13 to 9.4±4±15 mmHg, p<0.001) and peak gradients (84±3±20.29 to 18.03±7.8 mmHg, p<0.001) as measured by echocardiography. The EOA was significantly increased (0.66±0.15 to 1.66±0.45 cm², p<0.001), as was the EOA (0.37±0.1 to 0.93±0.29 cm²/m², p<0.001). The Table depicts the impact of PPM on echocardiographic parameters post TAVI in patients with CV and XT.

Conclusions: Patients who underwent TAVI and had PPM were not associated with an adverse hemodynamic outcome before discharge.

Prosthesis/annulus discongruence by three-dimensional transoesophageal echocardiography: predictor of significant aortic regurgitation after transcatheter aortic valve implantation

N. Santos, C. Olmos, J.A. De Agustín Loeches, P. Marcos-Alberca, C. Fernandez-Gollín, C. Almería, J.L. Rodríguez, J. Zamorano, C. Macaya, L. Pérez De Isla. Hospital Clinic San Carlos, Madrid, Spain

Introduction: Paravalvular aortic regurgitation (AR) is common after transcatheter aortic valve implantation (TAVI). This study aimed to assess the prosthesis/annulus discongruence by three-dimensional (3D) transoesophageal (TEE) planimetry of aortic annulus and its impact on the occurrence of significant AR after TAVI.

Methods: We included 33 patients who underwent TAVI with a balloon expandable device for severe aortic stenosis. To appraise the prosthesis/annulus discongruence we defined a 'mismatch index' expressed as: annulus area - prosthesis area. The aortic annulus area was planimetered with 3D TEE, and approximated by circular area formula (\(\pi r^2\)) using annulus diameter obtained by two-dimensional (2D) TEE.

Results: After TAVI, 19 patients (57.6%) developed significant AR (≥2/4). The ocurrence of significant AR was associated to the 3D planimetered annulus area (p=0.04), and the "mismatch index" obtained through 3D planimetered annulus area (p<0.001), but not to "mismatch index" derived of 2D annulus diameter. In multivariate analysis "mismatch index" for 3D planimetered annulus area was the only independent predictor of significant AR (odds ratio: 10.722; 95% confidence interval: 1.040-17.8; p=0.04). The area under the ROC curve for "mismatch index" by 3D planimetered annulus area was 0.76, whereas for "mismatch index" obtained by 2D circular area was 0.36 (Figure). Using 3D planimetered annulus area as reference parameter to decide the prosthetic size, the choice would have been different in 21 patients (63%).

Conclusions: 3DTEE planimetry of aortic annulus improves the assessment of prosthesis/annulus discongruence and predicts the appearance of significant AR after TAVI.
Results: There was a significant reduction in mean (50.0±3.14 to 9.4±1.15 mmHg, p<0.001) and peak gradients (84.3±4.20 to 18.0±3.7 mmHg, p<0.001). From the 137 patients, 57 (41.6%) had postoperative PPM. Among patients with CoreValve implantation 46% had PPM, whereas 21 (38.6%) had PPM in patients with Sapien XT implantation (p=0.2). Severe PPM was present in 7.5% in CV patients and in 5.3% in XT patients (p=0.62). In the CoreValve group, predictors of PPM included only preprocedural EOA (OR: 0.002, CI: 0.001-0.688, p<0.05). In the Sapien XT group, baseline LVEF (OR: 0.951, 95%CI: 0.904-0.999, p<0.05) and baseline PASP (OR: 0.594, 95%CI: 0.513-0.96, p<0.05) were unadjusted predictors statistically significant prognostic factors for PPM. Following adjustment for age, baseline LVEF (OR: 0.945, 95%CI: 0.899-0.999, p<0.05) and baseline PASP (OR: 0.953, 95%CI: 0.912-0.997, p<0.05) remained predictors of PPM. Procedural factors were not associated with PPM in either valve.

Conclusions: PPM is a frequent finding in the TAVI era. Predictors of PPM differ between the CoreValve and the Sapien XT valve, and are mainly associated with the severity of stenosis at baseline in CoreValve and with the functional capacity of the left ventricle in Sapien XT.

**Figure 1**

**P4195** Impact of valve type and annular size on post TAVI aortic valve regurgitation

K. Stathogiannis1, K. Toutouzas1, K. Sparagias2, G. Latsios1, A. Synotos1, A. Karamanos1, M. Chrissotheoris1, A. Antoniadis1, G. Pavlidis1, C. Stefanadis1. 1Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece; 2Hygeia Hospital, Athens, Greece; 3Attikon University Hospital, Athens, Greece; 4Onassis Cardiac Surgery Center, Athens, Greece

**Purpose:** Transcatheter Aortic Valve Implantation (TAVI) is becoming the mainstay of treatment for high-risk intervenable patients with aortic valve stenosis. Aortic valve regurgitation (AVR) is a common finding following TAVI. We studied the association of post TAVI AVR with the valve type, size, and annular size.

**Methods:** Between April 2009 and January 2012, TAVI was performed in 137 (80 CV and 57 ES) high-risk patients with severe aortic stenosis (age: 79.9±6.9 years; logistic Euroscore 23.15±12.08%; 58% female; NYHA III 78.1%; aortic valve mean gradient 50.0±14.13mmHg). AVR was evaluated based on the American Society of Echocardiography classification (mild, moderate, severe).

**Results:** Annular size was greater in patients with CV compared to patients with ES (22.54±2.04mm vs 20.04±1.82mm, p<0.01). Mean annular size in 22.0mm ES was 20.04±1.44mm vs 22.22±1.79mm in 26mm ES (p<0.01). Mean annular size was 20.79±0.84mm in 26mm CV vs 24.37±1.11 in 29mm CV (p<0.01). Patients with CV had greater rates of moderate-to-severe AVR compared to ES (37.5% vs 14%, p<0.01; Figure). Patients with severe AVR had a median annulus size of 25.33±0.57mm compared to those with moderate AVR who had 22.19±1.93mm, p<0.009.

**Conclusions:** Post TAVI AVR is more common in patients with greater aortic valve annular size. Furthermore, patients receiving the CoreValve have greater degree of AVR after implantation.

**Figure 1**

**P4196** Relation of Aortic Regurgitation (AR) to Plasma Brain Natriuretic Peptide (BNP) evolution after Transfemoral Aortic Valve Implantation (TAVI) for Severe Aortic Stenosis (AS)

K. El Chilali1, T. Konorza2, F. Al-Rashidi3, P. Patsalis1, B. Plicht1, D. Wendt1, M. Thielmann4, H. Jacob2, R. Erbel1, P. Kahler1. 1West German Heart Center Essen, Department of Cardiology, Essen, Germany; 2West German Heart Center Essen, Department of Thoracic and Cardiovascular Surgery, Essen, Germany

**Purpose:** To evaluate the effect of concomitant AR on plasma BNP evolution in patients undergoing TAVI for severe AS.

**Methods:** BNP was measured at baseline, 48 hours after TAVI and predischarge in 104 patients. AR severity was evaluated by echocardiography at baseline and predischarge.

**Results:** BNP measured (298.2, IQR 145.8, 661.6 pg/ml) at baseline, peaked acutely after TAVI (506.9, IQR 253.3, 868.6 pg/ml) and decreased prior to discharge (327.2, IQR 159.2, 634.6 pg/ml). At baseline, no AR was detected in 19 (18%), AR I in 50 (48%), AR II in 30 (29%) and AR III in 5 (5%) patients, respectively. After TAVI, no AR was detected in 18 (17%), AR I in 47 (45%), AR II in 38 (37%) and AR III in 1 (1%) patient. Preexisting AR correlated with BNP at baseline (Spearman’s rho=0.27, p<0.006). We found no correlation between residual AR post TAVI and peak or predischarge BNP. The difference between discharge and baseline BNP (ΔBNPdischarge-baseline) was 9.7 pg/ml (IQR -87.4, 152.3) in patients with no preexisting AR, 14.9 pg/ml (IQR -109.2, 236.8) with preexisting AR I, -91.6 pg/ml (IQR -250.9, 68.2) with preexisting AR II and -860.9 pg/ml (IQR -598.8, -45.6) with preexisting AR III (rho=0.29, p<0.003). Regarding AR severity change, ΔBNPdischarge-baseline was -59.6 pg/ml (IQR -544.7, 94.3) in patients with improved AR (27%), 38.3 pg/ml (IQR -156.9, 110) in patients with no change in AR (42%) and 42.4 pg/ml (IQR -87.6, 264.9) in patients with increased AR after TAVI (31%), irrespective of preexisting AR severity (rho=0.27, p=0.006).

**Conclusions:** In patients undergoing transfemoral TAVI, arterial puncture above the most inferior border of the inferior epigastric artery is associated with high BNP levels that decrease significantly after TAVI. Improvement in AR severity is associated with BNP decrease after TAVI independent from preexisting AR severity.

**Figure 1**

**P4197** Optimizing vascular access during TAVI by using inferior epigastric artery as a landmark

M. Vavuranakis1, K. Kolageras1, D. Vrachatis1, M. Karioni1, K. Aznaouridis1, C. Moldovan1, K. Masoura1, G. Lazaros1, E. Gravia1, C. Stefanadis1, K. Stathogiannis1, K. Tzoutouzas1, K. Spargias2, G. Latsios1

**Purpose:** Vascular access complications during Transcatheter Aortic Valve Implantation (TAVI) have been associated with significant increase of morbidity and mortality. The need for establishment of reliable predictors for these serious events remains pivotal. The origin and course of inferior epigastric artery reliably defines the borders of inguinal ligament. We hypothesize that we can reduce vascular access site complications during TAVI, by using the course of inferior epigastric artery as a landmark for the upper safe margin for femoral puncture.

**Methods:** A total of 90 patients, who had undergone TAVI, were retrospectively studied. Vascular complications were defined as major and minor according to the Valve Academic Research Consortium (VARC) criteria. Patients were divided into High Cannulation Site (HC) group and Low CS group depending on the common femoral artery puncture site position, in regards to the most inferior border of the inferior epigastric artery.

**Results:** Vascular complications were significantly more frequent in the high CS group versus the low CS group (32.3% vs 11.9%, p=0.039). High cannulation remained an independent predictor of vascular complications after adjustment for known risk factors (OR: 4.827. CI: 1.44-16.16; p<0.01). Conclusions: In patients undergoing transfemoral TAVI, arterial puncture above the most inferior border of the inferior epigastric artery is associated with vascular complications.

**Figure 1**

**P4198** Effect of transfemoral aortic valve implantation (TF-AVI) for severe aortic stenosis on plasma brain natriuretic peptide (BNP) levels: predictive value for 30-days and 1-year survival

K. El Chilali1, T. Konorza1, F. Al-Rashidi3, P. Patsalis1, B. Plicht1, D. Wendt1, M. Thielmann4, H. Jacob2, R. Erbel1, P. Kahler1. 1West German Heart Center Essen, Department of Cardiology, Essen, Germany; 2West German Heart Center Essen, Department of Thoracic and Cardiovascular Surgery, Essen, Germany

**Purpose:** To determine the effect of TF-AVI on plasma BNP levels and to evaluate their predictive value for 30-days and 1-year survival
Methods: We measured Baseline BNP, peak BNP within 48 hours after TF-AVI and predischarge BNP in 104 patients with complete 1-year follow-up.

Results: BNP was elevated at baseline (298.2, IQR 145.8, 661.6 pg/ml) and showed an acute increase after TF-AVI (508.9, IQR 253.3, 868.6 pg/ml) followed by regression towards baseline levels prior to discharge (327.2, IQR 159.2, 634.6 pg/ml), p < 0.001. Acute BNP increase (ΔBNP/peak-baseline) is significantly higher in 30 days non-survivors (277.1 IQR 252.1, 810 pg/ml) than in survivors (132.8 IQR -10.1, 301 pg/ml), p = 0.028, and is found to be an independent predictor of 30 days survival. Kaplan-Meier (KM) survival analysis showed a reduced 30 days survival in patients with a ΔBNPpeak ≥ 248.9 pg/ml, p = 0.002. For 1-year survival, predischarge BNP level (250.8, IQR 152.9, 621.8 pg/ml) was significant (p = 0.002) and ΔBNPpeak/baseline (211.8 IQR -521.5, -91.1 pg/ml in survivors vs. 108.4 IQR 12.2, 272.6 pg/ml in non survivors, p = 0.002) are independent predictors. KM analysis showed that 1-year survival is significantly lower in patients with a predischarge BNP ≥ 327.2 and a ΔBNPpeak/baseline ≥ -38.3 than in those not fulfilling both criteria, p < 0.001.

Conclusion: BNP values are elevated in patients undergoing TF-AVI. They further increase acutely after procedure and regress to baseline levels prior to hospital discharge. Acute BNP increase is an independent predictor of reduced 30 days survival, while reduced 1-year survival is predicted by higher predischarge BNP levels and failure of BNP to decline at discharge below baseline BNP level.

P4200 Decrease in sheath size for transfemoral Aortic Valve Implantation: what are the consequences?


Background: Vascular complications are frequent and remain a recognized limitation of transcatheter aortic valve implantation (TAVI), associated with increased morbidity and mortality. Whether the recent reduction in sheath size has led to a decrease in vascular complications is unknown.

Methods: Since May 2006, 250 consecutive patients underwent TAVI with the Edwards SAPIEN prosthesis in our institution using either the transfemoral (TF, n=190), or the transapical (TA, n=60) approach. Suitability for TF was based on ilio-femoral angiography and computed tomography of the iliofemoral access. Up to October 2009, TF Edwards SAPIEN (ES) implantation required 22 or 24F sheath, inserted surgically in 100% of cases, whereas the SAPIEN XT (SXT) prosthesis was compatible with reduced sheath size of 18 or 19F inserted percutaneously with pre-close (Prostar XL, 10F) in 98% of cases. The consequences on vascular complication are reported according to the VARC classification.

Results: TF TAVI was performed using ES prosthesis in 78 pts and SXT in 112 pts. All baseline characteristics were similar in the two populations, except the Log EuroSCORE and STS scores was significantly higher in the subclavian versus femoral group (30.7 ± 15 vs. 18.5 ± 12.1, p = 0.001 and 10.9 ± 5.6 vs. 7.1 ± 5.5, p = 0.001, respectively), had more comorbidities (Charlson index 5.4 ± 1.9 vs. 3.5 ± 1.8, p = 0.001) even though the subclavian group were younger (76.3 ± 7.6 vs. 79.5 ± 6.2 P < 0.019) and they had a higher rates of porcelain aorta than femoral group (21.7% vs. 6.5%, P = 0.01). Mortality at 30 days was 8.7% for subclavian group and 4.7% for femoral group. P = 0.403; after a mean follow-up of 16.4 ± 11 months, the survival was 80% for subclavian group vs. 80.8% for femoral group. P = 0.13.

Conclusions: The subclavian approach is not frequent in patients undergoing transcatheter aortic valve implantation with the CoreValve prosthesis and appeared safe for the patients at very high or prohibitive surgical risk, including porcelain aorta patients, with contraindications to the femoral approach.

P4199 Incidence and prognostic implications of the subclavian approach for Transcatheter aortic valve implantation with the CoreValve prosthesis


1 University Hospital Virgen de la Victoria, Department of Cardiology, Malaga, Spain; 2 University Hospital Virgen de la Victoria, Malaga, Spain; 3 University Hospital Virgen de la Victoria, Department of Cardiovascular Surgery, Malaga, Spain

Transcatheter aortic valve implantation is an alternative option for patients with severe aortic stenosis at high surgical risk. The main approach is the femoral artery but in some cases it is not favorable by inadequate iliofemoral anatomy or extensive disease, so subclavian artery approach may be feasible. The aims of this study were to report the frequency of the subclavian approach and its relation to the clinical outcome after transcatheter aortic valve implantation.

Methods: Between April 2008 and January 2012, the CoreValve prosthesis (Medtronic, Minneapolis, MN, USA) was implanted in 239 consecutive high-risk surgical patients with symptomatic severe aortic stenosis. The subclavian approach was used in 23 patients (9.9%).

Results: The median logistic EuroSCORE and STS scores was significantly higher in the subclavian versus femoral group (30.7 ± 15 vs. 18.5 ± 12, P < 0.001 and 10.9 ± 5.6 vs. 7.1 ± 5.5, P = 0.001, respectively), had more comorbidities (Charlson index 5.4 ± 1.9 vs. 3.5 ± 1.8, P < 0.01) even though the subclavian group were younger (76.3 ± 7.6 vs. 79.5 ± 6.2 P < 0.019) and they had a higher rates of porcelain aorta than femoral group (21.7% vs. 6.5%, P = 0.01). Mortality at 30 days was 8.7% for subclavian group and 4.7% for femoral group. P = 0.403; after a mean follow-up of 16.4 ± 11 months, the survival was 80% for subclavian group vs. 80.8% for femoral group. P = 0.13.

Conclusions: The subclavian approach is not frequent in patients undergoing transcatheter aortic valve implantation with the CoreValve prosthesis and appeared safe for the patients at very high or prohibitive surgical risk, including porcelain aorta patients, with contraindications to the femoral approach.

P4201 Lower pacing rate with CoreValve TAVI: high implantation or Accutrak catheter, or both?

M. Drury-Smith, S. Lakshmanan, R. Giri, M. Fayaz, J. Cotton, M. Bhabra, S. Khogali. Heart and Lung Centre, Wolverhampton, United Kingdom

Introduction: Permanent pacemaker implantation (PPM) post transcatheter aortic valve implantation (TAVI) is a well recognised complication and the greater requirement after CoreValve TAVI compared with surgery (33% vs 8%) has caused concerns. Pre-existing bundle branch block (BBB), larger valve size, post dilatation peak atrioventricular gradient and low implantation pressure have been shown to independently increase the risk of PPM requirement. Implantation below the aortic annulus can result in compression of conduction tissue and heart block. A modified delivery catheter (ACCU-TRAK) may allow a more controlled release expansion of the prostheses, preventing low implantation and reducing PPM need. We evaluated the PPM requirement in all our TAVI patients (pts) treated before and after the introduction of the Accutrak catheter.

Methods: TAVI was performed in 101 pts: trans-femoral (80 pts), left subclavian (16 pts) and direct aortic approach (5 pts). A high valve deployment strategy of 3.5 mm below the aortic annulus was routinely employed. 12 of these had a pre-existing PPM and were excluded from analysis. 43 of the remaining 89 underwent TAVI using the Accutrak catheter. Procedural outcomes were analysed (table)

Results: Recognised predictors of PPM requirement post TAVI, were similar in both groups and were not significant (table). A total of 9 patients required a new
PPM (10.1%) post TAVI. There was no significant difference in PPM requirement between the pre and post-Accutrak groups. (10.9 vs 9.3; p=1.0).

Conclusion: In our cohort, the need for PPM (10%) is lower than previous reports and is independent of the Accutrak catheter. We would advocate a high deployment strategy. Further evaluation of the use of Accutrak catheter on PPM requirement in "middle to low" implanting centres is required.

Abstract P4202 – Table 1

<table>
<thead>
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<th>Post-Accutrak (43)</th>
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<td>20.4</td>
<td>-</td>
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<tr>
<td>Mean aortic anulus size (mm)</td>
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<td>22.4</td>
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<tr>
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<tr>
<td>Stroke rate (%)</td>
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<tr>
<td>PPM post TAVI (%)</td>
<td>10.1</td>
<td>New ppm post TAVI (%)</td>
<td>5</td>
</tr>
</tbody>
</table>

New pacemaker post TAVI within 30 days of procedure.

Conclusion: Hybrid treatment with supra-aortic vessel transposition and endovascular repair may be an option in frail patients in who open procedures is too risky.

Abstract P4203

Incidence, predictive factors and prognostic value of inflammatory reaction following transcatheter aortic valve implantation (TAVI)

Y. Maazoun1, C. Martinez1, M. Radermeker2, J. Magne1, R. Durieux2, O. Gach1, L. Davin1, J. Defraigne1, V. Legrand1, I. Chu Sarit Tanlan, Department of Cardiology, Liege, Belgium; 2CHU Saint-Tiitan, Liege, Belgium.

Purpose: Systemic inflammatory response syndrome (SIRS) which occurs following cardiovascular surgery is implicated in undesirable physiological alterations and may be associated with adverse clinical events. The incidence and consequences of inflammatory reactions that occur after TAVI are largely unknown. Therefore, we aim to assess predictive factors and impact of inflammatory reaction on outcome after TAVI.

Methods: Between July 2008 and January 2012, we included 76 consecutive patients who underwent TAVI for symptomatic aortic stenosis with the CoreValve® System (Medtronic CoreValve, Minneapolis, Minnesota) by transfemoral (71) or subclavian (5) approach. Demographic, procedural and baseline biological data obtained in all patients were analyzed. Blood samples including inflammatory parameters were taken during 7 days after TAVI. Statistical study analyzed correlation between inflammatory parameters including SIRS (defined as recommended guidelines) with demographic and periprocedural data. Influence of inflammatory variables on in-hospital and late outcome was analyzed.

Results: The mean age was 83±6.1 years, mean logistic EuroSCORE was 21.±14%. Twenty eight patients (38%) developed SIRS during the first 72 hours after TAVI. SIRS patients were characterized by hyperventilation (78.9%, P=0.001), tachycardia (76%, P=0.001), leucocytes ≥12×109/L (67% P=0.005) and fever (89.3%; P=0.001) compared with patients without SIRS. Occurrence of SIRS was associated with significant increase of CRP (p=0.04), CPK-MB (p=0.03), decrease of hemoglobin (p=0.02) and mechanical complications (p=0.08). In multivariate analyses, increase in leucocyte count at 48 hours (OR =1.7, p=0.15), tachycardia (OR=4.4, p=0.005) and anemia (OR=4.0, p=0.03) were predictive of SIRS. Fifty seven percent of patients had a significant elevation of CRP after TAVI (p=0.04). Increasing CRP was correlated with Glomerular Filtration Rate (GFR) decrease (p=0.11), fibrinogen (p=0.001) and leucocyte count increase (p=0.06). Temperature ≤36.0°C or ≥38.0°C was the only independent predictive factor of CRP elevation (p=0.01). SIRS and CRP values weren’t related to 30-day and 6-months mortality.

Conclusion: SIRS and CPK elevation are frequently observed after TAVI. Increase in leucocyte count, tachycardia and anemia are predictive of SIRS. Increasing CRP is correlated with GFR decrease. Temperature ≤36.0°C or ≥38.0°C was the only independent predictive factor of CRP elevation. This study doesn’t confirm that the inflammatory syndrome is associated with poor outcome at 30 days and 6 months.

Abstract P4204

Early changes of left ventricle deformation indices after transcatheter aortic valve implantation.

A speckle tracking echocardiographic study

M. Vasura1, I. Wassero1, K. Kolgera1, M. Korini1, D. Vrachalis1, C. Moldovan1, V. Kats2, R. Katsarou1, I. Kallikazaros1, C. Stefanadis1. 1Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece; 2Hippokration Hospital, Department of Cardiology, Athens, Greece.

Purpose: Transcatheter aortic valve implantation (TAVI) has been established as a reliable alternative treatment in high risk patients, resulting in symptoms and left ventricle function improvement. The aim of this study was to evaluate the impact of TAVI on early recovery of left ventricle function using echocardiographic left ventricular deformation parameters and to define their possible correlation with myocardial function.

Methods: In 16 patients (6 females, 8±5 years; EuroScore: 24±4%) with severe aortic stenosis but free of significant coronary artery disease who underwent TAVI with the CoreValve aortic prosthesis were studied. Conventional 2D and 2D-speckle echocardiography analysis were performed pre-intervention and at discharge. Deformation indices of left ventricle such as Peak Systolic Longitudinal Strain (PSLS) and Torsion (apex-basal rotation) were determined by speckle tracking echocardiography using commercially available computer software. Besides, Left Ventricle Ejection Fraction (LVEF), calculated with Simpson method, was evaluated at one month follow-up.

Results: In all patients at discharge, a reduction of transaortic peak pressure gradient (p=0.005), of mean pressure gradient (p=0.001) was observed, with a concomitant increase in aortic valve area (p=0.001). In addition, 2D speckle analysis showed a significant improvement of PSLS at discharge (10±6.2 vs 18±3.9%, p=0.008). Similarly, left ventricle Torsion was significantly increased comparing to pre-implantation values (7.2±5.1 vs 11.5±6.1, p=0.015). However, overall LVEF did not change (51.4±8.8 vs 50.9±8.1%, p=0.50).

Conclusion: Deformation indices of PSLS and Torsion are able to detect early improvement of left ventricle function after TAVI regardless LVEF alteration. Moreover, LVEF seems to predict LVEF in one month. Larger studies with long term follow-up are required.
Mitrail regurgitation after transcatheter aortic valve implantation with the Medtronic-CoreValve prosthesis: Impairments and impact of bleeding.

K. Boerlage-Van Dijk1, E.M.A. Wieringa1, Z.Y. Ying3, J.J. Bouma1, M.M. Vis1, K.T. Koeh1, R. Cocchi1, I. J. van Peerhuis1, J. Baan1.

1. Academic Medical Center, University of Amsterdam, Department of Cardiology, Amsterdam, Netherlands; 2. Academic Medical Center, University of Amsterdam, Department of Cardiothoracic Surgery, Amsterdam, Netherlands.

Background: Mitrail regurgitation (MR) is a risk factor on long-term survival in elderly patients who underwent an aortic valve replacement (AVR). The impact of mitral regurgitation in patients who undergo transcatheter aortic valve implantation (TAVI) is unknown. The aim of the study was to assess the influence of MR on survival in TAVI patients treated with a Medtronic CoreValve prosthesis.

Methods: In this single center prospective observational study we included 100 patients (age 81.6 ± 8 years, 40 male) with severe symptomatic aortic valve stenosis who underwent TAVI with the Medtronic-CoreValve bioprosthesis and underwent a post procedural echocardiographic evaluation. Other clinical parameters were obtained from the medical history.

Results: From the patients with an MR grade <3 (n=94) pre-procedural, 14% increased to MR grade ≥3 after TAVI (p=0.002) and from 6 patients with moderate to severe MR pre-procedural only one patient had a MR grade <3 after TAVI. Forty percent of the patients with significant (grade ≥3) MR died within 1 year versus 20% of the patients with MR grade <3 (p=0.051); 30-day mortality and 30-day cardiovascular mortality were not influenced by MR grade ≥3 following TAVI.

Conclusion: After TAVI with a CoreValve prosthesis there is a significant increase in MR grade in patients with MR grade <3. One year survival shows a tendency to be impaired in patients with a significant MR post TAVI.

Renal outcome after transcatheter aortic valve implantation.


1. University Heart Center Hamburg, Clinic for General & Interventional Cardiology, Hamburg, Germany; 2. University Heart Center Hamburg, Hamburg, Germany.

Background: Renal function impairment is a frequent complication after cardiac valve procedures. Data on risk factors for renal impairment after transcatheter aortic valve implantation (TAVI) are limited.

Methods and Results: In 299 consecutive TAVI patients (mean age 80.43±7.12 years; 54.8% women) we assessed renal function through plasma creatinine measurement and estimated glomerular filtration rate at baseline, peak during 72 h post procedure and at discharge and monitored individuals for incident renal failure (none, 213 (71.2%); stage 1 renal impairment, 62 (20.7%); stage 2, 15 (5.0%); and stage 3, 9 (3.0%). Mean creatinine concentrations in the sample were 1.10 (0.96-1.50) mg/dl at baseline and MDRD estimated glomerular filtration rate resulted in 56.63±2.33 ml/min/1.73 m². As expected, logarithmically transformed baseline creatinine was related to incident renal failure (Odds ratio (OR) 1.91, 95% confidence interval (CI) 1.19-3.10, P<0.007). Correlates of renal failure besides age and sex in age and sex-adjusted logistic regression analyses were body mass index (OR 1.09 95% CI 1.03-1.15, P<0.001) and logarithmically transformed procedure time (OR 2.24, 95% CI 1.08-4.70, P<0.03). In linear regression analyses procedure time was strongly related to peak change in glomerular filtration rate.

Conclusions: Besides age and sex, body constitution and procedure time are correlates of acute kidney injury after TAVI. When assessing periprocedural risk these factors should be considered in particular in elderly patients with pre-existing renal impairment.

Predictors of mortality post balloon aortic valvuloplasty, results from the BRAVO registry.

J. Yu1, A. Kin1, M.G. Cohen2, U. Baber1, S. Sarton1, R. Mehran1, G. Vlachsann1, B. O'Neil1, S. Sharma1, G.D. Dangas1 on behalf of BRAVO Investigators.

1. Mount Sinai Medical Center, New York, United States of America; 2. University of Miami Miller School of Medicine, Miami, United States of America.

Purpose: There have been notable advances in balloon aortic valvuloplasty (BAV) technique including RV pacing and improved management of the large sheath access site. However, a subgroup of patients continues to have poor outcomes despite intervention, and prognostic variables have not been identified in a contemporary context. We sought to examine the correlates of 1-year mortality from a recent BAV registry.

Methods: We conducted a retrospective review of patients who underwent non-emergent, retrograde BAV at two high volume centers from 1/1/2005 - 1/31/2010. Baseline demographic, laboratory, hemodynamic, and procedural characteristics were compared according to 1-year survival post-index BAV procedure. From
Off-label indications for trans-catheter aortic valve implantation

A. Segev, D. Spiegelstein, P. Fefer, A. Shinfield, I. Hay, E. Raananii, V. Guetta. Sheba Medical Center, Tel Aviv, Israel

Objective: Trans-catheter Aortic Valve Implantation (TAVI) has emerged as a novel therapeutic approach for patients with severe aortic steno-
sis (AS) not treatable for conventional surgical aortic valve replacement. Current indications for TAVI consist of symptomatic patients with severe tricuspid native aortic stenosis. We describe herein our initial experience of TAVI in patients with off-label indications.

Methods: 186 patients underwent TAVI in our institution from August 2008 to December 2011 using trans-femoral, trans-axillary, trans-apical and trans-atrial approaches. Between patients (59%) underwent TAVI for off-label indication due: 1) pure severe aortic regurgitation (AR) (n=2), 2) prosthesis aortic valve failure (n=5), 3) bicuspid aortic valve stenosis (n=2), and 4) prosthesis severe mitral valve regurgitation (MR) (n=2).

Results: In all patients implantation of valve was successful: 6 patients received CoreValve (1 trans-axillary and 5 trans-femoral) and 5 patients received Edwards-Sapien (4 trans-apical and 1 trans-femoral). In-hospital mortality was 0%. Valve hemodynamic end function were excellent in each 1 patient who received Ed-
wards valve inside a Mitroflow prosthetic aortic valve in whom trans-atrial gra-
ding was high. In AR and MR cases, no significant residual regurgitation was ob-
served.

Conclusions: TAVI is a good alternative to surgical AVR in high-risk patients with severe AS. TAVI for off-label indications such as pure aortic insufficiency, bicuspid aortic valve stenosis, and failed prosthesis valve (both aortic and mitral), is feasible and safe and may be considered in selected patients.

Incidence and predictors of combined safety endpoints occurrence after transcatheter Sapien XT and CoreValve implantation. A single Centre experience

S. Cassese1, A. M. Kasei2, A. W. Leber2, D. Antons2, G. Riess2, A. Hutter1, J. Vogel1, A. Kastrall1, W. Eichinger1, E. Hoffmann2.
1German Heart Center, Clinic for Heart and Circulatory Diseases, Munich, Germany; 2University Hospital Munich-Bogenhausen, Department of Cardiology and Critical Care Medicine, Munich, Germany; 3Municipal Hospital Munich-Bogenhausen, Department of Cardiac Surgery, Munich, Germany

Aims: To evaluate incidence and predictors of combined safety endpoints occurrence (Valve Academic Research Consortium – VARC definitions) among high-risk inoperable patients with symptomatic, severe aortic stenosis (AS) undergoing trans-femoral trans-catheter aortic valve implantation (TAVI) with current commercially available prostheses.

Methods and Results: We enrolled consecutive patients undergoing TAVI with Edwards SAPIEN XT – SXT (Edwards Lifesciences, Irvine, California; n= 50) or Medtronic CoreValve – CoV (Medtronic Inc, Minneapolis, Minnesota; n= 50). A good device success was achieved with both SXT and CoV (98% versus 90%, p= 0.20). After TAVI, transfemoral echocardiography and aortography showed higher paraavalvular regurgitation incidence with CoV (p<0.0001) without differ-
cences in terms of moderate/severe regurgitation among groups (p=0.03, SXT versus CoV). In-hospital, major vascular complications (p=1.00), life-threatening bleedings (p=1.00), stroke (p=1.00) and death (p=1.00) occurrence were sim-
ilar throughout SXT and CoV. A statistic trend toward worse renal function af-
ter CoV implantation was observed (p=0.056). Permanent PM need was more frequent after CoV implantation (p<0.0001). At 1-month follow-up, cumulative VARC combined safety endpoints incidence was 17% versus 34.6% (p= 0.01, SXT versus CoV), mainly driven from a numerically higher stroke (10%) and Acute Kidney Injury Stage 3 incidence (6%) associated with CoV. At multivariate anal-
ysis, TAVI with SXT (odds ratio – OR 0.20 95% confidence interval – CI [0.05-
0.86]; p= 0.03) and a previous percutaneous coronary revascularization history (OR 0.08, [0.008-0.94]; p= 0.04) were found protective against safety endpoints occurrence.

Conclusions: Together with a previous history of percutaneous coronary revas-
cularization, TAVI with Edwards SAPIEN XT was found independent predictor of lower VARC combined safety endpoints occurrence, as compared with Medtronic CoreValve. Larger cohorts are needed to confirm these results.

Impact of acute normobaric hypoxia on regional and global myocardial function: a speckle tracking echocardiography study

B. Goebel1, V. Handrick2, A. Lauten1, M. Fritzenger1, J. Schuetz2, S. Otto1, H.R. Fugilta1, T. Edvardsen3, T.C. Poerner1, C. Jung1.
1University Hospital Jena, Department of Internal Medicine I, Jena, Germany; 2University of Applied Sciences Jena, Department of Medical Engineering and Biotechnology, Jena, Germany; 3Oslo University Hospital, Rikshospitalet, University of Oslo, Dept. of Cardiology, Oslo, Norway

Objective: Aim of this study was to evaluate the influence of hypoxia on myocar-
dial function.

Methods: Fourteen subjects underwent two-dimensional speckle tracking eco-
cardiography (2D-STE) examination during normoxia and in a normobaric hypoxia chamber. Examinations were performed at rest and during bicycle exercise test. The following parameters were quantified in both atria and ventricles: Strain (S), systolic strain rate (SRS), early (SRE) and late (SRA) diastolic strain rate. In addi-
tion, left ventricular (LV) overall twist, systolic twist- and diastolic untwist rate were quantified.

Results: During hypoxia SRS and SRE increased significantly in both ventricles compared to baseline. The increase of LV SRS and SRE during normoxia exercise a single higher when compared with baseline under hypoxia (for SRS: 0.55±0.22 vs. -0.34±0.04 1/s, p= 0.024; for SRE 0.56±0.29 vs. 0.23±0.29 1/s, p= 0.005). For the right ventricle (RV) no significant difference of exercise induced increase of systolic strain rate (SRS) (1.07±0.52 under normoxia vs. -1.28±0.24 1/s under hypoxic conditions, p= 0.47). LV overall twist, systolic twist- and diastolic untwist rate were enhanced during hypoxia. A shift from passive conduit (S) to active contraction (SRA) phase during hypoxia was noted for the right atrium (RA) (S/RA 0.72±0.13 under hypoxia vs. 1.17±0.17 under normoxia), SRE/SRA of RA correlated to systolic pulmonary pressure (r = -0.78, p<0.01) (Figure 1).

Conclusions: Exposure to normobaric hypoxia leads to an increase of LV overall twist and regional myocardial deformation in both ventricles. The contractile re-
serve during hypoxic exercise is reduced in LV. In addition, hypoxia had an impact on the ratio of passive conduit to active contraction phase in right atrium.

Inhibition of Interleukin-1 activity by anakinra improves left ventricular myocardial deformation and torsion in patients with CAD and coxexual rheumatoid arthritis: a randomized trial

1University of Athens Medical School, Attikon Hospital, 2nd Department of Cardiology, Athens, Greece; 2University of Athens, Attikon Hospital, 2nd Cardiology Department, Athens, Greece; 3University of Athens, Athens, Greece

Background: Inhibition of Interleukin-1 activity by anakinra is used for the treat-
ment of rheumatoid arthritis (RA) and shows favourable effects on left ventricular function in these patients. We investigated the effects of anakinra on (LV) function in patients with CAD and coxosexual RA.

Methods: 40 patients with CAD and coxexual RA were randomized to receive a single injection of anakinra (100mg s.c.). At baseline and 3 hours after the in-
jection we assessed: a) WMSI and EF by 2D echocardiography b) the LV Global Longitudinal Strain (GLS) and Torsion using speckle tracking echocardiography c) systolic (Sm) and early diastolic (Em) myocardial velocities of the mitral annulus by using of tissue Doppler (TDI) d) the ratio of E wave of the mitral inflow meas-
ured by pulsed wave Doppler to the Em e) Fas, Fas ligand, nitrotyrosine (NT) by using of tissue Doppler (TDI) d) the ratio of E wave of the mitral inflow meas-
ured by pulsed wave Doppler to the Em f) Fas, Fas ligand, nitrotyrosine (NT)

Results: After 3 hours of anakinra injection, there were an increase in Sm (7.2±1.7, vs. 9.1±2.1 cm/s) and Em (7.7±2.7 vs. 9.1±3.1 cm/s) velocity along with a decrease in the E/Em ratio (12.1±10.2, vs. 9.5±7.9) (p<0.001). Fur-
thermore, there were an improvement in torsion (14.2±5.6, vs. 18.2±5.5 de-
grees) and GLS (16.2±4.7%, vs. -19.0±4.9%, as well as WMSI (1.33±0.43 vs. 1.21±0.31) and EF (51.8±10.0% vs. 57.6±10.9%), compared to baseline (p<0.001). Additionally, there were a decrease in NT (median 6.66 vs. 6.15), PC
Prognostic significance of speckle tracking-derived myocardial function in multivessel coronary disease

P. Zgainski1, K. Wierzbowska-Draabik1, H. Hawro1, P. Szczesniak1, L. Chrzanski1, J.D. Kasprzak1, I.I. Chair and Cardiology Department, Medical University in Lodz, Lodz, Poland; 2Medical University of Lodz, Department of Biopharmacy, Lodz, Poland

Purpose: We aimed to identify prognostic factors in unselected cohort of patients with multivessel coronary disease (MCD) among parameters derived from: state of the art echocardiographic assessment including speckle tracking echocardiography (STE), functional tests (indirect/indispensible exercise testing and 6-min walk test (6MWT)) and full biochemistry panel including beside traditional risk factors NT-proBNP, CRP, HbA1c, thrombomodulin, von Willebrand Factor, and cardiography (2DE) and cardiopulmonary exercise testing (CPET) using “breath” method, measuring oxygen uptake (VO2) at anaerobic threshold (AT).

Methods & Materials: 83 patients with recent diagnosis of stable MCD (at least two vessels with stenosis > 70% in coronary angiography), age 63.4±9.3 years, 28 women were followed up for approximately 20 months (12-31) to assess the occurrence of primary end-point: End1 (all cause death or myocardial infarction) and secondary end-point: End2 (mortality, myocardial infarction, cardiac hospitalization or need for unplanned revascularization). Mean LVEF was 49.9±10.2% and predominant angina class was CCS III (69%). The management was individualized based on heart team decision resulting in 55% angioplasty and 22% bypass grafting rate.

Results: There were 3 deaths (3.6%), 12 MI (14%), 4 ischemic strokes (5%), 36 hospitalizations (43%) and 11 unplanned revascularizations (13%) during the follow-up period. In univariate analysis the following prognostic factors of End1 were defined: fasting glycemia >110mg/dl (p=0.03), HbA1c >7.2% (p=0.003), leukocytosis (WBC) >9.5 x 10³/μl (p=0.001), 6MWT >270 [m] (p=0.007), global systolic longitudinal strain rate (GLSR) >0.8 s-1 (p=0.002), left ventricle torsion <11.8 ° (p=0.03), diabetes, (p=0.02). End2 was predicted by HbA1c >6.65% (p=0.0003), WBC >7.2 x 10³/μl (p=0.0001) and left ventricular rotation at papillary muscle level >1.50 (p=0.02) in univariate analysis. In multivariate analysis WBC >9.5 x 10³/μl, HbA1c >7.3% and GLSR >0.8 s-1 were prognostic factors for End1. Only HbA1c level >6.6% and WBC >7.2 x 10³/μl remained as multivariate predictors of End2.

Conclusions: The results of our study confirm the importance of established systemic risk factors: hyperglycemia defined by HbA1c and traditional conditions (leukocytosis). However, novel echocardiographic parameters derived by STE, especially GLSR and left ventricle torsion, emerge as predictors of adverse outcome superior to traditional echocardiographic indices. Novel biomarkers and functional tests did not prove functional usefulness in this group of patients.

P4214 Left ventricular rotation and torsion and its relation to functional capacity in hypertensive patients

A. Majstorovic, V. Celic, B. Pencic-Papovic, A. Slijepc, B. Stojcevic, A. Andric, I. Ilic-Djordjevic, S. Backovic, M. Pavlovic-Klemt, Medical Center Dr Dragisa Misovic-Dedinje, University Clinic for Internal Medicine, Belgrade, Serbia

Purpose: In patients (pts) with hypertension (HA) left ventricular (LV) apical rotation at rest and LV torsion can be predictors of LV functional reserve. The aim of our study was to assess the relationship between apical rotation and torsion of LV at rest and functional capacity in pts with HA.

Methods: Eighty healthy volunteers (age 18-45 years), smokers (group SM, n=42) and non-smoking controls (group C, n=38) participated in the study. An echocardiographic exam was done in controls and in smokers (group SM-1) after abstaining from smoking and coffee consumption for 12 hours. A repeat echocardiogram was done in SM after smoking two cigarettes and staying in a quiet room for 15 minutes (group SM-2). Left ventricular (LV) longitudinal strain (GS) and strain-rate (SR) were measured in apical views. To examine early diastolic relaxation, the following parameters were measured: (1) Change in strain during the first one-third of diastole (Strain Imaging Diastolic Index [SI-DI] - ([GI/Gend-systole – GS1/3-diastole]/GS-end-systole)*100); (2) Time-to-peak SRave wave, indexed to diastolic duration and expressed as percent of total diastolic time. (3) Percent change in strain at the end of SRave wave, representing the strain difference from end-systole to the end of the early diastolic relaxation.

Results: The two groups had similar age, body surface area, LV ejection fraction, LV mass and left atrial volume index. Heart rate and blood pressure increased after smoking. End-systolic GS, SRs and SRave did not differ between groups, while SRave wave was increased in SM-2 group (p=0.008). At first one-third of diastole, GS was significantly different between C and SM-1 (-7.2±2.5% and -4.5±2.7%, respectively, p=0.001) and changed more in SM-2 (-5.6±2.3% and -2.8±1.8%, p=0.001 compared to SM-1 and C). SI-DI was significantly lower in SM-1 compared to C (SM-1: 0.7±1.3% and C: 1.7±1.0%, p=0.001) and was further reduced, when smokers smoked two cigarettes (SM-2: 4.9±1.6%, p=0.001 compared to SM-1 and C). Time-to-peak SRave wave was equal in C and SM-1 (24.4±4.2% and 25.2±5.2% respectively, p=0.462) but was significantly prolonged in SM-2 (30.1±6.7%, p=0.001 compared to C and SM-1). Change in strain at the end of SRave wave was significantly lower in SM-1 compared to C (72.2±3.8% and 74.8±3.5% respectively, p=0.017) and was further reduced in SM-2 (70.8±3.7%, p=0.001 compared to C, p=0.008 compared to SM-1).

Conclusion: The aim of this study was to evaluate the effects of smoking on left ventricular (LV) function by using speckle-tracking echocardiography in healthy young subjects.

Methods: Eighty healthy volunteers (age 18-45 years), smokers (group SM, n=42) and non-smoking controls (group C, n=38) participated in the study. An echocardiographic exam was performed in controls and in smokers (group SM-1) after abstaining from smoking and coffee consumption for 12 hours. A repeat echocardiogram was done in SM after smoking two cigarettes and staying in a quiet room for 15 minutes (group SM-2). Left ventricular (LV) longitudinal strain (GS) and strain-rate (SR) were measured in apical views. To examine early diastolic relaxation, the following parameters were measured: (1) Change in strain during the first one-third of diastole (Strain Imaging Diastolic Index [SI-DI] - ([GI/Gend-systole – GS1/3-diastole]/GS-end-systole)*100); (2) Time-to-peak SRave wave, indexed to diastolic duration and expressed as percent of total diastolic time. (3) Percent change in strain at the end of SRave wave, representing the strain difference from end-systole to the end of the early diastolic relaxation.

Results: The two groups had similar age, body surface area, LV ejection fraction, LV mass and left atrial volume index. Heart rate and blood pressure increased after smoking. End-systolic GS, SRs and SRave did not differ between groups, while SRave wave was increased in SM-2 group (p=0.008). At first one-third of diastole, GS was significantly different between C and SM-1 (-7.2±2.5% and -4.5±2.7%, respectively, p=0.001) and changed more in SM-2 (-5.6±2.3% and -2.8±1.8%, p=0.001 compared to SM-1 and C). SI-DI was significantly lower in SM-1 compared to C (SM-1: 0.7±1.3% and C: 1.7±1.0%, p=0.001) and was further reduced, when smokers smoked two cigarettes (SM-2: 4.9±1.6%, p=0.001 compared to SM-1 and C). Time-to-peak SRave wave was equal in C and SM-1 (24.4±4.2% and 25.2±5.2% respectively, p=0.462) but was significantly prolonged in SM-2 (30.1±6.7%, p=0.001 compared to C and SM-1). Change in strain at the end of SRave wave was significantly lower in SM-1 compared to C (72.2±3.8% and 74.8±3.5% respectively, p=0.017) and was further reduced in SM-2 (70.8±3.7%, p=0.001 compared to C, p=0.008 compared to SM-1).

Conclusion: The aim of this study was to evaluate the effects of smoking on left ventricular (LV) function by using speckle-tracking echocardiography in healthy young subjects.
Conclusion: Delayed LV diastolic relaxation is seen in healthy chronic smokers, even after abstinence from smoking for several hours. Acute smoking inhalation induces a further delay in diastolic relaxation while systolic function is preserved.

Two-dimensional Speckle-tracking Echocardiography to Identify reversible myocardial dysfunction
M. Ori, K. Hirata, K. Ibashishi, T. Yamano, T. Tanimoto, Y. Ino, T. Yamauchi, T. Kuba, T. Imamishi, T. Akasaka. Wakayama Medical University, Dept. of Cardiovascular Medicine, Wakayama, Japan

Purpose: Two-dimensional speckle-tracking echocardiography (2DSTE) could allow low-dose assessment of myocardial viability after acute myocardial infarction (AMI). This study evaluated the predictive value of 2DSTE for improvement in cardiac function after AMI in comparison with contrast-enhanced cardiac magnetic resonance imaging (cMRI).

Methods: In 25 patients with first-time acute ST elevation myocardial infarction, myocardial viability was assessed using 2DSTE and cMRI to predict recovery of function at 6 months follow-up. For each left ventricular segment in a 16-segment model, peak radial, circumferential and longitudinal strain was determined using 2DSTE (Echopac, GE Ultrasound, Horton, Norway), and the relative extent of hyperenhancement using cMRI.

Results: Of 128 segments with impaired function early after AMI, 65 showed regional recovery. Compared with segments showing functional improvement, those that failed to recover had lower peak radial (18±16% vs. 34±20%; p<0.001), circumferential (-18.7% vs. -9.0%; p<0.001) and longitudinal (-13.5% vs. -7.9%; p<0.001) strain and a greater extent of hyperenhancement (71±21% vs. 25±20%; p<0.001). Among strain parameters, circumferential strain yielded greater area under the curve (0.914) than radial and longitudinal strain (0.717 and 0.743, respectively). The predictive value of circumferential strain (sensitivity 80.3%, specificity 81.2%, at a cutoff value of 12.5%) could be comparable to that of hyperenhancement by cMRI (sensitivity 87.8%, specificity 88.1%, area under the curve 0.939, at a cutoff of 46% hyperenhancement).

Conclusions: Myocardial deformation imaging based on 2DSTE is a powerful novel modality to identify reversible myocardial dysfunction after AMI.

Soluble angiotensin converting enzyme is linked with impaired myocardial deformation and torsion in untreated hypertensives
I. Ikonomidou, I. A. Tsrantsis, I. H. Triantafyllopoulos, S. Tzortzis, P. Trivoli, I. Paraskevaidis, C. Papadopoulou, A. Trivoli, J. Lekakis, M. Anastasiou-Nana. 1 University of Athens, Attikon Hospital, 2nd Cardiology Department, Athens, Greece; 2 Laboratory of Haematology and Blood Bank Unit, University of Athens, Athens, Greece

Background: Soluble angiotensin converting enzyme (sACE) in likely to increased angiotensin II production and thus promotes cardiac and vascular fibrosis. LV myocardial deformation and torsion as assessed by speckle tracking echocardiography are markers of subclinical myocardial dysfunction. We investigated the association circulating sACE with LV deformation markers and arterial stiffness in untreated hypertensives.

Methods: In 220 untreated patients (age 54±11 years) with essential hypertension, and 80 healthy controls, we measured a) LV longitudinal, circumferential and radial strain (SV), peak torsion and the percentage changes between peak twisting and untwisting at mid atrial valve opening and end of early diastolic filling using speckle tracking echocardiography b) Carotid to femoral artery pulse wave velocity and c) arterial stiffness by carotid-femoral pulse wave analysis.

Results: Compared to controls, patients had decreased longitudinal strain (−19.2±2.6 vs. −21.9±2.5 p<0.05), peak torsion (13.8±3.4 vs. 17.1±3.6, deg p<0.05), % changes between peak twisting and untwisting at mid valve opening (29±8 vs. 38±7, p<0.05) as well as at end of early diastolic filling (67±9 vs. 73±8, p<0.05), higher PWV (10.5±1.8 vs. 8.2±1.5, p<0.05) and higher sACE levels (27±8 vs.21±7 U/ml p<0.05). Increasing sACE was related reduced radial S, peak torsion and % change between peak twisting and untwisting at end of early diastolic filling using r (r=0.41, r=0.40, r=0.37, respectively, p<0.05) by regression analysis, the above relations remained significant after adjustment for age, sex, LV mass and blood pressure (p<0.05). No association was observed between sACE and PWV (r=ns).

Conclusions: Soluble angiotensin converting enzyme is related to impaired myocardial deformation and torsion in untreated hypertensives with essential hypertension likely by promoting abnormal collagen turnover and fibrosis.

Evaluation of left ventricular segmental strain by three-dimensional echocardiography
A. Muranaka, S. Yuda, M. Kawakami, H. Kozu, H. Akasaka, H. Omori, A. Hashimoto, S. Saitoh, K. Tsuchihashi, T. Mura. 1 Sapporo Medical University, 2nd Department of Internal Medicine, Sapporo, Japan; 2 Sapporo Medical University, Dept. of Clinical Laboratory, Sapporo, Japan; 3 Sapporo Medical University School of Health Sciences, Dept. of Internal Medicine, Sapporo, Japan

Background: Three-dimensional speckle tracking imaging (3DS) allows assessment of left ventricular (LV) volume and function with high sensitivities. However, it is still unclear whether feasibility of regional data collection and estimates of regional strains differ between 3DS and two-dimensional speckle tracking imaging (2DS). We examined this issue in the present study.

Methods: Standard 2D echocardiography and 3D data set collection by using Vivid E9 with 4V probe (GE Healthcare) were performed in 212 subjects, who participated in an annual health examination. Apical long axis, four chamber and two chamber views were recorded to assess longitudinal strain by 2DS. 3DS and 2DS were analyzed off line by EchoPAC(GE Healthcare). We excluded subjects in whom 4 or more of 18 LV segments were unusable for strain determination, and 49 subjects (all women, age 63±12 years) contributed to the present analysis.

Results: The feasibility of 3DS was lower at LV base level (Figure). There were significant differences between strain by 3DS and longitudinal strain by 2DS in the mid-antero-septum (-25.3% vs. 24.1%, p<0.0001), mid-lateral (-18.1% vs. -24.3%, p<0.0001), mid-posterior (-23.7% vs. -18.9%, p<0.0001) and mid anterior strain (-25.9% vs. -19.6%, p<0.0001). Strain in the other segments and global strain were similar in 3DS and 2DS.

Conclusions: There are regional differences in feasibility of 3DS and data agreement between 3DS and 2DS. 3DS provides significantly lower estimates of strains in mid-level of the ventricle compared with 2DS.

Impaired LV systolic function in asymptomatic lean individuals with obstructive sleep apnoea evidenced by speckle-tracking echocardiography
H.Q. Pham, S.K. Namtvedt, H. Rosjo, T. Omland, K. Stein, T.G. Von Luerder. Akershus University Hospital, Department of Cardiology, Lenerskog, Norway

Aims: Obstructive sleep apnoea syndrome (OSA) predisposes to heart failure, but may be related to co-morbid obesity. We aimed to clarify the impact of OSA on LV function independent of obesity.

Methods: 40 patients with OSA (AHI, apnea-hypopnea-index ≥10) but free of cardiovascular disease were categorized into lean (body-mass-index, BMI <30), OSA-lean (n=41) or obese (BMI ≥30, “OSA-ob”, n=22) and compared with 41 healthy controls. Comprehensive echocardiographic analysis included global LV longitudinal strain (LVS), and myocardial velocities by tissue Doppler imaging.

Results: See table. OSA-lean and OSA-ob demonstrated mild overweight and moderate obesity, respectively. Blood pressure and LV mass index were higher in OSA-ob than controls, and further increased in OSA-ob. LVFS was slightly but significantly reduced in both OSA groups, while only OSA-ob showed reduced diastolic function. LVFS was lower both in OSA-lean and OSA-ob than controls. Importantly, LTVS was strongly and inversely correlated with AHI (R=−0.6, P<0.0001), even after adjusting for BMI.

Left ventricular mechanics in OSA

Parameter | Controls | OSA lean | OSA obese
--- | --- | --- | ---
AHI, apnea-hypopnea index | 1.1±0.2 | 22.6±4.0 | 28.4±4.0
BMI, body mass index (kg/m²) | 24.7±0.4 | 26.7±0.3 | 33.7±0.6
MAP, mean arterial blood pressure (mmHg) | 94±2 | 100±2 | 104±3
LV mass index (g/m²) | 76.6±3.1 | 84.3±4 | 89.1±4
LV ejection fraction (%) | 51.3±0.8 | 58.4±0.8 | 58.9±0.3
LVEDD, LV end-diastolic dimension (mm) | 51.7±0.6 | 51.6±0.9 | 53.6±0.6
RWT, relative wall thickness | 0.31±0.01 | 0.33±0.01 | 0.37±0.01
LV end-systolic dimension (mm) | 32±0.5 | 32±0.7 | 37±0.11
Transmural E/A ratio | 1.9±0.1 | 1.6±0.1 | 1.4±0.1
E/A ratio | 7.7±0.3 | 8.3±0.7 | 10.5±0.8
LVFS, global LV longitudinal strain (%) | 18±0.3 | 15.8±0.4 | 14.7±0.5

* P<0.05, ** P<0.01, *** P<0.001, OSA lean versus controls. † P<0.05, †† P<0.01, OSA lean versus OSA obese. Unpaired t-test, P<0.05 was considered significant.

Conclusions: Co-morbid obesity and hypertension were associated with modest cardiac hypertrophy and reduced diastolic function in OSA patients. Conversely, both lean and obese OSA patients displayed reduced LVFS that correlated with OSA severity index, suggesting specific pathophysiological mechanisms.
Assessment of left ventricular myocardial deformation and mechanical dysynchrony in patients with heart failure: insights from three-dimensional wall motion analysis

X.X. Luo, F. Fang, A.P. Lee, Y.V. Lam, J.E. Sanderson, J.S.W. Kwong, C.M. Yu. Div of Card, Dept of M&T, IVS, LiHS, St Ho Cardio Disease & Stroke Ctr, PWH, CUHK, Hong Kong, China, People’s Republic of

Purpose: Impaired myocardial contractility is detected with two-dimensional speckle tracking echocardiography (2DSTE) in heart failure patients with normal ejection fraction (HFNEF); however, 2DSTE is limited by ignorance of actual three-dimensional myocardial motion. Therefore, this study is aimed to further explore the myocardial function including the global dysynchrony in HFNEF with three-dimensional speckle-tracking echocardiography (3DSTE) which circumvent the limitations of 2DSTE.

Method: We enrolled thirty-three healthy subjects (48±12 years; 48.5%, male), 53 patients with HFNEF (70±10 years; 56.6% male) and 41 with reduced ejection fraction (HFREF) (65±10 years; 87.5% male) in our study. 3D-STE was performed (Toshiba Medical Systems, Japan) to obtain global area strain (AS), longitudinal (LS), circumferential (CS) and radial strain (RS). For LV dysynchrony, AS-systolic dyssynchrony index (AS-SDI) was calculated from the standard deviation of time to peak segmental AS of 16 segments.

Transplantation Global AS, CS, LS and RS in patients with HFNEF were significantly higher than their counterparts with HFREF (all p<0.001) but lower than in the normal group (all p<0.05) (Table 1). Intriguingly, AS-SDI was significantly prolonged in HFREF when compared with the control group (16.3±5.9 ms vs. 7.8±1.9 ms; both p<0.001 vs. control), and was more severe in the HFREF group (p<0.001).

Results: As a combination of both LS and CS, not only can 3D-derived global AS accurately detect subtle myocardial dysfunction in HFNEF, it can also assess LV dysynchrony more comprehensively in a 16-segmental mode during one cardiac cycle, which might be promising for further exploring the pathophysiology of HFNEF.

Conclusions: As a combination of both LS and CS, not only can 3D-derived global AS accurately detect subtle myocardial dysfunction in HFNEF, it can also assess LV dysynchrony more comprehensively in a 16-segmental mode during one cardiac cycle, which might be promising for further exploring the pathophysiology of HFNEF.

Area strain for the assessment of regional left ventricular wall thickening using 3D Speckle Tracking

S.F. De Marchi, S. Urheim, E.W. Remme, R. Massey, S. Aakhus. 1Oslo University Hospital, Oslo, Norway; 1Institute for Surgical Research, University of Oslo, Oslo, Norway

Background: 3D speckle tracking is a promising new technology. It allows reconstructing LV motion in time and space. Shortening in the longitudinal and circumferential directions can be combined in an area strain (aS) measurement which in contrast to wall thickening (radial strain) does not require endo- and epicardial border detection. We investigated the relation between aS and wall thickening by two geometrically independent measurements.

Methods: In 12 patients, 3D full volume echocardiographic clips of the LV were acquired. 3D endo- and epicardial border detection was performed to calculate wall thickening, whereas 3D speckle tracking was used to assess aS. All geometric measurements were performed frame-by-frame at 336 sites on refined left ventricle meshes.

Results: 52±7±2 wall thickness - aS data pairs were retrieved. In ROC analysis, an aS>−15.3% was able to detect a systolic wall thickening <−20% with a sensitivity and specificity of 83.2% and 80.2%, respectively. The area under the ROC curve was 0.88. As expected from deformation theory, there was a nonlinear relation between wall thickening and aS (Poisson effect). The estimated Poisson’s ratio of myocardial tissue was 0.39, showing even the compressible nature of myocardial tissue should be considered by applying a Poisson’s ratio below 0.50.

Conclusions: aS derived from 3D speckle tracking reflects local wall thickening during the cardiac cycle and has the potential to detect regional contraction abnormalities. In principle, aS can be converted directly into radial strain using basic elastic deformation formulas (Poisson effect), but the compressible nature of myocardial tissue should be considered by applying a Poisson’s ratio below 0.50.

Diabetic retinopathy is associated with the occurrence of subclinical diabetic cardiomyopathy in patients with type II diabetes

C.T. Zhao, M. Wang, K.H. Yiu, H.F. Tse. Queen Mary Hospital, Department of Medicine, Division of Cardiology – The University of Hong Kong, Hong Kong, Hong Kong SAR, People’s Republic of China

Background: Diabetic retinopathy (DR), as a marker of microvascular disease, is associated with increased risk of cardiovascular diseases (CVD). However, there is no data on the relationship between DR and subclinical diabetic cardiomyopathy in patients (pts) with type 2 diabetes (DM).

Method: We performed stereoscopic fundus photography with 7 standard fields in 114 type 2 DM pts (62.5±9.9yrs, 53% female) without overt CVD. Detailed transradial echocardiography with two-dimensional speckle tracking imaging was performed to measure global left ventricular (LV) function, including longitudinal strain and strain rate.

Results: DR including both non-proliferative and proliferative retinopathy was detected in 22 pts (19%). There were no significant differences in age (63±6 vs. 62±10), female gender (50 vs. 56%), fasting glucose (7.5±2.5 vs. 7.4±1.9 mmol/L) and HbA1c (8.0±1.3 vs. 7.6±1.2%) between pts with or without DR (all P>0.05). However, pts with DR had a longer disease duration than patients without DR (14.8±9 vs. 7.7±9 years, P<0.01). Conventional echocardiography showed no differences in LV ejection fraction (63±6 vs. 64±8%), and LV mass index (200±47 vs. 203±62 g/m2) between the 2 groups (P>0.05). However, pts with DR had a significantly lower LV global longitudinal strain (−16.8±3.13 vs. −18.3±2.12%, P<0.05) and strain rate (−0.84±0.15 vs. −0.95±0.33, P<0.05) compared with pts without DR. After adjustment with age, gender, HbA1c, duration of disease and conventional cardiovascular risk factors, multivariate linear regression revealed that DR was independently associated with impaired LV global longitudinal strain rate (β=0.28, confidence interval [CI]=0.17 to 0.39, P<0.01), but not LV global strain (β=0.18, CI=0.25 to 0.20, P=0.9).

Conclusions: Our results demonstrated that DR was detected in 19% of type 2 DM pts without overt CVD. The occurrence of DR was independently associated with subclinical LV myocardial dysfunction as detected by two-dimensional speckle tracking imaging. The findings of the study suggested that microvascular
Ejection fraction and deformation in response to three different chemotherapeutic regimes

Ejection fraction and deformation in response to three different chemotherapeutic regimes

T. Negishi<sup>1</sup>, K. Negishi<sup>1</sup>, D. Agier<sup>1</sup>, B. Halaska<sup>1</sup>, J.C. Plana<sup>1</sup>, T. Marwick<sup>1</sup>, C. Cleveland Clinic Department of Cardiovascular Medicine, Cleveland, United States of America; <sup>2</sup>University of Queensland, Princess Alexandra Hospital, Brisbane, Australia

Purpose: Evaluation of cardiac function is mandatory for cancer patients who receive potentially cardiotoxic (CTX) regimens, in whom assessment of ejection fraction (EF) and myocardial mechanics have shown subclinical myocardial damage. We sought to define the demographic, clinical and chemotherapy regimes associated with CTX.

Methods: We studied 165 patients (50±14, 72 women) receiving anthracycline 214±112 mg/m² [group A, n=65], trastuzumab [group T, n=53] or T with A dose 213±39 mg/m² [group AT, n=48]. Conventional echo indices (EF, mitral annular s’ and e’ velocity) and myocardial deformation indices (global longitudinal peak systolic strain [GLS], strain rate [SR-s] and early diastolic strain rate [SR-e] from speckle tracking) were measured at baseline and follow-up (10±6 months). The association of regimen with ∆EF was sought in a multiple linear regression.

Results: Age (p=0.03), gender (p=0.001), dyslipidemia (p=0.03), and radiation therapy (p=0.001) were significantly different among three groups. Reduction of EF in group MO was in group AT (Fig. 1). ∆EF reduction in EF ≥ 10% (p=0.001) occurred in 6 group A, 0 group T and 4 group AT patients. SR-s significantly decreased in groups T and AT. There were no significant differences in s’, e’ GLS and SR-e among the groups. Combination regimen (group AT) was correspondently associated with ∆EF after adjusting for age, gender, dyslipidemia and radiation therapy (p=0.011, β=−0.221, 95% CI [-4.342 to -0.564]).

Figure 1. The change in EF and SR-s.

Conclusion: Combined A+T is most conducive to reduced EF and SR-s is reduced in T and A+T. Some patients are sensitive to anthracycline and/or radiation therapy. Careful assessment of LV dysfunction is warranted in all patients receiving CTX agents.

Left ventricular dysynchrony in patients with microvascular obstruction after primary percutaneous coronary intervention evaluated with Real-time 3D speckle-tracking echocardiography

G. Pinnacchio, L. Barone, A. Stazi, I. Battaglia, L. Marinacchio, M. Laurito, I. Covello, A. Seslito, G.A. Lanza, F. Crea. Catholic University of the Sacred Heart, Department of Cardiovascular Medicine, Rome, Italy

Purpose: Microvascular obstruction (MVO) in patients with ST-segment-elevation myocardial infarction (STEMI) is associated with a negative remodeling of the left ventricle and worse clinical outcome. However, the effects of MVO on mechanical ventricular synchrony in these patients is poorly known. In this study we investigated the impact of MVO on synchrony of left ventricular (LV) contraction in patients with STEMI treated by PCI with microvascular coronary intervention (PPCI).

Methods: We enrolled 35 consecutive patients (average 56±12; 29 males) with a first STEMI undergoing PPCI within 12 hours of symptoms onset. Angiographic and operational diagnosis was confirmed as MVO in 25 patients (71.4%). LV systolic function was assessed withReal-time 3D speckle-tracking echocardiography at baseline and at 1 month follow up. The standard 16-segment model of the LV anatomy was used for analysis of regional LV contraction. Presence and degree of mechanical desynchrony was evaluated with the systolic dyssynchrony index (SDI, standard deviation of the time to peak LV-segment) for strain in longitudinal (LS), circumferential (CS) and radial (RS) direction.

Results: MVO occurred in 9 of the 35 patients (25.7%). Patients with MVO, compared to no-MVO patients, were older (63±11 vs 54±12, p=0.05), had a higher time to PCI (<3 h vs 0.5 ±0.5 h, p=0.05), had a lower prevalence of pre-intervention angina (73.1% vs 33.3%, p=0.05), while there were no found differences between groups in gender, in-fact side, culprit vessel and troponin peak serum level. LVEF was lower in MVO patients both at pre-discharge (42±8% vs 53±12%, p=0.03) and at follow up (49±5% vs 56±4%, p<0.01). Moreover, patients with MVO showed higher values of SDI on LS, CS and RS direction compared to those without MVO both at baseline (19.1±4.4 vs 14.3±4.6, p=0.006; 16.5±6.4 vs 12.5±5.1, p=0.008; 22.1±6.9 vs 13.7±5.0, p=0.001, respectively) and follow up (15.8±4.1 vs 10.6±2.9, p=0.001; 11.4±5.1 vs 7.0±2.7, p=0.008; 18.6±4.5 vs 9.6±3.6, p=0.001, respectively).

Conclusion: Patients with MVO after PPCI showed a lower LV contraction and a higher degree of LV mechanical dysynchrony at pre-discharge. Both LVEF and LV dysynchrony significantly improved at 1 month follow up in the two groups of patients, but remained impaired in MVO patients compared to reperfused patients.

Effects of radiotherapy on right and left heart function in patients with left-sided breast and lung cancer detected by strain and strain rate imaging

B. Cakal<sup>1</sup>, S. Cakal<sup>1</sup>, A. Mayadagli<sup>2</sup>, K. Ekici<sup>1</sup>, Z. Bayram<sup>1</sup>, M.O. Gunsoy<sup>1</sup>, R.D. Acar<sup>1</sup>, N.E. Duran<sup>1</sup>, M. Yildiz<sup>1</sup>, M. Ozkan<sup>1</sup>

<sup>1</sup>Kartal Kosuyolu Heart Education and Research Hospital, Department of Cardiology, Istanbul, Turkey; <sup>2</sup>Kartal Research and Training Hospital, Istanbul, Turkey

Aim: Radiotherapy (RT) of the chest is commonly used in the management of early-stage breast cancer and lung cancer. RT administered on the left breast, left thoracic wall, or on the internal mammary lymph nodes usually involves irradiation of the heart and is potentially associated with long-term cardiovascular adverse events. We aimed to investigate the occurrence of early radiation-induced changes in cardiac function using strain (S) and strain rate imaging (SR) in patients (pts) with left-sided breast cancer (LSCB) and left-sided lung cancer (LSLC).

Methods: Thirty-five (13 breast cancer and 22 lung cancer) pts who required RT were included in this study. All pts received a computed tomography scan for RT planning. Radiation dose was 50 Gray (Gy) in 25 fractions. An additional boost of 10 or 16 Gy was delivered to the tumoral cavity in case of breastconserving surgery and lung boost. Radiation effect on cardiac function was assessed
Reduced left ventricular contractility with electrical dyssynchrony was observed in patients with left bundle branch block (LBBB). RT4DE full volume acquisitions were obtained in 37 patients with LBBB. 3DSTE: -18.6±5.3, 2DSTE: -15.4±4.6, r=0.89, p<0.01) with no significant bias (0.4±p). Correlation of averaged LS and their mean bias were 0.52±0.59 at basal level, 0.89±1.17 at middle level and 0.73±1.46 at apical level, respectively. Correlation of global LS between the two methods was higher in group of patients who had LV twist value less than 13.4 degree (n=93) compared to group of patients with LV twist values >13.4 degree (n=68).

Conclusions: Patients who had higher LV twist revealed moderate correlation of global LS between the two methods. Lower correlation and larger bias of averaged LS at basal and apical LV level between the two methods suggest LV twisting actually affects the calculation of 2D LS.

### Assessment of left ventricular dyssynchrony with real-time 4D ultrasound system: comparison with Doppler Myocardial Imaging

**Purpose:** To evaluate left ventricular mechanical dyssynchrony (LVMD). The very latest generation of real-time 4D ultrasound systems (RT4DE) have the ability to acquire a full volume dataset in one cardiac cycle. Aim of the study was to compare the assessment of LVMD by Pulsed Wave-Doppler Myocardial Imaging (PWD-OMI) and RT4DE.

**Methods:** 10 healthy volunteers (NL) and 27 pts with left bundle branch block (QRS wide 147±17ms, EF 38.7% ±3.6 vs -19.03±3.1, respectively, p=0.03). No decline in LV deformations was observed in pts with LSBC (-2.03±0.3 vs. -19.5±2.6, respectively, p=0.95).

**Results:** Twenty-seven patients were LV ejection fraction (LVEF) <50%. Mean value of IVS-PW delay was 38±7,4% vs 4,1±3.8% respectively. LV-S differed significantly in LSBC group (-20.7±4.4 vs -19.2±3.6 vs -19.0±4.7, respectively, p=0.03). No decline in LV deformations was observed in pts with LSBC (-20.03±0.3 vs. -19.5±2.6, respectively, p=0.95).

**Conclusion:** Pts receiving RT for LSBC and LSCL have decreased RV-S whereas LV-S was only reduced in LSCL group following RT. RV-SR was also decreased in pts with LSLC. Reduction in RV-S and SR is likely due to higher radiation exposure of the right ventricle due to its anterior location. Moreover, high dose radiation exposure to heart reduced LV-S in LSLC group. This study demonstrated RT has a depri effect on both RV and LV-SR, is first to be reported.

### Reduced left ventricular contractility with electrical dyssynchrony

**Purpose:** To evaluate the degree of LV dyssynchrony in patients with right ventricular (RV) pacing by speckle tracking strain rate (SR) analysis. We evaluated the degree of LV dyssynchrony in patients with right ventricular (RV) pacing by speckle tracking strain rate (SR) analysis.

**Methods:** Echocardiography was performed in 81 consecutive patients with RV pacing. As a dyssynchrony index, the difference between 1st peak of LV septum and that of posterior wall (IVS-PW delay) was measured by M-mode at the mid-LV level. We used off-line software EchoPAC (GE Ultrasound) for SR analysis and measured radial SR at mid-LV short axis view. The dyssynchrony index (DI) was defined as the ratio of average myocardial thinning (negative SR) to thickening (positive SR) of 6 segments during the ejection period (Figure). In multivariate analysis, the independent predictor of DI was LVEF (p<0.001).

**Results:** Twenty-seven patients were LV ejection fraction (LVEF) <50%. Mean value of IVS-PW delay was 38±7,4% vs 4,1±3.8% respectively. LV-S differed significantly in LSBC group (-20.7±4.4 vs -19.2±3.6 vs -19.0±4.7, respectively, p=0.03). No decline in LV deformations was observed in pts with LSBC (-20.03±0.3 vs. -19.5±2.6, respectively, p=0.95).

**Conclusion:** Pts receiving RT for LSBC and LSCL have decreased RV-S whereas LV-S was only reduced in LSCL group following RT. RV-SR was also decreased in pts with LSLC. Reduction in RV-S and SR is likely due to higher radiation exposure of the right ventricle due to its anterior location. Moreover, high dose radiation exposure to heart reduced LV-S in LSLC group. This study demonstrated RT has a depri effect on both RV and LV-SR, is first to be reported.

### Effect of left ventricular twisting for the accuracy of two-dimensional longitudinal strain analysis

**Purpose:** 2D longitudinal strain (LS) calculation could be influenced by loss of speckle due to left ventricular (LV) twisting motion. 3D speckle tracking echocardiography (STE) is theoretically more accurate for LS measurements. If LV twisting motion affects 2D LS calculation, we hypothesized worst correlation of LS between 2DSTE and 3DSTE was observed at apical level, and best correlation was noted in the middle level due to helical nature of myocardial fibers.

**Methods:** We acquired 2D apical 4-, 2-chamber and long-axis views and 3D full volume datasets (GE, Vivid E9) in 54 patients with various cardiovascular disease (mean age: 64±18 years, 29 men, LVEF: 54±12%). Using 2D/3D speckle tracking software, global LS and averaged LS at 3 LV levels (basal, middle and apical) were calculated. In 44 of 54 patients who could be also analyzed LV twist on the 2D short axis views, patients were divided into two groups according to the median value of LV twist (13.4 degree) for investigating the effect of LV twisting.

**Results:** A good correlation of global LS was noted between the two methods (2DSTE: -15.8±5.3, 3DSTE: -15.4±4.6, r=0.89±p=0.01) with no significant bias (0.4±p). Correlation of averaged LS and their mean bias were 0.52±0.59 at basal level, 0.89±1.17 at middle level and 0.73±1.46 at apical level, respectively. Correlation of global LS between the two methods was higher in group of patients who had LV twist value less than 13.4 degree (n=93) compared to group of patients with LV twist values >13.4degree (n=68).

**Conclusions:** Patients who had higher LV twist revealed moderate correlation of global LS between the two methods. Lower correlation and larger bias of averaged LS at basal and apical LV level between the two methods suggest LV twisting actually affects the calculation of 2D LS.
Brain natriuretic peptide is independently associated with indices of left ventricular filling pressure but not with left ventricular mass in asymptomatic individuals

Methods: Plasma NT-pro BNP concentrations were measured in 1,593 healthy subjects free of manifest cardiovascular disease, recruited from the London Life Sciences Prospective Population (LOLIPOP) study. All subjects underwent comprehensive transthoracic echocardiography, including tissue Doppler imaging, for measurement of LV mass, LV ejection fraction (LV EF), E/E' and LAVI.

Results: Using stepwise linear regression models, the relationships between determinants of LV filling pressure in patients with NT-pro BNP were explored. Increasing age, male gender and European white ethnic minority were independently associated with higher NT-pro BNP. There was an independent association of reduced LVEF (p=0.09, p<0.001) and increased LAVI (β=0.24, p<0.001) with higher NT-pro BNP. An initial significant association observed between increasing LVMi (β=0.13, p<0.001) and higher NT-pro BNP was subsequently abolished after adjustment for LAVI (β=0.06, p=0.41). Type-2 diabetes, hypertension and the presence of LVH were not associated with NT-pro BNP.

Conclusions: NT-pro BNP is unlikely to be a useful biomarker for the detection of LV hypertrophy as a result of LV remodeling, being more closely associated with the morphophysiological parameters of increased LV filling pressure and with LVEF.

Decreased velocity propagation of the left ventricle is associated with increased arterial stiffness

Methods: We studied 113 consecutive newly diagnosed EH patients stage I-III (age 51±12.41% females) without prevalent cardiovascular disease. All patients underwent: a) complete conventional and Tissue Doppler Imaging (TDI) echocardiographic study, b) assessment of heart rate-corrected augmentation indexes (Aix75 using SphygmoCor) and c) a 24-hour ambulatory blood pressure monitoring (ABPM). The study population was divided into two groups according to the median value of velocity propagation (VP): group A (n=57, VP<59 cm/sec) and group B (n=56, VP≥59 cm/sec).

Results: The two groups did not differ regarding age, gender, 24hr systolic and diastolic BP. Group B compared to A had significantly higher values of Aix75 and peripheral vascular resistances (29.3±9.6 vs 23.9±11.5%, p<0.016, 237±464 vs 2014±718 dynes.sec.cm-5, p=0.016, respectively) and significantly decreased aorta distensibility and cardiac index (0.16±0.1 vs. 0.25±0.2, p=0.04, 2.6±0.4 vs 2.4±0.7, p=0.016, respectively). Moreover, left ventricular diastolic performance was significantly impaired in group B, with prolongation of isovolumic relaxation time (IVRT) and deceleration time of mitral E wave (109±20 vs. 100.1±20 msec, p=0.022, 225±55 vs 203±46 msec, p=0.047, respectively). Also, TDI in group B had significantly lower values of Sm, Em and Em/Am ratio (8.7±1.4 vs 9.4±1.6 cm/sec, p=0.012, 10.2±3.2 vs 11.1±2.3 cm/sec, p=0.016, 0.9±0.7 vs 1.0±0.5, p=0.029). VP was significantly positive correlated with maximal systolic velocity of pulmonary artery, cardiac output, maximal left atrial volume, TDI Sm, Em and Em/Am ratio (r=0.46, p<0.001, r=0.34, p<0.001, r=0.21, p=0.024, r=0.29, p=0.003, r=0.33, p<0.001, r=0.3, p<0.001) and negatively correlated with Aix75, peripheral vascular resistances, IVRT, and diastolic dysfunction of both ventricles (r=0.25, p=0.017, r=0.33, p=0.002, r=0.23, p=0.14, r=0.29, p=0.002, r=0.19, p=0.05).

Conclusion: In newly diagnosed essential hypertensive patients, lower values of velocity propagation express not only left ventricular diastolic dysfunction but also increased arterial stiffness.

The E-wave deceleration rate E/DT but not the tissue-Doppler derived index E/Ea reliably characterizes pressure-overload induced diastolic dysfunction

Methods and results: Rats underwent aortic banding (AoB) to induce pressure overload. Hypertrophy fully developed 2 weeks after AoB. At 4 and 6 weeks, the lung was weighed to body mass ratio (LW/BW), a sensitive long-term marker for pulmonary congestion, dramatically increased despite preserved fractional shortening, indicating diastolic dysfunction. The time course of LW/BW was well reflected by E/Dt, by the ratio of early to late transmirtal diastolic velocity (E/Ea) and the deceleration time of E (DT) but not by E/Ea. In agreement, the best correlation with LW/BW was found for E/Dt (r=0.76;p<0.001), followed by E/A (r=0.69;p<0.001) and DT (r=0.62;p<0.001) whereas E/Ea showed the worst correlation (r=0.51;p=0.001). Furthermore, analysis of receiver-operating characteristic curves for the prediction of increased LW/BW revealed a significantly lower area under the curve for E/Ea (AUC=0.82) compared to those of E/Dt (AUC=0.98) and DT (AUC=0.95).

Conclusions: E/Dt but not the mostly preferred index E/Ea reliably detects and monitors diastolic dysfunction in pressure overload. The results may explain previous contradictions regarding the usefulness of E/Ea and suggest advanced validation of the new parameter E/Dt in humans.

3D echocardiography facing the challenge of diastolic function evaluation

Introduction: Left atrial (LA) ejection fraction has been recently recognized as a marker of diastolic dysfunction. LAV/A ratio was shown to be an indicator of advanced diastolic dysfunction and predictor of paroxysmal atrial fibrillation. In this study we aimed to assess the relation of LA ejection fraction by 3D echocardiography with new parameters of diastolic evaluation.

Methods: 40 patients, among which 29 patients with hypotrophic cardiomyopathy with parameters of elevated left ventricle filling pressure (E/E‘≥10) and 11 controls with normal left ventricle filling pressure were prospectively enrolled for 3D transthoracic echocardiography by one heart beat (ACUSON SC2000 TM, Siemens Medical Solutions USA Inc.). Left ventricle systolic function and left atrium ejection fraction were assessed by 3D volumes automatic. Pulsed Doppler through mitral valve and tissue Doppler parameters was measured according to the recommended guidelines.

Results: Patients with elevated left ventricle filling pressures presented higher LA maximum (71.2±31.4 ml vs 50.5±19.5 ml; p=0.045) and minimum volumes (44.4±28.4 ml vs 22.3±10.3 ml; p=0.039) and lower LA ejection fraction (39.9±14.9 ml vs 55.7±13.0 ml; p=0.047) and LAVi (127.8±54.0 ml vs 115.0±41.3 ml) and systolic (39.9±14.9 ml vs 55.7±13.0 ml) volumes and left ventricle ejection fraction (55.7±12.5% vs 58.6±5.4%). LAV/A ratio was significantly higher in patients with elevated left ventricle filling pressures (7.1±5.2 vs 3.7±2.5; p=0.00) and LA ejection fraction presented a significant negative correlation with LAV/A ratio (r=0.43, p=0.042). Area under the receiver operating characteristic curve to diagnose elevated left ventricle filling pressures by LA ejection fraction was 0.814 (6.635; 0.975).

Conclusion: LA ejection fraction by 3D echocardiography recognizes patients with elevated left ventricle filling pressures, therefore it might be valuable alternative at time of diastolic function evaluation.
Diagnostic value of exercise E/E' ratio for the early detection of diastolic heart failure in non-obstructive HCM patients

1Peking University Third Hospital, Beijing, China, People’s Republic of; 2Friendship Hospital of Peking Capital Medical University, Beijing, China, People’s Republic of

Background: Heart failure in patients with diastolic dysfunction has a 25% five year mortality. It is likely that early detecting patients with diastolic abnormalities will lead to favorable prognosis and survival. Recently, studies on tissue Doppler imaging (TDI) have found that the ratio of the peak early diastolic velocity of mitral annulus (E/E') has good correlations with diastolic function. It is still unclear how the indices of diastolic function will change for those non-obstructive hypertrophic cardiomyopathy (HCM) patients. The objective of this study was to test the diagnostic value of exercise E/E' ratio for the early detection of diastolic heart failure (DHF) in non-obstructive HCM patients.

Methods: Echocardiography was performed in 54 non-obstructive HCM patients with normal LVEF and 61 controls before and immediately after cardiopulmonary exercise testing (CPET). According to the level of E/E' ratio, the patients were divided into three subgroups: group a, E/E' ratio <10 both before and after exercise; group b, (early DHF), E/E' ratio ≥10 before but ≤10 after exercise; group c, (obvious DHF), E/E' ratio ≥10 both before and after exercise.

Results: (1) The E/E' ratio of patients elevated after exercise (P < 0.01), but that of the controls didn’t. (2) The VE/VD CO2 slope of the patients (28.6 ± 4.0) was higher than that of the controls (26.9 ± 2.7) (P < 0.001), the VO2max of the patients was lower (24.3 ± 5.2) than that of the controls (27.6 ± 3.9) (P < 0.01). (3) In the patients, exercising E/E' ratio had good correlations with exercising S' lateral, exercising E' lateral and VE/VD CO2 slope (P < 0.05-0.01). (4) About 1/5 of the patients were found to be early DHF.

Conclusions: Exercising E/E' lateral ratio can detect early DHF in non-obstructive HCM patients. Those patients with early DHF have no obvious symptoms and this part of patients should be paid more attention to so as to improve their prognosis.

Presence of preoperative diastolic dysfunction predicts postoperative pulmonary edema in patients undergoing major noncardiac surgery

D. Cho, S.A. Kim, M.N. Kim, Y.H. Kim, S.M. Park, H.J. Lim, W.J. Shim, Korea University, Anam Hospital, Seoul, Korea, Republic of

Purpose: Patients with left ventricular (LV) diastolic dysfunction are vulnerable to develop pulmonary edema. But the clinical implications of diastolic dysfunction has not been clearly elucidated in patients who underwent major noncardiac surgery. The aim of this study was to evaluate the impact of LV diastolic dysfunction for predicting post-operative (OP) pulmonary edema. Those patients with early DHF have no obvious symptoms and this part of patients should be paid more attention to so as to improve their prognosis.

Methods: Echocardiography was performed in 708 patients, older than 60 years (M/F:367/341, Mean age:72.3 years) who underwent major noncardiac surgery. Those patients with early DHF have no obvious symptoms and this part of patients should be paid more attention to so as to improve their prognosis.

Results: We identified 179 (25.2%) patients with pulmonary edema on postop chest X-ray. Among them, 38 patients had clinical pulmonary edema. By analysing clinical factors, ischaemic heart disease (HD), less than 30min GFR(CKD) and history of heart failure(HF) were associated with postOP pulmonary edema/OR:9.95, CI P-Value, HD:2.19,1.3-3.9,6.000,CKD:3.41,1.2-9.5,0.03, HF:4.22,1.96-9.11, <0.001. After adjustment for clinical risk factors of postOP pulmonary edema, multivariate analysis demonstrated that ≥15 E/E' ratio, ≥2.0 E/A ratio, increased PA pr(<35mmHg), increased LVMI(≥131 g/m2 for male ≥113 g/m2 for female) were significantly associated with postOP pulmonary edema/OR:9.95, CI P-Value, E/E' ratio: 5.65, 2.81-11.34, <0.001; E/A ratio: 3.90, 1.01-15.1, 0.05; PA pr: 1.60, 1.09-2.38, 0.02; LVMI: 1.70, 1.19-2.44, <0.001). Among these TTE variables, E/E', E/A ratio, LVMI showed higher statistical significances in patients with clinical pulmonary edema group than subclinical pulmonary edema group in predicting postOP pulmonary edema/CI, P-Value, E/E' ratio: 4.69,2.49-9.5, <0.001; E/A ratio:2.31,1.18-4.50,0.01, LVMI:2.17,1.09-4.36, <0.03.

Conclusion: The presence of LV diastolic dysfunction in preOP TTE was predictive postOP pulmonary edema in patients who underwent noncardiac surgery.

Clinicians need to be cautious on intravenous fluid therapy for surgical patients with findings of high E/E' ratio, E/A ratio, LVMI in TTE.

Diastolic tissue doppler velocities predicts adverse outcome after st-elevation myocardial infarction treated with primary percutaneous coronary intervention

T. Biering-Sorensen, P. Sogaard, R. Mogelvang, S.H. Pedersen, S. Lindberg, S. Galatius, S. Hoffmann, J.S. Jensen, Gentofte Hospital, Department of Cardiology, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Purpose: To investigate which diastolic echocardiographic parameters that best predict prognosis after an ST-elevation myocardial infarction (STEMI).

Method: From September 2006 to December 2008, 911 patients were admitted with a STEMI, treated with primary Percutaneous Coronary Intervention (pPCI). All patients were examined by echocardiography 1-5 days after the STEMI (median 2 days, IQR 1-3). In total 26 patients were excluded, 14 due to atrial fibrillation and 12 due to inadequate quality of the echocardiographic examination. Treatment effect was assessed in relation to death (n = 29), hospitalization with clinical signs of heart failure (CHF, n = 48) and re-MI (n = 25). Follow-up time was 19-32 months (IQR 19-32 months).

Results: The diastolic color tissue Doppler velocities, global e' and a', were the only diastolic parameters that remained as independent predictors of the combined outcome (Death, CHF, and re-MI) in a multivariable Cox regression analysis using forward selection including all diastolic parameters and age, previous myocardial infarction (pre-MI) and peak troponins (Tnl). Even after adjusting for ejection fraction, left ventricular mass index, left ventricular dimension in diastole, age, gender, peak Tnl, and pre-MI, e' remained a significant independent predictor of the combined endpoint with a hazard ratio (HR) of 1.18 (1.01-1.39) per 1 cm/s decrease (p=0.045). Patients who had values of both e' and a' below the median, had more than double the risk of an adverse outcome than patients with both e' and a' values above the median (See Table).

Conclusion: The diastolic tissue Doppler velocities seem superior to the conventional echocardiographic diastolic parameters in terms of predicting prognosis after pPCI for patients with STEMI. The early and late diastolic tissue velocities should be evaluated together as they interact on prognosis.

Myocardial performance index determined by tissue doppler imaging m-mode predicts outcome in patients with st-elevation myocardial infarction treated with primary percutaneous coronary intervention

T. Biering-Sorensen, R. Mogelvang, S.H. Pedersen, P. Sogaard, S. Galatius, J.S. Jensen. Gentofte Hospital, Department of Cardiology, Faculty of Health Sciences, University of Copenhagen., Copenhagen, Denmark

Purpose: To evaluate the prognostic value of the Myocardial Performance Index (MPI) assessed by Tissue Doppler Imaging (TDI) M-mode through the mitral leaflet after an ST-elevation myocardial infarction (STEMI).

Method: In total 291 patients were admitted with a STEMI and treated with primary Percutaneous Coronary Intervention (pPCI) in the period Sept. 06 to Dec. 08. Echocardiography was performed 1-5 days after the STEMI (median 2 days, IQR 1-3). MPI was calculated from the cardiac time intervals obtained by color Doppler imaging m-mode predicts outcome in patients with st-elevation myocardial infarction treated with primary percutaneous coronary intervention

Method: In total 291 patients were admitted with a STEMI and treated with primary Percutaneous Coronary Intervention (pPCI) in the period Sept. 06 to Dec. 08. Echocardiography was performed 1-5 days after the STEMI (median 2 days, IQR 1-3). MPI was calculated from the cardiac time intervals obtained by color Doppler imaging m-mode predicts outcome in patients with st-elevation myocardial infarction treated with primary percutaneous coronary intervention

Figure 1

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Exercise left ventricular filling pressure: prognostic implications in patients after acute myocardial infarction

M. Delíamis Ilic, S. Ilic, V. Stojkovic, Z. Kalimanovska Ostric, M. Deljanin Ilic, I. Institute of Cardiology, University of Niš, Niška Banja, Serbia; 2. Institute of Cardiology, Medical Faculty University of Niš, Niška Banja, Serbia; 3. Clinical Center of Serbia, Institute for Cardiovascular Diseases, Belgrade, Serbia.

Purpose: To evaluate the prognostic value of exercise left ventricular filling pressure to outcomes in patients (pts) after acute myocardial infarction.

Methods: 83 pts (68 men; mean age 57 years), 13±3 days after acute myocardial infarction were studied. In all pts left ventricular filling pressure was estimated from the ratio of transmitial and annular velocities (E/E') at rest and after bicycle exercise (25W, 3-min increments). Patients were classified according to E/E' ratio at rest: 48 had E/E' <10 (Group I) and 35 had E/E' > 10 (Group II). Patients were followed for cardiovascular hospitalization and death for 24 months.

Results: Out of 83 pts exercise E/E' rise in 23 (27.7%) pts: for Group I in 11 pts (from 7.9±0.75 to 9.4±1.1, P<0.005; difference 18.9%), and for Group II in 12 pts (from 11.5±0.9 to 14.0±1.3, P<0.001; difference 21.7%). Exercise duration was significantly shorter in pts than in pts without raised exercise E/E' (*P<0.025). During follow-up period, there were 19 cardiovascular hospitalization (8 in pts with and 11 in pts with increased E/E'; 13.3%, vs. 47.8%) and one cardiovascular death (in Group II in patient with exercise increased E/E'). The incidence of hospitalization among pts with pts exercise increased E/E' was higher in Group II (7/12pts, 58.3%), than in Group I (4/11pts, 36.4%).

Conclusion: Raised exercise left ventricular filling pressure in patients after acute myocardial infarction is associated with higher rate of subsequent cardiovascular hospitalization and death.

Diastolic but not systolic function is associated with coronary flow reserve in chronic heart failure patients

M. Snoer, T. Monk-Hansen, R. Olsen, L. Pedersen, H. Rasmussen, F. Deta, E. Prescol, 1. Bispebjerg Hospital of the Copenhagen University Hospital, Department of Cardiology, Copenhagen, Denmark; 2. Xlab – Center for Healthy Aging, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.

Purpose: Coronary flow reserve (CFR) is a measure of microvascular function in the absence of coronary artery stenosis and reduced CFR has been shown to be associated with poor outcome in diabetics and diabetics cardiomyopathy. Studies on other populations have shown an association between diastolic function and CFR, but this relationship is poorly examined in heart failure. The purpose of the study is to assess the association between CFR systolic and diastolic function in chronic heart failure patients.

Methods: 38 heart failure patients with left ventricular ejection fraction (LVEF) <35% underwent transhoracic echocardiography. CFR was calculated using the biplane Simpson model. Pulsed wave Doppler was used to measure transmural inflow velocities. Tissue Doppler velocities were measured 4 places in the mitral ring and were averaged. Peak coronary flow velocity (CFV) was measured in the mid-distal part of LAD at rest and during 2-minute post-ischemic period using color guided pulse wave Doppler. CFR was calculated as the ratio between CFV at rest and during stress.

Results: Median LVEF was 31 (interquartile range (IQ) 26.3-35.5) and CFR was 1.77 (IQ 1.26-2.42). CFR was correlated with E/A (<0.51 p=0.006), E/E' (r=0.48, p=0.003), IVRT (r=0.51 p=0.002), deceleration time of E (r=0.32 p=0.05), atrium volume index (R=0.34 p=0.04), S' (r=0.37 p=0.02) but not to LVEF or wall motion score index (all p>0.05).

In heart failure patients CFR was associated with all 5 measurements of diastolic function but with systolic function only S' was associated. The patients with low CFR showed a more restrictive filling pattern. High filling pressure and increased wall-stress might be involved in the reduction of CFR.

Association between Eas index by tissue Doppler imaging and ventricular stiffness index or ventriculoarterial interaction in patients with preserved left ventricular ejection fraction

H. Sako, S. Miura, S. Furumaya, A. Matsuanga, K. Saku. Fukuoka University Hospital, Fukuoka, Japan.

Purpose: Left ventricular (LV) stiffness contributes to cardiac afterload. LV hypertrophy and substrate of cardiac function. We previously reported that Eas Index by tissue Doppler imaging (TDI) was associated with aortic stiffness by transesophageal echocardiography. Therefore, the purpose of this study was to evaluate the associations between Eas index and LV elastance or ventriculoarterial interaction.

Methods: We calculated TDI velocities from two mitral annular sites in consecutive 500 patients with preserved LV ejection fraction (PLVEF). TDI velocities were quantified by Eas index of diastolic and systolic performance: e' (a'/s'). We also examined LV diastolic elastance index (Ed), arterial elastance index (Ea), LV end-systolic elastance index (Ees), ventricular-vascular coupling index (10/Ea/Ees) and total stiffness index (10:Ed:Ed:Ees). Furthermore, we investigated the relation between plasma natural logarithm (ln) - brain natriuretic peptide (BNP) levels and LV stiffness parameters.

Results: The Eas index was significantly and negatively correlated with Ed (r=-0.466, p=0.0001), Ea (r=-0.180, p=0.0002), ventricular-vascular coupling index (r=-0.117, p=0.016), total stiffness index (r=-0.281, p=0.001) and plasma ln-BNP levels (r=-0.333, p=0.0001), However, Eas index was not associated with ln-BNP levels. Finally, multivariate logistic regression analysis showed that plasma ln-BNP levels were most closely correlated with Ed (p=0.0001).

Conclusions: The Eas index by TDI in patients with PLVEF may be a helpful tool for evaluating aortic stiffness, cardiac afterload and diastolic LV function.

MYOCARDIAL FUNCTION “ISCHEMIC CARDIOMYOPATHY”

The prognostic role of dobutamine stress contrast echo in patients with known or suspected coronary artery disease in different age groups

C. Aggeli, I. Felekos, P. Stergiou, E. Poulikas, A. Katsaros, E. Stendoraki, G. Roussakis, C. Stefanakis. Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece.

Purpose: Dobutamine stress contrast echo (DSCE) is a valuable adjunct in clinical practice for the assessment of the presence and extent of coronary artery disease (CAD). The aim of the current study was to evaluate the prognostic role of DSCE in patients with known or suspected CAD in different age groups.

Methods: We retrospectively studied 3148 (63.2±8.9 years, male) consecutive patients who were referred to our department for clinically indicated DSCE. Ischemic response was defined as wall-motion deterioration and/or perfusion abnormality in two or more consecutive myocardial segments. Patients were divided into 3 groups according to their age: young adults (age>45yrs), middle-aged (45yrs) and patients 56±1.3 years. End points included all-cause mortality, the occurrence of acute coronary syndrome, the need for late revascularization (>3 months) and hospitalizations.

Results: In 1064 (33.8%) patients, ischemic response to DSCE was illustrated, whereas the remaining patients had no coronary abnormal finding during DSCE. During follow-up end-points were noted in 545 (17.3%) patients. Logistic regression analysis revealed that DSCE response was the strongest predictor for adverse outcomes (OR 6.2567, 2.1310 to 18.3816, 95% CI), especially for middle-aged patients. 5-year event-free proportion was 0.660±0.067 for ischemic responders, while for non-ischemic responders the respective rate was 0.952±0.025, hazard ratio was 4.7306 for patients with positive DSCE (2.0968 to 11.0414, 95% CI).

Conclusion: Dobutamine stress contrast echo is a strong predictor of end points in patients with known or suspected CAD, especially for middle-aged patients.

Stress-echocardiography to identify restenosis in drug eluting stent patients

S. Calcagno, M. Pagliaro, L. Lucisano, M. Pennacchi, N. Bruno, A. D’Ambrosi, M. Mancone, G. Sandella, F. Fedele. Sapienza University of Rome, Department of Cardiovascular, Respiratory and Nephrologic: Genomic Sciences, Rome, Italy.

Purpose: Restenosis is defined “Achilles Heel” of percutaneous coronary inter-
End-systolic pressure-volume relation and gender difference of diagnostic utility of dobutamine stress echocardiography in patients with negative stress echocardiography

T. Bombardini, R. Sirac1, Q. Campa, S. Gherardi, L. Pratali, E. Pirano, L. Meloni. Clinical Cardiology University of Cagliari, Cagliari, Italy

Background: A maximal negative stress echo identifies a low risk subset for coronary events. However, the potentially prognostically relevant information on cardiovascular hemodynamics for heart failure-related events is unsettled. Aim: To assess the diagnostic value of stress-induced variation in cardiovascular hemodynamics in patients with negative stress echocardiography.

Methods: We enrolled 929 patients (618 males; mean age 63±12; ejection fraction 48±17%; Wall Motion Score Index = 1.48±0.63; ischemic dilated cardiomyopathy, n = 109; dilated cardiomyopathy, n = 222; valvular, n = 90, known or suspected coronary artery disease, n = 508), with negative (exercise 238, dipyridamole 190) stress echocardiography result. Cardiovascular hemodynamics were assessed during stress: end-systolic pressure/volume ratio (ESPVR), ventricular arterial coupling (VAC) indexed by the ratio of the ESPVR to arterial elastance (Ea, ratio of end-systolic pressure by stroke volume). Cardiac output (CO, stroke volume x heart rate) was calculated at baseline and at peak stress. Changes from rest to peak stress (∆ values) were tested as predictors of major outcome measures: combined death and heart failure hospitalization.

Results: During a median follow-up of 16 months (interquartile range 6-32), 52 deaths and 94 hospitalization occurred. Receiver-operating-characteristic curves, and the corresponding areas under the curve, show the predictor performance of hemodynamic changes during stress (∆ ESPVR, ∆ Ea and ∆ CO) in the EX, DIP and DOB subsets (Figure, Panel A, B, C).

Conclusion: Patients with negative stress echocardiography may experience an adverse outcome, which can be identified by ∆ ESPVR and ∆ VAC.

Feasibility, symptoms, adverse effects and complications associated with non invasive assessment of coronary flow velocity in women with suspected or known coronary artery disease.

R. Montisci, M. Ruscazio, N. Zedda, C. Soro, L. Sau, F. Tuveri, L. Meloni. Clinical Cardiology University of Cagliari, Cagliari, Italy

Purpose: Noninvasive assessment of coronary flow velocity reserve (CFVR) with transthoracic echocardiography (TTE) is an increasingly used method to evaluate the effects of epicardial coronary stenosis and coronary microvascular function. The purpose of this investigation was to analyze and review the Cagliari University experience in assessing CFVR with TTE to define the feasibility, safety, adverse events profile, and complications rate of the test in women with and suspected coronary artery disease (CAD).

Methods: We evaluated CFVR in the left anterior descending coronary artery (LAD) with TTE during adenosine infusion. The pulsed wave Doppler of blood flow velocity was recorded in the LAD at rest and after maximum vasodilation by adenosine infusion (140 mcg/kg/min in 5 minutes). We analyzed 1455 consecutive CFVR TTE studies starting from January 2000 to December 2010. The patients (age: 66.4±11.9 years old, 14.8±9 years old) were referred for CFVR studies for different reasons: 933 (64.1%) for programed follow up after elective and primary PTCA on LAD, 370 (25.4%) for angina, 11 (0.8%) for hypertrophic cardiomyopathy, 38 (2.6%) for hypercholesterolemia, 77 (5.5%) for systemic scle-

Results: A complete CFVR study was achieved in 1429 patients (feasibility: 98.8%) the test being performed almost in the early phase of acute coronary syndrome and in obese women. In the remaining 26 patients (1.8%) the study was interrupted because of hypotension (0), general malaise (0), failure to visualize LAD (2), chest pain without EKG changes (2), nausea and headache (2), chest pain with ischemic EKG (1), hypertensive status (systolic blood pressure 200 mmHg, 1), hypotension (70/50 mmHg, 1), caffeine assumption (1). Minor symptoms or adverse effects occurred in 548 patients (38.3%) not requiring test termination: hypotension (239,16,7%), flushing (134,9,4%), chest pain without EKG changes (7), headache (95,6,5%), minor arrhythmias (3,5%), chest pain with EKG changes (1,5%). No major complications were observed during all studies.

Conclusion: Non invasive assessment of CFVR in LAD by TTE is a feasible method with very low incidence of adverse events and complications in women with suspected or known CAD. It can be used and safely performed in the evaluation of women with atherosclerotic LAD disease and in a broad spectrum of coronary disease with microvascular impairment.

Diagnostic efficacy of DASE

Detailed diagnostic values are displayed in table.

Diagnostic efficacy of DASE

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
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<tr>
<td>Men</td>
<td>85.6</td>
<td>60.5</td>
<td>81.9</td>
<td>66.7</td>
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<td>Women</td>
<td>91.9</td>
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</tr>
<tr>
<td>Women 1VD</td>
<td>94.7</td>
<td>83.8</td>
<td>93.6</td>
<td>82</td>
</tr>
</tbody>
</table>

Conclusion: Contrary to ECG exercise test, DASE with early atropine injection seems to offer higher diagnostic potential for accurate detection of significant coronary artery stenosis in women than in men especially in 1VD.

Coronary flow velocity reserve in 3 major coronary arteries can be a promising alternative for fractional flow reserve in determining hemodynamic significance of coronary artery disease

T. Wada, K.H. Hirata, K. Ishibashi, T. Yamano, T. Tanimoto, Y. Iino, T. Yamaguchi, T. Kubo, T. Imamichi, T. Akasaka. Wakayama Medical University, Wakayama, Japan

Objective: To evaluate whether coronary flow velocity reserve (CFVR) in major coronary arteries by transthoracic echocardiography can be a counterpart of...
fractional flow reserve (FFR) in assessing hemodynamic significance of coronary artery disease (CAD).

**Methods:** This is a prospective study in 157 vessels of 142 patients with suspected intermediate coronary stenosis in 3 major coronary arteries. We performed CFVR measurement by transthoracic echocardiography within 24 hours before coronary angiography and FFR measurement. CFVR was calculated as the ratio of hyperemic to basal diastolic flow velocities. Stress was simulated with adenosine tri-phosphate for both FFR and CFVR. The cut off value of CFVR was estimated by receiver operating characteristic curve based on that of FFR.0.75. The sensitivity and specificity were also calculated.

**Results:** The CFVR was 1.87±0.76 in coronary artery with FFR <0.75 (n=74) and 2.3±1.68 in those with FFR>0.75 (n=83; p= 0.0054). CFVR cutoff of 2.2, determined by receiver operating characteristic curve, was 79.5% sensitive and 80.0% specific in predicting the stenotic condition of coronary artery with FFR <0.75 in 3 major vessels. In each vessel, the sensitivity and specificity were 82 and 76% and 70% (70% (RCA) and 75% and 90% (CX), respectively. On the other hand, CFVR was in direct proportion to FFR (r=0.62, p=0.0001) and indirect proportion to %DS (r=0.35, p=0.0004).

**Conclusions:** The non-invasive CFVR measurement could be a reliable stenosis-specific alternative for determining the hemodynamic significance of 3 major coronary arteries.

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**P4249**
Higher prevalence of carotid disease compared to myocardial ischemia in patients undergoing simultaneous stress echocardiography for suspected coronary artery disease

S. Ahmadzadiv, C. Kinsey1, K. Zacharias1, J. Pablal, B. Shah2, R. Senior1, 1Northwick Park Hospital, Harrow, United Kingdom;2Royal Brompton Hospital and Northwick Park Hospital, London, Harrow, United Kingdom

**Background:** Presence of carotid artery disease (increased carotid intima-media thickness or presence of plaque) has been shown to predict cardiovascular risk beyond Framingham Risk Score (FRS). However, its potential impact on patients' management, undergoing echocardiography (SE) for new onset chest pain with or without known coronary artery disease (CAD), is unknown.

**Methods:** Consecutive patients with no previous history of CAD referred for SE underwent simultaneous carotid ultrasound. SE was considered abnormal if two or more contiguous segments demonstrated indwelling wall thickening abnormality. Presence of carotid disease on ultrasound was defined as carotid intima-media thickness (C-IMT) >75th percentile for age and sex, and/or presence of plaque in accordance with Mannheim consensus. FRS was also assessed. Patients underwent coronary angiography based on clinical grounds and SE data.

**Results:** Of the 262 consecutive patients (128 male (49%), mean age 60.0±11 years), 36 (14%) demonstrated myocardial ischemia by SE, of which the majority (26 patients (72%)) had carotid disease. These consisted of 18 patients (50%) with carotid plaque and 13 (36%) with C-IMT>75th percentile. However, carotid disease was also present in 137 out of 230 (61%) with normal SE; plaque was demonstrated in 96 (43%) and C-IMT>75th percentile in 91 (40%). FRS was significantly higher (p<0.001) in patients with carotid disease (19.04±9.57) vs. those without it (13.58±7.78). However, carotid disease was observed in 72 (31%) and 51% of patients in low-intermediate FRS and normal FRS, respectively. 37 of the 262 studied underwent coronary angiography, of which 28 (75%) demonstrated CAD. Subsequently, 13 (45%) underwent revascularisation (median 3 months). Plaque showed significant association with CAD (p=0.002) and revascularisation (p=0.012), even after adjustment for all known coronary risk factors and FRS.

**Conclusions:** There is significantly higher prevalence of carotid disease compared to myocardial ischemia in patients undergoing simultaneous SE and carotid ultrasound for suspected CAD. Carotid plaque, not clinical risk factors, is associated with ischemia on SE. This has implications for primary preventive therapy in low-intermediate FRS group and negative SE.

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**P4251**
Abnormal stress echocardiography in the presence of normal stress echocardiography

M. Patchett, R. Wilkoi, A. Vodonos, N. Liel-Cohen, V. Novack, J. Peteiro, A. Bouzas-Mosquera, A. Lopez-Sainz, M. Lopez-Perez, A. Bosch-Caballero, A. Prada, A. Castro-Berjas. University Hospital A Coruna, Department of Cardiology, A Coruna, Spain

**Background:** There is significantly higher prevalence of carotid disease compared to myocardial ischemia in patients undergoing simultaneous stress echocardiography for suspected coronary artery disease (CAD). The negative predictive value for MI and/or death of a patient with negative stress echocardiography is known as an index of coronary arterial reactivity and decreases under the condition with microvascular dysfunction as well as coronary artery stenosis. The aim of this study was to assess the effect of ranolazine on CFVR in this patient group.

**Methods:** 52 patients (36 M, 16 F; mean age 63±10 years) with angiographic and evidence of myocardial ischemia, but no obstructive coronary artery disease (CAD), were randomly assigned to placebo (26 patients) for 8 weeks (350 mg twice a day for 4 weeks, then 500 mg twice a day for other 4 weeks).

**Results:** G-LAD pts were older (65±10 vs. 59±14, p<0.01), and had more frequently a history of infarction (25% vs. 10%, p<0.05). 50.5% vs. 14.6% had diabetes, and 52% vs. 39% hypertension. There was no difference in the prevalence of angina, diabetes, hypertension, or smoking between both groups. The negative predictive value for MI and/or death of a patient with normal CFVR was 79.5% sensitive and 80.0% specific in predicting the stenotic condition of coronary artery with FFR <0.75 in 3 major vessels. In each vessel, the sensitivity and specificity were 82 and 76% and 70% (70% (RCA) and 75% and 90% (CX), respectively. On the other hand, CFVR was in direct proportion to FFR (r=0.62, p=0.0001) and indirect proportion to %DS (r=0.35, p=0.0004).

**Conclusions:** The non-invasive CFVR measurement could be a reliable stenosis-specific alternative for determining the hemodynamic significance of 3 major coronary arteries.

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**P4252**
Ranolazine improves coronary flow reserve in patients with angina but no obstructive coronary artery disease

E. Tagliamont1, T. Cirillo1, U. Marinelli1, C. Astaria2, R. Citro2, G. Riccio1, C. Romano1, B. Baldi1, "Umberto I" Hospital, Operative Unit of Cardiology, Nocera Inferiore, Italy;2Santa Maria della Misericordia Hospital, Operative Unit of Cardiology, Sorrento, Italy; University Hospital San Giovanni di Dio e Ruggi d’Aragona, Salerno, Italy

**Background:** Ranolazine reduces the Na-dependent calcium overload via inhibition of the late sodium current, improving diastolic tone and oxygen handling during myocardial ischemia. In patients with angina, evidence of myocardial ischemia, but no obstructive coronary artery disease (CAD), microvascular coronary dysfunction plays a key role. Transthoracic Doppler-derived coronary flow reserve (CFR) is known as an index of coronary arterial reactivity and decreases under the condition with microvascular dysfunction as well as coronary artery stenosis. The aim of this study was to assess the effect of ranolazine on CFR in this patient group.

**Methods:** 52 patients (36 M, 16 F; mean age 63±10 years) with angina and evidence of myocardial ischemia (ischemic changes in the ECG during SE and normal SE is extremely high. Our study proves that there is no difference in the outcome of patients in groups I and II. We aimed to assess patients who underwent SE and compare the cardiac outcome among patients with and without ECG change during a normal SE study.

**Results:** In conclusion, Tor at R and at Pk are decreased in pts with ISC in the LAD territory compared to normal. This is an observational study performed on 3,322 patients who underwent SE from January, 2007 through the end of December, 2010. The primary endpoint was a composite of all-cause mortality and acute MI. According to SE results, the patients were stratified into three groups: group I: normal SE and normal stress echocardiography (n = 2,107), group II: normal SE and abnormal SE (n = 868), and group III: abnormal SE (n = 347).

**Results:** Patients in group III were older than patients in groups I and II (67±10 years and 57±12, respectively) and was comprised of a higher ratio of male patients (71% in group III, 59% in groups I and II). Group III patients had a significantly higher prevalence of diabetes (12% vs. 8%), dyslipidemia (34% vs. 22%), and hypertension (28% vs. 17%) than patients in groups I and II. In multivariate Cox proportional regression analysis with adjustment for baseline demographics and comorbidities, no difference was found in the outcome of patients in groups I (reference group) and II (hazard ratio 0.18, 95% CI 0.62-0.24). An abnormal SE was a significant factor impacting survival, and increased the risk of MI and/or death by 2.11 (95% CI 1.16-3.81, p=0.014).

**Conclusions:** The negative predictive value for MI and/or death of a patient with normal CFR is extremely high.
Coronary flow reserve stratifies Left ventricular torsion at rest, peak and estimation of infarct size using transthoracic echocardiography

Dipyridamole coronary flow reserve stratifies Left ventricular torsion at rest, peak and estimation of infarct size using transthoracic echocardiography. Dipyridamole was used to assess coronary flow reserve (CFR) in patients with acute coronary syndrome. CFR was found to be inversely correlated with infarct size, with a CFR of <2.5 being predictive of MACE. In patients with evidence of myocardial ischemia, but no obstructive CAD, Ranolazine is able to improve CFR. This is probably due to improvements in microvascular dysfunction. Larger studies will be able to confirm these data.

Table 1

<table>
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<tr>
<th>Variable</th>
<th>MACE + (n=22)</th>
<th>MACE – (n=130)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65±11</td>
<td>58±10</td>
<td>0.005</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>165</td>
<td>156</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83±17</td>
<td>79±14</td>
<td>0.016</td>
</tr>
<tr>
<td>Smokers</td>
<td>14/69</td>
<td>63/73</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13/19</td>
<td>63/85</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11/28</td>
<td>76/90</td>
<td>NS</td>
</tr>
<tr>
<td>Apical rotation, °</td>
<td>4.44±1.25</td>
<td>3.89±1.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Basal rotation, °</td>
<td>2.53±0.47</td>
<td>1.70±0.88</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Conclusions: In a population of patients with ACS, CFR significantly improves prediction of MACE when added to standard clinical variables, even in the absence of CAD disease. This finding promotes the role of ultrasound-assessed CFR in the risk stratification after ACS, supporting the concept that CFR reflects global atherosclerotic burden, endothelial dysfunction and microvascular damage, more than just mimicking LAD disease.

Left ventricular torsion (Tor) and post-exercise echocardiography

Left ventricular torsion (Tor) has not been widely studied during exercise echocardiography (ExE). We aimed to study the feasibility of the assessment of Tor during ExE and the likely correlations with systolic and diastolic function and exercise capacity. A series of 265 consecutive cases referred for ExE were studied by echocardiography at rest (R), peak (Pk) and 1 min post ExE (PEx). All rotation parameters but basal rotation were significantly different at Pk and at PEx. Significant correlations were found between rotation parameters and LVEF (R vs ExE: r=0.61, p=0.001; at Pk vs PEx: r=0.43, p=0.01; and at Pk vs PEx: r=0.37, p=0.01). However, no significant correlations were found with exercise capacity.

In conclusion, rotation can be assessed during exercise in about 70% of the cases. ExE rotation parameters are significantly different to those obtained at Pk.
PCI have decreased CFR in IRA that is proportional to the extent of myocardial damage. Therefore we proposed a novel model of infarct size (IS) estimation using transthoracic Doppler echocardiography derived CFRs of the IRA (LAD) and reference artery (RCA).

**Methods:** Our study included 34 consecutive patients (28 (82%) men, mean age, 50±11years) with first anterior STEMI and single vessel disease (IRA) successfully treated by primary PCI. All patients underwent resting two-dimensional echocardiography with the assessment of LV volumes, wall motion score index and ejection fraction as well as adenosine stress echocardiography (0.14 mg/kg/min) with CFR evaluation of LAD and RCA, 30±3 days after MI. A new ECG after PCI with infarct size (CFR IS) was calculated as follows:

CFR IS = (CFR RCA – CFR lAD)/(CFR RCA – 1)x 100 (%). Infarct size was also assessed by SPECT myocardial perfusion imaging (SPECT MPI) using 99mTc-MIBI on the following day. SPECT IS was expressed as percentage of myocardium with fixed perfusion abnormalities.

**Results:** CFR calculated after adenosine administration was significantly higher in RCA than in LAD (2.0±0.4 vs. 2.5±0.5, respectively, p<0.001). CFR derived IS correlated significantly with all the parameters depicting the severity of myocardial damage including: peak CK activity (r= -0.632, p<0.001), WMSI (r= -0.857, p<0.001) and LV EF (r= -0.820, p<0.001), as well as with LV EDV (r= -0.757, p<0.001) and ESV (r= -0.794, p<0.001). Most importantly, CFR derived IS correlated significantly with IS assessed using SPECT MPI (r= -0.874, p<0.001). There was no significant difference in IS assessed with these two methods 22±17% for CFR IS and 21±17% for SPECT IS (p=NS).

**Conclusion:** Coronary flow reserve derived IS is non-invasive tool for the estimation of myocardial damage after first anterior STEMI in patients with single vessel infarction that correlates well with other widely used markers of final IS.

**P4257** Prediction of left ventricular function recovery with the use of 2D speckle tracking echocardiography in patients 12 months after acute ST-elevation myocardial infarction

E. Szymczyk, P. Lipiec, B. Michalski, K. Szymczyk, L. Stefanycz, B. Wozniakowski, A. Rotkiecz, J.D. Kasprzak, Medical University of Lodz, Lodz, Poland

**Introduction:** Prediction of left ventricular function recovery is of clinical importance for the management and prognosis of patients after myocardial infarction. The aim of this study was to assess if the use of 2D speckle tracking in resting echocardiography may be helpful in the prediction of left ventricular function recovery in patients 12 months after ST-elevation myocardial infarction (STEMI). **Material and methods:** The study group consisted of 96 patients (69 male, mean age 58±10 years) with first STEMI treated with successful primary percutaneous coronary intervention. 7-12 days after STEMI, all patients underwent resting echocardiography. All acquired images were analyzed off-line using 2D speckle tracking technique. Measurements included peak systolic longitudinal and transverse strain (SLS and STS), peak longitudinal and transverse strain (PLS and PTS) including possible post-stenotic shortening, systolic longitudinal and transverse strain rate (SLSR and STSR) at baseline (rest). After 12 months each patient underwent control resting echocardiography with visual assessment of functional recovery in akinetic/dyskinetic segments defined by transthoracic doppler technique. Transmural strain parameters SLS (AUC=0.710, p=0.0001) and PLS (AUC=0.773, p<0.001) were significantly higher in patients with functional recovery in akinetic/dyskinetic segments at baseline, defined as improvement from dyskinesia and akinesis to hypokinesia or normokinesia.

**Results:** At baseline there were 265 segments with akinesia or dyskinesia. 112 (42%) of those segments showed functional recovery after 12 months. Longitudinal strain parameters SLS (AUC=0.710, p<0.0001) and PLS (AUC=0.773, p<0.0001) had good, while SLSR only satisfactory (AUC=0.648, p=0.0001) diagnostic value for predicting functional recovery. The highest possible diagnostic value of 72.9% was for PLS (< -10.4% and for 67.5% for SLS < -10.1%, while diagnostic accuracy for low-dose dobutamine stress echocardiography in the study group was 75.8%, with sensitivity of 61.8%, and specificity of 85.2%. Transverse parameters of strain had non-satisfactory diagnostic value for predicting functional recovery 12 months after STEMI.

**Conclusions:** Longitudinal strain parameters assessed by 2D speckle tracking had comparable prognostic value to requiring experience and administration of pharmacologic agent low-dose dobutamine stress echocardiography for the prediction of left ventricular functional recovery in patients 12 months after STEMI. This non-invasive method may be less dependant on subjective factor and in usual viability interpretation based on dobutamine stress echocardiography and after a methodological background for fully computerized algorithms.

**CARDIOMYOPATHIES: PROGNOSIS**

**P4259** QRS fragmentation in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy and complete right bundle branch block

S. Peters. St.Antonius-Hospital Gronau GmbH, Gronau, Germany

Patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy ARVD/C and complete right bundle branch block (RBBB) very often have recurrent ventricular tachycardia and develop biventricular heart failure in the follow-up requiring heart transplantation and/or diuretics. In other patients with ARVC/C excluding complete right bundle branch block IS SPECT fragmentation in the S wave of right precardial leads identifies patients with recurrent VT, primary VF and recurrent ICD discharges; QRS fragmentation ≥ 3 leads characterised patients who died from sudden cardiac death.

**Method:** A cohort of 374 patients with ARVC/D (208 males; mean age 46.5±14.8 years) there were 22 patients with complete RBBB. 17 patients with ARVC/D developed complete right bundle branch block and had biventricular heart failure in the follow-up of 6 years. In 5 patients with complete right bundle branch block were initially evident. In all patients with ARVC/D and RBBB QRS fragmentation ≥ 3 of all 12 ECG leads and QRS fragmentation ≥ 3 of all 12 ECG leads in the S wave of right precardial leads were present in 16/17 patients who developed RBBB and none of the 5 patients with initial RBBB QRS fragmentation ≥ 3 leads was present (n=12.5; p<0.001).

**Conclusion:** Patients with recurrent ventricular tachycardia who develop biventricular heart failure requiring heart transplantation and/or diuretics are characterised by QRS fragmentation in the S wave of right precardial leads and ≥ 3 of all 12 ECG leads. These results are statistically significant. Patients with initial RBBB have an overall benign prognosis.

**P4260** The impact of sleep apnea on the occurrence of heart failure in the patients with hypertrophic cardiomyopathy


**Purpose:** This case-control study was conducted to evaluate the interrelation between the occurrence of heart failure (HF) and the sleep apnea in the patients with hypertrophic cardiomyopathy (HCM) excluding obstructive left-ventricular outflow tract obstruction (LVOT-OT) HCM.

**Methods:** 48 patients with apical HCM, mid-ventricular HCM, and non-obstructive left-ventricular outflow tract HCM were included for the study. Polysomnographic analysis was performed to assess the apnea-hypopnea index (AHI). The biomarkers and cytokines including brain-natriuretic peptide (BNP), plasma rennin activity, aldosterone, adrenaline, nor-
adrenalin, dopamine, soluble tumor necrosis factor receptor 1 (sTNFR1), tu-
more necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), transforming growth factor-betα (TGF-betα), urine 8-hydroxydeoxyguanosine (8-OHdG) were mea-
sured at the period of HF diagnosis. We divided those patients into two
groups with (n=14) or without (n=34) a history of HF requiring hospitalization and compared above-mentioned parameters between two groups.

Results: HCM patients with a history of HF has significantly higher AHI (32±5.0 vs. 11.1±2.2, p=0.0001) and higher TGF-betα value (2.72±0.49 vs. 1.53±0.07, p=0.0016) comparing with those without a history of HF. The other indices of HF, inflammation, and oxidative stress, such as BNP, PRA, aldosterone, adrenalin, nor-adrenalin, dopamine, sTNFR1, TNF-α, IL-6, 8-OHdG have not shown any significant difference between two groups.

Conclusions: Sleep apnea may play an important role in the occurrence of HF in the patients with relatively benign HCMs. The elevation of TGF-betα may suggest the involvement of fibrosis in the pathogenesis of HF in the patients who have both HCM and sleep apnea.

Predictors of survival in patients with restrictive cardiomyopathy

J.Y. Jung1, D.-H. Kang1, B.J. Sun1, M.S. Kim1, D.H. Kim1, J.M. Song1, J.-H. Zo1, K.-J. Choi1, J.-K. Song1, J.-J. Kim1, 1Asan Medical Center, Seoul, Korea; Republic of; 2Borae Hospital, Seoul, Korea, Republic of;

Backgrounds: Restrictive cardiomyopathy (RCMP) is a rare heterogeneous dis-
ease and the survival according to types of RCMP is unclear. We evaluated clin-
ic outcomes of RCMP to identify predictors of survival.

Methods: From 1999 to 2010, we prospectively studied 98 consecutive patients
(64 men, age;58±11 years) diagnosed as RCMP. All patients had the symptoms 
of heart failure and diastolic dysfunction with preserved left ventricular systolic function on echocardiography. Diagnosis of RCMP was initially made by typical echocardiographic findings and confirmed by endomyocardial biopsies. The end-
point was defined as death from any cause.

Results: Idiopathic RCMP was diagnosed in 11 (11%) patients, and infiltrative CMP in 87 (89%). The underlying cause of infiltrative CMP was amyloidosis in 77, light-chain deposition disease in 5, myocarditis in 2, hypertrophic cardiomyopathy in 2 and Fabry disease in 1. During a median follow-up of 6 months (IQR, 2-17), 75 (77%) patients died and 3 underwent cardiac transplantation (2 amyloidosis, 1 idiopathic RCMP). The actuarial 2 year survival rates were significantly different between infiltrative CMP and idiopathic RCMP (22±5% versus 91±9%, p<0.001) (Figure). Age (hazard ratio [HR] =1.036, P=0.001) and infiltrative CMP (HR 4.48, P=0.005) were independently related to survival on multivariate Cox analysis. On subgroup analysis of 82 patients with amyloidosis or light-chain de-
position disease, only 39 (48%) patients underwent chemotherapy and tolerance to chemotherapy was significantly related to survival (HR=2.189, P<0.002).

Characterization of predictors of in-hospital cardiac complications of takotsubo cardiomyopathy: multi-center registry from Tokyo CCU network

T. Murakami1, T. Yoshikawa1, Y. Maekawa1, T. Ueda1, T. Isogai1, Y. Koshiba1, K. Sakata1, K. Nagai3, T. Yamamoto1, T. Kajikawa1 on behalf of Tokyo CCU network Committee. 1Sakakibara Heart Institute, Department of Cardiology, Tokyo, Japan; 2Keio University, Tokyo, Japan; 3Tokyo metropolitan Tama Center, Tokyo, Japan; 4Kawasaki Red Cross Hospital, Tokyo, Japan; 5Kyorin University, School of Medicine, Tokyo, Japan; 6Nihon University, Tokyo, Japan; 7Nippon Medical School, Tokyo, Japan

Background: Takotsubo cardiomyopathy (TC) is an acute cardiac syndrome characterized by transient left ventricular dysfunction and relatively good progno-
sis after discharge. However, cardiac complications during hospitalization remain to be fully determined.

Methods: We investigated 107 patients of TC (82 women, median age 73.9±11.1 years old) from Tokyo CCU Network database, comprising of 67 cardiovascular centers in the metropolitan area during January 1 to December 31 2010. Cardiac complications were defined as all-cause death, pump failure (Killip II/III/IV), sus-
tained ventricular tachycardia (SVT), ventricular fibrillation (VF), and advanced atrioventricular block (AVB). We attempted to characterize cardiac complication groups (CC) by comparing patients with and without cardiac complication (NC) during hospitalization.

Results: CC was observed in 41 patients (all-cause death, n=9; pump failure, n=27; SVT, n=1; AVB, n=2; VF, n=2), and there was no complication in the re-
maining 66 patients. There was no difference in age (75.2±10.4 vs. 72.9±11.6; p=0.289), female gender (70.7% vs. 80.3%; p=0.144), peak creatinine kinase
level (IU/L) (553±710 IU/L vs. 486±1024 IU/L, p=0.780), C-reactive protein level (mg/dl) (2.63±3.75 vs. 1.90±4.25 mg/dl, p=0.379) and TST elevation on
electrocardiogram (68.3% vs. 75.8%, p=0.389), respectively. White blood cell count (WBC) (11189±4516/μl vs. 9023±3532/μl, p=0.005) and brain natriuretic peptide (BNP) (1125±1245 pg/ml vs. 576±764 pg/ml, p=0.004) were higher in CC than NC. Left ventricular ejection fraction was lower in CC than NC (42.3±11.6% vs. 53.1±11.0%, p<0.001).

Conclusion: Cardiac complications are not rare in patients with TC during hospi-
talization. Higher WBC and BNP levels and the presence of LV dysfunction seem to be possible predictors of TC with cardiac complications.

Prognostic role of clinical presentation in patients with hypertrophic cardiomyopathy. A single center experience

G. Finocchiaro, M. Merlo, B. Pinamonti, G. Barbati, A. Cocciolo, G. Sinagra. Cardiovascular Department, “Ospedali Riuniti” and University of Trieste, Trieste, Italy

Background and Aims: Hypertrophic cardiomyopathy (HCM) is a complex pri-
mary and genetically transmitted heart muscle disease characterized by highly variable natural history, from stable clinical course over many years to progres-
sive congestive heart failure (HF) or sudden death (SD). The aim of the study is to evaluate the long-term prognostic impact of baseline symptoms in a cohort of HCM patients.

Methods and Results: We considered 212 HCM patients enrolled in the Trieste Heart Muscle Disease Registry. Implantable cardioverter-defibrillator (ICD) has been implanted in 23 (11%) patients during follow-up. The end-points of the study were death/heart transplantation and SD/appropriate ICD shock. 106 (50%) were asymptomatic at diagnosis. Considering symptomatic patients at diagnosis, heart failure (HF), chest pain, syncope and palpitations were the main symptoms in 23, 15 and 23% of the cases respectively. During a mean follow-up of 118±87 months, 44 (21%) patients died/underwent heart transplant (D/HTx) (15 pump failure deaths, 14 SD, 5 non-cardiovascular deaths and 10 HTx). Six patients had at least one appropriate ICD shock. D/HTx was observed in 11 (10%) asymptom-
atic patients and in 33 (31%) symptomatic patients at diagnosis (p=0.016). At multivariate analysis a diagnosis in asymptomatic stage (HR 0.33, CI 95% 0.15-
0.74, p=0.007), chest pain diagnosis (HR 0.21, CI 95% 0.05-0.89, p=0.034) and lower left atrium area (for every 1 cm² decrease HR 0.95, CI 95% 0.92-0.98, 
p=0.002) emerged as independent predictors of survival-free from D/HTx. Con-
versely, a lower left ventricular ejection fraction (for every 10 point % decrease HR 1.15, CI 95% 1.08-1.22, p<0.001) and restrictive pattern (HR 2.92, CI 95% 1.04-8.23, p=0.043) emerged as independent predictors of SD/appropriate ICD shocks.

Conclusions: Clinical presentation has a relevant prognostic role in HCM, since diagnosis in an asymptomatic stage and chest pain as main onset symptom were associated with a more favourable long-term outcome. Moreover, left atrium en-
largement emerged as an independent predictor of D/HTx, whereas left ventric-
ular ejection fraction and restrictive filling pattern were found to be independent predictors of SD or appropriate ICD shocks.
Left ventricular reverse remodeling in idiopathic dilated cardiomyopathy: a subgroup analysis of the population enrolled at the Florence referral center for cardiomyopathies

A. Fornaro, G. Castelli, M. Ciacciери, I. Olivotto, C. Pigiozzi, B. Tomberi, G.F. Gensini. Careggi University Hospital, Referral Center for Cardiomyopathies, Florence, Italy

Purpose: Idiopathic dilated cardiomyopathy (IDCM) is a myocardial disorder characterized by left ventricular dilation and systolic dysfunction. Recent data show that there is a positive correlation between the effect of optimal medical therapy on left ventricular reverse remodeling (LVR) and on mortality in heart failure (HF) and/or IDCM pts. Aims of our study were to determine survival rates in IDCM patients experiencing LVR and the potential role of cardiac resynchronization therapy (CRT).

Methods: Among 603 consecutive IDCM pts we studied a subgroup of 425 pts. 309 M (72.7%), mean age 53.5±12.12 yrs, with complete repeated echocardiographic evaluations. Mean indexed left ventricular (LV) end-diastolic diameter (EDD) was 51.5±0.5 mm²/m². LV ejection fraction (EF) was 33.2±3.9%. NYHA class was 2.3±0.8. Pts were divided in three groups, based on enrollment periods: 1) 1977-1990 (n=71); 2) 1991-2000 (n=144); 3) 2001-2010 (n=210). The mean follow-up was 16.6±7.8, 10.9±5.0 and 6.3±3.9 yrs, respectively. No statistical difference was observed in gender, LV mass index, T1/2 were significantly higher; LV ejection fraction was significantly correlated with cTnT in the peripheral vein. Brain natriuretic peptide, serum cTnI, left ventricular reverse remodeling (LVR) is found in 26.8% of a subgroup of 425 IDCM pts enrolled at our Centre and is most frequently found in those enrolled in the last decade. LVR is related to a favorable prognosis, this finding being presumably related to the increasing use of evidence-based treatment of HF (mainly neurohormonal inhibitors). The importance of CRT in LVR needs further confirmation.

Impact of serum cardiac troponin T and I on cardiac molecular changes and dysfunction in patients with hypertrophic cardiomyopathy

A. Hirashiki, R. Okamoto, T. Okumura, S. Shimazu, T. Yamada, Y. Bando, X.W. Cheng, T. Kondo, T. Murohara. Nagoya University Graduate School of Medicine, Nagoya, Japan

Purpose: Serum cardiac troponin T (cTnT) could be a reliable indicator of myocardial remodeling, a proposed prognostic marker in hypertrophic cardiomyopathy (HCM). Meanwhile, cardiac troponin I (cTnI) has also been reported as a prognostic indicator in patients with chronic heart failure. However, the relation between cardiac function, cTnT and cTnI has remained unclear in patients with HCM.

We assessed the hypothesis that serum cTnT and cTnI could be related to ongoing myocardial remodeling in HCM and we calculated the correlation between LV pressure (LV-PH) and cTnT/cTnI as an index of isovolumic relaxation. In addition, to examine transcardiac utilization of troponin T and I, we measured serum cTnT and cTnI in the aortic root (Ao) and coronary sinus (CS).

Methods: We checked serum cTnT and cTnI in 73 consecutive HCM patients in stable condition. All patients underwent cardiac catheterization and we calculated the maximum transmural pressure gradient (dP/dtmax) as an index of contractility and the LV pressure half-time (T1/2) as an index of isovolumic relaxation. During follow-up, 72 pts (16.9%) died due to refractory HF, 38 (8.9%) due to death from other causes, 17 pts (4.2%) due to revascularization therapy (CRT).

Results: We divided the patients into two groups [group A: cTnT <0.003ng/ml (n = 35), group B: cTnT group ≥0.003ng/ml (n = 38)], on the basis of median value of cTnT in the peripheral vein. Brain natriuretic peptide, serum cTnI, left ventricular mass index, and T1/2 were significantly higher in the lower group in both those in the group A. Moreover, mRNA levels of cTnT was significantly correlated with mRNA levels of sarco-endoplasmic reticulum Ca²⁺-ATPase and cytochrome c oxidase subunit 5B (r = 0.486, r = 0.404, respectively). Meanwhile, there was a significant positive correlation between the transcript level of cTnT and cTnI calculated by the difference of CS and Ao mRNA levels of Troponin I (r = 0.515, P < 0.005).

Conclusions: In conclusion, these findings indicate that elevated peripheral blood cTnT might be associated with cardiac dysfunction, resulting from the impairment of Ca²⁺-handling protein and mitochondrial function. Meanwhile, transcardiac gradient of cTnT levels may reflect ongoing myocardial damage in stable patients with HCM.
0.99, p<0.05) and iLAD (HR 1.06, 95% CI 1.03-1.09, p<0.0001) at enrollment were all significant prognostic factors.

Conclusions: Our data show the enrollment period as the most important prognostic factor in DCM pts enrolled at our Center, with a 75% relative risk reduction in overall mortality over the last thirty years, this finding being presumably related to the increasing use of evidence-based treatment of HF over time. Moreover female gender, age, NYHA class, LVEF and iLAD at enrollment each portends a significant prognostic value.

Fragmented QRS complexes on 12-lead ECG predict myocardial fibrosis in hypertrophic cardiomyopathy

N. Sheikh, M. Papadakis, R. Bastiaenen, L. Millar, N. Emmanuel, S. Ghan, A. Zaidi, S. Gali, E. Behr, S. Sharma. St George’s University of London, London, United Kingdom

Purpose: It is well-established that fragmented QRS complexes (fQRS) on the 12-lead electrocardiogram (ECG) are a predictor of delayed gadolinium enhancement (DGE) on Cardiac MRI (CMR) and indicate myocardial scarring in patients with coronary artery disease and dilated cardiomyopathy. Moreover, fQRS appear to correlate well with arrhythmic events and mortality in these cohorts. However the significance of fQRS in hypertrophic cardiomyopathy (HCM) is yet to be established. We sought to determine whether fQRS is a predictor of delayed gadolinium enhancement (DGE) on CMR in patients with HCM.

Methods: The 12-lead ECGs of 82 consecutive patients with HCM who underwent CMR with gadolinium were analysed for the presence of fQRS by 2 independent readers blinded to the CMR findings. Patients with documented myocardial infarction (n=3) were excluded from further analysis. The ECGs were correlated to CMR findings, and patients separated into DGE positive (DGE+ve; n=44) and negative (DGE-ve; n=35) groups. ECG territories of fQRS were correlated with myocardial segments of DGE on CMR, in order to determine whether areas of DGE were affected by fQRS.

Results: Patients from the DGE+ve and DGE-ve groups were of similar gender (75% vs. 77% male respectively, p=0.10) and age (54±19 vs. 57±11 years respectively, p=0.41). Fragmented QRS complexes were significantly more prevalent in the DGE+ve group than in the DGE-ve group (68.2% vs. 14.3%, p<0.001). The positive predictive value (PPV) of fQRS for DGE on CMR was 85.7%, with a specificity of 86.7%, sensitivity of 68.2% and negative predictive value of 68.2%. In the DGE+ve group with fQRS (n=30), fQRS ECG lead territory was predictive of regions of DGE on CMR in 73.3% (n=22) of patients.

Conclusions: The presence of fQRS on 12-lead ECG correlates with DGE on CMR in patients with HCM with high specificity and PPV. Electrocardiographic territories containing fragmentation also correlate with myocardial segments of DGE on CMR. This simple, inexpensive method may therefore be valuable for predicting scar or fibrosis in patients with HCM. Future work should focus on correlating fQRS with risk factors and events to determine its use in risk stratification.

Importance of hypertrophy pattern in sudden death risk stratification among patients suffering from hypertrophic cardiomyopathy

E. Pagourelas1, G.K. Efthimiadis2, D.G. Parcharidou3, T.D. Gossios1, H. Kavrousa1, I.H. Styliadis1,2, Aristotle University, Hippokration Hospital, 2nd Propedeutic Dept of Internal Med., Cardiology Unit, Thessaloniki, Greece;1 Aristotle University of Thessaloniki, 1st Department of Cardiology, Thessaloniki, Greece

Purpose: To investigate differences in sudden death (SD) and associated arrhythmic events (ventricular tachycardia/fibrillation, resuscitated cardiac arrest and appropriate defibrillator discharge) rates among four discrete hypertrophic cardiomyopathy (HCM) phenotypes (asymmetric basal septal hypertrophy (ASH), left ventricular outflow tract obstruction (LVOTO) at rest, midventricular hypertrophy/obstruction (MVO) and apical hypertrophy (APH)) and to challenge the importance of hypertrophy type in SD prediction.

Methods: Hypertrophy phenotypes were recognized by means of echocardiography and MRI in 423 HCM patients (49.3±17.2 years, 66.2% male) followed up for a median of 84 months (7 years, range 6 to 480 months). Cumulative SD event rates through follow-up were estimated by Kaplan-Meier method and differences were assessed by log rank test. To identify independent predictors of the study outcome, univariate and multiple Cox proportional hazard models were adopted. p-values <0.05 were considered significant.

Results: ASH was discovered in 259 patients (61.2%), LVOTO in 88 (20.8%), APH in 42 (9.9%) and MVO in 34 (8%). SD events rates among groups are shown in Figure 1. Presence of MVO strongly predicted SD and associated arrhythmic events [Adjusted Hazard Ratio (HR): 3.3, 95% CI (1.26-8.85), p=0.016] independently of the 5 established risk markers for SD (family history of SD, syncope, non sustained ventricular tachycardia, abnormal blood pressure response during exercise and maximum wall thickness >3.0 cm).

Conclusions: HCM phenotype is associated with SD and lethal arrhythmic events and should be taken into consideration during SD risk stratification. Especially, high adverse outcome rate connected to MVO necessitates early recognition and appropriate therapeutic interventions.

Tissue Doppler imaging and prognosis in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy

H. Kitaoaka, T. Kubo, K. Hayashi, Y. Baba, N. Yamazaki, Y. Matsumura, T. Furuno, Y. Doi, Kochi Medical School, Kochi, Japan

Aims: Assessment of left ventricular (LV) systolic and diastolic functions by tissue Doppler imaging (TDI) has been reported to be useful for predicting the prognosis in patients with hypertrophic cardiomyopathy (HCM). The purpose of this study was to evaluate the clinical significance of TDI parameters for prediction of cardiovascular events in asymptomatic or mildly symptomatic patients with HCM.

Methods and results: Eighty-five HCM patients (52 males, 55.6±14.6 yrs.) belonging to New York Heart Association (NYHA) functional class I or II were enrolled in this study. Patients with LV systolic dysfunction or a clinically documented history of atrial fibrillation were excluded. The combined end-points were HCM-related death, admission for heart failure or stroke, new episode of atrial fibrillation and aortic valve replacement, which were defined as aortic stenosis and/or significant aortic insufficiency. The study population comprised 42 individuals with hypertrophic obstructive cardiomyopathy (HOCM), 39 with non obstructive HCM and 4 with isolated right ventricular hypertrophy. Peak systolic, early diastolic (e’), and late diastolic (a’), tissue Doppler imaging velocities were lower in patients who experienced cardiovascular events; moreover, E/e’ was higher in these patients. The event-free curve in patients with a high E/e’ value was significantly worse than that in patients with a low E/e’ value (Figure). Multivariate analysis revealed the deceleration times of E and E/e’ to be independent predictors of cardiovascular events.

Conclusions: Assessment of diastolic function by TDI is useful for risk stratification in HCM patients with no or mild symptoms. TDI measurements should be incorporated into the clinical management of HCM.

Prognostic role of a high-sensitivity cardiac troponin T marker in patients with dilated cardiomyopathy

Y. Baba, T. Kubo, S. Yamanaka, Y. Nakashima, Y. Ochi, N. Yamazaki, Y. Matsumura, T. Furuno, H. Kitaoaka, Y. Doi, Kochi Medical School, Kochi, Japan

Purpose: Although serum high-sensitivity cardiac troponin T (hs-cTnT) has become a well established diagnostic and prognostic marker in acute coronary syndromes, its prognostic significance of a hs-cTnT marker in dilated cardiomyopathy (DCM) is unclear. The aim of this study was determine whether hs-cTnT can be a reliable prognostic marker of cardiac events in DCM.

Methods: We performed clinical evaluation including measurement of hs-cTnT in 55 patients with DCM. The normal range of hs-cTnT is less than or equal to 0.014 ng/ml. During a mean follow-up period of 5.0±1.7 years, there were 17 cardiac events: heart failure deaths in seven, sudden cardiac deaths in two and hospitalization for heart failure in eight. Patients with abnormal hs-cTnT values (0.014 ng/ml) had significantly more frequent cardiac events than did those with low hs-cTnT values (hazard ratio: 8.3, 95% confidence interval: 2.9 to 23.8, p<0.001). We divided the patients into four groups by hs-cTnT levels: nonmeasurable levels (<0.001 ng/ml), very low levels (0.001-0.023 ng/ml), low levels (0.023-0.028 ng/ml) and very high levels (0.028 ng/ml or more).

Results: Serum concentration of hs-cTnT was 0.017±0.023 ng/ml. During a mean follow-up period of 5.0±1.7 years, there were 17 cardiac events: heart failure deaths in seven, sudden cardiac deaths in two and hospitalization for heart failure in eight. Patients with abnormal hs-cTnT values (0.014 ng/ml) had significantly more frequent cardiac events than did those with low hs-cTnT values (hazard ratio: 8.3, 95% confidence interval: 2.9 to 23.8, p<0.001). We divided the patients into four groups by hs-cTnT levels: nonmeasurable levels (<0.001 ng/ml), very low levels (0.001-0.023 ng/ml), low levels (0.023-0.028 ng/ml) and very high levels (0.028 ng/ml or more).

Conclusions: hs-cTnT may be a useful and independent predictor of cardiac events in DCM.
Background: Detecting subclinical cardiac involvement in CA patients by advanced non-invasive techniques might be favorable for improving outcome.

Methods: Longitudinal, circumferential and radial peak systolic strain (Syst) were assessed by speckle tracking imaging (STI) in 44 biopsy-proven CA patients and 30 normal controls. Patients were divided into compensated (n=18) and decompensated (n=26) group based on clinical assessment and followed-up for a median period of 345 days.

Results: Ejection fraction (EF) was preserved while longitudinal Syst (LSyst) was significantly reduced in both CA groups. An intra-wall gradient with lower basal LSyst and higher apical LSyst was documented in CA patients. NYHA class, LV wall-thickness and diastolic dysfunction increased, while EF, septal mitral annular displacement and tricuspid plane annular systolic excursion decreased in proportion with increasing number of segments with reduced LSyst. Patchy distributed late enhancement detected by cardiac magnetic-resonance imaging in the LV was evidenced in 71% CA patients. Incidence of death or heart transplantation was significantly higher in decompensated (65%) group than in compensated CA group (22%, P<0.001) during follow-up. Mortality risk increased with increasing number of segments with reduced LSyst (risk ratio: 2.4, 95% CI: 1.4-3.9).

Conclusions: Global LV function is preserved but regional longitudinal function is severely compromised in CA patients featuring a characteristic base-to-apex gradient within one wall. Increasing number of segments with abnormal deformation is associated with adverse remodeling and poorer prognosis in CA patients.
in type non-A: (2) Intraventricular obstruction (15%), ventricular thrombi formation (4%), cardiac rupture (1%) and recurrence in acute phase (2%) were observed only in type A TCM, though the prevalences of pulmonary edema, pump failure and arrhythmic death were similar in the two types of TCM. (3) During long-term follow-up (24±25 months), recurrence (type A+1% vs. type non-A+4%) and cardiac death (type A+2% vs. type non-A+0%) were rare in both types of TCM.

Conclusions: Patient characteristics and long-term prognosis were similar in type A and type non-A TCMs. However, there were differences in frequent triggers and incidences of acute complications between the two types of TCM. Attention should be paid to occult pectomatomy in type non-A TCM, and acute complications such as intracardial thrombi and acute recurrence of TCM need to be closely monitored in type A TCM, especially in cases with intraventricular obstruction.

P4276 Prognostic value of the admission ECG for predicting complications in patients with tako-tsubo cardiomyopathy

B. Schneider, U. Desch, J. Stein. Sana Klinikum, Luebeck, Germany

Purpose: Tako-tsubo cardiomyopathy (TTCA) mimics acute myocardial infarction. A substantial number of patients develop adverse events during the acute course of TTA.

This study assessed the prognostic value of the admission ECG for predicting complications in patients with TTA.

Methods: A TCM is defined as the new onset of myocardial dysfunction within 48 h of the onset of symptoms. The incidence of TTA was 6.9 per 100,000 patients per year.

The study included 76 TTA patients (69±7 months; 70±12 years). A total of 37% patients (49±7) developed one event (n=17) or more (n=20) adverse events such as pulmonary oedema (n=14), cardiogenic shock (n=4), ventricular tachycardia (n=7), atrial fibrillation (n=14), right ventricular involvement (n=15), intraventricular pressure gradient (n=8), thrombus and/or stroke (n=6), or death (n=2).

Results: The admission ECG was compared in patients with and without adverse events.

- Patients with adverse events were older (73±12 years vs 67±12 years, p=0.05) and more frequently female (52% vs 14%, p=0.05).
- There was a higher rise in troponin (9.4±6.0 vs 6.1±5.7 times the upper limit of normal, p=0.05) and a lower left ventricular ejection fraction (47±19 vs 55±13%, p=0.007) in patients with adverse events. Angiographic ballooning pattern and left ventricular end-diastolic pressure were not different.

Conclusions: Time from symptom onset to first ECG (7.5±2.7 vs 9.3±9.8 hours, p=ns) was similar in both groups. Patients with adverse events had a higher heart rate on admission (97±25 vs 82±18/min, p=0.003), and there was a trend towards a higher number of leads with ST-segment elevation (4.4±2.5 vs 3.5±2.3 leads, p=0.09) and a greater magnitude of ST-segment elevation (0.64±0.51 vs 0.48±0.36 mV).

The number of patients with ST-elevation in V3 (89% vs 74%) and V4 (60% vs 39%, p=0.02) was observed in patients with adverse events. Regarding ST-elevation in the other leads, occurrence of an abnormal Q wave (32% vs 30%), reciprocal ST-segment depression (27% vs 28%) or T-wave inversion on the admission ECG there was no difference among both groups. Patients with adverse events, however, presented with a longer QTc interval (491±54 vs 460±54 msec, p=0.02).

Conclusion: Almost half of the patients with TTA develop adverse events. Especially elderly females with a high heart rate and a prolonged QTc interval on the admission ECG are at increased risk for developing complications during the acute course of TTA.

P4277 Long-term follow-up of 99 patients after transcatheter ablation of septal hypertrophy (TASH) for HOCM: No evidence for the induction of an arrhythmogenic substrate

T. Lawrence1, M. Schlosser2, S. Gottschalk2, C. Leuner2,
H. Kuhn1, C. Stellbrink1, 1University of Witten-Herdecke, Dept. of Cardiology, Witten-Herdecke, Germany; 2Dept. of Cardiology, Klinikum Bielefeld, Germany, Bielefeld, Germany

Background and Aim of the study: Prognosis after surgical myectomy for HOCM is beneficial even in long-term follow-up. However, after TASH only mid-term follow-up data is available so far. In the present study we systematically analyzed the mortality in a 7 year follow-up after TASH.

Methods: All patients who underwent TASH treatment at our institution within the year 2004 were included in the study (n=103, age 57.6±15 years). Follow-up was performed by telephone contact with either the patients or their general practitioners. Only 4 patients who lived abroad (Syria, Australia, Turkey, Italy) were lost in follow-up and were excluded from the study.

Results: Left ventricular outflow tract (LVOT) obstruction decreased significantly after the injection of 0.9±0.3 ml of ethanol (LVOT gradient at rest pre vs. post TASH: 76.0±17.5 mmHg, after provocation pre vs. post TASH: 163.6±60.4 mmHg, p<0.0001 for all). No patient died during the TASH-procedure or during the hospital stay. In 10 patients TASH was a redo intervention. During a mean follow-up time of 6.5±1.4 years 10 patients died. 7 patients died from non-cardiac reasons (5.3±0.8 years after TASH) and 3 patients died suddenly (2, 9 and 79 months after TASH at the age of 57, 47 and 78 years). In this study population the yearly total mortality was 1.6%, the yearly sudden death rate 0.4% and the in hospital mortality 0.0%.

Conclusion: Prognosis after TASH is excellent even in long-term follow-up. The sudden death rate in this study population is lower compared to untreated HOCM patients. There is no evidence for the induction of an arrhythmogenic substrate after alcohol ablation.

P4278 Identification of patients with idiopathic dilated cardiomyopathy and SCD-HeFT inclusion criteria who could be considered for early ICD implantation

M. Zechcin1, A. Pipetta1, M. Merlo1, C. Lutman1, A. D. Lendara2, D. Gregori3, G. Barbat1, L. Vitali Serdoz1, A. Balulati1, G. Sinagra1,
1Cardiovascular Department, “Ospedali Riuniti” and University of Trieste, Trieste, Italy; 2A.S.S. n. 1, Cardiovascular Center, Trieste, Italy; 2University of Padua, Department of Experimental Medicine and Public Health, Padua, Italy

Purpose: To identify patients with recently diagnosed idiopathic dilated cardiomyopathy (IDC) and symptomatic heart failure unlikely to improve despite medical treatment introduction/optimization and who could be considered for early ICD implantation.

Methods and Results: 189 consecutive patients with IDC and SCD-HeFT criteria (LV ejection fraction <0.35 and NYHA classes III—IV) evaluated at the time of the start of beta-blocker treatment were enrolled in the Trieste Heart Muscle Disease Registry. After optimization of medical treatment only 58 patients (31%) maintained SCD-HeFT criteria 6 months later, whereas 131 patients were no longer in the registry (n=12, 6%, 4 died suddenly). According to the multivariable analysis, the presence at first observation of an end-diastolic LV volume >110 ml/m² (OR=2.63; 95% CI: 1.29-5.60), lower systolic blood pressure (OR for interquartile difference=1.36; 95% CI: 1.33-1.40), a larger indexed left atrial diameter (OR for interquartile difference=1.72; 95% CI: 1.07-2.78), the presence of left bundle branch block (OR=2.17; 95% CI: 1.06-4.43) and the presence of significant single-vessel (OR=2.18, 1.05-4.5) significantly predicted the persistence of ICD indications or death 6 months later. Considering these parameters a model for the probability of non improvement estimation was developed.

Conclusions: In IDC, only a minority of patients still have SCD-HeFT criteria after optimization of medical treatment or die in the meanwhile; applying simple clinical parameters it is possible to identify this patients, who could be considered for earlier ICD implantation.

P4279 Surgical correction of HOCM in patients with severe hypertrophy and septal myocardial fibrosis

K.V. Borisov. Medical Center of the Executive Office of the President of Russian Federation, Moscow, Russian Federation

Purpose: The mechanism of sudden death in HOCM is ventricular tachycardia/fibrillation emanating from areas of fibrosis. The classic Morrow technique for HOCM in patients with extreme left ventricular hypertrophy, right ventricular obstruction and myocardial fibrosis is not effective. A new technique of HOCM surgical correction in patients with severe hypertrophy and septal myocardial fibrosis was proposed.

Methods: The excision of the asymmetrical hypertrophied area of the interventricular septum (IVS) causing LVOT and RVOT obstruction simultaneously was performed from the conal part of the RV corresponding to the zone of the LV. This excision was carried out on the right side of the IVS and not through the whole IVS thickness. The areas of septal myocardial fibrosis were removed corresponding to the zone of delayed enhancement (DE) imaging. Septal myocardial fibrosis was detected by cardiovascular magnetic resonance with DE imaging after gadolinium infusion. 11 patients with biventricular obstruction, severe hypertrophy (NYHA Class 3) and episodes of ventricular tachycardia (VT) underwent this procedure. Ages ranged from 18 to 38 years. The follow-up period was 25±7 months.

Results: 9 patients were free of symptoms (NYHA class 1) and 2 patients had only mild limitations. The mean echocardiographic LVOT gradient decreased from 87.9±12.8 to 96.6±3.4 mmHg, the mean value of gradient in RVOT was reduced from 44.6±5.7 to 41.4±1.4 mmHg. Echocardiographically determined septal thickness was reduced from 35.8±3.2 to 19.2±2.1 mm. Sinus rhythm was maintained in 10 patients. The end of His bundle right branch was noted in all patients after surgery. VT was not registered. None of the patients needed implantation of cardioverter-defibrillator.

Conclusion: This novel technique of HOCM surgical correction proved the precise removal of the areas of septal fibrosis and effective elimination of simultaneous LVOT and RVOT obstruction in patients with severe hypertrophy. A major advantage is that injuries, in particular to the conduction system, are easily avoided.
Long-term recovery of atrioventricular conduction after percutaneous transluminal septal myocardial ablation in patients with hypertrophic obstructive cardiomyopathy

A. Axelsson1, K. Weibring1, O. Havdrup2, H. Kelbak1, E. Jorgensen1, S. Helqvist1, L. Kober1, H. Bundgaard1, M.K. Jensen1.
1Rigshospitalet - Copenhagen University Hospital, Heart Centre, Department of Cardiology, Copenhagen, Denmark; 2Department of Cardiology, Roskilde sygehus, Roskilde, Denmark

Objectives: Lesion of the atrioventricular (AV) conduction system is a well known adverse effect of percutaneous transluminal septal myocardial ablation (PTSMA) in patients with hypertrophic obstructive cardiomyopathy (HOCM). Implantation of permanent pacemakers (PM) following PTSMA has been reported in 3 to 8% of patients, but data determining potential long-term AV recovery is sparse.

Methods: The AV-conduction was evaluated by ECG and 48 hours Holter recording at long-term follow-up 4.8±3.6 years after PTSMA. In patients with a PM or implantable cardioverter defibrillator (ICD) the device was adjusted to back-up VVI-mode frequency 40. Documented high grade AV block defined as 2nd or 3rd degree was registered.

Results: Eighty six of 101 consecutive patients undergoing first time PTSMA from 1999-2011 (age 61±12 years) had no implantable device at baseline. Left bundle branch block was present in 7% and right bundle branch block in 13% of the patients at baseline. Twenty eight percent (24/86) of the patients without a device at baseline had a PM implanted for high grade AV block 6.4±2.9 days after PTSMA. Ninety-nine percent (73/74) of patients with a PM implanted after PTSMA had high grade AV block. Patients who had a PM implanted in relation to PTSMA were significantly older (66±10 vs. 59±13 years, p=0.02) and they had higher incidence of a right AV block during the procedure (67% vs. 33%, p=<0.01) than those who did not.

Eight patients with PTSMA-related PMs were diseased at the time of follow-up and two patients declined participation in the long-term evaluation of AV conduction. In 43% (6/14) of patients 48 hour Holter recordings did not reveal high grade AV block which suggests post-discharge recovery of the AV conduction. No significant differences in baseline characteristics were found between patients with and without documented high grade AV block (p=0.04).

Conclusions: After first time PTSMA a PM was implanted due to AV block in 28% of patients with no previously implanted device. The long-term evaluation of AV conduction showed spontaneous recovery in 43% of these patients. This post-discharge recovery of the AV-conduction after PTSMA might suggest the potential for a more conservative pacemaker strategy.

P4281
Long-term outcomes after heart transplantation for Emery-Dreiffuss muscular dystrophy

J.M. Kracht, A.J. Gay, C. Nafeh-Bizet, M. Redonnet, F. Bouchart, P.V. Utzler, F. Dognet, A. Tabley, F. Anselme, J.P. Bessou, University Hospital of Rouen - Hospital Charles Nicolle, Rouen, France

Background: Emery-Dreiffuss muscular dystrophy (EDMD) is an hereditary syn- drome related to mutations in lamin A/C gene (LMNA) and is characterised by se- vere dilated cardiomyopathy, mostly slight peripheral muscular dystrophy, supra- ventricular arrhythmia and atrio-ventricular (AV) block. Transplantation for EDMD is rarely reported in the ISHLT registry. We aim to study outcomes after heart transplantation (HTx) for end-stage heart failure in twelve EDMD patients.

Methods: 12 cases of HTx performed for EDMD confirmed by genetic analysis in a single institution between 1997 and 2011 were compared to 12 patients age, sex and year of transplantation matched. Survival curves were analysed by Kaplan-Meier method.

Results: Before transplantation, EDMD patients had similar age (56 vs 57 yo, p=0.81), sex ratio (42% male), pre-transplantation NYHA functional class III (p=0.207), left ventricular ejection fraction (LVEF=33% vs 32%, p=0.89), higher rate of supra-ventricular arrhythmia (100% vs 45%, p=0.002) and AV block (58% vs 12.5%, p=0.042) compared to non-EDMD. After HTx, NYHA functional class was similar (I, p=1.00), LVEF (72±5.91% vs 69±11.3%, p=0.49), rejection rejection rate (19±3.8% vs 40±8.2% by year, p=0.45), infection rate (14% vs 6% by year, p=0.087), renal function (eGFR=89±5 vs 66±37 ml/min, p=0.22) were similar after HTx in EDMD and non-EDMD group. Survival rate at 1 year, 2 years, 5 years were not significantly different (respectively 91.6%, 90.9%, 81.5% versus 100%, 100%, 100%, p=0.146). 42% EDMD patients had slight muscular dysfunc- tion, comparable with good quality of life.

Conclusion: Despite reluctance for heart transplantation in end-stage HF pa- tients with EDMD, long term outcomes are similar to non EDMD patients at 1,2 and 5-year follow-up in our institution.

P4282
Distinguishing 320-slice CT-detected focal fibrotic lesions and non-fibrotic lesions in hypertrophic cardiomyopathy by assessment of regional myocardial-strain using two-dimensional Speckle-tracking

A. Kataoka, N. Funabashi, S. Horie, M. Takahashi, K. Ozawa, M. Uehara, H. Takeshi, Y. Kobayashi, Chiba University Graduate School of Medicine, Department of Cardiovascular Science and Medicine, Chiba, Japan

Purpose: To distinguish focal fibrotic and non-fibrotic-lesions in LVM in HCM subjects, we compared myocardial-regional-peak-strain-values using two-dimensional speckle-tracking trans thoracic-echocardiography (TTE) in 320-slice-CT-detected fibrotic, non-fibrotic and normal-control-lesions.

Methods: Forty subjects (20-consecutive-HCM-subjects (mean 59.1 years), 20- healthy-controls (mean 61.4years) underwent speckle-tracking TTE, and analysis of regional-peak-longitudinal (LS) and transverse-strain (TS) in each of 17-LVM-segments (American-Heart-Association-classification). In HCM-subjects, fibrotic-lesions were identified by early-phase defective-enhancement and late- phase abnormal-enhancement by 320-slice-CT. Regional-peak-LS and TS were measured in MSCI-detected fibrotic and non-fibrotic LVM-lesions.

Results: In 20-HCM-subjects, 318-lesions (93.0%) yielded good-tracking on TTE. Regional-peak-LS values were significantly lower in fibrotic-lesions than in non-fibrotic-lesions in HCM-subjects and controls (5.6±2.9%, 11.1±5.7%, 14.6±6.2%, respectively), furthermore these were significantly lower in non-fibrotic-lesions in HCM-subjects than controls (P<0.001). However there were no significant-differences of regional-peak-TS among fibrotic and non-fibrotic-lesions in HCM-subjects and controls (10.0±12.7%, 13.2±9.4%, 14.6±11.1%, respectively).

Figure 1. Strain images with and without fibrosis

Conclusion: Regional-peak-LS by speckle-tracking provides useful-information noninvasively to distinguish fibrotic from non-fibrotic-lesions in LVM in HCM subjects on 320-slice-CT and normal LVM in normal-health controls.

P4283
Hidden right ventricular dysfunction in asymptomatic first-degree relatives of arrhythmogenic right ventricular cardiomyopathy assessed by two-dimensional Speckle-tracking, compared with strain Doppler

R. Arconza, S. Cornenale Pinto, P. Caso, O. Rapisarda, C. Cavallaro, F. Vecchione, A. D'Oriofino, M. Cavallaro, R. Cabalito, Complex Unit of Cardiology, Non invasive Cardiology, Chair of Cardiology, Second University of Naples, Naples, Italy

Purpose: According to modifications of criteria of ARVC, proposed to facilitate clinical diagnosis in first-degree relatives, who often have incomplete expression of the disease, the diagnosis of familial ARVC is based on one of the following findings: either mild global dilatation or reduction in RV ejection fraction (EF) with normal LV or mild segmental dilatation of the RV or regional RV hypokinesis. The potential utility of Strain-Strain rate (S-SR) Doppler and two-dimensional (2D) to quantitatively assess: (P<0.001) function in asymptomatic family members of ARVC, with apparently normal RV, was evaluated.

Methods: 80 subjects were studied:40 first degree ARVC relatives with normal RV at standard echocardiography and 40 healthy controls. By E9-GE LV EF, LV diameters and volumes, RV dimension, fractional area change (FAC%) and RVOT fractional shortening (RVTot%), RA volume were measured. By DTI velocity of (both P<0.001) LV systolic- and diastolic wave (S) at tricuspid annulus were measured. Longitudinal systolic RV SR-Doppler and 2D SR in apical 4 and 2-chambers views were measured at level of RV free wall segments, all LV seg- ments and RA wall. Circumferential and radial systolic LV 2D S-SR were mea- sured in middle short axis view. By 3D echocardiography with volumetric probe we measured RA and RV volumes.

Results: No significant differences were found between relatives and controls for RV dimensions (1.9±0.3 vs 2.0±0.3 cm3), RVFAC (50±12 vs 51±11%) and RVOTTs (64.8±13 vs 65.3±14%, RA max volumes by 2D (39±8.5 vs 37±7.5 ml; index: 20.3±4.5 vs 8.7±6 ml/m²) and by 3D (52±9.6 vs ±51±8 ml; index: 27.4±5.9 vs 88.0±6 ml/m²), 3D RV end-diastolic (31±10.5 vs 33±11 ml/m²)
Cardiac sarcoidosis has characteristic distribution of late gadolinium enhancement in magnetic resonance imaging in comparison with idiopathic dilated cardiomyopathy

M. Sano1, H. Satoh1, K. Shikiri2, M. Saitome1, T. Ushihara1, H. Katoh1, H. Hayashi1. 1Hamamatsu University School of Medicine, Department of Cardiology, Hamamatsu, Japan; 2Hamamatsu University School of Medicine, Department of Emergency Medicine, Hamamatsu, Japan

Purpose: Late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) imaging is useful for the early diagnosis of cardiac sarcoidosis (CS). However, since some patients with dilated cardiomyopathy (DCM) also exhibit LGE, the differential diagnosis is sometimes difficult. This study aimed to identify the characteristic distribution of myocardial LGE in CS and to compare LGE patterns in CS with DCM.

Methods: Eighty-one patients with suspect of CS and 52 patients with DCM underwent CMR imaging. The intra-left ventricular (LV) and intra-mural distribution of LGE was compared.

Results: LGE was present at 22 patients (27%) with suspect of CS and 30 patients (58%) with DCM. In patients with CS, LGE was distributed into all LV segments, whereas LGE localized mainly in basal inter-ventricular septum in patients with DCM. The intra-mural analysis demonstrated that LGE was distributed into subepicardial to subendocardial layers in patients with CS, whereas LGE localized mainly in the mid-ventricular layer in patients with DCM. Especially, subepicardial and subendocardial LGE (with spared mid-ventricular layer), circumferential subepicardial LGE, and nodular (transmural) LGE were characteristic patterns in CS. The specificity and sensitivity were 23% and 97% in subepicardial and subendocardial LGE, 18% and 97% in circumferential subepicardial LGE, and 36% and 97% in nodular LGE, respectively.

Conclusions: In patients with CS, LGE-CMR showed more diffuse distribution of LGE compared with patients with DCM. The characteristic patterns of LGE distribution can help differential diagnosis of CS from DCM.
Diabetes mellitus and cardiac complications in thalassemia major patients

A. Pepe1, A. Meloni1, G. Rosati2, V. Carusolo2, L. Cuccia3, A. Spisani3, E. Chiodo3, V. Postlano1, M. Lombardi1, M.R. Gambirini2, 2Fondazione G.Monasterio CNR-Regione Toscana and Institute of Clinical Physiology, Pisa, Italy; 3Epidemiology and Biostatistics Unit, Institute of Clinical Physiology, CNR, Pisa, Italy; 1Unità Operativa Dipartimentale Talassemia, P.O. "S. Luigi-Curra" - ARNAS Garbaldi, Catania, Italy; 4Serv. Prenvenz. Diagnosi e Cura Talassemia, Ospedale "G. di Cristina", Palermo, Italy; 5Unità Microcitemia, A.O.R.N. Cardarelli, Napoli, Italy; 6Servizio Radiologia Ospedaleria-Universitaria, Arcipretale "S. Anna", Ferrara, Italy; 7Pediatría, Adolesscentologia e Talassemia, Arcipretale "S.Ana", Ferrara, Italy

Purpose: The relationship between diabetes mellitus (DM) and cardiac complications has never been systematically studied in thalassemia major (TM). Our aim was to evaluate in a large retrospective historical cohort of TM if DM was associated with an higher risk of heart complications.

Methods: We compared 86 TM patients affected by DM with 709 TM patients without DM consecutively included in the Myocardial Iron Overload in Thalassemia (MIOT) data base where the clinical history is recorded from the birth to the first T1 cardiovascular magnetic resonance (CMR) years 2006-2010. Myocardial iron overload (MIO) was evaluated by T2* multislice technique. Biventricular function was quantitatively evaluated by cine images. Myocardial fibrosis was evaluated by late gadolinium enhancement. All considered cardiac events were definitively evaluated at the end of the study.

Results: In DM patients versus no DM patients we found a significantly higher frequency of cardiac complications (46.5% vs 16.9%, p<0.0001), heart failure (HF) (30.2% vs 11.7%, P<0.0001), hypokinetic arhythmias (18.6% vs 5.5%, P<0.0001), and myocardial fibrosis (29.9% vs 18.4%, P=0.008). DM patients had a significant higher risk of cardiac complications, HF, hypokinetic arhythmias and myocardial fibrosis, also adjusting for the absence of MIO (all 16 cardiac segments with T2*>20 ms) and for the covariates significantly different between groups and significantly associated to the dependent variable (Table 1).

Conclusions: DM increases the risk for cardiac complications, HF, hypokinetic arhythmias and myocardial fibrosis.

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Left ventricular hypertrophia in individuals with sickle cell anaemia: pathology or physiology?

S. Gatti1, N. Von Niekerk1, M. Reed2, A. Cox3, A. Zaidi1, S. Ghani3, M. Papadakis4, M. Ahmed3, T. Vaneberg1, S. Sharma4, 1University Hospital Lewisham, London, United Kingdom; 2St George's University of London, London, United Kingdom

Introduction: Left ventricular noncompaction (LVNC) cardiomyopathy is rare amongst Caucasians but studies in African/Afro-Caribbean origin (black) heart failure patients demonstrate that a high proportion fulfill criteria for LVNC (30%). Recent observations in elite athletes, have also demonstrated a 3-fold greater prevalence of increased LV trabeculations (LVHT) amongst black athletes compared with Caucasian athletes, with almost 15% fulfilling echocardiographic criteria for LVNC. We postulate that the LVHT observed in black individuals represents an ethnically determined cardiac response to increased preload. Sickle cell anemia is associated with an increased preload and a high cardiac output. The aim of this study was to evaluate the prevalence of LVHT amongst homozygous sickle cell disease patients.

Methods: Between 2005 and 2012, 99 consecutive normotensive sickle cell patients (53% male) underwent echocardiography. Echocardiograms were analysed for trabeculations defined as localised protrusions of the ventricular wall ≥3 mm in thickness associated with intertrabecular recesses and previously published criteria for LVNC. The results were compared with 132 healthy black controls (55% male).

Results: Sickle cell patients were older compared with controls (33±11 years vs 21±6 years; p<0.0001) with no difference in systolic BP (118±11mmHg vs 120±15mmHg; p=0.165) in either group. Sickle cell patients had a mean Hb level of 8.6±1.2g/dl (range 5.5g/dl-11.6g/dl). Sickle cell patients displayed a higher prevalence of LVHT compared with controls (28.3% vs 12.1%; p=0.0002). Of the sickle cell patients, 20.8% fulfilled conventional Chin et al and 10% Jenni et al criteria for LVNC. None of the controls fulfilled the published LVNC criteria.

Sickle cell patients with LVHT exhibited a larger LV cavity size compared to controls with LVHT (51.7mm±6.0mm; range 44-66mm vs 47.1mm±6.0mm; range 38-54mm; p<0.0001) but showed no difference in LVIDd compared with Sickle cell patients without LVHT (mean LVIDd was 51±1.1mm ± 5.6mm vs 51.9±6.1mm; p=0.604). There were no differences in LV systolic or diastolic function in sickle cell patients with or without LVHT (EF by Simpson was 61%±8.1% vs 61%±8.4%;p=0.985; E/A ratio was 2.0±0.8 vs 1.7±0.6; p=0.111 and MV deceleration 191±36ms vs 194±51ms; p=0.792).

Conclusion: The high prevalence of LVHT in sickle cell patients compared with black controls further reinforces the likelihood of this morphological anomaly representing a physiological response to increased cardiac preload and endorses the need for robust criteria for diagnosing LVNC in black individuals.

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T1 mapping in differentiation of diffuse myocardial disease in hypertrophic and dilative cardiomyopathy


Background: T1 mapping was proposed as potentially valuable in quantitative assessment of diffuse myocardial fibrosis. We aimed to determine its role in differentiation of healthy myocardium from diffuse fibrosis clinical setting.

Methods and results: Thirty-nine subjects with known hypertrophic (HCM) or dilative cardiomyopathy (DCM) were enrolled (age 47±7.4 years). Twenty-five age-gender matched subjects with low pre-test likelihood of cardiomyopathy served as controls. Single equatorial short-axis slice T1 mapping was performed on a 3 Tesla scanner prior and after 3 minutes after administration of 2.0 mmol/l gadobutrol. We quantified T1 values within the septal myocardium between the native and the post-contrast myocardium (R1) as 1/T1 and the R1 differences between the native and post-contrast myocardium (ΔRR). R1 native was significantly shorter in cardiomyopathies compared to control subjects (p<0.01). Conversely, post-contrast R1 were significantly longer in cardiomyopathies with time points (p<0.01). ΔRRs were significantly higher in cardiomyopathies in comparison to controls.

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Table 1

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Covariates: age, gender, co-morbidity, age and sibling co-morbidity
Effect of physical exercise on cardiac remodeling and oxidative stress in diabetic rats


Purpose: Oxidative stress is one of the main mechanisms involved in the pathogenesis of diabetic cardiomyopathy. Studies suggest that physical exercise (PE) improves myocardial glucose homeostasis and reduces myocardial damage from diabetes mellitus (DM). The aim of this study was to evaluate the effect of PE on myocardial oxidative stress and in vivo and in vitro cardiac structure and function in diabetic rats.

Methods: Male Wistar rats were divided into three groups: control sedentary (CS, n=15), diabetic sedentary (DS, n=15), and diabetic trained (DT, n=15). Diabetes mellitus was induced by intraperitoneal injection of streptozotocin (50mg/kg, single dose). Physical training was performed 5 times a week for 8 weeks in a treadmill. At the end of the experimental period, rats underwent echocardiography. Myocardial function was evaluated in left ventricular (LV) papillary muscle preparations during isometric contractions. Oxidative stress was measured in LV myocardial samples using ANOVA. ANCOVA was used to compare echocardiographic and oxidative stress parameters, and ANCOVA for papillary muscle parameters using physical training provided 24 hour urine and fasting blood serum samples which were analyzed for copper/ceruloplasmin/zinc using the highly sensitive and widely validated technique of Inductively Coupled Plasma Mass Spectrometry.

Results: Changes between CFR LAD and CFR RCA in non obstructive HCM (2.22±1.60 vs. 2.27±1.7; DS 17.4±7; DT 107.7±7; DS 80.7±17*; DT 113.7±7.1*) were significant (p<0.001 vs. CS; #: p<0.05 vs. DS).

Conclusions: Exercising did not improve oxidative stress and in vitro and in vivo cardiac structure and function in diabetic rats. Left atrium diameter was enlarged in diabetic rats and unchanged in controls at all time-points (p>0.01). ROC analysis revealed that R1 native was able to distinguish between healthy and diseased myocardium (AUC: 0.98; 95% CI: 0.96-1.00; p<0.001) with a sensitivity of 100%, specificity of 68%, diagnostic accuracy 96%, positive predictive value 93%, and negative predictive value 100%. R110min and ∆R110min performed best among the postcontrast values, however with lower predict values.

Cyclophilin A expression in endomyocardial biopsies predicts clinical outcome of patients with congestive heart failure

C.S. Zuern1, K.A.L. Mueller1, P. Seiser1, K. Klingel2, R. Kandolf2, A. Bauer1, M. Gawaz1, A.E. May1, A. Bauer1, M. Gawaz1, A.E. May1, 1Medizinische Universitaetsklinik Tubingen, Tubingen, Germany; 2Eberhard-Karls University Tubingen, Institute of Pathology, Department of Molecular Pathology, Tubingen, Germany

Purpose: Recently, we have identified Cyclophilin A (CypA) and its extraacellular receptor EMPRRIN (CD147) as novel diagnostic markers of inflammatory cardiomyopathies. Here, we evaluated the prognostic relevance of CypA and EMPRRIN expression in endomyocardial biopsies of consecutive patients with congestive heart failure.

Methods: We enrolled 227 unselected patients with congestive heart failure undergoing endomyocardial biopsy for diagnostic reasons. Biopsies were analyzed using established histopathological and immunohistochemical criteria together with CypA and EMPRRIN staining. Study endpoint was the composite of all-cause mortality, heart transplantation, malignant arrhythmia, and heart failure-related rehospitalization.

Results: CypA was significantly enhanced in patients with inflammatory cardiomyopathy (n=127) as compared to patients with non-inflammatory cardiomyopathy (n=100, p<0.001). In contrast, expression of EMPRRIN was similar in both subgroups (p=0.081). During a mean follow-up of 16.3 months 60 patients (27%) reached the endpoint. Of all clinical (ejection fraction, NYHA functional class), laboratory (BNP) and immunohistological parameters tested (CypA, EMPRRIN, CD 68, CD3, MHC II, virus genome), CypA was identified as the only independent predictor for the primary endpoint yielding a relative risk of 2.55 (95% CI 1.25-5.25; p=0.018) figure) as well as a relative risk of 4.7 for all-cause mortality and heart transplantation alone (95% CI 1.19-15; p=0.038). Subgroup analysis also revealed CyPA as a predictor of clinical outcome in patients with non-inflammatory cardiomyopathy suggesting that CyPA is a prognostically relevant marker of myocardial damage beyond inflammation.

Cardiomyopathies: imaging / Cardiomyopathies: pathophysiology

Dual assessment of coronary flow reserve in non obstructive hypertrophic cardiomyopathy: patophysiological characteristics


Microvascular dysfunction reflected by the decreased coronary flow reserve (CFR) is a common finding in hypertrophic cardiomyopathy (HCM) and is related with unfavorable long-term outcome. Elevated LV filling pressure and wall stress (as a result of diastolic dysfunction) might additionally aggravate CFR. Plasma levels of NT-pro-BNP and the ratio of early to midventricular flow velocity to early diastolic lateral mitral annulus velocity (E/e') have been shown to be accurate noninvasive predictors of the abnormal LV wall stress and elevated LV filling pressure. Therefore, the aim of the current study was to examine: 1. Possible regional difference in CFR and CFR/E/e' in patients with nonobstructive HCM and controls, and 2. Whether CFR and CFR/E/e' best distinguish between controls and patients with cardiomyopathy.

Methods: In 41 pts (mean age 46.2±16 yrs;19 male) with asymmetric non obstructive HCM (HCM) and is related with unfavorable long-term outcome. Elevated LV filling pressure and wall stress (as a result of diastolic dysfunction) might additionally aggravate CFR. Plasma levels of NT-pro-BNP and the ratio of early to midventricular flow velocity to early diastolic lateral mitral annulus velocity (E/e') have been shown to be accurate noninvasive predictors of the abnormal LV wall stress and elevated LV filling pressure. Therefore, the aim of the current study was to examine: 1. Possible regional difference in CFR and CFR/E/e' in patients with nonobstructive HCM and controls, and 2. Whether CFR and CFR/E/e' best distinguish between controls and patients with cardiomyopathy.

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Methods: In 41 pts (mean age 46.2±16 yrs;19 male) with asymmetric non obstructive HCM (HCM) and is related with unfavorable long-term outcome. Elevated LV filling pressure and wall stress (as a result of diastolic dysfunction) might additionally aggravate CFR. Plasma levels of NT-pro-BNP and the ratio of early to midventricular flow velocity to early diastolic lateral mitral annulus velocity (E/e') have been shown to be accurate noninvasive predictors of the abnormal LV wall stress and elevated LV filling pressure. Therefore, the aim of the current study was to examine: 1. Possible regional difference in CFR and CFR/E/e' in patients with nonobstructive HCM and controls, and 2. Whether CFR and CFR/E/e' best distinguish between controls and patients with cardiomyopathy.
serum caeruloplasmin (Table 1). Serum zinc trended higher in healthy volunteers compared with HCM patients. There were no significant differences in urinary zinc or copper between the two groups.

Table 1. Differences in copper and zinc in patients with HCM compared with healthy volunteers.

<table>
<thead>
<tr>
<th>Copper Status</th>
<th>HCM Patients</th>
<th>Healthy Volunteers</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Copper umol/L</td>
<td>19.6 ± 3.43SD</td>
<td>18.7 ± 3.62SD</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum Zinc umol/L</td>
<td>18.28 ± 5.43SD</td>
<td>23.7 ± 0.73SD</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum Caeruloplasmin g/L</td>
<td>0.24 ± 0.05SD</td>
<td>0.20 ± 0.04SD</td>
<td>0.02</td>
</tr>
<tr>
<td>Urinary Copper umol/24 hours</td>
<td>0.36 ± 0.09SD</td>
<td>0.33 ± 0.11SD</td>
<td>0.51</td>
</tr>
<tr>
<td>Urinary Zinc umol/24 hours</td>
<td>8.23 ± 0.52SD</td>
<td>6.99 ± 0.96SD</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Conclusion: HCM patients exhibit overtly altered copper homeostasis. Coupled with the previous observation of LHV and fibrosis regression induced by copper chelation therapy these findings provide a mechanistic basis for copper chelation therapy to be tested in HCM.

P4295 Tyrosyl-tRNA synthetase: peculiarities of myocardial expression and autoimmune reactions at dilated cardiomyopathy

D.V. Ribaenko1, I.U. U. Kondratik2, V.I. Bobyk2, L.L. Sidork2, A.L. Kornelyuk2. 1NISC “Institute of Cardiology named after M.I. Strazhesko” MAS of Ukraine, Kyiv, Ukraine; 2Institute of Molecular Biology and Genetics of NAS of Ukraine, Kyiv, Ukraine.

Background: Aminoacyl-tRNA synthetases (ARS) are enzymes that play not only a leading role at the first prebiosomal step of protein biosynthesis, but may participate in binding of immune and autoimmune reactions. Antibodies (Abs) directed against ARSs are associated with different disease (myositis, arthritis, heart failure etc.). Moreover, the catalytic N-terminal module of tyrosyl-tRNA synthetase (TyrRS) may functions as immunemodulating factor (similar interleukin-8) and C-terminal non-catalytic domain - as endothelial and monocyte activating polypeptide like EMPAT II. The aim of investigation was to study the expression of TyrRS in myocardium and to examine the peculiarities of autoimmune reactions against full-size TyrRS and its N- and C-terminal modules at dilated cardiomyopathy (DCM).

Materials and methods: Recombinant proteins full-size TyrRS and its N- and C-terminal modules were isolated from the bacterial strains based on Escherichia coli BL21(DE3)pLy5E. TyrRS expression in myocardium was identified by Western blot analysis in pathomorphologic specimens of three DCM-affected human myocardium and samples of myocardium of three practically healthy men who died from cardiac trauma as a control. The level of specific circulating Abs against full-size TyrRS and its C- and N-terminal modules were measured by ELISA method in sera of 30 DCM patients with CHF, II-III functional NYHA classes, chronically treated with beta-blocker, inhibitor ACE, diuretic. Sera of 20 healthy donors were examined as a control. To study the effect of auto-Abs, purified from DCM pts sera with immunofluorochromaty, on TyrRS enzymatic activity we analyzed parameters changes of aminoacylation reaction of cognated tRNA catalyzed by TyrRS.

Results: The increased expression (on 43%) of TyrRS was revealed in totally lysed and especially in nuclear subfraction of DCM-affected cardiomyocytes in compared to control. The increased level (for 29.3%) of IgG class auto-Abs against full-size TyrRS, against N- and C-terminal modules for 18.5% and 65.5% respectively were found in blood serum of DCM patients, compared with healthy donors. The degrees of DCM sera IgM Abs elevation against full-size TyrRS and its isolated N- and C-terminal modules were 18.5%, 38.8% and 14.7%, respectively. Our results also revealed that auto-Abs against full-size TyrRS purified from DCM pts sera in vitro dosed a possible dependent stimulating effect (practically twice enhancement) on TyrRS enzymatic activity.

Conclusion: These results demonstrated a novel antigen-target at DCM - tyrosyl-tRNA synthetase and revealed its potential role at disease development.

P4296 Cardiotoxic anticancer agents induce an increase in myocardial weight: a pathophysiologic study of isolated cardiac mechanics

M. Arao1, M. Sekine1, K. Setsuda2, K. Mizuno1. 1Tokyo Metropolitan Matsuura Hospital, Department of Internal Medicine, Tokyo, Japan; 2Tokyo Metropolitan Komagome Hospital, Department of Cardiology, Tokyo, Japan.

Purpose: Administration of cardiotoxic anticancer agents results in a dose-dependent and significant increase in left ventricular mass (LVM). This study investigated the precise cardiac mechanisms that occur with this phenomenon in an effort to predict safe doses of anticancer agents.

Methods: A total of 229 consecutive patients with breast cancer (all females; mean age: 51.8±7 years) who completed adjuvant chemotherapy with three drugs (epirubicin, paclitaxel, and fluorouracil (CEF)); CEF over a 60-month period were studied. Echocardiography was performed before and after several cycles of CEF.

The left atrial diameter (LAD), LV diameter in diastole/systole (LVDds/LV), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), interventricular septal thickness (IVST), posterior wall thickness (PWT), LV ejection fraction (LVEF), stroke volume (SV), ratio of early to late ventricular filling velocity (E/A), mitral annulus velocity (e’), Tei index (TI), LVM index (LVMI), diameter of inferior vena cava (IVC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated. The relationships between the total amount of CEF (3CEF/LVM) and the rate of change (%) in the LVM (LVM, LVEDV, LVESV), LVEF, IVST, IVC, PWT, (PWT), and LV and LVSV were also investigated.

Results: No significant changes were observed in indices of cardiac function, such as LVEF, Tei-Index, A/E ratio, e’ and IVC. By contrast, anticancer treatment result in significant increases in the LVDS/LVEDV, LVESV, IVST, PWT, SV, LVM (142.8±2.5 vs. 167.3±2.8; P<0.0000000000000001), and LVMI (92.8±1.5 vs. 78.7±1.7; p<0.000000000000001) and a significant decrease in BP. Moreover, 3CEF/LVM correlated with 3IVST (r=0.47,P<0.0000000000000001), y=0.52x+21, and 3LVMI=0.45, y=0.55x-21).

Conclusions: A cardiotoxic anticancer regimen result in an increase in LVM, with a tendency towards concentric hypertrophy. Based on observed data, the relationship between CEF dose, LVM, and LVMI can be represented by the following formula: 3CEF/LVM=1.7+0.18×3LVMI. Further, in order to maintain the LVMI at less than 130 g/m², the following CEF dose formula should be used: 3CEF/LVM=3.26+3.46×LVMI.

CARDIOMYOPATHIES: DIAGNOSIS

P4297 A French registry of takotsubo syndrome in non-academic hospitals (OFFSET)

L. Belli1, J.J. Dujardin2, M. Hanssen1, S. Cattan1, F. Albert2, J.-L. Georges1, X. Marcaggi3, D. Logeais4, J.F. Aubert5, M. Mula6 on behalf of Collège National des Cardiologues des Hôpitaux Français. 1Hospital, Annecy, France; 2Hospital, Douai, France; 3Hospital, Hagueneau, France; 4Hospital, Montpellier, France; 5Hospital, Chartres, France; 6Hospital, Versailles, France; 7Hospital, Vichy, France; 8University Hospital, Paris, France; 9St Joseph - St Luc Hospital, Lyon, France; 10French Society of Cardiology, Paris, France.

Purpose: Takotsubo syndrome remains the subject of investigation. We report on the management of and processes of care in consecutive patients with Takotsubo syndrome using data from a French registry (OFFSET).

Methods: Between November 2010 and December 2011, 15 non-academic hospitals with a high volume of percutaneous coronary procedures (>1000) included consecutive patients diagnosed with Takotsubo syndrome according to the Mayo clinic diagnostic criteria.

Results: A total of 121 patients were enrolled: 89% were women and the mean age was 72±12 years. Most of the women (89%) >50 years old, 8% of patients had diabetes, 30% were current smokers and 52% had hypertension. Symptoms of Takotsubo syndrome were chest pain (81%), dyspnea (27%) and/or syncope (5%). The mean maximum troponin level was 7.8 ng/mL and the mean maximum B-type natriuretic peptide level was 1013 pg/mL. ECG showed a negative T wave in 73%, ST elevation in 42% and/or a new Q wave in 29% of patients. One patient was treated with fibrinolysis. Coronary angiography was performed in all patients. Coronary arteries were angiographically normal in 78% of patients and showed >50% stenosis in 22%. Left ventricle (LV) angiography showed typical ballooning in 73% of patients. The mean LV ejection fraction was 42±13% on echocardiography and 46±10% on angiography. The target event was identified in 55% of the patients: mental stress in 61% and physical stress in 46% and/or syncope (5%). In-hospital treatment included nitrates, (11% of patients), unfractonated heparin (25%), low-molecular-weight heparin (79%), aspirin (91%), antplatelet (82%) and angiotensin-converting enzyme/angiotensin receptor inhibitors (ACE/ARB) (75%). None of the patients died during hospitalization.

Conclusions: These observational data from 15 non-academic French hospitals provide insights into the characteristics of patients with Takotsubo syndrome and current processes of care for this population. Furthermore, they offer an opportunity for comparison with data from patients with acute myocardial infarction.

P4298 Syncope in hypertrophic cardiomyopathy: the diagnostic role of flow mediated dilation

M. Rognagni1, A. Capria2, S. Verbena3, M. Macini1, L. Zenilli1, I. Cazzoli4, F. Romeo5. 1Tor Vergata Polyclinic, Rome, Italy.

Introduction: Hypertrophic Cardiomyopathy (HCM) is an inherited myocardial disease characterized by unexplained increased left ventricular wall thickness associated with nondilated ventricular chambers in the absence of other cardiac or systemic disease. Syncope occurs in approximately 15–25% of patients with HCM. The principal causes can be arrhythmia and a primary haemodynamic mechanism. Abnormal blood pressure response during exercise and left ventricular outflow tract obstruction are the most important haemodynamic mech-
The extent and consequences of diagnostic uncertainty in individuals assessed for arrhythmogenic right ventricular cardiomyopathy

D. Lee, P. Brennan, S. Lord. Newcastle upon Tyne Hospitals NHS foundation trust, Newcastle upon Tyne, United Kingdom

Purpose: The diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) can only be made with certainty in the early stages of the disease from a combination of clinical features, echocardiography findings, and histopathological confirmation. However, this diagnosis can often be challenging, particularly in the later stages of the disease. The aim of this study was to assess the diagnostic uncertainty in individuals with ARVC.

Results: The diagnostic uncertainty was assessed using a combination of clinical, echocardiographic, and histopathological criteria. The diagnostic uncertainty was highest in patients with later-stage disease, where the clinical features were less specific. The diagnostic uncertainty was also highest in patients with a combination of clinical and echocardiographic features, where the histopathological confirmation was less likely.

Conclusions: The diagnostic uncertainty in individuals with ARVC is high, particularly in the later stages of the disease. This highlights the need for further research to improve the diagnostic accuracy of ARVC.

Performance of task force diagnostic criteria for identification of symptomatic patients in the Nordic arrhythmogenic right ventricular cardiomyopathy registry

1. Aarhus University Hospital, Aalborg, Denmark; 2Rigshospitalet - Copenhagen University Hospital, Copenhagen, Denmark; 3University of Oslo, Rikshospitalet University Hospital, Oslo, Norway; 4Karolinska University Hospital, Stockholm, Sweden; 5Aalborg Hospital of the Aarhus University Hospital, Aalborg, Denmark; 6Gentofte University Hospital, Copenhagen, Denmark

Purpose: To assess the performance of the task force diagnostic criteria for ARVC in the Nordic ARVC Registry.

Results: The performance of the task force diagnostic criteria was assessed using a combination of clinical, echocardiographic, and histopathological criteria. The diagnostic criteria showed a sensitivity of 86.7% and a specificity of 75.8% for the identification of symptomatic patients with ARVC.

Conclusions: The task force diagnostic criteria for ARVC show good performance in the Nordic ARVC Registry.
The impact of dynamic intraventricular obstruction on left ventricular mechanics in hypertrophic cardiomyopathy

M. Rosca1, B.A. Pepescu2, M. Gurzun2, A. Calin1, C.C. Beladan1, E. Gurea3, I.M. Coman1, C. Gheorghiu3. 1University of Medicine and Pharmacy, Bucharest, Romania; 2Institute of Cardiovascular Diseases "Prof. Dr. C.C. Iulius", Bucharest, Romania

Background: LV twisting and untwisting are integral components of ventricular contraction, relaxation, and filling. In hypertrophic cardiomyopathy (HCM), myocardial fibrous disarray, interstitial fibrosis and dynamic obstruction could influence left ventricular (LV) mechanics. Data regarding the impact of the dynamic LV outflow tract (LVOT) obstruction on LV mechanics are limited and discordant.

Purpose: To assess LV mechanics in patients (pts) with obstructive (HOCM) and non-obstructive (NHCM) HCM versus normal subjects.

Methods: We prospectively enrolled 35 pts (52±15 years, 16 men) with HCM (19 with HOCM and 16 with NHCM, according to the presence/absence of a dynamic LVOT gradient of > 30 mmHg) and 36 age- and gender-matched normal subjects (47±12 years, 12 men). Pts with apical HCM have been excluded. A comprehensive echocardiogram was performed in all. LV filling pressures were assessed using the E/e'average ratio. Global longitudinal LV strain (GLS) and LV torsion parameters have been assessed by speckle tracking echocardiography. Peak basal and apical rotation and backrotation rates, LV peak torsion and peak LV untwisting rate were determined. Time intervals from peak R wave (ECG) to each of them were measured and normalized to the RR interval. Mitral regurgitation (MR) severity was assessed.

Results: Pts with HOCM were older (p=0.009) and had more severe MR (p=0.01) than pts with NHCM. There were no significant differences between HOCM and NHCM pts regarding LV mass, E/e ratio, systolic and diastolic mitral valve velocities, GLS, and LV mass for all. Compared to normal subjects, pts with HOCM, unlike pts with NHCM, had higher values for apical LV rotation (21.7±8.5 vs 16.4±6.3, p=0.01) and backrotation rate (p=0.00) and basal Urotorion (p=0.04) and LVtorsion (3.7±1.3 vs 2.8±1.8°/cm, p=0.002). Time to peak LV untwisting rate was significantly longer than in normal subjects in both HOCM and NHCM pts (p=0.001 and p=0.01, respectively). In pts, LVtorsion was related to age (p=0.49, r=-0.20), GLS (r=0.67, p<0.001), Urotorion (r=-0.42, p=0.01) and the presence of dynamic obstruction (r=0.38, p=0.02). In multivariate analysis LVtorsion was independently correlated with GLS (p=0.05, p=0.03) and the presence of dynamic obstruction (p=0.32, p=0.04).

Conclusions: In pts with HCM, LVOT obstruction is related to changes in LV mechanics: increased apical and basal rotation, increased LV torsion, and delayed LV untwisting. Increased LV torsion is independently related to the presence of dynamic LVOT obstruction. These findings could provide new insights into the pathophysiology of HCM.

Prevalence of psychiatric disorders in Tako-Tsubo cardiomyopathy

D. Dojen1, S. Moschetta1, P. Moceri1, F. Bernascoski2, T. Tibi3, P. Cerboni1, E. Ferranti1. 1University Hospital of Nice - Hospital Pasteur, Nice, France; 2Hôpital La Fontaine, Antibes, France; 3Hospital Center of Cannes, Cannes, France

Purpose: Tako-Tsubo cardiomyopathy (TTC) involves transient left ventricular dysfunction, generally subsequent to stress. Most often, it affects postmenopausal women, and filling. Prevalence of psychiatric disorders has been forwarded as an explanation of the deleterious and disproportionate catecholergic response to stress. However, this prevalence has never been clearly established.

The aim of our study was to determine the prevalence of psychiatric disorders in TTC.

Methods: A history of psychiatric problems and psychotropic treatment were examined prospectively in a population of 70 TTC patients recruited over 36 months in 3 hospital centers. These were compared with those of 53 anterior ST-segment elevation myocardial infarction (STEMI) and 51 anterior non-ST-segment elevation myocardial infarction (NSTEMI). These groups were matched for age and gender.

Results: Close on 61.4% of TTC presented a history of psychiatric problems versus 28.4% for ACS (p<0.001), i.e. 2.16-fold more. The most frequently encountered psychiatric disorders in TTC were anxiety (30%), depression (7%) and schizophrenia (3.2%). Long-term psychotropic treatment had been delivered to 47.9% of TTC patients versus 20.1% for ACS (p<0.001). The most commonly used psychotropic treatments in TTC were antidepressants (86%), anxiolytics (24%) and antipsychotics (17%).

Conclusion: The prevalence of psychiatric disorders in TTC is strong, as witnessed by the high intake of psychotropic treatments. Anxiety-related and depressive disorders are most often at issue. The observed elevated prevalence of cancer and chronic respiratory insufficiency could be partly responsible for these disorders.

Clinical characteristics and short-term outcome of patients with Tako-Tsubo syndrome and critical coronary stenosis: comparison with patients with Tako-Tsubo with normal coronary arteries

M. Previtali1, G. Crimi2, A. Valbusa3, A. Bartolini2, A. Repetto1, M. Rossi1, P. Rubartelli2, F. Chiarella3, L. Oltrona Visconti3. 1IRCCS Pol. S.Matteo University of Pavia, Pavia, Italy; 2ASIL Genova Ospedaliera Villa Scassi, Genova, Italy; 3IRCCS Azienda Ospedaliera San Martino – IST, Genova, Italy

Purpose: Takotsubo syndrome (TTS) may be associated with significant coronary artery disease (CAD), but the prevalence, clinical characteristics and outcome of TTS with CAD and the pathogenetic role of CAD are not well defined.

The aim of the study was to compare the clinical characteristics and short-term outcome of pts with TTS and critical CAD with those with TTS with no CAD and to assess the role of CAD in these pts.

Methods and Results: 184 consecutive pts (aged 71±12 yrs, 90% women) admitted with acute symptoms and ST-T changes who showed a reversible pattern on ECG were prospectively studied. Clinical characteristics of TTS with critical CAD and the pathogenetic role of CAD are not well defined. The aim of the study was to compare the clinical characteristics and short-term outcome of pts with TTS and critical CAD with those with TTS with no CAD and to assess the role of CAD in these pts.

Critical CAD (n=32) was detected in 184 consecutive pts (aged 71±12, p<0.001), more frequently men (19% vs 9.5%, ns), had a higher prevalence of ST-elevation at admission (93 vs 59%, p<0.01) and a lower LV ejection fraction (47±12% vs 58±11%, p<0.05). The mean number of psychotropics per patient was 0.78 in TT and 0.28 in CAD (p<0.001). The most commonly used psychotropic treatments were antidepressants (86%), anxiolytics (24%) and antipsychotics (17%).

Conclusion: The prevalence of psychiatric disorders in TTC is strong, as witnessed by the high intake of psychotropic treatments. Anxiety-related and depressive disorders are most often at issue. The observed elevated prevalence of cancer and chronic respiratory insufficiency could be partly responsible for these disorders.
Completely autologous biotube vascular grafts: eosin Y significantly promoted in vivo formation of functional biotubes in a short term

Y. Nakayama1, T. Tjurinaka1, T. Watanabe1, M. Yamana1, K. Kanda2, H. Yaku2, National Cardiovascular Center Research Institute, Osaka, Japan; 2Kyoto Prefectural University of Medicine, Kyoto, Japan

Objectives: In our previous study, in vivo tissue-engineered autologous tubular tissues “BIOTUBEs” could reconstruct to vascular tissues within several months after implantation. BIOTUBEs obtained from traditional silicon mold in dorsal subcutaneous pouches of animals for 1 month had homogeneous thin (less than 0.1 mm) connective tissue walls even though with high burst strength (ca. 10 mmHg) and equivalent compliance to that of native arteries. We challenged the possibility of extremely short-term preparation of BIOTUBEs by controlled release of eosin Y.

Methods and Results: Micropored acrylate tubes (diameter: 4 mm, length: 4 cm, pore size: 0.5 mm) filled with a PBS solution of agar (0.3%) including eosin Y (1%), as molds for BIOTUBEs, were placed into dorsal subcutaneous pouches of Beagle dogs (ca. 10 kg) for 1 week. Eosin Y was continuously released through the matrix for the period of 1 week. BIOTUBEs in mainly consisting of collagen and fibroblasts, with extremely thick wall (thickness: 0.5 – 1 mm) and rich angiogenesis were obtained. Their elastic modulus was similar (1 ± 0.1% of T) to that of native arteries. BIOTUBEs were easily handled by using standard microsurgery. There were no major discrepancies in surgical handling between the biotubes and native arteries. After blood circulation was re-established, periodic cycles of inflation and deflation of the grafts were noted.

Conclusion: Only 1-week preparation of BIOTUBE vascular grafts with thick wall in surgical handling between the biotubes and native arteries. "BIOTUBEs" could reconstruct to vascular tissues within several months after implantation, and could be used as an instant regenerative medicine.

VASCULAR BIOLOGY I

Angiotensin II inhibits ecSOD and ATPTA and upregulates oxidative stress via toll-like receptor 4

T. Nakashima1, S. Umemoto2, T. Okamoto3, S. Matsuda3, T. Fukuda4, M. Matsuoka5, Y. Yamaguchi University Graduate School of Medicine, Department of Medicine and Clinical Science, Ube, Japan; 2Yamaguchi University Hospital, Ube, Japan; 3Yamaguchi University, Graduate School of Medical Science Research Center, Ube, Japan; 4Yamaguchi Prefectural University, Faculty of Nutrition and Nutrition, Yamaguchi, Japan; 5University of Illinois at Chicago, Chicago, United States of America

Aims: Toll-like receptor 4 (TLR4) and angiotensin II (AngII) involve the production of reactive oxygen species (ROS) in the vascular wall. AngII has been also shown to increase antioxidant enzyme extracellular superoxide dismutase (ec-SOD) through the copper efflux transporter ATPTA. However, the role of TLR4 in AngII-induced ROS production on the regulation of ecSOD remains unknown.

Methods: TLR4-deficient (TLR4−/−) and wild-type (WT) mice were subjected to pressure overload by AngII or norepinephrine (NE). We also examined the effects of AngII receptor type 1 (AT1) receptor antagonist irbesartan, which had no effects on TLR4−/− mice. The AngII infusion-induced increase in systolic BP in all drug-treated groups in comparison with those in the control TLR4−/− and WT mice (p<0.05). Little difference in BP was observed among the drug-treated groups. Furthermore, the control TLR4−/− and WT mice showed similar levels of the W/L ratio. In WT mice, AngII induced the increase in the W/L ratio compared to that in the control mice (p<0.05). However, in TLR4−/− mice, AngII-induced ROS production on the regulation of ecSOD remains unknown.

Results: The control TLR4−/− and WT mice showed similar body weight and heart rate, and drug treatment did not affect these indices. AngII and NE similarly increased systolic BP (14.9±6.9 and M1: 28.1±6.9, p<0.05) compared to sham controls (14.9±3.9 pos. cells/vessel, n=18), M1-MAC initially only increase slightly, compared to those in the untreated rats (3.6±1.9 vs. 9.0±0.8 pos. cells/vessel, n=18). At later time points (3d, 7d, 14d, 28d), both subpopulations further increased in number, whereas the proportion of the perivascular space (14d M2: 37.5±6.9 and M1: 21.8±16 pos. cells/vessel, n=18), was changed. The local distribution of the subpopulations changes during the arteriogenic process. Whereas M1-MAC are detected adjacent to the media, M2-MAC are present in the outer perivascular region of collateral vessel. In mice the distribution of MAC within collateral vessel did not reflect the composition of circulating monocytes. However, suppressing inflammatory monocytes (M1) with DEX impairs perfusion recovery (36.7±5 vs. 61.9±5% in sham controls; n=5; p<0.05), whereas IL10 application significantly increases perfusion (81±5% vs. n=5; p<0.05).

Conclusion: The distinct early increase and spatial distribution of M2-MAC support the idea that this subtype plays a predominant role during collateral remodeling. This investigation demonstrates that a forced shift towards M2-MAC improves the arteriogenic response.

Insulin induced vasoreactivity is impaired after short-term high fat feeding and is dependent on perivascular adipose tissue as well as resistance artery properties

R. Meijer1, E.C. Sarre1, J.S. Yudkin2, C.A.F. Alt2, J.E. Barrett3, V.W. Van Hinsbergh3, Y.M. Smulders1, E.C. Erinag3, 1VU University Medical Center, Department of Internal Medicine, Amsterdam, Netherlands; 2Department of Medicine, University College London, London, United Kingdom; 3VU University Medical Center, Institute for Cardiovascular Research, Laboratory of Vascular Biology, Amsterdam, Netherlands; 4Division of Endocrinology and Metabolism, University of Virginia Health System, Charlottesville, VA, United States of America

Purpose: Perivascular adipose tissue (PVAT) contractile properties are lost in obesity, thereby negatively impacting microvascular function. Here, we studied whether a two-week high fat diet (HFD) affects insulin-mediated microvascular function as well as PVAT properties in- and ex- vivo, in the pre-obese state in mice.

Methods: C57Bl/6 mice were assigned chow or high fat diet for two weeks. Insulin-induced microvascular recruitment was studied using Contrast Enhanced Ultrasound during a hyperinsulinaemic euglycaemic clamp. Insulin-induced vasoreactivity was further studied in chow and HFD rats. Perivascular adipose tissue (PVAT) from the pre-obese state in mice was evaluated by transplanting bone-marrow from ubiquitin GFP expressing mice to irradiated C57Bl6 mice before the diet.

Results: Short-term HFD did not increase total body weight compared to chow mice. Epidydimal adipose tissue mass was 70% heavier in HFD compared to chow mice, whereas PVAT was increased more than threefold from 0.07±0.02 mg to 0.24±0.07 mg, p=0.04. In vivo, insulin increased microvascular blood volume in chow, but not in HFD mice. Insulin did not mediate perfusion in nor in HFD in the absence of PVAT. In the presence of chow PVAT, there was vasodilation in chow RA (48±20%), but no vasoreactivity in HFD RA (7±10%), p<0.02. Incubation with HFD PVAT did not induce vasodilation in chow RA (+46%) or HFD RA (+21%), p=0.1. Also, differences between chow RA + chow PVAT and chow RA + HFD PVAT were significant (p<0.01). There was no difference between HFD RA with either chow or HFD PVAT (p=0.46). Western-blot experiments revealed there is no effect of short-term HFD on Akt-phosphorylation.

C. Troidl1, G. Jung2, K. Troidl3, J. Hoffmann1, S. Voss1, H. Netl2, W. Schaper2, C.W. Hamm1, T. Schmitz-Rixen1, H. Moellmann1, 1Kernhoff Heart and Thorax Center, Bad Nauheim, Germany; 2Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany; 3Justus-Leibig University Giessen, Medical Clinic I, Cardiology, Giessen, Germany; 4Johann Wolfgang Goethe-University Hosp., Division of Vascular & Endovascular Surgery, Frankfurt am Main, Germany

The temporal and spatial distribution of macrophage subpopulations during arteriogenesis

Insulin induced vasoreactivity is impaired after short-term high fat feeding and is dependent on perivascular adipose tissue as well as resistance artery properties

Vascular biology I 745
in RA. GFP-positive cells in PVAT were more abundant after two weeks of HFD than after Chow diet.

**Conclusions:** Two weeks HFD blunts insulin-induced microvascular recruitment. The ex-vivo data suggest that this can be attributed both to a loss of vasodilator capacity of RA in response to insulin, as well as altered PVAT properties. Furthermore, the phenotype of PVAT changes due to influx of inflammatory cells after a short HFD.

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**Saphenous vein aorto-coronary bypass graft atherosclerosis in patients with chronic kidney disease: more clarification, but less vasoconstrictor potential**

T. Baar1, P. Kleinbongard1, T. Konorza2, S. Moehlenkamp2, D. Boese1, H. Degen1, J. Hippler1, M. Haude1, R. Erbel1, G. Heusch1.

1. University of Essen Medical School, Institute of Pathophysiology, Essen, Germany; 2. West German Heart Center Essen, Department of Cardiology, Essen, Germany; 3. Krankenhaus Bethanien, Moers, Germany; 4. Lukas Hospital, Medical Clinic I, Cardiology, Neuss, Germany; 5. Institute of Environment Analytical Chemistry, University of Duisburg-Essen, Essen, Germany

**Purpose:** Atherosclerotic coronary arteries are more calcified in patients with than without chronic kidney disease (CKD). The role of chronic microvascular obstruction in patients with and without CKD during stenting for saphenous vein aorto-coronary bypass graft (SVG) stenosis under protection with epicardial (PMPs) and endomyocardial (EMP) microvesicles.

**Methods:** In patients with and without CKD (n=20/20), SVG calcification was determined from virtual histology using intravascular ultrasound analysis before stenting. Coronary arterial blood was retrieved during stent implantation and divided into particulate debris and plasma. The calcium concentration of particulate debris was analyzed by flame atomic absorption spectrometry. The concentrations of catecholamines, endothelin, serotonin, tissue factor, thromboxane, and nitric oxide were determined using a bioassay of rat mesenteric arteries with intact (E+) and denuded (E-) endothelium, the vasoconstrictor response to coronary aspirate plasma was quantified and normalized to that by potassium chloride (KClmax = 100%).

**Results:** There was more dense calcium in patients with than without CKD (15±3.3 vs. 3±1.1% of plaque volume). Patients with CKD had more particulate debris and coronary calcification than patients without CKD. In contrast, the release of serotonin was less in patients with than without CKD (0.40±0.16 μmol/L vs. 1.2±0.3 μmol/L), whereas that of catecholamines, endothelin, tissue factor, thromboxane, and TNF-α was not different. Aspirate plasma from patients with CKD induced less vasoconstriction of rat mesenteric arteries than from patients without CKD (E+ 26.7%; E- 26.7% vs. E+ 68.12%; E- 95.16% of maximum KCl-induced vasoconstriction).

**Conclusion:** Atherosclerosis of patients with CKD is more calcified, but the aspirate has surprisingly less serotonin and vasoconstrictor potential.

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**Comparison of circulating microparticles counts in patients with acute coronary syndrome with two methodologies**


1. University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; 2. University Hospital Virgen de la Arrixaca, Murcia, Spain

**Background:** Circulating microparticles (MPs) are increased in cardiovascular disease and have become promising biomarkers in many pathological situations. Measurement of plasmatic MPs is not standardized and most studies have focussed on relatively large MPs due to technological limitations. We following compare two flow cytometric methodologies for the enumeration and characterization of MPs in acute coronary syndrome (ACS) patients and its changes during 30 days.

**Methods:** We recruited 113 ACS patients (aged 68±12 years, 64% males; sodium citrate platelet poor plasma was collected within 24h of percutaneous coronary intervention (PCI). Day 1 and Day 30 (n=38) post-PCI. Aliquots of samples were processed in two different flow cytometers (FCM), avoiding pre-analytical issues. Polystyrene beads (0.1-0.5 μm) were used to size the MP gate in both FCMs. CD41a+ platelet MPs (PMPs), CD14+ endothelial MPs (EMP) and CD14+ monocyte MPs (mMPs) were quantified in a high resolution Apogee A50 FCM and in a conventional FCM (FACS Calibur) with a 0.5 μm detection limitation. Data was acquired in both protocols less than 5% CytoCounts beads were used for absolute counts in FACS Calibur FCM.

**Results:** MPs counts were significantly higher when the samples were processed with a FACS Calibur FCM, mainly PMPs (p<0.005). However, there were no differences in detected MPs counts following PCI (PMPs p=0.50, EMPs p=0.40, MMPs p=0.24).

When small-size MPs (0.1-0.5 μm) were quantified in a high sensitive FCM, a significant increase in EMPs and EMPs (p<0.012 and p<0.005, respectively) was found during the follow-up period (Table), but MMPs' remained constant (p=0.81).

**Conclusion:** Latest generation of FCMs likely display higher sensitivity for MPs, mainly due to lower detection limits and background noise. The size of polystyrene beads is not comparable to biological size of MPs and therefore conventional FCMs might not reliably detect MPs. In the search of MPs as potential biomarkers, technological improvements should not be underestimated.

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**Fibrin-related thrombosis risk in type 2 diabetes: relationship with vascular pathology and drug therapy**


1. University Hospital Aachen, RWTH, Internal Medicine I, Pulmonology & Vascular Medicine, Aachen, Germany; 2. University of Leeds, Leeds, United Kingdom; 3. University of Edinburgh, Edinburgh, United Kingdom; 4. Western General Hospital, Metabolic Unit, Edinburgh, United Kingdom

**Purpose:** The formation of a platelet-rich fibrin clot represents the final step in the process of thrombosis and the development of atherothrombotic disease. MP-related deposition to vascular ischaemia. Our aim was to investigate the effects of vascular disease, metabolic factors and drug therapy on clot structure/fibrinolysis in a large cohort of diabetes subjects.

**Methods:** A total of 385 participants of the Edinburgh type 2 Diabetes Study [age 68 (range 60-75) years, 450 males] were recruited and five parameters of clot structure/fibrinolysis were assessed using a dynamic evi and turbidimetric assay and confocal microscopy.

**Results:** Female gender was associated with longer clot formation time compared with males [562.6±6 and 516.7±7 sec, respectively; p<0.001], which may be related to higher maximum absorbance [0.37±0.005 and 0.34±0.005 respectively; p<0.001] and/or impaired clot lysis time [803.20 and 665.12 seconds, respectively; p<0.001]. Gender differences were confirmed by confocal microscopy and were still evident after adjusting for fibrinogen and plasminogen activator inhibitor (PAI-1) plasma levels. Age was associated with denser clots in men with a paradoxical enhancement in fibrinolysis, possibly related to lower PAI-1 levels. Male subjects with coronary artery disease had higher clot maximum absorbance.
compared with those without history of ischaemia (0.35±0.008 and 0.33±0.006 au., respectively; p=0.04), and displayed longer clot formation time (573±15 and 522±7 sec respectively, p<0.01). Clot formation time predicted previous ischemic events in women and men [OR 1.22 (1.07, 1.38) and 1.33 (1.15, 1.50), respectively], after controlling for traditional risk factors. Body mass index and waist circumference predicted clot structure parameters in women, whereas HbA1c was a predictor in men. Low ankle brachial index was associated with thrombogenic clots regardless of gender. Metformin therapy was associated with beneficidal effects on clot structure parameters, particularly in women, whereas insulin treatment was associated with thrombogenic clots in men. Aspirin, a known fibrinolytic agent, demonstrated little effect on clot structure/function.

Conclusions: Women with diabetes have a thrombogenic clot structure compared with men and gender-specific associations are detected between clotting parameters and cardiovascular risk factors/treatment. Improved clotting parameters with metformin therapy and the relatively minimal effect of aspirin may partly explain cardioprotection by the former and reduced clinical efficacy of the latter in diabetes.

**P4315 Molecular mechanism of tissue factor regulation through RAGE-MT1-MMP axis in HMGB-1 stimulated-endothelial cells**

K. Sugimoto1, T. Ishibashi1, Y. Takuwa2, Y. Takeishi1, F. Fukushima Medical University, Fukushima, Japan; 2Kanazawa University School of Medicine, Kanazawa, Japan

**Backgrounds:** The atherosclerosis is understood as a blood vessel inflammation. HMGB-1 is one of the mediators released from necrotic cells or macrophages that receives inflammatory stimulus. It plays a key role in the systemic inflammation. Tissue factor (TF), a physiological initiator of coagulation cascade, is known to lead to inflammation which promotes the thrombus formation in the onset of acute coronary syndrome. We recently have shown that silencing of membrane type1 MMP (MT1-MMP) suppressed the advanced glycation endproducts (AGE) triggered TF protein expression and phosphorylation of NF-κB in smooth muscle cells. These results suggest that MT1-MMP also regulates to inflammatory conditions in vascular wall. However, it is still unclear about the association of HMGB-1 and MT1-MMP mediated TF expression. In this study, we investigated the molecular mechanism of TF expression in response to HMGB-1 stimulation and the involvement of MT1-MMP in endothelial cells.

**Methods:** Cultured human aortic endothelial cells were stimulated with 50μg/ml HMGB-1. The protein levels of TF and phosphorylated NF-κB were determined by Western blotting. The MT1-MMP activity was measured by ELISA. MT1-MMP expression was silenced by small interfering RNA (siRNA). GTP-loading of RhoA and Rac1 was assessed by pull-down assays.

**Results:** HMGB-1 increased MT1-MMP activity and activated small GTP binding protein RhoA and Rac1 within 5minutes in endothelial cells, which was inhibited by silencing of receptor for AGE (RAGE) or MT1-MMP. TF protein expression was regulated by RhoA activation as well as Rac1 dependent NF-κB or phosphorylation in HMGB-1 stimulated endothelial cells. siRNA to RAGE or MT1-MMP suppressed NF-κB phosphorylation and TF protein expression mediated via RhoA and Rac1 activation induced by HMGB-1.

**Conclusion:** We clarified that RAGE/MT1-MMP axis modified the HMGB-1 mediated TF expression through RhoA and Rac1 activation and NF-κB phosphorylation in endothelial cells. These results suggested that MT1-MMP was involved in vascular inflammation and might be a good target for treating acute coronary syndrome.

**P4316 Pharmakokinetic interactions between clopidogrel and rosuvastatin: effects on vascular protection in subjects with coronary heart disease**


**Background/Objectives:** Genetic polymorphisms in the hepatic cytochrome P450 (CYP2C19) affect the antiplatelet effects of clopidogrel. Rosuvastatin is partially metabolized by the same cytochrome. We hypothesized that pharmacokinetic interactions between these drugs might affect their individual effects on vascular protection.

**Methods:** Patients with stable coronary heart disease (N=20) were submitted to four consecutive 1-wk therapeutic regimens: aspirin, rosuvastatin 40 mg, rosuvastatin 40 mg plus clopidogrel 75 mg, or clopidogrel 75 mg alone. A loading dose of 300 mg clopidogrel was given in the first day. Biochemistry, platelet function (multiplatelet analyzer), flow-mediated dilation (ultrasound of the brachial artery), endothelial progenitor cells, and microparticles (flow-citometry) were assessed at baseline, after 2-wks of treatment (clopidogrel bid, n=17) or placebo (n=19) for four weeks. Different EPC subpopulations were enumerated by flow cytometry using triple staining (CD34, CD133, Kinase domain receptor, KDR) at baseline at the end of treatment. Viability was assessed by 7AAD and Annexin V-staining.

**Results:** Baseline E1 levels correlated significantly with C-reactive protein levels. Patients with E1 levels above the median had higher levels of CD34+CD133+ and CD34+KDR+ EPC (Table 1). There was no difference in markers of EPC apoptosis or circulating markers of endothelial damage between patients with E1 levels below or above the median. Four weeks treatment with bosentan did not change EPC levels.

**Conclusion:** Among patients with type 2 diabetes and vascular disease, high plasma levels of E1 is associated with higher number of EPC, possibly reflecting activation of an endothelial cell repair mechanism triggered by vascular damage. The recruitment of EPC does not seem to be related to a pro-apoptotic mechanism.

**P4317 Endothelial progenitor cells in relation to endothelin-1 and endothelin receptor blockade: a randomized controlled trial**

C. Jung, A. Raffles, J. Pernow. Karolinska Institutet, Stockholm, Sweden

**Aims:** Endothelial progenitor cells (EPC) represent an endogenous repair mechanism involving remodeling and reangiogenesis. Patients with both diabetes and vascular disease associated with endothelin dysfunction have low numbers of circulating EPC. The endothelium-derived peptide, endothelin-1 (ET-1), is increased in diabetic patients and vascular comorbidities whereas bosentan has been suggested to contribute to endothelin dysfunction in this condition. Therefore, we investigated the relation between EPC and plasma ET-1 and the effect of dual ET-1 receptor antagonist treatment on the number of EPC.

**Methods:** In this double blind study patients with type 2 diabetes mellitus and microalbuminuria were randomized to treatment with the dual ETA/ETB receptor antagonist bosentan (125 mg bid, n=17) or placebo (n=19) for four weeks. Different EPC subpopulations were enumerated by flow cytometry using triple staining (CD34, CD133, Kinase domain receptor, KDR) at baseline at the end of treatment. Viability was assessed by 7AAD and Annexin V-staining.

**Results:** Baseline ET-1 levels correlated significantly with C-reactive protein levels. Patients with ET-1 levels above the median value had higher levels of CD34+CD133+ and CD34+KDR+ EPC (Table 1). There was no difference in markers of EPC apoptosis or circulating markers of endothelial damage between patients with ET-1 levels below or above the median. Four weeks treatment with bosentan did not change EPC levels.

**Conclusion:** Among patients with type 2 diabetes and vascular disease, high plasma levels of ET-1 is associated with higher number of EPC, possibly reflecting activation of an endothelial cell repair mechanism triggered by vascular damage. The recruitment of EPC does not seem to be related to a pro-apoptotic mechanism.

**P4318 Soluble adenylyl cyclase controls oxidative-stress-induced apoptosis of smooth muscle cells**

S. Kumar, A. Appukutan, H.P. Reusch, Y. Laidov. Ruhr-University Bochum, Dpt. of Clinical Pharmacology, Bochum, Germany

**Aims:** Apoptosis of vascular smooth muscle cells (VSMC) in advanced atherosclerotic plaques is an important cause of plaque instability and may result in plaque rupture followed by thrombosis and sudden death. Within several pro-apoptotic factors, enhanced reactive oxygen species generation has been suggested as a cause for VSMC death and plaque instability. However, the precise mechanism of oxidative stress-induced VSMC apoptosis is still poorly understood. CAMP signaling pathway has been shown to play a pro-apoptotic response to different stress stimuli. Until now, it was attributed exclusively to the activity of the G-protein-responsive transmembrane adenylyl cyclase. Aside from this cyclase, mammalian cells also express soluble adenylyl cyclase (sAC). Therefore, to investigate the role of sAC in apoptosis of VSMC was the aim of the present study. For this purpose, oxidative stress was induced in VSMC derived from ratal aorta by treatment either with H2O2 (200 μM) or DMNQ (inducer of mitochondrial superoxide production, 30 μM) for 6 hours. Both treatments led to pronounced release of mitochondrial cytochrome c, caspase-9-3 deactivation and caspase-3 activation. Suppression of sAC activity by treatment with 30 μM K74 (a specific inhibitor of sAC) or sAC-knockdown (shRNA-transfection) prevented the pro-apoptotic effects of H2O2 and DMNQ. Similarly, inhibition of protein kinase A prevented the stress-induced apoptosis of VSMC. Analysis of the underlying cellular mechanisms revealed that sAC-inhibition or knockdown led to a pronounced rise in phosphorylation of p38 mitogen-activated protein kinase under oxidative stress accompanied by p38-dependent phosphorylation/inactivation of the pro-apoptotic protein JNK.

**Results:** Baseline ET-1 levels correlated significantly with C-reactive protein levels. Patients with ET-1 levels above the median value had higher levels of CD34+CD133+ and CD34+KDR+ EPC (Table 1). There was no difference in markers of EPC apoptosis or circulating markers of endothelial damage between patients with ET-1 levels below or above the median. Four weeks treatment with bosentan did not change EPC levels.

**Conclusion:** Among patients with type 2 diabetes and vascular disease, high plasma levels of ET-1 is associated with higher number of EPC, possibly reflecting activation of an endothelial cell repair mechanism triggered by vascular damage. The recruitment of EPC does not seem to be related to a pro-apoptotic mechanism.
The p110alpha subunit of PI 3-kinase is crucially involved in neointima formation by mediating smooth muscle cell proliferation, migration and survival.

J. Jesus1, M. Vanlier1, E. Berghausen2, E. Caglayan3, H. Ten Freyhaus1, O. Leppaenen2, J. Zhao1, S. Rosenkrantz1, 1Cologne University Hospital - Heart Center, Clinic III for Internal Medicine, Cologne, Germany; 2Uppsala University, Uppsala, Sweden; 3Harvard Medical School, Boston, United States of America

The proliferation, migration and survival of vascular smooth muscle cells (SMCs) are essential for the neointima formation following balloon angioplasty. In this context, growth factors such as platelet-derived growth factor (PDGF) that activate receptor tyrosine kinases (RTKs) play a significant role. RTKs activated by growth factors are largely mediated by activation of phosphatidylinositol 3'-kinase (PI3K). Previously, we were able to demonstrate that in vitro inhibition of the catalytic PI3K subunit p110alpha (p110alpha) reduced H2O2 (25 μM) induced apoptosis of WT SMCs by 30% (n=4) whereas PDGF had only poor effects on H2O2 induced apoptosis of heterozygous SMCs (22% ± 13%, n=3, not significant). In conclusion, our results indicate that the p110alpha subunit of PI3K, is crucial for growth factor-mediated proliferation, migration and survival of SMCs in restenosis following balloon angioplasty. Therefore, p110alpha represents a promising therapeutic target.

P4319

Neutrophils contribute to DVT formation by forming procoagulant and prothrombotic neutrophil extracellular traps

K. Stark1, M.L. Von Bruel1, A. Steinhart2, S. Chandrasarti1, M. Lorenz1, R. Coletti1, S. Pfleider1, D. Massberg1, B. Engelmann1, S. Massberg3, 1German Heart Center, Munich, Germany; 2Ludwig-Maximilians University, Institute of Clinical Chemistry, Munich, Germany

Objective: Neutrophils have been primarily implicated in host defence, but it is increasingly recognised, that they also contribute to coagulation. One mechanism how they could do that is exposure of Neutrophil extracellular traps (NET). These extracellular DNA structures have been found in deep venous thrombosis (DVT), but their role in thrombus formation in vivo is unclear. In this study we wanted to assess the dynamics of NET formation in vivo and their impact on DVT development in a murine flow reduction model of the inferior vena cava (IVC).

Methods: Thrombosis was induced in C57Bl/6 mice by placing a narrowing figure eight around the IVC, resulting in a reduction of blood flow velocity (n=16). NET formation in vivo was visualised by intravital 2-photon microscopy. Thrombogenesis and NET formation were quantified in GFP+/−, Dnase and hepatic treated animals (n=7 each). The ability of NETs to bind and activate factor XIII was assessed in vitro.

Results: Neutrophils were recruited very early after initiation of flow reduction in the IVC, supported by platelets. NET formation in the IVC, triggered by platelets, could be detected in vivo as early as 3h after flow reduction. We found that NETs were binding platelets, tissue factor, and fibrinogen, demonstrating a concentration of procoagulatory and prothrombotic factors on their surface. This is highlighted by the fact that coinoculation of activated platelets and neutrophils resulted in significant FXII activation. Inhibition of NETs by an antibody directed against the H2A-H2B-DNA complex significantly attenuated FXII activation. The functional impact of NETs for DVT formation is indicated by the finding that disruption of NETs by DNase treatment resulted not only in a reduced number of NETs, but also in a markedly reduced thrombus weight compared to control. Surprisingly, injection of heparin resulted in a diminished number of NETs inside the IVC, which could add to its antithrombotic effect (n=3).

Conclusion: Here we show that neutrophils contribute to DVT by NET formation, which is triggered by adhered platelets. This provides a platform for platelet adhesion and concentration of procoagulatory factors on their surface, linking inflammation and thrombosis at the cellular level. Thus, disruption of NETs could be an interesting new therapeutic approach for prophylaxis and treatment of DVT.

P4320

VASCULAR BIOLOGY II

Small-size circulating microparticles in post myocardial infarction patients: changes over 30 days and relationship to the fibrinolytic status

S. Montero-Garcia1, E. Shantsila1, L. Tapp1, B.J. Wrigley1, F. Marin1, G.Y.H. Lip1, 1University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; 2University Hospital Virgen de la Arrixaca, Murcia, Spain

Background: Recent data suggest that circulating microparticles (MPs) contribute to inflammation, coagulation and vascular repair. The dynamics of MPs counts follows 5Tevision myocardial infarction (STEMI) and their relation to levels/activity of fibrinolytic factors are unknown. We studied trends on MP levels following STEMI and their relation to parameters of fibrinolytic system in consecutive patients.

Methods: Citrated platelet poor plasma was obtained from 48 STEMI patients and 40 “control” patients with stable CAD. In STEMI, study parameters were measured within 24h of primary percutaneous coronary intervention (PCI) (day1) and days 3, 7 and 30 after admission. Small-size (0.1-0.5 μm) apoptotic annexin V-binding MPs (AnV-MPs), CD42b+ platelet MPs (pMPs), CD144+ endothelial MPs (eMPs) and CD144+ monocyte MPs (mMPs) were quantified using a high resolution Agape A50 flow cytometer. Fibrinolytic parameters (tissue-type [tPA] and urokinase-type plasminogen activator, plasminogen activator inhibitor-1 anti- gen/activity and thrombin activatable fibrinolysis inhibitor [TAFI]) were analysed by ELISA.

Results: Small-size AnV-MPs and eMPs were significantly reduced at admission (p<0.001, p<0.007 and p<0.028, respectively) but no changes...
in mMPs during the follow-up period. MP levels 30 days after STEMI were different from values seen in stable CAD (p=NS).

On linear regression analysis, AnV-MP levels were negatively associated with TIMP levels on day 30 (p=0.013 and p=0.016, respectively).

**Conclusion:** Small-size eMPs and apoptotic MPs are significantly down-regulated on admission with STEMI, possibly due to their increased consumption through interaction with thrombus/damaged myocardium. Different types of MPs are linked to parameters of the fibrinolytic system. These findings indicate pathophysiological roles for small-size MPs in STEMI and may potentially become therapeutic targets.

### Table 1. Dynamics of MPs counts in STEMI patients

<table>
<thead>
<tr>
<th>Group</th>
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<th>Day 7</th>
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**Purpose:** Leptin is assumed to contribute to the pathogenesis of atherosclerosis, through interaction with its receptor ObR on vascular cells. However, no quantitative data on its expression in human plaques has been reported so far and its impact on plaque vulnerability remains unclear. In the present study, we investigated this link in patients with carotid artery disease and hypothesized that leptin could play an active role in this process via its effects on human vascular smooth muscle cells (VSMC).

**Methods:** Carotid plaque specimen were collected from 60 patients undergoing carotid endarterectomy. Each sample was evaluated by ELISA and q-PCR for leptin and ObR expression, by histology and immunohistochemistry for detection of leptin, ObR, VSMC, collagen, macrophages, cell proliferation (Ki67) and by Western Blot for ERK signaling pathway mediating cell migration and proliferation. The effects of leptin (0-100 ng/mL) on human VSMC migration, proliferation, collagen synthesis and ERK signaling were investigated in cell culture.

**Results:** Leptin and its receptor were co-localized with plaque VSMCs by immunofluorescence. Intraplaque leptin was correlated, negatively with plaque VSMCs and played an active role in plaque stability via its effects on human vascular smooth muscle cells phenotype.

**Conclusions:** These results, for the first time, suggest that leptin could actively contribute to carotid plaque stability via various effects on human VSMCs.

### Table 2 – Dynamics of MPs counts in STEMI patients

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**Purpose:** Lack of JunD promotes oxidative stress-induced vascular aging

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**Methods:** Endothelium-dependent relaxation to acetylcholine (Ach, 10-9-10-6 mol/L) was assessed in aortic rings from young (6 months old) and old (22 months old) male JunD−/− and wild-type (WT) mice. Nitr oxide (NO), superoxide anion (O2−) and peroxynitrite (ONOO−) were measured with chemiluminescence and radiolabeled nitrotyrosine and cyclic GMP levels were assessed with specific siRNA-mediated knockdown of JunD was performed in young and old JunD−/− mice.

**Conclusions:** The Annexin I/PSR-dependent pathway was detected as a crucial mechanism for MP uptake by target cells.

### Table 3 – Dynamics of MPs counts in STEMI patients

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**Purpose:** Endothelial Microparticulates (EMP) are taken up in an Annexin I/PSR dependent pathway by target cells and promote endothelial regeneration

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<td>pMP</td>
<td>3.7 ± 0.28</td>
<td>4.1 ± 0.16</td>
<td>6.2 ± 0.18</td>
</tr>
<tr>
<td>AnV-MP</td>
<td>5.1 ± 0.3</td>
<td>0.2 ± 0.2</td>
<td>0.3 ± 0.18</td>
</tr>
<tr>
<td>p value</td>
<td>p&lt;0.05 vs. day 7</td>
<td>p&lt;0.05 vs. day 30</td>
<td></td>
</tr>
</tbody>
</table>
Recently, perivascular adipose tissue (PVAT) has been shown to play a crucial role in the development of atherosclerosis; however, the effects of AT1 on PVAT properties and their functional relevance in atherogenesis remain undefined.

Methods: 

Results: We examined the functional consequence of ATR1 deletion in perivascular adipocytes (PVAT) and subcutaneous adipocytes (SAT) with regard to adipose tissue inflammation, proliferation, and fatty acid metabolism. The absence of AT1 in PVAT led to an inflammation and proliferation phenotype, suggesting that AT1 is fundamentally implicated in the terminal differentiation of periaortic adipocytes.

Conclusions: This study demonstrates that AT1 regulates the expression levels of late stage of adipocyte differentiation marker genes in PVAT, suggesting that AT1-mediated modulation of periaortic adipocyte differentiation could be a novel therapeutic target for the prevention of atherosclerosis.

Kreupell-like factor 4 is downregulated in circulating monocyte subsets of patients with Coronary Artery Disease


The zinc finger transcription factor Krueppel-like factor 4 (KLF4) is involved in the regulation of important cell functions, including proliferation, differentiation or activation. Monocytes (Mo) are essential mediators of cardiovascular repair processes, and human Mo can be divided in CD14+CD16- mo and CD16+ mo (consisting of CD14+CD16+ and CD14+CD16- mo). For the CD16(-)CD14+ mo mouse analogues, i.e. Ly-6C(high)- and Ly-6C(low)-mo, it was shown that Ly-6C(high)-mo are crucial for phagocytosis and proteolysis of necrotic tissue in the early inflammatory phase after acute myocardial infarction (MI), whereas the reparative and proangiogenic properties of Ly-6C(low)-mo may promote healing of damaged myocardial tissue in the subsequent proliferative phase. So far, little is known about the expression and function of KLF4 in human Mo subsets. In the present study, KLF4 expression was quantified in circulating Mo subsets of healthy subjects (HS; n=18; 78% male; median age, 58 years) and patients with coronary artery disease (CAD; n=52; 77% male; 70 years) using flow cytometry. In HS, the number of KLF4 expressing cells was significantly lower in CD14+CD16- mo (51.0%) compared to CD14+CD16+ mo (73.0%; p<0.01) and CD14+CD16+ mo (72.5%; p<0.01). Although the same distribution pattern could be observed, the number of KLF4 expressing mo was significantly reduced in all 3 mo subsets of CAD patients (CD14+CD16- mo: 19.9%; p<0.01 vs. HS; CD14+CD16+ mo: 35.9%; p<0.01; CD14+CD16+ mo: 30.8%; p<0.001). Interestingly, the number of KLF4-expressing Mo, consistent for all 3 Mo subgroups, was found to correlate negatively with the leukocyte counts (p<0.01). Histochimical analyses of human myocardial tissue revealed that the number of KLF4 expressing mononuclear cells, presumably monocytes, was significantly increased in patients with acute MI (p=0.05 vs. old MI), and even more pronounced findings were detected in those with subacute MI (p=0.01 vs. old MI; p=0.05 vs. control). In summary, our findings demonstrate that the transcription factor KLF4 is highly expressed in CD16+ mo, i.e. an immune cell subtype with presumed reparative/repair functions, whereas KLF4 was downregulated in all 3 mo subsets of CAD patients. The observed accumulation of KLF4-positive cells in the acute MI phase after MI might indicate that KLF4 may play an important role in regulating immune cell functions during cardiovascular repair processes.

Is NGAL assessment in patients referred to renal artery stenting for atherosclerotic renal artery disease conclusive of clinical value? 

D. Rzeznik, T. Przewlocki, A. Kabak-Zembicka, A. Roslawiecka, A. Kozanecki, M. Kostkiewicz, K. Zmudka, P. Podolec. John Paul II Hospital, Department of Cardiac and Vascular Diseases, Krakow, Poland

Despite many trials, only a few predictors of outcome in patients referred to renal artery stenting (PTA) for renal artery stenosis (RAS) were identified. NGAL is a marker for immune function and predictor of outcomes after cardiac surgery procedures, however, it was not investigated in the setting of RAS. The present study aimed to assess clinical value of NGAL assessment in patients referred to PTA for RAS.

Methods: 78 patients with renovascular hypertension, aged 63.8±10.7, who underwent PTA for RAS (69-60%: 41 (53%) with eGFR<60ml/min and 25 (32%) after hypertension crisis. Clinical data, serum level of NGAL, creatinine (Cr) and BNP, mean systolic and diastolic blood pressure (SBP and DBP), left ventricle mass (LVM) and diastolic function (E/A, e’ velocity, E/e’ ratio) were analyzed before PTA. The incidences of cardiovascular (CV) death, myocardial infarction (MI), ischimic stroke, and coronary artery disease (CAD) (previous MI, Q-waveMI, 2Q:31-47.3; 3Q:47.4-69; 4Q>93 vs. 1Q<47.3; 2Q<47.4; 3Q<69; 4Q>93) were significantly reduced in PVAT, suggesting that PVAT has a strikingly different phenotype from the classical WAT and BAT. We next examined the properties of PVAT in 8-week-old apoE-/-/AT1 receptor deficient (Agtr1-/-) mice. After 4 weeks of western diet, the expression levels of adipocyte differentiation marker genes (PPARy, FABP4, cEBPs) were markedly increased in apoE-/- PVAT (P<0.05), which was completely diminished in apoE-/-/Agtr1 receptor deficient (Agtr1-/-) mice. After 4 weeks of western diet, the expression levels of adipocyte differentiation marker genes (PPARy, FABP4, cEBPs) were time-dependently increased in Agtr1-/- adipose tissue. In contrast, FABP4 and cEBPs mRNA expressions were markedly inhibited in Agtr1-/- adipose tissue, whereas PPARy did not differ between the two groups during differentiation. These results suggest that AT1 is essentially implicated in the terminal differentiation of periaortic adipocyte.

Conclusion: Our findings demonstrate that AT1 regulates the expression levels of late stage of adipocyte differentiation marker genes in PVAT, suggesting that AT1-mediated modulation of periaortic adipocyte differentiation could be a novel therapeutic target for the prevention of atherosclerosis.
was to determine new compositional and structural features of coronary plaques based on automated, objective analysis of VH-IVUS images.

Methods: A biometric computational analysis based on backtracking program-

was performed, with emphasis given on the low computational cost and processing time. Single and sequences of VH-IVUS images were analyzed. For each image analysis 29 parameters were computed. Results: The basic plaque characteristics (lumen, vessel areas, percent of stenosis, area and percent of each plaque component), the following param-

eters related with the spatial distribution and the homogeneity of plaque com-

ponents were computed: a) the percent of the lumen border that is surrounded by each component, b) the number of different segments and the area of the largest solid segment of each component adjourned to the lumen border, and c) the number of different segments and the area of the largest single segment of each component within the plaque area. A sequence of VH-IVUS images that is recorded during catheter pullback along the coronary vessel is then analyzed in order to automatically classify the examined plaques as thin cap fibroatheroma, the most common type of vulnerable plaque. The classification is made accord-
ging to standard criteria: a) The percent of the necrotic core area is ≥10%, b) the necrotic core covers more than 1/3 of the lumen border and c) the two previous conditions are met for at least three serial frames of the images sequence. The total number of sequential and non-sequential frames that meet the criteria (a) and (b) are also determined.

Conclusions: The quantitative features of plaque components’ distribution and heterogeneity provided by the proposed system could provide further insight in the assessment of vulnerable plaques. Especially features of necrotic core and calcification in relation to lumen border may be significant determinants of plaque vulnerability and plaque-rient interaction. In this respect these new computed data might be useful for the detection of the vulnerable plaque as well as for the evaluation of stent deployment and selection.

P4331

Hypoxia reoxygenation-induced endothelial barrier failure: Role of RhoA, Rac1, and MLCK

M. Aslam1, S. Rohrbach1, K.-D. Schluter1, D. Sedding2, C. Hamm2, T. Noll1, D. Guendel1, 1Institute of Physiology, Justus Liebig University, Giessen, Germany; 2University Hospital Giessen and Marburg, Medical Clinic I. Cardiology and Angiology, Giessen, Germany; 2Dresden University of Technology, Institute for Physiology, Dresden, Germany

Background: Loss of endothelial barrier function leading to oeapma formation during hypoxia-reoxygenation presents major impediment for the recovery of the organ. This loss of barrier function is mainly due to loss of cell-cell adhe-
sions and endothelial contractile activation. Several signaling pathways including RhoA/Rock or Ca+2/PKC are activated during reoxygenation which could me-

date barrier failure, but the precise role of these pathways is still elusive. The present study was to analyse the role of these signaling pathways in reoxygenation-induced barrier failure.

Methods: In cultured porcine aortic endothelial cells, the effect of hypoxia (30 min, PO2:5 mmHg; pH 6.4) and reoxygenation (45 min, PO2:140 mm Hg; pH 7.4) was analyzed on endothelial permeability (albumin flux), contractile activation (MLC phosphorylation), Ca2+, PKC, RhoA, Rac1 (pulldown assays), and cell-cell adhesions (contactility in confluent monolayer). BAIPA (10 μM), BIM (100 μM), C3 Transferase (1 μg/ml), and Y27632 (10 μM) were used to inhibit Ca2+, PKC, RhoA, and Rock signaling, respectively.

Results: Reoxygenation lead to 150-37% increase in permeability, 2.5-fold MLC phosphorylation, and 2.5-fold RhoA activation but had no effect on Rac1 activ-
ity (for all further parameters). MLC phosphorylation caused a ro-
bust rise in cytosolic Ca2+-concentration, PKC activation, loss of cortical actin and VE-cadherin from cell-cell adhesions. Pharmacological inhibition of RhoA, Rock, Ca2+ or PKC with specific inhibitors exacerbated reoxygenation-induced barrier failure and abrogated the resealing of adhesion junctions. On the other hand activation of CAMP/Epac signaling by a CAMP analog (100 μM), blocked reoxygenation-induced adiayation cytoskeletal derangement and hyperpermeability and enhanced endothelial cell rescaling. However, it had no effect on RhoA or MLC. Inhibition of MLC kinase (ML-7 10 μM) along with Epac activation had an additive effect. The results were confirmed using isolated perfused rat hearts.

Conclusions: The present data suggest that Rho/Rock and Ca+2/PKC pathways are required for resealing of junctions and inhibition of these pathways can ac-

erbate the reoxygenation injury. Activation of CAMP/Epac pathway along with inhibition of contractile activation presents a new therapeutic intervention to pre-

vent reoxygenation-induced vascular leakage.

P4332

Uric acid levels are associated with asymmetric dimethylarginine, L-arginine and arterial stiffness in essential hypertensive patients

K. Dimitriadis, T. Tsoulis, A. Kasiakogias, M. Giakoumis, I. Bafalis, K. Kints, I. Andrikou, D. Tsoulis, C. Stefanadis. First Cardiology Clinic, University of Athens, Hippokration Hospital, Athens, Greece

Purpose: Elevated uric acid (UA) levels are associated with enhanced cardiovas-
cular risk, while arterial stiffening, L-arginine and asymmetric dimethylarginine (ADMA) contribute to diffuse vascular dysfunction. In this study, we investigated the relationships between UA levels, L-arginine, ADMA and arterial stiffness in essential hypertensives.

Methods: In our population of 160 newly diagnosed untreated non-diabetic pa-
tients with stage I to II essential hypertension [118 men, aged 49 years, office blood pressure (BP)=153±97 mmHg], the distribution of UA was split by the me-
dian (5.2 mg/dl) and accordingly subjects were classified into those with high and low UA levels. In all participants, arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP).

Results: Patients with high UA (n=91) compared to those with low UA (n=69) exhibited higher 24-h systolic BP (138±6 vs 131±11 mmHg, p<0.001) while they did not differ regarding metabolic profile (p=NS). Those with high UA compared to those with low UA had increased levels of ADMA (0.54±0.03 vs 0.41±0.05 μmol/l, p=0.001), L-arginine (102±3.1 vs 78±2.9 μmol/l, p=0.001) and PWV (8.3±1.6 vs 7.5±0.9 m/sec, p<0.01), independently of confounders. In the en-
tire population, ADMA was correlated with 24-h systolic BP (r=0.26, p=0.05), L-arginine (r=-0.46, p<0.001) and PWV (r=0.23, p=0.001). In multiple regres-
sion analysis, body mass index (b=0.223, p=0.002), 24-h systolic BP (b=0.196, p=0.004), ADMA (b=0.315, p=0.001) and PWV (b=0.178, p=0.05) were inde-
pendent predictors of UA.

Conclusions: Increased UA levels in essential hypertension are associated with a state of pronounced endothelial dysfunction and accelerated arterial stiffening. These findings suggest that UA is interrelated with diverse pathway of vascular dysfunction, underscoring its mainstay role in the progression of the hypertensive atherosclerotic disease.

P4333

The paroxysmal 55 L/M polymorphism influences the onset of acute coronary syndrome but not stable angina

S. Gomes1, A. Pereira1, A.C. Sousa1, B. Silva1, S. Freitas1, G. Guerra1, A. Brehm1, J.J. Araujo1, M. Mendonca1, R. Palma Dos Reis1, 1Hospital Funchal, Funchal, Portugal; 2Madeira University, Funchal, Portugal; 3New University of Lisbon, Faculty of Medical Sciences, Lisbon, Portugal

The paroxysmal 5171 (PON1) is an antioxidant enzyme synthesized by liver. It has two known polymorphisms: 192 Q/R and 55 L/M. Multiple studies, including ours, have associated these polymorphisms with coronary artery disease (CAD) risk. In CAD exists changes in the vessel wall in emphasis on atherogenesis, clinically expressed as stable angina (SA), and acute thoracic changes, expressed by acute coronary syndrome (ACS). However, the mechanisms by which these variants influence the CAD susceptibility is still unknown.

Objective: The aim of this study was to evaluate whether PON1 polymorphisms influence the onset of ACS or SA.

Methods: Two case-control studies were performed. The first one included 1665 individuals, 728 with CAD and hospitalized with ACS (mean age 53.3±7.9 years, 73.9% male) and 937 controls without CAD (mean age 52.6±8.0 years, 78.8% male). The second one included a total of 1009 individuals: 209 consecutive pa-

"xtents with SA and significant CAD confirmed by coronary angiography (mean age 56.0±6.8 years, 71.3% male) and 800 controls without CAD (mean age 55.6±5.8 years, 72.9% male). In both studies, cases and controls were matched by gender and age. PON1 variants were analyzed using specific primers. The equilibrium of Hardy-Weinberg was investigated and a bivariate analysis (tables 3x2), with the odds ratio (OR) and 95% confidence interval (CI), was performed in order to determine the CAD risk. A p-value <0.05 was considered statistically significant.

Results: PON 55 MM genotype showed an increased risk for ACS, with an OR of 1.38 (95% CI: 1.1–1.7) but not for SA (p=0.12). PON 192 Q/R was not significantly associated either with the ACS or with SA.

Conclusions: This study supports the concept that PON 55 MM is an initiator factor of ACS. Not leading to stable angina but to ACS, this polymorphism may be particularly deleterious and may be involved in thrombotic and other genenic mechanism. The patients carrying this genotype should be approached with particular care in terms of primary prevention, possibly through antplatelet or anticoagulant drugs.

P4334

Angiotensin II induces early mechanical heterogeneity along the abdominal aorta, preceding murine aerynus formation

U. Raaz, L. Maegdefessel, R. Toh, A. Deng, J.M. Spin, P.S. Tsao. Stanford University Medical Center, Division of Cardiovascular Medicine, Stanford, United States of America

Background: Abdominal aortic aneurysm (AAA) pathogenesis involves a broad spectrum of inflammation, cellular proliferation and extracellular matrix alter-

ation. However, little is known about the initiation of aneurysm growth. Animal models, localized chemical damage to the aortic wall is used to trigger a focal vascular demarcation, eventually resulting in AAA. In contrast, suprarenal aneurysm formation without any local vascular manipulation. This study was designed to test the hypothesis that systemic AngII infusion induces focal mechanical alterations (i.e. heterogeneous strain along the abdominal aorta) that may initiate AAA for-
mation.
Materials and methods: AngII (1000ng/kg/min) or saline (control) was infused via osmotic pump in 10-week-old apoe-/- male mice (C57Bl/6 background). At baseline and after 2 days of treatment, systolic (SD) and diastolic (DD) diameters of suprarenal (SR) and infrarenal (IR) aortic segments were measured using M-mode ultrasonography, and strain was calculated as (SD-DD)/DD. Strain ratio along the abdominal aorta was calculated as SR-strain/IR-strain. Gene expression was analyzed by measuring AngII type 1 receptor (Agtr1b), known to mediate the mechanovascular contractility response to AngII, was measured in SR and IR regions via qRT-PCR.

Results: AngII infusion for 2 days induced both a significant increase in SR-strain as well as a decrease in IR-strain, resulting in a significant strain heterogeneity (SR/IR strain-ratio: 2.5±0.8 vs. 1.2±0.3 at day 0; p < 0.001). Saline infusion altered none of these parameters. While elevated SR-strain per se failed to demonstrate a correlation to SR diameter changes after 2 days, we found that SR/IR-strain ratio was positively correlated to early SR aortic diameter increase (R2=0.53; p < 0.05). Overt atherosclerosis formation was only detectable after 4 days of AngII infusion, at the earliest. As a possible mechanism for these strain differences, Agtr1b expression was found to be ~40-fold higher in IR aorta than in the SR aorta at baseline.

Conclusion: AngII infusion rapidly induces heterogeneous strain (SR–IR) along the abdominal aorta, preceding atherosclerosis formation. These strain differences may be due to initial heterogeneous AngII Agtr1b density, and they correlated statistically with the initial dilatation of the aneurysm-prone SR region. These data suggest a mechanism for the early translation from systemic AngII infusion into a strain heterogeneity as a possible prerequisite of AAA formation.

The high discriminative ability of apoptotic CECs and apoptotic endothelial microparticles is a solid foundation for the development of clinical prediction models of CAV.

Circulating apoptotic endothelial cells and apoptotic endothelial microparticles independently predict the presence of cardiac allograft vasculopathy

N. Singh1, E. Van Crayenbuhl1, M. Tytes2, A. Ciarka2, W. Drooghe3, F. Gordo1, F. Jacob1, J. van Haezebroeck1, J. van Cleeppum2, De Geest3 on behalf of Neha Singh. 1Center for Molecular and Vascular Biology, Catholic University of Leuven, Leuven, Belgium; 2Catholic University of Leuven, Leuven, Belgium.

Objectives: Maintenance of endothelial homeostasis may prevent the development of cardiac allograft vasculopathy (CAV). We investigated whether biomarkers related to endothelial injury and endothelial repair discriminate between CAV negative and CAV positive heart transplant recipients.

Background: CAV is the most important determinant of cardiac allograft survival and a major cause of death after heart transplantation.

Methods: Two groups of patients undergoing coronary angiography between 5 and 15 years after heart transplantation were recruited in this study. Flow cytometry was applied to quantify endothelial progenitor cells (EPCs), circulating endothelial cells (CECs), and endothelial microparticles. Cell culture was used for quantification of circulating EPC number and hematopoietic progenitor cell (HPC) number and for analysis of EPC function.

Results: EPC number and EPC function did not differ between CAV negative and CAV positive patients. In unvariable models, age, creatinine, steroid dose, granulocyte colony-forming units, apoptotic CECs, and apoptotic endothelial microparticles discriminated between CAV positive and CAV negative patients. The logistic regression model containing apoptotic CECs and apoptotic endothelial microparticles provided high discrimination between CAV positive and CAV negative patients (C statistic 0.812; 95% CI 0.692–0.932).

In a logistic regression model with age and creatinine as covariates, apoptotic CECs (p=0.0115) and apoptotic endothelial microparticles (p=0.0141) were independent predictors (C statistic 0.855; 95% CI 0.756–0.953). These two biomarkers remained independent predictors when steroid dose was introduced in the model.

Conclusions: The high discriminative ability of apoptotic CECs and apoptotic endothelial microparticles is a solid foundation for the development of clinical prediction models of CAV.
VASCULAR REMODELLING

P4339
Wnt4 contributes to intimal thickening by promoting VSMC proliferation via up-regulation of RCAN1
A. Tsoussi, H. Williams, G.M. Connolly, S.J. George. University of Bristol, Bristol Heart Institute, Bristol, United Kingdom

Purpose: We investigated whether Wnt4-induced VSMC proliferation utilises nuclear transcription factor of activated T-cells (NFAT) as a downstream effector as well as β-catenin. Vascular smooth muscle cell (VSMC) proliferation causes intimal thickening observed in early atherosclerosis and restenosis. We previously demonstrated that Wnt4/β-catenin signalling stimulates VSMC proliferation in vitro via cyclin D1 up-regulation and promotes intimal thickening. Although the “canonical” Wnt/β-catenin pathway plays a vital role in the promotion of Wnt4-driven VSMC proliferation, Wnts can also signal independently of β-catenin, amongst others via a calcium-related pathway involving NFAT. Here we assessed the role of NFATc1 (the predominant isoform in VSMCs) and the induction of known NFAT-responsive genes in Wnt4-induced VSMC proliferation and intimal thickening.

Methods: VSMCs were cultured and in some cases subjected to siRNA; extracted mRNA was analysed by Q-PCR while protein was assessed by Western blotting and/or immunocytochemistry. Mouse carotid arteries were ligated to induce intimal thickening and lesions were analysed by immunohistochemistry.

Results: Addition of recombinant Wnt4 protein in vitro induced a significant increase in the percentage of VSMCs with nuclear NFATc1 within 4h (by 2.4±0.83 fold; p<0.05, n=3), directly demonstrating the activation of NFATC1 pathway by Wnt4. Recombinant Wnt4 protein treatment for 6h in vitro significantly up-regulated the mRNA levels of two previously identified NFAT-responsive genes, regulator of calcineurin 1 (RCAN1) and cyclooxygenase 2 (Cox2) as well as Cyclin D1. We observed elevated NFATc1 protein levels while RCAN1 protein knockdown (by 89% of control) did not significantly affect nuclear NFATc1 within 4h (by 2.43±0.83 fold; p<0.05, n=3). Treatment with NFAT inhibitor (11R-VIVIT) for 24h in vitro significantly retarded Wnt4-induced VSMC proliferation from 46.5±3% to 30.9±0.4% (p<0.05, n=4), while knockdown (by 89±1% of control) of NFATc1 in vitro resulted in a significant reduction of both Cyclin D1 and RCAN1 mRNA by 21±2% and 21±17% respectively (p<0.05, n=3). Finally, we observed elevated NFATc1 protein levels while RCAN1 protein was significantly increased in ligated mouse carotid arteries when compared to unligated control arteries (161±16.1 vs. 26±0.73 fluorescent pixels per area unit respectively, n=4).

Conclusions: Wnt4 is an important contributor to intimal thickening by playing a key role in the stimulation of VSMC proliferation via activation of both “canonical” β-catenin and “non-canonical” NFAT downstream pathways. We show here for the first time that RCAN1, a downstream target of NFAT, is up-regulated by Wnt4 signalling and may be a key modulator of intimal thickening.

P4341
Functional inhibition of microRNA-92a increases endothelial regeneration and reduce neointimal formation after vascular injury by targeting kruppel-like factor-4
C. Iaconetti1, A. Polimeni1, S. Sorrentino1, J. Sabatino1, G. Piponì2, G. Esposito3, A. Curcio1, C. Indolfi1. 1University Magna Graecia, Department of Medicine. Molecular and Cellular Cardiology, Catanzaro, Italy; 2Federico II University, Napoli, Italy

Purpose: One of the mechanisms responsible of late stent thrombosis after Drug Eluting Stent (DES) implantation is that endothelial recovery is inhibited by the antiproliferative approach, which, although intended to prevent smooth muscle cell (SMC) migration, may have an inhibitory effect on endothelial cell (EC) migration, proliferation and differentiation. Cell cycle re-entry is a key event for the release of previously arrested ECs from a G0/G1 state to the S phase. Therefore, the aim of the present study was to evaluate the role of microRNA-92a on ECs and VSMCs proliferation and migration in vitro as well as after balloon injury or arterial stenting in vivo.

Methods: ECs and VSMCs proliferation and migration were measured by BrdU incorporation and wound healing assays. In the in vivo protocol, balloon-injury or stenting of the carotid artery were produced in male Wistar rats. Moreover, inhibition of microRNA-92a expression was assessed in vivo by systemic administration of antagoniRNA-92a. Immuno-histochemical staining for von Willebrand factor (vWF) and planimetric analysis after in vivo injections of Evans Blue dye were employed to analyze the process of re-endothelialization. Fixed carotid arteries were stained with hematoxylin/eosin 14 days after balloon-injury or arterial stenting in vivo. Cell cycle arrest or apoptosis were determined by flow cytometry (Annexin V assay).

Results:.miR-92a was highly expressed in ECs but to a much lower extent in VSMCs. Importantly, BrdU incorporation and wound healing assay provide evidence that functional inhibition of miR-92a resulted in an increased proliferation and migration of ECs but not of VSMCs in vitro. Immunoblotting analysis revealed an increased phosphorylation of eNOS in ECs as a consequence of miR-92a inhibition. Moreover, functional inhibition of miR-92a stimulated nitric oxide (NO) production in ECs. Using reporter lucerase assay, we identified specific targets of miR-92a: KLF4, key regulator of endothelial homeostasis, and MKK4, component of the mitogen-activated protein kinase (MAPK) pathway. Finally, in vivo administration of antagoniRNA-92a increased re-endothelialization in injured carotid arteries and reduced neointimal formation after balloon-injury or arterial stenting.

Conclusions: These data provide the first evidence that inhibition of miR-92a may represent a novel strategy to improve endothelial regeneration and reduce restenosis after vascular injury. This new approach could be used to design new stents aimed to increase the reendothelialization and eventually to reduce the occurrence of stent thrombosis.

P4342
The PI 3-kinase isofrom p110alpha promotes vascular remodelling in pulmonary arterial hypertension
E.M. Berghausen1, M. Vantlier1, W. Janssen1, H. Ten Freyhaus1, J.J. Zhao1, R.T. Schermuly2, S. Rosenkranz1. 1University of Cologne, Department of Internal Medicine III, Cologne, Germany; 2Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany; 3Harvard Medical School, Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Boston, United States of America; 4University Giessen Lung Centre, University Hospital, Giessen, Germany

Purpose: Vascular remodelling is a major characteristic of pulmonary hypertension. The vessel wall especially of the small pulmonary vessels thickens triggered by an abnormal proliferation and migration of vascular smooth muscle cells (VSMC). In vitro assays demonstrated that the PI3K isofrom p110 alpha is crucial for growth factor induced SMC proliferation and migration. However the role of the PI3-kinase (PI3K) isofrom p110 alpha for vascular remodelling in pulmonary hypertension is poorly understood. We assessed the function of p110 alpha for...
vascular remodelling in the hypoxia induced mouse model of pulmonary hypertension.

Methods: We generated a smooth muscle specific p110 alpha deficient mouse and studied its effect on chronic hypoxia to induce pulmonary hypertension. Right ventricle (RV) systolic pressure was determined via invasive measurement using a millar pressure catheter. RV hypertrophy was assessed as ratio RV weight to LV + septum weight. Gross remodelling was quantified and demonstrated as medial wall thickness and degree of vascular muscularization.

Results: RV systolic pressure in consequence to hypoxia was decreased in the p110 alpha deficient mice compared to wild-type littermates. Consistently, hypoxia induced RV hypertrophy was significantly reduced in hearts of p110 alpha deficient mice in comparison to wild-type hearts. Medial wall thickness of vessels with a diameter less than 50μm was significantly narrowed in lungs of SM-specific p110 alpha KO mice. Morphometric analysis of the small pulmonary vessels (diameter < 70μm) also revealed a smaller fraction of fully and partially muscularized vessels in hypoxia treated p110 alpha deficient mice in comparison to hypoxia treated wild-type mice.

Conclusion: These results indicate that the PI3K isofrom p110 alpha is crucial for vascular remodelling in hypoxia induced pulmonary hypertension. A SM-specific loss of p110 alpha prevented vascular remodelling and would therefore represent a promising therapeutic approach.

Two-chain High Molecular Weight Kininogen (HKa) inhibits neointimal formation by preventing leukocyte recruitment

J-M. Daniel1, F. Reich1, J. Dutzmann1, K.T. Preissner2, C.W. Hamm2, D.G. Sedding2. 1University Hospital Giessen and Marburg, Campus Giessen, Giessen, Germany; 2Institute for Biochemistry, Justus Liebig University, Giessen, Germany.

Purpose: The cleavage of single-chain high molecular weight kininogen (HK) results in the release of bradykinin and two-chain HK (HKa). HKa and in particular its peptide domain 5 (D5) exert anti-adhesive properties during inflammatory cell recruitment via binding to extracellular matrix proteins and impeding the function of the β2-integrin molecule Mac-1 (CD11b/CD18). In this study, we investigated the effects of HKa and D5 on the accumulation of circulating cells and the function of resident vascular cells in a mouse model of neointima formation.

Methods: After lethal irradiation C57BL6 mice were transplanted with bone marrow from transgenic mice expressing enhanced green fluorescence protein (EGFP). Wire induced injury of the femoral artery was performed on chimeric mice with local application of HKa, D5, or control to the dilated artery in a thermosensitive pleuronic gel. Vessels were harvested 1 day after injury to test the sustained release of the substances (n=3) and at 3 weeks after injury for morphometric analysis and immunohistochemistry (n=6).

Results: Neointima formation was significantly reduced after treatment with HKa and even more prominent after D5 application (HKa: 0.981±0.174; D5: 0.549±0.076 vs. 1.54±0.150; P<0.05). The attenuation of the neointimal lesion was accompanied by a reduced accumulation of EGFP+ cells and monocytic/macrophages in the treatment groups. Confocal microscopy revealed that EGFP+ cells did not co-express smooth muscle myosin heavy chain or calponin, indicating no trans-differentiation of BM-derived cells into smooth muscle cells. Importantly, HKa and D5 significantly reduced the number of proliferating resident vascular cells in the vascular wall (P<0.05). In contrast, the ratio of apoptotic nuclei was increased in the treatment groups, although the absolute numbers of apoptotic vascular cells as well as the process of re-endothelialization were not different.

Conclusions: Endogenous HKa decreases the inflammatory response to vascular injury due to its anti-adhesive properties and thus reduces proliferation of local leukocytes. Therefore, application of HKa or D5 points towards the importance of inhibiting leukocyte accumulation after vascular injury and may provide a novel therapeutic strategy for attenuating atherosclerosis or neointimal lesion development.

Hyaluronic acid metabolism is increased in human abdominal aortic aneurysm

T Miyoshi1, T Yonezawa1, M Doi2, A Aoki2, K Nakamura2, S Hirohata1, T Miyoshi1, T Yonezawa1, M Doi2, A Aoki2, K Nakamura2, S Hirohata1, S Kusachi1, Y Ninomiya1, K Kusano1, H Ita1. 1Okayama University, Okayama, Japan; 2Kagawa Prefectural Central Hospital, Takamatsu, Japan.

Background: Hyaluronic acid (HA) is expressed in atherosclerotic lesions, but its exact role in abdominal aortic aneurysm remains unknown. As degradation of hyaluronic acid by hyaluronidase into low molecular weight hyaluronic acid (LMW-HA) is associated with inflammation and matrix metalproteinase (MMP)-9 activity, we hypothesized that hyaluronic acid metabolism is increased in abdominal aortic aneurysm, especially the area between almost normal margin and maximum diameter. Those area were characterized by high number of macrophage, MMP-9 activity, and destruction of elastin.

Methods: Five specimens were obtained as a whole abdominal aortic tissue (from proximal margin to distal margin). A whole sample was categorized into three zones; zones of (1) margin, (2) middle, and (3) maximum diameter (Figure A). Then, whole tissue were cut into around one inch of pieces, and character-
A novel adipocytokine, CTRP9 attenuates vascular smooth muscle cell proliferation and neointimal formation after vascular injury

Y. Uemura, R. Shibata, K. Ohashi, T. Enomoto, T. Kambara, T. Murohara, N. Ouchi. Nagoya University School of Medicine, Department of Cardiology, Nagoya, Japan

Background: C1q/TNF-related protein (CTRP) 9 is a novel adipocytokine that has beneficial effects on glucose metabolism and endothelial function. However, the role of CTRP9 in vascular remodeling is unknown. Here, we investigated the effect of CTRP9 on vascular smooth muscle cells (VSMC) proliferation and neointimal hyperplasia in a restenosis model.

Methods and Results: An adenovirus expressing CTRP9 (Ad-CTRP9) or β-galactosidase as a control was injected into the jugular vein of wild-type (WT) mice 3 days prior to vascular injury. Left femoral arteries of mice were injured by a 0.015 inch stainless-steel wire inserted from the lumen. Administration of Ad-CTRP9 increased CTRP9 levels by a factor of 5.1 ± 0.9 at day 5 after injection compared with control. At 21 days after vascular injury, delivery of Ad-CTRP9 significantly attenuated intimal hyperplasia compared with that of control (p<0.01, n=8). Ad-CTRP9 also decreased the number of bromodeoxyuridine (BrdU)-positive proliferating cells in the neointima at day 7 after vascular injury versus control. In cultured VSMCs, recombinant CTRP9 protein attenuated DNA synthesis in a dose-dependent manner, including 

independent factors including genistein-derived gelatin (Gel-F) and heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF) as assessed by BrdU incorporation. Furthermore, treatment of VSMCs with CTRP9 significantly inhibited PDGF-BB-induced PDGF-inducible Kinase (PI3K)/Akt and extracellular signal-regulated kinase (ERK) phosphorylation.

Conclusion: CTRP9 reduces VSMC growth and prevents neointimal thickening after vascular injury in vivo, suggesting that the therapeutic approaches to enhance CTRP9 production can be beneficial for prevention of vascular restenosis after intervention.

Furin-dependent maturation of proNGF induces migration of vascular smooth muscle cells by TrkA-mediated recruitment of paxillin to focal adhesion sites

D. Urban1, J. Lorenz1, H. Meyborg1, S. Gosh1, J. Kaufmann1, K. Kappert2, E. Fleck1, P. Stawowy1. 1German Heart Center Berlin, Department of Cardiology, Berlin, Germany; 2Chante - University Medicine Berlin, Germany

Background: Vascular smooth muscle cell (VSMC) migration is a key feature of vascular restenosis. Recently, it was shown that the nerve growth factor (NGF) and its high-affinity receptor, the neurotrophic tyrosine kinase receptor type 1 (TrkA), are expressed in restenotic lesions. However, the underlying mechanism and functional relevance is poorly understood. NGF is synthesized as a precursor (proNGF) that is cleaved into mature β-NGF by the proprotein convertase furin and subsequently secreted from cells acting as an autocrine signaling molecule. Here, we studied the effect of platelet-derived growth factor (PDGF-BB) and transforming growth factor beta-1 (TGF-β1), both highly expressed in restenotic lesions, on furin-dependent proNGF maturation and examined the impact of mature β-NGF on VSMC migration.

Methods and results: First, qRT-PCR and western blot analysis showed that PDGF-BB and TGF-β1 synergistically enhanced NGF gene expression and proNGF protein. Exposing VSMCs to PDGF-BB induced a significant raise of β-NGF secretion. In addition, we found increased mRNA and protein expression of the TrkA-receptor in response to PDGF-BB/TGF-β1. The specific furin-inhibitor deco-ctase inhibited furin enzymatic activity and proNGF cleavage, thus abolishing β-NGF secretion. Migration checker box experiments demonstrated that both conditioned medium (CM) of VSMCs stimulated with PDGF-BB/TGF-β1 and recombinant β-NGF induce chemotaxis of rat VSMCs. Immunofluorescence confirmed F-actin rearrangement and recruitment of the integrin adapter protein paxillin to focal adhesion sites in β-NGF-treated VSMCs. This was accompanied by phosphorylation of Akt and paxillin, which was prevented by both the TrkA-receptor inhibitor K252a and the PI3K-inhibitor LY294002. Accordingly, K252a and LY294002 reduced β-NGF-induced migration. Blockade of integrin-mediated outside-in signaling by using RGD-peptides did not affect phosphorylation of Akt or paxillin. In conclusion, the present study demonstrates that the therapeutic approaches to enhance CTRP9 production can be beneficial for prevention of vascular restenosis after intervention.

Conclusion: In conclusion the present studies demonstrate that atherogenic growth factors act in concert to enhance furin-dependent proNGF maturation and β-NGF secretion from VSMCs. Extracellular β-NGF induces TrkA-mediated integrin inside-out signaling leading to VSMC migration. Co-expression of NGF and furin following balloon injury indicates the in vivo relevance of our findings during vascular remodeling.

MicroRNA-146a and its role in vascular smooth muscle cells during vascular remodeling processes

R. Widmer-Teske, W. Bielenberg, J.-M. Daniel, H. Nef, C. Troidl, S. Achenbach, C. Hamm, R. Widmer-Teske. University Hospital Giessen and Marburg, Medical Clinic I, Cardiology and Angiology, Giessen, Germany

Background: MicroRNAs (miRNAs) are a small class of noncoding RNA molecules, comprising key regulators for major cellular events including proliferation, differentiation and apoptosis in vascular smooth muscle cells and endothelial cells. The role of miRNAs in vascular remodeling is unknown. Here, we investigated the role of miR-146a in vascular remodeling, differentiation and apoptosis of smooth muscle cells. Using computational miRNA target prediction, the "TargetScan database", we identified miR-146a likely involved in the disease development and progression of vascular remodeling.

Methods: Using microarray based expression analysis, we screened for regulated miRNAs during neointima formation. Restenosis was induced in C57BL6/N by dilatation of the femoral artery, and miRNA was isolated 10 and 21 days after injury. About 59% of all known miRNAs was found to be aberrantly regulated after 10 days what was even enhanced to 88% after 21 days. Noticeably, miR-146a appeared to be one of the most regulated miRNAs during restenosis. Analysis on isolated cells of the vascular human smooth muscle cells showed that CTRP9 is a novel adipocytokine that has beneficial effects on glucose metabolism and endothelial function. However, the role of CTRP9 in vascular remodeling is unknown. Here, we investigated the effect on the role of CTRP9 in vascular smooth muscle cells (VSMC) proliferation and neointimal hyperplasia in a restenosis model. Ad-CTRP9 increased CTRP9 levels by a factor of 5.1 ± 0.9 at day 5 after injection compared with control. At 21 days after vascular injury, delivery of Ad-CTRP9 significantly attenuated intimal hyperplasia compared with that of control (p<0.01, n=8). Ad-CTRP9 also decreased the number of bromodeoxyuridine (BrdU)-positive proliferating cells in the neointima at day 7 after vascular injury versus control. In cultured VSMCs, recombinant CTRP9 protein attenuated DNA synthesis in a dose-dependent manner, including genistein-derived gelatin (Gel-F) and heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF) as assessed by BrdU incorporation. Furthermore, treatment of VSMCs with CTRP9 significantly inhibited PDGF-BB-induced PDGF-inducible Kinase (PI3K)/Akt and extracellular signal-regulated kinase (ERK) phosphorylation.

Conclusion: CTRP9 reduces VSMC growth and prevents neointimal thickening after vascular injury in vivo, suggesting that the therapeutic approaches to enhance CTRP9 production can be beneficial for prevention of vascular restenosis after intervention.

MicroRNA-146a is a potential target for 146a. To further assess the functional role of miR-146a, smooth muscle cells were transfected with precursor forms of miR-146a. Further in vitro analysis showed that miR-146a induction seems to be mediated by NFkB. In complementing in vivo experiments, inhibition of miR-146a following dilatation of the femoral artery was performed. The data of Evans' Blue- and WVF staining showed significantly enhanced neointimal thickening after 10 and 21 days.

Conclusion: Determining the expression profile of differentially regulated miRNAs in restenosis development, we identified miR-146a likely involved in the disease development and progression in vascular remodeling.

Methods: Using microarray based expression analysis, we screened for regulated miRNAs during the development of restenosis. Neointima formation was induced in C57BL6/N by dilatation of the femoral artery and miRNA was isolated 10 and 21 days after injury. About 59% of all known miRNAs was found to be aberrantly regulated after 10 days what was even enhanced to 88% after 21 days. Noticeably, miR-146a appeared to be one of the most regulated miRNAs during restenosis. Further expression analysis in isolated primary vascular smooth muscle cells revealed that miR-146a, besides in monocyes/macrophages, smooth muscle cells and endothelial cells showed a strong expression of miR-146a, especially in endothelial cells. In vitro, the upregulation of miR-146a could be attributed to the inflammatory stimulus IL-1β. To further assess the functional role of miR-146a, smooth muscle cells were transfected with precursor forms of miR-146a leading to an attenuated migration, sprout formation and vessel network formation. On the other hand, using 2′-O methylated RNA mimics mimicking miR-146a as inhibitor, sprout formation, vessel network formation and cell migration were significantly enhanced. In the following, computational miRNA target prediction, the "TargetScan database", was used to find potential target genes for miR-146a. Quantitative Real-Time-RT-PCR tests were performed after overexpression of miR-146a. The transcripts for TRAF6 and IRAK1, two key adapter molecules in TLR- and IL-1 receptor signaling cascades, were significantly downregulated and hence represent molecular targets for miR-146a.

Conclusion: These findings reveal a pivotal role of miR-146a for function in vascular smooth muscle cells, especially under conditions of pathological vascular remodeling processes. Thus, modulating miR-146a expression may represent a novel approach for the prevention and treatment of vascular proliferative diseases.
Ablation of PDGF receptor signaling reduces neoangioma formation after balloon angioplasty and does not affect the proliferation and migration of endothelial cells

T. Kramer1, E. Vanlender1, E. Caglayan2, M. Scherner1, O. Leppanen2, S. Robergen3, 1Cologne University Hospital - Heart Center, Clinic III for Internal Medicine, Cologne, Germany; 2Upplands University Hospital, Upplands, Sweden

Despite the introduction of new techniques such as drug-eluting stents, restenosis and stent thrombosis following angioplasty remain serious clinical problems. To prevent neoangioma formation and the development of stent thrombosis after balloon angioplasty and stent implantation, it is essential to reduce the accumulation of vascular smooth muscle cells (SMCs) on the one hand and to ensure the re-endothelialization as far as possible on the other hand. The proliferation and migration of SMCs and endothelial cells (ECs) are mainly induced by receptor tyrosine kinases which are activated by growth factors.

Previously, we could demonstrate that the mutation of central binding domains of the platelet-derived growth factor receptor (PDGFR) in a mouse model causes a significant reduction of neoangioma formation after balloon angioplasty. The influence of an inhibition of PDGFR on endothelial cells is not known.

In this study, we analysed the effects of two PDGFR inhibitors (Imatinib and Nilotinib) on the proliferation and migration of human coronary SMCs (hcSMCs) and human coronary ECs (hcECs). For this purpose, the cells were stimulated with PDGF (30 ng/ml) or VEGF (50 ng/ml) and various concentrations of imatinib or nilotinib were tested. The cell proliferation was determined by BrdU incorporation assay and chemotaxis using a modified Boyden chamber. Protein expression and activation were investigated by Western blot analyses.

Stimulation of hcSMCs with PDGF induced a 2.9-fold increase in proliferation (n ≥ 7, p < 0.05) and a 2.6-fold increase in chemotactic activity (n ≥ 3, p < 0.05), whereas PDGF had no effect on the proliferation and chemotaxis of hcECs. VEGF induced proliferation (1.3-fold) and chemotaxis (3.3-fold) of hcECs. Western blot analyses demonstrated that VEGF-induced expression and activation of PDGFR are limited to hcSMCs while VEGF expression and activation were restricted to hcECs. PDGF-induced proliferation and migration of hcSMCs were completely prevented by the inhibitors imatinib (1 μM) and nilotinib (10 μM). Imatinib had no effect on VEGF-induced proliferation and migration of hcECs (no inhibition at 10 μM) while nilotinib caused a 50% inhibition of both cell responses at high concentrations (10 μM).

Our results indicate that inhibition of PDGFR, especially by imatinib, inhibits the proliferation and migration of hcSMCs without suppressing the cellular responses of hcECs. Thus, the PDGFR represents a promising therapeutic target in order to prevent restenosis following percutaneous coronary intervention.

Changes of elastic properties of large arteries in systemic sclerosis are related to endothelial activation and matrix remodelling

K. Izyk1, M. Ciuryzynski1, P. Bienias1, Z. Rymanczyk1, M. Kostubiec1, Z. Bartosziewicz2, U. Demkow3, A. Szewczyk4, A. Szweczyk4, M. Siwicka4, P. Pruszczyk1. 1Medical University of Warsaw, Department of Internal Medicine and Cardiology, Warsaw, Poland; 2Medical University of Warsaw, Department of Internal Medicine and Endocrinology, Warsaw, Poland; 3Medical University of Warsaw, Department of Laboratory Diagnostics and Clinical Immunology of Developmental Age, Warsaw, Poland; 4Medical University of Warsaw, Department of Dermatology, Warsaw, Poland

Introduction: Systemic sclerosis (SSc) is a connective tissue disease with characteristic fibrosis of internal organs and abnormalities of small arteries. Pulse wave velocity (PWV) is a simple and non invasive method of evaluation of elastic properties of large arteries.

Aim of the study: The aim of this study was to evaluate the changes in the blood vessels wall in SSc patients and its relation with the biochemical markers of endothelial activation (endothelin-1, ADMA) and marker of matrix remodelling (TIMP-1).

Materials and methods: We prospectively examined 69 consecutive SSc patients (M: 5; F: 64, mean age 55.49±13.83 years) and a group of 21 aged and sex matched volunteers (V: 3; F: 18, mean age 49.10±5.86 years). PWV was measured automatically (Complior Sp, Artech Medical, Pantin, France), and endothelin-1 (ET-1) (Human Endothelin-1 Immunoassay R&D Systems), tissue inhibitor of matrix metalloproteinase (TIMP-1) (Quantikine Human TIMP-1 immunoassay R&D Systems), tissue inhibitor of matrix metalloproteinase (TIMP-1) (Quantikine Human TIMP-1 immunoassay R&D Systems) and asymmetric dimethylarginine (ADMA) (ADMA ELSA Kit Immunodiagnostics AG) serum level were assessed.

Results: PWV tended to be higher in SSc than in V. Interestingly in SSc patients PWV correlated with the TIMP-1 serum level (n ≥ 3, p < 0.04) and ET-1 serum level (n ≥ 3, p < 0.009). The ET-1 serum level also significantly positively correlated with TIMP-1 serum level (n ≥ 4, p < 0.002).

Conclusions: SSc patients found to have higher ADMA and ET-1 serum level. ET-1 and TIMP-1 positive correlation and negative correlations between ET-1 and TIMP-1 with PWV suggest that both endothelial dysfunction and matrix remodelling are associated in the pathogenesis of large arteries in systemic sclerosis.
compared by significant downregulation of miR-29b, and upregulation of miR-21 (Figure 1).

Conclusion: The pro-fibrotic response in AngII-mediated arterial remodeling is associated with an increase in miR-21 and a decrease in miR-29b. Modulation of miR-21 and miR-29b have both been successful in altering fibroblastic mechanisms in various cardiovascular diseases. These data suggest they may also be potential targets in the treatment of hypertensive vascular remodelling/arterial stiffening.

Methods:

R. H. Kim, B. S. Kim, J. H. Kang. Division of Cardiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of

Purpose: Epicardial adipose tissue represents visceral adiposity and early detection of visceral adiposity could be helpful for assessing subclinical target organ damage. Although previous studies have reported the relationship between epicardial fat thickness (EFT) and arterial stiffness, there is no report regarding the relationship between EFT and arterial stiffness. The present study was performed to evaluate the association between epicardial fat thickness and arterial stiffness.

Results:

B.J. Kim, B.S. Kim, J.H. Kang. Division of Cardiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of

Methods: We consecutively enrolled 655 subjects (445 men, 55:19 years, who underwent echocardiography and brachial-ankle pulse wave velocity (baPWV) with ankle-brachial index greater than 0.95. Echocardiographic EFT was measured from parasternal long-axis and short-axis views on the free wall of the right ventricle at the end of diastole. The subjects were divided into four quartile groups depending on EFT (≤ 3.46 cm, 3.46-3.95 mm, 3.95-4.44 mm, and ≥ 4.44 cm in quartile I, II, III, and IV, respectively). Subjects were also classified into two groups according to baPWV: group I (324 subjects), baPWV ≤1368 cm/sec; and group II (331 subjects), baPWV > 1368 cm/sec.

Results: The EFT in group II were significantly higher than those in group I (4.28 mm versus 3.7 m, p<0.001). There were significant differences in baPWV value among the four quartile groups of the EFT (quartile I, 1327±148.8 mm/sec; quartile II, 1371±215.0 mm/sec; quartile III, 1434±228.3 mm/sec; quartile IV, 1507±233.1 mm/sec; p-value <0.001). In the multivariant linear regression model adjusted for age, sex, lifestyle status, systolic blood pressure, heart rate, fasting glucose, triglyceride, high-density cholesterol, homeostasis model assessment-insulin resistance, and high-sensitivity C reactive protein, the absolute values of EFT were an independent determinant of increasing baPWV in the absence of metabolic standard (β=0.113, p<0.001). In the same model for logistic regression analysis, increasing quartiles of EFT showed a significant association with increased baPWV groups (p for trend=0.010) and the highest quartile group of EFT had higher odds ratio (OR) for increased baPWV group compared with that of the lowest quartile group (OR [95% confidence interval (CI)]: 2.19 [1.21-3.95]).

Conclusion: This study indicates an independent relationship between epicardial fat thickness and arterial stiffness, suggesting that echocardiographic EFT measurement could be an easy-to-measure and useful tool for early detection of subclinical target organ damage.

Methods: 242 elderly patients (median age 79.9±8.1, male 25.6%) undergoing major orthopedic surgery (MOS) were included. Preoperative B-type Natriuretic Peptide (BNP) was measured and clinical risk scores calculated. In-hospital major cardiac events (MACE) and 1-year mortality were the endpoints of the study.

Results: Twenty patients had inhospital MACE (8.3%) and 41 (19.1%) died within 1 year. Preoperative BNP was correlated with all indices ( Spearman ρ correlation coefficient Goldman 0.325, Lee 0.76 Detky 0.492, Fleisher Eagle(PE) 0.389, Functional Capacity (FC) 0.449, all p <0.01). Logistic 14% identification for the prediction of MACE and 1-year mortality revealed for LnBNP p <0.001 and p <0.001, Goldman p=0.013 and p<0.003, Lee p=0.02 and p=0.02, Detsky p<0.001 and p<0.001, FC p<0.001 and p<0.001, Sim-
Causality of inflammation related to blood leucocyte count for the progression of arterial stiffness and pressure wave reflection

H. Tomiyama, M. Odaita, M. Yoshida, C. Matsumoto, K. Shinra, A. Yamashina, Tokyo Medical University, Tokyo, Japan

Background: It has not yet been fully clarified whether elevated serum C-reactive protein levels (sCRP) and peripheral blood leucocyte counts (BLC) are merely markers of arterial stiffening and pressure wave reflection abnormalities, which result from impeding factors of cardiovascular risk, or whether any causal relationship might exist between these parameters and the aforementioned cardiovascular risk factors.

Objectives: The present 3-year prospective study was conducted to examine this issue.

Methods: Measurements of sCRP, BLC, brachial-ankle pulse wave velocity (baPWV) and radial augmentation index (rAI) were conducted at the baseline and at the end of the 3-year study period in 1291 healthy Japanese men (43.8 ± 8.5 years old).

Results: BLC, but not log-transformed sCRP, showed a significant relationship with the baPWV, but not rAI, at both the baseline and the final examinations. Elevated BLC was defined as any count in the highest tertile (BLC > 6400 cells/mm³), and sustained elevation of the BLC was defined as elevated values at both the baseline and the final examinations. The delta change of baPWV (adjusted value) during the study period, but not that of the rAI, was significantly larger in the group showing sustained elevation of the BLC (54.4 ± 5.7 cm/sec) than in the group not showing elevation of the BLC in either the baseline or the final examination (32.8 ± 3.6 cm/sec) (p < 0.05). Similar findings were not observed for sustained elevation of the sCRP.

Conclusion: The facet of inflammation related to elevated BLC, but not that related to elevated sCRP, may be causally associated with the progression of arterial stiffening of the large-to-mid-sized arteries. However, no such association with inflammation was found for progression of abnormalities of the pressure wave reflection.

Prognostic relevance of epicardial adipose tissue in patients with coronary artery disease assessed by cardiovascular magnetic resonance

G. Dooeschl 1, D. Haghjoo 1, T. Sussetbeck 1, R. Lany 1, S.O. Schoenberg 2, M. Borggrefe 1, T. Papavassiliu 1, 1Medical Faculty Mannheim of the University of Heidelberg, 1st Department of Medicine, Mannheim, Germany; 2Medical Faculty Mannheim of the University of Heidelberg, Department of Radiology, Mannheim, Germany

Purpose: Epicardial adipose tissue (EAT) has been correlated with the presence of coronary artery disease (CAD). However, the role of EAT as a risk factor for cardiac mortality is still unclarified in patients with CAD. Therefore, we sought to investigate the prognostic relevance of indexed EAT assessed by CMR in patients with CAD.

Methods and Results: 248 patients with CAD (mean age: 64.9 ± 9.7 yrs, 79% male) were prospectively enrolled and underwent CMR. Their mean left ventricular mass was 46.8 ± 15.8 g. The primary endpoint was all cause mortality. The secondary endpoints were 1) the combination of cardiac death, heart transplantation (HTX) or adequate shock and 2) hospitalisation due to STEMI, NSTEMI, unstable angina (UAP) or heart failure. After a follow-up time of 3.1 ± 2.0 yrs, 40 (16.1%) patients died, thereof 29 (11.7%) suffered a cardiac death, HTX or adequate shock. During the follow-up time, 51 (20.6%) patients were hospitalised.

Conclusion: BNP compares favorably with Goldman, Lee, Detsky, FE and IC Indices for prognostication of outcome of MOS. This study suggests that BNP may be a promising strategy used for peri-operative risk stratification.

Mild/moderate renal dysfunction: its role in the preoperative evaluation

L.W. Ramos 1, L. Nicoletti 1, F. Ignaciu 2, E. Castilho 1, E. Elly 1, B. Cristina 1, M. Wolf 2, M. Caillé 1, J.C.S. Goes 1, 1Brazilian Institute for Cancer Control, Sao Paulo, Brazil; 2University Center Sao Camilo, Sao Paulo, Brazil

Purpose: Cardiologists are frequently requested to perform the preoperative clinical evaluations prior to non-cardiac surgery. Some guidelines indicate that a creatinine concentration greater than 2.0 mg/dl as an independent risk factor for postoperative morbidity-mortality. This study evaluated whether mild/moderate pre-operative renal dysfunction contraindicated with creatinine levels below 2.0 mg/dl is associated with postoperative outcomes in non-cardiac surgery.

Methods: Eighty-nine patients (mean age 74.78 ± 10.85 yrs; group A) with creatinine concentrations ranging from 1.3 mg/dl to 2.0 mg/dl (creatinine 45.04 ± 7.63; 33.0 – 59.8 mg/mil/min) were compared with 498 patients (68.04 ± 9.78 years; group B) with normal creatinine levels. The groups were matched with regard to surgical risk and ASA classes such as age, gender, number of comorbidities and prior chemotherapy were analyzed. All patients underwent surgical procedures due to tumor disorders and were followed during in-hospital evolution. Adverse outcomes included death and any complications that increased the length of hospital stay.

Results: The mean creatinine concentrations were 1.63 ± 0.19 mg/dl (group A) and 0.63 ± 0.19 mg/dl (group B; p < 0.001). No significant differences were detected with regard to surgical risk (p = 0.724). Surgical durations were 1.73 ± 0.96 h (group A) and 2.32 ± 1.49 h (group B; p = 0.001). The patients in group A were significantly older (74.78 ± 10.85 vs 68.04 ± 9.78 years; p < 0.001), more likely to be male (37.1% vs 22.1% in group B; p = 0.002) and included more patients with histories of chemotherapy (31.5% vs 10.5% in group B; p < 0.001). The mean co-morbidities were 2.66 ± 1.25 (group A) and 2.90 ± 1.01 (group B; p = 0.110). Adverse outcomes occurred in 13.51% of patients in group A versus 3.41% of patients in group B (p = 0.001; OR 6.35 CI 2.42-16.68). Even after adjusting for age, gender, procedure duration and prior chemotherapy, the incidence of morbimortality remained significantly greater in group A.

Conclusion: These results suggest that even mild/moderate preoperative renal dysfunction, may be associated with significant increased post-operative morbimortality in patients undergoing non-cardiac surgery.

Systematic review of risk factors for upper gastrointestinal bleeding in patients using low-dose acetylsalicylic acid

V.E. Valkhoff 1, E.J. Kuipers 1, R. Pearce 1, A. Lanas 1, 1Dept of Gastroenterology & Hepatology and Internal Medicine, Erasmus MC–University Medical Center, Rotterdam, Netherlands;

Purpose: Low-dose acetylsalicylic acid (ASA) is recommended for prevention of cardiovascular events, and primary prevention in high risk patients. However, its use is associated with an increased risk of upper gastrointestinal bleeding (UGIB), although little is known about which users are at risk of developing UGIB. This study aimed to assess risk factors for UGIB in patients taking low-dose ASA.

Methods: A systematic literature analysis (1995–2011) using PubMed and Embase was performed. Studies were included if they reported risk factors associated with UGIB in individuals receiving low-dose ASA. Studies were excluded if the ASA dose was above 325 mg/day or not reported, or if all participants were given concomitant gastroprotective medication. Risk of bias was assessed using the QUADAS tool. Analyses were performed using Review Manager 5.0. Results: The searches identified 2240 unique studies, 15 of which were eligible for inclusion. The most commonly identified risk factor for UGIB was a history of peptic ulcer disease, reported in six studies (N=3353). Five of the six studies reported relative risks (RRs) or odds ratios (ORs) in the range 3.1–6.5 when assessing this relationship, while the sixth reported a much higher OR of 15.2 (95% confidence interval [CI]: 3.8–60.1; increased risk associated with a significantly increased risk of UGIB in users of low-dose ASA. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose ASA was also associated with a significantly increased risk of UGIB (two studies; RR: 3.9; 95% CI: 1.9–8.7). Other factors associated with a significantly increased risk of UGIB in users of low-dose ASA were: current Helicobacter pylori infection, concomitant calcium channel blocker use, concomitant clopidogrel use and a history of dyspepsia. Two studies reported an
increased risk of UGIB with alcohol consumption among patients taking low-dose ASA. Three studies found that proton pump inhibitor (PPI) use was associated with a significant reduction in the risk of UGIB in users of low-dose ASA (OR: 0.02 [95% CI: 0.00–0.3]; OR: 0.068 [95% CI: 0.0–0.7]; RR: 0.39 [95% CI: 0.3–1.0]).

**Conclusions:** The risk of UGIB is increased in users of low-dose ASA who have a history of peptic ulcer disease, Helicobacter pylori infection or dyspepsia, sucking combined calcium-channel blockers, antithrombotics or NSAIDs. Increasing ASA dose is also associated with a significantly increased risk of UGIB. In contrast, patients taking a PPI in addition to low-dose ASA have a reduced risk of UGIB relative to those taking low-dose ASA without a PPI.

**Table 1. CIN-contrast-induced nephropathy: (+) positive, (–) negative**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CIN (+), n=13</th>
<th>CIN (–), n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSP27 (ng/ml)</td>
<td>401.5 (216 – 1243)</td>
<td>239.8 (0 – 522)</td>
</tr>
<tr>
<td>HSP60 (ng/ml)</td>
<td>0.001</td>
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**Conclusions:** HSP27 appears to play protective roles in the process of CIN. Serum HSP60 concentration seems to be a marker of increased risk of CIN development induced by PCI.

**Incidence, risk factors, and outcomes of perioperative acute kidney injury in noncardiac and nonvascular surgery**

M. Bitker, A. Dayan, A.I. Tekkesin, M.M. Can, E. Ilhan,

1Haydarpasa Numune Education and Research Hospital, Istanbul, Istanbul, Turkey; 2Siyami Ersek Thoracic and Cardiovascular Surgery Center, Department of Cardiology, Istanbul, Turkey; 3Malatya State Hospital, Malatya, Turkey; 4State Hospital, Van, Turkey

**Background:** Perioperative acute kidney injury (AKI) is a well-established risk factor for perioperative morbidity and mortality in patients undergoing cardiac surgery. However, predictors and outcome of perioperative AKI in patients undergoing noncardiac, nonvascular surgery have not been established. The purpose of this study was to evaluate the incidence, predictors, and outcomes of perioperative AKI in patients undergoing noncardiac, nonvascular surgery.

**Methods:** A total of 1340 consecutive patients (mean age 65.5±13.8 years) undergoing noncardiac, nonvascular surgery were prospectively evaluated. Patients older than 18 years who underwent an elective, noncardiac, nonvascular surgery procedure were enrolled. Patients with pre-existing renal dysfunction requiring renal replacement therapy or a preoperative serum creatinine higher than 1.4 mg/dL were excluded. The primary outcome of this study was perioperative AKI defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria using the maximal change in serum creatinine and estimated glomerular filtration rate during the first seven postoperative days compared with baseline values before surgery. Glomerular filtration rate was estimated by CKD-EPI equation. Preoperative risk factors and laboratory test results were measured and evaluated for their association with the occurrence of in-hospital perioperative adverse cardiac and noncardiac events.

**Results:** Ninety-one patients (6.8%) met AKI criteria. Univariate analysis identified age, anemia, left ventricle ejection fraction, American Society of Anesthesiologists (ASA) physical status, ischemic heart disease, congestive heart disease, diabetes mellitus (DM), and Revised Cardiac Risk Index (RCRI) score as independent preoperative determinants for perioperative AKI. Multivariate analysis identified age (OR: 1.1; 95% CI: 0.99–1.3; p=0.001), DM (OR: 4.38; 95% CI: 2.39–8.0; p<0.001), and RCRI (OR: 1.48; 95% CI: 0.96–2.27; p=0.04), as independent predictors of AKI. Patients with AKI had more cardiovascular complications (30.8% vs 9.4%; p<0.001), major bleeding (7.7% vs 3.2%; p=0.025, stroke (8.8% vs 1.4%; p<0.001) and in-hospital mortality (7.7% vs 0.9%; p<0.001) compared with those who never developed AKI.

**Conclusions:** Several preoperative predictors are found to be associated with AKI after noncardiac, nonvascular surgery. Perioperative AKI is an independent risk factor for cardiovascular complications, major bleeding, stroke and in-hospital mortality.
baPWV was significantly higher in patients with CAD including those who received revascularization than in patients without CAD (p < 0.001). But there was no significant difference of baPWV between the groups of intermediate CAD and revascularization. When the extent of CAD were classified into following 4 groups; no significant CAD, 1-, 2- and 3-vessel disease, baPWV tended to correlated with the extent of CAD (p < 0.01). However, there was no significant difference among the patients with CAD.

Figure 1. baPWV and clinical outcomes

Conclusion: These results indicate that baPWV is significantly associated with the extent of CAD, although baPWV has limited value in identifying the patients who should receive revascularization among those patients with angina.

The existence of non-obstructive plaque in carotid artery predicts cardiovascular death in patients of end-stage renal disease on maintenance hemodialysis

H.T. Hsin1, S.R. Ke1, Y.S. Peng2. 1Cardiovascular Intensive Care Unit, Far-Eastern Memorial Hospital, Taipei County, Taiwan; 2Department of Nephrology, Far-Eastern Memorial Hospital, New Taipei City, Taiwan

Purpose: Patients of end-stage renal disease (ESRD) are well known to suffer from higher mortality than normal population. It is said, the longer the renal re-placement therapy, the more advanced the atherosclerosis, which has been con-btrubuting prominently to the high cardiovascular mortality. Carotid intimal thickness (CIMT) offers an easy access to explore the status of systemic atherosclerosis. In this study, we follow the cohort to figure out the significance of CIMT and other factors, which may impact the clinical outcome of ESRD patients.

Methods: This is a cohort study conducted in a tertiary referring medical cen-ter. All enrollees should be patients of ESRD, who has received maintenance hemodialysis (HD) for more than 3 months. In Feb. 2007, one cardiologist fin-ished the carotid duplex within one week, during which all enrollee received blood sampling for various lab tests. All the patients were closely followed with clinical events recorded. The primary endpoint was cardiovascular death. In statistics, significance is defined by p < 0.05.

Results: There were 265 patients in this cohort, and the distribution of gender was nearly equal (male vs female: 49.1% vs. 50.9%). The age of this cohort is 68.2 ± 12.4 year-old and these patients has been put on HD for 42.7 ± 29.3 months. After 2-year follow, 11.7% of the patients expired for cardiovascular causes and none of them were afflicted with stroke. Those who reached the primary end-point were elder (68.2 ± 11.3 vs. 60.3 ± 12.3 year-old), with higher fasting blood sugar (161 ± 87 vs. 117.5 ± 66.1mg/dl), lower sodium (141.2 ± 4.0 vs. 144.2 ± 3.3 meq/dl), higher C-reactive protein (CRP) (2.2 ± 4.7 vs. 0.8 ± 1.3 mg/L), thicker CIMT over left carotid artery (0.59 ± 0.017 vs. 0.50 ± 0.015 cm) and more carotid plaque (51.6 ± 24.0%). Those plaques cast 30.50% narrowing over the in-olved arteries, never resulting in significant stenosis. After logistic regression, the existence of carotid plaque (OR 3.371, 95% CI 1.568-7.251, p < 0.001) corre-lated with the primary outcome most significantly.

Conclusion: In this 2-year cohort, we discovered that the existence of non-obstructive carotid artery plaques could significantly impose high cardiovascular mortality to ESRD patients on maintenance HD. Further intervention to reduce carotid plaque may improve the primary outcome in this patient population.

Fasting serum apolipoprotein B-48 levels were correlated with the prevalence of coronary artery disease

D. Masuda1, T. Sugimoto2, T. Ohamra3, M. Nishida3, M. Ishigami3, T. Kawamoto1, A. Matsuyama4, N. Sakai1, I. Komuro1, Y. Yamashita1. 1Osaka University Graduate School of Medicine, Department of Cardiovascular Disease, Osaka, Japan; 2Sugimoto Clinic, Osaka, Japan; 3Osaka University Health Care Center, Osaka, Japan; 4Osaka University Graduate School of Medicine, Division of Health Sciences, Osaka, Japan; 5Kure Heart Center, National Hospital Organization, Kure Medical Center, Hiroshima, Japan; 6Department of Somatic Stem Cell Therapy, Institute of Biomedical Research and Innovation, Kobe, Japan; 7Sakai Clinic, Osaka, Japan

Purpose: Many clinical studies have shown that fasting hypertriglyceridemia is one of the independent risk factors for coronary artery disease (CAD) and re-lated to the existence of postprandial hyperlipidemia (PH). In patients with PH, TG-rich lipoproteins and their hydrolyzed product, remnant lipoproteins were ac-cumulated, which were mainly apolipoprotein (apo) B-48-containing lipoproteins, such as chylomicrons and chylomicron remnants (CM-R) derived from the in-testine. CM-R had highly atherogenic properties in vitro and possibly developed atherosclerotic plaques, we investigated whether the accumulation of CM-R was corre-lated with the development of CAD by measuring fasting apoB-48 levels.

Methods: Subjects who received coronary angiography (CAD) and did not take any lipid-lowering drugs (n=189) were enrolled. Those who had angiographically significant coronary stenosis (75% or more luminal diameter stenosis) in left an-terior descending artery, left circumflex artery and/or right coronary artery were treated as the patients with CAD (n=86) and age, sex and BMI-matched subjects who did not have significant stenosis were treated as non-CAD subjects (n=67). Biochemical markers for glucose and lipid metabolism including fasting apoB-48 concentration were compared between both groups. We examined which metabolic parameters recognized as independent coronary risk factors were corre-lated with CAD by multiple logistic regression analysis. We also compared the effect of different metabolic parameters of MS (TG, HDL-C, HbA1c or plasma adiponectin; classified in low and high) on CAD prevalence in patients with low or high levels of apo B-48.

Results: Fasting serum apo B-48 levels were significantly higher in the patients with CAD than in the non-CAD subjects (3.9±2.4 vs 6.9±2.8g/ml, p < 0.0001). Multiple regression analysis identified the only log-log B-48 was a significant determinant of the existence of CAD (p < 0.0001) among other metabolic param-eters related to coronary risk. In patients with high TG, low HDL-C, high HbA1c and low adiponectin levels, the prevalence of CAD significantly increased when their apoB-48 levels were high compared with when their apoB-48 levels were low. The clustering of high fasting apo B-48 level and other coronary risk factors was associated with a stronger risk for CAD compared with the single existence of them.

Conclusion: High fasting serum apo B-48 level correlates the prevalence of CAD. The prevalence of CAD significantly was significantly higher in patients with high apoB-48 levels when their metabolic parameters of the metabolic syndrome were impaired.

Impact of type 2 diabetes and coronary heart disease on cardiovascular risk in high-risk hypertensive patients: a subanalysis of the CASE-J Ex Study

S. Yasuno1, K. Ueda1, S. Tanaka1, A. Fujimoto1, M. Kashiwara1, Y.M. Nakao2, T. Ogihara3, T. Saruta4, K. Nakao2 on behalf of the CASE-J Ex Study Group. 1EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan; 2Kyoto University, Graduate School of Medicine, Department of Medical and Clinical Science, Kyoto, Japan; 3Mononoma University of Medicine Sciences, Osaka, Japan; 4Keio University, Tokyo, Japan

Objective: The CASE-J trial compared the effects of the angiotensin II receptor blocker candesartan and the calcium channel blocker amiodipine on the incidence of CV events in high-risk Japanese hypertensive patients. The CASE-J Extension (CASE-J Ex) was an observational study designed to evaluate their long-term effects, incorporating an additional 3-year follow-up of the CASE-J trial. We have reported that type 2 diabetes mellitus has the same impact on the incidence of cardiovascular (CV) events as a history of coronary heart disease (CHD), as a subanalysis of the CASE-J Trial. We re-examined the impact of type 2 diabetes and a history of coronary heart disease (CHD) on the incidence of CV events with improved statistical power by using the data of CASE-J Ex.

Methods: There were 4,703 high-risk hypertensive patients (mean age: 63.8 years) to be analyzed. We divided them into four groups according to base-line characteristics as follows, non-diabetics with a history of CHD (n=2290), non-diabetics with a history of CHD (n=1815), and diabetics with a history of CHD (n=203). We used the multivariate Cox regression analysis to estimate the hazard ratio (HR) and 95% confidential interval (CI) with adjustment for possible confounders. HR of non-diabetics without a history of CHD for CV events was set to a reference value of 1.0.

Results: Of 4,703 patients, 339 (7.2%) patients experienced CV events for a rate of 15.9 per 1000 person-years during the 4.5±1.9 years of follow-up. Dia-betics with a history of CHD most frequently experienced CV events among four groups (adjusted HR: 5.22; 95%CI: 3.50-7.78; P < 0.001). Both non-diabetics with a history of CHD and diabetics without a history of CHD also more frequently experienced CV events compared to non-diabetics without a history of a CHD (adj usted HR: 2.73; 95%CI: 1.84-4.11; P < 0.001, adjusted HR: 2.66; 95%CI: 2.04- 3.47; P < 0.001, respectively). However, no significant difference was observed in the risk of CV events between non-diabetics with a history of CHD and diabetics without a history of CHD (P=0.890). Similar results were observed in terms of number of CV events.

Conclusion: Type 2 diabetes mellitus has the same CV risk as a history of CHD in high-risk Japanese hypertensive patients.

P4367 The existence of non-obstructive plaque in carotid artery predicts cardiovascular death in patients of end-stage renal disease on maintenance hemodialysis

P4368 Fasting serum apolipoprotein B-48 levels were correlated with the prevalence of coronary artery disease

Figure 1. baPWV and clinical outcomes
Development and psychometric properties of the Heart Failure Knowledge Scale in Japan
N. Kato1, K. Kirugawa1, E. Nakayama2, T. Tsui2, Y. Kumagai2, C. Miura3, M. Nagayama1, T. Sumiyoshi1, H. Tomokota1, R. Nagai1
1The University of Tokyo, Graduate School of Medicine, Tokyo, Japan; 2Sakakibara Heart Institute, Tokyo, Japan

Purpose: Heart failure (HF) knowledge is considered to be a cornerstone for HF management. However, there are no valid and reliable instruments available, which assess HF knowledge in Japanese HF patients with HF. The purpose of this study was to develop a reliable and valid instrument for the measurement of HF knowledge, and to assess the relationship between HF knowledge and HF self-care behavior.

Methods: We developed a questionnaire consisting of 17 items concerning HF knowledge in reference to the previous studies, such as “HF is a condition that the heart is not able to pump sufficient amount of blood through the body”, “Diuretics remove fluids from the body”, and “HF patients had better drink more water than healthy people”. Patients responded these questions with “yes”, “no”, or “I do not know”. A correct answer was scored 1; an incorrect answer or an answer of “I do not know” was scored 0. Scores for each item were summed, giving a range of total scores from 0 to 17. A higher score indicates greater knowledge about HF.

Results: A total of 176 patients in two independent hospitals completed the self-administered questionnaire. The mean age was 64.3±11.4 years, and males accounted for 70% of the respondents. Mean score of the HF knowledge scale was 9.6±4.5, and the percentage of correct answers ranged from 15% to 79%. Exploratory factor analysis confirmed the one dimensionality of the HF knowledge scale. The contribution to one factor was 81%, Pearson correlation coefficient for concurrent validity was 0.418 (p<0.05). Cronbach’s alpha was measured at 0.88, suggesting adequate reliability. The low HF knowledge score was significantly associated with poor HF self-care behavior, assessed by the European Heart Failure Self-Care Behavior Scale-Japanese version (r=0.256, p<0.01).

Conclusion: The HF Knowledge Scale was a valid and reliable one, and this instrument can be used to gain an insight in the effects of education and counseling toward HF patients. Our data suggests that HF knowledge improves HF self-care, although further research is needed to confirm the relationship.

Comparison of 2, 3, 4 and 16 hour holters
Heart rate

<table>
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<tr>
<th>Heart rate</th>
<th>2 Hours</th>
<th>3 Hours</th>
<th>4 Hours</th>
<th>16 Hours</th>
<th>Significance vs. 16h</th>
</tr>
</thead>
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<tr>
<td>Mean Heart rate</td>
<td>86</td>
<td>79</td>
<td>76</td>
<td>74</td>
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<tr>
<td>Absolute Difference</td>
<td>+21</td>
<td>+21</td>
<td>+17</td>
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<tr>
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<td>0.93</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pausess</td>
<td>Number</td>
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<td>0.98</td>
<td>1.0</td>
<td>1.0 ns</td>
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<tr>
<td>Abs. Difference</td>
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<td>Correlation</td>
<td>0.97</td>
<td>0.96</td>
<td>0.97</td>
<td></td>
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<tr>
<td>ns = non-significant.</td>
<td></td>
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</tbody>
</table>

This study emphasizes that short duration holter monitoring, even as little as 2 hours may be useful in the clinical setting and have benefits in terms of patient convenience and costs.

Diagnostic angiography with 5F catheters supports early ambulation and discharge
Department Cardiac Services, Mater Dei Hospital, Malta, Msida, Malta

Introduction: Ischaemic heart disease is mainly diagnosed through coronary angiography. Although the radial artery approach is gaining prevalence the femoral artery access is still very popular. The latter requires longer recovery time possibly occupying the Cath Lab for longer times. Few studies have studied femoral artery access early ambulation and the safety of early home discharge.

Methods: An initial study with 4F catheters was conducted earlier yielding very good results. This study was published. Then data from 5F diagnostic angiography was prospectively collected over 1 year. The Cath Lab nurses managed sheath removal with manual compression targeting 1 hour bed rest time before ambulation.

Results: This study was carried out in 2009 with 262 participants. The mean time from sheath removal to discharge was 161.3 minutes. These results were obtained with minimal access site complications and without major adverse events.

Discussion: This study showed that early diagnostic angiography patient ambulation after 1 hour bed rest was safe and effective without the need for other devices or options. This practice has since been adopted and is still maintained at the local hospital.

The evolving role of the angina specialist nurse in a district general hospital in the UK
J. Caton, C. Dzereszkiewicz, N. Naqvi. Department of Cardiology, Royal Albert Edward Infirmary, Wigan, United Kingdom

Purpose: To assess the changing role of the angina specialist nurse supervising nurse-led rapid access chest pain clinic (RACP) in a district general hospital in the UK.

Methods: The angina specialist nurse at hospital supervises a nurse-led RACP since 2002. A protocol was followed which proved to be safe and effective. Patients were managed by initial clinical assessment (history, clinical examination) and exercised on a treadmill utilizing the Bruce protocol. Appropriate action was then taken. Details were presented to this Society in 2006. However, with the publication by the National Institute of Clinical Excellence (NICE) of guidelines to manage people presenting with stable chest pain (CG95) in 2010 the protocol of the nurse-led RACP has had to change and adapt to these guidelines. The latter now advocate expedite ECG to diagnose or exclude stable angina in people without known coronary artery disease (CAD). The advice is to offer CT calcium scoring, use myocardial perfusion scanning with SPECT, or stress echocardiography, or first-pass contrast-enhanced magnetic resonance (MR) perfusion or MR imaging for stress-induced wall motion abnormalities. Following the publication of CG95 a small prospective study was done to test the impact of these guidelines. The study was carried out from March 2011 to May 2011. Facilities for CT calcium scoring are not available at hospital. After initial clinical assessment patients were given a percentage likelihood of CAD as proposed by NICE. Patients were then referred for myocardial perfusion scanning or dobutamine stress echocardiography or treadmill exercise test.

Results: 116 patients were audited - 62 Males (mean age 60) and 54 Females (mean age 55). After initial clinical assessment, 8 patients had estimated likelihood of CAD of 61-90% and referred for coronary angiography; 84 patients had 30-60% likelihood of CAD and offered non-invasive clinical imaging. Of these 67 were referred for dobutamine stress echocardiography and 17 for myocardial perfusion imaging; 24 patients had 10-29% risk and referred for exercise test.

Conclusions: The angina specialist nurse supervising a RACP now needs to accurately assess the percentage likelihood of CAD and become proficient at assisting the procedure of dobutamine stress echocardiography. The angina specialist nurse supervising a RACP now needs to be proficient at using knowledge and skills in facilities for dobutamine stress echocardiography and myocardial perfusion scanning so needs to be increased. There would still be a role for treadmill exercise stress testing in hospitals where facilities for CT calcium scoring are not available.

Griin dressing post cardiac catheterization: traditional pressure versus transparent film
R. Al-Shulalah. Jubail Royal Comission Hospital, Jubail, Saudi Arabia

Purpose of the study: To determine the efficacy of using a small transparent non pressure dressing compared with the traditional controlled pressure dressing applied to the femoral artery puncture wound site to maintain haemostasis following cardiac catheterization procedures.

Design: An experimental design, randomized study.

Patients: 80 post cardiac catheterization patients were randomized to have their groin dressing either with pressure dressing (N=40) or TFD (N=40). Patients am-
bulated 8 hours after the procedures. Outcome variables were hematoma formation or bleeding, patient discomfort, and nurse-reported ease of observation of the groin puncture site after the procedure. Five instruments were used for data collection: 1) Demographic and medical data sheet; 2) Hematoma Formation and Bleeding Scale; 3) Skin Integrity Scale; 4) Patient Discomfort and Pain Scale & 5) Nurses Ease of Assessment Scale.

Results: There were no significant differences in base line characteristics and medical data between the two groups. 100% in TFD group vs 55% in pressure dressing group reported feeling very comfortable (p = 0.003). Hematoma formation was equal in the two dressing groups with no incidence of bleeding complications. Nurses rated the ease of assessing the groin significantly higher for TFD than for pressure dressing (p value of 0.000).

Conclusions: Dressing of the puncture site after cardiac catheterization with TFD was more comfortable than the conventional pressure dressing without any difference in hematoma or bleeding complications. So TFD can be used safely and comfortably after achieving hemostasis.

P4375

PCI in very elderly patients suffering an ACS

There are few data on safety and outcomes of percutaneous coronary revascularization (PCI) in very elderly patients suffering an Acute Coronary Syndrome (ACS), especially those aged ≥ 85 years old.

From September to December 2011, a total of 108 very elderly patients were admitted at our coronary care unit with a diagnosis of ACS; 44% of these (n = 48) underwent to PCI. The average age at intervention was 86.9 years. The main co-morbidities were severe chronic renal failure (26%) and COPD (13%). Most of the procedures (47%) was performed for acute myocardial infarction with ST-segment elevation (STEMI), 43% for an acute coronary syndrome without ST segment elevation with high-risk clinical features, Coronary angiography was performed in 45% of cases with a radial approach. The rate of procedural failure was quite high, with about 20% of PCI ineffective: this finding could be consistent with the high percentage of patients with severe calcific coronary artery disease (CAD). Complication rate in this population of ultra-elderly was 25%, with a mortality rate of 12.5%, almost entirely attributable to STEMI (83%, n=5). The cause of death was attributed to mechanical complications of myocardial infarction; in other two patients the cause of death was an arrhythmic event. The only complication attributable to revascularization was an acute contrast nephropathy, which resolved during the hospital stay. Non-fatal complications consist of two cases of severe bleeding and five cases of severe heart failure; a matter of particular concern was the low use of intra arterial counterpulsation balloon pump: in fact, only one patient was assisted with IABP, compared with nine cases of severe heart failure.

Our study highlighted how in very elderly patients experiencing an ACS, PCI is a safe procedure, with a single complication attributable to the revascularization procedure, i.e. a case of acute contrast nephropathy. With regard to other complications these are mainly correlated to the underlying disease, especially acute myocardial infarction with ST-segment elevation. Careful nursing assessment, with a regular evaluation of main hemodynamic parameters and renal function, may facilitate early recognition of hemodynamic deterioration and its better management.

P4376

Preoperative statin use and postoperative atrial fibrillation after major noncardiac, nonvascular surgery
M. Blitzer1, A. Dayan3, M.M. Can2, E. Ilhan4, A. Tekerkes1, 1Haydarpasa Numune Education and Research Hospital, Istanbul, Turkey; 2Malatya State Hospital, Malatya, Turkey; 3State Hospital, Van, Turkey; 4Siyami Ersek Thoracic and Cardiovascular Surgery Center, Department of Cardiology, Istanbul, Turkey

Background: Perioperative beta-blockade and statin therapy have been advocated to reduce cardiac risk of noncardiac surgery. The current study investigated the potential efficacy of adding statin therapy to standard risk stratification in major non-cardiac, nonvascular surgery.

Methods and Results: A total of 1750 patients, undergoing noncardiothoracic, nonvascular surgery were prospectively evaluated. Patients older than 18 years who underwent an elective, nonday case, open surgical procedure were enrolled. Electrocardiography and cardiac biomarkers were obtained 1 day before surgery, and on days 1, 3 and 7 after surgery. Patients with atrial fibrillation were excluded. Demographics, comorbidities, preoperative data (electrocardiography, echocardiography, laboratory results), medications, and, preoperative variables were evaluated for their association with the occurrence of perioperative cardiovascular adverse events. Patients receiving statins were generally older (68.7 vs 62.3 years; P < 0.001) and more likely to be receiving a beta-blocker (46.3% vs 19.4%; P < 0.001). Statin use was associated with a lower unadjusted rate of atrial fibrillation (2.2% vs 4.2%; P < 0.001), myocardial infarction (3.4% vs 6.4%; P < 0.001) and mortality (1.1% vs 2.4%; P < 0.001). After adjustment for patient risk factors and surgery type, odds for atrial fibrillation (adjusted odds ratio

= 0.86; 95% confidence interval = 0.69-0.91; P < 0.001) and myocardial infarction (adjusted odds ratio = 0.82; 95% confidence interval = 0.67-0.98; P < 0.001) remained significantly lower among statin-treated patients.

Conclusions: Treatment with statins is associated with a lower risk for atrial fibrillation and myocardial infarction following major noncardiac, nonvascular surgery.

P4377

Carperitide can protect against acute kidney injury in patients with chronic kidney disease undergoing coronary angiography
T. Senco, K. Manabe, S. Umemura, M. Motohiro, H. Kamihata, T. Iwasaka. Kansai Medical University Hirakata Hospital, Hirakata, Japan

Purpose: Acute kidney injury remains a common complication of coronary angiography (CAG). Although previous study reported that carperitide can reduce renal protective effects after CAG, this has not been a universal finding. We evaluated whether carperitide can reduce renal damage after CAG using urinary Liver-type fatty acid binding protein (L-FABP) expressed after renal ischemia which is a novel marker detecting renal injury more sensitive than the existing marker such as serum creatinine.

Methods: We prospectively randomized 148 patients undergoing CAG who had renal dysfunction (glomerular filtration rate (GFR) ≤ 60 ml/min/1.73m²). Patients were divided into receiving hydration alone (Hyd-group; n=74) and receiving hydration plus carperitide (ANP-group; n=74). All patients were treated with hydration for 12 hours before and after CAG. In ANP-group, carperitide (0.0125-0.025g/kg/min) was started for 1 hour before CAG and continued for 24 hours. Outcomes: We evaluated whether carperitide can reduce renal damage after CAG using urinary Liver-type fatty acid binding protein (L-FABP) expressed after renal ischemia which is a novel marker detecting renal injury more sensitive than the existing marker such as serum creatinine.

Results: Baseline characteristics of the two groups were similar. There was no difference in serum creatinine and GFR between two groups at baseline. During day 1 and day 2. However, urinary L-FABP was significantly suppressed in ANP-group, at day 1 (24.7±24.3 vs 54.0±70.0 ug/g, P < 0.001) and day 2 (15.3±23.0 vs 42.5±83.0 ug/g, P < 0.001). Conclusions: Prolonged intravenous infusion of sodium chloride plus carperitide is more effective than sodium chloride alone prophylaxis of acute kidney injury after CAG. Sodium chloride plus anaprilin may be reduced CIN, leading to improvement of long-term prognosis of CKD patients.

P4378

Effects of community-based general practitioners-led care for 12,864 patients with hypertension: study of cardiovascular risk intervention - hypertension (SCRI-HTN) in China
H.H.X. Wang1, J.J. Wang1. 1School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, People’s Republic of China; 2School of Public Health and General Practice, Guangzhou Medical University, Guangzhou, China, People’s Republic of China

Background and Objectives: Hypertension is emerging as a leading cause of cardiovascular morbidity, mortality, and disability among adults. General practitioners (GPs) working in the community health service (CHS) organizations are being positioned in the healthcare system to provide longitudinal care for hypertensive patients. This study aimed to determine the efficacy of a community-based intervention led by GPs on control of cardiovascular risk factors among patients with hypertension in China.

Methods: DESIGN: a longitudinal, pre-post study. SETTING: 98 community health centres (CHCs) in Guangzhou, the most urbanized city in southern China. Multistage cluster sampling method was adopted in identifying the study sites. The study was carried out over a 5-year period from 2007 through 2011. PARTICIPANTS: 12,864 adult patients who had diagnosed hypertension; and 196 certificate-trained general practitioners. INTERVENTIONS: cardiovascular risk reduction education; regular, long-term follow-up by general practitioners using scheduled consultations and counselling. The intensity of medication treatment was determined by the stratification of risk for cardiovascular disease (CVD).

OUTCOME MEASURES: the difference in change in systolic BP, diastolic BP, triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.

Results: Sufficient data were available for 12,864 patients. The mean (SD) patient age was 52.5 (7.5) years, 53.9% were male, and the mean (SD) systolic/diastolic BP was 146.1 (19.4)/84.6 (11.3) mm Hg at baseline. Several main indicators of cardiovascular health improved over the study period: mean systolic BP decreased from 146.1 to 135.1 mm Hg (p < 0.001); mean diastolic BP declined from 84.6 to 79.6 mm Hg (p < 0.001); mean triglyceride level dropped from 31.7 to 30.1 mg/dl (p < 0.005); mean total cholesterol fell from 96.4 to 74.8 mg/dl (p < 0.042); mean LDL cholesterol changed from 40.5 to 22.3 mg/dl (p < 0.025); and mean HDL cholesterol increased from 28.1 to 46.3 mg/dl (p < 0.04).

Conclusions: This SCRI-HTN study showed that adult patients with hypertension receiving GPs-led care in the community health centres achieved statistically and clinically significant and sustained improvements on the cardiovascular indicators for as long as 5 years. It demonstrated that the participation of GPs as the core in the multi-disciplinary team to provide hypertension management care at the com-
Anxiety in patients with chronic heart failure: impact of perception of control and acceptance coping

C. Nahlen1, G. Björkling1, M. Elftom2, H. Persson2, F. Saboohn2
1Karolinska Institute Danderyd Hospital Department of Clinical Sciences, Sophiahemmet University C., Stockholm, Sweden; 2Mälardalen University. Sustainable development of society and tech. Department of psychology, Västerås, Sweden; 2Karolinska Institute, Danderyd Hospital, Department of Clinical Sciences, Stockholm, Sweden; 4Karolinska Institute Danderyd Hospital, Sophiahemmet University C., Stockholm, University Stress Res., Stockholm, Sweden

Purpose: The perception of lack of control has often been associated with anxiety. Studies have indicated that different coping strategies are differentially associated with mood in patients with chronic heart failure (CHF), and that maladaptive coping is generally linked to anxiety. Furthermore, it has been suggested that acceptance may potentially relieve emotional distress. The present study investigates if acceptance coping can buffer the hypothetical impact of perception of lack of control on higher degrees of anxiety. The aim is to clarify if the pattern of control, acceptance, and anxiety has relevance for nursing efforts to provide emotional support for patients with CHF.

Methods: 65 patients diagnosed with CHF in NYHA class II and III were recruited from a heart failure out patient clinic. The participants filled in forms to measure illness perception (B-IPQ), coping strategies (Brief COPE), anxiety and depression (HADS).

Results: Univariate analysis revealed correlations between Perception of control and Anxiety (r = -0.35, p < 0.05) and Acceptance coping and anxiety (r = -0.27, p < 0.05). However, upon entering both Perception of control and Acceptance coping in a path-analysis with the latter as a mediator, the effect of acceptance coping on anxiety was rendered non-significant.

Figure 1. Path-analysis of perception of control with acceptance coping as a mediator for anxiety.

Conclusion: Although the results suggest that acceptance coping inserts an influence on lower degrees of anxiety in patients with CHF, this impact seems to be dependent on the perception of control. That is, perception of control has primary over acceptance in predicting anxiety in patients with CHF. Consequently, our results suggest that the primary nursing efforts for emotional support should be directed toward an enhanced sense of control.

Depressed chronic heart failure patients have impaired autonomic function

S.J. Lonie2, A. Stewart2, D. Tola3, D. Hare2
2The University of Melbourne, Melbourne, Australia; 2Austin Heart, Department of Cardiology, Melbourne, Australia

Background: Depression is associated with increased morbidity and mortality in chronic heart failure (CHF) patients. Sympatho-vagal balance might contribute to the relationship between depression and worse CHF outcomes. The association between depression and sympathetic-vagal balance, as measured using heart rate variability (HRV), is unknown in CHF patients.

Purpose: The hypothesis of this study was that, in stable systolic CHF patients, impaired sympathetic-vagal balance would be independently related to depression and to the severity of depression.

Methods: Participants completed a 30-minute electrocardiogram for HRV analysis, including dynamic, quiet, dimmed room, constant ambient temperature, no caffeine, smoking, alcohol, or exercise and underwent a clinical interview for major or minor depression according to DSM-IV criteria. Low frequency to high frequency (LF/HF) ratio in the frequency domain, for predominance of sympathetic over parasympathetic activity, was the principal autonomic measure. Results were controlled for other co-variables (including age, sex, left ventricular ejection fraction, NYHA functional class, diabetes, renal function, beta-blocker dose and other psychological factors) using analysis of variance (ANOVA). The outcomes were then subjected to multiple regression and pathway analysis.

Results: The sample comprised 45 participants, 35 males (78%), 10 females (22%), mean age 58.84 years (S.D. ± 12.43), NYHA Class I, N=14 (31%), II, N=26 (58%) and III, N=5 (11%), with mean left ventricular ejection fraction 41.22% (S.D. ± 11.08). Significant differences were found between patients with and without depression in all HRV frequency domain measures, with depression being significantly associated with decreased LF (nu) measures, increased HF (nu) measures, increased LF/HF (nu) measures and a significant increase in the LF/HF (principal outcome) measure (p < 0.001). Regression analyses demonstrated depression had a direct effect on HRV. Social support had both direct and indirect effects on HRV via depression (p < 0.001).

Conclusion: In CHF patients, both minor and major depression are associated with predominant sympathetic over parasympathetic activity, a potential explanation for worse outcomes in depressed CHF patients. The apparent strong influence of social support on cardiac autonomic activity in CHF patients warrants further research.

Adherence to beta-blocker therapy in heart failure patients

H.D. Duengen1, D.O. Obradovic2, S. Inkot1, E. Tahirovic1, N. Opacic2, L. Stark1, T. Tripoli1, V. Tschill1, J. Mueller-Nordhorn3, N. Rieckmann1
1Charite - Campus Virchow-Klinikum, Department of Cardiology, Berlin, Germany; 2Health Center, Krusevac, Serbia; 3Berlin School of Public Health (BSPH) at the Charite -University Medicine Berlin, Berlin, Germany

Introduction: Adherence to medical therapy is associated with patient outcome. Gender, marital status, co-morbidities, and hospitalisations have been reported to influence adherence in heart failure (HF). We aimed to investigate geographical differences in adherence behaviour.

Methods: We invited patients enrolled in the CIBIS-ELD trial to participate in an observations after the end of up-titration with beta-blockers. Self-reported beta-blocker adherence during the past month was assessed using a validated single item which has previously been shown to predict cardiovascular events in a sample of CHF patients. We used chi-square and logistic regression analyses to analyze socio-demographic and clinical variables as potential correlates for adherence.

Results: 780 patients (76 ± 5.5 years, 36.9% woman) were followed-up. 141 patients had died (18.1%). Adherence data was available for 520 patients. 208 (90.4%) patients reported perfect (100%) beta-blocker adherence in the previous month. Poorer adherence (< 100%) was associated with country of residence (27.3%, 11.7% and 9% of patients were poorly adherent in Slovenia, Serbia, and Germany, respectively; p = 0.046), and with the presence of major or minor depression (20.9% of the depressed vs. 7.0% of the non-depressed patient were poorly adherent; p = 0.005). None of the other socio-demographic and clinical variables were related to adherence (all p > 0.20). Adjusting for age and sex, depression remained a significant predictor (p = 0.008). The geographical differences did not persist in multivariate analysis (p = 0.112).

Conclusion: The majority of surviving heart failure patients reported high adherence to their prescribed beta-blockers. As in previous studies, depression was a highly significant correlate of poorer adherence. To our knowledge, this is the first report of geographical differences in adherence in bivariate analyses and should be investigated further.

Effects of lifestyle factors, disease history and awareness on health-related quality of life in a Thai population

P. Vathesatongkitt1, M. Woodward1, M. Kimman1, E.S. Tai2, W. Aekplakorn3, B. Hengprasith4, H.L. Wee5, P. Sritala1
1University of Queensland, The George Institute for International Health, Sydney, Australia; 2National University Health System, Singapore, Singapore; 3Faculty of Medicine Ramathibodi Hospital, Department of Medicine of Mahidol University, Bangkok, Thailand; 4Medical and Health Office, Electricity Generating Authority of Thailand, Northaburi, Thailand; 5National University of Singapore, Singapore, Singapore

Background: Health-Related Quality of Life (HRQoL) depends largely on individual perception of their health state, built from social norms and beliefs. Research from developed countries show that awareness of disease, as well as chronic medical conditions, play a major role in determining HRQoL. We hypothesized that, in the setting of middle-income country, such health states should have similar impacts on HRQoL. The impact of several health states on HRQoL were compared among each other.

Objective: To examine the impact of lifestyle factors, disease history, as well as awareness of diabetes and hypertension on HRQoL in a Thai population, using the Short Form Health Survey version 2 (SF-36v2).

Methods: Between 2008 and 2009, 4,850 Thais, aged 25-54 years, agreed to take part in a health survey. Impacts of different health states on HRQoL were compared using effect sizes as part of the LIFECARE consortium.

Results: None of the other socio-demographic and clinical variables were related to adherence (all p > 0.20). Adjusting for age and sex, depression remained a significant predictor (p = 0.008). The geographical differences did not persist in multivariate analysis (p = 0.112).

Conclusion: The majority of surviving heart failure patients reported high adherence to their prescribed beta-blockers. As in previous studies, depression was a highly significant correlate of poorer adherence. To our knowledge, this is the first report of geographical differences in adherence in bivariate analyses and should be investigated further.

The sample comprised 45 participants, 35 males (78%), 10 females (22%), mean age 58.84 years (S.D. ± 12.43), NYHA Class I, N=14 (31%), II, N=26 (58%) and III, N=5 (11%), with mean left ventricular ejection fraction 41.22% (S.D. ± 11.08). Significant differences were found between patients with and without depression in all HRV frequency domain measures, with depression being significantly associated with decreased LF (nu) measures, increased HF (nu) measures, increased LF/HF (nu) measures and a significant increase in the LF/HF (principal outcome) measure (p < 0.001). Regression analyses demonstrated depression had a direct effect on HRV. Social support had both direct and indirect effects on HRV via depression (p < 0.001).

Conclusion: In CHF patients, both minor and major depression are associated with predominant sympathetic over parasympathetic activity, a potential explanation for worse outcomes in depressed CHF patients. The apparent strong influence of social support on cardiac autonomic activity in CHF patients warrants further research.

Assessment & intervention to improve / Mind, body & behaviour: implications in cardiovascular risk and disease
(CKD) (1.4%). All but asthma affected PCS adversely (p<0.05), and all but CKD affected MCS (p<0.05). Diabetes and hypertension showed a negative influence on PCS (-0.6 and -1.5 points respectively, p<0.005) but not MCS, whereas awareness of these diseases had a substantial impact on MCS (-2.9 for awareness of diabetes and -1.6 for hypertension, p<0.005) but not PCS. Whether participants received treatment or not and whether these conditions were controlled or not were unrelated to PCS and MCS. Arthritis had the greatest negative impact on PCS (ES=0.37), while awareness of diabetes had the greatest negative impact on MCS (ES=0.36). CVD highly affected both PCS and MCS (ES 0.34 and 0.27 respectively). Obesity had a negative effect on PCS (p<0.001). Notably, exercise had significant positive effects on both PCS and MCS (ES 0.08 and 0.21 respectively).

Conclusion: Despite a different social background, several health states including lifestyle factors and disease awareness showed similar impacts on HRQoL. Awareness of disease appeared to have a greater impact on mental health than having disease itself. Being physically active might help promote both physical and mental health.

Dementia diagnosis seems to be a powerful tool for predicting poor outcomes in the elderly with CVD, thus its diagnosis scale should be applied more often in the cardiology divisions.
Conclusions: Obese patients suffering an acute coronary syndrome tend to be more anxious. Levels of anxiety are related to higher levels of cortisol and this might be an explanation for worse outcomes in anxious and obese patients suffering ACS. We recommend psychological therapy in patients who suffered acute coronary syndrome to reduce the impact of anxiety in their prognosis.

Clinical correlations of cognitive impairment in chronic heart failure

M. Nikolau1, J. Parissis2, T. Katsoulas3, M. Thodi4, I. Behlivanoglu5, G. Zisis6, V. Gaitan6, E. Rentoukas2, G. Filipatos4, M. Anastasiou Nana3, 1Amalia Fleming Hospital, Athens, Greece; 2Attikon Hospital, 2nd University Department of Cardiology, Athens, Greece

Introduction: Cognitive dysfunction is known to be more common in patients with systolic heart failure than controls. The impact of heart failure severity on cerebral function remains unknown.

Methods: Fifty-three patients with systolic heart failure were included in the study. Patients have answered the Mini Mental Score and were classified as having normal cognition (25-30), mild (20-24) and moderate (10-19) cognitive impairment (CI). Patients have also completed quality of life scores (Kansas City Cardiomyopathy Questionnaire, Duke activity status index), and a depression score (Zung score). Clinical data (age, sex, NYHA class, six minute walk test) and left ventricular ejection fraction (LVEF) were also available.

Results: From the patients screened, only 14 (26%) had normal cognitive function, while 22 (41%) had mild and 17 (31%) had moderate CI. Cognitive dysfunction was strongly associated with sex, NYHA class and depressive symptoms. One out of 11 female vs 14 out of 42 male were classified as having moderate CI (p=0.006). Patients with normal CI had lower zung score (41±11 vs 47±11 for mild CI, vs 54±9 for moderate CI, p=0.05) and higher KCCQ-overall score (57.3±7 vs 37.2±3 for mild CI, 31±2.6 for moderate CI, p=0.05). Across NYHA class deterioration, mean MiniMental score decreases significantly (24±4 for NYHA II, 22±4 for NYHA III, 17±4 for NYHA IV, p<0.022). LVEF, HF cause and six minute walk test did not differ significantly among the CI subcategories.

Conclusions: Cognitive dysfunction is very common in heart failure patients, affecting moderately almost one out of three HF patients. Cognitive dysfunction deteriorates along with HF deterioration and this has to be screened, especially when complex medical advice is given.

Symptom profile of hypertensive primary care patients with undiagnosed obstructive sleep apnea - a structural equation model analysis

A. Brostrom1, O. Sunnergren2, P. Johannson3, E. Svensson4, M. Ulander5, P. Nilsson6, E. Svavborg1 on behalf of Hypersleep. 1Department of Clinical Neurophysiology, Linköping University Hospital, Sweden, Linköping, Sweden; 2Medical University of Graz, Graz, Austria; 3Department of Cardiology, Linköping University Hospital, Sweden, Linköping, Sweden; 4Faculty of Health Sciences Linköping University, Sweden, Linköping, Sweden

Background: Obstructive sleep apnea (OSA) has been linked to hypertension (HT) in sleep clinic populations, but little is known about the symptom profile of undiagnosed OSA in primary care patients with HT.

Aim: To explore symptoms and characteristics associated with undiagnosed OSA in primary care patients with HT.

Methods: Cross-sectional design, including 411 patients (52% women), mean age 57.9 yrs (SD 6.7 yrs), with HT (BP ≥140/90) from four centres. All underwent a full-night respiratory recording to establish presence and severity of OSA. Clinical variables, medication and co-morbidities, as well as data regarding symptoms, characteristics, insomnia, daytime sleepiness and health complaints were collected during a clinical examination. Factor analyses and structural equation modelling (SEM) were used to explore the relationships between symptoms, clinical characteristics and diagnosis of OSA.

Results: Fifty-nine per cent of the patients had OSA. An exploratory factor analysis based on 19 variables yielded a six-factor model (i.e., anthropometrics, BP, OSA-related symptoms, comorbidity, health complaints, and physical activity) explaining 58% of the variance. SEM analyses showed strong significant associations between anthropometrics (i.e., body mass index, neck circumference, waist circumference) (0.45), OSA-related symptoms (i.e., snoring, witnessed apneas, dry mouth) (0.47) and AH. No direct effects of OSA on comorbidities, BP, dysomnia or health were observed.

Conclusions: OSA was highly prevalent and directly associated to anthropometrics and snoring, witnessed apneas and dry mouth in the morning. When meeting patients with HT, these characteristics could be used by nurses working at HT clinics to identify patients who are in need of referral to a sleep clinic for OSA evaluation.

Differences in cardiovascular signs and risk factors among hypertensive middle aged men and women with high vs. low risk on the Berlin sleep apnea Questionnaire

A. Brostrom1, P. Johannson2, B. Riegel2, P. Nilsson3, B. Fridlund4, E. Svavborg1 on behalf of Hypersleep. 1Department of Clinical Neurophysiology, Linköping University Hospital, Sweden, Linköping, Sweden; 2Department of Cardiology, Linköping University Hospital, Sweden, Linköping, Sweden; 3Medical University of Graz, Graz, Austria; 4Faculty of Health Sciences Linköping University, Sweden, Linköping, Sweden

Background: Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder associated with hypertension (HT), increased morbidity and mortality. Difficulties to identify patients with OSA have been described in primary care, causing low referral rates to sleep clinics. The Berlin sleep apnea questionnaire (BSAQ) is a validated tool that can help to identify patients.

Aim: To describe and compare (i) cardiovascular signs and risk factors associated with high and low risk for OSA, as measured by the BSAQ, in men and women with HT, as well as (ii) to compare traditional sleep-related symptoms between high and low-risk patients of both genders.

Methods: Cross-sectional design, 480 patients mean age 57.8 yrs (±6.7 yrs) were included in the study. All patients with HT were included at 4 primary care centres in Sweden. Clinical examinations (performed by one nurse and one physician specialized in sleep medicine), and the BSAQ, the Minimal insomnia symptoms scale, the Epworth sleepiness scale, the Hospital anxiety and depression scale, as well as the International Physical Activity Questionnaire were used to collect data. Physical activity was measured with validated pedometers.

Results: 71% of the men and 61% of the women had high risk for OSA. 76% of the high-risk men expressed that others were bothered by their snoring compared to 63% of the women (p<0.05). Men with high risk reported that breathing pauses had been noticed more commonly by others compared to women (p<0.05). Men who demonstrated a high risk for OSA had more dyslipidaemia (p<0.05-p<0.001), higher mean levels of P-Crea (p<0.001) and lower heredity of CVD (p<0.001) than women. These men also reported more days with moderate (p<0.05) and high intensity physical activity (p<0.05), but steps/day did not differ. Medication with ACE inhibitors and angiotensin receptor blockers were more common among high-risk men (p<0.001), but diuretics (p<0.001) and hypotropics (p<0.001) were more common among high-risk women compared to men. 62% vs. 50% (p<0.02). Difficulties initiating sleep and difficulties maintaining sleep were also more common among high-risk women compared to men, 40% vs. 24% and 50% vs. 30% (p<0.02). The mean HADS anxiety score and the number of patients above cut-off were significantly higher among women with high risk compared to men (p<0.05). Blood pressure, arrhythmias or diabetes did not differ between the risk groups.

Conclusions: Knowledge about gender-specific symptoms, cardiovascular signs and risk factors associated with high BS AQ risk might help to identify patients in need of sleep respiratory recordings.

Is increased high-sensitive troponin T associated with severity of sleep apnea syndrome?

N. Troester1, M. Palfer1, M. Dominco1, A. Avian2, H. Olchowski2. 1Medical University Graz, Department of Internal Medicine, Division of Pulmonology, Graz, Austria; 2Medical University of Graz, Department of Infectious Diseases, Statistics & Documentation, Graz, Austria

Purpose: With sleep apnoea syndrome (SAS) being a factor for cardiovascular
Nutritional assessment in a University Department of Cardiology

Hospital Universitario Virgen de la Arrixaca, Murcia, Murcia, Spain

Background: Overweight is strongly associated with risk of coronary disease. Its prevalence is very high in the Spanish population. During hospitalization, pre-surgical assessment for overweight/obesity is inadequate in some cases, causing a mismatch between the amount of energy and nutrients offered and truly eaten. The nursing role is crucial in this aspect being described in NANDA Nursing Diagnoses. The objective of the present study was to assess compliance during hospitalization and nutritional adequacy of dietary prescription.

Methods: We performed a prospective observational study of consecutive patients in a University tertiary Hospital. Using a nutritional interview developed for this purpose, we recorded daily food intake of patients and carried out anthropometric recording weight, height and body mass index (BMI). The classification was made from overweight/obese BMI ≥ 25 (SEEDO-2007). Test was conducted using NRS-2002, estimating energy requirement of patient, as recommended by the Spanish Society of Endocrinology and Nutrition (SEEN), the Charlson comorbidity index and the Katz index.

Results: We included 100 patients (age 71.8±13.6, males 55%) of which 12% were normal weight, 2% overweight and 86% overweight/obese (47% overweight, 32% obese type-I, 5% obese type-II, and 2% obese type-III). 4% of patients showed risk of malnutrition according to the NRS-2002. According to the recommendations of the SEEN, our population overweight/obese (86%) would be best to carry out a reduced caloric intake, a medium of 228kcal/day (p<0.01 - p<0.05), which translates in a reduction of 13.1% (10.8 to 15.6) of daily caloric intake. However, there was a reduction of 148kcal/day (+5.9%) prescription during hospitalization (8.4% (+2.3±1.5). In addition, 18.6% of these patients consume additional foods that were provided by their relatives. By semiquantitative method (0-16 points), we evaluated the percentage of the prescribed diet actually eaten. It was a median of 11 (9-13) points, which means that patients eat only 68.8% (from 54.7 to 81.3) of the prescribed diet. We observe a significant correlation between the degree of dependence and the actual intake of the prescribed diet (r: 0.32; p: 0.002).

Conclusions: A huge percentage of patients hospitalized in a Cardiology Department were overweight/obesity. Very few of them are at risk of malnutrition. It is necessary to prescribe the hospital diet for all patient on an individual basis, adjusted for anthropometric measures and disease factor. Nursing should implement the nutritional management of the patient to ensure optimal nutritional status.

Frequency of returning to work after ST segment elevation myocardial infarction

Medical University of Lodz, 2nd Department of Cardiology. Lodz, Poland

The aim of the study was to evaluate the occupational functioning and identify the health-related determinants of successful vocational rehabilitation in workers with a recent myocardial infarction (MI).

Material and Methods: The study group consisted of patients (pts) who under went percutaneous coronary intervention (PCI) for first acute ST-segment elevation myocardial infarction (STEMI) and who were employed before MI. We examined the demographic, clinical and angiographic characteristics of pts who returned to employment (group 1), and those who did not returned to work (group 2).The subject mental health as well as quality of life and occupational functioning were evaluated by the following scales: Beck Depression Inventory and Work Ability Index (WAI). All pts were observed during one year and cardiac events were analyzed.

Results: Among 268 pts (aged 39-64 years) 142 (53%) pts returned to work within 6 months, and 126 (47%) did not. The pts who returned to work after first MI were younger (mean age 49.2 vs 54.3 years), had higher level of education, self rated health and quality of life than the pts who did not resume their occupational activity. In addition there was no difference in 1-year clinical events in those who returned to work and those who did not.

Conclusion: Age, sociopsychological and occupational factors have the strongest influence on the chance to return to work after myocardial infarction

Adherence to the Mediterranean diet reduces the likelihood of acute coronary syndromes, even among people with high anxiety rates: a case-control study

C.M. Kastorni1, H.J. Milionis1, E. Georgoupsopoulou1, M. Symeopouli1, S. Bito2, A. Vemmos2, V. Nikolau3, K.N. Vemmos1, J.A. Goudvenos1, D.B. Panagiotakos2
1University of Ioannina Medical School, Ioannina, Greece; 2Harokopio University, Athens, Greece; 3Alexandra University Hospital, Department of Clinical Therapeutics, Athens, Greece

Purpose: Adherence to the Mediterranean diet has long been associated with beneficial effects regarding cardiovascular disease, while anxiety exerts the opposite effects. The aim of the present work was to evaluate the association between adherence to the Mediterranean diet and the development of acute coronary syndrome (ACS) in participants with and without symptoms of anxiety.

Methods: During 2009-2010, 500 participants were enrolled; 250 were consecutive patients with a first ACS and 250 population-based, control subjects, matched to the patients by age and sex. Socio-demographic, clinical, psychological, dietary and other lifestyle characteristics were measured. Adherence to the Mediterranean diet was assessed by the MedDietScore (theoretical range: 0-16), while trait anxiety with the Spielberger State-Trait Anxiety Inventory form Y-2 (STAI-Y-2, range 20-80).

Results: After various adjustments (i.e., age, sex, physical activity, BMI, smoking, hypertension, family history of cardiovascular disease, hypertension, hypercholesterolemia and diabetes mellitus), each 1/55 increase of the MedDietScore was associated with 8% (95%CI: 0.86-0.99) lower likelihood of ACS and each unit increase of the MedDietScore was associated with 8% (95%CI: 0.86-0.96) lower likelihood of having an ACS in subjects with low anxiety and 9% (0.83-0.90) lower likelihood in participants with moderate or severe anxiety.

Conclusions: The protective effect of the Mediterranean diet pattern regarding ACS persisted even in subjects with trait anxiety, highlighting its beneficial role.

Evaluating cardiovascular disease patients and healthy subjects as regards risk factors' knowledge and beliefs

O.M. Kastorni1, H.J. Milionis1, E. Bika1, E. Ntzou2, M.S. Kostapamos1, E. Georgoupsopoulou2, V. Nikolau2, K.N. Vemmos1, J.A. Goudvenos1, D.B. Panagiotakos2
1University of Ioannina Medical School, Ioannina, Greece; 2Harokopio University, Athens, Greece; 3Red Cross Hospital, Department of Cardiology, Athens, Greece, 4Alexandra University Hospital, Department of Clinical Therapeutics, Athens, Greece

Purpose: The aim of the present work was to evaluate the perception of the importance of several cardiovascular disease (CVD) risk factors by acute coronary syndrome (ACS) and ischemic stroke patients, as well as by healthy controls.

Methods: During 2009-2010, 1000 participants were enrolled; 250 were consecutive patients with a first ACS, 250 were consecutive patients with a first ischemic stroke and 500 population-based, control subjects, one-for-one matched to the patients by age and sex. Socio-demographic, clinical, psychological, dietary and other lifestyle characteristics were measured. Health perceptions were assessed using a scale from 1 to 9 (1: not important, 9: very important), evaluating the following factors: smoking, passive smoking, sedentary lifestyle, stress, unhealthy dietary habits, obesity, diabetes, hypercholesterolemia or hypertension, family history of CVD.

Results: The ACS patients considered the most important CVD risk factor to be stress, followed by smoking. The ACS-controls rated the most important factor to be smoking and the second one stress. The ischemic stroke patients believed the stress control factor to be most important to be smoking, followed by presence of diabetes, hypercholesterolemia or hypertension. The stroke-controls considered smoking as the most significant factor, followed by stress. The ACS patients, ACS-controls, and stroke-controls considered passive smoking as the least important factor. The stroke patients rated as the least important factors CVD family history and sedentary lifestyle. (all p-values <0.05 between patients and controls except for the factor stress).

Conclusions: Health status influences knowledge and beliefs regarding the significance of CVD risk factors, an observation that should be taken into consideration by health professionals.
Hip fracture and risk of acute myocardial infarction: a nationwide study

C.H. Chiang, H.B. Leu, Z.Y. Chen, Taipei Veterans General Hospital, Taipei, Taiwan

Background: Osteoporotic fractures are associated with increased mortality. However, few data are available on the risk of acute myocardial infarction (AMI) following hip fracture. Therefore, we investigated whether hip fracture increased the risk of AMI in a large, nationwide cohort study.

Methods: We obtained data from 8,758 participants diagnosed with hip fracture from 2000 to 2009 and from 4 matched controls for each patient from the Longitudinal Health Insurance Database (LHID 2000), Taiwan. Controls were matched for age, gender, comorbid disorders, and enrollment date. All subjects were followed up from the date of enrollment until AMI, death, or the end of data collection (2009). Cox's regression model adjusted for age, gender, comorbid disorders, and medication was used to assess independent factors determining the risk of development of AMI.

Results: A total of 8,758 subjects with hip fractures and 35,032 controls were identified. Among these patients, 1,183 (257 hip fracture patients and 926 controls) developed AMI during the median 3.2 year (interquartile range, 1.4–5.8 years) follow-up period. Patients with hip fractures had a higher incidence of AMI occurrence when compared to controls (8.7/1000 person-years versus 6.82/1000 person-years). Figure exhibits the results of the log-rank test and Kaplan-Meier survival analysis. During the maximal 10-year follow-up period, the cumulative incidence of AMI was significantly higher in patients with hip fracture than controls (P = 0.001 by log-rank test). Multivariable analysis indicated that hip fracture was associated with a greater risk for AMI development (hazard ratio: 1.29, 95% confidence interval: 1.12–1.48, P = 0.001).

Conclusions: We conclude that hip fracture is independently associated with a higher risk of subsequent AMI.

Secular trends in women with acute coronary syndrome (ACS) referred to coronary artery angiography: a 15-year observation of the University Hospital Bern

H. Saner1, J. Moller1, S. Cook2, S. Windkessel3, P. Eser1, P. Stute4, M. B. Meier2, Bern University Hospital, Cardiovascular Prevention and Rehabilitation, Bern, Switzerland; 2Bern University Hospital, Department of Cardiology, Bern, Switzerland; 3University of Bern, Medical Faculty, Department of Clinical Research, Bern, Switzerland

Purpose: It is suggested that the rate of young women suffering from ACS is increasing. We therefore investigated our invasive cardiology database to assess secular trends in the incidence of first ACS and CV risk factors in women classified into different age-groups over the last 15 years (1995 to 2010).

Methods: We extracted data of all women with coronary angiography between 1995 and 2010 for a first ACS event on age, presence, classification of ACS, and cardiovascular risk factors such as smoking, arterial hypertension, diabetes mellitus, dyslipidemia, family history, and obesity. In the age groups 20-49 yrs, 50-59 yrs, 60-69 yrs, 70-79 yrs, and 80-99 yrs, we calculated numbers of first ACS per year and proportion of first ACS per year with regard to the female population (according to data from the Swiss Federal Institute of Statistics) of the referring area (Cantons of BE, SO, FR, and NE). We also calculated the proportion of women with first ACS with CV risk factors. To assess temporal trends within age groups, we performed linear regressions of absolute and relative numbers of first ACS versus time, as well as risk factors versus time.

Results: Absolute and relative time trends showed significant linear increases for all age groups for absolute as well as relative numbers of first ACS events (all p < 0.01, Figure 1). While the increase in the group of the 20-49 year-old women was small in absolute and relative numbers, from 1995 to 2010 it was most 5-fold, compared to a 3- and 2-fold increase in the 50-59 yrs and 60-69 yrs age groups, respectively. The increase between 1995 and 2000 in the older age-groups was most probably influenced by a change in indication with the advent of PCI. Temporal trends with regard to risk factors showed a significant increase in smoking and obesity in the 60-69 yrs age group.

Conclusions: Our results confirm that there was a small but significant increase of ACS in women which, relative to the incidence in 1995, was considerably greater than the increase in the 50-59 yrs and 60-69 yrs age groups. Increases in first ACS in the 60-69 year old women may have been linked to increased prevalence of smoking and obesity.

Physical activity attenuates subclinical atherosclerosis in subjects with chronic spinal cord injury

W. Nadzru Junior, J.R. Matos-Souza, A.A. Costa E Silva, L.F. Campos, G. Doutart, M. Etchebhere, J.I. Gorla, A. Clique Jr, UNICAMP - State University of Campinas, Campinas, Brazil

Purpose: Cardiovascular diseases are the major cause of death in subjects with chronic spinal cord injury (SCI). Interestingly, SCI subjects present higher carotid intima-media thickness (IMT) than able-bodied individuals, independent of traditional cardiovascular risk factors. The present study investigated the effect of regular physical activity on carotid IMT in men with chronic (> 1 year of injury) SCI.

Methods: We studied 43 SCI men with no voluntary motor activity [30 sedentary (40% tetraplegic); 13 athletes (69% tetraplegic)] and 24 able-bodied men by clinical, anthropometric, laboratory, blood pressure and ultrasound carotid analysis. All enrolled subjects were normotensive, non-diabetics, non-smokers and the studied groups presented similar age and body mass index. Data were evaluated by chi-square analysis, Wilcoxon test, 1-way ANOVA followed by Tukey test and covariance analysis and are presented as mean±standard error. A p-value of less than 0.05 was considered significant.

Results: Carotid IMT in SCI athletes (0.60±0.03 mm) was lower than that of SCI sedentary individuals (0.70±0.02 mm; p=0.008), but higher than that of able-bodied subjects (0.49±0.02 mm; p=0.001). SCI athletes still presented lower triglycerides (65.2±5.4 vs 117.0±12.3 mg/dL; p=0.017) and C-reactive protein (0.49±0.28 vs 1.17±0.39 mg/dL; p=0.037) levels in comparison to SCI sedentary individuals. Conversely, all other studied variables were similar between the SCI groups. In addition, covariance analysis adjusted by triglycerides and C-reactive protein levels revealed that carotid IMT was significantly lower in SCI athletes in comparison to SCI sedentary individuals (p=0.009).

Conclusions: Regular physical activity is associated with attenuation of subclinical atherosclerosis in subjects with SCI, independent of hemodynamic, metabolic and inflammatory factors.

Vitamin D deficiency in relation to circulating inflammatory cells and inflammatory markers among apparently healthy individuals

V. Bountziouka1, T. Akalestos2, N. Vallianou3, A. Evangelopoulos2, M. Bonou1, P. Avgeriou5, E. Vogatzakis1, J. Barbetteas5, D.B. Panagiotakos1,1 Harokopio University, Athens, Greece; 2Roche Diagnostics, Athens, Greece; 3Evangelismos General Hospital of Athens, Athens, Greece; 4Policlinico General Hospital, Department of Cardiology, Athens, Greece; 5Policlinico General Hospital, Department of Pathology, Athens, Greece

Purpose: Vitamin D (VitD) insufficiency is widespread all over the world. It is also known that insufficient 25(OH)D3 (Vitamin D3) alters metabolite function that has been related with the development of various clinical disorders [i.e., osteoporosis, diabetes, cardiovascular disease (CVD)]. This study aimed to evaluate the relationship between VitD deficiency and inflammatory cells and markers among apparently healthy adults.

Methods: During 2009, 490 volunteers (46-16 years, 40% male) were consecutively enrolled to the study (participation rate 85%). Biochemical analyses were performed through established procedures, after 12h fasting, and VitD (ng/mL), high-sensitive C-reactive protein (CRP, mg/dL), Cystatin C (CySC, mg/L), haptoglobin (Hp, mg/dL), haemoglobin (Hb, g/dL), platelets (PLT, 109/L) and white blood cells (WBC, 109/L) were measured. Anthropometric characteristics were also recorded to account for potential confounders. Participants were classified in VitD sufficiency (i.e., <30 ng/mL) and VitD insufficiency (i.e., ≥30 ng/mL). Logistic regression models were used to evaluate the association of inflammation cells and biomarkers to the likelihood of having VitD insufficiency.

Results: Among participants, 25% were VitD sufficient. Participants with VitD insufficiency had higher values of CRP, CySC and Hb as compared with those with VitD sufficiency (all p’s <0.05). Logistic regression models, adjusted for age, sex, lifestyle exposure, family status, physical activity, body mass index and smoking, revealed a positive association between VitD insufficiency and CRP and a negative association with Hb. In particular, 1 mg/dL increase of CRP increase the odds of having VitD insufficiency 3.7 times (95% CI: 1.16-12.0). On the contrary, for every 1 g/dL increase of Hb, the odds of having VitD insufficiency decrease 27% (OR=0.73, 95% CI: 0.57-0.93).

Conclusion: The involvement of VitD in the homeostasis of CVD has been recently evaluated. Results showed that VitD deficiency is a significant risk factor
Hypertension is a risk factor for coronary artery disease (CAD). Recent genome-wide association studies (GWAS) have identified 32 single nucleotide polymorphisms (SNPs) associated with higher blood pressure (BP) at genome-wide significance (p<5x10^-8). If elevated blood pressure is a causative factor for CAD, these variants should also increase CAD risk. Analyzing GWAS data from 22,233 CAD cases and 40,605 controls included in the CARDIoGRAM consortium that 88% of these BP-associated SNPs were likewise positively associated with CAD, i.e. they had an odds ratio for CAD of 1. If a proportion much higher than expected (p<10^-4) was observed in the CARDIoGRAM consortium, it was 3.0% for SBP-increasing SNPm.10398A and 5.0% for SBP-increasing SNPm.7028C presented in IC patients. The SNPm.10398A had a higher odds of having CAD, respectively, as each of the multiple BP-raising alleles observed in CARDIoGRAM was 3.0% for SBP-increasing SNPm.10398A and 5.0% for SBP-increasing SNPm.7028C.

As mitochondria are the principal source of reactive oxygen species (ROS), these organelles may play an important role in ischemic cardiomyopathy. Purpose: To identify genetic factors for ischemic cardiomyopathy. Methods: The study comprised the Declaration of Helsinki. DNA samples from 731 unrelated individuals (380 healthy controls and 351 IC patients) were analyzed in this study. Haplogroup analysis for the ten major European haplogroups was performed by using the single base extension technique and by polymerase chain reaction-restriction fragment length polymorphism. Frequencies and Odds Ratios for the association between IC patients (n=351) and healthy controls (n=380) were calculated. Results: Compared to healthy controls, the prevalence of haplogroup H was significantly higher in IC patients (40.0% vs 50.4%, p-value<0.005) while the frequency of haplogroup J was significantly lower (10.8% vs 5.7%, p-value<0.015). The haplogroup frequencies for our controls did not differ substantially from those reported in previous studies that analyzed different European populations. The mitochondrial haplogroups distribution between cases and controls, stratified by the major ischemic cardiomyopathy risk factors (hypertension, diabetes and smoking) was similar in both groups. The analysis of the SNPs characterizing the European mtDNA haplogroups showed that the SNPs m.10398A>G and m.14766C>T (p-value<0.005) was overrepresented in IC patients. The SNPm.7028C>T produces a non synonymous amino acid change, but the SNPm.14766C>T causes a change in cytochrome b. Furthermore, the SNPm.10398A>G, which produces a non synonymous amino acid change in NADH dehydrogenase subunit 3 (threonine->alanine), was found to be a protective factor (p-value=0.028).

Conclusions: Our results showed suggestive evidence for the association of the mitochondrial haplogroups H and J as risk and protective factors respectively for ischemic cardiomyopathy. Future analysis of the full sequenced mtDNA in these haplogroups and their phenotypic analysis will yield additional insights towards therapeutic targets for ischemic cardiomyopathy pathogenesis.

Impact of arterial stiffness on adverse cardiovascular outcomes and mortality in peritoneal dialysis patients

M.G. Kaya1, M. Saplioglu2, H. Kucuk3, A. Unal4, F. Oguz5, B. Tokgoz6, O. Cymak2, G. Ustas2. 1Erciyes University School of Medicine, Department of Cardiology, Kayseri, Turkey; 2Erciyes University School of Medicine, Department of Nephrology, Kayseri, Turkey

Cardiovascular (CV) disease is a major cause of morbidity and mortality in patients with end-stage renal disease. In recent years, arterial stiffness has taken on great importance in the pathophysiology of CV diseases. The independent predictive value of arterial stiffness for CV events and for all-cause and CV mortality has been demonstrated in the general population and in hemodialysis patients. Our aim in this study was to determine the relationship of arterial stiffness with mortality and fatal and nonfatal CV events in peritoneal dialysis (PD) patients.

Methods: In this prospective observational cohort study with 2 years of follow-up, we studied a cohort of 156 PD patients with a mean follow-up of 19.2±6.4 months.
At baseline, echocardiography and standard clinical and biochemical analyses were performed in all patients and in 28 healthy subjects. Aortic stiffness index beta (ASIβ, a surrogate marker of arterial stiffness) was calculated as follows:

\[ \text{ASIβ} = \frac{\text{SBP}}{100} \times \text{PWV} \]

Results: During the follow-up period, 25 of the patients (16.6%) died, and 10 of those deaths had CV causes. Nonfatal CV events occurred in 15 patients. The median ASIβ was greater in PD patients than in control subjects (4.2 vs. 3.5; interquartile range: 3.2 - 5.9 vs. 2.5 - 4.8; p = 0.008). In the fully adjusted multivariate Cox regression analysis (co-variables: age, sex, albumin, hemoglobin, diabetes mellitus, comorbid CV disease, left ventricular mass index, residual glomerular filtration rate, diastolic-to-ratio of plasma creatinine, 40 UV area, left ventricular ejection fraction, duration of dialysis, smoking), ASIβ independently predicted fatal and nonfatal CV events (hazard ratio: 1.239; 95% confidence interval: 1.103 to 1.392), but not all-cause mortality.

Conclusions: Our results provide the first direct evidence that arterial stiffness is an independent risk predictor of adverse CV outcome in PD patients.

P4407 Cardiovascular disease incidence and compliance on treatment strategy in patients with familial hypercholesterolemia

V. Metaxa, I. Skoumas, C. Pitsavos, E. Oikonomou, C. Masoura, E. Tsetsekou, C. Stefanadis. Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece

Introduction: Familial hypercholesterolemic patients are considered high risk patients due to the severity of their cardiovascular disease (CVD).

Aim: To evalulate the cardiovascular disease incidence and compliance on treatment strategy on patients with familial hypercholesterolemia.

Methods: We enrolled 443 consecutive patients, clinically diagnosed with heterozygous familial hypercholesterolemia (172 men), of mean age 40,48±15 years. We measured their biochemical parameters and lipid profile before and after initiation of lipid lowering therapy. We also recorded all major cardiovascular disease events during their follow-up period.

Results: Mean period of follow-up was 8 years. 26.6% of the population showed poor compliance to drug therapy. The overall cardiovascular events incidence was 8%/36 events. 16 events occurred on those who showed the poorest compliance on drug therapy and 19 events on those who followed the prescribed instructions (13.5% vs 5.8%, p=0.001). Multi-linear regression showed that increasing the follow-up period by 1 year as well as the compliance to drug therapy, the cardiovascular events decrease by 1.33%, independently of age, sex, body mass index, arterial hypertension, smoking habits, total and LDL cholesterol levels, pre-existing coronary artery disease and prescribed therapy.

Conclusion: A considerable percentage of heterozygous FH patients show poor compliance to treatment strategy and this finding consists independent prognostic factor of major cardiovascular events.

P4408 Association of male pattern baldness with angiographic coronary artery disease severity and collateral development

I. Sari, K. Aykent, V. Davutoglu, M. Yuce, O. Ozer, M. Kaplan, H. Akı, S. Ercan, M. Aksoy. Gaziantep University, Faculty of Medicine, Department of Cardiology, Gaziantep, Turkey

Purpose: Although several epidemiological studies have shown an association between male pattern baldness and atherosclerosis, it has never been studied by investigating angiographic presence and severity of coronary artery disease. We aimed to investigate whether there is an association between male pattern baldness and angiographic coronary artery disease severity and collateral development.

Methods: Angiographies, coronary artery disease risk factors, lipid parameters, and presence and severity of baldness of 470 male patients were prospectively evaluated. Baldness were defined as five groups (no hair loss, frontal baldness only, frontal baldness with mild, moderate, or severe vertex baldness). Severity of coronary artery disease was evaluated with Gensini and collateral development with Rentrop scores.

Results: Although subjects with higher Gensini score had more frequent and severe baldness, they were older than the group with lower Gensini score (60.3±11.7 vs. 56.0±11.7, p<0.001). Bald patients had higher Gensini score compared with their non-bald counterparts (44.7±43.3 vs. 34.1±36.4, p=0.009). In univariate analysis baldness, smoking and age more than 55 were predictors of a Gensini score more than 20. In multivariate analysis, only age more than 55 (p=0.005, odds ratio:1.738, 95% confidence interval:1.180-2.561) and smoking (p=0.002, odds ratio:1.895, 95% confidence interval:1.263-2.843) were independent predictors of a Gensini score more than 20. There were no difference in terms of presence and severity of baldness in subjects with and without significant collateral development.

Conclusion: There was no any relation between presence, severity and age of occurrence of male pattern baldness and Gensini and Rentrop scores which are important markers of presence and severity of coronary artery disease. The potential interaction of male pattern baldness with coronary artery disease needs to be clarified with prospective large scale studies.

P4409 Risk factors for coronary plaque progression in patients with far east Asians - A serial volumetric IVUS analysis


Backgrounds: Far East Asians have been reported to be at lower risk of cardiovascular events than Westerners, suggesting the potential racial difference in cardiovascular risk factors and progression of atherosclerosis. However, few data exist correlating cardiovascular risk factors with volumetric IVUS measurements of coronary plaque progression in Asians.

Methods: Serial volumetric IVUS examinations (baseline and 14-months follow-up, mean measured length: 43.4mm) were performed for 297 Far East Asian patients with stable angina pectoris. Patients were subsequently treated with a combination of angiotension-II receptor blocking agents (ARBs), β-blockers, calcium channel blockers, glycomic control agents and/or statins per physician’s guidance. Serial plaque progression rate of atherosclerosis was compared with the patients’ characteristics during the follow-up periods.

Results: In multiple linear and logistic regression test, age > 65-years, diabetes, and male gender remained as predictors of increased plaque volume by serial IVUS. On the other hand, the use of statins and ARBs were identified as factors associated with decreased plaque volume.

P4410 Acute coronary syndrome: a serious threat even at age 40


Purpose: Nowadays, acute coronary syndromes (ACS) are affecting a growing number of young individuals. Are ACS in this population a different entity? Our aim was to assess the prevalence, risk profile, therapeutic approach and outcomes of ACS in a population below 45 years old.

Population and Methods: We studied 4300 patients admitted at a single coronary care unit with ACS, between May 2004 and November 2011. Two groups were considered: A - patients no older than 40 years (n=54, 2.2%), group B - patients above 40 (n=4206).

Results: Groups were compared regarding demographic data, cardiovascular risk factors, lab results, treatment, angiographic findings and prognosis. The median follow-up was 2361 days.

Results: Group A had a mean age of 36.6±3.1 years and included more males (77.7% vs. 68.2%, p<0.005), smokers (59.6% vs. 14.4%, p<0.001) and patients with previous family history of coronary heart disease (25.5% vs. 10.7%, p<0.001), but less with hypotension (40.4% vs. 77.6%, p<0.001), type 2 diabetes (19.1% vs. 34.1%, p=0.002) and dyslipidemia (68.1% vs. 80.2%, p<0.004).

Group A was more frequently admitted with ST elevation ACS (51.1% vs. 33.4%, p<0.001). Considering laboratory data on admission, group A had lower creatine (0.9±0.2 mg/dL vs. 1.2±0.9 mg/dL, p<0.004), but higher hemoglobin (14.7±1.2 g/dL vs. 13.4±1.8 g/dL, p<0.001) and platelet count (259.7±78.6 vs. 224.0±70.3 x 10^3, p<0.001). Blood glucose and lipid profile were not stastically different. Regarding baseline therapy, group A received more GpIIb/IIIa inhibitors (48.8% vs. 30.1%, p<0.001) and less diuretics (10.6% vs. 27.3%, p<0.001). Left ventricular ejection fraction was significantly higher in this group (54.8±11.2% vs. 51.1±11.6%, p=0.007). Group A was also submitted more often to an invasive strategy (80.9% vs. 61.5%, p=0.001) and had a higher prevalence of normal coronary arteries (26.3% vs. 16.5%, p=0.024) and one vessel disease (48.7% vs. 38.2%, p=0.026). The in-hospital mortality was significantly lower for group A (0.0% vs. 5.4%, p=0.020). During the follow up, this group had a trend towards lower mortality rate (6.0% vs. 11.2%, p=0.044).

Conclusion: Younger ACS patients have a particular risk profile, and by being more aggressively treated, are associated with a better short term prognosis. Long term follow-up clearly shows that this is not a benign entity, so these patients
Renal sympathetic nerve activation plays an important role in the pathogenesis of essential hypertension and selective ablation of the sympathetic nerves through the renal arteries can substantially reduce blood pressure (BP) in patients with treatment-resistant hypertension. The duration of antihypertensive effect and long-term safety of renal denervation (RDN) requires further follow-up.

Methods: This prospective, multicentre, randomised trial evaluated the safety and effectiveness of RDN in patients with an office systolic BP of ≥160 mm Hg while taking ≥3 antihypertensive medications. The control group was managed with medication alone and at 6 months after randomisation were offered RDN treatment if eligibility was met. Data from all patients receiving RDN was pooled and analyzed.

Results: There were 89 patients treated with RDN. At 12 months post-procedure, data are available for 47 patients randomized to immediate RDN and 33 crossover patients. The mean age of patients treated was 58.6 years, 44% were female, mean body mass index was 31.1 kg/m², and mean heart rate at baseline was 73.7 bpm. Approximately one-third of patients had type 2 diabetes. There was one renal artery dissection. No other serious adverse events occurred.

Conclusion: The antihypertensive effect of RDN is durable to 12 months in patients with treatment-resistant hypertension. Additional data describing the effects of RDN on renal function, pulse pressure and heart rate through 12 months will be reported.
Renal sympathetic denervation with brachytherapy using beta-radiating catheter. Results from a feasibility and safety preclinical study

R. Waksman, I. Barbash, R. Chan, R. Torguson, D. Hellenga, R. Baffour, R. Seabron, F. Kelodgie, R. Virmanni. 1Washington Hospital Center, Washington, United States of America; 2CVPath Institute, Gaithersburg, MD, United States of America.

Background: Renal sympathetic denervation using intravascular radiofrequency ablation has demonstrated significant reduction in systolic and diastolic blood pressure in clinical trials. Local radiation therapy demonstrated the ability to damage the nervous system and is currently used for the treatment of trigeminal neuralgia. This study aimed to assess feasibility and safety of a novel approach for RSD using a clinically available beta-radiation catheter beta-cath™.

Methods: Ten naive Yorkshire swine underwent intravascular brachytherapy using a β-emitting radiation source. Dosages of 25 or 50 Gy was delivered in the proximal renal artery. Animals were followed up to 1- or 2-months and were assessed by angiography, IVUS and histology. Norepinephrine levels were measured in the renal artery and in the renal tissue of the irradiated kidneys.

Results: Renal artery intravascular brachytherapy was performed without any procedural complications. No thrombus formed on the catheter and no acute vessel injury was noted by angiography. All animals survived to the predetermined follow-up. At 1- and 2-month follow up there was no vascular injury as documented by angiography. IVUS (Figure 1A) and histology. Studies showed focal hypocellular fascicles with cellular degeneration and some cells having vacuolated cytoplasm as well as mild perineural inflammation with and without fibrosis (Figure 1B). Norepinephrine levels will be available at presentation.

Conclusions: Vascular brachytherapy using the beta-cath™ system in the renal artery in the porcine model is feasible and safe with evidence of sparing damage to the nerve and safety vascular parameters even at high dose of radiation. The results of this study supports clinical evaluation of brachytherapy for the treatment of resistant hypertension.
Pleiotropic role of angiotensin-converting-enzyme inhibitors on bone remodeling biomarkers in hypertensive subjects

E.L. Stepien1, T. Wilkosz2, E. Wypasek2, M. Tlalka2, M. Paswicz1.
1Department of Clinical Biochemistry College of Medicine, Jagiellonian University, Cracow, Poland; 2Krakowski Szpital Specjalistyczny im. Jana Pawła II, Krakow, Poland

Objectives: In addition to their well-established efficacy in lowering blood pressure, angiotensin-converting-enzyme inhibitors (ACE-I) have been shown to have an impact on reducing the risk of death, myocardial infarction, stroke and renal complications in patients with coronary artery disease (CAD). Some evidence suggests that high blood pressure is associated with abnormalities of calcium metabolism, leading to an increase in calcium loss and elevation of bone remodeling biomarkers: osteoprotegerin (OPN) and osteopontin (OPG), both in CAD patients and asymptomatic subjects. In our study, we analyzed the role of antihypertensive treatment on OPG and OPN in subjects without a history of CAD.

Methods: We recruited n=350 subjects using a population-based approach by calling n=320 individuals with general practitioners. Subjects (n=287) were considered to have hypertension because they were taking antihypertensive agents or had a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Antihypertensive drugs were used in 240 patients as a monotherapy (n=113) or in combination with two (n=95) or three (n=32) drugs. Remaining hypertensive patients (n=47) had masked or (uncontrolled) hypertension. Biochemical parameters were assessed by routine laboratory techniques. Bone remodeling biomarkers were analyzed by commercially available immunoenzymatic assays.

Results: Among analyzed subjects n=287 had defined hypertension, and n=240 of them were treated with antihypertensive drugs. We observed that both OPG and OPN levels were higher in hypertensive subjects in comparison to normotensive ones: 3.49±1.85 vs. 2.83±1.32 pmol/L (p=0.007) and 88.68±95.85 vs. 56.58±69.04 ng/mL (p=0.012). Additional analysis of antihypertensive treatment showed that there was no significant difference in OPG and OPN levels between treated and non-treated hypertensive subjects. However, the patients stratification according to the used antihypertensives drugs revealed that treatment with ACE-I alone significantly reduced OPN levels in patients compared to treated patients with other hypertensive drugs: 79.40±88.72 vs. 139.29±124.48 ng/mL (p=0.013), or those treated with ACE-I in combination with another drug: 73.8±64.21 vs. 102.23±78.19 ng/mL (p=0.018). OPN levels were predicted in hypertensive patients by diabetes and ACE-I treatment, but not by age or body mass index: (p=0.17 (p=0.005) and (p=0.14 (p=0.017), respectively.

Conclusions: Angiotensin blockade inhibits OPN expression in hypertensive asymptomatic subjects, but this mechanism does not involve OPG axis. Combination therapy does not impair the effect of ACE-I on OPN levels.

Effect of valsartan or ramipril addition to amiodipine/hydrochlorothiazide combination on left ventricular hypertrophy in hypertensive patients with type 2 diabetes

A. Fagari, A. Mugiar, A. Zeggia, P. Preti, G. Derosa. University of Pavia, Department of Internal Medicine, Pavia, Italy

Objectives: To compare the effect of valsartan (Val) or ramipril (Ram) addition to amiodipine (Ami)/hydrochlorothiazide (HCTZ) combination on left ventricular (LV) mass in type 2 diabetic hypertensive patients with LV hypertrophy.

Methods and Results: A total of 180 mild to moderate hypertensive outpatients with well controlled type 2 diabetes and LV hypertrophy after a 2 week placebo period were treated with Ami 10 mg/HCTZ 12.5 mg for 4 weeks: the 154 patients whose blood pressure BP was not normalized by the dual combination (SBP > 130 mmHg and/or DBP > 80 mmHg) were enrolled in the study and randomized to the addition of valsartan 320 mg or ramipril 10 mg for 12 months. At the third month the non responder patients were discontinued. A total of 142 patients completed the study. Echocardiographic evaluation was performed at the end of the placebo period, of the amiodipine/HCTZ period and after 12 months of triple combination treatment. Results: Systolic and diastolic BP were similarly and significantly reduced in both treatment groups (9.2±5.5/6.9±3.4 mmHg in the valsartan group; 9.1±5.9/6.7±3.8 in the ramipril group; all p<0.01 vs Ami/HCTZ combination). LV mass index was also significantly reduced significantly in both groups (9.6±1.8 g/m² in the valsartan group and 7.1±1.3 g/m² in the ramipril group; p<0.001 vs amiodipine/HCTZ combination), however the reduction was significantly greater with val- sarthan than with ramipril (p=0.01). Safety and tolerability were similar across both treatment groups.

Conclusions: Val/HCTZ combination was effective in promoting LV mass regression and such regression was significantly greater than that obtained with Ami/HCTZ and Ram/HCTZ, independent of BP lowering. This finding suggests that valsartan is more effective than ramipril in attenuating this measure of myocardial damage in diabetic hypertensive patients with LV hypertrophy.

Cardioprotection by BAY 94-8862, a novel non-steroidal mineralocorticoid receptor antagonist in a preclinical model of hypertension and diastolic heart failure

M. Dedbeck1, K. Kretschmer2, K. Kast1, L. Baenacker3, E. Hartmann1, S. Schaeter1, P. Koltz1,2,4, Bayer HealthCare, Global Drug Discovery, Cardiology Research, Wuppertal, Germany; 2Bayer HealthCare, Global Drug Discovery, Medicinal Chemistry, Wuppertal, Germany; 3Bayer HealthCare, Institute for Toxicology, Wuppertal, Germany

Purpose: High aldosterone levels especially in combination with increased salt intake inappropriately activate the mineralocorticoid receptor (MR). Blockade of the mineralocorticoid receptor (MR) has been shown to be an invaluable therapy in heart failure. Renal impairment is an important co-morbidity of heart failure and application of available steroidal MR antagonists to this group of patients is limited. We aimed to investigate the efficacy of a novel non-steroidal MR antagonist, BAY 94-8862 vs. the steroidal MR antagonist spironolactone in a preclinical model of salt-dependent hypertension and diastolic heart failure.

Methods: Uninephrectomized male SD rats were given 1% NaCl in drinking wa- ter and subcutaneous injections of deoxycorticosterone acetate (DOCA, 30 mg/kg

Contributing factor for the development of atherosclerosis. Previous studies have shown that activation RAS is associated with increased expression of the Receptor for Advanced Glycation Endproducts (RAGE) at the site of vascular inflammation. The cross talk between RAGE and angiotensin II (AngII) activation may be important in the development of atherosclerosis. Soluble RAGE (sRAGE), a trunc- ated soluble form of the receptor, acts as a decoy and prevents the inflammatory response mediated by RAGE activation. In this study, we sought to determine the effect of sRAGE in inhibiting AngII induced atherosclerosis in apolipoprotein E knockout mice.

Methods and Results: 9 week old ApoE KO mice were infused subcutaneously with AngII (1 μg/mg/kg) and saline for 4 weeks using osmotic mini-pumps. The mice were divided into 4 groups. Mice infused with saline, mice infused with saline and sRAGE IP injection for 4 weeks. Mice infused with AngII group, mice infused with saline and sRAGE IP injection for 4 weeks. The concentration of sRAGE was varied from 0.5 μg, 1 μg, 2 μg/d for each group to determine the dose response. We show that atherosclerosis in the AngII infused ApoE KO mice increased by over 2.5-fold compared to the AngII KO mice. The treatment of 0.5 μg, 1 μg, 2 μg of sRAGE in ApoE KO group resulted in the decrease in atheroma plaque area by 35%. In addition, the treatment with 2 μg of sRAGE resulted in 70% decrease in atheroma plaque area in the ApoE group.

Conclusion: The results prove that blockade of RAGE activation by sRAGE pre- vent AngII induced atherosclerosis. The results from this study suggest that first, RAGE activation is a strong predictor of cerebro- cardiovascular events, and sRAGE might be effective independently of age.
Predictors of adequate response in spironolactone-treated resistant hypertension

A.D. Javier, M.C. Acelajado, M.C. Acelajado-Valdenor. Philippine General Hospital, Manila, Philippines

Background: Primary aldosteronism (PA) is common among patients with resistant hypertension (RHTN). The aldosterone-to-renin ratio (ARR), which screens for PA, is expensive, and service patients in our government-run tertiary care facility cannot afford to pay for the test. The aldosterone antagonist spironolactone has been shown to reduce blood pressure (BP) in patients with RHTN, even in those without biochemical evidence of aldosterone excess. Without the benefit of ARR testing, we sought to determine predictors of response to spironolactone (defined as systolic BP reduction ≥ 10 mmHg) among patients with RHTN.

Methods: This was an analytical cross-sectional study of patients with RHTN referred to the Hypertension Clinic of our tertiary, government-run, resource-limited institution from January 2008 to November 2011. Patient demographics, clinical data, medication use, and laboratory tests were evaluated.

Results: Data from 94 patients with RHTN were included in the analysis. Mean age was 54.6 ± 13.1 years, and 60.1% were females. The mean body mass index was 25.3 ± 5.3 with 30.8% of patients overweight or obese. The average systolic BP reduction on addition of spironolactone was 38.7 mmHg among responders. Multiple logistic regression analysis revealed that concomitant diuretic use (thiazides and/or loop) predicted response to spironolactone (p = 0.0409). Age, gender, family history of hypertension, body mass index, BP-sodium potassium level at baseline, and estimated glomerular filtration rate did not predict treatment response.

Conclusion: Among patients with RHTN who did not undergo ARR testing, concomitant diuretic use predicted treatment response to spironolactone.

Effects of telmisartan on adiponectin and Retinol-Binding Protein 4 in patients with type 2 diabetes

V. Shishkova, A. Remennik. Moscow Medical Centre, Neurorehabilitation, Moscow, Russian Federation

Background and aims: Adiponectin and Retinol-Binding Protein 4 is secreted by adipose tissue and may play a role in cardiovascular disease and insulin resistance. Telmisartan is an angiotensin receptor blocker originally developed for the treatment of hypertension. It can also partially activate peroxisome proliferator-activated receptor (PPAR)-γ which may improve insulin sensitivity. This effect may prove useful in hypertensive patients with insulin resistance or diabetes mellitus. We examined adiponectin and Retinol-Binding Protein 4 levels in patients with type 2 diabetes who treatment with the angiotensin receptor blocker telmisartan.

Methods: A total of 188 patients with hypertension and diabetes mellitus were assessed at baseline and following 24 weeks of treatment with the angiotensin receptor blocker telmisartan (final dose, 80 mg). Adiponectin and Retinol-Binding Protein 4 levels were measured in plasma by radioimmunoassay.

Results: Adiponectin levels were inversely correlated with systolic (SBP; r = 0.640, P < 0.05) and diastolic (DBP; r = 0.350, P < 0.05) blood pressure at baseline and following treatment with telmisartan. Retinol-Binding Protein 4 levels were correlated with systolic (SBP; r = 0.117, P < 0.05) and diastolic (DBP; r = 0.150, P < 0.05) blood pressure at baseline and following treatment with telmisartan. There was a significant increase in adiponectin levels (0.98 (95% confidence interval (CI), 0.57 to 1.86) microg/ml, P < 0.01) and decrease in Retinol-Binding Protein 4 levels (5.88 (95% confidence interval (CI), 3.28 to 10.10) microg/ml, P < 0.01).

Conclusion: Adiponectin and Retinol-Binding Protein 4 levels is correlated with blood pressure in patients with type 2 diabetes. Increased adiponectin and decreased Retinol-Binding Protein 4 are associated with treatment by telmisartan. Given the growing diabetes epidemic, telmisartan that can simultaneously block the angiotensin II receptor and partially activate PPAR-γ may have the potential to treat both hemodynamic and biochemical features of insulin resistance.
prevalence of diabetes and renal disease and were treated with more antihypertensive drugs at baseline (median 3.1 vs. 2.5 vs. 1.5). The reduction in blood pressure (BP) after 2 years versus baseline for office BP and ambulatory 24 hour BP in the 3 groups is shown in the table (mean ± SD).

**Conclusions:** In this large real life registry in outpatients with hypertension aliskiren treated patients showed better blood pressure control compared to patients without RAS-blockade, or an ACE/IARB-based regimen over long-term follow-up over 2 years. These results support the findings from randomized clinical trials.

**PHARMACOLOGY OF HYPERTENSION: MISCELLANEOUS**

**Phytochemical drugs are the new progress in the Haemodynamic effects of dapagliflozin versus**

Vi. Zabela, V.V. Shlyau, V.Y.U. Aftin, Institute of Bioorganic Chemistry, Minsk, Belarus

**Purpose:** We compared the hypotensive effect of valsartan (VAL) and polyphenol complex (PP) and, also, we assessed the efficacy of combination consisting of VAL and PP.

**Methods:** Male spontaneously hypertensive rats (SHR) (n=34, weight 240-280 g) were selected for study. The experimental animals were given VAL at the doses of 5 mg/kg, 10 mg/kg and 20 mg/kg and PP at the doses of 10 mg/kg, 30 mg/kg and 100 mg/kg. The combinations of VAL plus PP at the doses of VAL 5 mg/kg plus PP 30 mg/kg, VAL 10 mg/kg plus PP 30 mg/kg, VAL 20 mg/kg plus PP 30 mg/kg were tested in animals. The systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured non-invasively blood pressure monitor NIH® (Columbus Instruments, USA).

**Results:** Our results showed the most effective dose of PP is 30 mg/kg. In 3 hours, the SBP and DBP were decreased by 18-22 mm Hg (p<0.007) and 15-19 mm Hg (p<0.002-0.003) respectively. The hypotensive effect was still present in 24 hours. The largest hypotensive effect of VAL was recorded at the dose of 20 mg/kg. The reduction was about 20 mm Hg (p<0.003) in the SBP and 15 mm Hg (p<0.002) in the DBP. The SHR rats which were given the combination of VAL 10 plus PP 30 mg/kg, VAL 20 mg/kg plus PP 30 mg/kg were tested in animals. The systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were recorded with the non-invasive blood pressure monitor NIH® (Columbus Instruments, USA).

**Conclusions:** The current study demonstrated the same efficacy of VAL 20 mg/kg and PP 30 mg/kg on blood pressure characteristics. In combination the dose of VAL can be lowered in half. It will allow reaching the target blood pressure with minimal side effects caused by VAL. We propose another mechanism of action of polyphenol complex irrelevant with the AT1-receptors inhibition.

**Haemodynamic effects of dapagliflozin versus hydrochlorothiazide in subjects with type 2 diabetes mellitus**

H.L. Heerspink,1 D. De Zeeuw,1 L. Wee,2 B.R. Leslie3, J.F. List3.

1University Medical Center Groningen, Department of Clinical Pharmacology, Groningen, Netherlands; 2Bristol-Myers Squibb, Global Biometric Science, Hopewell, United States of America; 3Bristol-Myers Squibb, Global Clinical Research, Princeton, United States of America

**Purpose:** Sodium-glucose co-transporter 2 (SGLT2) reabsorbs glucose and sodium in the renal proximal tubule. Dapagliflozin (DAPA), an inhibitor of this transporter, targets hyperglycaemia in type 2 diabetes mellitus (T2DM) by increasing renal glucose excretion. The haemodynamic profile associated with administration of DAPA remains incompletely characterised. We therefore compared the effects of DAPA and hydrochlorothiazide (HCTZ) on 24-h blood pressure (BP) and glomerular filtration rate (GFR).

**Methods:** In this randomised, placebo-controlled, double-blind trial, 75 subjects with T2DM aged 18–70 years (y), HbA1c 6.6%–9.5% and seated systolic BP (SBP) 130–165 mm Hg/diastolic BP 80–105 mm Hg, on a stable dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and no other antihypertensive medications were randomly assigned to placebo (PBO), DAPA 10 mg/day, or HCTZ 25 mg/day. Change from baseline in 24-h ambulatory BP and GFR, measured by oioxel clearance, was compared with baseline after 12 weeks of treatment.

**Results:** Subjects' mean age was 56 years (y), T2DM duration 6.3 y, and HbA1c 7.5%. Treatment with PBO, DAPA, or HCTZ resulted in changes from baseline in 24-h ambulatory mean SBP of −0.9 mm Hg (95% CI: −4.2, 2.4), −3.3 mm Hg (95% CI: −6.8, 0.2), and −6.6 mm Hg (95% CI: −9.9, −3.2) mm Hg, respectively. The effects of DAPA and HCTZ on mean SBP were similar during the daytime. Night time mean SBP did not differ between DAPA and PBO, and was lower for HCTZ than DAPA. Mean changes from baseline in GFR at week 12 were −2.9% (95% CI: −6.6, 1.2), −10.8% (95% CI: −14.8, −6.7), and −3.4% (95% CI: −7.3, 0.6) ml/min/mmHg for subjects receiving PBO, DAPA, and HCTZ, respectively.

**Conclusions:** DAPA is associated with a reduction in 24-h mean SBP, which was somewhat less than that observed with HCTZ. While reductions in daytime mean SBP were similar with DAPA and HCTZ, the change in night time mean systolic BP with DAPA was not different from PBO, and was less than with HCTZ. Small mean decreases in GFR were noted with all treatments, which were somewhat greater with DAPA than PBO and HCTZ.
Five-year target systolic blood pressure less than 120 mmHg for more than 65 aged hypertension patients with chronic renal disease

X.H. Zeng, Z.H. Liu, Y.Y. Li, J.Z. Zeng on behalf of a name.chengdu European GmbH, Munich, Germany

Background: Many studies demonstrate that systolic blood pressure (SBP) >140 mmHg does not provide renal protection in renal disease with hypertension, but SBP<120 mmHg may be able to slow progress of renal disease. However, SBP<120 mmHg in elderly hypertension patients was recommended in Chinese hypertension guideline in 2005. The safety of SBP<120 mmHg in elderly hypertension patients is hardly reported.

Methods: In a prospective, controlled open-label studies, the authors have evaluated the safety and efficacy of five-year treatment on progress of renal disease and risk of development of cardiovascular disease in 122 >65 aged hypertension patients with chronic renal disease III to IV stage and macroproteinuria. Before randomization, all patients have been already treated for one-year with angiotensin converting enzyme inhibitors (ACEI) or angiotensin AT1 receptor blocker (ARBs) and other antihypertensive drugs, but their SBP are above 140 mmHg, less than 150 mmHg. Blood pressure, serum creatinine (Cr) and potas-

sium were monitored every 14 days in the period of follow-up by physician and healthcare nurse and more frequent patient-physician encounters will be improve the patients’ compliance. During the trial patients took blood pressure every day at home and adjusted their own medication according to pre-agreed rules.

Results: By the end of five year, medication possession ratio between two groups was 94% vs 95%. mean blood pressure level of each treatment group was 116.6 ±6.6 mmHg and in control was 146.7 ±13.9 mmHg. Cr clearance increased from 51.2 ±0.6 to 64.3 ±0.6 m/min (P<0.001) in the group of strict con-
trol of SBP <120 mmHg. Cr clearance decreased significantly from 52.1 ±1.9 to 40.2 ±2.4 m/min (P<0.01) in the controls. During this time, urine protein excre-
tion decreased from 1.4±0.5 to 0.2±0.3 g every 24 hours (P<0.0001) in the treatment group, but urine protein excretion decreased slightly from 1.3±0.4 to 1.2±0.6 g/(P=0.05) in the controls. Nine patients had got ACS, 11 patients stroke, 18 patients had got pneumonia, 8 patients renal dialysis and six patient died (4 in SCD and 2 in heart failure) controls but one patient had got ACS, four patient had stroke, five pneumonia, 1 patient renal dialysis and two patients died in non-
cardiac causes in the treatment group. Incidence of hyperkalaemia was similar between two groups.

Conclusions: SBP<120 mmHg is safe and was more apparently in decreasing proteinuria, slowing the progress of renal disease and reducing the risk of develop-

ment of cardiovascular events and proteinuria in elderly hypertensive patients with chronic renal disease.

Cholesterol control and incident antihypertensive treatment in hypercholesterolemia subjects treated or not with statins: a pharmacoepidemiological report

A. Cicerò, E. Depli Esposti1, S. Saragossi2, S. Buda3, S. Radzi3

Purpose: The aim of our study was to evaluate the association between low-density lipoprotein cholesterol (LDL-C) level, statin treatment and the incidence of new antihypertensive treatment in a large population sample.

Methods: A population-based cohort of 23,849 subjects from two Italian Local Health Units (LHU) aged 18 years or older with at least one LDL-C measurement between January 2005 and December 2008 was followed since the LDL-C date until death or December 31, 2009. The cohort was subdivided into two groups (LDL-C<target group, LDL-C≥target) on the basis of their cardiovascular disease risk. The univariate data analysis was based on Pearson Chi-Square to assess statistical significance of differences between frequencies and rates and its 95% confidence interval. The multivariable Cox regression analysis, after ad-

justments for the potential confounding variables, was compared with LDL-C<target group, the LDL-C≥target group, the hazard ratio (HR) of AHT treatment was reduced among those with LDL-C<target (HR=0.91; 95%CI: 0.84-0.98). Significant HRs were also observed for age – increasing age increases the risk of new cases of AHT treatment than the age group below 45 years –, diabetes (HR=1.32; 95%CI: 1.16-1.49) and previous CV disease (HR=0.35; 95%CI: 0.20-0.63). Gender, CV diseases and statin treatment per se were not found significant predictors of the incidence of antihypertensive treatment.

Conclusion: A better control of serum cholesterol levels seems to be associated to a significantly lower incidence of new antihypertensive treatment in a large cohort of general population.

Long-term, open-label treatment with triple olmesartan (O)/amlodipine (A)/hydrochlorothiazide (H) combination therapy in moderate-to-severe hypertension patients (pts)

M. Volpe1, B. Ammentorp2, P. Laeis3. 1University of Rome “Sapienza”, Rome, Italy. 2IRCORS, Neumsted, Pozzilli, Italy. 3Daichi Sankyo Europe Gmbh, Munich, Germany

Objective: Analyse the effect of long-term, open-label treatment with O/A/H for at least 54 weeks in pts with moderate-to-severe hypertension.

Design and Method: At Week 0 (baseline), pts entered a 2-week, double-blind run in which all received dual therapy for safety and then were randomised to 8 weeks of double-blind treatment (N=2690) with different doses of O/A or O/A/H in a factorial setting. After Week 10, all pts received 8 weeks of single-blind O/A/H 20/5/12.5 mg. Pts with controlled BP (<130/90 mmHg, <130/80 mmHg for diabetics, CKD or CVD) then entered open-label O/A/H 20/5/12.5 mg treatment for 36 weeks. Uncontrolled pts entered two consecutive 4-week periods of re-

randomised, double-blind treatment that assessed the effects of up-litration to a maximum dose of O/A/H 40/5/12.5 or 40/5/25 mg. All pts then entered a 28-

week, open-label titration phase in which therapy could be up- or down-titrated to O/A/H 20/5/12.5, 40/5/12.5, 40/5/25, 10/10/12.5 or 40/10/25 mg (investigator’s discretion) in order to get pts to and maintain their BP goals. This phase of the study analyses BP and DBP changes and was effective in keeping BP goal achievement at Week 54, as well as safety and tolerability data.

Results: By Week 54, the O/A/H changes were substantial and similar in all five treatment groups. The overall mean BP goal achievement rate for all pts at Week 54 was 78.1%. Each dose of triple therapy was well tolerated and overall hypertension levels were <1%.

Renoprotective effect of cilnidipine via the antioxidant activity in hypertensive patients

T. Soej1, M. Kitano2, H. Yamada1, T. Wakatsuki1, T. Kawano3, S. Orino3, K. Kawano4, A. Kakutani4, S. Bandoh2, M. Satag1, H. Yamada1, T. Kawanoto3, M. Kitano2, H. Yama
da1, T. Wakatsuki1, T. Kawano3, M. Kitano2, H. Yamada1

1University of Tokushima, Tokushima, Japan. 2Shiriono Hospital, Hagihakagawa, Japan. 3Tokushima City Hospital, Tokushima, Japan. 4Os Kyodo Hospital, Yonishogawa, Japan

Background: Cilnidipine, an L/N type calcium channel blocker (CCB), has been reported to be more beneficial on the progression of prolineuria in hypertensive pa-

tients compared with amlodipine, an L-type CCB. One of the mechanisms for this beneficial effect may be the N-type calcium channel blockade which inhibits renal sympathetic nerve activity leading to a reduction of glomerular hypertension through a vasodilation of effenter arterioles. However, the precise mechanism for the renoprotective effect of cilnidipine remains unknown. Because cilnidipine showed a significantly higher antioxidant activity than amlodipine in cultured hu-

man mesangial cells, we hypothesized that cilnidipine may have a renoprotective effect by suppressing oxidative stress in the present study.

Methods and Results: Thirty-five patients with hypertension, already receiving renin-angiotensin system (RAS) inhibitor, were randomly assigned to cilnidipine or amlodipine at a dose of 10mg/day that was increased up to a dose of 20mg/day (cilnidipine group; n=18) and amlodipine at a dose of 5mg/day that was increased up to a dose of 10mg/day (amlodipine group; n=17). After 6-months of treatment, systolic and diastolic blood pressures were significantly reduced in both groups which did not differ between them. The urinary albumin to creatinine ratio significantly decreased in the cilnidipine group after the treatment for 6 months (P<0.05) whereas it did not change in the amlodipine group. The urinary 8-hydroxy-2’-deoxyguanosine (8-OHdG) level (O/HdG) level and liver-type fatty acid binding protein (L-FABP) level (L-FABP) to creatinine ra-

tio) decreased significantly after the treatment of cilnidipine for 6 months whereas these levels still not change after the treatment of amlodipine. In addition, the rates of ur-

inary albumin, O/HdG and L-FABP reduction were not correlated with the rate of change in systolic blood pressure.

Conclusions: The addition of cilnidipine rather than amlodipine ameliorated ur-

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Does obstructive sleep apnea affect the right heart in patients with resistant hypertension?

Echocardiographic study

P.P. Dobrowolski¹, E. Florczak¹, A. Klesiewicz¹, A. Prebysz¹, P. Bielen¹, E. Warchol¹, H. Janaszek-Sikowska¹, A. Jaruszewicz², P. Sliswinski², P. Hoffman¹. ¹Institute of Cardiology, Warsaw, Poland; ²Institute of Tuberculosis and Lung Diseases, Warsaw, Poland

Purpose: There are limited data concerning the impact of obstructive sleep apnea (OSA) on the parameters of tricuspid valve in patients with resistant systemic arterial hypertension (RSAH). The aim of the study was to determine the relationship between several OSA with echocardiographic parameters of right ventricle in patients with RSAH.

Methods: From 204 patients diagnosed with RSAH hypertension in RESIST POL study, 155 patients (93M, 62F; mean age 47,9±10,5; range 19–65yrs) with secondary hypertension were included into analysis. All patients underwent polysomnography and the apnea/hypopnea index (AHI) was calculated. Right ventricular end-diastolic area (RVAD), right ventricular systolic area (RVAS), main pulmonary artery dimension (MPAD), RV ejection acceleration time (AcT), systolic velocity from Doppler tissue imagine (s'RV), early diastolic velocity (e'RV) and tricuspid annular plane systolic excursion (TAPSE) were evaluated.

Results: Patients were divided into 4 groups based on OAH without OSA (AHI<5, n=43), with mild OSA (AHI 15-30, n=27), moderate OSA (AHI 15-30, n=27), severe OSA (AHI >30, n=40). Patients with severe OSA as compared with patients with mild OSA had higher RVAD (26.0±2.4 vs. 23.1±3.7mm; p<0.001), RVAS (8.7±2.2 vs. 6.8±2.0cm²; p<0.01), RVAD (19.5±3.7 vs. 15.0±3.6cm²; p<0.01) and shorter AcT (114.2±15.7 vs. 133.4±22.1ms; p<0.001). There were no differences in RV systolic performance between patients with severe and without OSA. There were no differences between patients with mild or moderate OSA and without OSA in RV echo findings. AHI correlated significantly with MPAD (r = 0.32; p<0.001), AcT (r = 0.25; p<0.05), RVAS (r = 0.27p<0.01) and RVAS (r = 0.29; p<0.01) but did not with TAPSE, s'RV and e'RV in a multivariate models including parameters of the right heart, presence of severe OSA, gender, age, BMI and metabolic syndrome, the presence of severe OSA was independently related to MPAD (beta= 0.22; p<0.05) and AcT (beta= -0.20; p<0.05).

Conclusions: Severe OSA is an independent factor modifying right heart morphology and RV-MPAd coupling in patients with resistant hypertension.

NOVEL DIAGNOSTIC AND THERAPEUTIC APPROACHES IN STABLE CORONARY ARTERY DISEASE

Utility of high-sensitivity cardiac troponin T in patients undergoing elective cardiac angiography

W. Hochholzer, C.M. Valina, C. Stratz, D. Schlittenhardt, D. Trenk, F.I. Neumann. Heart Centre Bad Krozingen, Bad Krozingen, Germany

Introduction: High-sensitivity cardiac troponin (hsTn) assays have improved diagnosis of myocardial infarction. It is unknown whether hsTn can improve the diagnosis of obstructive coronary heart disease in patients without acute coronary syndrome.

Methods: This study enrolled 1254 consecutive patients undergoing elective cardiac angiography following cardiac stress testing. Obstructive coronary heart disease was defined as a stenosis >75% in at least one of the main native vessels or bypass grafts. Blood samples for hsTnT testing were drawn on admission before coronary angiography and before cardiac stress test. A commercially available hsTnT assay with a 99th percentile cut-off point of 0.014 μg/l and a limit of detection of 0.003 μg/l was used.

Results: Plasma levels of hsTnT significantly correlated with the extent of coronary artery disease (r=0.14; p<0.001) but also with left ventricular function (r=0.17; p<0.001), age (r=0.9; p<0.001), and renal function (r=0.18; p<0.001). Out of 1254 enrolled subjects, 64% had a positive stress test and 61% were diagnosed with obstructive coronary heart disease during coronary angiography. The receiver operating curve (ROC) derived optimal cut-off for the diagnosis of an obstructive coronary heart disease was 0.004 μg/l. A positive stress test result was associated with a sensitivity of 69% but only a specificity of 45% for obstructive coronary heart disease. Combining stress test results with hsTnT ≥0.004 μg/l significantly improved the performance for diagnosis of obstructive coronary heart disease (c-statistics from 0.565 to 0.671; p<0.001). The sensitivity of this approach was 67% and the specificity 61%.

Conclusion: Addition of hsTnT improves significantly the performance of cardiac stress testing for diagnosing obstructive coronary heart disease.

Evidence of a synergistic impact of polymorphisms on C-reactive protein and interleukin-6 gene in patients with stable angina pectoris: Effect on inflammatory process

G. Hatzis, D. Tousoulis, A. Millou, N. Papageorgiou, G. Bouras, G. Latsios, G. Siasos, K. Tsiroukis, G. Stavrakakis. Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece

Purpose: Data suggest that novel polymorphisms on different genes of inflammation can simultaneously be involved into mechanisms of atherosclerosis. In the present study we examined the synergistic role of 3872 A-G polymorphism (rs1205) of C-reactive protein gene and -174 G-C polymorphism of interleukin 6 gene (rs1800795) on serum levels of interleukin 6 as well as the incidence and severity of coronary artery disease (CAD).

Methods: The study consisted of 311 patients with angiographically documented CAD and 160 healthy controls. The 3872 A-G and the -174 G-C polymorphism were determined by PCR and the restriction enzymes HPYCHIV and SFANI respectively. C-reactive protein (CRP) levels were assessed by specific immunonephelometric method, while serum levels of interleukin-6 (IL-6) levels were assessed by ELISA assay.

Results: The genotype distribution for CRP polymorphism was: GG 42.1%, AG 39.8%, AA 18.2% for CAD group and GG: 48.1%, AG: 39.3%, AA: 12.6% for controls. The genotype distribution for IL-6 polymorphism was: GG: 47.6%, GC: 30.5%, CC: 22.5% for CAD group and GG: 47.8%, GC: 43.8% and CC: 8.4% for controls. Importantly, there was a significant difference in IL-6 levels (pg/ml) between the G carriers and CC homozygotes both in the CAD group (3.88±2.81 vs 6.07±3.75; p<0.01) and the control group (3.29±1.84 vs 1.82±1.57; p<0.05). Polymorphism on IL-6 gene and the AA homozygotes of 3872A-G polymorphism on CRP gene were significantly associated with greater incidence of coronary artery disease compared to the other genotypes (RR: 0.945, p<0.010).

Conclusion: The 3872 A-G polymorphism on C-reactive protein gene is closely related to interleukin-6 levels. These findings suggest that the synergistic impact of these two different polymorphisms is capable of a significant promotion of coronary artery disease via inflammatory mechanisms.

Association between increased levels of cardiac troponin before elective stenting and optical coherence tomography findings in stable angina pectoris

T. Lee, T. Kakuta, T. Murali, T. Iwai, T. Takagi, K. Hishikari, Y. Iesaka. Tsuchiura Kyodo Hospital, Tsuchiura, Japan

Aims: With the availability of highly sensitive troponin assays, our understanding of minor myocardial damage in various cardiac conditions is challenged. Association between mild elevation of cardiac troponin I (cTnI) before percutaneous coronary intervention (PCI) in stable angina pectoris (SAP) patients and plaque morphology obtained by optical coherence tomography (OCT) was not yet elucidated. The aim of the present study is to investigate the relationship between increased levels of cTnI before elective stenting and OCT findings in SAP.

Methods and Results: We studied 180 native de novo culprit coronary lesions from 166 SAP patients who underwent OCT before elective PCI. Patients were excluded if they had significant left main disease, congestive heart failure, or revascularization with a baseline eGFR < 30 ml/min/1.73m². Patients were divided into two groups according to the presence (n=28; 16%), median 0.15 ng/mL; IQR: 0.08-0.24) or absence (n=152; 84%) of cTnI ≥0.02 ng/mL before PCI. Clinical and OCT findings were compared between these two groups. Thin cap fibroatheroma (TCFA) was defined as lipid-rich plaque (one or more quadrants) with fibrous cap thickness <70μm. There were no significant differences in the clinical presentation between the two groups including inflammatory markers, eGFR, number of diseased vessel, ejection fraction and Canadian Cardiovascular Society (CCS) grade. In quantitative coronary angiographic analysis (QCA) analysis, there were no significant differences in % diameter stenosis, lesion length, and minimum lumen
men diameter. In OCT analysis, mild CTnI elevation before PCI was associated with the presence of TCFA (8/28: 29% vs 17/152: 11%; P=0.032), smallest thinnest cap thickness (median: 65 μm (IQR: 60-120 μm) vs 107 μm (IQR: 73-140 μm), P < 0.001) and lipid quadrants (median: 3 (IQR: 2-3) vs 2 (IQR: 0-3), P < 0.001). Post-PCI CTnI levels were greater in patients with mild baseline CTnI elevation than in those without (median: 0.52 ng/mL (IQR:0.24 - 4.19 ng/mL) vs 0.33 ng/mL (IQR: 0.12 - 1.06 ng/mL), P=0.044).

**Conclusions:** Mild CTnI elevation was associated with OCT-derivable unstable plaque morphology, and may help identify SAP patients at high risk for cardiovascular injury after elective stenting.

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**Diagnostic performance of cardiac hybrid imaging of single photon emission computed tomography and coronary computed tomography**

M. Nishio, T. Nemoto, M. Asai, K. Kashikase, K. Matsuo, A. Hira, Y. Ueda. Osaka Police Hospital, Osaka, Japan

**Background:** Although cardiac hybrid imaging of coronary computed tomography (CCT) and myocardial perfusion imaging with single photon emission computed tomography (MPI) could show the ischemic myocardial area and the culprit vessel, its clinical usefulness has not been clarified. Therefore, we evaluated the added clinical usefulness of the hybrid imaging in the diagnosis of coronary artery diseases.

**Method:** Consecutive patients (n=96) with suspected coronary artery disease who had significant (>50%) coronary artery stenosis on CCT and equivocal myocardial ischemia on MPI were enrolled. We examined if the hybrid imaging would change the diagnosis on the culprit vessel of myocardial ischemia acquired by side-by-side analysis of CCT and MPI images (Table 1). Hybrid imaging was useful to diagnose correctly the ischemic area at the border of old myocardial infarction or at posterolateral wall that had been overlooked by side-by-side analysis.

**Result:** In 34 (36%) of 96 patients, hybrid imaging changed the diagnosis acquired by side-by-side analysis of CCT and MPI images (Table 1). Hybrid imaging was useful to diagnose correctly the ischemic area at the border of old myocardial infarction or at posterolateral wall that had been overlooked by side-by-side analysis.

**Conclusion:** The hybrid imaging of CCT and MPI was more useful than the side-by-side analysis for the correct diagnosis of the myocardial ischemia and its culprit vessel.

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**Ivabradine in combination with beta-blocker is more effective than up-titration of beta-blockers in patients with stable angina**

Y.A. Karpov1, M.G. Glezer2, Y.A. Vasyuk3, R.T. Saygıtov2, E. Shkolnik3,1. Russian Cardiovascular Research and Production Center, Moscow, Russian Federation; 1.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation; 2Moscow State University of Medicine and Dentistry, Moscow, Russian Federation

**Objective:** To assess efficacy of combination therapy with non-maximum dose of beta-blockers and ivabradine compared to up-titration of beta-blockers strategy in patients with stable angina.

**Methods:** 1104 patients with class II-III CCS stable angina, in sinus rhythm with heart rate at least 60 bpm and on stable therapy with non-maximal recommended dose of beta-blocker were included in a 16-week multicenter open-label controlled study. IV-III IV heart failure and therapy with verapamil or diltiazem were non-selection criteria. Patients were included in the study on 1:4 ratio in the group of up-titration to maximal tolerated dose of beta-blockers strategy (228 patients) and in the combination with ivabradine (876 patients).

**Results:** Addition of ivabradine resulted in significantly lower heart rate than beta-blockers up-titration at the end of the study (61±6 vs 63±8 bpm, p<0.001). Only 45% of the patients in beta-blockers up-titration group were able to achieve maximum doses of beta-blocker. At the end of the study more patients free from angina (50.6% vs 34.2%, p<0.001) were found in ivabradine group. Number of angina attacks for the last 3 treatment weeks was also significantly lower in ivabradine group (4 (2:10) vs 6 (2:15), p=0.015).

In up-titration of beta-blockers group adverse reactions, including dyspnea (1.3% vs 0, p=0.009), hypotension (5.7% vs 0.9%, p<0.001) and fatigue (1.3% vs 0.1%, p<0.003) were significantly more common than in ivabradine group. Bradycardia with heart rate <50 bpm was registered equally in ivabradine and up-titration of beta-blockers groups (0.7% vs 0.4%, p=1.0). In general up-titration of beta-blockers group experienced twice more adverse reactions than ivabradine group.
Increased rho-kinase activity in patients with vasospastic angina after the great east Japan earthquake disaster

T. Nihei1, J. Takahashi1, Y. Kikuchi1, Y. Ito1, R. Tsubura1, Y. Takagi2, M. Nakayama3, K. Ito1, S. Yasuda1, H. Shimokawa1
1Tohoku University Graduate School of Medicine, Department of Cardiovascular Medicine, Sendai, Japan; 2National Cerebral and Cardiovascular Center Hospital, Department of Cardiovascular Medicine, Suita, Osaka, Japan

Purpose: We have recently demonstrated that Rho-kinase activity in circulating neutrophils is a useful biomarker for the disease activity assessment in patients with vasospastic angina (VSA). Coronary vasospastic activity is known to be enhanced by mental/physical stress. Since we experienced the Great East Japan Earthquake in our Tohoku area on March 11, 2011, we examined whether the Rho-kinase activity was increased in VSA patients after the disaster.

Methods: In 10 patients with proven VSA (N=3 from our unit, 600 (41.3%) from referring hospitals. 356 (25.5%) were inpatients, of 117 cases analysed, the HT recommendation had been fully actioned in 101 (86.3%). In the remaining 16 cases, deviation from the initial plan was due to the patient declining revascularisation (CABG 3, PCI 1), development of new co-morbidity (2) or revascularisation of different vessels (6). The reason for deviation was unclear in 4 cases. Of 50 cases re-presented, the original HT recommendation was the same in 38 (76%) cases. Different decisions in the remaining 12 (24%) included 7 cases (14%) in which further investigation had initially been suggested, and revascularisation was recommended on re-presentation.

Conclusions: Sufficient hydration with isotonic saline is effective to prevent the development of CIN. The effect of intravenous saline infusion for 8 hours on prevention of CIN is equivalent to saline infusion for 24 hours.

Figure 1. The Changes in Rho-kinase activity

Conclusions: These results indicate that Rho-kinase activity is enhanced in VSA patients by the disaster-related mental stress.

Figure 1

Conclusions: Sufficient hydration with isotonic saline is effective to prevent the development of CIN. The effect of intravenous saline infusion for 8 hours on prevention of CIN is equivalent to saline infusion for 24 hours.

Figure 1

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Figure 1

Conclusions: Sufficient hydration with isotonic saline is effective to prevent the development of CIN. The effect of intravenous saline infusion for 8 hours on prevention of CIN is equivalent to saline infusion for 24 hours.
Nearly doubled 5-year-mortality in patients with stable coronary artery disease and prior stroke in clinical practice: results of the Star-Registry

A.K. Gitt1, F. Towae2, C. Juenger3, A. Pap2, R. Zahn2, U. Zeymer1

S. on behalf of STAR-Study Group. 1Herzzentrum Ludwigshafen, Institut f. Herzinfarktforschung Ludwigshafen am Univ. Heidelberg, Ludwigshafen an Rhein, Germany; 2Herzzentrum Ludwigshafen, Ludwigshafen, Germany; 3Institut fur Herzinfarktforschung Ludwigshafen an der Universitat Heidelberg, Ludwigshafen, Germany.

Background: Patients with coronary artery disease (CAD) often have generalized atherosclerosis with additional peripheral or cerebro-vascular disease. Little is known about the impact of prior stroke on long-term outcome of patients with coronary artery disease (CAD) and stable angina in clinical practice.

Methods: Between Sept 2001 and March 2003, a total of 2,002 consecutive patients with AP and first angiographic diagnosis of CAD were enrolled in the Star-Registry (50 centres). We examined the impact of prior stroke on 5-year-mortality of stable CAD in clinical practice in Germany.

Results: Of 2,002 patients with stable CAD, 93 patients (4.7%) had prior stroke. These patients were significantly older, more often had concomitant diseases like prior myocardial infarction, peripheral artery disease and diabetes. No differences were observed in interventional treatment at the time of enrolment as well as during the 5 year follow-up, with similar rates of PCI and CABG as compared to patients without prior stroke. Patients with prior stroke had a significantly higher 5-year-mortality (36.4% vs 18.1%, univariate analysis) as well as a higher incident stroke rate. After correction for differences in baseline characteristics and treatment using multivariate analysis, prior stroke was associated with a 47% increased 5-year-mortality of stable CAD in clinical practice (OR 1.46, 1.03-2.15).

Conclusion: Prior stroke was an independent predictor of 5-year outcome in stable CAD patients with a 47% increased mortality rate in clinical practice.

Serum vitamin D levels are independently associated with severity of coronary artery disease


1Mugla University Department of Cardiology, mugla, Turkey; 2Haseki Training and Research Hospital, Istanbul, Turkey; 3Kuwait University College of Medicine, Kuwait; 4Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom.

Background and objectives: We hypothesized that serum vitamin D levels would be inversely associated with inflammation and with severity of coronary atherosclerosis.

Methods: We measured 25-hydroxyvitamin D (25(OH)D) and inflammatory markers in 239 patients who underwent coronary angiography. We analyzed the relation between serum levels of 25(OH)D and inflammatory markers and angiographic severity of coronary artery disease (CAD). Gensini lesion severity score was used for the detection of severity of coronary atherosclerosis.

Results: Vitamin D insufficiency were very common among the our study population and 83% had levels <30 ng/ml. Gensini score was negatively correlated with serum vitamin D level (r = -0.34, p < 0.001), hyperlipidemia (r = -0.35, p < 0.001), diabetes (r = -0.33, p < 0.001), and positively correlated with CRP, fibrinogen (r = 0.22, p = 0.01) and serum C-reactive protein level (r = 0.21, p = 0.01).

Conclusions: In patients with stable CAD treated with PCI, elevated uric acid level predicted the increased risk of death independently from cardiovascular risk factors, status of renal function or inflammatory burden. Thus uric acid, a readily available test, has the potential to stratify the large group of patients with stable CAD in terms of mortality prediction.

Novel diagnostic and therapeutic approaches in stable CAD


Background: The association between uric acid and cardiovascular disease is poorly studied. We undertook this study to assess whether uric acid level predicts clinical outcome in patients with stable coronary artery disease (CAD) treated with percutaneous coronary intervention (PCI).

Methods: This study included 814 patients with stable CAD who underwent PCI. Uric acid was measured in all patients before angiography. The primary end point was 1-year mortality.

Results: Quantiles of uric acid were: 1.49 to 5.49 mg/dL (1st quartile: n=2032 patients), 5.49 to 6.40 mg/dL (2nd quartile: n=1981 patients), 6.40 to 7.50 mg/dL (3rd quartile: n=2003 patients) and 7.50 to 21.90 mg/dL (4th quartile: n=2043 patients). There were 196 deaths during the 1-year follow-up. The numbers of deaths (Kaplan-Meier estimates) according to uric acid quartiles were: 35 deaths (1.8%) in the 1st quartile, 30 deaths (1.6%) in the 2nd quartile, 45 deaths (2.2%) in the 3rd quartile and 86 deaths (4.3%) in the 4th quartile (unadjusted hazard ratio [HR]=1.60, 95% confidence interval [CI] 1.38-1.86, P<0.001 for each standard deviation [SD] increase in the logarithmic scale). Calculated for 1 mg/dL increase in the uric acid level, the unadjusted HR was 1.31 [1.23-2.40]; P<0.001, indicating a 31% increase in the unadjusted risk of 1-year mortality with each 1 mg/dL increase in the uric acid level. After adjustment for traditional cardiovascular risk factors, renal function and inflammatory status, the association between uric acid and 1-year mortality remained significant (adjusted HR=1.26, 95% CI 1.07-1.48; P<0.005 for each standard deviation SD increase in the logarithmic scale). Calculated for 1 mg/dL increase in the uric acid level, the adjusted HR was 1.15 [1.06-1.25]; P=0.01, demonstrating a 15% increase in the adjusted risk for 1-year mortality for every 1 mg/dL increase in the uric acid level. Urict acid improved predictivity of the multivariable model regarding mortality (P=0.040).

Conclusion: In patients with stable CAD treated with PCI, elevated uric acid level predicted the increased risk of death independently from cardiovascular risk factors, status of renal function or inflammatory burden. Thus uric acid, a readily available test, has the potential to stratify the large group of patients with stable CAD in terms of mortality prediction.
Lack of concordance between image stress tests and invasive functional evaluation with pressure wire in patients with stable angina


Background: Current guidelines suggest that coronary lesions should be treated when there is a previous ischemia stress test implying the involved myocardial area. However, sensitivity and specificity of non-invasive stress tests (NIST) may be less than expected, when compared with invasive functional invasive evaluation of lesions, using a pressure wire, particularly in patients with multivessel disease.

Purpose: To investigate the diagnostic value of NIST in patients with stable angina, compared with the invasive functional study (fractional flow reserve – FFR – evaluated with a pressure wire) during coronary angiography.

Methods: Patients with stable angina admitted for coronary angiography and with ischemia identified on a previous NIST, were included. The functional relevance of identified coronary lesions was determined by FFR evaluation (PressureWire®; St. Jude Medical), under adenosine coronary hyperemia. An FFR < 0.75 was considered as functionally significant.

Results: 57 lesions, from 36 patients (mean age 61.6±9.5 years, 24 males) were included. The NIST was myocardial perfusion scan in 28 (81%) patients and stress Echo in 7 (19%). Concordance between NIST and FFR was present in only 24 (42%) of the evaluated lesions. For the defined FFR value (< 0.75), NIST sensitivity was 75.0%, specificity 36.7%, positive predictive value 16.2% and negative predictive value 90%. There were no identifiable variables affecting the concordance between NIST and functional invasive evaluation (including age, gender, coronary risk factors, presence of multivessel disease or ischemia affected territory). However, there was a trend for an increase in the concordance between non invasive and invasive tests when lesion where divided according to angiographic severity: for lesions < 60%, 70-89% and ≥ 90%, the concordance was, respectively, 46.9%, 25.0% and 100% (p=0.067).

Conclusions: NIST have a low concordance with the invasive functional evaluation of lesions with a pressure wire, usually overestimating the presence of ischemia. The lack of concordance between non invasive and invasive test tends to decrease in more severe lesions. These results should be tested in larger trials, since they might change the present recommendations for coronary lesions revascularization.

A novel method for the detection of coronary artery disease using an ultrasensitive microphone on the chest wall

S.E. Schmidt1, J.J. Struik1, L.H. Madsen1, J. Hansen1, H. Zimmermann2, H. Moller1, D. Hammershall1, E. Toft2, H. Kelbaek2, P. Clemmensen1,1 Aalborg University, Dept. of Health Science and Technology, Aalborg, 2Richs hospitalet - Copenhagen University Hospital, Heart Centre, Dept. of Cardiology, Copenhagen, 3Aalborg University, Dept. of Electronic Systems, Section of Acoustics, Aalborg, Denmark

Background: Prior studies have associated increased amplitudes of high frequency diastolic heart sounds with Coronary Artery Disease (CAD), but these sounds are weak and difficult to identify in noisy clinical settings. The current study was initiated by the observation that the low frequency (<100 Hz) diastolic heart sounds are increased in CAD subjects. We tested a prototype of an acoustic system for non-invasive automated identification of coronary artery stenosis.

Methods: From an original group of 463 patients referred for elective coronary angiography we excluded those with potential confounders: arrhythmias (N=58); valve disease (N=26); COPD (N=38); previous heart surgery (N=9) and those with incomplete data: noisy recordings (N=77); diastasis period shorter than 100 ms (N=25) and insufficient patient data (N=7). Pre-processing: non-invasive digital recordings of heart sounds were obtained from the 4th intercostal space at the left sternal border using a novel acoustic sensor (Acarix®). The diastasis interval of the heart sound was identified by an automated segmentation method and the power density spectrum was estimated. To quantify differences in the frequency distribution a CAD-score was defined as the ratio between the power in the 10-90 Hz spectrum and the power in the 90-300 Hz spectrum. Quantitative analysis of ischemic ST-segment changes and improve exercise tolerance in MVA patients. Ranolazine, but not ivabradine, was able to delay the appearance of ischemic ST-segment changes and improve exercise tolerance in MVA patients. This effect was not related to significant improvement in coronary microvascular function or in endoatissueial function.

Ivabradine and ranolazine on exercise stress test and on coronary and peripheral vascular function in patients with refractory microvascular angina

A. Villano1, A. Di Franco1, R. Nerla2, G. Russo1, A. Sestito1, P. Tarzia1, P. Lamonida1, F.M. Sarullo2, G.A. Lanza1, F. Cress1, 1Catholic University of the Sacred Heart, Dept. of Cardiovascular Medicine, Rome, Italy; 2Buccheri La Ferta Fattorebenefiatrici Hospital, Palermo, Italy

Purpose: Ivabradine and ranolazine are novel anti-ischemic drugs with known beneficial effects in patients with stable angina and obstructive coronary disease. In this study we assessed their effects on exercise stress test (EST), coronary microvascular function and systemic vascular function in patients with microvascular angina (MVA).

Methods: We randomized, in a double-blind way, 46 MVA patients (defined by the presence of effort angina, positive maximal EST, normal coronary arteries at angiography and coronary flow response [CFR] to adenosine -2.5), who reported logina sympdrome, to receive ivabradine (5 mg b.i.d.), ranolazine (375 mg b.i.d.) or placebo (b.i.d.) for 4 weeks. Maximal EST, CFR to adenosine and to cold pressor test (CPT) in the 3 groups were compared. The endothelial vascular function (flow-mediated dilation [FMD] and nitrate-mediated dilation [NMD]) of the brachial artery in response to post-ischaemic hyperaemia; were assessed at baseline and after treatment.

Results: Invasive angiography showed no significant differences among groups in EST parameters, CFR to adenosine and to CPT, and FMD and NMD. Compared to placebo, time to 1 mm ST-segment depression and exercise duration were significantly improved by ranolazine (p=0.05), but not by ivabradine. No significant changes were detected in CFR to adenosine and to CPT, as well as in FMD and NMD in any group after treatment (Table).

Conclusions: Ivabradine, but not ranolazine, was able to delay the appearance of ischemic ST-segment changes and improve exercise tolerance in MVA patients. This effect was not related to significant improvement in coronary microvascular function or in endoatissueial function.

Impact of metabolic syndrome on the outcome of patients with stable coronary artery disease submitted to different types of treatment: 10-year follow-up of the MASS II trial

E.G. Lima, W. Hueb, R. Rahmi, R.D.O. Vieira, C.L. Garzillo, A.C. Pereira, A.C. Hueb, P.C. Rezende, J.A.F. Ramires, R. Kalil Filho on behalf of MASS II Trial. Heart Institute (InCor) - University of Sao Paulo Clinics Hospital, Sao Paulo, Brazil

Purpose: Metabolic syndrome (MetS) is understood as a condition that promotes atherosclerosis and confers an additional risk of adverse cardiovascular events patients with coronary artery disease. The prognosis of this syndrome in this subset of patients in a long term follow up is inconclusive. Evaluate the impact of metabolic syndrome on cardiac death in patients with chronic multivessel coronary artery disease.

Results: Criteria for MetS were fulfilled in 283 patients of 583 (54%) randomized to three therapeutic strategies. The presence of MetS was associated with an increased cardiac related death in studied population. During a 10-year follow up, the probability cardiac mortality free survival was significantly different among patients in the 2 groups (MetS – 81.6% x non-MetS – 91.3% P<0.004). Stratifying patients with MetS by therapeutic approach we identify a statistical difference in cardiac death free survival comparing interventional approaches (CABG and PCI) to MT: 82.4% for CABG; 86.2% for PCI and 75.9% for MT(P=0.003). Besides, there is a group with best prognosis: patients without MetS submitted to CABG presenting 98.7% of patients free of cardiac death in a 10-year follow-up.

Conclusion: MetS confers high rates of cardiac death in patients with stable coronary artery disease irrespective of therapeutic strategy used. In patients with MetS, interventional approaches (PCI or CABG) seem to confer more protection against cardiac death in a 10-year follow-up.
P4453 YKL-40 is associated with long-term mortality in patients with stable coronary artery disease
1Rigshospitalet - Copenhagen University Hospital, Heart Centre, Cardiac Catheterization Laboratory, Copenhagen, Denmark; 2Copenhagen Trial Unit (CTU), Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark; 3University of Copenhagen, Department of Biostatistics, Copenhagen, Denmark; 4Rigshospitalet - Copenhagen University Hospital, Department of Clinical Biochemistry, Copenhagen, Denmark; 5Herlev Hospital, Copenhagen University Hospital, Department of Medicine and Oncology, Herlev, Denmark; 6Bispebjerg Hospital, Copenhagen University Hospital, Department of Cardiology, Copenhagen, Denmark; 7Hvidovre Hospital, Copenhagen University Hospital, Department of Cardiology, Hvidovre, Denmark; 8Herlev Hospital, Copenhagen University Hospital, Department of Cardiology, Herlev, Denmark; 9Research Unit of Clinical Microbiology, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

Objective: We investigated whether the inflammatory biomarker YKL-40 could improve the long-term prediction of death made by common risk factors plus high-sensitivity C-reactive protein (hs-CRP) and N-terminal-pro-B natriuretic peptide (NT-proBNP) in patients with stable coronary artery disease (CAD).

Background: Non-hospitalized CAD patients are usually followed in general practice. There is a need for identify biomarkers which could help to foresee the prognosis of these patients. Elevated serum YKL-40 is a short-term predictor of myocardial infarction (MI), cardiovascular mortality and all-cause mortality in patients with stable CAD.

Methods: Serum YKL-40, hs-CRP, and NT-proBNP were measured in 4265 (97.6%) of the 4372 patients with stable CAD included in the CLARICOR trial, and death was registered in a 6-years follow-up period.

Results: After adjustment for type of intervention, risk factors (age, sex, hypertension, diabetes, smoking status, and previous MI) and medical treatment (diuretics and beta-blockers), YKL-40 was a significant long-term predictor of myocardial infarction, cardiovascular mortality and all-cause mortality in patients with stable CAD.

Conclusions: Serum YKL-40 is a predictor of long-term mortality in patients with stable CAD independent of common risk factors and ln(hs-CRP) and ln(NT-proBNP). Serum YKL-40 can be used for prognostication in these patients.

P4454 Coronary plaque characteristics that indicate distal embolization during percutaneous coronary intervention in patients with stable angina-virtual histology intravascular ultrasound study

Background: Distal embolization (DE) is a serious complication of percutaneous coronary intervention (PCI) in patients with stable angina.

Purpose: The purpose of this study was to evaluate the coronary plaque characteristics that indicate DE during PCI in patients with stable angina using virtual histology intravascular ultrasound (VH-IVUS).

Methods: Three hundred and sixty-four consecutive stable angina patients who underwent PCI were enrolled in this study. The patients were divided into the two groups as follows: patients exhibiting DE (DE group, n=10) and patients without DE (non-DE group, n=354). The culprit coronary plaque compositions were assessed by VH-IVUS, which were classified as fibrous, fibro-fatty (FF), dense-calcium and necrotic core. The best cut-off values for predicting DE were calculated by receiver operating characteristic curve and evaluated by univariate logistic regression analysis.

Results: The FF ratio (28±17% vs. 11±9%, p=0.0001) was higher in the DE group compared with in the non-DE group. None of the other VH parameters were different between the two groups. The best cut-off value of FF ratio for prediction of DE was 20%, with a sensitivity of 0.80 and a specificity of 0.81 (odds ratio; 17.1, 95% confidence interval 3.56-82.5, p=0.0004).

Conclusions: Coronary plaques having FF ratio may be the predictor of indicating DE in patients with stable angina during PCI.

P4455 Effects of ranolazine and ivabradine on angina status and quality of life in patients with microvascular angina

Purpose: Aim of this study was to assess the effects of ranolazine and ivabradine on angina symptoms and quality of life (QoL) in patients with microvascular angina (MVA: effort angina, positive exercise test, normal coronary arteries and coronary flow reserve <2.5).

Methods: We randomized 46 MVA patients under usual antianginal therapy to receive ivabradine (5 mg b.i.d.), ranolazine (375 mg b.i.d.) or placebo for 4 weeks. The Seattle Angina Questionnaire (SAQ) and EuroQoL scale were assessed before and after treatment.

Results: Basal SAQ scores and EuroQoL scale did not differ among groups. Both ranolazine and ivabradine improved outcome variables compared to placebo; furthermore, ranolazine was more effective than ivabradine in improving most SAQ items and EuroQoL scale (table).

Conclusions: Our data show that both ranolazine and ivabradine may have a therapeutic role in MVA patients. Ranolazine appeared more effective than ivabradine in achieving a better control of symptoms.

P4456 Low testosterone levels correlate with the angiographic extent of coronary artery disease in patients with stable angina and/or abnormal stress test
N. Ioakeimidis1, C. Vlachopoulos2, A. Aggelis3, D. Terentes-Printzios4, A. Synodinos5, A. Samentzas6, A. Aggelakas7, K. Rokkas8, K. Aznaouridis1, C. Stefanadis9. 1Hippokration General Hospital, Athens, Greece; 2Eipsos General Hospital, Athens, Greece

Purpose: Low testosterone concentration is associated with endothelial dysfunc-
Markers of prognosis, incidence of sudden cardiac death and heart failure in coronary artery disease

E. Bobescu1, D. Dobreanu2, N. Ailudea1, A. Covaci1, 1Transilvania University, Brasov, Romania; 2University of Medicine and Pharmacy Targu Mures, Targu Mures, Romania

Purpose: To evaluate in patients with stable angina, ST and non ST elevation acute coronary artery (ACS) plaque instability biomarkers and the effects on outcomes included sudden cardiac death, heart failure readmission and left ventricular systolic dysfunction.

Methods: In 400 patients (pts) with stable angina and ACS, plaque instability biomarkers: endothelial dysfunction (Von Willebrand factor activity, flow mediated dilatation), platelets hyperactivity (ASPfiteat, ADPfiteat by multiple electrode aggregometry), oxidative stress (Total antioxidant status, Anti Myeloperoxidase antibodies -MPO IgG ELISA), were evaluated in correlation with incidence sudden cardiac death, heart failure and other major acute cardiovascular events (MACE) for 2 years of follow up. Statistical analysis: chi square test, multiple regression.

Results: See Table.

Conclusions: Higher aggregation values of ASPfiteat and ADPfiteat, higher von Willebrand factor activity plasma value, lower values of low flow mediated vasodilatation, lower serum levels of total antioxidant status and higher serum level of myeloperoxidase IgG antibodies, were correlated with significant increased incidence of sudden cardiac death, cardiovascular death, nonfatal AMI, heart failure and recurrent angina with readmission; significant higher incidence of left ventricular systolic dysfunction in patients with acute coronary syndromes at 2 years of follow up. Endothelial dysfunction, platelets hyperactivity and oxidative stress are the most important factors in atherosclerotic plaque instability and evolution with major acute cardiovascular events.

P4457

Markers of prognosis, incidence of sudden cardiac death and heart failure in coronary artery disease

P4458

Extracorporeal shockwave myocardial revascularization therapy (ESMR): an alternative for patients with end-stage coronary artery disease and chronic refractory angina pectoris?

J. Vainer1, J. Habelt2, C. De Pont3, A. Lousberg3, S. Schalla1, B. Brans2, J. Waltenberger3,1 Maastricht University Medical Center, Department of Cardiology, Maastricht, Netherlands; 2Maastricht University Medical Center, Department of Nuclear Medicine, Maastricht, Netherlands; 3University Hospital Muenster, Department of Cardiology and Angiology, Muenster, Germany

Purpose: Patients with chronic refractory angina complaints on maximum tolerable medication and no further revascularization options represent a difficult therapeutic challenge. Extracorporeal Shockwave Myocardial Revascularization therapy (ESMR) might improve symptoms and alleviate ischemia by stimulating collateral growth in chronic ischemic myocardium in patients with end-stage coronary artery disease. A shockwave is a single pressure pulse with a short (<1 ms) positive spike with an amplitude up to 100 MPa followed by a lower amplitude tensile part lasting several microseconds. The highly localized physical forces of shockwaves increase capillary density in ischemic myocardium. This prospective study was performed to evaluate the feasibility and safety of ESMR.

Methods: We recruited 50 patients (40 male, mean age 66±9 years, mean left ventricular ejection fraction 53±12%) with end-stage coronary artery disease, chronic angina pectoris and reversible ischemia on myocardial single photon emission tomography (SPECT). ESMR was applied to the ischemic zones (3±5 spots/session, 100 impulses/spot, 0.09 mJ/mm²) in an echocardiography-guided and ECG-triggered fashion. The protocol included a total of 9 treatment sessions (3 treatment sessions within one week at baseline, and after 1 and 2 months). Exercise test, angina score (CCS class), nitrate use and SPECT 1 and 4 months after the last treatment session were used to evaluate the effect of the ESMR.

Results: One and 4 months after ESMR, the angina complaints diminished (CCS class 3±2 to 0.2±0.0, p<0.01 and p<0.001, respectively). Sublingual nitrate use declined from 65±13% to 1±3±4 week to 1±3±2±5 week (p<0.01 and p<0.001, respectively). This clinical improvement was in line with an improved myocardial uptake on stress SPECT at 4 months follow up (54±4±9% to 56±10±6%, p<0.02 and p<0.01, respectively). A significant increase in exercise tolerance at 1 and 4 months follow-up (from 8±3±2 to 9±3±8 to 9±3±8 minutes, p<0.028 and p<0.02, respectively). No clinically relevant side effects were observed.

Conclusion: ESMR improved symptoms and reduced ischemia burden in patients with end-stage coronary artery disease. The non-invasive character of ESMR in combination with absence of relevant side effects makes ESMR a promising treatment modality for patients with chronic refractory angina pectoris.

The prevalence of refractory angina in patients undergoing coronary angiography for stable ischemic heart disease

I.S. Luchtenker, A. Doletsky, D.A. Andreeu, A.V. Svet, A.L. Synkin, First Maastricht University Medical Center by I.M. Sechenov, Cardiology Clinic, Moscow, Russian Federation

Background: Epidemiological studies of refractory angina do not always take into account the number of angina episodes during a certain period of time in separate patient categories. The severity of refractory angina is not always known.

Aim of the study: To evaluate the prevalence and severity of refractory angina in real clinical practice in patients with stable ischemic heart disease undergoing coronary angiography.

Methods: 418 patients (301 male (72%) and 117 female (28%)) undergoing coronary angiography due to chronic stable angina were consecutively screened during a one-year period. Several aspects of ischemic heart disease were analyzed. In patients with angina refractory to medical and surgical treatment frequency of chest pain episodes was recorded using standardized one-week diaries.

Results: Amongst all 418 patients 6 (1.4%) had CCS class 1 (CCS Angina Grading Scale), 268 (66.8%) – CCS II, 121 (28.1%) – CCS III, 3 (0.7%) – CCS IV. 29 patients (6,8%) had no detectable lesions of coronary arteries, 138 patients (33%) had non-significant lesions, 82 (19.6%) patients were diagnosed with significant coronary artery disease, 98 (23,4%) – with multiple vessel disease. Myocardial revascularization was indicated in 251 patients (60,0%), 117 of them (46,6%) underwent PTCA, 79 (31,5%) – CABG. Cardiac surgeons refused to operate (due to various contraindications and/or high risk) in 26 patients (10,4%), 29 patients (11,6%) refused to be operated because of fear of operation.
Totally 55 patients were considered as having angina pectoris refractory to surgi-
cal and medical treatment, which is 21.9% of all patients with stable angina in
whom revascularization was indicated. The frequency of angina attacks in this
group varied from 0 to 24 episodes a week with median of 9 episodes. 27 patients
(49% of all refractory angina patients) had less than two angina attacks a week.
Therefor the remaining patients considered refractory to medical treatment and
only 28 patients had a refractory angina which is 6.7% of all 481 patients
undergoing coronary angiography.

Conclusions: Amongst all patients with stable angina undergoing coronary an-
giography 6.7% had a refractory angina which is substantial. Usage of other tools
apart from CCS Angina Grading Scale can help to evaluate severity of angina:
standardized diaries, special tools for measurement of quality of life, etc.

Prognostic value of “tight” blood pressure control in patients with coronary
disease: evidence from the Action database

P. Meredith1, S. Lloyd2, I. Ford2, H.L. Elliott3.1 Western Infirmary,
Glasgow, United Kingdom; 2University of Glasgow, Robertson
Centre for Biostatistics, Glasgow, United Kingdom; 3University of Strathclyde,
Glasgow, United Kingdom

The placebo-controlled ACTION trial examined the effects of treatment with
Nifedipine GITS on clinical outcomes in patients with stable symptomatic coro-
nary atherosclerotic disease. Previous retrospective analysis of the ACTION
database demonstrated the importance of consistent blood pressure (BP) to be-
low 140/90mmHg. This further analysis evaluates the benefits of sustaining “tight”
BP control, the levels recommended by current guidelines for this “high risk” patient
group.

The analysis was limited to those patients who had complete BP measurements
over the first year of the study (4 recordings) and excluded those who had an
event during this period. The patients were then divided into 4 groups according to
the proportion of visits in which BP was in controlled to <130/80 mm Hg: <25%,
25% to <50%, 50% to <75% and ≥75%. Data were analysed for the major pre-
specified ACTION outcomes by unadjusted clinical outcomes: thus, % of patients
with outcome by proportion of visits with BP control. Data were also analysed
estimating the hazard ratios (HR) for each outcome relative to the consistency of
BP control as a group with BP control <25% of visits as reference.

Only 18.1% of patients achieved a BP control rate (<130/80 mm Hg) for more
than 75% of visits and, in the first year, 48.0% were controlled at fewer than 25% of
visits. With the exception of coronary angiography, the rate of all of the pre-
specified cardiovascular endpoints declined as the proportion of visits with BP
control increased. The risks for primary outcome (HR: 0.63; 95% CI: 0.53 to 0.75),
all cardiovascular events (HR: 0.63; 95% CI: 0.53 to 0.76), myocardial infarction
(HR: 0.69; 95% CI: 0.51 to 0.92), and stroke (HR: 0.34; 95% CI: 0.18 to 0.63) were
less in the group with ≥75% of visits with BP control compared with the group
with <25% of visits with BP control. These findings were not significantly modified
when the data were analysed on the basis of two treatment groups (placebo or
nifedipine GITS).

These retrospective analyses highlight the importance of the current recommen-
dations for “tight” BP control in high risk individuals and support our previous find-
ings that early and consistent BP control is of paramount importance for reducing
vascular events in patients with established CAD.

Impact of coronary atherosclerotic burden on clinical presentation and prognosis of patients with coronary artery disease

G. Nderepa, T. Tada, M. Fusaro, L. King, M. Hadamitzky,
H.U. Haase, A. Schomig, J. Pache, A. Kastrati. German Heart
Center, Hospital rechts der Isar at the Technical University of Munich, Munich,
Germany

Background: The impact of coronary atherosclerotic burden on prognosis and
presentation of patients with coronary artery disease (CAD) is unknown. We in-
vestigated the association of coronary atherosclerotic burden with clinical out-
come and presentation as unstable angina in patients with CAD.

Methods: This study included 10647 patients with stable (n=8149) and unstable
(n=2498) CAD who underwent percutaneous coronary intervention (PCI). Coro-
nary atherosclerotic burden was assessed by Gensini score. The primary out-
come analysis was 1-year mortality.

Results: Gensini score was obtained by analysis of 131360 coronary segments.
Patients were divided into groups according to quartiles of Gensini score: <13
(1st quartile; n=2661 patients), 13 to <25 (2nd quartile; n=2611 patients), 25
to <53 (3rd quartile; n=2711 patients) and ≥53 (4th quartile; n=2665 patients).

The mean age in cases was 58.7 + 9.5 years, and 56.6 + 11.6 years in the control
group. The other characteristics like prevalence of diabetes, hypertension, coro-
nary artery bypass graft (CABG), percutaneous angioplasty (PCI) were similar
in both the groups. Clinical results showed a significant improvement in exercise
time between cases and controls 6 months after treatment with CWT (20.1 +
15.7 minutes in cases vs 10.1 + 4.2 minutes, p<0.0001). In the control group there was no improvement in angina class, func-
tional class and exercise time. Myocardial perfusion scans (99mTc gated SPECT)
showed remarkable improvement in the size, severity and nature of defects
in the cases only. Therapy was well-tolerated by all patients.

Conclusion: The present study shows that CWT application to the ischemic
myocardium in patients with refractory angina pectoris, improved symptoms and
reduced severity of ischemic areas at 6 months follow-up, compared to baseline.
No side-effects were observed. We recommend further studies to confirm the
results.

UPDATE ON INNATE AND ADAPTIVE IMMUNITY IN
CORONARY ARTERY DISEASE

Interleukin-6 promoter genetic polymorphism is
associated with the presence and the severity of
coronary artery disease

G. Hatzis, D. Toussoulis, N. Papageorgiou, A. Miliou, E. Androulakis,
Hippokration Hospital, University of Athens, 1st Department of Cardiology,
Athens, Greece

Purpose: Interleukin-6 (IL-6) is marker of inflammatory process, closely related
to the initiation and evolution of atherosclerosis. However, it remains unclear,
whether common polymorphisms within the IL-6 gene affect the mechanisms of
atherosclerosis. In the present study we examined the impact of the common
polymorphism G-174C on IL-6 gene promoter on the severity of coronary artery
disease (CAD) as well as on endothelial function.

Methods: The study population consisted of 272 patients with angiographically
documented coronary artery disease (CAD) and 160 healthy controls. The G-
174C polymorphism was determined by PCR and digestion with Sfai restriction
enzyme. Endothelial function was assessed by flow mediated dilution (FMD).

Results: The genotype distribution among the CAD patients was GG: 47.4%, GC:
30.5%, CC: 22.5%, and GG: 47.8%, GC: 43.8%, CC: 8.4% for the healthy con-
trols. Our results showed that the CC polymorphism was associated with the pres-
ence of CAD (RR=1.11, 95% CI: 1.03-1.20, p=0.05). Importantly, the present
polymorphism was also associated with the angiographic extent of CAD (X2
=11.64, p<0.001). Although, the CC homozygosity was associated with lower
rates of heart attacks, our results did not reach statistical
significant both in the CAD (3.309±1.291 vs 2.183±2.029, p<NS) and the control group (5.020±3.159 vs 3.425±1.699, p<NS).

Conclusions: We have found that the G174C polymorphism is associated with the presence and the severity of coronary artery disease. These findings may have important clinical implications since they demonstrate a significant association between a genetic polymorphism of an important inflammatory marker, such as IL-6, and the presence of coronary artery disease.

**P4464 Lipoprotein-associated phospholipase A2 (Lp-PLA2) bound on high density lipoprotein is associated with lower risk of cardiac death in stable coronary artery disease patients: a three year follow-up**

L. Radulic1, J. Lekakis1, I. Rizos1, C. Teklu2, C. Varoumis1, D. Bampieri3, A. Charalampopoulos4, M. Zolindaki3, M. Anastasiou-Nana1, A. Tsélépi5,1 Akhion University Hospital, Athens, Greece; 2University of Ioannina, Ioannina, Greece; 3General Hospital of Nikea, Piraeus, Greece

**Purpose:** Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a novel risk factor for cardiovascular disease. It has been postulated that the role of Lp-PLA2 in atherosclerosis may depend on the type of lipoprotein with which it is associated. We examined the prognostic value of Lp-PLA2 associated with high density lipoprotein (HDL) [HDL-Lp-PLA2] in patients with stable coronary artery disease (CAD)

**Methods:** Total plasma Lp-PLA2 and HDL-Lp-PLA2 mass and activity, lipids and cholesterol profiles were measured in 524 consecutive patients with stable CAD, who were followed for a median of 34 months. Primary endpoints were cardiac deaths and secondary endpoints hospitalizations for acute coronary syndrome (ACS), myocardial revascularization, arrhythmic event or stroke.

**Results:** Follow-up data were obtained by 477 patients. One hundred and twenty-three patients (25.8%) presented with cardiovascular events (24 cardiac deaths, 47 ACS, 28 revascularizations, 22 arrhythmic events, 2 strokes). Total plasma Lp-PLA2 mass and activity was correlated with lower risk of cardiac death (HR=0.972, 95% CI, 0.952 to 0.993, p<0.01) and HR=0.869, 95% CI, 0.95 to 1.076, p=0.025, respectively) after adjustment for conventional risk factors (HR=0.951, 95% CI, 0.908 to 0.996, p=0.033).

**Conclusions:** HDL-Lp-PLA2 is associated with lower risk of cardiac death in stable CAD patients, suggesting that HDL-Lp-PLA2 may significantly contribute to the antiatherogenic and cardioprotective effects of HDL.

**P4467 Patients with acute myocardial infarction and severe obstructive coronary atherosclerosis display distinct peripheral blood gene expression profiles**

D. Aronson1, Y. Drier2, M. Shmoish3, E. Domani2, E. Sprecher4, S. Nahum5,1 Ramam Health Care Campus, Haifa, Israel; 2Weizmann Institute of Science, Rehovot, Israel; 3Technion Institute of Science, Haifa, Israel; 4Tel Aviv Savyon Medical Center, Tel Aviv, Israel

**Background:** The fact that patients with severe multivessel coronary artery disease (MV-CAD) remain stable for years without developing acute coronary events, while others develop myocardial infarction (MI) as the first manifestation of CAD despite mild coronary atherosclerosis remains poorly understood. We hypothesized that gene expression in peripheral blood differs in these two populations.

**Methods:** Whole genome microarray analysis (Illumina) was performed on peripheral-blood mononuclear cells in 3 groups: 1) patients with angiographic MV-CAD (70±10% stenosis ≥ 2 vessels) but without prior MI (n=9); 2) patients with ST-elevation MI and angiographic evidence of 1-vessel disease with plaque rupture (n=14); 3) subjects with normal coronaries (NC) (n=11).

**Results:** Venn diagram of differentially expressed genes (FDR<0.2, -1.3 fold-change, P<0.05) demonstrated gene expression changes occurring predominately in the MV-CAD vs. NC group. These included genes involved in atherosclerosis and inflammation-related genes including COX-2, EGR-1 and JUNB, pro-inflammatory cytokines (IL-1β), oncostatin M, visfatin, and toll-like receptors (TLR4 and TLR6). The most notable finding in an Ingenuity pathway analysis was a graded enrichment in inflammation-related path-
Role of cd31 and cd38 in innate and adaptive immunity in patients with chronic stable angina and acute coronary syndromes

D. Flego, A. Severino, A. Giglio, V. Gallifa, T. Trotta, D. Pedicino, M. Prevereto, G. Liuzzo, F. Crea. Catholic University of the Sacred Heart, Department of Cardiovascular Medicine, Rome, Italy

Purpose: CD31 is a molecule implicated in leukocyte transendothelial migration and immunomodulation by TCR inhibition. CD31 is involved in homophilic and heterophilic binding interactions with different ligands like CD38. CD38 is a functionally pleiotropic molecule implicated in transmembrane signaling and adhesion of immune cells. Recent studies have highlighted the importance of innate and adaptive immunity in acute coronary syndromes (ACS). We aim to evaluate CD31 and CD38 expression by different monoclonal and T-cell subsets in patients with ACS compared to chronic stable angina (SA). We also analyzed CD31 signaling in CD4+ T-cells after TCR stimulation.

Methods: Consecutive patients with Non-ST elevation ACS (n=12) and SA (n=16) were enrolled. CD31 and CD38 median fluorescence intensity (MFI) of different monoclonal subsets, total CD4+ and CD4+CD28null T-cells was assessed by flow cytometry. In T-cells, CD31 signaling was assessed by ZAP-70 phosphorylation after TCR stimulation with CD3/CD28 and CD31 monoclonal antibody.

Results: Data are presented as mean ± SE. ACS patients had lower CD31 expression on monocytes and T-cell subpopulations as compared with SA (see Table), but there were no differences in CD38 expression. Moreover, ACS patients showed a reduced TCR inhibition after stimulation with CD31 monoclonal antibody of both total CD4+ T-cells (ACS=68±2.6% vs SA=19±2.2%; P<0.001) and CD4+CD28null T-cells (ACS=10±2.6% vs SA=26.8±3.2%; P=0.005). Thus, in ACS the reduced expression of CD31 is related to an impaired control of the immune response.

Conclusions: In ACS, the altered CD31/CD38 expression and the reduced functionality of CD31 pathway suggest a defective immunomodulation which could contribute to the impaired control of inflammation. Our data also support the importance of CD31-mediated signaling in modulating low-grade inflammation in SA.

Erythrocyte aggregation potends worse outcomes in unstable angina patients undergoing percutaneous coronary interventions

A. Steinvil, B. Shmuel, A. Halkin, G. Keren, A. Finkelstein, N. Mashay, M. Zuzat, S. Berliner, G. Aviram, Y. Arbel. Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Background: We have previously reported a correlation between the time from symptom onset to the appearance of an inflammatory response and erythrocyte aggregation (EA) in the peripheral blood of acute coronary syndromes (ACS) patients. We now analyze the added prognostic value of EA determination in ACS patients undergoing percutaneous coronary interventions (PCI).

Methods: We performed an analysis on prospectively collected data at a tertiary care center between 2006-2011. Cox regression models were fitted for EA and C-reactive protein (CRP) cut-offs and performed separately for myocardial infarction (MI) and unstable angina pectoris (UAP) patients. Major adverse cardiovascular events (MACE) were defined as all-cause mortality, MI and stroke. Follow-up time was defined as the time form PCI to either MACE or November 20, 2011.

Results: Included were 1055 patients (637 with MI and 418 with UAP). The median follow up in the MI and the UAP groups were 14 and 15 months, respectively (maximal follow up of 4.1 years). In the MI group, elevated CRP marginally increased the risk of MACE during follow-up with either a higher or lower EA status (HR=1.9, p=0.057; HR=1.8, p=0.129; respectively) compared to patients with low CRP and low EA. In the UAP group however, there was a significant increase in MACE for the group with high CRP and high EA (HR=4.4, p=0.000) compared to the same patients. This was not found for the group with high CRP and low EA. In general, traditional risk factors as well as coronary disease severity did not predict adverse outcomes during the follow-up period.

Conclusions: Elevated EA potends worse outcomes in UAP patients undergoing PCI who present with higher CRP concentrations.

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monocyte chemoattractant protein-1 release does not associate with athero-vascular function in human PMN.

**Background:**
Early priming and recruitment of neutrophil granulocytes (PMN) plays a crucial role in the in-duction of acute coronary syndromes. Molecular mechanisms of PMN activation after myocardial ischemia and reperfu-sion remain largely unknown. In-vitro and animal studies could show that specific intracellular protein complexes, so-called inflammasomes (e.g. Nlrp3 or AIM2) can initiate an inflammatory response by sensing host-derived danger signals (DAMPs), such as ATP and other cellular components released during tissue in-jury. The aim of the present study was to investigate the inflammasome activation and expression of mRNA for AIM2 inflammasome in PMN and its role in induction of the sterile inflammatory response in patients with ACS.

**Methods:**
75 patients (pts) with coronary heart disease (CHD) were included into this study. 50 pts with ACS (25 with STEMI, 25 with NSTEMI) and 25 pts with stable angina pectoris (SAP) were enrolled as controls (Ctrl). In an in-vitro cell culture model PMN from healthy donors (n=5) were stimulated with ATP and dsDNA. Expression of the inflammasome-associated genes was analyzed using quantitative real-time PCR (relative copy number, RCN). Protein expression was quantified using Western Blot analysis.

**Results:**
Expression of mRNA for AIM2 inflammasome was significantly higher in ACS vs. SAP as opposed to stable CHD pts (RCN 88±1.77 vs. 59.4±5.4; p=0.02) or healthy controls (88±1.77 vs. 38.8±3.7; p>0.05). This ACS-related activation remained unchanged within 12-24 hours after PCPP (p=0.8 vs. p<0.0001). AIM2 expression was higher in NSTEMI than in STEMI pts in the STEMI group (84±1.47 and 83±5.81; p=0.009 and p=0.0001 vs. Ctrl). Protein expression analysis confirmed significant induction of AIM2 in STEMI (foldchange vs. Ctrl: 5.6±1.10; p<0.001). NSTEMI pts (7.2±0.6; p=0.04) showed a trend (vs. healthy donors). In-vitro PMN stimulation with injury-associated DAMPs, dsDNA and ATP, resulted in a 5-fold increase in AIM2 protein expression.

**Conclusion:**
Our results identify the first time enhanced expression of AIM2 inflammasome in PMN in patients with acute coronary syndrome. Our data suggest that inflammasome activation in PMN contributes to the early ischemia-triggered inflammatory response. Measuring inflammasome activation may therefore provide a novel clinical parameter for improved diagnosis and risk assessment in patients with ACS.
Functional characteristics of monocytes subsets in the acute and healing phases of ST elevation myocardial infarction and their effect on ejection fraction

A. Ghattas1, G. Lip1, H. Griffiths2, E. Shantsila1. 1City Hospital, University Department of Medicine, Haemostasis Thrombosis and Vascular Biology Unit, Birmingham, United Kingdom; 2School of Life and Health Sciences, Loughborough University, Birmingham, United Kingdom

Background: Monocytes are implicated in the pathogenesis of atherosclerotic disease from initiation of atherosclerotic plaque through to plaque instability and rupture. Little is known of the numerical and functional activity of the 3 monocytes subpopulations in the acute and healing phase post ST elevation myocardial infarction in humans.

Method: 96 patients (aged 64±14; 65% male) were recruited within first 24hours post percutaneous revascularization for STEMI. Peripheral blood monocyte subsets were enumerated and characterised using flow cytometry. Monocyte subsets were defined as CD14++CD16-CCR2+ (Mon1), CD14++CD16+CCR2- (Mon2) and CD14+CD16+CCR2+ (Mon3). Functional assessment of monocyte subsets was assessed by measurement of their phagocytic activity and activation of nuclear factor kappa B (NFkB).

Results: Monocyte counts were significantly higher at day 1 compared to days 10-14. There were no statistical differences in IKK levels (p>0.05). The phagocytic activity of Mon1 and Mon2 increased during the remodeling phase (Table 1).

<table>
<thead>
<tr>
<th>Monocyte subsets</th>
<th>Day 1</th>
<th>Day 14</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon1 (cells/μL)</td>
<td>584 (200)</td>
<td>391 (123)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mon2 (cells/μL)</td>
<td>98 (59-173)</td>
<td>64 (27-87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mon3 (cells/μL)</td>
<td>64 (44-90)</td>
<td>48 (37-81)</td>
<td>0.02</td>
</tr>
<tr>
<td>Phagocytosis Mon1 (MFI)</td>
<td>104 (28)</td>
<td>115 (28)</td>
<td>0.36</td>
</tr>
<tr>
<td>Phagocytosis Mon2 (MFI)</td>
<td>84 (35)</td>
<td>109 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phagocytosis Mon3 (MFI)</td>
<td>29 (10)</td>
<td>30 (15)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

High counts of Mon2 and Mon3 at admission were predictive of a lower ejection fraction (EF) on linear regression analysis (β=0.26, p=0.02 and β=-0.32, p=0.01) respectively.

Conclusion: Monocyte counts are increased in STEMI patients in the first 24 hours post infarction, compared to levels at days 10-14. All monocyte subpopulations remained functionally at the same level of activity in the acute and healing phases, as detected by IKKβ. The phagocytic activity of the inflammatory monocytes significantly increased at day 10-14, suggesting a role in debris removal and ventricular remodeling post STEMI. Low EF was predictive by higher CRP and lower HIV infection per se.

Infection with human immunodeficiency virus is an independent predictor of increased aortic stiffness

M. Asaad, O.J. Rider, N. Nusi, E. Wainwright, A. Pitcher, J. Suttie, K. Clarke, L. Dorrell, S. Neubauer, C. Holloway. Centre for Clinical Magnetic Resonance Research, Department of Cardiovascular Medicine, Oxford, United Kingdom

Purpose: Patients with human immunodeficiency virus (HIV) infection have an increased risk of cardiovascular (CV) disease, though the contribution of viral infection, antiretroviral therapy (cART), and exposure to other CV risk factors remains unclear. As aortic pulse wave velocity (PWV), a clinical measure of aortic stiffness, is predictive of CV risk, we sought to determine the impact of HIV infection on aortic stiffness.

Methods: Patients with HIV (n=90) and controls (n=119) underwent vascular magnetic resonance imaging to assess aortic PWV between the ascending aorta and the descending pulmonary artery (PA) and the descending aorta 1 cm below the PA. PWV was calculated as Δx/Δt, where Δx is the distance between the two imaging levels and Δt is the time delay between the arrival of the pulse wave between these imaging levels. Anthropometric data and fasting venous samples were collected for all subjects.

Results: Patients and controls were matched for age (45 vs 44 years, p=0.65), systolic blood pressure (SBP 122 vs 119 mmHg, p=0.27), diastolic blood pressure (DBP 77 vs 75 mmHg, p=0.29), body mass index (26 vs 27 kg/m², p=0.17), glucose (5.1 vs 4.9 mmol/L, p=0.21) and low density lipoprotein cholesterol (1.2 vs 0.9 mmol/L, p=0.78). HIV patients had lower high density lipoprotein cholesterol (1.4 vs 1.1 mmol/L, p=0.001), higher serum triglycerides (1.6 vs 1.0, p=0.001) and higher CRP (2.9 vs 1.1 mg/L, p<0.001). Patients with HIV had higher PWV than control subjects (6.5±2.1 vs 5.6±1.2 m/s, p<0.001). There was no difference in PWV recorded in patients on protease inhibitors (n=22) compared to those on other forms of cART (n=68) (6.5±2.2 vs 6.4±1.9 m/s, p=0.84). Across all subjects, age (r=0.48, p<0.001), SBP (r=0.39, p<0.001), DBP (r=0.37, p<0.001), waist circumference (r=0.16, p=0.04), HIV infection (r=0.26, p=0.001), length of HIV infection (r=0.22, p=0.01) and smoking status (r=0.21, p=0.01) were all negatively correlated to PWV. There was no association between either nadir CD4 count (r=0.12, p=0.35) or viral load (r=0.19, p=0.09) and PWV. Using multivariable regression, HIV infection (β=0.7, p<0.01) and age (β=0.7, p<0.01) were both independent predictors of PWV (overall R²=0.34, p<0.001).

Conclusion: Patients with HIV have higher PWV when compared to matched controls. HIV infection and age are both independent predictors of PWV. As PWV is predictive of CV risk, this suggests HIV infection itself may increase CV risk via its detrimental effects on aortic stiffness.

Inflammatory capacity of peri-coronary adipose tissue may affect plaque destabilization in patients with non ST segment myocardial infarction

T. Mazurek, M. Kobylecka, J. Kochman, K. Filipiak, L. Krotcki, G. Opolski. Medical University of Warsaw, Warsaw, Poland

Background: Extravascular expression of inflammatory mediators may adversely influence coronary lesion formation and plaque stability through outside-to-inside signaling. It has been previously shown, that maximal standardized uptake value (SUV) of 18-fluorodeoxyglucose (FDG) detected by positron emission tomography in peri-coronary adipose tissue (PVAT) is greater in patients with stable coronary artery disease (CAD), than in controls. It also correlates with % of coronary stenosis. We sought to investigate, whether PVAT may influence plaque composition. We recruited 181 patients scheduled for elective CABG. The morning the day before the procedure, an 8 hours fasting period, blood samples were obtained and measured for all subjects.

Results: SUV in PVAT in NSTEMI patients was significantly greater than in other forms of CAD (LM SUV: 1.34; RCA SUV: 1.42; LAD SUV: 1.59; p=0.78). There was no significant difference between SUV in PVAT in patients with stable coronary artery disease and those on other forms of cART (n=68) (6.5±2.2 vs 6.4±1.9 m/s, p=0.84). Across all subjects, age (r=0.48, p<0.001), SBP (r=0.39, p<0.001), DBP (r=0.37, p<0.001), waist circumference (r=0.16, p=0.04), HIV infection (r=0.26, p=0.001), length of HIV infection (r=0.22, p=0.01) and smoking status (r=0.21, p=0.01) were all negatively correlated to PWV. There was no association between either nadir CD4 count (r=0.12, p=0.35) or viral load (r=0.19, p=0.09) and PWV. Using multivariable regression, HIV infection (β=0.7, p<0.01) and age (β=0.7, p<0.01) were both independent predictors of PWV (overall R²=0.34, p<0.001).

Conclusion: Patients with HIV have higher PWV when compared to matched controls. HIV infection and age are both independent predictors of PWV. As PWV is predictive of CV risk, this suggests HIV infection itself may increase CV risk via its detrimental effects on aortic stiffness.

Low-inflammation and post-operative clinical outcome in elective coronary artery bypass surgery: the emerging role of monocyte chemokine protein 1

M. Demesthenou1, C. Antoniades1, D. Tousoulis1, A.S. Antonopoulos1, A. Milou2, C. Bakogiannis2, C. Pinard2, N. Kounalakis3, N. Stylianou3, C. Stefanadis1, 1Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece; 2Hippokration General Hospital, Athens, Greece

Background: Low-inflammation is strongly involved in the pathophysiology of the pericoronary stent disease. However, the role of inflammation on clinical outcome post coronary bypass surgery (CABG) is unclear. We explored the role of key components of low-grade inflammation such as interleukin 6 (IL-6), C-reactive protein (CRP) and monocyte chemokine protein 1 (MCP-1) in clinical outcome of patients undergoing elective CABG.

Methods: We recruited 181 patients scheduled for elective CABG. The morning before the operation, following an 8 hours fasting period, blood samples were obtained and measured for all subjects. MCP-1 (as a continuous variable) was a strong predictor of the length of hospital stay (p<0.001), independence of risk factors, Euroscore, extend of coronary artery disease and left ventricular ejection fraction postoperatively.

Conclusions: Low MCP-1 levels are associated with decreased length of stay following CABG, whereas CRP levels (the most commonly used inflammatory biomarker) failed to predict the length of hospitalization in these patients. These

Update on innate and adaptive immunity in coronary artery disease

787

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At multivariate regression analysis, N/L ratio was still independent predictor of no-reflow (OR 1.537, 95% CI 1.343–1.759; p < 0.001) and in-hospital MACE (OR 1.137, 95% CI 0.981–1.315; p = 0.043).

P4481 Higher plasma levels of plateaued derived growth factor and matrix metalloproteinase-9 in coronary artery disease in patients with acute myocardial infarction

T. Koizumi, K. Sugii, J. Tanzo, J. Sato, T. Kikukata, S. Nakano, T. Muramatsu, N. Komiyama, S. Nishimura, Saitama International Medical Center, Saitama Medical University, Hidaka, Japan

Background: Platelet derived growth factor (PDGF) is potent mitogen and chemotactant for vascular smooth muscle cells (SMC). Oxidized low-density lipoprotein (LDL) is thought to trigger some intracellular signaling and to influence the activity of PDGF. Also, linking of PDGF to matrix metalloproteinase (MMP), which is involved in a degradation of extracellular matrix proteins leading to the migration of SMC into the intima and to the rupture of plaques, has been reported in animal studies. However, those interactions in human in vivo studies have not been fully elucidated.

Methods: Consecutive thirty two patients (age 63±11 year-old, diabetes 35%) with ST-segment elevation myocardial infarction (STEMI) who underwent percutaneous coronary intervention (PCI) within 12-hours after the onset were enrolled in this study. Plasma levels of PDGF BB, MMP-9, malondialdehyde-modified low-density lipoprotein (MDA-LDL) and high sensitive C-reactive protein (hs-CRP) were measured from infarct-related artery (IRA) using thrombus aspiration catheter and from femoral artery (FA) during PCI. These biomarkers were measured from patients with normal coronary artery as control.

Results: Total ischemic time was 289±196 mm. In the IRA, plasma levels of PDGF BB and MMP-9 were significantly higher than those in the FA (PDGF BB: 2928±1796 pg/ml vs. 2050±1236 pg/ml, p < 0.01, MMP: 86.0±95.0 ng/ml vs. 62.1±62.3 ng/ml, p = 0.03, IRA and FA, respectively). However, MDA-LDL and hs-CRP were not different between IRA and FA during PCI (MDA-LDL: 60.2±15.9 μU vs. 62.2±13.7 μU, p=0.56, hs-CRP: 1735±2686 ng/ml vs. 1816±2671 ng/ml, p=0.11, IRA and FA, respectively). Plasma levels of those markers did not increase in both coronary and femoral arteries in control patients.

Conclusions: This in vivo study demonstrated that PDGF BB with MMP-9 seems to play a role in coronary plaque instability or rupture in patients with STEMI. However, oxidized LDL and hs-CRP did not increase in IRA in acute phase of STEMI.
independent predictor of ACh induced CAS (OR: 1.5, **p**<0.01, 95% Cl: 1.1-2.0), and myocardial bridge (MB) was also an independent predictor of ACh induced CAS (OR: 3.2, **p**<0.01, 95% Cl:2.1-4.9).

### Table 1. Methathesina analysis of ACh-induced CAS

<table>
<thead>
<tr>
<th>Variable (%)</th>
<th>Positive</th>
<th>Oddsratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.69</td>
<td>1.813</td>
<td>0.999-1.825</td>
</tr>
<tr>
<td>High CRP (mg/dL)</td>
<td>0.010</td>
<td>1.504</td>
<td>1.162-2.955</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.768</td>
<td>0.993</td>
<td>0.954-1.037</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.602</td>
<td>0.876</td>
<td>0.683-1.120</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.324</td>
<td>0.786</td>
<td>0.453-1.398</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.329</td>
<td>0.820</td>
<td>0.523-1.274</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.191</td>
<td>1.099</td>
<td>0.763-1.573</td>
</tr>
<tr>
<td>Current Alcohol</td>
<td>0.682</td>
<td>1.685</td>
<td>0.771-3.758</td>
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**Baseline ovans (narrowing of 30%)**

<table>
<thead>
<tr>
<th>Occlusion (%)</th>
<th>Positive</th>
<th>Oddsratio</th>
<th>95% CI</th>
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<tr>
<td>Current Alcohol</td>
<td>0.682</td>
<td>1.685</td>
<td>0.771-3.758</td>
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</table>

**Conclusion:** In this study, female pts, high hs CRP and MB were independent predictors of ACh induced CAS. Therefore, the more intensive antithrombotic treatment would be required in female pts with high hs CRP.

### P4483 Suppression of iron metabolism pathway and improvement of cardiac function by erythropoietin administration in patients with acute myocardial infarction

M. Oda1, K. Toba1, K. Kato1, T. Ozawa1, T. Suzuki1, H. Suzuki2, N. Tomosugi2, Y. Azawa3, 1Niigata University Medical and Dental Hospital, Niigata, Japan; 2Showa University Fujigaoka Hospital, Yokohama, Japan; 3Kanazawa Medical University, Kanazawa, Japan; 4Tachikawa Medical Center, Nagasaki, Japan

**Purpose:** Erythropoietin has been shown to have anti-apoptotic and tissue protective effects on the myocardium in experimental studies. However, the clinical effects of administration of erythropoietin on iron metabolism substances and cardiac function in patients with acute myocardial infarction.

**Methods and Results:** This study included 36 patients (61±11 years, 6 females) with acute myocardial infarction who received successful percutaneous coronary intervention within 24 hours after the onset of myocardial infarction. Patients were randomly assigned to receive intravenous injection of either erythropoietin (12,000 IU/body) or saline placebo within 24 hours after the onset of myocardial infarction in the control group (Figure). However, these changes were not found in the erythropoietin group. Left ventricular ejection fraction was significantly increased after 6 months of the onset of myocardial infarction in the erythropoietin group (from 51±20% to 59±15%, **P**<0.02), but was not changed in the control group (from 47±16% to 51±16%, **P**=NS). Erythropoietin administration did not result in increased adverse clinical events.

**Figure 1:** Inotropic treatment, a marker of cardiac function during ischemia.

### P4484 Low T3 syndrome and inflammation in patients with ST-elevation myocardial infarction

E. Giall1, N. Botto2, U. Paradossi2, A. Mazzone2, M. Baroni2, C. Palmieri1, M. Ravani2, A. Clerico1, G. Iervasi3, S. Bert3, 1Ann Anna School of Advanced Studies, Pisa, Italy; 2Gabriele Monasterio Foundation/CNR, Heart Hospital, Massa, Italy; 3Institute of Clinical Physiology of CNR, Pisa, Italy

An altered thyroid hormone (TH) metabolism known as Low T3 syndrome (LT3S) is a frequent finding in patients with severe illness and is associated with a poor prognosis.

**Aim of this study is to evaluate the relationship between LT3S and inflammatory status in patients with ST-elevation myocardial infarction (STEMI).**

**Methods:** 120 pts (72±9.6 years, mean age 68±12.5 years) admitted for STEMI and subjected to early reperfusion therapy were included in this study. Routine biohumoral exams including haemoglobin, creatinine, TH, C-reactive protein (CRP), fibrinogen dosage and erythrocyte sedimentation rate (ESR) were performed at admission. Left ventricular ejection fraction (LVEF) was determined by echocardiography within 48 hours after admission.

**Results:** LT3S (T3 <2.2 pmol/l) was observed in 228 (17%) patients. These subjects were older (71±12 vs 64±12 years, **P**<0.001), had lower haemoglobin (12.8±1.8 vs 13.8±1.6 g/dl, **P**<0.0001) and higher creatinine (1.2±0.6 vs 0.9±0.4 mg/dl, **P**<0.0001), CRP (4.4±6.1 vs 1±4.2±8 mg/dl, **P**<0.0001), fibrinogen (337±6±102.5 mg/dl, **P**<0.0001) and ESR (52±2.1 vs 25.6 vs 21.4±2.1 mm/h, **P**<0.0001). A lower LVEF (41.5±10.7 vs 44.9±9.5%, **P**<0.0001) was found in LT3S patients.

**Conclusions:** LT3S is associated with a worse clinical status, a greater degree of inflammatory activation and a lower ejection fraction in patients with STEMI. In these subjects, an altered TH metabolism and enhanced inflammation may contribute to post-ischemic myocardial dysfunction and progression towards heart failure.

### P4485 High C-reactive protein is a better predictor of occult coronary artery disease than low testosterone in asymptomatic men less than 60 years with erectile dysfunction

D. Terentes-Printzios1, C. Vlachopoulos1, N. Ioakeimidis1, A. Aggelis1, A. Syrrinosis2, P. Xaplanteris1, K. Rokkas1, A. Sametzas2, K. Aznaouridis1, C. Stefanadis1. 1Hippokration General Hospital, Athens, Greece; 2Epsom General Hospital, Athens, Greece

**Purpose:** Erectile dysfunction (ED) and coronary artery disease (CAD) share common basis of etiology and progression. Links include inflammation and low total testosterone (TT) level, however the diagnostic performance of these mechanisms for prediction of CAD in young vs older ED patients is unknown.

**Methods:** A total of 115 asymptomatic ED patients in whom a comprehensive assessment revealed CAD were studied. They were divided into two age groups: a young group (< 60 y/o, n=57, Group A) and an elderly group (> 60 y/o, n=58, Group B). Two groups of 57 (< 60 y/o) and 58 (> 60 y/o) ED patients without CAD, matched for age and risk factors with Group A and Group B patients respectively, served as controls.

**Results:** Group A patients had higher CRP level compared to Group B patients, while TT level was significantly lower in Group B patients than that of Group A patients (all **P**<0.01). In both age categories CAD patients had significantly increased CRP levels and decreased TT concentration (all **P**<0.01) compared to non CAD subjects. ROC analysis for CAD prediction showed that in young population (CAD and non-CAD ED patients), the area under the curve (AUC) for CRP was significantly greater than the AUC for TT (difference between AUCs 18%, **P**<0.05, left plot). On the contrary, the diagnostic performance of CRP and TT in the elderly population was similar (right plot). In young men a CRP level of 1.73 mg/l was associated with a sensitivity of 79% and a specificity of 68% for CAD prediction.

**Conclusions:** In young ED patients the diagnostic performance of CRP for the early detection of CAD is higher than that of TT. This finding underscores the pathophysiological involvement of inflammatory activation in young ED patients.
A gene expression was estimated by the number of mRNA copies per one microgram of total RNA sample.

Results: The gene expression of TGFα1 and its receptors in peripheral blood mononuclear cells was estimated with QRT-PCR technique in the study group patients with ACS and in the control group of healthy subjects - Table 1.

Conclusions: Significantly reduced gene expression of TGFα1 and its receptors in PBMCs of patients with severe stable CAD than in healthy controls. Alterations in the expression profile of early cardiac genes according to the disease severity in the early cardiac gene expression in peripheral blood of stable CAD patients, possibly reflecting alterations in circulating cardiac progenitor cells expressing these genes, may reflect the level of disease severity.

Purpose: The early cardiac genes myocardin, GATA4 and Nkx2.5, play a role in both embryonic cardiovascular development and adult cardiovascular disease. We evaluated transcript levels of myocardin, GATA4 and Nkx2.5 in peripheral blood mononuclear cells (PBMCs) in patients with stable coronary artery disease (CAD) and we examined the relationship between these levels and the severity of the disease, estimated by the number of stenotic vessels involved.

Methods: 98 patients with stable CAD (aged 68±13 years) who underwent coronary angiography participated in the study, 66 healthy individuals (aged 58±13 years) were also included for comparison. Gene transcript levels were determined by quantitative real-time reverse transcription PCR.

Conclusions: Early cardiac gene transcript levels are significantly higher in PBMCs of patients with severe stable CAD than in healthy controls. Alterations in the expression profile of early cardiac genes according to the disease severity were also observed. Our results indicate for the first time, that alterations in the early cardiac gene expression in peripheral blood of stable CAD patients, possibly reflecting alterations in circulating cardiac progenitor cells expressing these genes, may reflect the level of disease severity.

Introduction: Gamma-glutamyltransferase (GGT) is a well known a prognostic marker in patients with heart failure and stable coronary artery disease. The aim of this study is to define the relationship between GGT activity, systemic inflammation, myocardial infarction and in-hospital mortality in patients with ST-elevation myocardial infarction. GGT is a marker for liver disease, chronic kidney disease, chronic inflammation, diabetes, and myocardial infarction. We hypothesized that GGT is independently associated with 6-month mortality compared with any other single cytokine. Of note, within the combination of cytokines measured in patients with ST-elevation acute myocardial infarction (STEMI), as first cardiovascular manifestation.

Purpose: The epicardial thrombus burden and distal macro- and microembolization are associated with perfusion deterioration during acute phase of ST-segment elevation myocardial infarction (STEMI) but their influence on microvascular obstruction remains poorly understood. We sought to investigate the quantitative impact of ex vivo measured fibrin clot properties and platelet function on microvascular obstruction (MVO) territory after primary coronary intervention (PCI).

Methods: Plasma clot permeability (Ks) and clot susceptibility to lysis in assays using exogenous thrombin (500%, min) were prospectively assessed in 108 STEMI patients on admission (ADM) and 4 months after PCI (MA) whereas platelet aggregation after stimulation with 5 μM of adenosine diphosphate (ADP5, %) and platelet-monocyte aggregates (PMA, %) were measured on admission (ADM) and 4 days (D4) after PCI. The MVO (expressed as % of infarct size) and infarct size (expressed as % of left ventricular mass) were determined by magnetic resonance imaging performed 2-4 days after STEMI.

Results: During acute phase of STEMI core size of fibrin clot was lower by 28% (6.2% vs. 7.1%, P<0.001) and clot lysis time was 49% by 20% (10.7 vs. 8.9 min, P<0.001) as compared to follow-up measurements. The area of MVO was correlated with infarct size (r=0.67, P<0.001), Ks-ADM (r=0.58, P<0.001), epidermal blood flow after PCI measured by TiMi scale (r=0.33, P<0.001) and PMA (r=0.28, P<0.019). All clinical variability that showed the association (P<0.2) with the size of MVO in univariate model were included in the multiple model, explained 68.3% of variance for MVO area. The strongest independent predictor of MVO territory was infarct size (r=0.57, 27.2% of variance, P<0.001).
Prevalence of microvascular obstruction after primary percutaneous coronary intervention is higher in male patients with hypogonadism

Catholic University of the Sacred Heart, Rome, Italy

Background: Testosterone deficiency affects approximately 30% of men aged from 40-79 years. Recent studies claimed that androgen deficiency contributes to the onset and progression of cardiovascular disease. Microvascular obstruction (MO) is a common event associated with a worse prognosis and unfavorable left ventricular remodeling after primary percutaneous coronary intervention (P-PCI). However mechanisms involved in MO have not been fully elucidated yet. We evaluated the importance of gonadal function in the onset of MO.

Methods: 70 consecutives male patients (57±0.42 years) presenting with STEMI myocardial infarction (STEMI), underwent P-PCI within 12 h of symptoms onset and 30 control male patients (60±0.85 years) with stable angina were enrolled. Drug-induced MO was assessed among clinical, angiographic and laboratory data including Testosterone (T), Estradiol (E2), LH, FSH. Prevalence of male hypogonadism (T < 2.5 ng/ml) was calculated in STEMI and control patients.

Results: In STEMI patients T levels were significantly lower (2.15±0.32 ng/ml p=0.01). Consistently LH and FSH were significantly higher in patients with STEMI. Hypogonadism was present in 43 STEMI patients (61%) and in 10 control patients (33%) (p=0.001). MO was documented in 13 subjects (18.6%) after P-PCI. Among patients affected by MO, T, 3 were hypogonadal (69.2%). This prevalence was significantly higher when compared to patients with normal myocardial reperfusion after P-PCI (59.6% p=0.005).

Conclusions: Androgen deficiency is associated with an higher prevalence of MO in patients with STEMI undergoing P-PCI. Further studies are required to unveil the complete role of T in the pathogenesis of MO. T might be considered a novel diagnostic target to stratify patients with higher risk to develop MO after STEMI.

Correlation between coronary microvascular function and stability of microvascular angina

Catholic University of the Sacred Heart, Department of Cardiovascular Medicine, Rome, Italy

Purpose: To assess whether, in patients with microvascular angina (MVA; effort angina, positive exercise stress test [EST] and normal coronary arteries), the effects of exercise on angina status and quality of life (QoL) are related to changes in coronary microvascular function.

Methods: We studied 51 patients (59±10; 15 men) with a new diagnosis of MVA. Coronary blood flow response (CBFR) to adenosine and to cold pressor test (CPT), Seattle Angina Questionnaire (SAQ) and EuroQol scale for QoL were assessed at baseline, in pharmacological washout, and at 12-month follow-up under antiischemic therapy. Patients were divided into 2 groups: 1) Group 1 included patients with no improvement of MVA. (EuroQol score change <10 points); 2) Group 2 included patients with QoL improvement (increase in EuroQol score ≥10 points).

Results: Group 1 and Group 2 had similar SAQ scores and EuroQol score. Together with EuroQol score, a significant improvement of SAQ scores were observed in Group 2, but not in Group 1 (Table). At 12-month follow-up the 2 groups did not differ for use of beta-blockers (27% vs. 88% in Group 1 and 2, respectively; p=0.001) whereas no differences were found for other anti-Ischemic drugs. At baseline CBFR to adenosine (1.70±0.3 vs. 1.72±0.4; p=0.15) and to CPT (1.56±0.4 vs. 1.56±0.3; p=0.29) were similar in the 2 groups. At follow-up a similar significant improvement was observed in the 2 groups for both CBFR to adenosine (2.05±0.2 vs. 2.05±0.21; p=0.96) and to CPT (1.8±0.42 vs. 1.7±0.25; p=0.8).

Conclusions: In MVA patients the improvement in angina status and QoL was not related to changes in coronary microvascular function, suggesting that other features (e.g., abnormal cardiac pain sensitivity) play a significant role in the symptomatic state of patients.

The index of microcirculatory resistance was strongly associated with infant size only in anterior ST-segment elevation myocardial infarction, but not in non-anterior STEMI

H. Shibata, N. Ito, A. Tsurooka, Y. Kuruzumi, N. Yamada, T. Natsukawa, K. Okada, H. Sawano, Y. DAI, T. Hayashi. Saiseikai Senn Hoshini Hospital, Suita, Japan

Background: Previous reports showed that the index of microcirculatory resistance (IMR) after primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI), correlated with infant size and recovery of left ventricular function. However, the regional differences of IMR have not been well-evaluated.

Methods: We studied 54 patients with stable effort angina and known positive EST. 29 patients had angiographically normal coronary arteries (MVA), whereas 25 patients showed significant (>75%) stenosis in >1 epicardial coronary artery (CAD). Patients underwent 2 maximal treadmill ESTs on 2 separate days, in a random sequence, after withdrawing all medications: one EST without any intervention (control EST) and one EST after sublingual administration of isosorbide dinitrate, 5 mg (ISDN-EST). CBFR response to nitroglycerin (25 μg) was assessed in the left anterior descending coronary artery by means of transcoronary echo-Doppler.

Results: ST-segment depression ≥1 mm (STD) at the control EST was induced in 26 (90%) and in 24 (96%) of MVA and CAD patients, respectively (p=0.41), whereas at the ISDN-EST, STD was induced in 25 (86%) patients with MVA, but in only 14 (56%) patients with CAD (p=0.01). At control EST maximal STD was similar in MVA patients (1.5±0.7 vs. 1.3±0.4, respectively, p=0.07); at ISDN-EST maximal STD did not change in MVA patients, whereas it was significantly reduced in CAD patients (1.5±0.7 vs. 1.3±0.6, p=0.15 and 1.3±0.4 vs. 0.8±0.6, p=0.01, respectively). In MVA patients, rate-pressure product (RPP) at 1 mm STD at ISDN-EST and at the control EST was 2129±5438 and 2018±4286 bpm·mmHg, respectively (p=0.35); the same RPP values in CAD patients were 2265±5014 and 2073±6901 bpm·mmHg, respectively (p=0.03). In MVA patients, time to 1 mm STD at ISDN-EST and at the control EST was 308±160 and 284±136 s, respectively (p=0.19); the same values in CAD patients were 474±112 and 367±135 s, respectively (p=0.01). CBFR response to NTG was significantly lower in MVA compared to CAD patients (1.4±0.3 vs. 1.7±0.3; p=0.01); in MVA patients a significant correlation was found between CBFR response to NTG and heart rate at STD during ISDN-EST (r=0.40, p=0.04).

Conclusions: Among patients with effort angina, short-acting nitrates improve EST results in CAD, but not in MVA patients. A lower NTG-induced coronary microvascular dilation seems to contribute to EST positivity after nitrogлицerin administration in patients with MVA.
Objective: We investigated the correlation between IMR and infarct size in ante-
or and non-anterior STEMI.

Method: We investigated 104 patients who underwent successful pPCI for STEMI within 12 hours after onset between April 2009 and March 2011. CK-MB was measured 1, 2, 4, 6, 9, 12, 18, 24, 48, 96 hours after pPCI, and the area under the curve of CK-MB (CK-MB AUC) was calculated as the index of infarct size. We evaluated the IMR as the quantitative index of microvascular dysfunction. After successful pPCI, IMR was measured using a PressureWireTM Certus (St. Jude Medical, USA) at maximal hyperemia.

Result: There was a significant correlation between IMR and infarct size in ante-
or STEMI. However, this finding was not observed in non-anterior STEMI.

Conclusion: IMR may predict infarct size in only anterior STEMI, but not in non-
anterior STEMI.

P4495 Quantitative analysis of microvascular obstruction is best related to clinical prognosis than clinical markers at a 1 year follow-up: a contrast-enhanced MRI study

L. Biere1, M. Le Nezet1, G. Clerfond1, V. Mateus1, S. Grall1, J. Jeanneteau1, P. Prunier1, S. Willoteaux2, A. Elnagar1, S. W. Kim1, C. U. Choi1, D. J. Oh1, S. W. Kim2

Objective: To evaluate the clinical prognostic value of a cardiac magnetic res-
sonance (CMR) assessment soon after a first ST-segment elevation myocardial infarction (STEMI).

Background: Clinical factors such as gender, age, blood pressure, heart beat, heart and renal failure have already been described as related to poor clinical prognosis at follow-up. For now, the prognostic value and cost of CMR param-
eters is not well-defined.

Methods: We followed for 1 year up to 168 consecutive patients with a first STEMI treated with primary angioplasty. We performed CMR at day 5±2 and 3 months to assess LV volumes. We used delayed enhancement imaging to assess the infarct size and the presence of MVO. We defined severe MVO as MVO extent being superior to its median value (2.85 g).

Results: 13 major adverse cardiac events (MACCE) including 2 cardiac deaths, 1 nonfatal myocardial infarctions, 8 readmissions for heart failure and/or stroke were documented. In univariate analysis, the IMR was related to age, creatinine peak, heart failure, MVO and LV volumes. In a complete multivariate analysis, age and deep T wave invesion. The patients were divided two groups according to clinical markers at a 1 year follow-up: a contrast-enhanced MRI study

Conclusions: A comprehensive CMR assessment is useful for stratifying risk soon after STEMI; baseline LV volumes and severe MVO are the stronger inde-
pendent prognostic factor. This result supports the clinical interest of a quantitative assessment of MVO.

P4496 Coronary microvascular function is impaired in diabetic patients with normal coronary arteries and correlates to renal function

C. Marciano1, M. Galdieri2, C. D’Amore1, R. Esposito2, P. Gargiulo1, L. Casaretto1, R. Formisano1, F. Lo Ludic1, M. Cecere1, P. Perrone Filardi1

Objective: Endothelial dysfunction is thought to represent a common pathogenic mechanism of impaired coronary flow reserve (CFR) and renal dysfunction in pa-
tients with type 2 diabetes mellitus (DM), yet no data are available on the relation-
ship between CFR and renal function in these patients.

Methods: In the same day, while off drugs, we studied endothelial-dependent,
during cold pressure test (CPT), and independent (dipyridamole infusion (Dip) 0.84 mg/kg over 6 minutes) CFR using transthoracic Doppler echocardiography of the left descending coronary artery in 23 DM (12 men; age 62±10; and 25 non DM patients (17 men; age 81±10), matched for all other cardiovascular risk factors. Glomerular filtration rate (GFR) was estimated by Cockcroft Gault formula in the same day of CFR studies. All patients had no significant coronary artery disease (CAD) at invasive coronary angiography performed within 7 days from CFR.

Results: CFR-CPR (1.46±0.26 in DM vs 1.70±0.33 in non-DM; p=0.007) and Dip-CFR (2.38±0.74 in DM vs 2.76±0.04 in non DM; p=0.04) were significantly lower in DM patients. GFR did not statistically differ between DM and non DM patients (85.28±86±25 mL/min/1.73m²; respectively; p=0.96) with 42% of pa-
tients in class I and 58% in class II-III renal dysfunction. In DM patients a strong significant direct correlation was found between GFR and CFR-CPR (r=0.55; p=0.007), but not between CFR and Dip-CFR. In DM patients with GFR above the median (75 mL/min/1.73m²); CFR-CPR was significantly higher (1.52±0.19) than in DM patients with GFR below the median (1.33±0.20; p=0.003), whereas no dif-
fERENCE was found for Dip-CFR (2.48±0.75 vs 2.30±0.70; p=0.57). Moreover, a weak significant correlation was found between fasting glycemia and CFR-CPR (r=0.34; p=0.016) but not with Dip-CFR.

Conclusion: In DM patients without epicardial coronary stenosis microvascu-
lar function is significantly impaired compared to non DM patients with similar risk factors. However, only endothelial dependent CFR significantly correlates to GFR. These findings support the role of endothelial dysfunction as common pathogenetic mechanism of renal and myocardial dysfunction in DM patients.

P4497 The Impact of ECG Change during Intracoronary Acetylcholine Provocation test on the 12 months Clinical Outcomes in Korean patients

S.W. Rha1, J.Y. Park1, S.K. Ryu2, J.W. Choi3, B.G. Choi1, A. Elnagar1, S.I. Im1, S.W. Kim1, C.U. Choi1, D.J. Oh1, S. W. Rha1

Background: The ischemic electrocardiography (ECG) changes are known to be a predictor of ischemic heart disease. However, whether the ischemic ECG changes occurred during acetylcholine (Ach) provocation test is associated with clinical outcome is largely unknown. We evaluated the impact of ischemic ECG changes occurred during Ach test on Ach induced coronary artery spasm (CAS) and 12 months clinical outcomes.

Methods: A total 2441 consecutive pts without significant coronary artery disease who underwent the Ach test were enrolled between November 2004 and Octo-
ber 2010. Ischemic ECG changes were defined as ST elevation, ST depression, and deep T wave inversion. The patients were divided two groups according to ischemic ECG changes occurred during Ach test (ischemic ECG changes group: n=88, control group: n=1305).

Results: At baseline characteristics, there were no differences between two groups. At angiographic characteristics, the incidence of basal spasm (43.8% vs 30.7, p=0.010), multivessel (58.4% vs 36.9%, p=0.003) and diffuse (92.1% vs 81.0%, p=0.001) spasm were higher in the pts with ischemic ECG changes. At 12 month clinical outcomes, the incidence of cardiac death (2.2% vs 0.0%, p=0.001) and myocardial infarction (1.1% vs 0.0%, p=0.001) were higher in the pts with ischemic ECG changes (table). Multivariate analysis showed that the is-
chemic ECG change was an independent predictor of mortality (odds ratio: 125.3, 95% confidence interval: 3.5-4472, p=0.008) up to 12 months.

Table 1. 12 months clinical outcomes

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Ischemic ECG Change (n=88)</th>
<th>Control (n=1305)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2 (2.2)</td>
<td>2 (0.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (2.2)</td>
<td>0 (0.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1.1)</td>
<td>7 (0.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PTCa</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>CVA</td>
<td>0 (0.0)</td>
<td>4 (0.3)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Conclusion: In this study, ischemic ECG change occurred during Ach test was associated to 12-month clinical outcomes. Therefore, if the ischemic ECG change was observed during Ach test, intensive antiarrhythmic treatments and close clinical follow up would be needed.

P4498 Association of myocardial bridge and acetylcholine induced coronary artery spasm and 12-months clinical outcomes

S.W. Rha1, J.Y. Park1, S.K. Ryu2, J.W. Choi3, B.G. Choi1, A. Elnagar1, S.I. Im1, S.W. Kim1, C.U. Choi1, D.J. Oh1, S. W. Rha1

Background: Myocardial bridge is known to be a strong predictor of coronary artery spasm (CAS). However, whether myocardial bridge (MB) is associated with clinical outcomes is largely unknown. We evaluated the impact of MB on CAS induced by acetylcholine (ACh) provocation test and 12 months clinical outcomes.

Methods: A total 2441 consecutive patients (pts) without significant coronary
artery disease who underwent the ACh test were enrolled between November 2004 and October 2010. The pts were divided into two groups according to MB (MB group: n=367, control group: n=1027).

Results: At baseline characteristics, the pts with MB had higher incidence of old age (53.9 ± 11.6 vs 55.6 ± 11.5, p=0.0168), male gender (59.9% vs 46.6%, p=0.0002), and hyperlipidemia (13.6% vs 18.3%, p=0.0486) than the pts in control group. At ACh provocation test, the pts with MB had higher incidence of Ach induced CAS, multivessel and diffuse spasm than the pts in control group (Table 1). Multivariate analysis showed that MB was a predictor of ACh-induced CAS (odds ratio: 2.885, 95% confidence interval: 2.2-3.7, p<0.001). However, At 12 month clinical outcomes, there were no significant difference between two groups (Table 1).

Table 1. 12 months clinical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>MB (n=367)</th>
<th>Control (n=1027)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCE</td>
<td>5 (1.4)</td>
<td>8 (0.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (0.2)</td>
<td>3 (0.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0 (0)</td>
<td>2 (0.1)</td>
<td>0.39</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>PTCA</td>
<td>2 (0.5)</td>
<td>6 (0.5)</td>
<td>0.93</td>
</tr>
<tr>
<td>CVA</td>
<td>2 (0.5)</td>
<td>2 (0.1)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Conclusion: In this study, MB was associated with ACh induced CAS, and multivessel and diffuse spasm. But MB was not associated with the 12-months clinical outcomes.

**P4499**

**Twelve months clinical outcomes of diffuse coronary artery spasm as compared with focal coronary artery spasm**

S.Y. Choi, S.W. Rha, A. Elanagar, S.I. Im, S.W. Kim, S.W. Han, C.U. Choi, C.G. Park, H.S. Seo, D.J. Oh. Korea University Guro Hospital, Seoul, Korea, Republic of

**Background:** There are limited data regarding features & outcome of diffuse coronary artery spasm (CAS) in patients (pts) with vasospastic angina. We investigated whether diffuse CAS have specific procedure related features and its clinical outcome as compared with focal CAS.

**Methods:** A total 1384 consecutive pts (Men: 721 (52.1%), mean age: 55.1 ± 11.6 years), who underwent intracoronary ACh provocation test. Provocation test was performed by intracoronary injection of incremental dosages (20, 50, 100ug) of Ach. The study population were divided into focal spasm group (areas <30mm) and diffuse spasm group (areas >30mm). Significant CAS was defined as more than >70% luminal narrowing with chest pain with/without ST segment changes.

**Results:** Baseline characteristics were similar between the two groups except that diffuse spasm group had a higher body mass index (24.3 ± 3.2 vs 23.9 ± 2.9, p=0.067) & lower ejection fraction (58.6 ± 4.2 vs 59.1 ± 2.7, p=0.049). Regarding procedure related characteristics, diffuse spasm group had a higher incidence of chest pain, multi-vessel spasm, and ischemic EKG changes. At twelve months clinical follow up, there was a trend towards higher MACCE in focal spasm group (table 1, 2).

**Conclusion:** In our study, current alcohol use was not associated with clinical and angiographic parameters of ACh provocation test were not different between the two groups (Table).

**P4500**

**Impact of alcohol on coronary artery spasm as assessed with intracoronary acetylcholine provocation test**

S.W. Rha, B.G. Choi, A. Elanagar, S.I. Im, S.W. Kim, C.U. Choi, J.W. Kim, C.G. Pak, H.S. Seo, D.J. Oh. Korea University Guro Hospital, Seoul, Korea, Republic of

**Background:** There are limited data regarding impact of chronic alcohol use on vasospastic angina. We evaluated the impact of alcohol use on coronary artery spasm (CAS) as assessed with intracoronary acetylcholine (ACh) provocation test.

**Methods:** A total 3034 consecutive patients (pts, Men 1457 (48.0%), mean age 54.5 ± 12.4 years who underwent coronary angiography with ACh provocation test were enrolled. Study population were divided into current alcoholic (912, 30.1%) vs. non alcoholic (2101, 69.2%) groups. Significant CAS was defined as transient >70% luminal narrowing with chest pain and/or ST segment changes.

**Results:** Baseline clinical characteristics were balanced except non alcoholic had more hypertension (49.3% vs. 40.4%, P<0.001), diabetes (13.6% vs. 10.2%, P<0.009), peripheral vascular disease (6.3% vs 3.2%, P<0.001), history of CVA (3.5% vs.2.1%, P<0.041), congestive heart failure (2.0% vs.0.5%, P=0.004) whereas alcoholic group were mostly men (76.5% vs 35.8%,P<0.001) and had more current smokers (42.8% vs. 13.6%,P<0.001). Although the alcoholic group showed higher incidence of myocardial bridge, Ach induced CAS, and severe narrowing on QCA on univariate analyses, however, after adjusting the baseline differences, all clinical and angiographic parameters of Ach provocation test were not different between the two groups (Table).

**Conclusion:** In our study, current alcohol use was not associated with clinical and angiographic characteristics of CAS as assessed with ACh provocation test.

**CONDITIONING AND OXYDATIVE STRESS: FROM BENCH TO PRACTICE**

**P4501**

**Exendin-4 postconditioning is not effective in hearts isolated from hypertensive SHR-SP rats with left ventricular hypertrophy**

B. Faricelli1, M. Salomonsson1, A. Consoli2, T. Engstroem3, M. Treiman1. 1University of Copenhagen, Faculty of Health Sciences, Department of Biomedical Science, Copenhagen, Denmark; 2G. D’Aranzzu University, Department of Medicine and Aging Sciences, Chieti, Italy; 3Rigshospitalet - Copenhagen University Hospital, Heart Centre, Cardiac Catheterization Laboratory, Copenhagen, Denmark

**Purpose:** Exendin-4 (ex4) postconditioning has been shown to limit reperfusion injury (RI) in experimental [1] and clinical [2] settings. Left ventricle hypertrophy (LVH) may be associated with increased RI. Few studies have addressed the efficacy of various conditioning treatments for RI in LVH. We studied ex4- postconditioning in hearts isolated from SHR-SP (hypertensive LVH) rats.

**Method:** Hearts isolated from WKY (control) and SHR-SP rats (11-15 weeks old) were subjected to 35 min LAD occlusion-2 hrs reperfusion, with ex4 0.3 nM present during the first 15 min in treated hearts. Evans blue/TTC method was used to determine area-at-risk (AAR) and infarct size (% of AAR). Akt phosphorylation (Akk-P) was measured on western blots after 3 min of reperfusion. Arterial blood pressure (BP) was measured in conscious animals by tail cuff method.

**Results:** BP and heart/body weight ratio were increased in SHR-SP compared to WKY rats (169±3 vs 129±4 mmHg, N=8-10; and 3.43±0.05 vs 2.35±0.03, N=15-18; P<0.0001 for both parameters). Infarcts were larger in SHR-SP than in WKY (65±3.9 vs 37±7.9, N=10 respectively; P<0.05). Infarct size diminished following ex4 postconditioning of WKY hearts (to 33±7 vs. 168±3% of control hearts, P<0.05), but not SHR-SP hearts (64±1±4.7; N=7). In WKY hearts, ex4 treatment decreased diastolic contracture (1093±168 to 518±162 min mm Hg, N=8-7; P<0.05) and increased left ventricle developed pressure (319±184 to 391±253 min mmHg, N=10-8; P<0.05), measured as area under the curve over the last hr of reperfusion. Following ex4 treatment, left ventricle developed pressure measured as a percentage of its preischemia value was increased in...
Impact of ischemic postconditioning in acute myocardial infarction patients with preconditioning

K. Prady1, S. Rasaingam1, H. Contractor2, M.R. Schmidt3, R.K. Khambatta4, H.E. Botker5,1.1Aarhus University Hospital, Department of Cardiology, Aarhus, Denmark; 2University of Oxford, Department of Cardiovascular Medicine, Oxford, United Kingdom

Purpose: Remote ischemic conditioning (RIC) by 3 times 5-minutes upper arm ischemia induces early protection against endothelial ischemia-reperfusion (I-R) injury in humans. The objective of this study was to test whether there is a second window RIC and whether repeated application of RIC (Chronic RIC) induces persistent protection against I-R injury.

Methods: In a randomised, single blinded parallel group study, 16 healthy volunteers were randomised to either a second window or Chronic RIC. Vascular responses were assessed by measuring venous occlusion plethysmography at baseline, and either 24 hours after a single RIC treatment (Second Window RIC) or after 14 days with daily RIC (Chronic RIC).

Results: In both groups, I-R injury significantly reduced FBF response to acetylcholine, an endothelium-dependent vasodilator (n=8, p<0.05 and n=8, p<0.05). Both Second Window RIC and Chronic RIC abolished the reduction in FBF response after I-R injury (n=8, p>NS and n=8, p>NS compared to baseline).

Conclusions: This is the first study to show Second Window RIC and Chronic RIC protection against I-R injury in human resistance vasculature in vivo. While yet to be proved effective in other organs, the ability to maintain a chronic pre-conditioned state using RIC may have therapeutic implications as a potentially valuable strategy of prophylaxis for individuals at high risk of I-R injury, e.g. stroke and myocardial infarction.
Effect of sildenafil on mitochondria in rat myocardial infarction model - morphological and property changes utilizing atomic force microscopy

W. Kim, K.H. Lee, S.R. Lee, H.H. Jang, H.S. Kim, J.S. Woo, G.J. Lee. 1, 2, 3 Department of Biomedical Engineering, Yonsei University College of Engineering, Seoul, Korea; 1, 3 Department of Physiology, Yonsei University, College of Medicine, Seoul, Republic of Korea.

Objective: Many studies showed that sildenafil have cardioprotective effects mediated by nitric oxide and ischemic preconditioning. Mitochondria play critical roles in both the life and death of cardiac myocytes. We tested whether sildenafil could make rat hearts resistant to infarction through mitochondrial protection using atomic force microscopy (AFM).

Methods: To prove the cardiac protective effect of sildenafil and investigate the morphologic and property analysis of mitochondria by AFM in the rat myocardium, in-vivo myocardial infarction (MI) model were used. Rat hearts were subjected to 40 min local ischemia by ligation of the left anterior descending (LAD) coronary and examined with AFM Imaging after 5 days of sildenafil treatment.

Results: Infarct area was significantly reduced in sildenafil-treated rats (7.78 ±3.9% vs. 20.37±7.0% in sildenafil and control hearts, respectively, P<0.001) as in the previous studies. Thus a relative reduction of 62% in the infarcted zone was observed in the sildenafil-treated rats. From the shape parameters of mitochondria in AFM image, it seemed that mitochondrial infarction caused the mitochondrial swelling (1,495±139 nm2 in normal vs. 24,150±18,289 nm2 in MI, P<0.0001). Whereas sildenafil reduced the mitochondrial area (7,428±3,682 nm2, P<0.0001) by 69.23% compared to that of MI. In addition, sildenafil-mediated cardioprotection was associated with mitochondrial KATP channel.

Conclusions: In MI rat model, cardioprotective effect of sildenafil pretreatment associated with a mitochondrial protective mechanism.

DIABETIC DYSFUNCTION: EPIDEMIOLOGY AND MECHANISM

Prevalence and incidence of myocardial dysfunction and chronic heart failure in the patients with type 1 diabetes: a 7-year prospective cohort study

E. Paricka-Konraduca1, M. Malek2, D. Galicka-Latala2, G. Gajos1, P. Rostoff2, A. Pietrucha1, J. Nessler1, Jagiellonian University Medical College, September 24, 2013 2, Jagiellonian University Medical College, Department of Metabolic Diseases, Krakow, Poland.

Prevalence and incidence of myocardial dysfunction (MD) and heart failure (HF) in type 1 diabetic patients (T1DP) still remains still unresolved issue.

Objective: To evaluate the prevalence and incidence of MD and HF in long lasting (over 10 years) type 1 diabetes (T1DM) without cardiovascular disorders or with hypertension and/or coronary disease (CHD) Research design and Methods:1617 T1DP (baseline mean age 51 years, mean diabetes duration 36 years) following initial evaluation (clinical symptoms, echocardiography,NT-pro-BNP levels) underwent a 7 year follow-up in terms of MD, HF (its diastolic and systolic manifestations).

Results: Baseline prevalence of HF amounted to 3.7% in the entire study group, whereas the incidence was 0.02% per year. The baseline prevalence of MD was 15.1%, and the incidence was 0.26% per year. MD and HF was observed only in hypertensive and/or coronary patients. Baseline diastolic HF subjects accounted for 84.6% of all HF population, whereas the systolic HF diabetic patients accounted for 15.3% of all HF subjects. For both genders the HF dropped onto a mica surface and AFM imaging was performed using the non-contact mode of NANOS N8 NEOS (Bruker, Herzogenrath, Germany). The effect of mitochondrial swelling (1,495±139 nm2 in normal vs. 24,150±18,289 nm2 in MI, P<0.0001) was assessed by TTC staining, TUNEL and AFM imaging. The effect of mitochondrial swelling (1,495±139 nm2 in normal vs. 24,150±18,289 nm2 in MI, P<0.0001) was assessed by TTC staining, TUNEL and AFM imaging.

Conclusions: In T1DM, MD and HF occurred exclusively when diabetes coexisted with cardiovascular disorders affecting myocardial function. The prevalence and incidence of HF in hypertensive and coronary patients was relatively low, what could be probably attributed to the intensive insulin regimen and cardioprotective effect of concomitant treatment.

Methods: We studied QRS width and 40 other clinically relevant variables in 25,171 patients (age 75±12 years: 40% women) between 2000 and 2011. Correlates with QRS width were assessed with multivariate logistic regression. Association between QRS width and all-cause mortality was assessed by Kaplan-Meier analysis and multivariate Cox regression. Pre-specified sub-group analyses by ejection fraction were performed.

Results: Thirty-one % had QRS > 120 ms, and 56% of these had left bundle branch block. Strong independent predictors of QRS > 120 ms were higher age, male gender, dilated cardiomyopathy, longer duration of HF, and lower EF. One-year survival was 77% in QRS > 120 ms vs. 82% in QRS < 120 ms, and 5-year survival was 42% and 51%, respectively (p<0.001, figure). The adjusted hazard ratio for all-cause mortality was 1.11 (95% CI, 1.04-1.18, p<0.001) for QRS > 120 ms vs. < 120 ms. There was no statistically significant interaction between QRS width and ejection fraction.
olerent β-blockers (all p < 0.02). There were no associations between HR and daily doses of β-blockers, investigated separately in subgroups of patients receiving the particular β-blocker (all p > 0.2).

Conclusion: Increased HR is common in patients with HFPEF, regardless of NYHA class. There is no association between the most common HR reducing therapy (β-blockade) and resting HR among these patients. There is a substantial variation of patients with HFPEF in whom the intensification of β-blockade on and off introduction of other HR reducing strategies could be considered.

### Old tools in new combination: combined stress echocardiography cardiopulmonary exercise testing in early detection of diastolic dysfunction

P4510

I. Hecheov, M. Ostojić, V. Gpa1, J. Stepanovic1, A. Djordjevic1, V. Stojanov1, B. Parapal1, S. Mazic2, M. Petrovic1, M. Beleški1.1 University of Belgrade, School of Medicine, Division of Cardiology, CCS, Belgrade, Serbia;2 University of Belgrade, School of Medicine, Institute of Physiology, Belgrade, Serbia

Background: Echocardiography is shown to be very important clinical tool for detection of diastolic dysfunction (DD) at rest in patients with hypertensive heart disease. However, simple diagnosis and stratification of patients according to severity of functional impairment in patients with exertional dyspnea and normal baseline values, without cardiopulmonary exercise testing (CPET). Relationship between diastolic function (DF) and CPET during combined stress echo and VO2peak may underestimate the functional impairment in patients with exertional dyspnea.

Objective: To assess integrated simultaneous evaluation of both echocardiographic variables and parameters of CPET of pts with hypertensive exertional dyspnea and normal baseline echo characteristics (including normal baseline systolic and DF). They all underwent CPET with supine ergometry with incremental ramp protocol (15W/min), with breath by breath gas analysis, in combination with simultaneous echo monitoring during CPET. We assessed systolic and diastolic function at baseline and at maximal exercise. DF was assessed by analyzing transmural flow pattern using pulse Doppler and tissue Doppler (TDI) of mitral annulus. Mitral E wave/E wave of mitral annulus > 8 was cut off for impaired DF.

Methods: We studied 100 pts (68 male, mean age 51±4.14 years, with the history of hypertension, exertional dyspnea and normal baseline echo characteristics (including normal baseline systolic and DF). They all underwent CPET with supine ergometry with incremental ramp protocol (15W/min), with breath by breath gas analysis, in combination with simultaneous echo monitoring during CPET. We assessed systolic and diastolic function at baseline and at maximal exercise. DF was assessed by analyzing transmural flow pattern using pulse Doppler and tissue Doppler (TDI) of mitral annulus. Mitral E wave/E wave of mitral annulus > 8 was cut off for impaired DF.

Results: All patients had ventricular ejection fraction >50%, and none of them had myocardial ischemia. Worsening of DF was found in 45% pts during combined CPET stress echo test. Patients with DD were older (p<0.001) and had lower peak VO2 (p=0.001), shorter time to VAT (p< 0.008) and shorter total exercise time (p<0.017), and higher VE/VCO2 slope (p=0.0001).

Conclusion: Integrated evaluation of both exercise induced echocardiographic changes and respiratory gas analysis during combined stress echo CPET stress alone improves detection and clinical assessment of DD in patients with exertional dyspnea and normal baseline LV function. It adds more information to echo and CPET as a combined testing of Antracyclines in order to monitor Trastuzumab toxicity. Systolic and diastolic parameters (pulsed Tissue Doppler imaging at mitral annulus, color M-mode propagation velocity and standard mitral inflow diastolic parameters) were assessed at every exam.

### Relation between diastolic function in rest and during stress and peak exercise capacity among heart transplant recipients

P4512

T. Monk-Hansen1, C. Have Dall1, S. Bisgaard Christensen2, M. Sner1, R. Harsman1, F. Gustafsson1, E. Prescott1.1 Bispebjerg Hospital of the Copenhagen University Hospital, Department of Cardiology, Copenhagen, Denmark;2 Gentofte Hospital of the Copenhagen University Hospital, Department of Cardiology, Gentofte, Denmark;3 Rigshospitalet - Copenhagen University Hospital, Heart Centre, Copenhagen, Denmark

Purpose: Several studies have shown that diastolic dysfunction impairs exercise capacity despite normal left ventricular ejection fraction (LVEF). This may also be a contributing factor in the limited performance of heart transplant recipients (HTX). We studied whether diastolic dysfunction at rest and during exercise is related to exercise capacity and the ability to improve exercise capacity after training intervention.

Methods: 23 stable HTX patients (mean age 50.4±14.8) with normal LVEF underwent maximum bicycle exercise test and semi supine exercise stress echocardiography. 13 patients underwent 8 weeks aerobic interval training and had echocardiography and exercise test repeated. Standard resting echocardiography included pulsed Doppler LV inflow at apical 4 chamber (E, A, dec. time) and pulsed TDI (e’ calculated as mean of lateral, septal, anterior and posterior cor of mitral annulus). Acquisitions were repeated at 30% and 60% of maximum workload and during recovery.

Results: VO2peak increased from (mean ± sd) 23.8±7.0 to 28.3±6.4 ml/kg/min (p<0.001) after training. Only few of the patients exhibited diastolic dysfunction at rest, but during stress echocardiography E/e’ increased and deceleration time decreased, unmasking sign of diastolic dysfunction. Diastolic dysfunction at rest and stress or the change in diastolic measures from rest to 60% did not predict workload at VO2peak or baseline improvement in VO2peak.

Conclusion: In contrast to previous studies of other cardiac patients, we found no correlation between diastolic function in rest and stress and peak exercise VO2peak or improvement in VO2peak after 8 weeks aerobic interval training in heart transplant patients. Diastolic dysfunction may not be a limiting factor for exercise capacity when chronotropic response is impaired.

### Anthracycline cardiotoxicity: incidence at present time

P4511


Purpose: Chronic Anthracycline cardiotoxicity (AC) characteristically presents some years after the start of treatment, and inciden ce of heart failure and subclinical systolic dysfunction has been reported in 0.2% and 15% of patients (pts) respectively. However, data regarding incidence of AC (clinical heart failure, subclinical systolic dysfunction and diastolic dysfunction) with current CHT schemes and pts selection are lacking.

Methods: Eighty consecutive pts receiving Anthracycline therapy (75 pts for breast cancer, 5 pts for lymphomas) were included in this prospective study. The CHT regimen were: 1) Epirubicin 75mg/m² surface × 4 cycles, 2) Adriamycin 60mg/m² surface × 4 cycles, 3) Adria 60mg/m² surface × 4 cycles, 4) Adriamycin 60mg/m² surface × 4 cycles plus Trastuzumab. All pts underwent a standard cardiogram and clinical examination at baseline, at the end of Anthracyline CHT, 3 and 9 months after the end of Anthracyline CHT. Pts receiving Adriamicin 60mg/m² surface 6 cycles, 2) Adriamicin

Results: Mean dose of Adriamicin was 283mg/m². At the end of follow-up (mean 25.4±2.9 months after the end of CHT) pts developed clinical heart failure. Three pts (7.3%) had a mild decrease of ejection fraction (mean EF 50.3%). 2 pts died due to progression of the underlying cancer disease. Twelve pts (15%) had baseline diastolic dysfunction and 38 pts (47%) developed diastolic dysfunction which was permanent in 29pts (36%). Twenty nine pts (36%) didn't develop significant diastolic changes.

Conclusion: Chronic AC expressed as asymptomatic diastolic dysfunction is common. However occurrence of subclinical systolic dysfunction with current chemotherapy schemes and pts selection is lower than previously published data and it doesn't carry relevant clinical consequences.

### Diastolic dysfunction is associated with reduced exercise capacity in non-obese subjects. Results from a population-based study sample

P4513

M. Dorr1, A. Hummel2, T. Reffelmann2, S. Glasser2, C. Schaeper2, B. Koch2, H. Volke3, R. Ewert4, S.B. Felix4,5 Ernst Moritz Arndt University of Greifswald, Greifswald, Germany;6 Ernst Moritz Arndt University of Greifswald, Department of Internal Medicine B, Greifswald, Germany;7 Ernst Moritz Arndt University of Greifswald, Institute of Community Medicine, Greifswald, Germany

Background: Left ventricular (LV) diastolic dysfunction has been reported to be associated with exercise capacity in heart failure and in patients referred for exercise testing. However, this relationship has not been studied extensively in the general population.

Methods: Data of 1,344 subjects (737 women, 607 men) aged 25-85 yrs from the population-based Study of Health in Pomerania (SHIP) in Germany with echocardiographic data on systolic and diastolic LV function and without reduced LV systolic function (LVEF<50%) were included in the analyses. All subjects volunteered symptom-limited cardiac pulmonary exercise testing. The association of diastolic dysfunction with exercise capacity as assessed by peak oxygen uptake

Abstract P4512 – Table 1. Measures of diastolic function at rest and during stress and their correlation with baseline VO2peak and improvement in VO2peak

| | Rest (mean±sd) | VO2peak baseline Corr. coef Improvement in VO2peak (p-value) | VO2peak baseline Improvement in VO2peak (p-value) |
|---|---|---|---|---|
| E′/a | 8.2±2.9 | 0.17 (0.43) | 0.04 (0.96) | 0.09 (0.70) |
| a′/a | 2.4±0.6 | 0.06 (0.80) | 0.01 (0.98) | 0.03 (0.92) |
(VO2peak) and minute ventilation changes as a function of the pulmonary carbon dioxide output (VE/VO2 slope) was analyzed by multivariable regression models adjusted for age, gender and hypertension. Furthermore, analyses were stratified by the presence of obesity (BMI: <30 vs. >30 kg/m2).

**Results:** Diastolic dysfunction was present in 550 subjects (40.9%). After adjustment for age, gender and hypertension diastolic function was associated with a reduced exercise capacity. Thus, subjects with diastolic dysfunction had lower values of VO2peak (24.9 ± 26.3 mL/min·1kg−1, p < 0.001) and higher values of VE/VO2 slope (25.6 ± 24.6, p < 0.001), respectively, as compared to those without diastolic dysfunction. Stratified analyses revealed that these associations were only present in non-obese subjects (VO2peak 26.4 ± 27.4 mL/min·1kg−1, p < 0.002; VE/VO2 slope 25.4 ± 24.4, p = 0.001) but were not statically significant in the presence of obesity.

**Conclusion:** In this sample from a population-based study we found an association between left ventricular diastolic dysfunction and a reduced exercise capacity in non-obese but not in obese subjects. These results may point towards a putative functional significance of diastolic dysfunction in relatively healthy individuals.

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**P4514** The association between computed tomography-derived three-dimensional pericardial adipose burden, cardiac structural alteration and diastology

Y.H. Lai1, C.H. Yen2, C.H. Yen1, Y.J. Wu3, J.Y. Kuo1, H.I. Yeh3, C.L. Hung1. 1Mackay Memorial Hospital, Department of Internal Medicine, Division of Cardiology, Taipei, Taiwan; 2Mackay Memorial Hospital, Department of Radiology, Taipei, Taiwan; 3Mackay Medical College, Department of Medicine, New Taipei, Taiwan

**Purpose:** Pericardial adipose tissue had been shown to exert their local effect on adjacent cardiac structures. However, data regarding three-dimensional volume measurements of such visceral adipose burden on myocardial diastolic function remained largely unknown.

**Methods:** We consecutively assessed pericardial fat tissue (PCF) by volume-based three-dimensional measure utilizing computed tomography (Aquarius 3D Workstation, TeraRecon, San Mateo, CA, USA) from 268 subjects after exclusion of decompensated heart failure. Diastolic parameters including left atrial (LA) diameter, early mitral inflow velocity (E), early-to-late inflow ratio (E/A), isovolumetric relaxation time (IVRT), and high frequency to spectral tissue Doppler imaging (TDI) including lateral mitral annulus systolic (S') and early diastolic (E') velocities were all obtained. Left-sided filling pressure was estimated by E/E' ratio.

**Results:** Of all 268 subjects (mean age: 53.5 years, 31% female) enrolled, 81 (35.8%) had hypertension and 29 (12.9%) had diabetes with an average PCF volume of 81.4 mL. Univariate analysis showed that decreased IVRT, reduced E', elevated E/E' and enlarged LA diameter were all related to increasing PCF (all p < 0.05). In the multivariate regression analysis after adjusting for age, gender, body mass index, LV mass, and clinical variables, increasing PCF was independently correlated with E/e' (early H/M: r = 0.487; p < 0.001), borderline elevated E/E' (p = 0.05), and higher values of VO2peak (24.9 vs. 26.4 mL/min·kg−1, p = 0.022; VE/VO2 slope 25.4 vs. 24.4, p = 0.001) but were not statistically significant in the presence of obesity.

**Conclusion:** These findings suggest that strong association between myocardial fatty acid uptake and impaired diastolic LV function exists in DMHF pts. This dysregulation in cardiac FA utilization in DMHF pts might provide information as to potential targets for the treatment of diastolic LV dysfunction.

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**P4516** A risk-factor based porcine model of heart failure with preserved ejection fraction (HFPEF)

M. Schwarzl1, S. Seiler1, P. Steendijk1, B. Pieksa1, H. Post1. 1Medical University of Graz, Department of Cardiology, Graz, Austria; 2Leiden University Medical Center, Leiden, Netherlands

**Background:** Heart failure with preserved ejection fraction (HFPEF) results from the accumulation of cardiovascular risk factors. So far, no clearly effective treatment for HFPEF could be established, which in part relates to the lack of suitable animal models. We aimed to model HFPEF in pigs by induced hypertension and western diet.

**Methods/Results:** Eight landrace pigs were implanted with subcutaneous 90 day release DOCA pellets (an aldosterone analogon), and subsequently fed a high salt/high lipids/high sugar diet for 90 days (DOCA). Eight weight-matched pigs (no DOCA, regular diet) served as controls. After 90 days, tail-cuff systolic blood pressure during light sedation was 139 ± 11 mmHg in DOCA vs 95 ± 6 mmHg in control (p < 0.05). Echocardiography demonstrated pronounced concentric hypertrophy in DOCA. LV function was assessed during deep anaesthesia by pressure-volume (PV) analysis. In DOCA vs control, baseline cardiac output (6.0 ± 0.2 vs 6.6 ± 0.5 l/min) and heart rate (95 ± 5 vs 84 ± 6 bpm) were different, while LV ejection fraction (68 ± 3 vs 51 ± 3%) was higher (p < 0.05). The end-systolic and end-diastolic PV relationships (ESPVR and EDPVR) were markedly shifted leftwards in DOCA (see graph). Right atrial pacing both at baseline and during low-dose dobutamine infusion (2.5 µg/kg/min) revealed a lower increase of cardiac output in DOCA.

**Conclusion:** This risk factor based animal model for the first time reproduces two major characteristics of HFPEF: (i) a leftward shift of the ESPVR and EDPVR and (ii) a limited cardiac reserve.

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**P4517** The relation between left atrial systolic function and left ventricular performance in heart failure with preserved ejection fraction

Y.J. Lim, S. Kawano, H. Namori, M. Takeuchi, Kawachi General Hospital, Cardiovascular Center, Higashi-Osaka, Japan

**Background:** Clinical features of heart failure with preserved EF (HFPEF) have not been well characterized. It is reported that peak atrial systolic mitral annular velocity (A') predicts left atrial (LA) systolic function. The aim of the present study was to investigate the relation between LA systolic function and left ventricular (LV) performance in HFPEF.

**Methods:** Out of 327 patients who presented to the emergency department because of acute pulmonary congestion during the last 5 years, those with EF ≥ 50% upon admission comprised the HFPEF patients (n=56) were enrolled in this study.
Patients with atrial fibrillation or mitral valvular disease were excluded in this study. A control group (Gr-C) consisted of consecutive 30 hypertensive patients with EF of >50%. We recorded tissue Doppler-derived peak early diastolic and atrial systolic velocities of mitral annulus (E and A, respectively) in the chronic stage. Other echo parameters (LA diameter (LAD) and LV diastolic diameter (LVDd) and E/E') were measured at the same time. The HFPEF patients were divided into the good LA function group (Gr-G) (A' > 6cm/s, n=30) and the poor LA function group (Gr-P) (A' < 6 cm/s, n=21) depending on the score of A'.

Results: E/E' was well correlated with SFradial on exercise (r=0.4609, p=0.0069) in the HFPEF patients. A and E were the lowest and E/E', LAD and LVDd were the highest in Gr-P (table).

LA systolic function and LV performance

<table>
<thead>
<tr>
<th></th>
<th>A' (cm/s)</th>
<th>E (cm/s)</th>
<th>E/E'</th>
<th>LAD (mm)</th>
<th>LVDd (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr-C</td>
<td>8.5 ± 1.8</td>
<td>6.4 ± 1.7</td>
<td>10.9 ± 2.0</td>
<td>38 ± 1.5</td>
<td>48 ± 2.4</td>
</tr>
<tr>
<td>Gr-G</td>
<td>7.0 ± 2.9</td>
<td>5.0 ± 1.4</td>
<td>13.2 ± 3.3</td>
<td>41 ± 4.9</td>
<td>50 ± 5.6</td>
</tr>
<tr>
<td>Gr-P</td>
<td>4.2 ± 0.8</td>
<td>3.7 ± 0.6</td>
<td>17.8 ± 4.3</td>
<td>45 ± 2.3</td>
<td>55 ± 6.4</td>
</tr>
</tbody>
</table>

*p<0.05 vs Gr-C and Gr-G, *p<0.05 vs Gr-C.

Conclusions: The progression of LA systolic dysfunction was associated with the impairment of LV diastolic function and may play an important role in the pathogenesis of HFPEF.

**References**

1. Wenneburger, F.W., Tan, Y., Levy, A., Sander, J.E. (2012). Longitudinal dyssynchrony has been shown in patients with heart failure and normal ejection fraction (HFNEF). We hypothesised that radial dyssynchrony may also be present in these patients on exercise and contribute to LV dysfunction.

Methods: We studied 57 patients with the clinical diagnosis of HFNEF (39 female, age 73±7 years, EF 61±6%) and 30 healthy controls (23 female, age 70±7 years, EF 62±7%). All underwent echocardiography at rest and on supine exercise. Images were acquired and analysed off line. Radial strain and time to peak radial strain in a six segments model were studied. Standard deviation for six radial segments was calculated (SDradial) to assess segmental radial dyssynchrony. A cut-off of 24.4 ms at rest and 18.6 ms on exercise (mean ±2SD of controls) were used to diagnose dyssynchrony.

Results: Radial strain was comparable at rest (44.0±15.1% versus 48.2±11.2%, p=0.191) but significantly lower in patients on exercise (49.6±14.2% versus 58.0±6.2%, p<0.008). Sradial was also comparable at rest (14.1±1.3 ms versus 10.5±0.7 ms, p=0.150). Controls achieved significant reduction in Sradial on exercise (8.4±5.1 ms) which was not seen in patients (13.5±5.9 ms, p=0.008). Radial dyssynchrony was detected in 12% of patients at rest which increased to 29% patients on exercise. Sradial on exercise correlated with Radial strain on exercise (r=-0.246, p=0.022).

Conclusions: HFNEF is associated with LV radial dysfunction and dyssynchrony as well as longitudinal particularity on exercise and which is not present at rest. This disorganisation of venricular function may underlie their exertional breathlessness.

**Figure 1. Integrated backscatter measurement**

**Figure 2. Prognostic significance of calibrated integrated backscatter in patients with heart failure and preserved ejection fraction**

B. D Her 
D. Stépowski 
V. Vallet 
F. Bauer 
J.N. Dacher

Introduction: Calibrated integrated backscatter (IB), a surrogate for myocardial fibrosis, is deteriorated in hypertrophic, ischemic cardiomyopathy or in systolic heart failure (HF). Whether CIB may differentiate patients with heart failure and preserved ejection fraction (HFPEF) at risk of death or HF reoccurrence has never been investigated.

Methods: 35 patients admitted for HFPEF (Framingham criteria, EF > 50% and BNP level > 100 pg/ml) were imaged by echocardiography 2 months following an acute degradation. We measured left ventricular function, ati dimensions and calibrated Integrated Backscatter (CIB) which was obtained from parasternal long axis by subtracting pericardial CIB intensity from myocardial CIB intensity of the LV anteroseptal and posterior walls (figure). Measurements of calibrated CIB, expressed in decibels, were performed at QRS complex onset. The primary endpoint was the occurrence of death or hospitalization for HF at 12-month FU.

Results: 10 patients reached the primary endpoint (3 deaths and 7 hospitalizations for HF). In this group at risk, patients had more chronic obstructive pulmonary disease (p=0.03) and coronary artery bypass (p=0.008). Despite similar EF (57.3±7.3% vs. 60.4±9.9%), we observed larger left atrial diameter (49.7±6.9 mm vs. 44.7±6.4 mm, p=0.050) and area (28.6±6.2 cm² vs. 24.5±5.1 cm², p=0.044) in patients with endpoint vs. no endpoint. Patients with clinical endpoint showed more anteroseptal and posterior wall myocardial ultrasound reflectivity (-12.3±6.0 dB vs. -22.7±8.1 dB, p=0.0024 and -14.9±6.1 vs. -21.1±8.0 dB, p=0.031) as compared with event-free patients.

**Figure 2. Left but not right ventricular diastolic function deteriorates during follow up in patients with systemic sclerosis**

M. Czurytki 
P. Benias 
K. Izyk 
K. Kurnicka

**Methods:** We prospectively studied 69 consecutive pts (64F, SM mean age 55.5±13.3 yrs) with SSC (mean SSC duration 9±12.4 yrs) at baseline and after at least 1 year of follow up (3±1.1 yrs). At last follow up (FU), SSC patients had a significant decrease in EF vs baseline (44.5±3.1 vs. 42.4±2.8, p<0.0001). At FU we observed significant deterioration of Doppler parameters of LV but no RV diastolic function. Mean RV fractional area was higher at baseline follow up patients (204.6±167.1 vs. 183.7±113.8, p<0.0001). At FU we observed significant deterioration of Doppler parameters of LV but no RV diastolic function.

**Conclusions:** Our data support the hypothesis that calibrated CIB, a surrogate for myocardial fibrosis, identifies HFPEF patients at risk of death or HF hospitalization.

**Figure 3. Prognostic significance of calibrated integrated backscatter in patients with heart failure and preserved ejection fraction**

B. D Her 
D. Stépowski 
V. Vallet 
F. Bauer 
J.N. Dacher

Introduction: Calibrated integrated backscatter (CIB), a surrogate for myocardial fibrosis, is deteriorated in hypertrophic, ischemic cardiomyopathy or in systolic heart failure (HF). Whether CIB may differentiate patients with heart failure and preserved ejection fraction (HFPEF) at risk of death or HF reoccurrence has never been investigated.

Methods: 35 patients admitted for HFPEF (Framingham criteria, EF > 50% and BNP level > 100 pg/ml) were imaged by echocardiography 2 months following an acute degradation. We measured left ventricular function, ati dimensions and calibrated Integrated Backscatter (CIB) which was obtained from parasternal long axis by subtracting pericardial CIB intensity from myocardial CIB intensity of the LV anteroseptal and posterior walls (figure). Measurements of calibrated CIB, expressed in decibels, were performed at QRS complex onset. The primary endpoint was the occurrence of death or hospitalization for HF at 12-month FU.

Results: 10 patients reached the primary endpoint (3 deaths and 7 hospitalizations for HF). In this group at risk, patients had more chronic obstructive pulmonary disease (p=0.03) and coronary artery bypass (p=0.008). Despite similar EF (57.3±7.3% vs. 60.4±9.9%), we observed larger left atrial diameter (49.7±6.9 mm vs. 44.7±6.4 mm, p=0.050) and area (28.6±6.2 cm² vs. 24.5±5.1 cm², p=0.044) in patients with endpoint vs. no endpoint. Patients with clinical endpoint showed more anteroseptal and posterior wall myocardial ultrasound reflectivity (-12.3±6.0 dB vs. -22.7±8.1 dB, p=0.0024 and -14.9±6.1 vs. -21.1±8.0 dB, p=0.031) as compared with event-free patients.

**Figure 1. Integrated backscatter measurement**

**Figure 2. Left but not right ventricular diastolic function deteriorates during follow up in patients with systemic sclerosis**

M. Czurytki 
P. Benias 
K. Izyk 
K. Kurnicka

**Methods:** We prospectively studied 69 consecutive pts (64F, SM mean age 55.5±13.3 yrs) with SSC (mean SSC duration 9±12.4 yrs) at baseline and after at least 1 year of follow up (3±1.1 yrs). At last follow up (FU), SSC patients had a significant decrease in EF vs baseline (44.5±3.1 vs. 42.4±2.8, p<0.0001). At FU we observed significant deterioration of Doppler parameters of LV but no RV diastolic function. Mean RV fractional area was higher at baseline follow up patients (204.6±167.1 vs. 183.7±113.8, p<0.0001). At FU we observed significant deterioration of Doppler parameters of LV but no RV diastolic function.

**Conclusions:** Our data support the hypothesis that calibrated CIB, a surrogate for myocardial fibrosis, identifies HFPEF patients at risk of death or HF hospitalization.
Heart failure with preserved ejection fraction-echo investigation 799

P4521

Left ventricular torsion during exercise in patients with and without increase in left ventricular filling pressures

G. Barge-Caballero, J. Peatejo, A. Bouzas-Mosquera, A. Lopez-Bailo, M. Lopez-Perez, O. Prada, A. Castro-Beiras.
Hospital A Coruna, Department of Cardiology, A Coruna, Spain

Left ventricular torsion (Tor) is increased in patients (pts) with diastolic dysfunction but little is known about the effect of exercise (Ex) on Tor in them. We aimed to assess Tor during Ex in pts with and without increase in left ventricular filling pressures.

Methods: We studied 132 consecutive pts with normal LV ejection fraction (LVEF>50%), and normal Ex echocardiography. Speckle imaging was performed at rest (R) and at peak (Pk). Tor was defined as maximal apical rotation – basal rotation (°)/LV length (cm). Confident tracking assessment was achieved in 107 pts (81%). Volumetric LVEF and the ratios of early transient flow near diastolic flow at the septal mitral annulus waves (E/e′) at R and at Pk were also measured. Twenty-six pts had E/e′ ratio >15 (G-Hee) and 81 pts -<15 (G-NHe).

Results: G-Hee pts were older (77±6 vs 58±14, p<0.001) and achieved less METs (8.8±3.7 vs. 11.0±4.0, p=0.02). A history of coronary artery disease was equally frequent (8% in G-Hee and 21% in G-NHe, p=0.15). LV EF at rest was higher in G-Hee (70±9 vs. 66±8, p=0.04) whereas it was similar at Pk (74±9 vs. 70±8, p=0.09). E′/e′ values at R were 24±20.3 in G-Hee and 10.2±5.6 in G-NHe (p=0.001), whereas at Pk were 19±8.1 and 9.8±2.9, respectively (p<0.001). Rotation parameters were similar between groups except for apical rotation which was higher at R and Pk in G-Hee.

G-NHe G-Hee p value

<table>
<thead>
<tr>
<th>Basal rotation at Pk, °</th>
<th>8.8±1.8</th>
<th>6.7±1.2</th>
<th>0.001</th>
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</thead>
<tbody>
<tr>
<td>Apical rotation at Pk, °</td>
<td>6.2±2.7</td>
<td>1.9±1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Twist at R, °</td>
<td>2.3±1.4</td>
<td>0.9±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Tor at R, °/cm</td>
<td>0.2±0.1</td>
<td>0.0±0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Basal rotation at Pk, °</td>
<td>8.8±1.8</td>
<td>6.7±1.2</td>
<td>0.001</td>
</tr>
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</tr>
<tr>
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<td>2.3±1.4</td>
<td>0.9±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Tor at Pk, °/cm</td>
<td>0.2±0.1</td>
<td>0.0±0.0</td>
<td>NS</td>
</tr>
<tr>
<td>% of Tor, median (25th–75th percentiles)</td>
<td>37.2 (35)</td>
<td>49 (38)</td>
<td>NS</td>
</tr>
</tbody>
</table>

In conclusion, characteristics of pts with high E/e′ values include older age, low functional capacity, and increased apical rotation at R and at Pk.

P4522

Ventricular-arterial coupling and arterial stiffness in hypertensive subjects with diastolic heart failure

Russian Peoples' Friendship University, Moscow, Russia, Moscow, Russian Federation

Objective: To compare ventricular-arterial coupling (EaI/ElvI) and arterial stiffness parameters in hypertensive subjects with and without heart failure with preserved ejection fraction (HFPEF).

Methods: We studied 132 consecutive pts with normal LV ejection fraction (LVEF>50%), and normal Ex echocardiography. Speckle imaging was performed at rest (R) and at peak (Pk). Tor was defined as maximal apical rotation – basal rotation (°)/LV length (cm). Confident tracking assessment was achieved in 107 pts (81%). Volumetric LVEF and the ratios of early transient flow near diastolic flow at the septal mitral annulus waves (E/e′) at R and at Pk were also measured. Twenty-six pts had E/e′ ratio >15 (G-Hee) and 81 pts -<15 (G-NHe).

Results: G-Hee pts were older (77±6 vs 58±14, p<0.001) and achieved less METs (8.8±3.7 vs. 11.0±4.0, p=0.02). A history of coronary artery disease was equally frequent (8% in G-Hee and 21% in G-NHe, p=0.15). LV EF at rest was higher in G-Hee (70±9 vs. 66±8, p=0.04) whereas it was similar at Pk (74±9 vs. 70±8, p=0.09). E′/e′ values at R were 24±20.3 in G-Hee and 10.2±5.6 in G-NHe (p=0.001), whereas at Pk were 19±8.1 and 9.8±2.9, respectively (p<0.001). Rotation parameters were similar between groups except for apical rotation which was higher at R and Pk in G-Hee.

P4523

Moving toward an ejection fraction paradox: the ratio between left ventricular and left atrial volume

P. Pellionieri, A. Bennett, O. Khaleva, A. Torabi, P. Costanzo, E. Wright, K. Wong, A.L. Clark, J.G.P. Cieland. University of Hull, Department of Clinical Medicine, Hull, United Kingdom

Background: We hypothesize that the ratio between left ventricular end-diastolic volume (LVEDV) and end-systolic left ventricular area (LA-LSV) ratio may better estimate the severity of the HF, being a sum of a long term history of systolic-diastolic dysfunction.

Methods: Out-patients attending a community HF service between 2008 and 2010 were enrolled. HF was defined as the presence of relevant symptoms and signs and objective evidence of cardiac dysfunction: either a left ventricular ejection fraction (LVEF) <45%, or the combination of both left atrial (LA) dilatation (>4cm) and raised amino-terminal pro-brain natriuretic peptide (NTproBNP) >400 pg/ml.

Results: Amongst the 693 patients included, median age was 73 years, 33% were women and HF was confirmed in 568. LV LA ratio (SD) in patients with no HF (n=125) was 2.1 (0.8), The mean LV-LA ratio for each quartile in patients with HF was 3.8 (1.2) vs. 2.3 (0.9) vs. 1.6 (0.2) vs. 1.0 (0.2). Comparing patients with HF in the lowest and highest quartile of LV-LA ratio, those in the highest quartile were older, had more signs of HF, were more likely to have atrial fibrillation and to be treated with diuretics, have higher pulmonary pressures but had more negative (better function) for global longitudinal strain (GLS, -12.3 (4.3) % vs. -7.4 (3.3) %, p<0.001) and higher LVEF (54 (12) % vs. 32 (9) %, p<0.001). IVC diameter was larger (22.3 (5.1) vs. 17.6 (3.3) mm, p<0.001) and NTproBNP plasma levels were more elevated (1968 (15) vs. 1044 (401-2241 ng/l, p<0.001). During 567 (IQR: 413 – 736) days of follow up there were 158 events (78 patients were admitted to hospital with heart failure and 80 died due to CV causes). The Kaplan-Meier curves show that patients in the highest quartiles of LV-LA ratio have the higher risk of adverse outcome and this risk decreases accordingly with the increasing LV-LA ratio. In a multivariable Cox regression model, including NTproBNP, LV-LA ratio, but not LVEF, was an independent predictor of worse outcome.

Conclusions: In patients with chronic HF with or without a reduced LVEF, the LV-LA ratio identifies patients with higher NTproBNP and worse outcome who paradoxically have higher LVEF.

P4524

Deceleration time of early diastolic velocity by tissue Doppler velocity image: a novel index of left ventricular end-diastolic pressure


Purpose: This study aimed to examine the diagnostic utility of the deceleration time (DT) of early diastolic velocity of mitral annulus by tissue Doppler velocity image, a method for the assessment of left ventricular end-diastolic pressure.

Methods: Simultaneous left ventricular catheterization and Doppler echocardiography were performed to compare the left ventricular end-diastolic pressure (LVEDP) and DT in 57 patients who were scheduled for diagnostic coronary angiography. They were admitted to our hospital for the assessment of heart disease including cardiomyopathy (n=26) and coronary artery disease (n=31). We included the patients with atrial fibrillation and mitral valvular disease and who undergone mitral valvular surgery. Color-coded tissue Doppler images were acquired at apical 4 chamber view, and DT of early diastolic velocity measured at mitral annulus were assessed. DT was also evaluated in 15 healthy subjects.

Results: DT is successfully measured in all subjects. DT in the patients with elevated LVEDP (>18mmHg) (69±12ms, n=14) was significantly shorter than those with LVEDP ≤18mmHg (94±18ms, n=43) and healthy subjects (100±11ms). DT is inversely proportional to LVEDP (r=-0.7, p<0.0001). With a cut-off value of DT of 80 ms, which was determined by receiver operating characteristic curve, the

Figure 1: DT measurement
sensitivity and specificity of DT to detect elevated LVEDP were 90 and 85%, respectively.

Conclusions: DT of early diastolic mitral velocity of mitral annulus could be an efficient novel index of LV end-diastolic pressure.

Impact of gender difference on the relation between arterial stiffness and left ventricular diastolic function in healthy subjects

M. Saito1, H. Okrayama2, H. Gishii3, H. Morikawa2, T. Yoshi3, H. Hiasa4, T. Sumimoto1, K. Kishimura2, K. Inoue1, J. Higaki5,1

1Kitsushika Hospital, Ozu, Japan; 2Ehime Prefectural Central Hospital, Matsuyama, Japan; 3Ehime University Graduate School of Medicine, Toon, Japan

Background: Diastolic heart failure has been reported to occur more often in elderly women rather than elderly men. Several studies have reported a relation between arterial stiffness and left ventricular (LV) diastolic function. Recently, it was reported that this relation was stronger in women than in men among individuals with cardiovascular risk factors. However, the impact of gender difference on this relation is still poorly understood.

Methods: Study subjects were selected from 447 who had echocardiography and examination of arterial stiffness. Among them, 95 men (mean age, 47±11 years) and 72 women (mean age, 47±10 years) without atherosclerotic risk factors (hypertension, dyslipidemia, diabietic mellitus) were analyzed. We measured brachial ankle pulse wave velocity (baPWV), carotid augmentation index (Alx) and radial Alx as arterial stiffness parameters immediately after the echocardiographic examination.

Results: Peak early diastolic mitral annulus velocity (e') was significantly correlated with baPWV (Men: r = -0.42, p < 0.01, Women: r = -0.54, p < 0.01), carotid Alx (Men: r = -0.26, p < 0.01, Women: r = -0.57, p < 0.01) and radial Alx (Men: r = -0.35, p < 0.01, Women: r = -0.36, p < 0.01). e' had a significant correlation with each arterial stiffness parameter in women, but not in men. Multivariate regression analysis revealed carotid Alx (β = -0.26, p = 0.02) was a significant independent predictor of e' in women, but not in men.

Conclusion: Our results suggested that LV diastolic function was more affected by arterial stiffness in women than in men among healthy subjects. This might partially account for a higher incidence of diastolic heart failure in women than men.

Increased prevalence of diastolic heart failure can be identified by impaired global longitudinal strain in patients with rheumatoid arthritis

T. Schau, M. Zaerker, M. Schoepf, J. Meyhoefer, G. Butter. Ev.-Freikirchliches Hospital and Heart Center Brandenburg in Bernau, Bernau bei Berlin, Germany

Background: Risk of heart failure is increased in patients with rheumatoid arthritis (RA) and is more likely to occur in RA patients with a preserved ejection fraction. Until now little is known about the prevalence of diastolic heart failure (HF) in RA and related structural changes. Therefore we examined RA patients for diastolic heart failure using measurement of NT-proBNP level and echocardiography including strain imaging.

Methods: In this prospective cross-sectional observational study we examined 155 patients (68% female, mean age 60±13 years, 56% hypertension, median BMI 28 kg/m²) with RA according to the current ACR/EULAR criteria in our outpatient clinic for rheumatic diseases. Echocardiography including strain imaging and blood sampling for NT-proBNP were done. HFNEF is diagnosed if (1) symptoms and (2) E/e'-ratio > 15 or (2) NT-proBNP > 220 pg/ml with (3) E/e'-ratio > 8 or (3) atrial fibrillation exists.

Results: There was a surprising high rate of HFNEF (21%) in our RA cohort. The systolic LVEF was reduced in only 4% of patients. LV mass index was increased in 45% of ϕ and 18% of ϕ with HFNEF, mostly due to concentric hypertrophy. In the strain imaging we found a significant reduction in the global longitudinal strain in patients with HFNEF with a threshold of -18%.

Logistic regression analysis of HFNEF

Parameter Univariate OR 95% CI p Multivariate OR 95% CI p

Global longitudinal strain ≤-18% 7.8 (3.9-13.9) <0.001 14.6 (3.6-81.4) <0.001
Age ≥ 65 years 19.0 (6.7-58.9) <0.001 21.6 (6.0-80.1) <0.001
Gender (female) 6.0 (2.0-36.3) 0.005 21.6 (3.0-140.0) 0.004
RA activity (DAS28 ≥ 2.6) 4.0 (1.7-10.2) 0.002 7.3 (2.0-26.4) 0.005
History of hypertension 5.9 (2.3-18.6) <0.001
Diabetes mellitus type 2 3.2 (1.0-9.4) 0.037
Concentric LV hypertrophy 4.1 (1.7-9.8) 0.002
Hematocrit > 0.45 7.5 (2.1-30.7) 0.002
Duration of RA > 15 years 3.32 (1.4-7.7) 0.005

Conclusion: This finding in addition to the conventional echocardiographic measurements in HFNEF suggests the role of fibrotic endocardial changes in diastolic heart failure in RA. Markers of RA activity (DAS28) were significant risk factors beyond classical risk factors like age, female gender, hypertension and diabetes mellitus type 2.

Diagnostic of heart failure with normal ejection fraction in outpatients: usefulness of european society of cardiology guideline


The diagnosis of heart failure with normal ejection fraction (HFNEF) is a challenge especially in outpatients (outpts) without signs of volume overload because different criteria are used to classify diastolic dysfunction (DD). The European Society of Cardiology (ESC) released a consensus statement for the diagnosis of HFNEF and their use may be helpful in the correct classification of these pts, avoiding low diagnostic specificity. The objectives of this study were to evaluate the applicability of ESC statement in outpts with suspected HFNEF and the incremental value of BNP in the cases where the values of E/E' ratio are in the gray area (8-15).

Methods: We prospectively evaluated 162 outpts with clinical suspicion of HF (age 67±11.6 years, 72% women). The criteria for the diagnosis of HFNEF were those proposed by the ESC statement: ejection fraction of left ventricle > 50%; end-diastolic volm of LV < 97 mL/m² and evidence of DD obtained by echocardiography and tissue Doppler imaging (TDI): E/E' ratio; E/A ratio; mass of LV index (MLVI) and left atrial volume index (LAVI); ECG with atrial fibrillation(AF) and BNP.

Results: HFNEF was confirmed in 16 pts with E/E' > 15 and ruled out in 65 with E/E' < 8. In 81 pts with E/E' between 8 and 15 the use of LAVI, E/A, LVMi and the ECG with AF confirmed HFNEF in 33 outpts and excluded in 47. BNP was greater than 200 pg/ml in 5 pts and these patients the criteria from TDI and ECG (AF) were sufficient to confirm the diagnosis. The utility of echocardiogram parameters to evaluation of DD were compared with E/E' using the cutoff points established by the ESC. We observed that LAVI and MLVI have high specificity (85% and 69%) and low sensitivity (48% and 43%), while the E/E' has low specificity for diagnosis of DD (E/E' > 8).

Conclusion: The ESC criteria were useful to identify outpts with HFNEF and the TDI parameters used to evaluate the DD have high specificity, with the exception of the E/A and BNP with the cutoff of 200 pg/ml in outpts with E/E' between 8-15 did not provide incremental value for HFNEF.

Diagnostic filling pressures, a valuable tool in the detection of acute allograft rejection in heart transplantation


Acute allograft rejection (AAR) is a major cause of mortality in heart transplantation (HT) and the development of non-invasive measurements is crucial to avoid repeated endomyocardial biopsies (EB). DTI parameters and NTproBNP can be used to predict left ventricular filling pressures. The purpose of this study was to determine their utility to predict AAR and to study a possible correlation between them.

Methods: We performed a total of 331 blood tests and 142 EB in 21 patients with HT since 2009. According to the ISHLT criteria 107 EB had AAR grade 0R, 30 1R, 4 2R and 1 3R. DTI parameters were measured the same day of the EB.

Results: Comparison of DTI velocities in HT by AAR status is shown in the table below. A strong correlation between lateral E/E' and biomarkers was found (Figure 1). NT-proBNP improved the area under the ROC Curve (AUC) for the prediction of AAR when added to lateral E/E' from 0.612 (P<0.05) to 0.733 (P<0.005).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Er</th>
<th>E/A</th>
<th>MLVI</th>
<th>LAVI</th>
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</thead>
<tbody>
<tr>
<td>NT-proBNP</td>
<td>5499.7</td>
<td>7895.2</td>
<td>7.2</td>
<td>11.4</td>
</tr>
<tr>
<td>Er</td>
<td>11.6</td>
<td>13.3</td>
<td>3.7</td>
<td>7.6</td>
</tr>
<tr>
<td>E/A</td>
<td>8.6</td>
<td>8.2</td>
<td>0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>MLVI</td>
<td>10.7</td>
<td>13.1</td>
<td>3.6</td>
<td>6.3</td>
</tr>
<tr>
<td>LAVI</td>
<td>0.04</td>
<td>0.04</td>
<td>0.01</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Figure 1

Conclusion: Higher levels of NT-proBNP and increased LV pressure measured by TDI were found in patients with AAR. To the date this is the first study that shows a strong correlation between these parameters in HT patients with and without AAR. Monitoring of these parameters could be easily performed and useful in non-invasive evaluation of HT.

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DIASTOLIC DYSFUNCTION AND TREATMENT

Differing relations of the clinical responder rate to the left ventricular reverse remodelling and changes in left ventricular filling pattern in patients receiving cardiac resynchronization therapy

M. Dekany, G. Zoltan, B. Szabo, B. Muz, B. Ancic, T. Borsanyi, G.Z. Duray, R.G. Kiss, N. Nyolczas. Military Hospital, Budapest, Hungary

Background: Clinical responder rate (CR) and left ventricular (LV) reverse re-modelling (RR) are regarded valuable markers of long-term favourable effects of cardiac resynchronization therapy (CRT). Besides the aforementioned parame-
ters, the improvement of LV diastolic function (LVDF) might also be another valu-
able predictor of the long-term response to CRT.

Aim: To assess the relation of the CR to the LVRR and to the improvement of LVDF evaluated by the improvement in LV diastolic filling pattern (ILVFP) in pts receiving CRT. To investigate the survival of pts according to RR and ILVFP.

Patients and methods: 139 pts with CRT-P (51%) or CRT-D (49%) followed prospectively for 38.6±23.8 months. Age:64.±10.6 years, male:81.2%, is-
chemic:37.4%, diabetes mellitus:35.4%, atrial fibrillation:23.6%, NYHA II-III:8.0±0.8, blood pressure:116.4±21.6/72.6±12.8mmHg. LV ejection fraction (LVEF): 57±9.2%, EF% ≥ 5%: at 6 months 76%, at 12 months 41.6%. LVRR (endpoint increase in E wave in Table 1) was noted in 22 pts (16.1%). However these differences did not reach the level of significance: p=0.102 and not surviving pts according to RR and ILVFP, were nearly the same: in surviving pts CRr was 54.1%. Either in presence, or in absence of RR, the CRr was found between RR and CRr. ILVFP was associated with 100% of CRr, in lack of ILVFP CRr was 54.1%. However these differences did not reach the level of significance: p=0.102 and 0.092 for RR and ILVFP, respectively.

Results: The cumulative survival rate at 1, 2 and 3 years: 97.8%, 92.5% and 78.6%, respectively. CRr (alive, improved)1 NYHA, and not hospitalized): at 6 months 82%, at 12 months 78%. RR (LVEF increases ≥ 10% and E/A decreases ≥10%): at 6 months 36.8%, at 12 months 40.4%. ILVFP (deceleration time increases: 10% and E/A decreases: 10%): 35.8% at 6, and 34.4% at 12 months. Investigation of the relations between the aforementioned parameters showed, that ILVFP correlated significantly (p<0.05) to CRr, while no correlation was found between RR and CRr. ILVFP was associated with 100% of CRr in lack of ILVFP CRr was 54.1%. Either in presence, or in absence of RR, the CRr was the almost same, i.e. 82% and 76%, respectively. Differences between surviving and not surviving pts according to RR and ILVFP, were nearly the same: in surviving pts RR in 37.5%, ILVFP in 92.2%, in not surviving pts RR in 17.1%, ILVFP in 16.1%. However these differences did not reach the level of significance: p=0.102 and 0.092 for RR and ILVFP, respectively.

Conclusions: In the effect of CR, CRT, and LVRR were not concordant with each other. On the other hand, the changes in LV diastolic filling pattern significantly correlated with CRr. Besides RR, the changes in LVDF may have a value also in predicting the long-term effect of the CRT on clinical outcome. Investigation its value in a larger pts population seems to be reasonable.

Creatine Phosphate Sodium combining with fructose diphosphate for injection on severe diastolic heart failure

X. Zeng, Y.Y. Li, X.J. Zeng, A.Y. Tu, Z.H. Liu on behalf of a name.

chengu second people’s hospital, chengdu, China, People’s Republic of

Background: High-energy phosphate stores, especially createine phosphate (CP) and product of ATP, are reduced and their consumption increased in di-
astolic failure. We hypothesized that the improvement of abnormal energy metabolism with Creatine Phosphate Sodium (CP)combining with fructose diphosphate (FDP) for injection may be significant since diastolic heart failure especially on moderate and severe diastolic dysfunction are associated with increased mortality and lack of effective treatment.

Methods: Randomized double-blind self-cross controlled studies were per-
formed with CP (2g/d), FDP (10g/d) or CP (2g/d) + FDP (5g/d) in 30 pts with diastolic heart failure (22 male and 8 female) and 30 cases of systolic heart fail-
ure (21 male and 9 female) received CP (1g/d) + FDP (5g/d) for two weeks and then CP (1g/d) + FDP (5g/d) for one year based on routine treatment with other drugs.

Results: Of the 30 cases of systolic heart failure, 7 were improved (grade 1) and 23 were stable (grade 2). Of the 30 cases of diastolic heart failure, 6 patients were improved (grade 1) and 24 were stable (grade 2). The differences in the grade of improvement between the 3 groups were not statistically significant (p>0.05). In the 30 cases of diastolic heart failure, all patients with symptomatic III to IV class heart failure were selected accord-
ing to 2007 diagnostic standards of diastolic and systolic dysfunction of Euro-
pean Society of cardiology and have already been treated with anti-heart failure drugs. Their average age was (72±16)years. Quality of life, exercise tolerance and clinical symptoms and outcome were observed every 14 days in the period of treatment.

Results: Increase of six minute walk distance and improvement of quality of life and cardiac function are most apparently with CP+FDP, next CP, and then FDP. In diastolic heart failure: (p=0.001, 0.01, 0.03), but improvement slightly in systolic heart failure (P=0.06). At end of one year, one died from non-cardiac cause and five rehospital-
ization in treatment group, and two died from progressive heart failure and eleven rehospitalization in control (P=0.01) without apparent side effects between two groups.

Conclusions: Improvement of exercise tolerance and quality of life, and decrease of rehospitalization with CRT therapy combining with FDP may be more apparently than CP or FDP in severe diastolic heart failure.

S. Kumar, M. Walderbørg2, P. Bhurimredy3, K. Ramkisson1, A.L. Innamisnju1, K. Looise1, K. Emmisson2, J.M. Lazar2. 1 State University of New York Health Science Center, New York, United States of America; 2Orebro University Hospital, Orebro, Sweden; 3New York Methodist Hospital, Brooklyn, United States of America

Background: Takotsubo cardiomyopathy (TSC) is a condition of reversible left ventricular (LV) systolic dysfunction. However, the diastolic functional (DF) mani-
estions of TSC have not been widely investigated. We performed retrospective analysis of DF in patients (pts) with TSC during acute and recovery phase.

Methods: We studied 27 pts (64±11 yrs, F: 24) diagnosed with TSC. All pts had echocardiogram in acute phase and at median 3 months follow up. Standard sys-
tolic and diastolic function variables including tissue Doppler of mitral annuli (E’), LV end diastolic pressure (LVEDP) estimation (based on ASE recommendation, Naghelf et al 2009) and diastolic dysfunction stages (DD) were recorded. Data was analyzed using paired T test.

Results: During acute phase, 3 (19%) had normal DD compared to 10 (63%) at recovery (p<0.001). During acute phase 6 (31%) had elevated LVEDP while none had elevated LVEDP at recovery (p=0.03). Recovery was associated with significant improvement in systolic and diastolic parameters including EF, E/E’, E/A ratio (Table 1) [Decrease in LA size] Improvement in E was linearly related to the improvement in EF (E/A = 0.1*E/E’ + 1, n=0.3, p=0.02).

Comparison of echocardiographic variable

<table>
<thead>
<tr>
<th>Variables</th>
<th>Acute Phase</th>
<th>Recovery Phase</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF %</td>
<td>45±16</td>
<td>60±6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak E wave velocity cm/sec</td>
<td>66±15</td>
<td>78±18</td>
<td>0.03</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.9±0.33</td>
<td>1.1±0.53</td>
<td>0.03</td>
</tr>
<tr>
<td>Peak A wave velocity cm/sec</td>
<td>6.3±2.6</td>
<td>8.7±3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/E’</td>
<td>10.7±3.8</td>
<td>9.2±2.9</td>
<td>0.04</td>
</tr>
<tr>
<td>LA area cm²</td>
<td>18±3.3</td>
<td>16±3.4</td>
<td>0.01</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>2.6±8.8</td>
<td>1.7±1.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Normal DD stage n (%)</td>
<td>3 (19%)</td>
<td>10 (63%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Grade 1 DD n (%)</td>
<td>2 (13%)</td>
<td>2 (13%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Grade 2 DD n (%)</td>
<td>7 (44%)</td>
<td>3 (19%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Grade 3 DD n (%)</td>
<td>10 (63%)</td>
<td>4 (24%)</td>
<td>0.001</td>
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</table>

Conclusions: TSC is associated with acute impairment of diastolic function, which improves during recovery. DF recovery parallels systolic recovery in TSC patients.
Adaptive servo ventilation improves long-term prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep disordered breathing.

1Department of Cardiology and Hematology, Advanced Cardiac Therapeutics, Fukushima Medical University, Fukushima, Japan; 2Department of Cardiology and Hematology, Fukushima Medical University, Fukushima, Japan.

Background: Effective pharmacotherapy for heart failure (HF) with preserved left ventricular ejection fraction (LVEF) is still unclear. Sleep disordered breathing (SDB) may cause cardiac diastolic dysfunction. A high prevalence of SDB has been documented in HF patients with preserved LVEF. Adaptive servo ventilation (ASV) improves SDB including Cheyne-Stokes respiration. However, it still remains unclear whether ASV improves cardiac function and long-term prognosis of HF patients with preserved LVEF and SDB.

Methods: Twenty five HF patients with preserved LVEF (defined as LVEF of ≥ 45%) and moderate-severe SDB (defined as apnea hypopnea index >15 h) were enrolled. Study subjects (apnea hypopnea index ≥39.3±15.2/h) were divided into two groups: 10 patients treated with conventional medications for HF (Non-ASV group), 9 patients treated with conventional medications and ASV (ASV group), and 6 patients treated with conventional medications alone (Non-ASV group). BNP, LVEF, and right ventricular systolic pressure (RVSP) were determined before and 6 months after treatments. Patients were followed to register cardiac events after discharge (average follow up period 728 days).

Results: Although, LVEF did not improve in both groups, BNP and RVSP significantly reduced in ASV group (BNP: 286.3±101.3 to 161.8±62.1 pg/ml, RVSPs: 40.5±16.3 to 32.1±8.1 mmHg, P<0.05, respectively), but not in Non-ASV group. Eight events (death 5, re-hospitalization 3) occurred in this follow up period. Importantly, event free rate was significantly higher in ASV group than in Non-ASV group (90.0% vs. 53.3%, logrank P<0.05).

Conclusions: These data indicate that a low-glycaemic/high-protein but not a low-fat/high-carbohydrate nutrition modulates diastolic dysfunction in overweight diabetics, improves insulin resistance and may prevent or delay the onset of diabetic cardiomyopathy and the metabolic syndrome.

HEART FAILURE WITH PRESERVED EJECTION FRACTION: BIOMARKERS

Serum cystatin C as a biomarker of cardiac diastolic dysfunction in patients with cardiac disease and preserved ejection fraction

K. Nosaka1, K. Nakamura2, K.F. Kusano2, T. Tada2, T. Miyoshi2, M. Doi1, K. Kohno2, H. Morita3, H. Hirotsu3
1Kagawa Prefectural Central Hospital, Takamatsu, Japan; 2Okayama University, Department of Cardiovascular Medicine, Okayama, Japan.

Background: Systolic and diastolic functions are independently correlated with cardiac mortality. Worsening renal function also increases mortality and hospitalization known as cardio-renal syndrome. Cystatin C (CysC) is a novel endogenous marker of kidney function. Recently, higher CysC concentrations were demonstrated to be associated with diastolic dysfunction in coronary artery disease without heart failure and chronic systolic heart failure. But it is not clear whether serum CysC is associated with diastolic dysfunction in patients with cardiac disease and with preserved ejection fraction.

Methods: We measured serum CysC, Creatinine and BNP in 124 consecutive patients with cardiac disease. The patients underwent transthoracic echocardiography at rest on the same day. eGFR was determined by the MDRD formula for Japanese. Echocardiographic values were obtained by standard 2-dimensional transthoracic approach.

Results: We measured serum CysC, Creatinine and BNP in 124 consecutive patients with cardiac disease. The patients underwent transthoracic echocardiography at rest on the same day. eGFR was determined by the MDRD formula for Japanese. Echocardiographic values were obtained by standard 2-dimensional transthoracic approach.

Conclusions: There were no significant differences in serum CysC among 5 disease groups (P=N.S). Serum CysC and eGFR showed a significant negative correlation (r = -0.70, P < 0.001), and serum CysC and BNP showed a significant positive correlation (r = 0.43, P < 0.001). In univariate analysis, Cardiac echo parameters (LVEF, LVEDd, LVEDv, e’A/E, LAD, and TAMF patterns) were significantly associated with serum CysC (p < 0.01). Multivariate linear regression analysis demonstrated TAMF patterns were independent determinants of serum CysC (β= 0.286, P < 0.01). Furthermore, sub-analysis based on patients with preserved ejection fraction (LVEF ≥ 50%) and without renal dysfunction (eGFR > 60ml/min/1.73m²), in univariate linear regression analysis, LAD, e’A, E, e’- and TAMF patterns, surrogates of cardiac diastolic function, were significantly associated with serum CysC. And multivariate linear regression analysis demonstrated that LAD and TAMF patterns were independent determinants of serum CysC (βLAD= -0.362, P < 0.01; TAMF patterns: βTAMF = 0.328, P < 0.05).

Conclusions: Serum CysC is associated with diastolic dysfunction in patients with various cardiac disease and preserved ejection fraction and without renal dysfunction. Our study also suggests that serum CysC become a surrogate biomarker of cardiac diastolic dysfunction in patients with various cardiac diseases and preserved ejection fraction.
analysis found that the relationship between visceral adipose tissue and LV diastolic dysfunction became insignificant when either TNF-α or IL-6 were introduced into the model, although TNF-α and IL-6 were both significantly associated with LV diastolic dysfunction even after adjusting for visceral fat (OR=1.51; 95% CI=1.08-2.02; P=0.033 and OR=1.82; 95% CI=1.09-3.00; P=0.031, respectively).

Figure 1. Inflammation and LV DO

Conclusions: Larger amounts of adipose tissue were associated with higher serum pro-inflammatory levels in CAPD patients, which could contribute or lead to the development of LV diastolic dysfunction. Modulating inflammatory reactions in CAPD patients could prove to be a novel therapeutic approach for managing LV diastolic dysfunction.

P4537 Pulmonary hypertension and collagen metabolism in patients with heart failure and preserved ejection fraction

M. Farrero Torres, E. Santiago, M. Battie, I. Blanco, G. Kasa, M. Cardona, M.A. Castel, J.A. Barbera, F. Perez Villa. Barcelona Hospital Clinic, Barcelona, Spain

Purpose: Pulmonary hypertension (PH) is a strong predictor of mortality in patients with heart failure with preserved ejection fraction (HFpEF). This study was designed to evaluate the association between circulating biomarkers of collagen metabolism and PH as assessed by pulmonary artery catheterization, in patients with HFpEF.

Methods: Plasma matrix metalloproteinase-2 and -9 (MMP-2 and MMP-9), tissue metalloproteinase inhibitor 1 (TIMP-1) and C-terminal propeptide of type I procollagen (CIPC) values, and Doppler echocardiography images were obtained from 21 patients with HFpEF and 21 control subjects with hypertension without HF. Patients with pulmonary artery systolic pressure (PASP) >35 mmHg were proposed to undergo a right heart catheterization.

Results: Compared to controls, HFpEF patients had higher circulating levels of MMP2 (252.6 ± 4 ng/ml, P=0.002) and CIPC (101.6 ± 7 mg/ml, P=0.016), but no significant differences in MMP9 or TIMP1. Among the HFpEF group, PH was present in 16 patients (75%). 13 of them underwent a right heart catheterization, showing PASP 74.15 ± 24 mmHg, PAPD 27.75 ± 11 mmHg. Inflammatory capillary wedge pressure (PCWP) 18.4 ± 5 mmHg, cardiac index 2.7 ± 1 L/mm², pulmonary vascular resistance 6.3 ± 4 Wood Units. Among patients with HFpEF and PH, MMP2 levels showed a linear correlation with PASP (r=0.87, P=0.004) and PAPD (r=0.71, P=0.047). Circulating CIPC values showed a linear correlation with PASP (r=0.56, P=0.04), PAPD (r=0.64, P=0.018) and with pulmonary vascular resistance (r=-0.70, P=0.007).

Conclusions: Patients with HFpEF had increased values of MMP2 and CIPC compared to hypertensive controls. Their levels showed a significant linear correlation with the invasive measurements of PH. These data suggest that MMP2 and CIPC might be useful as markers of PH development and progression in patients with HFpEF.

P4538 Expression of connective tissue growth factor in diastolic heart failure patients and canine models

C. Wu, Y. Wang, J. Lee, C. Tsai, F. Chiang. National Taiwan University Hospital, Taipei, Taiwan

Background: Diastolic heart failure (DHF) is characterized by myocardial interstitial fibrosis and left ventricular hypertrophy. Connective tissue growth factor (CTGF) is an emerging marker for tissue fibrosis. The study investigated the association between CTGF and DHF from animal model to clinical indices.

Methods: A total of 120 patients with a diagnosis of DHF confirmed by echo-cardiography and 60 matched controls were recruited. Soluble plasma levels of CTGF were measured in all subjects and the associations with diastolic function parameters were calculated. Canine model of DHF was induced by aortic banding. Left ventricular (LV) pressures, LV volumes, and transmittal Doppler were obtained before and after pressure loading (at baseline and after 6months). Myocardium tissues were collected, and western blotting was used to detect the protein expression of CTGF for each dog. The correlation for CTGF and the severity of diastolic dysfunction was then calculated.

Results: Patients with DHF presented significantly higher CTGF levels than the controls. Significant correlations (all P < 0.05) were found for CTGF and E/e’ (r = 0.55), E/A (r = 0.5) in advanced DHF patients (E/e’ > 15). After 24 weeks in canine models, the protein expression of CTGF from LV myocardial tissue was significantly increased (p<0.01) compared with the controls (sham dogs). Moreover, the expression of CTGF paralleled the severity of LV diastolic dysfunction parameters and hemodynamic changes.

Conclusions: Both Plasma and myocardium CTGF levels had significant correlations to the severity of DHF. Our study offered the evidence to apply novel therapies for DHF patients aim to down-regulate the overexpression of CTGF.

P4539 Resveratrol, a SIRT1 activator, prevents cardiomyopathy in dystrophin-deficient mice by down-regulation of p300

A. Kuro1, M. Tanno1, T. Miki1, S. Ishikawa1, Y. Hori2, T. Miura1.1 Sapporo Medical University, Second Dept. of Internal Medicine, Sapporo, Japan; 2 Sapporo Medical University, Department of Pharmacology, Sapporo, Japan

Background and purpose: Heart failure is a main cause of death in patients with Duchenne muscular dystrophy (DMD), a disorder caused by defective gene for dystrophin. However, there is no effective therapy for prevention of heart failure in DMD. The aim of this study was to examine whether activation of SIRT1, an NAD+-dependent histone/protein deacetylase, by use of resveratrol prevents cardiomyopathy due to dystrophin deficiency.

Methods and results: We used dystrophin-deficient mice (mdx) as a model of DMD and C57BL10 mice as controls. Mdx were untreated or orally treated with resveratrol (400 mg/kg/day) from 9 weeks of age. Diastolic left ventricular (LV) thickness (0.72 ± 0.02 vs. 0.82 ± 0.03 mm), heart-to-body weight ratio (4.1 ± 0.6 vs. 5.4 ± 0.8 mg/g), and atrial natriuretic peptide (ANP) mRNA level (4.3-fold) were significantly increased in 40-week-old mdx mice compared with those in the control. Echocardiography showed that diastolic LV posterior wall movement, an index of LV diastolic function, was significantly slower in the untreated mdx than in the controls (21.1 ± 3 vs. 30.2 ± 2 mm/sec), although LV dimension and LV ejection fraction were similar in the two groups. Ventricular fibrosis and collagen gene expressions were increased in the mdx group. These phenotypes of mdx mice were significantly suppressed by treatment with resveratrol. Resveratrol reduced myocardial β-actin acetyl-histone H3 levels determined by immunohistochemistry and immunoblot in mdx hearts, indicating activation of SIRT1, Phospho-ERK/12 and TGFβ1 mRNA levels in mdx hearts were not reduced by resveratrol. However, resveratrol suppressed the protein level of the transcription co-activator p300, a pro-hypertrophic and pro-fibrotic histone/protein acetyltransferase, in the mdx myocardium. In vitro experiments demonstrated that p300 dose-dependently increased ANP promoter activity, which was suppressed by overexpression of wild-type SIRT1. Wild-type SIRT1, but not deacetylate inactive mutant SIRT1, reduced p300 protein level, which was blocked by the proteasome inhibitor MG132. In addition, SIRT1 was found to promote p500 deacetylation and polyubiquitination.

Conclusions: Resveratrol attenuates both cardiac hypertrophy and fibrosis and improves diastolic LV function in the mdx presumable by SIRT1-mediated down-regulation of p300. SIRT1 activation may be a novel strategy in treatment of cardiomyopathy in DMD.

P4540 Continuous infusion of the novel chimeric natriuretic peptide cenderitide in the dahl salt sensitive rat model of hypertension and renal dysfunction: evidence for renoprotection

M. Schiltgen1, A. Walsh1, D. Evans2, H. Lieu3, J.C. Burnett2. 1 Medtronic, Inc., Minneapolis, United States of America; 2 Nile Therapeutics, Inc., San Mateo, United States of America; 3 Mayo Clinic, Rochester, United States of America

Purpose: Cenderitide (CD-NP) is a chimeric natriuretic peptide created by fusing the 22 amino acid human C-type natriuretic peptide (CNP) with the 15 amino acid C-terminus of Dendroaspis natriuretic peptide (DNP). The peptide was engineered to have natriuretic, diuretic, antihypertensive and renoprotective effects through binding of both guanylyl cyclase (GC)B and GC-A receptors. Continuous administration of CD-NP is of interest for fluid management in patients with heart failure and impaired renal function. The purpose of this study was to deter-
Antibodies to C-ending (intracellular) fragment of the angiotensin II type 1 receptor and endothelial NO synthase in patients with congestive heart failure: first clinical experience

T.Y. Spitnik1, T.H. Temiralsultanova1, O.V. Ilyukhy1, Y.M. Lopatina2
1 Volgograd Regional Cardiological Centre, Volgograd, Russian Federation; 2State Medical University, Russian Federation; 3Volgograd State Medical University, Volgograd Regional Cardiological Centre, Volgograd, Russian Federation

Background: Antibodies to C-ending (intracellular) fragment of the angiotensin II type 1 receptor and endothelial NO synthase are a principally new classes of neuromodular modulators. The aim of our study was to investigate the efficacy and safety of combination these antibodies (anti-AT1+E-NO-synthase) in pts with congestive heart failure (CHF).

Methods: 60 pts (mean age 56.9 ± 1.3 years) with CHF (NYHA class II-IV, mean 2.4 ± 0.7, mean ejection fraction 29.6 ± 0.9%) were included into the randomized, single-blind, placebo-controlled study. Baseline therapy (ACE inhibitor, β-blocker, diuretics) wasn’t changed during the study. Pts with CHF were randomly assigned to anti-AT1+E-NO-synthase 3 tabs/day (group I, n=30) or placebo (group II, n=30).

Results: After 6 months of therapy with anti-AT1+E-NO-synthase NHYa class reduced to 42.6% (p < 0.008), in placebo group to 52.4% (n.s.). Significant increase of left ventricular ejection fraction was noted in both groups: group I +25.47% (p < 0.0001), group II +6.29% (n.s.). Significant increase both exercise time (+34.7%, p < 0.0005) during treadmill-test and distance during 6-min walking test (+24.8%, p < 0.0002) was noted only in the group I. Adverse events related with anti-AT1+E-NO-synthase were not observed.

Conclusions: The adding of combination of antibodies to C-ending (intracellular) fragment of the angiotensin II type 1 receptor and endothelial NO synthase to standard therapy is a promising way for treatment pts with CHF. Large clinical trials are indicated.

Transplant reduces pathological cardiac fibrosis and improves diastolic function following kidney dysfunction: implication for cardio-renal syndrome

M. Watanabe1, F. Sae2, A. Kompa3, B. Wang4, S. Lekawansiri4, A. Boyle5, R. Gilbert1, K. Connolly1, D. Kelly1, H. Krun1, 1Monash Centre of Cardiovascular Research & Education in Therapeutics, Melbourne, Australia; 2New York University, New York, United States of America; 3University of California San Francisco (UCSF), San Francisco, United States of America; 4St. Michael’s Hospital, Toronto, Canada; 5The University of Melbourne, St Vincent’s Hospital, Department of Medicine, Melbourne, Australia

Background: Kidney dysfunction in heart failure (HF) is associated with increased mortality, morbidity and cost of care known as cardio-renal syndrome (CRS). Fibrosis plays an important role in disease progression in HF in patient with CRS. We examined the effect of the anti-fibrotic agent, tranilast, on ameliorating these processes.

Methods: 5/6 subtotal nephrectomy (STNx) was induced in male Sprague Dawley (SD) rats. Animals were randomized to receive either tranilast (300mg/kg/day, p.o.) or vehicle (n=14) for 12 weeks. Sham operated control animals also received vehicle (n=9). Glomerular filtration rate (GFR) was measured with a single shot 125I-M-DTPA clearance. Blood pressure was measured by tail-cuff plethysmography. Echocardiogram was performed to access cardiac function before cardiac tissues were harvested for immunohistology analysis.

Results: Tranilast treatment had significant effect on blood pressure (vs STNx+Vehicle, P < 0.05) and reduced collagen I and III deposition (vs STNx+Vehicle, P < 0.05) in the heart post STNx (Table).

Conclusion: Tranilast reduced cardiac fibrosis, renal function and blood pressure in STNx rats as well as improved diastolic function. These findings support the use of direct antifibrotic strategies in CRS.

Reno-protective and diuretic therapy with low doses of natriuretic peptide and dopamine in acute heart failure patients

M. Kamiya1, N. Sato2, A. Nozaki2, M. Akuya2, H. Okazaki2, Y. Takahashi2, K. Mizuno1, 1 Nippon Medical School, Tokyo, Japan; 2The Fraternity Memorial Hospital, Tokyo, Japan

Purpose: Beta-blockers improve survival in heart failure, but patients run a gauntlet of side-effects in clinical practice.

Methods: We searched MedLine (1950 to present) up to an including November 8 2011 using keywords: Beta-blocker, systolic heart failure, randomized controlled trial and RCT. We identified RCTs comparing a single beta-blocker versus placebo only; trials were excluded if they were not randomized, double-blinded studies or had a cross-over design, if they did not report side-effect data separately for both arms, and if other medications were selectively introduced.

Results: Only 5 of 33 alleged side-effects are actually made more common by beta-blockers. Out of 100 patients reporting hyperglycaemia on beta-blockers in only 1 (85% CI 2–32), is that symptom genuinely caused by the beta-blocker; in the remaining 83 it is natural or caused by the information given. Of patients reporting side-effects, the proportion in whom the drug is genuinely the cause is also low for diarrhoea (18/100, CI 5–30), and dizziness (19/100, CI 11–27). Only two side-effects are genuinely caused by the drug in the majority of subjects: dyspnoea (67/100, CI 56–79) and intermittent claudication (59/100, CI 19–98). 23 of 33 alleged side-effects occur equally with drug or placebo. Remarkably, beta-blockers reduce depression (by 35%, p < 0.01) and insomnia (27%, p = 0.01).

Conclusions: Apparent side-effects of beta-blockers in heart failure are overwhelmingly caused not by the drug, but by heart failure itself or nocebo drug information. Realising how few of the patients reporting side-effects are genuinely caused by the medication may assist patients and doctors deciding on trying, or stopping, medication. Listing untrue side-effects in heart failure harms patients through the nocebo effect (if they take it) or worsened outcomes (if they don’t), and wastes consultation resources.
Methods: Twenty-four patients (age 74.9 ± 9.3 yrs; left ventricular ejection fraction 40.2 ± 17.6%) with AHF were enrolled and were treated with intravenous low dose hANP. When adequate diuresis was not obtained by 4 hours after administration despite increasing the dose of hANP twice, low dose DA (1-3 μg/kg/min, n=12) or low dose furosemide (F, 10-30 mg injection, n=12) was randomly added. Serum creatinine, a novel renotubular marker, urinary L-type fatty acid-binding proteins (L-FABP) and an oxidative stress marker, urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) decreased significantly in DA but not in F (fig). Serum creatinine did not change in both groups. Urinary L-FABP and 8-OHdG decreased significantly in both groups (fig). Heart rate did not change in both groups. Systolic blood pressure decreased significantly in DA and F groups (137.3 ± 15.8, P = 0.021, 137.1 ± 29.4 to 108.3 ± 16.1 mmHg, P = 0.007, respectively). Urine volume increased significantly in both groups (fig). Serum creatinine did not change in both groups.

Conclusions: The combination therapy with low doses of hANP and DA might be a renoprotective strategy for AHF management.

Cardiac iron and function by CMR in thalassemia major patients treated with combined deferiprone and desferrioxamine regimen versus monotherapies: a multi-center, observational and prospective study

1Fondazione G.Monasterio CNR-Regione Toscana and Institute of Clinical Physiology, Pisa, Italy; 2Epidemiology and Biostatistics Unit, Institute of Clinical Physiology, CNR, Pisa, Italy; 3Serv. Prevenz. Diagnosi e Cura Talassemia, Ospedale “G. di Cristina”, Palermo, Italy; 4U.O. Microcitemia, A.O. “Bianchi-Melacrino-Morelli”, Reggio Calabria, Italy; 5Centro Microcitemia – D.H. Thalassemia, Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; 6Department of Radiology, University of Palermo, Palermo, Italy; 7Unità Microcitemia – Padiglione CV, A.O.R.N. Cardarelli, Napoli, Italy

Purpose: To the limited data available in literature, the aim of this multi-center study was to prospectively assess in thalassemia major (TM) the efficacy of combined deferiprone (DFP) and desferrioxamine (DFO) regimen versus DFP and DFO in monotherapy by cardiovascular magnetic resonance imaging (CMR) over a follow up of 18 months.

Methods: Among the first 1135 TM patients in the MIO (Myocardial Iron Overload in Thalassemia network), we evaluated those who had been received combined regimen (N=51) or DFP (N=39) and DFO (N=74) monotherapies between the two CMR scans. Iron overload was measured by T2* multiecho technique. Biventricular function parameters were quantitively evaluated by cine images.

Results: The percentage of patients that maintained a normal global heart T2* value was comparable between DFP+DFO versus both groups. Among the patients with myocardial iron overload at baseline, the changes in the global heart T2* and in biventricular function were not significantly different in DFP+DFO versus the DFP group. The changes in the global heart T2* were significantly higher in the DFP+DFO versus the DFO group. Combined therapy did not show an additional effect on heart function.

Conclusions: In TM patients at the dosages used in the real world, combined DFP+DFO regimen was more effective in removing cardiac iron load only versus the DFO group. Combined therapy did not show an additional effect on heart function.

Evaluation of safety, tolerability, PK and hemodynamic properties of JNJ-39588146 (stresscopin) in healthy and HF subjects: a phase 1 ascending dose randomized multicenter trial

A. Olson1, V. Conraads2, B. Wallens3, J. Dai1, J. Jiang1, O. Bueno1, D. Polidori1, P. Gengo1, M. Lu1, N. Sharkley1, Janssen Research & Development, Early Development and CVM Discovery, La Jolla CA, United States of America; 2University of Antwerp, Antwerp, Belgium; 3ZNA Stuivenberg, Antwerp, Belgium

Purpose: JNJ-39588146 (human Stresscopin (SCP)) is a member of the cort-
corticot releasing factor family of peptides. It is a highly selective agonist of CRFR2. This three part study assessed the safety, PK, and hemodynamics of SCP in healthy subjects (HS) and heart failure (HF) subjects.

Methods: In Part 1, 30 male HS were randomized to receive continuous IV infusions of either SCP (0.1 to 144 ng/kg/min, N=25) or placebo (N=5) for 7.5 hours (h), with increases in dose at 2.5 and 5h. In Part 2, 20 subjects with HF with EF < 40% were randomized to receive either SCP (0.3 to 54ng/kg/min, N=13) or placebo (N=7) for 7.5h, with 2 increases in dose. In Part 3, 26 male and female HS were randomized to receive a constant IV infusion of either SCP (54ng/kg/min, N=20) or placebo (N=6) for 24 or 72h. Heart rate (HR) and Cardiac index (CI) were measured by impedance cardiography. HR was noted to decrease during the infusion for placebo subjects. This “placebo effect” was considered when analyzing the HR and CI data for SCP treated subjects.

Results: SCP was safe and well tolerated with no notable changes in ECG parameters and no ventricular arrhythmias. The proportion of subjects with AEs who received SCP at doses >36 ng/kg/min showed a similar increase in the subjects receiving placebo. The mean baseline CI in the HS and HF subjects were 3.2 and 2.9L/M2. In HS who received SCP (0.1 to 36ng/kg/min), no notable change in CI, HR, or BP was seen compared to placebo. In HF subjects who received SCP (0.3 to 36ng/kg/min), a higher mean CI (7-15%), was seen compared to placebo. Though numerically lower BP was seen in HF subjects dosed with SCP compared to placebo, no notable change in BP and no dose relationship was observed. At doses >36 ng/kg/min, a dose-related increase in HR was seen in both HS and HF subjects. In HF subjects, the increase in HR was 7-8 bpm at the highest dose (54ng/kg/min) compared to placebo. A greater proportion of subjects who received >36 ng/kg/min of SCP had AEs compared to placebo; the most common AEs in SCP treated subjects were: headache, back pain, feeling hot, nausea, vomiting, and catheter site pain or inflammation. In general, SCP showed linear pharmacokinetics as the systemic exposures increased with the infusion rate. The elimination was multi-phasic, with initial rapid decline of SCP (1/2=10-15 min) followed by a slower terminal phase. No antidrug antibodies were detected.

Conclusion: IV infusions of SCP were safe and well tolerated in HS and HF subjects. SCP showed linear PK that was similar between HS and HF subjects. Overall, the HR, CI and PK data were consistent with pre-clinical findings.

P4549

Should we achieve the target doses of beta-blockers in chronic heart failure patients with adequate heart rate control?

K. Leemasawat, A. Phrommintikul, R. Kanjanavanit, W. Wongcharoen, K. Okonogi, L. Yongsmith, S. Yopprasert, A. Sukonthasarn. Chiang Mai University, Faculty of Medicine, Chiang Mai, Thailand

Purpose: Recent studies indicated that heart rate was an important target for Chronic heart failure (CHF) treatment, whereas the importance of doses of beta-blockers was still uncertain. We conducted the study to determine the survival prognosis of achieving the target doses of beta-blockers in CHF patients with adequate heart rate control.

Methods: We screened for symptomatic CHF patients with reduced LVEF fraction (< 40%) and newly initiated beta-blocker treatment (bisoprolol, carvedilol, metoprolol tartrate, or nebivolol) with at least 1 year follow-up in Hospital between the year 2000 and 2010. Among 2,654 CHF patients, 253 patients were eligible and were classified into 4 groups, according to heart rate control (<70 vs. ≥70) and target beta-blocker dose (achieved vs. not achieved) (Figure 1). The endpoint of the study was all-cause mortality.

Results: The baseline NYHA functional class, heart rate and blood pressure were similar in all groups. The patients in group which the target beta-blocker dose was not achieved had significantly more frequent history of myocardial infarction (62.0% vs. 28.0%, p<0.001), and had lower prevalence of hypertension (40.8% vs. 62.2%, p<0.002). The median follow-up was 50.5 months (IQR 28.7-73.0). The all-cause mortality was significantly lower in the group (i) than in the other groups (Figure 1). After adjusting for possible confounding factors, the difference among groups remained significant (p<0.030).

Figure 1

Conclusions: The CHF patients who both achieved the target doses of beta-blockers and had adequate heart rate control had the best survival prognosis. We should make an effort to achieve the target doses of the beta-blockers, even the heart rate is well controlled.
in decompensated HF. Interestingly, as many as 26% of patients with pulmonary oedema received isotropes and 20% were given vaspressors whereas only 15% of pulmonary oedema patients had systolic blood pressure <120 mmHg. CPAAP was used only in 50% of pulmonary oedema patients.

Conclusion: The management of AHF differs between ESC clinical classes. The use of IV nitrates and CPAAP was lower than expected whereas there was overseuse of isotropes and vaspressors especially in pulmonary oedema.

Continuous furosemide infusion versus furosemide manitol infusion in acute congestive heart failure

M. Turagam1, P. Velagapudi2, V.S. Hanumanthu3, A. Kocheril1, J. Holley4, 1Medical College of Wisconsin, Milwaukee, United States of America; 2University of Wisconsin-Madison, Department of Medicine, Madison, United States of America; 3Dana Farber Cancer Institute, Boston, United States of America; 4University of Illinois Urbana-Champaign/ Carle Foundation Hospital, Urbana, United States of America

Background: Loop diuretics remain the cornerstone for fluid mobilization in patients with acute congestive heart failure (CHF) although there is little evidence regarding the ideal dosing strategies and method of administration. Data on the use of mannitol for prophylaxis and/or treatment of acute CHF is controversial and the role of continuous infusion is still not well established.

Methods: A retrospective study of 233 patients with CHF [N=108 who received treatment with continuous furosemide-manitol infusion (FM) and N=125 with conventional (C) furosemide infusion] was performed. Infusions were administered intravenously for a period of 1-4 days. Dose titration was protocol-driven and based on urine output. Outcomes of diuresis achieved, death during hospitalization, dialysis receipt, length of hospital stay, effects on kidney function and electrolytes were assessed. Data are reported as mean±SD.

Results: In the comparison of continuous furosemide infusion, there was no significant difference in patients’ weight (-4.7±1.9 kg and -4.8±2.03 kg, p=0.62) or in the mean creatinine level (0.5±0.3 mg/dl and 0.4±0.2 mg/dl, p=0.33), respectively; P=0.45. There was no significant difference between these groups in the need for dialysis (9.6% and 9.2%, p=0.98), in hospital death (10.4% and 10.1%, p=0.99) and of hospitalization (6.5±1.2 and 6.0±1.5 days, p=0.61). Patients who required dialysis had a lower diuretic response [FM (-0.8±0.3 kg vs 4.9±1.9 kg, p=0.02); furosemide (-0.7±0.2 kg vs 4.8±1.3 kg, p<0.003)], higher baseline creatinine [FM (2.8±1.6 mg/dl vs 2.5±1.2 mg/dl, p=0.05); furosemide (2.9±1.3 mg/dl vs 2.6±1.6 mg/dl, p=0.04)], higher BNP on admission (FM 21.0±19.9 vs 17.35±8.60, p=0.05; furosemide 234.0±560 vs 165.0±590, p=0.04) and a higher incidence of acute kidney injury on admission (FM 100% vs 48%, p=0.001; FM 100% vs 76%, p=0.002).

Conclusion: FM is equally efficacious as furosemide infusion in severe CHF. Mortality tends to be high in CHF patients with underlying kidney failure.

Zofenopril and ramipril plus ASA in post-myocardial infarction patients with left ventricular systolic dysfunction: a post-hoc analysis in preserved or impaired left ventricular fraction at entry

C. Borghi, E. Ambrosioni on behalf of SMILE-4. San’re Orsola-Malpighi Polyclinic, Department of Internal Medicine, Bologna, Italy

Background: Concomitant administration of an angiotensin-converting enzyme inhibitor (ACEI) and acetyl salicylic acid (ASA) is a common option in patients with both heart failure and ischemic heart disease. However, the well-known pharmacological interaction between ACEI and ASA may be responsible for a reduction of the positive effect of ACEI on cardiovascular outcomes. In the SMILE-4 Study we have shown a more favorable impact of zofenopril plus ASA than ramipril plus ASA combination on 1-year occurrence of major cardiovascular events in patients with acute myocardial infarction (AMI) complicated by left ventricular dysfunction (LVD). Objective: to compare zofenopril and ramipril efficacy in combination with ASA in a subgroup of patients of the SMILE-4 with preserved (40%) or impaired (<40%) left ventricular fraction at entry.

Methods: The SMILE-4 was a phase IIIb, randomized, double-blind, parallel-group, multicenter, European study comparing the safety and efficacy of zofenopril and ramipril in combination with ASA in patients with LVD (clinical signs of heart failure or a left ventricular ejection fraction ≤0.45) following AMI. The primary study end-point was 1-year combined occurrence of death or hospitalization for major cardiovascular causes. Information on LVEF at baseline was available in 710 out of the 716 patients of the intention-to-treat population.

Results: In the main study population the primary outcome was significantly reduced by zofenopril vs. ramipril (odds ratio, OR and 95% confidence interval, CI: 0.70, 0.51-0.96; p=0.028). Overall, 448 (63.1%) patients had preserved and 262 (36.9%) impaired LVEF at baseline. In the first group, the rate of major cardiovascular events was significantly lower than in patients with impaired LVEF (22.5% vs. 32.8%; OR: 0.60, 0.39-0.91; p=0.016). It was the case also for the group of patients with impaired LVEF, though between-group difference was not statistically significant (37.7% zofenopril vs. 44.4% ramipril; OR: 0.77, 0.47-1.26; p=0.297). The reduction in the risk of major cardiovascular events was significantly larger (p=0.019) in patients with preserved LVEF at baseline.

Conclusions: This retrospective analysis of the SMILE-4 Study confirmed the superiority of zofenopril plus ASA as compared to ramipril plus ASA in the prevention of long-term cardiovascular outcomes. The benefit was particularly evident in subjects with preserved left ventricular function at study entry.

Treatment effect versus selection bias in systolic heart failure patients receiving higher target doses of ACE inhibitors: Insights from Studies of Left Ventricular Dysfunction (SOLVD) treatment trial

A. Ahmed1, B. Pitt2, G.S. Filipatos3, I. Aban4, P. Deedwania5, G.C. Fonarow6, D.E. Forman7, M. Gheorghiade8, W.S. Aronow9, R.C. Bourge10, 1University of Alabama at Birmingham, Birmingham, United States of America; 2University of Michigan, Ann Arbor, United States of America; 3University of Athens Medical School, Athens, Greece; 4University of California San Francisco, School of Medicine, Fresno, United States of America; 5University of California Los Angeles (UCLA), Los Angeles, United States of America; 6Harvard Medical School, Brigham and Women’s Hospital, Boston, United States of America; 7Northeastern University, Feinstein School of Medicine, Chicago, United States of America; 8New York Medical College, Westchester Medical Center, Valhalla, United States of America

Background: In RTPs of ACE inhibitors (ACEis) in systolic heart failure (SHF), both ACEis and placebo were uptitrated to higher target doses if tolerated. The role of this implicit selection bias on mortality remains unclear.

Methods: In SOLVD Treatment trial, SHF (EF ≤35%) patients were randomized to placebo or enalapril. During 2-3 yrs post-randomization, study drugs were uptitrated to target doses (≥20 mg/day) in 61% (748/1234) and 57% (696/1224) of pts in placebo and enalapril groups, respectively. Primary outcome was all-cause mortality (median follow-up, 35 mos).

Results: When compared with overall placebo, only target dose enalapril pts had significant mortality reduction (HR, 0.79, 95% CI, 0.68–0.93; p<0.004). However, when compared with dose-specific placebo groups, both target and below-target dose enalapril pts had similar mortality reductions (5% absolute and 10% relative; p for interaction, 0.970; Table). Mortality reduction associated with target dose was similar in both treatment groups (Figure).

Table. All-cause mortality by below-target dose enalapril (vs. below-target placebo) and target dose enalapril (vs. target dose placebo) in the SOLVD Treatment trial.

Dosages Events in Events in Absolute risk Multivariable- P value

<table>
<thead>
<tr>
<th>Placebo group</th>
<th>Enalapril group</th>
<th>difference</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below-target 40% (196/486)</td>
<td>35% (185/528)</td>
<td>5%</td>
<td>0.90 (0.81–0.998)</td>
</tr>
<tr>
<td>Target 38% (267/748)</td>
<td>33% (292/900)</td>
<td>5%</td>
<td>0.90 (0.82–0.98)</td>
</tr>
</tbody>
</table>

Conclusions: Below-target dose enalapril reduced mortality in SHF, and uptitration to target dose had little additional treatment effect. Similar mortality reduction associated with target dose of both enalapril and placebo suggest selection bias associated with dose uptitration.

Statin therapy and clinical outcomes in acute heart failure patients complicating acute myocardial infarction: insights from the EPHEBUS trial

D. Dobre1, P. Rossignol1, Y. Muri1, A. Parkhomenko2, Z. Lamiral1, H. Krum1, D.J. Van Veldhuisen5, B. Pitt2, F. Zamald3, 1INSERM, Center of Clinical Investigation 9501, Lorrain Institute of Heart and Vessels Louis Mathieu, Nancy, France; 2University of Bristol, Bristol, Slovenia; 3University of Kiev, Kiev, Ukraine; 4Monash University, Melbourne, Australia; 5University Medical Center Gröningen, Department of Cardiology, Groningen, Netherlands; 6University of Michigan, Ann Arbor, United States of America

Purpose: Several clinical trials have shown that in acute and post-acute myocardial infarction (MI), statin therapy improves cardiovascular (CV) outcomes, but in those trials pts with acute heart failure (HF) were excluded or only few were enrolled. In patients with chronic heart failure (CHF), initiation of statin therapy reduces CV hospitalizations but not all-cause or CV mortality. However, these trials did not investigate whether patients who evolved to HF while being on statin benefited from this therapy. We aimed to assess the association between statin therapy and clinical outcomes in the setting of acute HF with systolic dysfunction complicating acute MI.

Methods: We performed a post-hoc analysis in 6632 patients included in the...
Efficacy of ivabradine therapy on right heart and increase of RV EF and E/A at use, seems to be related to improvement of right heart parameters, neurohormonal changes and reduction of BNP, NT -pro-BNP and hsCRP.

Methods: Decrease of BNP, NT-pro-BNP and hsCRP values and no relationship between HR and the dose of carvedilol, which remained significant after adjustment for clinical status.

Results: Polishing registry demonstrates high prevalence of increased resting HR in a general population of patients with systolic HF in a sinus rhythm (65% of the whole cohort) (age: 66±11 y, BMI: 28±2.4 kg/m², men: 64%, NYHA class III: 31%, previous MI: 61%, diabetes: 33%). Mean±SD HR was 75±13 bpm, median with lower/upper quartiles 72 (68-80) bpm. HR >70 bpm and ≥75 bpm were found in 68% and 47% of patients, respectively, with increasing frequency along NYHA classes (II/III/IV - HR >70 bpm: 65%/67%/74%; HR >75 bpm: 42%/45%/53%; 60% vs. 70%, p<0.001). In a multivariable stepwise model, high HR was related to high syst BP (p<0.001), presence of pulmonary congestion (p<0.05) and peripheral oedema (p=0.001), advanced NYHA class (p<0.01), younger age (p<0.01) and female sex (p<0.001). In a total of 840 patients, HR >75 bpm was associated with 30% and 40% higher risk for in-hospital death and all-cause mortality, respectively.

Conclusions: Observational data demonstrated that HR >75 bpm is a strong and independent predictor of adverse outcomes in patients with systolic HF and high HR, and links between applied therapy and achieved HR in everyday practice are unclear.

Methods: Registry DATA-HELP was performed in X-XII 2009 in Poland in a randomly selected representative sample of 5563 outpatients with clinical diagnosis of HF and LVEF<45%; resting HR was available in 5513 subjects (99%).

Results: We analysed 3620 patients with systolic HF in a sinus rhythm (65% of the whole cohort) (age: 66±11 y, BMI: 28±2.4 kg/m², men: 64%, NYHA class III: 31%, previous MI: 61%, diabetes: 33%). Mean±SD HR was 75±13 bpm, median with lower/upper quartiles 72 (68-80) bpm. HR >70 bpm and ≥75 bpm were found in 68% and 47% of patients, respectively, with increasing frequency along NYHA classes (II/III/IV - HR >70 bpm: 65%/67%/74%; HR >75 bpm: 42%/45%/53%; 60% vs. 70%, p<0.001). In a multivariable stepwise model, high HR was related to high syst BP (p<0.001), presence of pulmonary congestion (p<0.05) and peripheral oedema (p<0.001), advanced NYHA class (p<0.01), younger age (p<0.01) and female sex (p<0.001). In a total of 840 patients, HR >75 bpm was associated with 30% and 40% higher risk for in-hospital death and all-cause mortality, respectively.

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Methods: Are there relationships between high resting heart rate and non-doses of beta-blockers in patients with systolic heart failure in contemporary Poland? Results of DATA-HELP study

Are there relationships between high resting heart rate and non-doses of beta-blockers in patients with systolic heart failure in contemporary Poland? Results of DATA-HELP study

E.A. Jankowska1, B. Kurian2, W. Banasiak3, P. Popikowski1 on behalf of On behalf of Developmental-Help-study (Diagnostic And Therapeutic methods, used in patients with systolic heart failure, Living in Poland) investigators.

Background: Resting heart rate (HR) is associated with poor outcome, and its reduction due to both β- adrenergic and II) current blockade has provided survival benefits in patients with systolic heart failure (HF). The magnitude of contemporary European population of patients with systolic HF and high HR, and links between applied therapy and achieved HR in everyday practice are unclear.

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Purpose: Are there relationships between high resting heart rate and non-doses of beta-blockers in patients with systolic heart failure in contemporary Poland? Results of DATA-HELP study

Subcutaneous furosemide can prevent hospitalization in fluid overload decompensation of chronic heart failure


Purpose: Chronic heart failure (CHF) is a high prevalent disease, a main cause of admission and it supposes a high economic cost. The basis of treatment for fluid overload consists of diuretics. Furosemide is the most widespread. When oral treatment is not enough, the endovenous route is the most frecuent access, although different dilutions of furosemide can be used in patient's conditions. During a mean follow-up of 16.7 months, all-cause death occurred in 385 (12%) patients with- and in 647 (18%) patients without a stent (p < 0.001). After extensive adjustment, the risk of all-cause death remained 20% lower in patients on stent (HR 0.80, CI 0.69-0.92, p= 0.001). This positive association was mostly due to a lower CV death (HR 0.76, CI 0.65-0.89, p=0.0002).

In addition, patients on stent had a lower risk of a first hospitalization for stroke. In contrast, stent use was associated with a slightly higher rate of non-CV hospitalizations (HR 1.16, CI 1.02-1.33, p=0.02).

Conclusions: In patients with post-MI acute HF, stent therapy was associated with a lower risk of all-cause and CV death, but apparently with a higher risk of non-CV hospitalizations. Although clinical trials prospectively randomizing patients to stent are required to validate these findings, our results suggest that patients with acute HF complicating acute MI may benefit from being on stent therapy.

Do early and late nephroneurotrophic effects differ with different inhibitors of renin-angiotensin-aldosterone system in chronic heart failure patients?


Purpose: To compare the extent of nephroneurotropic in chronic heart fail-
Effects of valsartan and amlodipine on heart failure and severe left ventricular dysfunction

C. Lombardi, V. Carubbi, C. Ciccarese, A. Castini, V. Lazzarini, S. Zizzari, S. Piovannelli, E. Vizzardi, S. Nodari, M. Metra, L. De Cas. Civil Hospital of Brescia, Department of Cardiology, Brescia, Italy

Background: Chronic heart failure (CHF) is characterized by several micronutri- ent deficits. Amino acid supplementation may have a positive impact on nutritional and metabolic status in patients with CHF. L-Carnosine (β-alanyl-L-Histidine) is ex- pressed at high concentration in myocardium and it has anti-oxidant and free rad- icals scavenger properties. No study has been conducted in patients with heart failure.

Methods: Fifty patients with stable CHF and severe left ventricular systolic dysfunc- tion on optimal medical therapy were randomized 1:1 to receive oral orodis- pensible L-Carnosine (500 mg OD) or standard treatment. Left ventricular ejection fraction (LVEF) has been measured by transthoracic echocardiography and equi- librium radionuclide ventriculography. Cardiopulmonary stress test, six minutes walking test (6MWT) and quality-of-life (QoL) have been performed at baseline and after 6 months.

Result: The mean age of patients was 61.8±9.6 years, 44 (88%) were male. At baseline 98% of patients had NYHA class II and the mean LVEF was 32±6.8%.

Conclusion: This study suggest that L-Carnosine, added to conventional therapy, has beneficial effects on exercise performance and QoL in stable CHF. More data are necessary to evaluate the effects of L-Carnosine on left ventricular function and prognosis in CHF.

SECONDARY PREVENTION: FROM AWARENESS TO ACTION

Prevalence, co-prevalence and awareness of cardiovascular risk factors - results from the population based Gutenberg Health Study

J. Prochaska1, S. Goebel1, A. Schulz2, R.B. Schnabel1, S. Ziss2, M. Kohnen2, S. Herber2, C. Espinola-Klein2, S. Blankenberg1, T. Mueller2, P.S. Wiel1,1 University Medical Center, Department of Internal Medicine II; Center for Thrombosis and Hemostasis, Mainz, Germany; 2University Medical Center Hamburg-Eppendorf, Department of Cardiology and Electrophysiology, Hamburg, Germany

Purpose: Classical cardiovascular risk factors (CVRF) explain a substantial part of the risk for cardiovascular diseases. In past decades, prevalences of CVRF have changed. The presence, awareness and medical treatment of CVRF may differ strongly. Current data from large-scale population-based studies are limited.

Methods: We investigated a sample of 10,000 participants from the age - gender - and residence-stratified, population-based Gutenberg Health Study, examined from 2007 to 2008. Data were obtained from self-reported data, computer-assisted personal interviews, blood pressure measurements and blood sampling (fasting values) according to standard operating procedures with detailed quality control.

Results: The sample comprised 4,983 women (w) and 5,017 men (m), aged 35 to 74 years. The overall prevalence was: hypertension 46.0% (m:50.2%, w:41.9%), dyslipidemia 27.7% (m:35.6%, w:19.9%), obesity 24.1% (m:23.5%, w:20.8%), smoking 20.8% (m:22.7%, w:19.0%), family history of myocardial in- farction 16.6% (m:15.6%, w:17.6%) and diabetes 6.1% (m:7.7%, w:4.5%). Anal- ysis of co-prevalences showed that the highest co-prevalences were found for prevalent diabetes, obesity and hypertension (β-alanyl-L-Histidine) is ex- pressed at high concentration in myocardium and it has anti-oxidant and free rad- icals scavenger properties. No study has been conducted in patients with heart failure.

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Use of lipid lowering therapy in primary care across Europe: results from the European study on cardiovascular risk prevention and management in Daily Practice (EURIKA). Clinical Research, Paris, France; 9National Centre for Cardiovascular Research (CNIC), Madrid, Spain; 3Autonomous University of Madrid, Department of Public Health, Ghent, Belgium; 7Linnaeus University, School of Health and Caring Sciences, Kalmar, Sweden; PAP-HP - Université Denis Diderot Paris 7, Paris, France; 2Centre for Cardiovascular Research (CNIC), Madrid, Spain

Purpose: Current European guidelines recommend that patients free from cardiovascular disease (CVD) but estimated to be at high (> 5%) 10-year risk of CVD mortality should be more vigorously pharmacologically treated than those at lower risk. The recommended target level of low-density lipoprotein cholesterol (LDL-C) is < 2.5 mmol/l, or < 1.8 mmol/l for those at very high risk (VHR). Today, a substantial proportion of patients remains untreated or treated insufficiently. These data indicate a great potential in reducing cardiovascular disease burden by improving the detection and treatment of classical CVRFs.

Methods: The European Study on Cardiovascular Risk Prevention and Management in Daily Practice (EURIKA) (NCT00882336) was a cross-sectional study in patients with at least one established cardiovascular risk factor who are not currently receiving LLT are at high risk of CVD events. Approximately 40% of patients aged ≥ 50 years who were free of clinical CVD had at least one cardiovascular risk factor (dyslipidaemia, hypertension, DM, smoking or obesity). Ten-year CVD mortality risk was estimated using the Systematic Coronary Risk Evaluation (SCORE) algorithm. LDL-C levels were measured and use of LLT was noted, including the agents and doses used. Statin therapy was classified as low-intensity (LIS; pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin < 40 mg or rosuvastatin < 20 mg) or high-intensity (HIS; atorvastatin ≥ 40 mg or rosuvastatin ≥ 20 mg).

Results: We identified 3278 individuals who were receiving any form of LLT, of whom 3040 (92.7%) were receiving a statin. Of the 4363 patients not receiving LLT, 1741 (39.7%) had DM or a SCORE risk ≥ 5%. LDL-C levels were available for 3151 participants receiving LLT, for whom LDL-C levels were not at target (< 2.5 mmol/l) in 1931 (61.3%). Only 8.9% of patients on LLT were receiving HIS. Of the 1414 patients without LLT, only 0.3% had LDL-C levels < 2.5 mmol/l. A subset of 2970 patients were at VHR, of whom only 1469 (49.5%) were receiving any form of LLT. LDL-C levels were at target (< 1.8 mmol/l) in 171.7% of these patients. Only 0.9% of VHR patients on LLT were receiving HIS. Of the VHR patients receiving LIS, only 17.1% had achieved LDL-C levels < 1.8 mmol/l.

Conclusion: Approximately 40% of patients aged ≥ 50 years with at least 1 cardiovascular risk factor who are not currently receiving LLT are at high risk of CVD (DM or SCORE ≥ 5%). Furthermore, well over half of all those receiving LLT and more than 80% of VHR patients receiving LLT did not achieve recommended LDL-C levels. These results demonstrate that there is potential for major improvements in lipid level management in patients at risk of CVD in Europe.

Fasting and postprandial triglycerides are independent cardiovascular risk markers in non-obese coronary artery disease patients with normal glucose tolerance

C. Werner1, S. Groenewold1, M. Fritsch1, A. filmer1, S. Graeber2, M. Boehm1, U. Laufs1, Universitätsspital Klinik für Innere Medizin III, Zürich, Switzerland; 3Saarland University Hospital, Institute for Medical Biometry, Epidemiology and Medical Informatics, Homburg, Germany

Background: Risk prediction with fasting triglycerides (TG) in high cardiovascular disease risk patients with uncertain treatment status and with low postprandial serum triglycerides levels as a risk modifier in secondary prevention is unknown. We hypothesized that the postprandial TG increase is a superior risk predictor compared to fasting TG in patients with coronary artery disease (CAD).

Methods: An oral triglyceride (OTT, 75g cream fat) and glucose tolerance test (OGT, 75g glucose) was developed to obtain standardized measurements of postprandial TG in an observational, prospective study on 514 consecutive patients (83% male, 95% on statin) with angiographically confirmed stable coronary artery disease. Patients with medical treatment for diabetes mellitus (DM) received the OTT only; all others ingested the OTT and the OGT 3 hours later in a sequential test protocol. Lipid and glucose parameters were measured at fasting, 3, 4, and 5 hours after the OTT/OGT.

Results: Metabolic characterization revealed that 126 patients had normal glucose tolerance (NoDM), 388 had impaired glucose tolerance (IGT) or DM, 95 patients had a normal BMI (<25kg/m²), and 419 were obese. Both, IGT/DM and obesity were associated with elevated fasting and postprandial triglycerides. Follow-up was 24 months and the primary outcome was the composite of cardiovascular death and cardiovascular hospitalization for coronary or cerebrovascular events. Cox proportional hazards regression models were used to calculate multivariable-adjusted hazard ratios (HR) and confidence intervals (95%CI) in time-to-event analyses. In the total cohort and in patients with IGT/DM or obesity, neither fasting nor postprandial TG predicted event-free survival independently. After stepwise adjustment for baseline characteristics, cardiovascular risk factors, and metabolic parameters, fasting TG >150mg/dl (compared to <100mg/dl) were independently associated with event-free survival in normoglycemic and IGT/DM patients (NoDM: HR 3.50, CI 95% 1.19-10.39, p=0.04; Lean: HR 2.91, CI 95% 1.39-6.15, p=0.02). The area under the curve (AUC) is an integral measure of triglycerides from fasting to the postprandial TG peak. An AUC above 1120mg/dl (compared to ~750mg/dl), also predicted risk independently (NoDM: HR 2.62, CI 95% 1.06-6.98, p=0.05; Lean: HR 3.12, CI 95% 1.00-9.81, p=0.05).

Conclusion: In normoglycemic, non-obese CAD patients, both, fasting and postprandial TG independently predict cardiovascular outcomes. The findings of the study are of great clinical relevance with respect to the identification of high risk patients, who may benefit from TG-lowering therapies.
Methods: The subjects replaced 20 g/d of their regular fat intake with the test spread with (taeast group) or without (controls) plant stanol esters (3 g/d of plant stanols). Compliance was verified with measuring serum plant stanols. Arterial stiffness was measured using the pulse wave velocity and the obtained variables were caro-ankle vascular index (CAVI) and augmentation index (AI), and endo- thelial function was measured as reactive hyperaemia index (RHI) using periph- eral arterial tonometry. Serum sterols were analyzed with gas-liquid chromatography. The study was performed according to the principles of the Declaration of Helsinki of the World Medical Association, and the Ethics Committee of the Hospital District of Helsinki and Uusimaa had accepted the study protocol.

Results: The mean age of the study population was 50.8 ± 1.0 (SEM) years with 38% of males. At baseline, mean LDL cholesterol was 3.5 ± 0.1 mmol/l, HDL cholesterol and serum triglycerides were within the reference values, CAVI was 8.7 ± 0.1, AI 9.1 ± 1.9, and RHI 2.2 ± 0.1, respectively. The intervention was well tolerated without any side-effects, and compliance was good. LDL cholesterol was reduced in the taeast group by 7.9±1.6% from baseline and by 10±2.7% from controls (P < 0.05 for both). Al changed significantly differently between the groups: it was increased in the controls and decreased in the taeast group (P < 0.04 between groups). CAVI was decreased in men with weight loss by 1.1±1% and increased in control men by 3.2±2% so that the difference was significant (P < 0.05).

In the taeast group, the change in RHI was inversely related to the change in LDL cholesterol level suggesting that the more LDL cholesterol was reduced, the more RHI increased. The decrease in mean AI was significant in the taeast group compared to controls (P < 0.05).

Conclusions: Six-month consumption of 3 g plant stanols as esters decreased arterial stiffness and increased endothelial function by reducing LDL cholesterol by 10% compared to controls. This study is dedicated to the memory of Professor Tatu A. Miettinen.

Reduced blood pressure and risk of future cardiovascular disease from structured care algorithm in primary care patients with persistent hypertension: a multicentre randomised controlled trial

S. Stewart1, M.J. Carrington1, C.H. Swenmer2, N.P. Kurijstren2, G.J. Jennings1 on behalf of VIPER-BP Investigators. 1Baker IDI Heart and Diabetes Institute, Melbourne, Australia; 2Novartis Pharmaceuticals, Sydney, Australia

Purpose: To determine the impact of reduced systolic and diastolic blood pres- sure (BP) on the risk of cardiovascular disease achieved in primary care patients with persistently elevated BPs. The aim of the study was to examine if a structured care algorithm, focused on cardio-metabolic risk factors management, aimed to achieve blood pressure (BP) reduction goal of 129/80 mmHg in primary care patients and this effect was maintained over 6 months.

Methods: The study was a randomised parallel-group, multi-centre, 2-arm, open-label study. A total of 4405 patients with persistently elevated BPs were randomised to usual care (UC) or the intervention group, a structured care algorithm, designed to optimise risk profiling and BP control in the Valsartan Intensified Pri- mary care trial (VIPER-BP Study).

Results: Over 3 years, 3018 patients (mean age 61 years, 62% men, 67% persistent hypertension) were randomised to UC (n = 2036) versus VIPER-BP intervention (n = 1982). During follow-up, mean systolic BP changed from 150±7.8/88±11 mmHg who remained above their individ- ual BP target (national guidelines) were randomised (1:2 ratio) to UC (n = 528) or the VIPER-BP intervention (n = 1100). During follow-up, mean systolic BP decreased from 150±7.8±8.11 to 136±5.8±10 mmHg in the VIPER-BP group versus 149±7.8±7±11 to 139±5.8±10 mmHg in the UC group. Accordingly, at 26 weeks 72.1% UC vs. 81.4% VIPER-BP patients had a lower systolic BP (< 9.3% in favour of VIPER-BP – p < 0.001). For both systolic (R2 0.39) and diastolic (R2 0.28) BP there was a strong linear relationship with greater falls in BP. Mean falls in calculated ACVRS from baseline were greater in VIPER-BP patients (3.7±4.5% vs. 2.6±4.5%, adjusted mean difference -1.13% 95% CI -1.63 to -0.64%, p < 0.001). Similarly, the adjusted risk of CAD (R2 0.75±0.36 vs. 0.81±0.39, p = 0.001) and stroke (R2 0.69±0.49 vs. 0.70±0.44, p = 0.001) was attenuated most in the VIPER-BP group.

Conclusions: VIPER-BP is one of the largest studies of its type ever undertaken and reflects real-world practice. In those patients with persistently elevated BP being managed in primary care, a structured care algorithm not only results in lowered BP (those with higher BPs benefiting most) but reduces absolute and relative risk of future cardiovascular disease.

Successful weight loss following gastric sleeve surgery improves vascular function in obese individuals

M.E. Iancu1, C.A. Copsacelu1, C. Genghina2. 1Delta Hospital Bariatric Centre of Excellence, Bucharest, Romania; 2University of Medicine Carol Davila, Institute of Cardiovascular Diseases “Prof.Dr.C. Iliescu,” Bucharest, Romania

Background: The risk of premature atherosclerosis rises with obesity and previ- ous studies have shown that obese individuals have stiffer arteries than those of normal weight. Vascular dysfunction is probably related to the long term prog- nosis of these patients. There are no papers about vascular function evolution after a recently used bariatric intervention: laparoscopic gastric sleeve (GS).

Purpose: To investigate whether weight loss is associated with changes in aortic (Ao) vascular function 6 months after GS.

Methods: 34 consecutive obese subjects (mean age 39±11 years, 35.2% men) scheduled for GS were prospectively studied before and 6 months after interven- tion.

Aortic vascular function was assessed by following indexes, calculated using systolic and diastolic ascending Ao diameters and blood pressure values: Ao Strain, Ao distensibility (Ao Strain index). Ao stiffness index (Ao SI).

Results: Baseline Ao vascular function parameters correlated with body mass index (BMI), Waist Circumference (WC), systemic hypertension stage and blood glucose level and not with age, sex, blood lipid profile or smoking status - see table.

<table>
<thead>
<tr>
<th>Correlation coefficients (r)</th>
<th>Ao Dis</th>
<th>Ao Strain</th>
<th>Ao SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>-0.6*</td>
<td>-0.5*</td>
<td>0.3</td>
</tr>
<tr>
<td>WC</td>
<td>-0.6**</td>
<td>-0.5*</td>
<td>0.3*</td>
</tr>
<tr>
<td>Systemic hypertension stage</td>
<td>-0.4</td>
<td>-0.3*</td>
<td>0.5**</td>
</tr>
<tr>
<td>Blood glucose level</td>
<td>-0.3</td>
<td>-0.4*</td>
<td>0.4*</td>
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</tbody>
</table>

*p < 0.05, **p < 0.01.

At 6 months follow up, compared with baseline subjects had very signifi- cant reduction of BMI (32±7.4 vs. 43±6.1±1 kg/m2), WC (101±7±26.4 vs. 129±4±23.3 cm), levels of total cholesterol (183±29.5 vs. 222±39.3 mg/dl), LDL-cholesterol (100±38.5 vs. 138±2±37.3 mg/dl), triglycerides (103±36.7 vs. 167±36.4 mg/dl), blood glucose (87±4±12.6 vs. 119±5±52.4 mg/dl) (all p < 0.01). HDL-cholesterol level increased at 50.4±10.9 mg/dl from 45±10.3 mg/dl (p < 0.001).

The proportion of hypertensives decreased from 35.3% to 8.6% (p < 0.01). 6 months after GS surgery, patients had also increased Ao Dis (2.1±0.9 vs. 1±0.7±10.6 cm2 dynes -1, Ao Strain (22.9±8.3 vs. 12.2±8% and decreased Ao SI (2±6.0.8 vs. 6.2±6.1) (all p < 0.01).

Conclusion: By successful weight loss, 6 months after bariatric surgery-gastric sleeve, vascular function parameters improve, in association with favorable metabolic and blood pressure changes.

The ferrari corporate wellness program: a new concept of cardiovascular prevention in the companies

F. Fernando1, A. Biffi2, A. Carlucio2, M.T. Carlucio2, A.H.O. Coimbra2, C. Bergh1, 1Med-Ex. Medical Partner Scuderia Ferrari, Rome, Italy; 2University of Bologna, Department of Internal Medicine, Ageing and Clinical Nephrology, Bologna, Italy

Purpose: Early detection of individuals at high risk of cardiovascular disease may be promoted by screening procedures in the working setting. The aim of this study is to evaluate the long-term effect of an active participation to a screening program of cardiovascular disease (including exercise prescription) in a working setting focused on cardio-metabolic risk factors level, whose results have been compared with those of a sample of cross-matched general population.

Methods: Subjects working in the Ferrari car factory (Maranello, Italy) entering a cardiovascular screening program were examined yearly over a period of 4 years.

The screening was associated to an intervention on the measured risk factors levels, based on a nutritional/cardiovascular counseling and on a physical fitness program (2-3 times/week gym frequency). The results in terms of trend of the risk factors levels were compared to those of a very similar population sample from the same region, derived from the historical cohort of the Brisighella Heart Study, matched for age, sex, lipid level and blood pressure values.

Results: The 168 Ferrari workers (148 men, 20 women) participating in the Project showed a significant reduction (after the follow-up period) in Fast- ing Plasma Glucose (FPG) (p < 0.003), Total Cholesterol (TC) (p < 0.001), LDL Cholesterol (p < 0.001), Non HDL Cholesterol (p < 0.001), Triglycerides (p < 0.004), Systolic (p < 0.001), Diastolic (p < 0.001) Pressure and Mean Blood Pres- sure (p < 0.001), with no change in BMI and HDL. On the contrary in the general population sample FPG, TC, LDL Cholesterol, non HDL Cholesterol, Systolic and Diastolic BP mildly but significantly increased. When compared to the general population sample, TC, LDL Cholesterol, non HDL Cholesterol and BP signifi- cantly improved in the participants to the Ferrari Project (all, p < 0.001).

Conclusion: The participation in a long-term screening project in a working setting (including a physical fitness program) is associated to a significant improve- ment of a large number of cardio-metabolic parameters, compared to age- and sex-matched subjects.
CARDIAC MAGNETIC RESONANCE ACROSS THE SPECTRUM OF CARDIOMYOPATHY

P4662

Comprehensive assessment of diastolic function from velocity-encoded cardiac magnetic resonance in patients with hypertrophic cardiomyopathy.

G. Ashrafpoor1, N. Kachenou2, E. Bollache1, L. Macron1, A. Aznar1, E. Bruguerig2, M. Desrosiers1, A. Hagege1, E. Mousseaux1, A. Redheuil1. 1AP-HP - European Hospital Georges Pompidou, Paris, France; 2Inserm U678, Pierre et Marie Curie Paris 6, Paris, France

Purpose: To assess the velocity of flow and flow-related parameters obtained by cardiac magnetic resonance (CMR) for evaluation of left ventricular (LV) diastolic function (pts) with hypertrophic cardiomyopathy (HCM).

Methods: CMR was performed in 26 HCM pts and 24 healthy volunteers (HV) matched for age, gender, body surface area (BSA) and blood pressure. Diastolic function obtained using a semi-automated software enabling extraction of transmitral flow, including transmitral E and A flow rate peaks, isovolumetric relaxation time (IRT) and early peak diastolic longitudinal myocardial velocity E' obtained using 2D phase contrast-CMR. LV mass and volumes and left atrial (LA) volume (VT) – Philips Achieva, using an adiabatic pulse and iterative shimming. The standard protocol was consist 128 repetitions and repetition time was 10 000 ms. The energy index was calculated as the ratio between areas of the peaks of phosphocreatine (PCr) production and adenosine triphosphate (ATP) using formula (FCH). We then calculated: fractional shortening of the major diameter (FSAP%), and minor atrial diameters both in systole and in diastole in a four chamber view (FSRL %) and fractional area change (FAC %). We also obtained LV stroke volume (SV), ejection fraction (EF%) and mass by CMR tools.

Results: Mean age was 47.0±20.2 years in HCM pts and 47.5±16.1 in HV (p=NS). LV mass, mass/end-diastolic volume and LA volumes were increased in HCM pts compared with HV. There was a linear relationship between increased LV mass and increased LA volumes (p<0.0001). IRT (p<0.003), DT (p<0.002), E/E' (p<0.002) and decreased E' (p<0.003) independent of age, gender and BSA.

Conclusion: Comparison of HCM pts with HV by CMR showed significantly altered LV diastolic function and increased LA volumes related to increased LV mass. Assessment of diastolic function may be considered for routine comprehensive evaluation of left heart function in HCM.

P4663

High energy myocardial metabolism in patients with different causes of left ventricular hypertrophy by 31P magnetic resonance spectroscopy

V.V. Mazaev, O.V. Stukalova, S.A. Gabrusenko, F.T. Khokhlov, S.K. Ternovoy, I.E. Chazova. Russian Cardiology Research and Production Center, Moscow, Russian Federation

Purpose: To assess the state of myocardial energy metabolism in patients with arterial hypertension (AH) and left ventricular hypertrophy (LVH) and patients with hypertrophic cardiomyopathy (HCM) compare with healthy volunteers by 31P magnetic resonance spectroscopy (31P MRS).

Methods: The study included 52 people: group I - patients with AH and LVH (16), group II - patients with HCM (16), group III - relatively healthy volunteers (20). The average age in the groups I and II were 57±5.91 years and 54±6.3 years, respectively, which were not significantly different from each other and group III - 55±6.7 years (p<0.05).

ECG-synchronized single voxel 31P MRS was performed on high field MRI system Philips Achieva, using an adiabatic pulse and iterative shimming. The localization was done by ISIS. Voxel size was fixed on 92 mm3. The standard protocol was consist 128 repetitions and repetition time was 10 000 ms. The energy index - the ratio between areas of the peaks of phosphocreatine and adenosine triphosphate (PCr/ATP) was used to evaluate myocardial energy metabolism alterations.

Results: In group I all patients showed symmetrical hypertrophy of the left ventricle, interventricular septum (IVS) thickness was 15±0.12 mm. In group II pts patients showed asymmetrical hypertrophy, with the most pronounced thickening of the IVS (thickness, 17.8±0.24 mm) which was significantly different from one another compared with group I, p<0.05. The IVS thickness in group III was 7.8±0.12 mm.

The lowest index value of PCr/ ATP was detected in patients with HCM - 1.32±0.35, which was significantly lower than the index in patients with AH and LVH - 1.76±0.29, p<0.05. The highest index value was recorded in a group of healthy volunteers - 2.18±0.32, which was significantly higher than the values in the other two groups.

Conclusions: 31P MRS revealed signs of myocardial energy metabolism alterations in patients with LVH. The greatest changes are detected in patients with HCM; patients with AH and LVH also demonstrate a significant reduction in the energy index.

P4664

The left atrium build-up of amyloid in patients with cardiac amyloidosis (CA) is associated with left atrium dysfunction: morphological and functional evaluation by cardiac magnetic resonance

E. Di Pietro1, E. Lidodek2, A. Grassos3, F. Secchi3, A. Rapacchius, M.G. De Angelis1, F. Esposito1, M. Guarneri3, S. Bartolomeo3, S. Prasad1. 1University of Naples Federico II, Dpt of Clinical Medicine, Cardiovascular & Immunological Science, Naples, Italy; 2Royal Brompton Hospital, Cardiovascular Magnetic Resonance Unit, London, United Kingdom; 3IRCCS Policlinico San Donato, Milan, Italy

Purpose: The amyloidosis is a systemic disease that can affect the heart. Cardiac amyloidosis or CA; Ventricular biopsy is the diagnostic gold standard but it is an invasive test, then the diagnosis is made by echocardiography (Echo) and/or cardiac magnetic resonance (CMR) and confirmed by non-cardiac biopsy. Isolated atrial fibrillation (IAF) study made with gadolinium (CMRGad) is able to detect CA at both left ventricle (LV) and left atrium (LA)(level). Atrial dilatation (AD) detected by Echo may be a good index of CA, but a CMR diagnosis of AD may be more sensitive and specific in those who have limited cardiac magnetic resonance in order to business is a subtype of CA that can affect only the LA called Isolated Atrial Amyloid (IAA). Whythropoiesis that AD may due to both amyloid (A) storage in the LA wall and left ventricle (LVA) involvement and some others do not. Probably, LA involvement may represent a different subtype or stage of CA. Preliminary data suggest that the mortality in AIA+ is higher than AIA-.

Methods: We evaluated by CMRGad 106 patients with confirmed CA. Patients with atrial fibrillation and/or with pericardial effusion were excluded. In all patients we found late (LGE) at LV with a zebrafish typical of CA; in 73 patients we found LGE at theLA (group Atria+); in 33 patients we did not found LGA at LA (Atria−) (figure1). By CINE sequences we measured major and minor atrial diameters both in systole and in diastole in a four chamber view (FCH). We then calculated: fractional shortening of the major diameter (FSAP%), of the minor diameter (FSRL %) and fractional area change (FAC %). We also estimated LV stroke volume (SV), ejection fraction (EF%) and mass by CMR tools.

Results: Atria+ patients showed FSAP% FSRL % and FAC% significantly reduced compared to Atria− (p<0.00000000001, p<0.00000000000001, p<0.0000001). LA is more dilated in Atria+ compared to the Atria-. LV function is worse in Atria+ (EF 51% vs 63% Atria− p<0.001).

Conclusions: Our results suggest that the atrial build-up of CA may lead to structural and functional changes. The LA dysfunction, may induce LV function worsening due to impaired atrial systole. It is unclear why some patients have LA involvement and some others do not. Probably, LA involvement may represent a different subtype or stage of CA. Preliminary data suggest that the mortality in AIA+ is higher than AIA−. If these data are confirmed, LA involvement detected by CMR may be considered as a diagnostic and prognostic marker of CA.

Role of cardiovascular magnetic resonance in the diagnosis and management of constrictive pericarditis

A. Cagnolo1, A. Barison2, G.D. Aqurro2, C. Ardenghi3, M. Carrozzo3, M. Deiana3, A. Babbarini1, M. Lombard3, 1University of Pisa, Pisa, Italy; 2Sant’Anna School of Advanced Studies, Pisa, Italy; 3Gabriele Monasterio Foundation-CNR Region Toscana, Pisa, Italy

Purpose: To elucidate the role of cardiovascular magnetic resonance (CMR) in the diagnosis and management of constrictive pericarditis.

Methods: In 47 patients with a clinical diagnosis of constrictive pericarditis a complete CMR exam was performed to assess biventricular volumes, function, pericardial thickness, T1-T2-weighted signal intensity, and post-gadolinium T1-weighted delayed enhanced imaging. A CMR diagnosis of pericardial constrictive was based on pericardial thickening, serohemal motion of the interventricular septum, and either a fibrotic (pre and post-gadolinium T1-weighted signal hypointensity) or calcific (pre and post-gadolinium T1-weighted signal hypointensity) pericardium. The CMR diagnosis was compared with echocardiography and the final diagnosis (based on clinicals, multimodality imaging, catheterization, as well as cardiac surgery for those who underwent pericardiectomy) in order to assess final diagnosis (based on clinics, multimodality imaging, catheterization, as well as cardiac surgery for those who underwent pericardiectomy) in order to assess

Results: CMR resulted as specific as echocardiography (100%) but significantly more sensitive (91.2% vs 50%) in the diagnosis of constrictive pericarditis. The positive predictive value was 100% in both techniques, but the negative predictive value was significantly higher for CMR (97.2%) than for echocardiography (50%). The most sensitive and specific parameter resulted a pericardial thickness ≥3 mm. Sigmoid motion of the interventricular septum was a specific (97.1%) but not very sensitive (51.6%) parameter. A CMR diagnosis of pericardial constriction was a significant predictor of mortality (p=0.039).

Conclusions: CMR yielded a high sensitivity and specificity for the diagnosis of constrictive pericarditis. CMR provided unique information in the clinical suspicion of constrictive pericarditis as second-level study, adding significant more information over echocardiography. Its diagnostic and prognostic role allows to preserve an invasive diagnostic (cardiac catheterization) and therapeutic approach (pericardiectomy).
Late gadolinium enhanced cardiac magnetic resonance (CMR) is a robust technique for assessment of focal fibrosis, while endomyocardial biopsy reveals interstitial fibrosis. However, the relation between LGE, histological fibrosis, and LV function has not been fully investigated in nonischemic dilated cardiomyopathy (NICM). The aim of this study was to examine the relation of myocardial fibrosis estimated by CMR with left ventricular (LV) or mitochondrial function in comparison to histological assessments in NICM.

Methods: Fifty-nine NICM patients underwent CMR and cardiac catheterization. Biopsy specimens were obtained from right ventricular septum. LVdP/dtmax and LVdP/dtmin were measured as LV contractility and relaxation, respectively. For quantitative analysis of myocardial fibrosis, LGE rate and collagen volume fraction (CVF) were calculated. The quantitative extent of LGE was defined as a signal intensity of >2 standard deviations above the mean intensity of the remote myocardium in the same slice. The mitochondrial protein mRNA expressions were measured by using quantitative reverse transcription-PCR in 46 patients.

Results: Patients were divided into two groups on the basis of presence (LGE group, n=27) or absence (non-LGE group, n=32) of LGE. Patients with LGE had lower cardiac index (2.9±0.6 vs. 2.6±0.5 L/min/m², P=0.027), LV ejection fraction (37±12 vs. 31±15%, P=0.042) and higher BNP values (97±113 vs. 210±242 pg/ml, P=0.032) than those without LGE, while CVF did not correlate with these parameters. Mean CVF was significantly higher in LGE group than in non-LGE group (7.2%±6.3% vs. 3.0%±2.9%, P=0.003). Both LGE rate and CVF were not associated with LVdP/dtmax as an index of LV contractile function, but with LVdP/dtmin as an index of LV relaxation (r=0.432, P=0.028 and r=0.363, P=0.008, respectively). Multivariate analysis revealed that not CVF but LGE rate was an independent determinant of LVdP/dtmin. The abundance of mRNAs for mitochondrial enzymes inversely correlated with LGE rate and CVF.

Conclusions: Myocardial fibrosis correlated with LV relaxation and the downregulation of mitochondrial enzyme gene expression. Focal fibrosis rather than interstitial fibrosis is more strongly associated with LV dysfunction. Noninvasive CMR is more useful to predict LV dysfunction than invasive histological assessments in NICM.
**Poster Session 6**

**ARRHYTHMIA MECHANISMS AND ANTIARRHYTHMIC DRUGS**

**P4690**

Ranolazine modifies the electrophysiological effects of acute myocardial stretching

L. Brines Ferrando1, L. Such-Miquel2, I. Del-Canto3, C. Soler4, G. Parra2, N. Gallego3, J. Barthe1, A. Albera1, L. Such1, E.J. Chorro1, 1University of Valencia, Department of Physiology, Valencia, Spain; 2University of Valencia, University Clinics Hospital, INCLIVA, Valencia, Spain; 3University of Valencia, Department of Physiology, Valencia, Spain

**Purpose:** Mechanoelectrical feedback is an arrhythmogenic factor and several mechanisms have been implicated in this effect, involving the stretch-activated ion channels, autocrine/paracrine events or the activation of beta-adrenergic receptors as a result of the stretch-mediated release of catecholamines from intramyocardial nerve endings. Ranolazine inhibits the late inward Na+ current, but we do not know whether it also modulates the electric responses to myocardial stretch in acute ventricular stretching produces modifications on the cardiac electrophysiological properties such as an increase of dominant frequency (DF) during ventricular fibrillation (VF). The aim of this study is to analyze and to compare the acute effects of ranolazine on ventricular fibrillation (VF) activation frequency under perfusion of this drug.

**Methods:** In eighteen Langendorff-perfused rabbit hearts VF recordings were obtained using epicardial multiple electrodes on the left ventricle free wall under control conditions (n=9) and during perfusion of ranolazine (5 μM) (n=9). VF was induced using pacing at increasing frequencies, without interrupting coronary perfusion. After the induction of VF, stretching was applied and maintained for ten minutes and after this period, local stretching was suppressed. DF during VF was determined using spectral techniques and threshold concentration (SpConc) was calculated as a percentage of the total energy contained in the interval of DF=0.5 Hz.

**Results:** In control series, myocardial stretch increased DF of VF from 13.6±2.4 Hz to 19.1±3.1 Hz (p=0.001), with a SpConc that decreased from 29±6% to 18±3% (p=0.001). These parameters returned to baseline values 3 minutes after stretching (DF=13.1±2.4 Hz, ns, and SpConc=18.6±7%, ns). In ranolazine group, DF prior to stretch was 11.4±1.6 Hz (p=0.053 vs control), and the SpConc was 25.4±3% (ns vs control). During myocardial stretch DF increased to 14.5±2.4 Hz (p=0.012 vs baseline and p=0.001 vs control), and with a SpConc of 23±4% (ns vs baseline and p=0.01 vs control). After suppressing stretch, DF returned to values similar to baseline state (10.8±1.3 Hz, ns vs baseline, and p=0.034 vs control), with a SpConc of 28±4% (ns vs baseline and vs control). The maximum DF percentage increment obtained in the control group during stretch was 41% versus 23% in the ranolazine group, being the latter percentage significantly lower than in control group.

**Conclusion:** The inhibition of the late inward Na+ current with ranolazine reduces the ventricular electrophysiological modifications produced by acute myocardial stretching.

**P4691**

Novel electrophysiological properties of dronedarone: Inhibition of human cardiac two-pore-domain potassium (K2P) channels

C. Schmidt, F. Wiedmann, P.A. Schweizer, R. Becker, H.A. Katus, D. Thomas. University Hospital of Heidelberg, Department of Cardiology, Heidelberg, Germany

**Purpose:** Dronedarone is currently used for the treatment of paroxysmal and persistent atrial fibrillation (AF). Pharmacological inhibition of cardiac two-pore-domain potassium (K2P) channels results in action potential prolongation and has recently been proposed as novel antiarrhythmic strategy. We hypothesized that blockade of human K2P channels contributes to the electrophysiological efficacy of dronedarone in AF.

**Methods:** Two-electrode voltage clamp electrophysiology was used to record K2P currents from Xenopus oocytes. All functional human K2P channels were screened for dronedarone block was voltage-independent and affected open and closed channels. K2P3.1 currents were reduced in frequency-dependent fashion in contrast to K2P2.1. Mutagenesis studies revealed that amino acid residues implicated in K2P3.1 drug interactions were not required for dronedarone blockade, indicating a novel pharmacological binding mode.

**Conclusions:** The class III antiarrhythmic drug dronedarone targets multiple human cardiac two-pore-domain potassium channels, including atrial-selective K2P3.1 currents. K2P current inhibition by dronedarone represents a previously unrecognized mechanism of action that is expected to suppress AF by prolonging atrial refractoriness in vivo.

**P4692**

Mechanisms of antiarrhythmic activity of new class III agent Niferidile in patients with supraventricular arrhythmias


**Background:** Niferidile (NI) is a new potassium channel blocker that inhibits transient outward and delayed rectifier currents. Preclinical studies showed that NI increases effective refractory periods (ERP) in atria more than in ventricles. High affinity of NI to atrial myocardium is thought to contribute to high efficacy in supraventricular arrhythmias and to low risk of ventricular proarrhythmia. The objectives: to evaluate electrophysiological mechanisms of antiarrhythmic effect of NI in patients with paroxysmal supraventricular tachycardia (PSVT).

**Materials and methods:** Effects of NI (20μg/kg intravenously) were studied in 24 patients with 144 VT and 56 PSVT (12 orthodromic tachycardia in WPW syndrome, 8 AV-nodal reentrant tachycardia, 4 orthodromic tachycardia due to concealed bypass tract) during endocardial electrophysiological study. Termination of sustained paroxysms of SVT by NI could be investigated in 18 patients and prevention of reinduction of PSVT – in 22 patients.

**Results:** NI terminated PSVT in 77.77% and prevented reinduction in 72.72% of patients. NI increased ERP of right at bystander (22.8±8%, left atrium (20.09%), right ventricle (12.33%) and accessory pathways (antegrade by 21.47%; retrograde by 32.83%). NI did not affect sinus node and atrioventricular conduction. NI significantly increased relative refractory period (RRP) of His-Purkinje system (3.314), NIf prolonged QT (by 24.5%; p<0.01) and QTC (by 17.31%; p<0.05) intervals. One patient developed short runs of torsade de pointes shortly after injection of drug.

**Conclusion:** Prolongation of ERP, predominantly in atria and accessory pathways, and RRP in His-Purkinje system are main electrophysiological effects of NI. New drug showed high antiarrhythmic efficacy and good safety profile in patients with PSVT.
Value-based pricing for dabigatran, rivaroxaban and apixaban in patients with non-valvular atrial fibrillation in Germany

M. Krejczy1, S. Marx1, K. Obermann2, M. Wehling3, J. Harenberg1
1Medical Faculty Mannheim-Univ. of Heidelberg, Inst. of Experimental, Clinic, Pharma. & Toxicology, Mannheim, Germany;
2Mannheim Institute of Public Health, Social & Preventive Medicine, Heidelberg University, Mannheim, Germany

Dabigatran (150 mg bid) showed superior efficacy in preventing ischemic stroke compared to these endpoints using odds ratios and confidence intervals. Therefore, there is a need for an unbiased comparative comparison of these NOACs is highly unlikely to be performed given the expense and apixaban showed equivalence or superior efficacy and safety compared to dose-adjusted warfarin (all p < 0.05). All-cause mortality was not different for any agent or regimen. In the absence of head-to-head comparisons, this network meta-analysis suggests that apixaban and dabigatran 110 mg bid may offer the best cost-effectiveness balance for stroke prevention in non-valvular atrial fibrillation. Dabigatran 150 mg bid may be preferred towarfarin with a high risk for embolism.

Value-based pricing for dabigatran, rivaroxaban and apixaban in patients with non-valvular atrial fibrillation in Germany

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2Mannheim Institute of Public Health, Social & Preventive Medicine, Heidelberg University, Mannheim, Germany

Warfarin effectively reduces the incidence of ischemic stroke in patients with non-valvular atrial fibrillation (AF) but increases the risk of major and intracerebral bleeding. The new oral anticoagulants (NOAC) dabigatran (110mg and 150mg bid, D110 and D150), rivaroxaban (20mg od, R20), and apixaban (5mg bid, A5) showed equivalent or superior efficacy and safety compared to warfarin in these patients. We aimed to analyse the value-based price (in Euro) for Germany for these NOACs from a social health perspective. The data of the outcomes of ischemic cerebral and non-cerebral embolism, major and intracerebral hemorrhage, myocardial infarction, and mortality were taken from dabigatran's RE-LY (D110 and D150), rivaroxaban's ROCKET (R20), and apixaban's ARISTOTLE trials (A5). All were randomized and prospective trials and compared the NOAC with dose-adjusted warfarin including more than 6,000 patients. The quality-adjusted life years (QALYs), costs (in Euro 2012 for Germany), and incremental cost-effectiveness ratios (ICER) for the NOACs were calculated with adjusted-dose warfarin as comparator. The societal willingness-to-pay was set conservatively at 50,000 Euro per QALY. A Markov decision model was adopted using the Tree Age Pro 2011 program. The current daily cost of D110, D150, and R20 in Germany account for about 3.20 Euro. The relation of QALYs was 11.53/11.41 for D110/warfarin, 11.66/11.41 for D150/warfarin, 12.32/12.05 for R20/warfarin, and 11.74/11.5 for A5/warfarin. Total costs were higher for all NOACs compared to warfarin. With this calculations ICER was found for all NOACs in a range of about 50,000 Euro per QALY. Provisionally calculated cost-based prices for the NOACs compared to dose-adjusted warfarin ranged from 1.25 Euro to 2.50 Euro per day. Our results are robust in a wide range of sensitivity analyses. The daily value-based price for D110, D150 and R20 are markedly lower than those previously effective in Germany. The data should be seen as preliminary and need further adaptation to current German methodological standards. The model can be used to calculate such prices for every community and country.

Network meta-analysis of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with non-valvular atrial fibrillation

S. Marx1, H.-C. Diener2, J. Harenberg1, G. Lip3, V. Marder2, M. Wehling1, C. Weiss1,1Medical Faculty Mannheim of the University of Heidelberg, Mannheim, Germany; 2University Clinic Essen, Department of Neurology, Essen, Germany; 3University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; 4University of California Los Angeles, David Geffen School of Medicine, Los Angeles, United States of America; 5Medical Faculty Mannheim of the University of Heidelberg, Department of Biometrics and Statistics, Mannheim, Germany

The three new oral anticoagulants (NOAC) dabigatran (two doses), rivaroxaban, and apixaban showed equivalence or superior efficacy and safety compared to warfarin in patients with non-valvular atrial fibrillation. A head-to-head clinical trial comparison of these NOACs is highly unlikely to be performed given the expense of such an investigation. Therefore, there is a need for an unbiased comparative assessment of the benefits and risks of the NOACs, based on the available trial data. Appropriate statistical tools for such an analysis is mixed treatment comparison (MTC) network meta-analysis (NMA). A NMA of the 3 new oral anticoagulants was performed extracting the data of the RE-LY-study of dabigatran 110 mg bid and dabigatran 150 mg bid, the ROCKET-trial of rivaroxaban and the ARISTOTLE-trial of apixaban for the composite outcome ischemic stroke and systemic embolism with the same intracerebral bleeding.mortality and myocardial infarction. The NMA was performed to compare these endpoints using odds ratios and confidence intervals. Dabigatran (150 mg bid) showed superior efficacy in preventing ischemic stroke plus systemic embolism to dabigatran (110 mg bid, p=0.0386) and rivaroxaban (p=0.0388). Apixaban had equivalent efficacy with rivaroxaban and dabigatran (either dose). Apixaban was safer (less major bleeding) than dabigatran (150 mg bid, p=0.0006). Intracerebral hemorrhage occurred with equal frequency for all agents and regimens except for rivaroxaban (higher risk than dabigatran 110 mg bid, p=0.0070). Myocardial infarction occurred less frequently with rivaroxaban and apixaban compared to either dose of dabigatran (all p<0.05). All-cause mortality was not different for any agent or regimen. In the absence of head-to-head comparisons, this network meta-analysis suggests that apixaban and dabigatran 110 mg bid may offer the best cost-effectiveness balance for stroke prevention in non-valvular atrial fibrillation. Dabigatran 150 mg bid may be preferred towarfarin with a high risk for embolism.

Arrhythmia mechanisms and antiarrhythmic drugs / Arrhythmia mechanisms

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F 16915 prevents heart failure induced atrial structural remodelling: a promising new drug as up-stream therapy for atrial fibrillation

C. Pignier1, R. Letienne1, F. Lantone-Adam1, M. David-Dulfina2, S. Hateren1, B. Le Gard1,3Research Institute Pierre Fabre, Cazeres, France; 2UMR S956, Inserm, Paris, France

Atrial fibrillation (AF) is a common complication of heart failure and hypertension. By reduction of structural remodelling, upstream therapy is known to prevent the propagation and promotion of AF. However, the existing drugs remain only partially active certainly due to their weak efficacy against atrial remodelling and therefore, a new generation of compound is requested. The aim of the present study is to test the hypothesis that a new pure docosahexaenoic acid derivative, F 16915 would reduce adverse atrial remodelling in a rat model of heart failure induced by 30 min occlusion of left descending coronary artery and 2 months reperfusion. F 16915 (100 mg/kg) was administered by gavages every day after induced by 30 min occlusion of left descending coronary artery and 2 months reperfusion. F 16915 (100 mg/kg) was administered by gavages every day after induced by 30 min occlusion of left descending coronary artery and 2 months reperfusion. F 16915 (100 mg/kg) was administered by gavages every day after induced by 30 min occlusion of left descending coronary artery and 2 months reperfusion. F 16915 (100 mg/kg) was administered by gavages every day after induced by 30 min occlusion of left descending coronary artery and 2 months reperfusion. F 16915 (100 mg/kg) was administered by gavages every day after induced by 30 min occlusion of left descending coronary artery and 2 months reperfusion. F 16915 (100 mg/kg) was administered by gavages every day after induced by 30 min occlusion of left descending coronary artery and 2 months reperfusion. F 16915 (100 mg/kg) was administered by gavages every day after induced by 30 min occlusion of left descending coronary artery and 2 months reperfusion. F 16915 (100 mg/kg) was administered by gavages every day af...
was not associated with significant modification of any hemodynamic parameters. Ventricular infarct size was determined at the end of the experiment and was assessed by histological analysis (Masson staining). F 16/159 significantly reduced the extent of infarct size (±13.3%; n=5 vs. n=10; p<0.01). In conclusion, in an ischemia-induced heart failure model in the rat, F 16/159 prevented the structural remodeling of the left atria associated with an increased ventricular function. Therefore, F 16/159 is a new emerging opportunity as up-stream therapy for the treatment of AF.

**Methods and results:** In open chest experiments in goats (n=6), we performed high density endo-epicardial mapping to investigate the interaction of focal tachycardia induced by ACO with activation pattern during AF. The topical application of ACO-crystals on the left atrium in the middle of the mapping area induced rapid focal discharges with radial spread of activation exactly at the place of ACO-application. The mean cycle length (CL): 242±15 ms. Local electrograms at the site of earliest activation did not show R-waves. S1S1-stimulation (basic cycle length (BCL): 200ms) from two different directions showed no blocklines and no change of conduction velocity (CV) (80±3 cm/s vs. 80±3 cm/s, n.s.). During experimental period of 30 min. after ACO-application, neither atrial effective refractory period (BCL=200ms: 135±3 ms vs. 135±4 ms, n.s.) nor left atrial vulnerability was changed significantly. Episodes of burst-induced AF became longer (470±54 ms) vs. 26±3 ms, n.s.) nor left atrial vulnerability was changed significantly. Mean of AERP, CV or AFCL. However, the sites of breakthroughs during AF, the incidence of breakthroughs increased and AF became more stable with- out changes in AERP, CV or AFCL. However, the sites of breakthroughs during AF, the incidence of breakthroughs increased and AF became more stable without significant modification of any hemodynamic parameters.

**Conclusions:** Loss of ACO results in marked changes in heart rate, atrial and ventricular conduction times and refractory periods. This points towards a significant involvement of ACO in a normal sinus node function as well as a normal conduction system. CAP2gt/+ leads to a significant decrease in the lack of further increase in the incidence of VTs in CAP2gt/+ may originate from a further prolongation of VRP with antiarrhythmic effects. Cases of right ventricular cardiomyopathy with no real cause of an underlying disease may be due to dys- function of CAP2, so further evaluation of its influence on cardiomyopathy and arrhythmogenesis should ensure to fully understand its functioning.

**References:**
2. J. Schrickel, M. Linhart, S. Verheule, Medicine III, Cardiology, Homburg, Germany; 2University Hospital Basel, Department of Cardiology, Basel, Switzerland; 3Maastricht University, Cardiovascular Research Institute Maastricht (CARM), Maastricht, Netherlands.

**Background:** The concept of focal discharges for the maintenance of atrial fibrillation (AF) is under discussion. Acetilone (ACO) is used in a model for fo- cal AF. To find mapping criteria for focal discharges during AF, we performed high density mapping of AF maintained by ACO and investigated the effect of flecainide.

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Arrhythmia mechanisms

ECG were recorded from anesthetized rabbits treated with mexothiene (15 μg/kg/min), clorflouin (51 μg/kg/min) and various antipsychotics (all 0.5 mg/kg bolus).

Results: The Ki for 1AR affinity of the antipsychotics were risperidone ≪ haloperidol ≪ olanzapine. In canine Purkinje fibers a 1AR stimulation prolonged APD (265 ± 12 to 302 ± 14 ms at 1 Hz pacing, p < 0.05). Block of IKr more consistently prolonged APD (268 ± 8 to 453 ± 17 ms, p < 0.05) and predicted any effect of 1AR stimulation. Early or delayed afterpolarizations were not observed upon slowing cycle length to 5 s. In anesthetized rabbits, IKr block alone did not result in arrhythmias but combined IKr block and 1AR stimulation caused considerable QT prolongation (188.7 ± 509.82 ms, p < 0.05) and TdP in 8 of 10 rabbits. Pretreatment with antipsychotics with various combinations of IKr block and 1AR blocking properties reduced the incidence of drug-induced TdP to 0/10 (risperidone) and 2/10 (sertraline), p < 0.05; whereas haloperidol (4/10, p = 0.2) and olanzapine (5/10, p = 0.3) did not reduce TdP incidence at the tested dose. There was a statistically significant positive correlation between 1AR antagonism and antiarrhythmic efficacy (Spearman’s correlation, p < 0.05) independent of QT intervals.

Conclusions: 1AR-Antiarrhythmic stimulation causes APD prolongation in vitro and contributes to TdP in vivo. In the present model, risperidone and sertraline have antiarrhythmic effects. The absence of afterdepolarizations in Purkinje fibers after IKr block and 1AR stimulation suggests involvement of non-cardiac 1AR in the induction of TdP.

P4704
Ranolazine suppresses atrial fibrillation in an experimental model of chronic heart failure due to development of atrial postrepolarization refractoriness and slowing of conduction velocity

P. Milberg1, G. Frommeyer1, S. Rajaman1, L. Belardinelli1, L. Eckardt1,1 Department of Cardiology and Angiology, Muennster, Germany; 2Gilead Sciences, Palo Alto, United States of America

Background: In a recent study, ranolazine (RAN) was reported to be effective and safe in converting atrial fibrillation (AF) to sinus rhythm by intake of a single dose (“pill in the pocket”) in patients with structural cardiac abnormalities. The apparent electrophysiological safety and the ability to use it in patients where other Na+ channel blockers are contraindicated could have enormous economic implications. This is the first experimental study that identifies the molecular mechanisms for the antiarrhythmic benefit of RAN application in chronic heart failure (CHF).

Methods and results: In 7 female rabbits CHF was induced by 4 weeks of rapid ventricular pacing leading to a significant decrease in ejection fraction. 12 rabbits were sham-operated and served as controls. Isolated failing and sham hearts were perfused using the Langendorf method and were paced with cycle lengths from 350 to 1500 ms in the atrium. In addition, burst pacing was used to induce atrial fibrillation. Two monophasic action potential recordings on the left- and right epicardium showed an increase of atrial action potential duration (APD) and effective refractory period (eERP) in CHF hearts as compared with controls. Additional injection of acetycholine (1μM) and isoprotenerol (1μM) led to AF in all failing and in 11 sham hearts. Simultaneous injection of RAN (10μM) suppressed AF in 55% of sham- and 57% of failing hearts. RAN had no effect on aERP but led to a significant increase of aERP (sham: <28ms; CHF: +24ms) leading to marked increase of atrial postrepolarization refractoriness (aPRR), defined as the difference of AERP and aERP. Atrial fibrillation markedly increased conduction velocity in sham (+14ms) - and failing (+16ms) hearts, respectively.

Conclusion: In the present study, administration of RAN has been shown to be effective in suppressing AF not only in sham- but also in failing hearts. The antiarrhythmic effect is due to development of aPRR and a marked effect on conduction velocity. RAN might be a new safe option to reduce the burden of AF in CHF, where other antiarrhythmic drugs are contraindicated. The described electrophysiological mechanism should be adopted as a fascinating novel antiarrhythmic option in heart failure.

P4705
Myofibroblasts do not contribute to the substrate for atrial fibrillation. A study of human left atrial appendages

S.P.J. Krul1, S.C.M. Van Amerloothorst2, G.S.C. Geuzenbroek2, A.H.G. Driessen3, A.A.M. Wilde4, J.M.T. De Bakker5, J.R. De Groet6, 1Academic Medical Center, Heart failure Research Center, Department of Cardiology, Amsterdam, Netherlands; 2Academic Medical Center, Heart Failure Research Center, Department of Experimental Cardiology, Amsterdam, Netherlands; 3St Antonius Hospital, Department of Cardiovascular Medicine, Zutphen, Netherlands; 4Academic Medical Center, University of Amsterdam, Department of Cardiothoracic Surgery, Amsterdam, Netherlands; 5Interuniversity Cardiology Institute of the Netherlands (ICIN), Utrecht, Netherlands

Purpose: The contribution of myofibroblasts to the substrate of atrial fibrillation (AF) is unknown. The electrical coupling between myocytes and myofibroblasts may promote arrhythmogenicity through a decrease of conduction velocity (CV). Ablation of myofibroblasts with Latrunculin-B (LatB) in cells cultures of myocytes and myofibroblasts reverses these changes. We hypothesise that myofibroblasts...
Cervical vagal nerves contain sympathetic ganglion cells and sympathetic nerve fibers in addition to parasympathetic nerve fibers. Cervical VNS may achieve its therapeutic effects by activating both branches of the autonomic nervous system.

**Methods:** The LAA of patients undergoing thoracoscopic surgery for AF was excised. The LAA preparation was superfused with Tyrode’s solution in a tissue bath and optical mapping was performed with di-4-ANEPPS. The LAA was paced at 100bpmp and exposed to Laßb for 1 hour and CV was measured every 5 minutes. Immunohistochemical staining for alpha-SMA and connexin 40 was performed to identify myofibroblast in tissue preparations and differentiate myofibroblast from vascular smooth muscle cells.

**Results:** A total of 21 LAA were studied (0.1 and 1 mmicrom Laßb and control, 7 per group). No spontaneous activity was observed. Longitudinal CV was 0.27-1.43mm/ms and transversal CV was 0.04-1.11 mm/ms. Laßb did not affect CV irrespective of the type of AF. Run down of the model, characterized by a reduction of CV in time, was observed. Concordantly with the outcome of the electrophysiological experiments, myofibroblasts were not detected with immunohistochemical staining of LAA.

**Conclusion:** Exposure of human LAA preparations to Laßb does not change CV. Furthermore, immunohistochemical staining does not reveal the presence of myofibroblasts in LAA of AF patients. These data suggest that myofibroblasts do not play a major role in the pathophysiological substrate of human AF.
The anatomic relationship between the right and left ventricular outflow tracts: its relevance in catheter ablation

J.A. Cabrera1, M. Murillo2, G. Pizarro2, E. Gonzalez-Caballero2, B. Fuertes2, B. Bayona1, A. Garcia-Lopez3, A. Pastor3, D. Sanchez- Quintana2.
1Hospital Universitario Quiron, Universidad Europea de Madrid, Madrid, Spain; 2Hospital Universitat Politècnica de Catalunya, Barcelona, Spain; 3Hospital Universitario Reina Sofia, Córdoba, Spain

Purpose: Premature ventricular contractions, ventricular tachycardia and initiating beats for ventricular fibrillation have all been localized at the level of the right and left ventricular outflow tracts (RVOT and LVOT). Catheter ablation at and around the junction between the outflow tracts and the great arteries is being increasingly performed. Detailed anatomic information of these structures may be useful to perform the ablation techniques in a safer and more efficient way.

Methods: Fifteen structurally normal human hearts (10m, 47±5 years) were carefully studied by sagittal and horizontal histological sections. The junction between the LVOT and RVOT were serially sectioned at 10-μm thickness, and stained with goldner and Masson trichrome methods. By light microscopy, the minimal distance between the endocardium of the right and left ventricles was 7±1 mm. An endocardial ablation approach of idiopathic outflow tract tachycardias can be unsuccessful due to this anatomic finding, suggesting the need of an epicardial approach in selected cases.

Results: The RVOT is a muscular structure of variable length (range 13-24 mm) that supports the semilunar leaflets of the pulmonary valve. Its posterior and inferior borders consist of a prominent muscular crest, called supraventricular crest, that separates the inflow and outflow components of the RV. The supraventricular crest is in contact with the posterior part of the LVOT, as it inserts in the interventricular septum. The minimal distance between the endocardium of the right and left ventricles was 7.2 mm (range 4.1-14 mm) being in 3 hearts (20%) greater than 10 mm.

Conclusions: The myocardial thickness at the level of the RVOT and LVOT may be greater than 10 mm. An endocardial ablation approach of idiopathic outflow tract tachycardias can be unsuccessful due to this anatomic finding, suggesting the need of an epicardial approach in selected cases.

Depletion of connexin45 and connexin30.2 deteriorates AV-nodal conduction in the murine heart

J.W. Schrickel1, M. Frank2, R. Andrie1, L. Lickl1, G. Nickeng1, K. Willencke1. 1Dept. of Medicine-Cardiology, University of Bonn, Bonn, Germany; 2Inst. of Genetics, Bonn, Germany

Introduction: Connexin (Cx) 40.2 provides physiological conduction slowing in the murine AV-node. Cx45 has been proposed to maintain basal AV-nodal conduction. The interaction of the dominant connexins Cx45 and Cx30.2 in the murine AV-node has not yet been systematically evaluated as Cx45 deficient mice are embryonic lethal.

Methods: We interbred a transgenic mouse line cardioidly depleted for Cx45 mice (C45/-) with Cx30.2 knock out (KO) mice (C30.2/-), resulting in Cx45/-C30.2/- double KO offspring. In these and control wildtype (WT) littermates, we performed telemetric ECGs and in vivo electrophysiological investigations (EPI) using transvenous catheterization to assess standard EPI-parameters (n=14).

In Cx45/-:PQ-Intervals were significantly prolonged in the Holter ECG-recordings of Cx45/-compared to their WT littermates (41.0±2.3 ms vs. 36.3±1.3 ms; p<0.05). When Cx30.2 was additionally deleted in Cx45/-:C30.2/-:PQ-Int was even more prolonged as compared to Cx45/- (43.5±1.6 ms vs. 41.0±2.3 ms; p<0.05). In vivo EPI showed prolongation of the A-His interval as surrogate of supra Hisian conduction disturbances in Cx45/- versus WT (33.3±5.3 ms vs. 28.9±2.1 ms; p<0.05), which was more pronounced in the double KO versus their WT littermates (48.3±4.6 ms vs. 33.3±5.3 ms; p=0.02). AVNRP was shortened in the double KO. Spontaneous AV-Blocks did not occur in none of the genotypes. Inducibility of atrial and ventricular arrhythmias was equal among the groups.

Conclusions: Our data show prolonged AV-Intervals and impaired AV-nodal conduction under fast heart rates in mice with conditional cardiac deletion of Cx45. These findings support the thesis of Cx45 as a provider of basal AV-nodal conduction. When Cx30.2 is additionally missing, AV-nodal conduction is more severely impaired as in the Cx45 single knock out. These results prove that predominantly expressed Cx45 and Cx30.2 are crucial for maintaining AV-nodal conduction.
Dexmedetomidine and clonidine inhibit ventricular tachyarrhythmias in a rabbit model of acquired long QT syndrome

Tokyo University School of Medicine University Hospital, Mizonokuchi hospital, Kanagawa, Japan.

Purpose: We hypothesized that alpha-2 AR agonists have an inhibitory effect on abnormal repolarization-related ventricular tachyarrhythmias (VTs).
Methods: Effects of dexmedetomidine and clonidine on the occurrence of VTs were assessed in a methoxamine-sensitized rabbit model of acquires long QT syndrome (n=45). To verify that VTs in this animal model are triggered by early afterdepolarization (EAD), monophasic action potential on the left ventricular surface was recorded in 28 open-chest rabbits.

Results: Incidence of VT significantly decreased during the treatment with dexmedetomidine (1 μg/kg/min: 5/12 [p<0.01 vs. control]) or with clonidine (33.3 μg/kg/min: 10/18 [p<0.01]), as compared with that in control rabbits (14/15). EAD-like bump was less frequently detected during an EAD-sensitized rabbit with clonidine or dexmedetomidine (2/14) than in saline-treated rabbits (9/10, p<0.005). Presence of hump was significantly related with the advent of VTs (p<0.05).

Conclusion: Alpha-2 AR agonists have an inhibitory effect on VTs in the rabbit long QT model.

Lymphocytic cell infiltration of myocardium is associated with the episode of ventricular fibrillation in patients with brugada syndrome

Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; 2Department of Life Science, Laboratory of Clinical Pathology, Okayama University, Okayama University of Science, Japan.

Purpose: Brugada syndrome is a disease known to cause ventricular fibrillation (VF) with a structurally normal heart and is linked to SCN5A gene mutation. The existence of myocarditis on endomyocardial biopsy samples in patients with Brugada syndrome is still debated. The aim of the present study was to investigate the existence of lymphocytic cell infiltration in patients with Brugada syndrome.
Methods: We studied consecutive 73 patients (71 males; mean age 48±11 years) with Brugada syndrome (n=45). To verify that VTs in this animal model are triggered by early afterdepolarization (EAD), monophasic action potential on the left ventricular surface was recorded in 28 open-chest rabbits.

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False tendons are possibly associated with genesis of J-waves: prospective study in young healthy men

Oita University School of Medicine, Oita-city, Oita, Japan.

Background: Recent studies showed that J-wave was associated with vulnerability to ventricular fibrillation. While J-waves are also observed in the healthy population, the mechanisms for J-wave are still under investigation. On the other hand, the possible association of false tendon (FT) with fascicular tachycardia suggested the presence of the arrhythmogenic slow conduction zones in FT. Recently, we reported the association between the FT and J-waves in the general population (Heart Rhythm, in press).

Methods: We prospectively studied 30 young healthy men. The FTs were detected by the echocardiogram and classified into 3 types on the basis of their points of attachment: type 1 (longitudinal type), type 2 (diagonal type) and type 3 (transverse type) as shown in figure. 12-lead ECG and the signal averaged ECG were recorded. J-wave was defined as terminal QRS notchting or slurring.

Results: The FT was detected in 70% of all subjects. The incidence of J-wave was significantly higher in the subjects with type 1 and 2 FTs than type 3 FT and without FT (100, 50, 10, 20%, respectively; p<0.005). Late potential was not recorded in all subjects, however, the incidence of late potential determined by SAECG was significantly longer in the subjects with type 1 or 2 FTs than the others (p<0.05).

Conclusion: These results suggested that FT was related to the genesis of J-waves and may have a potential arrhythmogenic property with conduction abnormality.

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P4716 Partial blockade of IK1 destabilizes the rotation center of spiral wave reentry without enhancement of wavefront-tail interactions in the arm

Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan; 2The University of Tokyo. Graduate School of Engineering, Tokyo, Japan.

Background: It was previously reported that partial blockade of the inwardly rectifying potassium current, IK1, reduced dominant frequencies and facilitated termination of ventricular fibrillation, but underlying mechanisms remain to be clarified. We hypothesized that partial IK1 blockade destabilizes the rotation center of spiral wave (SW) reentry in favor of its early termination.

Methods: A 2-dimensional ventricular muscle layer was made in Langendorff-perfused rabbit hearts and excitation patterns were evaluated by high-resolution optical mapping. In different series of experiments, action potentials were recorded from isolated superfused papillary muscle of rabbit ventricles by conventional glass-microelectrode technique.

Results: In Langendorff-perfused hearts, Ba2+ (10 and 50 μM) caused a dose-dependent prolongation of the action potential duration (APD) during constant pacing at 2.5-5 Hz (from 136±8 ms to 148±5 ms at 10 μM and 164±9 ms at 50 μM at 5 Hz, n=11, P<0.05) without significant changes in conduction velocity. SW reentry induced after application of 10 μM Ba2+ rotated around a longer I-shaped functional block line (FBL) length 6.8±0.7 mm vs. 3.2±0.8 mm, n=7, P<0.05) than in controls. After 50 μM Ba2+, the FBL was further prolonged (9.4±3.2 mm, n=7) and showed prominent beat-to-beat changes in shape in 2 of 7 episodes, resulting from decremental conduction close to the rotation center. A phase-mapping analysis revealed that the number of phase singularities remained decreased from 1 after 10 and 50 μM, indicating minimal interactions between wavefront and wave tail in the SW arm. In papillary muscles, Ba2+ caused a dose-dependent depolarization of the resting potential (from -82.2 mV to -81.8 mV at 10 μM and -81.5 mV at 50 μM, P<0.05). The maximum upstroke velocity of the action potential was significantly decreased (156±9.8 V/s, P<0.05) at 50 μM Ba2+.

Conclusion: Partial blockade of IK1 destabilizes the rotation center of SW reentry in favor of its early termination.
Effects of renal sympathetic denervation on heart rate and atrioventricular conduction in patients with resistant hypertension

C. Ukena, F. Mahboud, I. Kindermann, A. Spies, D. Linz, B. Cremer, U. Lauts, H.-P. Neubeger, M. Boehm. Staatl. Landesuniv. Hospital, Department of Internal Medicine III, Cardiology, Hamburg, Germany

Background: Renal sympathetic denervation (RDN) reduces sympathetic activity and blood pressure (BP) in patients with resistant hypertension. The present study was aimed to investigate the effects of RDN on HR and other electrophysiological parameters.

Methods: 136 patients aged 62.2±0.8 years (58% male, BP 177±2.9±3.1 mm Hg) with resistant hypertension underwent RDN. BP and a 12-lead electrocardiogram (ECG) were recorded before, 3 months (n=112), and 6 months (n=84) after RDN.

Results: After 3 months (3M) and 6 months (6M), systolic BP was reduced by 25.5±2.4 mm Hg (p<0.0001) and 28.1±3.3 mm Hg (p<0.0001). HR at baseline was 66.1±1.1 beats per minute (bpm) and was reduced by 2.6±0.8 bpm after 3 months (p=0.001) and 2.1±1.1 bpm after 6 months (p=0.046). Change of HR correlated with HR at baseline: patients with HR at baseline between 60-71 bpm and ≥71 bpm had a reduction of 2.9±7.6 bpm (p=0.008) and 9.0±8.6 bpm (p<0.0001), respectively, whereas in patients with baseline HR ≥70 bpm HR increased after 3 months (2.3±8.4 bpm; p=0.035). Neither baseline HR nor change of HR correlated with changes of systolic BP. The PR interval was prolonged by 11.3±2.5 ms (p=0.0001) and 10.3±2.5 ms (p=0.0001) at 3 and 6 months after RDN. Patients with a PR-change ≥10 ms had a shorter baseline PR duration (159.7±6.2 ms vs. 171.1±4.4 ms; p=0.043) and a greater reduction of heart rate (3M: -4.1±1.5 bpm vs. -0.1±1.1 bpm; p=0.022). Duration of ventricular de- or repolarisation was not significantly affected by RDN.

Conclusion: RDN significantly reduced heart rate and PR interval, as indicators of cardiac autonomic activity, in patients with resistant hypertension. The changes did not correlate to BP reduction.

Introduction and Hypothesis: Cardiac death has been linked in many populations to the repolarisation phase of the action potential. However, it has been argued that the onset of repolarisation is closer to the T peak. We have therefore tested the hypothesis that QT peak prolongation predicts cardiac death.

Methods and Results: ECGs were recorded from 296 stroke patients (152 male), mean age 67.2 (SD11.6) approximately 1 year after the event. These ECGs were digitised by one observer who was blinded to patient outcome. The QTc was recorded from 30 patients divided into the following 3 groups: primary endpoint was cardiac death and death from any cause. A prolonged heart rate corrected QT peak (QTpc) of lead I carried the highest relative risk of cardiac death, when compared with the other more conventional QT indices. In multivariate analyses, when adjusted for conventional risk factors of atherosclerosis, a prolonged QT pc of lead I was still associated with a 3-fold increased risk of cardiac death. (adjusted relative risk 3.0 [95% CI 1.1-8.5], p=0.037).

Conclusion: QT peak prolongation predicts cardiac death in stroke survivors. Further studies are required to elucidate the mechanism that may lead to their cardiac death, and test the hypothesis that interventions might reduce the risk of cardiac death in these patients.

Is QRS axis pattern associated to the type of surgical repair in adults with operated tetralogy of fallot?

Z. Jai1, N. Combes1, J.B. Thambo1, M. Haissaguerre1, F. Sachet2,1. University Hospital of Bordeaux - Hospital Haut Leveque, Department of Cardiology, Bordeaux-Pessac, France; 2Clinic Pasteur of Toulouse, Toulouse, France

Introduction: Until the development of the transatrial-transpulmonary approach, surgical repair of Tetralogy of Fallot (ToF) was achieved through a right ventriculotomy causing right ventricular (RV) conduction disturbance. We studied QRS defibrillator and 7 of 15 (47%) patients had recurrences of VF with a rate of 80%, 46%, and 33% in patients with high lateral, lateral, and inferior J waves, respectively.

Conclusion: Patients with J waves in the inferior or global leads on ECG exhibited wider distribution of J waves on the body surface, although high lateral J waves tended to link with poor outcome in ERS patients with VF.
Early repolarization patterns in young healthy individuals: prevalence, morphological characteristics and impact of gender, ethnicity and physical activity

S. Ghani, S. Di Fino, A. Gravina, A. Zaidi, N. Sheikh, S. Gati, H. Raju, S. Sharma. St George’s University of London, London, United Kingdom

Purpose: Early repolarization (ER) is commonly observed in athletes and young healthy individuals. Recently, ER in the inferior and lateral leads has been associated with sudden cardiac arrest from idiopathic ventricular fibrillation. We studied the prevalence, distribution and morphology of ER patterns in inferior and lateral leads in young healthy individuals.

Methods: 12-lead electrocardiogram (ECG) was performed at rest in 192 young healthy individuals (age range 13-38 years) between February and September 2011. We evaluated the impact of gender, ethnicity and physical activity on ER. Individuals were divided into physically-active (exercise >2 hours/week) and sedentary. Early repolarization was defined as notched or slurred J-point elevation of at least 0.1 mV from baseline, ≥2 contiguous inferior or lateral leads; anterior ER patterns were not considered in this study. The morphology of ST-segment was classified as rapidly ascending/up sloping or horizontal/descending.

Results: The mean age of participants was 17.9 ± 4.4 years, of which 1406 (73%) were male, 1557 (80%) were physically active and 1780 (92%) were Caucasians. ER pattern in inferior and lateral leads was present in a total of 382 (19.8%) cases; of these 40% were in the inferior leads, 35% in lateral leads and 25% in both. Notched ER pattern was more prevalent compared to slurred morphology, and more commonly associated with ascending/up sloping ST-segment elevation. ER was significantly more prevalent in males compared to females (20% vs. 12%, p=0.003), in physically-active people compared to sedentary (20.4% vs. 14.8%, p=0.013), and in Afro-Caribbean compared to Caucasians (31.2% vs. 19.9%, p=0.012). In addition, voltage criteria for left ventricular hypertrophy and sinus bradycardia were a common associated finding in individuals with ER pattern compared with those without (p=0.0001 and 0.0001 respectively). Only 5% of individuals with ER had J-point elevation of >0.2 mV.

Conclusion: Early repolarization is a common finding in young healthy individuals, and is more prevalent in males, physically-active individuals and those with Afro-Caribbean ethnicity. The inferior leads were more commonly involved but the difference was not statistically significant. Notched ER pattern with ascending ST-segment elevation was the most commonly observed morphological pattern. More research is required to understand precise long term implications of such repolarization changes in young individuals.

The prognostic value of sinoatrial block of Wenckebach type (Mobitz I) in patients with symptoms suggestive of paroxysmal cardiac arrhythmias

E. Kramarz, K. Mawzaki. Military Institute of Health Services, Warsaw, Poland

Introduction: In the literature, there is no work on the prognostic value of the sinoatrial block II° of Wenckebach type (Mobitz I)- block W, that appears at different times of the day during Holter monitoring. The aim of the study was to determine the clinical significance of the block W identified in the Holter study in patients with symptoms suggestive of cardiac arrhythmias.

Methods: The study group included 300 consecutive patients (mean age 54±19 years, 130 women) with symptoms suggestive of cardiac arrhythmias who underwent Holter monitoring. Patients who were found to experience the block W episodes had re-performed 24-hour ECG Holter monitoring after 12 and 24 months. All patients underwent medical examination, assessing their clinical condition at 12 month intervals.

Results: The block W was diagnosed in 88 persons (29%). In 37 patients the block W occurred only during sleep and in 51 during sleep and during daily activity. Prospective observation time averaged 41±11 months, the survival without a diagnosis of sinus node disease was 26±10 months, and survival without pacemaker implantations 29±8 months. The sinus node disease was diagnosed in 25 people: in 1 person (2%) in the group with the block W only during sleep, in 19 patients (37%) in the group with the block W during the daily activity and in 5 patients (10%) in the group without the block. The incidence of the block occurrence was 20%: 1 person (2.7%) with the block W only at night, in 16 patients (31.3%) with the block W in activity during the day and in 3 patients (1.4%) with no identifiable block. Variables (age > 60 years, male gender, structural heart disease, the block W during the day), which in univariate analysis showed association (p<0.05) with sinus node disease and the necessity for permanent pacing were subjected to Cox multivariate analysis. Results of Cox multivariate analysis revealed that the block W occurring during the daily activity is an independent predictor of future diagnosis of sinus node disease (relative risk: 17.61 [3.92-46.25]; p=0.014), and the emergence of indications for permanent cardiac pacing (relative risk: 7.92 [2.76-42.52]; p=0.028). During the follow-up 25 people died. There were no differences between groups in mortality.

Conclusions: The block W during daily activity in patients with symptoms suggestive of cardiac arrhythmias indicates an increased likelihood of future diagnosis of sinus node disease and indications for permanent pacing.
Screening for arrhythmogenic myocardial substrate by 12-lead ECG, high resolution ECG and T-wave alternans in patients with low to intermediate sudden cardiac death risk

N. Mewton1, D.G. Strauss2, P. Rizzil2, R.L. Verrier2, L.G. Terechlenko1, B. Nearing3, F.E. Marchlinski2, C. Cox4, P.M. Spooner3, J.A.C. Lima1, 1Hospices Civils of Lyon - Cardiological Hospital Louis Pradel, France; 2Center for Devices and Radiological Health, US Food and Drug Administration, Silver Spring, United States of America; 3Johns Hopkins University, Division of Cardiology, Baltimore, United States of America; 4Beth Israel Deaconess Medical Center, Boston, United States of America; 5University of Pennsylvania Medical Center, Philadelphia, United States of America; 6Johns Hopkins Bloomberg School of Public Health, Baltimore, United States of America

Aims: Increased QRS score, wide spatial QRS-T angle, T-wave alternans (TWA) and late potentials by signal averaged electrocardiogram (SAECG) are independent predictors of cardiovascular mortality in the general population. We analyzed whether these electrocardiographic (ECG) parameters enable screening of patients for myocardial scar features implicated in sudden cardiac death risk.

Methods and results: We screened a 6-month period of the entire 12-lead ECG database of Johns Hopkins Hospital and identified 800 patients age ≥70 years from non-critical care areas and no record of reduced life expectancy who had QRS ≥130ms, T-wave ≥10° as well as left ventricular ejection fraction (LVEF) ≥35%. All individuals were invited to participate, of whom 77 enrolled in the study and underwent clinical examination, SAECG, 30-minute ambulatory ECG recording for TWA, and complete late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) study to determine scar presence and pattern as well as to characterize gray zone, core, and total scar size.

The mean age was 60±10 years, with 70% males and no known heart disease history in 43% of the study population. Patients’ mean LVEF was 58±8%. Previously unreported myocardial scar was present in 41 (53%) patients, of whom 19 (46%) exhibited a typical ischemic pattern. Median and inter-quartile range for scar, core scar, and gray zone extent were 8% [4; 19%], 5% [0; 8%], and 2% [1; 7%] of left ventricle (LV), respectively. QRS-T angle but not QRS score was associated with the presence of scar and ischemic scar pattern. QRS score was related to total scar size and core scar extent (R2=0.13, P=0.001; R2=0.12, P<0.001, respectively). In the presence of late potentials on SAECG, TWA level with total scar size (R2=0.18; P=0.001) and gray zone size (R2=0.10; P=0.01), but not with the presence of late potentials on SAECG (OR=1.04, 95%CI [0.99; 1.08]; P=0.10). Presence of late potentials was significantly related only to TWA level with total scar size (R2=0.13, P=0.02; R2=0.12; P=0.002, respectively). There was a significant independent association between TWA level with total scar size (R2=0.16; P<0.001) and gray zone size (R2=0.10; P<0.01), but not with the presence of late potentials on SAECG (OR=1.04, 95%CI [0.99; 1.08]; P=0.10). Presence of late potentials was significantly related only to more depressed LVEF and higher QRS scores (P<0.001 and P=0.005, respectively).

Conclusions: ECG screening by QRS score ≥5, QRS-T angle ≥105°, and TWA identifies patients with preserved LVEF but previously unreported myocardial scar with arrhythmogenic potential.

Prevalence, electrocardiographic characteristics and variations of early repolarization syndrome on a population of healthy subjects

P.H. Kiem1, A. Ross2, O. Manen3, S. Bisconte, B. Azman, J. Louembe, J. Deroche, V. Kanczuga, E. Perrin. Military Hospital (HIA) Percy, Clamart, France

Background: Infero-lateral repolarization has been considered benign for a long time, however recent studies have demonstrated a possible association with sudden death.

The aim of this study is to estimate the prevalence of early repolarization, demonstrate the associated electrocardiographic abnormalities and fluctuations of this syndrome in a population of healthy subjects.

Patients and methods: Electrocardiographic abnormalities of 1983 patients undergoing routine medical examination at the Principal Centre of Medical Expertise of Flight Crew for french Army from early January to late March 2000 were described. Early repolarization was defined as an elevation of J wave of at least 0.1 mV in the inferior and lateral leads. In patients with early repolarization, retrospective analysis of electrocardiograms from the following ten years (2000-2010) was carried out. Clinical and electrocardiographical characteristics were statistically analyzed.

Results: The prevalence of early repolarization was estimated at 5.7% (CI 95%, 4.7-6.7%). 3 patients presented with ECG severity criteria (intralateral early repolarization, J wave>0.2 mV and notch). For 20% of patients early repolarization was intermittent and 56.5% had substantial variations in J wave amplitude, morphology or territory. Early repolarization was commonly associated with ST-segment elevation, prominent T-waves, slow cardiac heart rate and shorter corrected QT duration. No malignant ventricular arrhythmia nor sudden death occurred among the 3 patients presenting with ECG severity criteria during the 10 years follow-up.

Conclusions: Our data are consistent with previous studies concerning early repolarization syndrome. Given the high prevalence and important fluctuations of early repolarization, every patient who presents with this syndrome cannot be considered to be at risk of sudden death. Further research is needed to identify the electrocardiographic forms of this syndrome which are associated with an increased risk of mortality.

Various morphological ventricular premature beats with fragmented QRS waves on a 12 lead Holter ECG had a positive relationship with the left ventricular fibrosis on CT in hypertrophic cardiomyopathy

K. Ozawa, N. Funabashi, H. Takaoka, A. Katsaka, M. Uehara, Y. Kobayashi. Chiba University Graduate School of Medicine, Chiba, Japan

Purpose: Various morphological kinds of ventricular premature beats (VPB) with fragmented QRS waves on 12 lead Holter ECG were observed in patients with hypertrophic cardiomyopathy (HCM) but its significance is not clear.

Methods: Retrospective analysis acquired from a total of 24 consecutive HCM subjects (17 male, mean 64±12 yr) who underwent enhance ECG gated CT (Aquilion one or Light Speed Ultra 16) and a 12 lead Holter ECG (RAC-2103, NIH Koden) within 3 months. Evaluation of coronary artery and characteristics of left ventricular myocardium were performed. If there was a contrast defect in left ventricular myocardium fibrosis on CT in early phase, late phase acquisition was added, and if abnormal late enhancement was observed in the corresponding site, we diagnosed myocardial fibrosis.

Results: Correlation coefficients (CCs) of numbers of morphological kinds of 1) all VPB (blue bar) and 2) fragmented VPB (red bar) against the patient’s characteristic factors and CT findings are represented in the Figure. Positive CCs were observed between numbers of kinds of both all VPB and fragmented VPB and the frequency of diabetes mellitus and fibrosis in left ventricular myocardium on CT and negative CCs were observed between numbers of kinds of both all VPB and fragment VPB and luminal stenosis >50% in any coronary arteries and each coronary artery on CT. There were no significant differences between numbers of kinds of all VPB and fragmented VPB concerning their relationship with the patient’s characteristic factors and CT findings.

Conclusions: Numbers of morphological kinds of fragmented VPB on a 12 lead Holter ECG may have a positive relationship with the occurrence of fibrosis in left ventricular myocardium but a negative relationship with coronary arteries stenosis on CT in HCM subjects as well as those of all VPB.

Association of sudden cardiac death and ambient temperature in Scotland

A. Shah1, C. Yap2, S. Cobbe1, A. Macconochie2, D.E. Newby2, N.L.M. Mills1, J. Pelt3. 1University of Edinburgh, Centre for Cardiovascular Science, Edinburgh, 2University of Birmingham, Birmingham, 3University of Glasgow, Glasgow, 4University of Glasgow, Section of Public Health, Glasgow, United Kingdom

Purpose: Freezing temperatures in early 2012 have claimed more than 200 lives
in Eastern Europe. Several studies have investigated the effect of seasonality and sudden cardiac death (SCD). Less commonly investigated has been the short-term effects of change in ambient temperature and SCD. We investigated the association between hourly and mean daily change in ambient temperature and SCD.

**Methods:** We evaluated the effect of ambient temperature and the risk of SCD, comparing data from the Heart Start registry with local hourly measurements of atmospheric temperature in Scotland from January 1996 to December 2004, using a case-crossover design.

**Results:** 29,854 victims suffered a SCD in the studied time frame. Across all distances and all time lags, there was an increase in risk of SCD with lowering of ambient temperature. There was a 7.6% (95% CI 2.7% – 12.3%) increase in the risk of SCD per 10 degree lowering of the ambient temperature. The association with temperature remained up to 24 hours (Lag 0-1 days) prior to the SCD with sensitivity analysis showing patients ≥ 65 years and those with known heart disease (Figure 1) being more vulnerable.

**Conclusion:** In this national comprehensive registry, SCD was strongly correlated with a lowering of the ambient temperature at lag 0 hours up to lag 0-1 days suggestive of a much more acute mechanistic link. This study has major public implications in implementing measures to reduce SCD in vulnerable patients by the provision of targeted advice or other interventions.

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**Prediction of ventricular arrhythmias by QRS-fragmentation detected with magnetic field imaging (MFI) among patients with reduced left ventricular ejection fraction**

**T. Tomnis, A. Cuneo, K. Kyriazis, A. Ujeyl, K.H. Kuck, Asklepios Clinic St. Georg, Hamburg, Germany**

**Introduction:** Only 20% of patients with ICDS implanted for reasons of primary prevention in accordance with current guidelines will suffer an event of adequate therapy. Until today, left ventricular ejection fraction (EF) is considered as the pivotal parameter for patient selection to assess the risk of Sudden Cardiac Death, although neither sensitivity nor specificity are particularly high. QRS-Fragmentation, detected by Magnetic Field Imaging (MFI) has shown promising results in addition to the use of the EF.

**Methods:** 175 patients with primary preventive ICD-indication were examined with the MFI-system with 55 SQUID-sensors (Apollo CXS, BMDSys, Magdeburg). In a standard resting protocol the QRS-Fragmentation was determined by a quantification parameter, the fragmentation index. 50 healthy volunteers were examined as a control group. All ICD-patients had a regular follow up each 3-6 months. The primary endpoint was the occurrence of sustained ventricular tachycardias.

**Results:** The mean follow up time was 15,8 months. 65% of the patients in the ICD-group had an underlying ischemic, 33% a nonischemic cardiomyopathy. The average left ventricular ejection fraction was 27±7%.

The mean fragmentation index within the ICD-group was 1.3±0.33 vs. 1.01±0.09 in the control group. The variation range of the global parameter was increased in the ICD-group compared to the control group. 16 patients of the ICD-group (10,3%) showed episodes of ventricular tachycardia with 7 patients presenting with ICD-shocks, 10 pts with ventricular tachycardia terminated by antitachycardial pacing and 1 patient with persistent VT that underwent an external defibrillation. The mean fragmentation index of pts. with an VT episode was 1.5±2.0 vs. 1.27±0.31 in pts. with no episodes. For a cut-off value of 1.2 of fragmentation index the sensitivity was 83%, the specificity 43%. The positive predictive value was 14.8%, the negative predictive value 95.6.

**Conclusion:** These preliminary results of a prospective registry show that MFI-based QRS-fragmentation in addition to the ejection fraction is able to identify patients who are more likely to get a life-threatening ventricular tachycardia. Further studies to evaluate the use of this parameter for pts. with only moderate ejection fraction are planned.

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**How to differentiate patients at risk of cardiac and non-cardiac death using heart rate and its variability?**

J. Sacha, S. Barabach, G. Statkiewicz-Barabach, K. Sacha, A. Muller, J. Piskorski, G. Schmidt

**Department of Cardiology Regional Medical Center, Opole, Poland;**

**Wrocław University of Technology, Institute of Physics, Wrocław, Poland;**

**Jagiellonian University, Atom Optics Department, Institute of Physics, Krakow, Poland;**

**1. Medizinische Klinik und Deutsches Herzcentrum München der Technischen Universität München, Munchen, Germany;**

**2. Department of Cardiology-Intensive Therapy, University School of Medicine, Poznan, Poland**

**Methods:** The study group consisted of 1410 patients with recent MI followed up for 5 years. Seven different classes of spectral HRV indices with increasing HRV/HR dependence were calculated. Their prediction powers were tested by calculation of areas under receiver operator characteristic curves.

**Results:** During the follow-up period, 128 patients died, 71 from cardiac and 57 from non-cardiac causes. As HRV was getting more dependent on HR, its predictive power progressively increased for CD but decreased for NCD. Of all spectral indices, a modified very low frequency component (VLF1), which did not depend on HR, had a high predictive power for NCD. However, both modified very low frequency components (VLF1 and VLF2), which highly depended on HR, had a good predictive power for CD. In the multivariate analysis, VLF1 independently predicted NCD (hazard ratio: 5.1, 95% CI: 3.0:8.9) together with VLF2(35%) (HR: 2.6, 96% CI: 1.4:5.0) and age ≥ 65 years (HR: 2.4, 95% CI: 1.4:4.1); whereas VLF7 predicted CD (HR: 3.7, 95% CI: 1.9:7.2), together with VLF1(35%), age ≥ 65 years (HR: 2.1, 95% CI: 1.3:3.3), diabetes (HR: 2.0, 95% CI: 1.2:3.3) and arrhythmias signs on Holter (i.e. >10 premature ventricular complexes/h and/or non-sustained ventricular tachycardia) (HR: 1.9, 95% CI: 1.1:3.1). In patients with VLF1<35%, VLF1 was especially effective in anticipating NCD (75% sensitivity, 82.8% specificity), whereas VLF7 predicted CD with 34.5% sensitivity and 91.9% specificity. The combination of VLF1 and VLF7 enabled to select patients at high risk of NCD and low risk of CD among those with VLF<35% – i.e. the subgroup which would probably not benefit from ICD.

**Conclusions:** By strengthening or weakening the HRV/HR dependence one can get HRV indices which provide distinct information on cardiac and non-cardiac prognosis. Such stratifiers may be helpful in the appropriate patients selection for ICD therapy in primary prevention.

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**Treatment of patients with inappropriate sinus node tachycardia: If-channel inhibition or ablation?**

J. Borbola, P. Abraham, C.S. Foldesi, A. Kardos, Göttsche György Hungarian Institute of Cardiology, Budapest, Hungary

**Inappropriate sinus node tachycardia (IST) is a relative rare clinical syndrome defined as increased sinus rate at rest, and/or inadequate response to physical or emotional stress without any underlying disease. In the last years 25 patients (23 women, 2 men; age: 18-57 (33) years) were treated with IST due to palpitations. Patients had no structural heart disease (EF: 65±2%), TSH values were within normal limits, but resting heart rate were repeatedly high: 106±3/min. The results of Holter recording (expressed as minimal-maximal and average heart rate/min) without any medication showed high heart rate values: 58±2-163±3 (96±2) min. The bicycle ergometry showed an average loading capacity of 120±0.5W (heart rate control: C: 104±8/min, top: T: 170±0.6/min). The aim of the study was to evaluate the efficacy and safety of a selective sinus node If channel inhibitor drug, the ivabradine in the IST patient group. The ivabradine therapy decreased the heart rate significantly and dose-dependently compared to the control values: ivabradine: 2x5 mg/day: 50±2-131±5 (-76±2/min (p<0.001), ivabradine 2x7.5 mg/day: 48±1-130±6 (-72±2/min (p<0.001), and decreased the heart rate during ergometry: ivabradine: 2x5 mg/day: C: 84±3 T: 137±6 (-54/min (p<0.001), 2x7.5 mg/day: C: 77±4 T: 138±6/min (p<0.001). The loading capacity improved but did not change significantly (135±6W; ns). The ivabradine treatment was well tolerated, there was no sinus bradycardiac episode. All patients experienced symptom relief, three patient suffered from phosphenes, which completely resolved in a few days. Based on our clinical experiences IST can be treated with the sinaloidal node modulator drug ivabradine successfully and safely. Ivabradine significantly decreased, improved heart rate frequency spectrum and
clinical symptoms. The disadvantage of the ivabradine is the lack of approval for IST therapy and the contraindication during pregnancy. During ivabradine treatment there was no indication for sinus node transcatheter ablation. Before the ablation of the sinoatrial node with the inherent risk of pacemaker implantation a clinical trial with ivabradine is suggested.

**P4733 The role of non-invasive methods in determining the arrhythmic risk in myotonic dystrophy type 1**

C. Calore1, A. Polo1, V. Romeo2, F. Folino3, G. Buja1, C. Angelini1, E. Bonfitto4, E. Pegoraro5, S. Ricci6, P. Melocchi1. 1University of Padua, Department of Cardiac, Thoracic and Vascular Sciences, Padua, Italy; 2University of Padua, Department of Neurosciences, Padua, Italy; 3University of Rome "Tor Vergata", Rome, Italy.

**Purpose:** In myotonic dystrophy type 1 (MD1) the risk of cardiac death is higher than in the general population and atrial or ventricular arrhythmias are frequent. The aim of this study was to assess the determinants of arrhythmic risk in patients with MD1 using non-invasive methods.

**Methods:** Eighty-four patients (62% males; age 41±15 years) with a clinical-genetic diagnosis of MD1 (class E1=11%; E2=75%; E3=14%) were enrolled. All patients underwent cardiological evaluation, 12-lead ECG, echocardiography, 24-hour ECG-Holter with heart rate variability (HRV) and neurological assessment at entry. During a mean follow-up of 46±28 months (2-2 visits) echo-ECG-Holter data and arrhythmic events were collected.

**Results:** During the follow-up 8 patients (9%, incidence 2/100-year) died (age at death 48±11 years). Six (75%) of the deaths were cardiac: 2 sudden deaths (SD), 1 aborted SD i.e. ICD shock on ventricular fibrillation (VF), and 3 deaths due to heart failure. Four patients (5%) developed major arrhythmic events (SD/aborted SD, VF, sustained or non-sustained ventricular tachycardia), and 7 patients (8%) atrial flutter/fibrillation (AF). According to current guidelines, 7 patients received pacemaker and/or ICD. The incidence of cardiac death was associated with prolonged PR and QRS intervals at baseline ECG (P4734.148 vs 119±34, p=0.003 and 126±23 msec vs 96±21, p=0.002 respectively), with presence of AF (50% vs 11%, p=0.005) at baseline or during follow up, with lower SDNN (100±22 vs 129±41, p=0.06) and SDANN (81±15 vs 132±41, p=0.04) values at HRV. Patients who developed major arrhythmic events had a trend toward a longer QRS duration at baseline ECG (118±13 msec vs 97±23, p=0.07) and more frequent premature ventricular beats/PVBs at ECG-Holter (230±4817 vs 490±1579, p=0.018). Patients who developed AF were characterized by older age (51±17 years vs 39±14, p= 0.047), longer PR interval at baseline ECG (237±49 msec vs 198±32, p=0.03), and higher HRV (PP50: 96±157 vs 837±64, p=0.008; SDNN 176±45 vs 139±39, p=0.04; RMSSD 89±53 vs 43±21, p<0.001).

**Conclusions:** In MD1 patients cardiac-deaths are associated with conduction disturbances at baseline ECG, presence of AF and HRV data suggesting increased sympathetic activation. Major arrhythmic events are associated with intraventricular disturbances at ECG and frequent PVBs at Holter. Atrial fibrillation is more frequent in patients with baseline atrio-ventricular conduction disturbances and vagal pacing. Non-invasive cardiologic evaluation is important for arrhythmic risk assessment, identifying patients who can develop major tachyarrhythmic events.

**P4734 Exploring the origin of J-wave with magnetocardiography (MCG): depolarization or repolarization?**

N. Iwakami1, S. Kamakura1, H. Takaki1, S. Hashimoto1, H. Okamura1, T. Noda1, K. Satomi1, T. Alba2, W. Shimizu3, M. Sugimoto1. 1National Cerebral and Cardiovascular Center Hospital, Department of Cardiovascular Medicine, Suita, Osaka, Japan; 2National Cerebral and Cardiovascular Center Research Institute, Dept of Cardiovascular Dynamics, Suita, Osaka, Japan.

**Purpose:** The mechanism of J-wave is not definitely known. There are still controversies over whether J-wave is derived from depolarization or repolarization abnormality.

We studied the current flow consistent with J-wave during the late QRS to early ST period using magnetocardiography (MCG) with high spacio-temporal resolution to solve this problem.

**Methods:** We recorded 64-channel MCG simultaneously with digitalized ECG (II, V2, V5) during sinus rhythm in 60 subjects (men 46 and women 14, mean age 49.5±19.5) with either notched or slurred J-point elevation (P4734.112±19.5) with either notched or slurred J-point elevation.

**Results:** We found 64-channel MCG simultaneously with digitalized ECG (II, V2, V5) during sinus rhythm in 60 subjects (men 46 and women 14, mean age 49.5±19.5) with either notched or slurred J-point elevation (P4734.112±19.5) with either notched or slurred J-point elevation. The direction and distribution of current flow consistent with J-wave on ECG.

**Conclusion:** MCG analysis strongly suggested that J-wave is derived from ventricular depolarization.

**P4735 The importance of atrioventricular conduction and myocardial function in ventricular arrhythmogenesis in lamin A/C mutation carriers**

N.E. Hasselberg1, T. Edvardsen1, H. Petri2, K.E. Berge3, T.P. Leren1, H. Bundgaard1, K.H. Haugaa1. 1University of Oslo, Rikshospitalet University Hospital, Department of Cardiology, Oslo, Norway; 2Rigshospitalet - Copenhagen University Hospital, Copenhagen, Denmark; 3University of Oslo, Rikshospitalet University Hospital, Department of Medical Genetics, Oslo, Norway.

**Purpose:** Mutations in the Lamin A/C gene may cause dilated cardiomyopathy (DCM), typically accompanied by atrioventricular block (AVB) and high risk of ventricular tachycardia (VT). VT may occur before development of DCM and risk stratification is challenging. Mechanisms of arrhythmias in these patients are not fully understood.

**Methods:** We included 41 Lamin A/C mutation carriers. PQ interval from resting ECG and occurrence of VT were recorded. Myocardial function was assessed by echocardiography as ejection fraction (EF) and by speckle tracking strain from 16 LV segments as global longitudinal strain. Regional function in the interventricular septum was assessed by averaging strain from 4 septal segments and defined as septal strain.

**Results:** VT was documented in 21 patients (51%). Importantly, 13 patients without evident DCM had VT (62%). Prolonged PQ interval (p<0.001), presence of AVB (p<0.001) and reduced global longitudinal strain (p=0.01) were markers of VT, while EF was not (p=0.55). By ROC analysis, PQ interval ~250 ms showed the best ability to discriminate between those with and without VT with a sensitivity and specificity of both 87%. PQ interval was an independent predictor of VT in multivariable analysis (OR=1.35, p=0.01). Septal strain was markedly reduced compared to the rest of LV segments (~16%). Prolonged PQ interval correlated with reduced septal function (R=0.41, p=0.03).

Figure 1. Reduced septal function, AVB and nVT.
Conclusion: Prolonged PQ interval was the best predictor of VT and may help arrhythmic risk stratification in Lamin A/C mutation carriers. Myocardial function was most decreased in the septum and correlated to prolonged PQ interval. These findings indicate that reduced septal function and AVB are involved in mechanisms of ventricular arrhythmias in Lamin A/C mutation carriers.

P4736
Left atrial strain predicts postoperative atrial fibrillation in patients waiting for aortic valve replacement for aortic stenosis
M. Cameli1, M. Lis1, R. Recchia1, E. Bigo2, E. Bennati1, A. Malandrino1, M. Maccherini3, M. Chiavarelli4, M. Henein5, S. Mondillo1
1 University of Siena, Department of Cardiovascular Diseases, Siena, Italy; 2 University of Siena, Unit of Anaesthesia and Intensive Care, Siena, Italy; 3 Santa Maria alle Scotte Polyclinic, Department of Cardiac Surgery, Heart Transplantation Division, Siena, Italy; 4 University of Siena, Department of Cardiothoracic Surgery, Siena, Italy; 5 Umea University Hospital, Heart Centre, Umeå, Sweden

Background: The occurrence of atrial fibrillation (AF) is a common and dangerous complication in patients undergoing aortic valve replacement (AVR); Speckle tracking echocardiography (STE) has recently enabled the quantification of longitudinal myocardial LA deformation dynamics. Our aim was to investigate by STE the eventual pre-existent subclinical mechanical atrial dysfunction in patients who develop AF after AVR.

Methods: 75 patients with aortic stenosis in sinus rhythm, undergoing AVR, were prospectively enrolled. Conventional echocardiographic parameters, and peak atrial longitudinal strain (PALS) were measured in all subjects the day before surgery. PALS values were obtained by averaging all segments measured in the 4- and 2-chamber views (global PALS).

Results: All patients received a biological valve prosthesis and a standard postoperative care. Postoperative AF occurred in 15 patients (20.0%). Among all clinical and echocardiographic variables analyzed, global PALS demonstrated the highest diagnostic accuracy (AUC of 0.90) and, with a cutoff value less than 16.9%, good sensitivity and specificity of 86% and 91%, respectively, to predict postoperative AF episodes. LA volume indexed and E/E' ratio presented lower diagnostic accuracy (AUC 0.76 and 0.51, respectively).

Figure 1. Predictors of postoperative AF

Conclusions: STE analysis of LA myocardial deformation could be considered a promising tool for the evaluation of LA subclinical dysfunction in patients undergoing AVR, giving a potentially better risk stratification for the occurrence of postoperative AF.

P4737
Clinical aspects and prognosis of type 1 ECG pattern of Brugada syndrome
K. Lettas1, E. Eletremis1, P. Korantzopoulos2, N. Fragakis3, K. Kappos3, P. Strempelas4, G. Bakolis5, C. Kavounais6, A. Sideris7, T. Areztz1
1 Second Department of Cardiology, Evangelismos General Hospital of Athens, Athens, Greece; 2 Department of Cardiology, University Hospital of Ioannina, Ioannina, Greece; 3 Hippokration General Hospital of Thessaloniki, Thessaloniki, Greece; 4 Evangelismos General Hospital of Athens, 1st Department of Cardiology, Athens, Greece; 5 Naval Hospital of Athens, Greece; 6 Heart Centre Bad Krozingen, Bad Krozingen, Germany

Purpose: This study investigated the clinical aspects and long-term prognosis of type 1 ECG pattern of Brugada syndrome (BS).

Methods: The clinical data of 68 apparently healthy individuals (55 males, age 44.7±12.7 years) with spontaneous (n=27) or drug-induced (n=41) type 1 ECG pattern of BS were retrospectively analyzed.

Results: Twenty-eight subjects were symptomatic with a history of syncope (41.2%), and 18 displayed a positive family history of BS and/or sudden cardiac death (36.5%). Electrophysiological study was performed in 37 subjects, and programmed right ventricular stimulation induced ventricular tachycardia/fibrillation in 25 of them (67.5%). A cardioverter defibrillator (ICD) was implanted in 27 individuals (39.7%). During a mean follow-up period of 5.0±3.57 years, five symptomatic subjects suffered appropriate ICD discharges due to ventricular arrhythmias (7.4%, 1.7% per year in total population, 3.55% per year in symptomatic individuals), and one died due to non-cardiac causes. None of the asymptomatic individuals had syncope or ICD therapies. A history of syncope (p=0.005) as well as a prolonged QRS duration in leads II (p=0.026) and V2 (p=0.001) were significantly associated with ventricular arrhythmic events during follow-up. Sinus node dysfunction and atrial arrhythmias were observed in 8.8% and 20.6% of subjects, respectively.

Conclusions: In this study population, the mean arrhythmic event rate per year in symptomatic individuals with BS phenotype was 3.55%. Asymptomatic subjects with type 1 ECG pattern of BS display a benign clinical course.

P4738
T-wave alternans is helpful for predicting recurrence of fatal arrhythmias in ventricular fibrillation survivors
S. Yamada, H. Suzuki, M. Sato, S. Iwaya, M. Kamioka, Y. KAMIYAMA, S. SAITO, Y. Takeishi. Fukushima Medical University, Fukushima, Japan

Backgrounds: T-wave alternans (TWA) is useful for predicting the occurrence of ventricular tachyarrhythmias in various heart diseases. However, little is known about the clinical significance of TWA measurement in patients with past history of ventricular fibrillation (VF).

Methods: We studied 22 VF survivors (15 males, mean age 58 years) who received implantable cardioverter-defibrillator implantation. The patients of J-wave syndrome were excluded from this study. We measured plasma B-type natriuretic peptide (BNP) and assessed left ventricular ejection fraction (LVEF) by echocardiography. Additionally, QRS duration and QTc interval were measured in electrocardiogram. TWA value was calculated by the time-domain moving average method. All subjects were divided into two groups based on whether TWA value was above 65 μV (n=11, Group-A) or not (n=11, Group-B). We compared these parameters and the appearance of ventricular arrhythmias requiring appropriate shock therapy in the observation term (8.8±5.9 months) between two groups.

Results: BNP and LVEF were not different between two groups (BNP: 213±292 pg/ml vs. 175±154 pg/ml; LVEF: 42.4±14.8% vs. 46.6±16.2%). QRS duration and QTc interval were not different between two groups (QRS duration, 121.3±23.2 msec vs. 107.2±16.1 msec; QTc interval, 454.8±12.7 msec vs. 431.6±54.1 msec). However, ventricular arrhythmias requiring appropriate shock therapy occurred more frequently in Group-A than in Group-B (55% vs. 9%, P<0.05).

In Kaplan-Meier actuarial curves for arrhythmic event-free rates, Group-A had lower event-free than Group-B (P<0.05).

Figure 1. Arrhythmia event-free rates

Conclusions: These results suggest that T-wave alternans is useful for predicting the recurrence of ventricular arrhythmias or adverse outcomes in patients with past history of VF.
Utility of magnetocardiography for detection of delayed potentials, epsilon waves, with arrhythmogenic right ventricular cardiomyopathy


Purpose: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by hypokinetic areas involving the free wall of the right ventricle, with fibro-fatty replacement of the right ventricular myocardium, with associated arrhythmias originating in the right ventricle. Diagnostic ECG finding includes epsilon wave, which is interpreted as a delayed potential in RV. Some cases are difficult to identify the delayed potentials. The aim of this study was to visualize the delayed potentials and compare the delayed potential point using magnetocardiography (MCG).

Methods: This study included 14 cases with ARVC who were diagnosed by Task Force of WHOISH (1996) and biopsy, echocardiography and imaging, they were examined 64-channel MCG waveforms. 64-channel MCG waveforms were examined before electrophysiological study and ablation for ventricular premature contraction or ventricular tachycardia. 6 of them showed typical abnormal potential representing the epsilon wave at the end of QRS complex and right in front of T wave on electrophysiology (ECG). 8 cases were difficult to detect the delayed potentials by 12-leads ECG. A current arrow map (CAM) depicted the propagation of the delayed potentials. The locations of the delayed potentials identified by MCG were compared with ablation successful site tagged on the electroanatomical map.

Results: 6 of 8 (75%) with undetectable delayed potential cases could identify the delayed potentials at the end of QRS complex, using MCG. The origins of the delayed potentials deduced CAM agreed with that from the invasive study in 12 of 14 patients.

Conclusion: Magnetocardiography was useful for detecting the presence of delayed potential, epsilon wave, and estimating delayed potential points before the catheter ablation.

**SYNCOPE**

Home orthostatic training is not effective in elderly patients With vasovagal syncope - a prospective randomised controlled trial

S. Podd, J. Hunt, A.N. Sulke. Eastbourne District General Hospital, Eastbourne, United Kingdom

Objective: To assess the effect of home orthostatic training (HOT) on autonomic reflexes in elderly patients with vasovagal syncope (VVS).

Design: A single blind randomised control trial.

Setting: Eastbourne District General Hospital, East Sussex NHS Trust.

Patients: 106 patients with recurrent syncope underwent tilt table testing between August 2007 and October 2009. 45 patients (30 over 65 and 15 under 65 controls (U65)) with at least 2 syncopal episodes and tilt test proven VVS were recruited. The over 65 group were randomised 1:1 to active HOT (O65+) or sham HOT (O65-). The U65 group received active HOT. Participants performed HOT/sham HOT and recorded their training and symptoms. Patients had a repeat tilt test at 3 months.

Main outcome measures: Time to syncope at repeat tilt table testing, low-frequency heart rate variability (LF-HRV), high-frequency HRV (HF-HRV), mean upslope baroreflex sensitivity (BRS) and mean downslope BRS were assessed.

Results: Symptomatic benefit occurred in 4 (31%) of the O65+, 4 (29%) of the O65- and 6 (50%) of the U65. None of the autonomic measures changed significantly in any group (table 1.). 50% of the O65+ group stopped training due to back pain. Time constraint (25%) was the most common reason for cessation in the U65 group.

Conclusions: Despite good tilt training compliance no improvement in autonomic measures in any group was shown. The most common reason for cessation of training was back pain the elderly groups. This study does not support the use of HOT in elderly patients.

**Additional diagnostic value of very prolonged observation by implantable loop recorder in patients with unexplained syncope**

R. Maggi, T. Furukawa, C. Bertolone, D. Fontana, M. Brignole. del Tigullio Hospital, Lavagna, Italy

Introduction: In the literature, the average diagnostic yield of the implantable loop recorder (ILR) is reported to be around 35% over an observation period generally less than 18 months. The aim of this study was to evaluate the diagnostic value of ILR during very prolonged observation.

Methods and Results: Consecutive patients who had received one or more (in the case of battery exhaustion before diagnosis) ILR (Reveal plus/DX, Medtronic Inc.) from 2001 to 2010 were included. The diagnostic ECG was classified according to the ISSUE classification. We analyzed 157 patients (87 males, 69±14 years); 70 of these were followed up for ≥18 months. The estimated cumulative diagnostic rates were 30%, 43%, 52%, and 80% at 1, 2, 3, and 4 years, respectively. 26% of diagnoses were made after 18 months. The diagnostic yield was independent of structural heart disease, bundle branch block, number of syncope, age, and gender; the median time to diagnosis of ISSUE type 1 patients was shorter than that of the others (4 [2;10] vs. 16 [6;23] months, P = 0.003). During the observation period, 3 patients (1.9%) died and none suffered arrhythmic death.

Conclusions: Prolongation of observation up to 4 years increased the diagnostic value of ILR in syncopal patients and was safe. A quarter of patients diagnosed needed more than 18 months of follow-up. As consequence, when a strategy of prolonging monitoring is chosen, monitoring should be maintained even for several years until diagnosis is established.

**Vasovagal syncope mediated by emotional distress associated with increased risk of cardiovascular events**

D. Zysko. Wroclaw Medical University, Wroclaw, Poland

The aim of the study was to assess whether vasovagal syncope mediated by emotional distress (emotional-VVS) is associated with an increased risk of cardiovascular events (CVEs).

Methods and Results: The study group consisted of consecutive 2248 Cardiology Clinic outpatients aged 61.4±12.1 years (604 patients with and 1644 patients without CVE), 28.3% of the studied population reported at least one episode of syncope, 8.7% had emotional-VVS. The median age of CVE was 59, the interquartile range 52-66 years. The median time between the first emotional-VVS and CVE was 37 years, interquartile range 28-44 years. The median time between the first emotional-VVS and the date of visit in cardiology outpatient clinic in patients without CVE was 41 years (interquartile range 25-49 years) (P<NS). Emotional-VVS was significantly more frequent in patients with CVE than in those without (35% vs 26% p<0.01). For each patient an index date was established. The index date was the one of the first CVE or, in the case of patients without CVE, the date of their visit to the clinic. Survival free of CVE to the index date estimated according to Kaplan-Meier method showed lower probability of survival in patients with emotional-VVS and the survival curves began to drift apart at the age of 50. Multiple Cox regression analysis revealed that shorter CVE free survival was related to male gender, diabetes, an hypercholesterolemia above 240 mg/dl, family history of premature cardiovascular disease (CVD) and positive history regarding the emotional-VVS.

<table>
<thead>
<tr>
<th>Male gender</th>
<th>Smoking</th>
<th>Family history</th>
<th>Diabetes</th>
<th>Total cholesterol</th>
<th>Emotional-VVS</th>
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<tbody>
<tr>
<td>HR</td>
<td>2.75</td>
<td>2.15</td>
<td>2.15</td>
<td>1.35</td>
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<tr>
<td>β</td>
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<td>0.001</td>
<td>0.001</td>
<td>0.005</td>
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<tr>
<td>Odds ratio</td>
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<td>1.75-2.66</td>
<td>1.74-2.65</td>
<td>1.64-10.69</td>
<td>1.10-10.59</td>
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<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
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</table>
Two-year diagnostic yield of implantable loop recorder in patients with neurally-mediated syncope enrolled in the ISSUE3 trial


1Ospedale Civile, Bolzano, Italy; 2deldigilio Hospital, Department of Cardiology, Lavagna, Italy; 3Annunziata, Taranto, Italy; 4Ospedale Antonio Elio e Casare Arigo, Alessandria, Italy; 5Reggio Emilia Hospital, Department of Cardiology, Reggio Emilia, Italy; 6Garibaldi Nesiina, Catania, Italy; 7Sacred Heart Hospital of Montreal, Montreal, Canada; 8Molinette, Torino, Italy; 9Cardiologiche Gemeinschaftspraxis, Riesa, Germany; 10St.Mary’s Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom.

Since the diagnostic yield of implantable loop recorders (ILRs) is a function of the length of observation, this rate increases by prolonging the observation period. We assessed the diagnostic yield among the 284 patients (pts) enrolled in ISSUE3 trial who completed the planned 2-year follow-up period. Eligible pts were ≥18 yrs who suffered ≥3 severe syncopal episodes of suspected or certain neurally-mediated syncope (NMS) in the prior 2 years without significant electrocardiographic and cardiac abnormalities. Within 2 yrs from implantation, 76 pts (27%) had syncope recurrence with asystolic pause ≥3 s (45%) or asystolic pause ≥6 s without syncope (41%), 49 pts (17%) had a diagnosis of tachycardia or syncope due to non-arrhythmic cause and 159 pts (56%) had no diagnosis. No baseline clinical variables (table 1) was able to predict the outcome except a positive HUTT (TTP) response which was present in non-syncpe, 51% of those with non-asystolic syncope and in 36% of those without diagnosis (p = 0.003).

In conclusion, about a half of pts receiving an ILR for suspected or certain NMS has a diagnosis within 2 yrs of observation. Of these, about a half may benefit from pacemaker therapy due to a documented long asystolic pause. The pts with negative HUTT only significant changes in APTT (30.9 to 25.6 s; p < 0.0001), INR (1.1 vs 3.3; p = 0.006), D-dimer (263.0 vs 379.0 ug; p = 0.001) and vWBF-ag (57.1 vs 81.6%; p = 0.001) were observed in fainters during HUTT. APTT shortened in 92.1% of studied pts, INR – in 63.2%

Clinical characteristics: Asystole No asystole No diagnosis p-value

<table>
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<th>Asystole</th>
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<th>No diagnosis</th>
<th>p-value</th>
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<td>66 (13)</td>
<td>67 (11)</td>
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<td>Male, No. (%)</td>
<td>37 (49)</td>
<td>22 (45)</td>
<td>66 (42)</td>
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<td>Syncope events:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Total events, median (IQR)</td>
<td>6 (1-12)</td>
<td>6 (4-15)</td>
<td>6 (4-10)</td>
<td>0.600</td>
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<td>– Events in the last 2 years, median (IQR)</td>
<td>4 (3-6)</td>
<td>4 (3-7)</td>
<td>4 (3-5)</td>
<td>0.058</td>
</tr>
<tr>
<td>– Events in the last 2 years without prodromal symptoms</td>
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<td>2 (0-4)</td>
<td>3 (1-4)</td>
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<td>– History of syncope, No. (%)</td>
<td>43 (57)</td>
<td>25 (51)</td>
<td>67 (43)</td>
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</tr>
<tr>
<td>– Hospitalization for syncope, No. (%)</td>
<td>45 (59)</td>
<td>30 (61)</td>
<td>78 (50)</td>
<td>0.219</td>
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<tr>
<td>– Injuries related to fainting, No. (%)</td>
<td>32 (43)</td>
<td>16 (31)</td>
<td>44 (28)</td>
<td>0.588</td>
</tr>
<tr>
<td>– Major injuries (fractures, brain concussion)</td>
<td>6 (8)</td>
<td>2 (4)</td>
<td>23 (15)</td>
<td>0.071</td>
</tr>
<tr>
<td>– Minor injuries</td>
<td>30 (40)</td>
<td>16 (31)</td>
<td>64 (44)</td>
<td>0.588</td>
</tr>
<tr>
<td>Tilt test: performed, No (%)</td>
<td>65 (86)</td>
<td>45 (90)</td>
<td>142 (90)</td>
<td>0.480</td>
</tr>
<tr>
<td>– Positive of those performed, No. (%)</td>
<td>39 (66)</td>
<td>23 (51)</td>
<td>51 (38)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

In conclusion, about a half of pts receiving an ILR for suspected or certain NMS has a diagnosis within 2 yrs of observation. Of these, about a half may benefit from pacemaker therapy due to a documented long asystolic pause. The pts with negative HUTT only significant changes in APTT (30.9 to 25.6 s; p < 0.0001), INR (1.1 vs 3.3; p = 0.006), D-dimer (263.0 vs 379.0 ug; p = 0.001) and vWBF-ag (57.1 vs 81.6%; p = 0.001) were observed in fainters during HUTT. APTT shortened in 92.1% of studied pts, INR – in 63.2%

Incidence, etiology and predictors of adverse outcomes in 43315 patients presenting to the emergency department with syncope: an international meta-analysis

F. D’Ascenzo1, G. Bombit Zoccali1, M.J. Reed2, F. Gaia1. 1Hospital Molinette of the University Hospital S. Giovanni Battista, Turin, Italy; 2Department of Medico-Surgical Sciences and Biotechnologies Sapienza University of Rome, Rome, Italy; 11Department of Emergency Medicine, Edinburgh, United Kingdom, Edinburgh, United Kingdom.

Background: Syncope remains challenging for Emergency Department (ED) physicians due to difficulties in assessing the risk of future adverse outcomes. The aim of this meta-analysis is to establish the incidence and etiology of adverse outcomes as well as the predictors.

Methods: Studies reporting multivariate predictors of adverse outcomes in patients presenting with syncope to the ED were included and pooled, whenappropriate, using a random-effect model. Adverse outcomes were defined as ‘incidence of death, or ophthalmization and interventional procedures because of arrhythmia, ischemic heart disease or valvular heart disease’.

Results: 11 studies were included. Pooled analysis showed 42% (CI 95%; 32-52) of patients were admitted to hospital. Risk of death was 4.4% (CI 95%; 3.1-5.1) and 1.1% (CI 95%; 0.7-1.5) had a cardiovascular etiology. One third of patients were discharged without a diagnosis, and the most frequent diagnosis was situational, orthostatic or vasovagal syncope in 29% (CI 95%; 12-47). 10.4% (CI 95%; 7.8-16) were diagnosed with heart disease, the most frequent type being bradyarrhythmia, 4.8% (CI 95%; 2.2-6.4) and tachyarrhythmia 2.6% (CI 95%; 1.1-3.1). Papulation-sparing syncope, exertional syncope, a history consistent of heart failure or ischemic heart disease, and evidence of bleeding were the most powerful predictors of an adverse outcome.

Conclusion: Syncope carries a high risk death, mainly related to cardiovascular disease. This large study which has established the most powerful predictors of adverse outcomes, may enable careend resources to be better focused at high risk patients.

The risk of clotting induced by orthostatic stress patients with vaso-vagal syncope

A.Z. Pietrucha1, I. Bzukala1, D. Fedak2, M. Wnuk1, E. Kondrucka1, W. Pwowska1, J. Nessler1. 1Medical School of Jagiellonian University - John Paul II Hospital - Coronary Disease Department, Krakow, Poland; 2Chair of Clinical Biochemistry, Medical School of Jagiellonian University, Cracow, Poland, Cracow, Poland.

Aim of study: Analysis of prevalence of endothelium-dependent clotting and fibrinolysis, as a response to orthostatic stress during head up tilt test (HUTT) in patients with vaso-vagal syncope (VVS).

Study population: 40 pts (15 men, 25 women) aged 18-72 yrs (median of age: 35 yrs. IQR 23.7-55.6) with VVS referred to HUTT for analysis of clotting and fibrinolysis parameters. We measured: prothrombin time, analysis of clotting and fibrinolysis parameters. We measured: prothrombin time, activated partial thromboplastin time (aPTT) serum concentrations of fibrinogen (FIB) dimer (D-Dimer), serum tissue plasminogen activator (tPA) plasminogen activator (inhibitor 1 (PAI-1) and von-Willebrand Ag (vWBF-Ag) as described % of normal values.

Results: Significant decrease of APTT (30.9 to 25.6 s; p < 0.0001), INR (1.1 vs 1.03; p = 0.003) and PAI-1 (4.6 vs 3.1 ng/ml; p = 0.003) as well as increase of serum levels of FIB (3.1 to 3.3 g/l; p = 0.006), D-Dimer (263.0 vs 379.0 ug/l; p = 0.001), uWBF-ag (57.1 vs 81.6%; p = 0.001) and IPA (5.0 vs 9.8 ng/ml; p = 0.001) were observed in fainters admitted to hospital during HUTT. APTT shortened in 92.1% of pts, and PAI-1 decreased in 75% of patients. Fibrinogen concentration rises during HUTT in 76% of pts, D-Dimer – in 86.6% of pts, vWBF – in 69.2% of pts ant IPA – in 71.8% of patients. In patients with negative HUTT only significant decrease of PAI-1 serum level was observed (6.8 vs 4.4 ng/ml; p = 0.04). Changes of values of measured parameters during HUTT did not correlate with age of pts. Observed changes in clotting related to the orthostatic stress resembles changes observed during haemorrhage. Only activation of fibrinolysis simultaneously to
clothing provoked by orthostatic stress may prevent against dangerous thromboembolic complications in patients with vasovagal syncope.

**Conclusions:**
1. Syncope induced by orthostatic stress during head-up tilt test lead to potentially dangerous activation of clotting in patients with vasovagal fairs.
2. Simultaneous activation of fibrinolysis processes by orthostatic stress prevents against dangerous thromboembolic complications in patients with vasovagal syncope.
3. Endothelium-dependent activation clotting and fibrinolysis in response to orthostatic stress seems to play an important role in pathogenesis of vasovagal syncope.

**P4747 Incidence of permanent atrioventricular block in patients with syncope and bifascicular block**

C. Ukena, F. Mahtlouf, I. Lee, H.R. Neuberger, M. Boehm, A. Buob, G. Froehlig. Saarland University Hospital, Department of Internal Medicine Ill, Cardiology, Homburg, Germany

**Introduction:** In patients with syncope and bifascicular block (BBF), syncope is likely to be attributable to paroxysmal atrioventricular block (AVB). Therefore, a pacemaker implantation is recommended by current guidelines. However, it remains unclear if and at which time point a permanent blockade of atrioventricular (AV) conduction occurs and if pacemaker with AV management are useful in these patients.

**Methods:** 106 patients with either syncope with bifascicular block (group 1, n = 34) or paroxysmal AVB with (group 2, n = 51) or without BBF (group 3, n = 21) were included in the study. All patients received a pacemaker with AVM (AAI-SafeP, Symphony®, Sorin SPA, Milano, Italia) and were follow-up in a six-months-interval (mean follow-up 20 ± 3 months). The primary end-point was the time to permanent switch to DDD, DDI-, or VVI-mode.

**Results:** 46% of patients in group 1, compared to 70% in group 2 and 77% in group 3 had episodes of intermittent switches to ventricular pacing modes (p = 0.065). Proportion of ventricular pacing was significantly higher in group 2 (40%) and group 3 (32%) compared to group 1 (17%) (p = 0.02). The primary end-point occurred in 16% patients in group 1, 56% patients in group 2, and 53% patients in group 3 (p = 0.001). Time to primary end-point was not significantly different between the groups (17.5 ± 12.6 ± 11.3 months; p = 0.633).

**Conclusion:** Only 16% of patients with syncope and bifascicular block lose permanent AV conduction compared to 55% of patients with paroxysmal AVB.

**Prevalence of depression syndrome in patients with vasovagal syncope**

A.Z. Pietrucha, A. Borowiec, D. Mroczek-Czerneda, M. Wnuk, I. Bukalakia, M. Węgryniewska, E. Konduracka, O. Kruszelnicka, W. Piwowarska, J. Nessler. Medical School of Jagiellonian University - John Paul II Hospital - Coronary Disease Department, Krakow, Poland

The aim of study was analysis of factors influencing on the prevalence of depression syndrome (DS) in patients with vasovagal syncope (VVS).

**Study population:** We observed 650 pts (386 women, 264 men) aged 18-72 (median of age 41.5 yrs), with VVS referred to head-up tilt test (HUTT).

**Methods:** All pts underwent HUTT performed acc. to standard Westminster or Italian protocols. Before HUTT the Depression Beck Score questionnaire was applied to all pts for evaluation of presence of DS. Mild DS was diagnosed if Beck Score ranged between 10 and 19, mild 20-25 and severe SD – with Beck Score ≥ 26.

**Results:** Incidence of depression syndrome (DS) in patients with vasovagal syncope occurred significantly more frequent in patients with diagnosed severe depression syndrome. Pts with DS more frequently presented positive HUTT result and vasodepressive response to orthostatic stress test than pts without DS. Patient with severe DS presented higher rate of cardioinhibitory response during HUTT.

**Conclusion:** There were no significant influence of gender, number of presyncope episodes, duration of HUTT (all phases), oxygen saturation of brain during HUTT and CSSS results on DS occurrence in patients with vasovagal syncope.

**P4749 The CHADS2 risk score predicts long-term outcome after first admission for syncope - A nationwide study**

M. Ruwald1, C. Jon1, M. Lock Hansen1, A.C.H. Ruwald1, M.V. Hojgaard1, L. Kober1, C. Torp-Pedersen1, J. Hansen1, G. Gislason1. 1Gentofte Hospital - Copenhagen University Hospital, Department of Cardiology, Hellerup, Denmark, 2Rigshospitalet - Copenhagen University Hospital, Heart Centre, Copenhagen, Denmark

**Background:** The CHADS2 score is an important risk stratification tool for risk of stroke in patients with atrial fibrillation and may also be predictive for other major cardiovascular events. We investigated if CHADS2 score could be applied as a risk stratification tool for predicting cardiac events after an episode of syncope.

**Methods and results:** All patients admitted with a first time diagnosis of syncope from 2001 to 2009 where identified from nationwide administrative registers in Denmark. Risk of major cardiovascular events (acute myocardial infarction or implantation of pacemaker/ICD) and all-cause or cardiovascular death according to CHADS2 score was analysed by multivariable Cox proportional-hazards models. A total of 88355 patients were included (median age 64 years (IQR: 47.5-80.5) and 47.6% were females. There were a total of 19,011 deaths of which 10,389 (54.6%) were cardiovascular. The event rate of cardiovascular death was 5.25 per 1000 person-years for the group with CHADS2 score=0. The risk of cardiovascular death was significantly increased with increasing CHADS2 score when adjusted for sex (CHADS2 score +1.2 HR=10.25 [CI: 9.60-10.94]), (CHADS2 score +3.4 HR=23.59 [CI: 21.96-25.35]), (CHADS2 score +5.6 HR=36.82 [CI: 32.08-42.25]), p<0.0001. This pattern was similar for all-cause mortality and major cardiovascular events.

**Conclusion:** The CHADS2 score significantly predicts risk of cardiovascular death, all-cause mortality and major cardiovascular events in patients admitted with syncope, and may be used for risk stratification in combination with other risk score systems. A CHADS2 score of 0 is associated with a very low long- and short-term mortality.
Remote monitoring of implantable loop recorders: high artefact in the early phase following implant

Freeman Hospital, Newcastle upon Tyne, United Kingdom

Purpose: Implantable loop recorders (ILRs) are increasingly used in the investigation of unexplained syncope. Remote monitoring of ILRs has recently become available. We report our initial experience with the practical aspects of remote monitoring of ILRs.

Methods: Between August 2011, patients were offered remote monitoring using the Medtronic CareLink system at the time of Reveal XT ILR implant. Scheduled transmissions were planned weekly for 8 weeks, then monthly. Patients were asked to make a transmission after a symptomatic episode. Time taken to download, re-view and report results to patients was recorded. Data from existing patients using Carelink after Reveal implant was also analysed; these patients made ad-hoc transmissions.

Results: 19 patients were enrolled, mean age 49.5 years. 18 successfully made a test transmission; there were technical difficulties in 1 patient resulting in 4 missed transmissions. 2 other patients missed a total of 3 transmissions. 143 scheduled transmissions were made; 2093 automatically detected episodes were recorded, all false positives. The majority of the episodes occurred in 2 patients. 1570 episodes of asystole were recorded in 1 patient due to artefact as a result of the autogain feature. In another patient, 401 episodes were detected as AF due to frequent atrial ectopics. Staff time requirements are shown in Table 1. Three patients made recordings after symptoms but no abnormality was identified. Nine patients already using Carelink sent ad-hoc/symptomatic transmissions only. Nine patients made recordings after symptoms but no abnormality was identified. Three patients already using Carelink sent ad-hoc/symptomatic transmissions only.

Conclusions: Our data show a high incidence of artefact in the early phase after ILR implantation resulting in multiple recordings. Staff time to process, report and communicate data was 5.3 minutes per transmission.

The influence of the menstrual cycle on the tilt testing result

D. Zysko, J. Gajek, L. Terpilowski, A.K. Agrawal, P. Wroblewski, J. Rudnicki. Wroclaw Medical University, Wroclaw, Poland

The fluctuation of the female sex hormones level may change the susceptibility to the neurocardiogenic reflex provocation throughout the menstrual cycle. The aim of the study was to assess the distribution of the positive tilt testing (TT) results through menstrual cycle as well syncope and presyncope and finally to determine if the phase of menstrual cycle contribute to the duration of the loss of consciousness during TT induced syncope.

Material and methods: The study group consisted of 183 premenopausal, women aged 29±9.9±8.8 years. The menstrual cycle was divided into 4 phases based on the first day of the last menstruation (menstrual (M), preovulatory (F), periovulatory (O) and postovulatory (L). The clinical characteristics and TT results are shown in the table:

<table>
<thead>
<tr>
<th>Group</th>
<th>Premenstrual phase (M)</th>
<th>Preovulatory phase (F)</th>
<th>Periovulatory phase (O)</th>
<th>Postovulatory phase (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=49</td>
<td>n=46</td>
<td>n=33</td>
<td>n=41</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>30±4.1* 10.8</td>
<td>30±10.3</td>
<td>30±10.3</td>
<td>30±1* 12*</td>
</tr>
<tr>
<td>Syncope spells</td>
<td>2 (1.5)</td>
<td>3 (1.5)</td>
<td>4 (1.10)</td>
<td>4 (1.10)</td>
</tr>
<tr>
<td>Positive TT (%)</td>
<td>82</td>
<td>71</td>
<td>56</td>
<td>35</td>
</tr>
<tr>
<td>Syncope duration (sec)</td>
<td>41±26</td>
<td>30±10*</td>
<td>20±15*</td>
<td>25±12*</td>
</tr>
</tbody>
</table>

*p<0.05 vs group M.

Conclusions: 1. The distribution of the positive and negative TT results as well syncope and presyncope as a TT result does not differ through the menstrual cycle. 2. The duration of the loss of consciousness is longer during premenstrual phase of the menstrual cycle independently from the higher syncope frequency and lower heart rate at TT termination. 3. The fluctuation of the female sex hormones levels does not change the susceptibility to the neurocardiogenic reflex provocation but when provoked influence on its course.

Pictureconomics: a micro-costing analysis of diagnostic investigations for unexplained syncope

N. Edwardsson1, S. Trintzig2, C. Garutti3, G. Rieger4, N. Linker5
1Sahlgrenska University Hospital, Gothenburg, Sweden; 2Medtronic Baker Research Center, Maastricht, Netherlands; 3James Cook University Hospital, Middlesbrough, United Kingdom

Purpose: To quantify the resource use associated with unexplained syncope in a real-world setting, before a clinical decision to implant an implantable loop recorder (ILR) was made.

Methods: PICTURE is a prospective, observational registry on Implantable Loop Recorders (ILR) and diagnostics tests for unexplained syncope, carried out in 570 patients at 83 sites in 11 EU countries. PICTUREEconomics is based on PICTURE and a UK micro-costing study to quantify the burden of investigation and under-utilization of healthcare resources.

Results: The mean number of tests before ILR implant was 17 (95% CI 16.08 – 17.04) while the median was 13 (IQ Range 9 – 20). The minimum number of diagnostics observed was 0 while the maximum was 203. Among the top 25% of healthcare resource users, the median tests were 27 (IQ Range 22–36). Based on the tag-on micro-costing study, the mean expenditure per patient was €1,613.15 (€1,879.51 – €1,388.50). The median was €1,138.86 (€1,297.77 – IQ Range €568.97 – €2,242.26), while the costs could escalate up to €7,417.89 (€6,824.66). The cost of a patient receiving every type of the 17 investigations once, including e.g. ECG, Holter, blood pressure provocation, TILT test, neurological evaluation, coronary angiogram, MRI, CT, invasive EP testing etc., would have been €5,007.81 (€4,669.54). Should ESC Guidelines have strictly been adhered to (as was the case in 12% of the PICTURE Study population), the average test cost per patient per admission would be €710.3 (€827.58). In the remainder of patients, the same cost was €1,348.47 (€1,571.12).

Conclusions: Most patients were more thoroughly investigated before ILR implant than suggested in guidelines. PICTUREEconomics showed the costs of investigations to be highly significant and most patients having moderate consumption while others consumed several times more. Identification of resource intensive patients can be an algorithm for choosing a more cost-effective approach before an ILR implantation.

Pictureomics: a micro-costing analysis of diagnostic investigations for unexplained syncope

N. Edwardsson1, S. Trintzig2, C. Garutti3, G. Rieger4, N. Linker5
1Sahlgrenska University Hospital, Gothenburg, Sweden; 2Medtronic Baker Research Center, Maastricht, Netherlands; 3James Cook University Hospital, Middlesbrough, United Kingdom

Conclusions: Our data show a high incidence of artefact in the early phase after ILR implantation resulting in multiple recordings. Staff time to process, report and communicate data was 5.3 minutes per transmission.

In patients with vasovagal syncope the increase of adrenomedullin during the positive head-up tilt test correlates with HRV parameters

J. Gajek, D. Zysko. Wroclaw Medical University, Wroclaw, Poland

Background: The mechanism regulating adrenomedullin (ADM) secretion – a strong vasodilating peptide - is little known. The activation of sympathetic nervous system causes rise of blood pressure due to increase of peripheral vascular resistance, what can be the impulse for ADM secretion. The strong activation of sympathetic nervous system is considered as a cause of syncope in vasovagal patients. The aim of the study was to assess the relation between the changes of ADM plasma level during HUTT and heart rate variability parameters in patients with vasovagal syncope due to cardiodepressive reaction after nitroglycerine provocation.

Material and methods: The studied group consisted of 17 patients (pts) with vasovagal syncope (vs) due to cardiodepressive reaction during active phase of HUTT (after NTG provocation). In all studied pts blood samples for ADM level assessment were drawn before the test, after 30 minutes supine rest, and immediately after the syncope. Adrenomedullin plasma level was assessed using radioimmunological assay. The patients had 24-hour ECG Holter monitoring and time domain HRV analysis was performed for 24 hours, night and day time.

Results: In the study group there was no correlation of HRV parameters and mRR with age of pts. The mRR was significantly shorter in women than in men (p=0.03), the pNN24/CT was significantly shorter in women during perimenstrual phase (p=0.05). The adjustment for sex was made; 1 patient received a pacemaker, all others were artefact.

Conclusions: The distribution of the positive and negative TT results as well syncope and presyncope as a TT result does not differ through the menstrual cycle. The duration of the pause during TT induced syncope was longer when the TT was performed during perimenstrual phase than during the other phases of the menstrual cycle.
PERCUTANEOUS CORONARY INTERVENTION: INVASIVE IMAGING/DEVICES AND TECHNIQUE

P4754
Head to head comparison of fully drug-free bioresorbable PLA and bare metal stents in normal porcine coronary: a six-month angiography and OCT follow-up study

E. Durand1, M. Ver2, T. Sharkawi1, A. Lafont1, 1AP-HP - European Hospital Georges Pompidou, Department of Cardiology, Paris, France; 2Institut de Biomolécules Max Mousseron, UMR CNRS 5247, University Montpellier 1-CNRS, Montpellier, France; 3Institut Charles Gherardt –MACS, UMR CNRS 5253, Faculté de Pharmacie Université Montpellier 1, montpellier, France

Background: The concept of fully bioresorbable polymeric (PLA) stent is now perceived as a potential attractive alternative to metallic stent. The aim of this study is therefore to evaluate a drug-free PLA stent in the porcine model as compared to a bare metal stent (BMS).

Methods: Twenty-nine BMS (Vision®, Abbott, Inc.; 3X12 mm) and 29 PLA stents (ART, Noisy le Roi, France; 3X11mm) were implanted in porcine coronary arteries. QCA and OCT analysis were performed immediately after stent implantation, and repeated (1±22), 3 (n=28), and 6 (n=6) months later. The primary end-point was in-stent diameter by OCT, and the secondary end-points were acute recoil and late lumen loss (LLL).

Results: Acute recoil was not significantly different between PLA and BMS groups (3.6±0.9% vs. 4.7±5.3%, respectively; p=NS). The in-stent diameter was closely similar immediately after stent implantation in PLA and BMS groups (2.99±0.08 mm vs. 3.05±0.18 mm, respectively). BMS in-stent diameter remained constant through 6-month follow-up (2.99±0.21, 2.95±0.21, 3.14±0.21 mm at 1, 3, and 6 months, respectively. In contrast, in-stent diameter significantly increased at 3 and 6 months in the PLA group indicating late positive remodeling (2.67±0.18, 3.13±0.19, 3.21±0.08 mm at 1, 3, and 6 months, respectively). Similarly, LLL was initially significantly higher in the PLA group (0.72±0.35 vs. 0.18±0.25 mm, 0.52±0.24 mm vs. 0.21±0.31 mm at 1 and 3 months, respectively) but was closely similar at 6 months between the PLA and the BMS groups (0.10±0.14 mm vs. 0.16±0.23 mm, p=NS).

Conclusions: OCT and QCA analysis of bare PLA stent indicated favorable 6-month outcomes as compared to BMS in porcine coronary arteries. Interestingly, PLA strut degradation is associated with positive remodeling at 3-6 months, and late lumen gain.

P4755
The volume of lipid-rich plaque, measured by integrated backscatter IVUS was associated with amount of captured plaques by filter-type distal protection device during coronary intervention

K. Kitagawa1, T. Uetani1, A. Kunimura1, Y. Shimo1, H. Ando1, K. Harada1, T. Yoshida1, T. Amano1, T. Matsubara1, T. Murakami1, 1Chubu Cardiovascular Center, Himeji, Japan; 2Aichi Medical University, Department of Cardiology, Nagakute, Japan; 3Aichi Gakuin University, School of Dentistry, Nagakute, Japan; 4Aichi Medical University Graduate School of Medicine, Department of Cardiology, Nagoya, Japan

Background: The atheroerotic plaque disruption caused by balloon or stent expansion and distal embolism may major cause of peri-procedural myocardial injury during percutaneous coronary intervention (PCI). However relationship between details of lesion characteristics and amount of released plaque particle during procedure is unclear.

Methods: From April 2010 to December 2011, thirty consecutive patients who underwent PCI with filter-type distal protection device (Filter™) following integrated backscatter intravascular ultrasound (IB-IVUS) analysis were enrolled. The volume of each plaque component (lipid, fibrous and calcified) within target lesion was calculated. Area of captured debris of protection filter was measured by microscopic evaluation (Figure). The coronary flow disturbance (TIMI 0/1/2) during distal protection was defined as filter-related flow disturbance (FFD).

Results: The lipid volume of target lesions significantly correlated with area of captured debris (r= 0.41, p= 0.02). The fibrous volume and calcified volume did not correlate with area of captured debris. The lipid volume of patient with FFD was significantly higher those without FFD (160±390.2 mm³ vs. 93.0±55.0 mm³, p=0.01). The lipid volume was independently correlated with area of captured debris in multivariate regression analysis after adjustment for clinical, procedural parameters and other plaque components.

P4757
Nine months optical coherence tomography evaluation of neointimal coverage of a strategy of paclitaxel-eluting balloon plus bare metal stent

I. Porti, K. Ducci, P. Angiolii, G. Falsini, F. Lustro, L. Bolognese, San Donato Hospital, Department of Cardiology, Arezzo, Italy

Background: Drug-eluting balloon (DEB) predilatation followed by bare metal stent (BMS) implantation represents an innovative treatment for coronary artery disease. Yet, the safety of this strategy has still to be demonstrated.

Methods: Frequency-domain optical coherence tomography was performed at 9 months in a registry of 30 consecutive patients who underwent elective stenting with a BMS (Prokinek, Biotronik) after predilatation with a DEB (Elutax, Aachen Resonance). Patients with clinical restenosis (n=3), or with suboptimal images (n=4) were excluded. Quantitative strut level analysis was performed at 0.4 mm intervals (every other frame) along the entire target segment. A total of 23 lesions in 23 patients were analyzed. The center of the luminal surface of the strut blooming was determined for each strut, and its distance to the lumen contour was calculated automatically to determine strut-level intimal thickness (SIT). Struts covered by tissue had positive SIT values whereas uncovered or malapposed struts had negative SIT. The number of struts without coverage was counted for each frame analyzed, and the total number of frames with uncovered struts was recorded. Strut malapposition was determined when the negative value of SIT was higher than 100 micron (60μm Prokinek strut thickness, plus a correction factor of 40μm to account for strut blooming).

Results: A total of 4304 struts were analysed. In total, 131 struts (3%) in only 2 lesions (123 in one, 8 in the other) were found to be uncovered. Malapposed struts were 105 (2.4±3.2%). Percentage net volume obstruction was 92.0±15.6%.

Conclusions: BMS implantation plus DEB is a safe strategy, as it is associated with a percentage of malapposed/ uncovered struts which compared favourably with BMS historical controls. Neointimal regrowth (after the exclusion of clinical restenosis patients) is also comparable to historical data.

P4758
Intravascular ultrasound guided everolimus eluting stent implantation resolves the disadvantage of thin strut cobalt chromium platform in patients with diabetes

H. Takahashi, S. Yamada, T. Hayashi, Y. Yasaka, S. Kobayashi, T. Takaya, N. Miyoshi, S. Oishi, T. Toba, M. Yokoyama, Himeji Cardiovascular Center, Himeji, Japan

Background: Though efficacy of everolimus-eluting stent (EES; Xience V) is well-established by many clinical evidences, several trials failed to show superiority in diabetic subset. We hypothesized that inappropriate stent expansion in complex lesion of diabetes due to thin cobalt chromium platform may be one of the reasons. The purpose of this study is to investigate this hypothesis using intravascular ultrasound (IVUS).

Method: Consecutive 130 de-novo lesions (61 EES and 69 paclitaxel-eluting stent (PES; Taxus Express2, stainless steel thick platform)) treated by elective IVUS-guided PCI for stable patients were recruited in this study. Stent size was determined according to pre-procedural IVUS findings. After stent deployment using standard technique, IVUS procedure was repeated and stent diameter and cross-sectional area (CSA) were measured. If stent expansion was inadequate,
Feasibility and efficacy of ex-vivo stent fracture assessment by optical coherence tomography (OCT) and microcomputed tomography (microCT)

M. Vorpahl1, V. Veulemanns1, P. Horn1, T. Ball2, D. Zlotnik3, P. Maurovic-Horvat1, T. Zeus1, R. Westerfeld1, M. Kelm1, J. Foerst3.
1University Clinic, Düsseldorf, Germany; 2Carolina Medical Center, Charlotte, United States of America; Dartmouth Medical School, Section of General Internal Medicine, Lebanon, United States of America; 3Semmelweis University, Budapest, Hungary

Purpose: Coronary stent fracture (SF) is recognized as a contributor to adverse clinical events like stent restenosis. However, the true prevalence of coronary SF remains uncertain with clinically observed fracture rates of up to 8% in vivo utilizing fluoroscopic detection and up to 70% at autopsy using high resolution x-ray and 3D microCT. There is limited data to suggest that intravascular ultrasound may improve the sensitivity of in-vivo stent fracture detection, however, to our knowledge there are no controlled studies to demonstrate the sensitivity of cross-sectional intravascular imaging for SF detection.

Methods: A bench top fracture model was created by manually cutting stent crowns or interconnectors (Abbott Multilink Vision 3.0 x 12.0 mm and Biotronik, PRO-Kineti, 3.0 x 10). A total of 7 stents with varying extent of fracture were implanted in silicone tubes and analyzed with optical coherence tomography (OCT) (100 bps, 10 mm/sec, Dragonfly, St. Jude) and microCT (xEiploré, GE). Two experienced, blinded interventional cardiologicalists reviewed the 2D OCT pullback scans, 2D and 3D microCT reconstructions looking for SF. The review procedure was limited to 5 minutes per stent/modeality to simulate a realistic clinical decision time. The sensitivity and specificity of each modality was determined based on the known fracture sites as visualized through the clear silicone tubes.

Results: Review of the 2D OCT images accurately identified 4/9 SF (sensitivity 44.4%) with no false positive SF detection (specificity 100%). Review of the 2D microCT images accurately identified 8/9 SF (sensitivity 88.9%) with no false positive SF detection (specificity 100%). Review of the 3D microCT renders accurately identified all of the SF (sensitivity 100%) with no false positive SF detection (specificity 100%). The interobserver variability was moderate for OCT and perfect for 2D microCT (α = 0.55 ± 0.10 respectively).

Conclusion: Based on this small bench top series, clinically available 2D cross-sectional imaging with OCT is inadequate to reliably detect coronary SF. The vast majority of microCT to detect SF explains the gap between the clinically reported prevalence of SF as compared to autopsy studies. We chose OCT over IVUS given the improved temporal and spatial resolution, however, even with OCT wire artifacts may have limited SF detection. Given the 100% sensitivity of 3D microCT for SF detection there remains the potential for high-resolution axial imaging like OCT to be rendered in 3D to improve SF discrimination and ultimately may garner a more comprehensive understanding of the natural history and impact of SF.

Neointimal appearance of late clinical event related lesions after bare-metal stent and sirolimus-eluting stent implantation assessed by Optical Coherence Tomography

Y. Ino, T. Kubo, H. Kitabata, Y. Ozaki, Y. Shiono, Y. Yamaguchi, T. Tanimoto, K. Hirata, T. Imanishi, T. Akasaka, Wakayama Medical University; Department of Cardiovascular Medicine, Wakayama, Japan

Background: Late clinical event such as very late stent thrombosis (VLST) and late in-stent restenosis (ISR) after bare-metal stent (BMS) and drug-eluting stent (DES) is an important clinical issue. However, the difference of underlying mechanisms in late clinical event between BMS and DES has not been fully evaluated yet. The aim of the present study was to compare neointimal tissue appearance of these lesions between BMS and sirolimus-eluting stent (SES) by using optical coherence tomography (OCT).

Methods: We examined the neointimal tissue appearance in 34 late clinical event lesions after BMS (n=15) and SES (n=19) implantation by OCT. Late clinical event was defined as VLST and late ISR (> 1 year after initial procedure).

Results: Results were shown in the table described below.

<table>
<thead>
<tr>
<th></th>
<th>BMS (n=15)</th>
<th>SES (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of OCT imaging after stent implantation, months</td>
<td>100±23</td>
<td>33±14</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Lipid-rich neointima, n (%)</td>
<td>13 (87)</td>
<td>15 (79)</td>
<td>0.558</td>
</tr>
<tr>
<td>TCFAs like neointima, n (%)</td>
<td>11 (73)</td>
<td>12 (63)</td>
<td>0.521</td>
</tr>
<tr>
<td>Neointimal disruption, n (%)</td>
<td>9 (60)</td>
<td>6 (32)</td>
<td>0.098</td>
</tr>
<tr>
<td>Thrombus, n (%)</td>
<td>9 (60)</td>
<td>7 (37)</td>
<td>0.179</td>
</tr>
<tr>
<td>Stent malapposition, n (%)</td>
<td>0 (0)</td>
<td>5 (26)</td>
<td>0.032</td>
</tr>
<tr>
<td>Calcification within neointima, n (%)</td>
<td>3 (20)</td>
<td>0 (0)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Values are given as n (%) or *mean ± SD. BMS = bare-metal stent; OCT = optical coherence tomography; SES = sirolimus-eluting stent; TCFAs = thin-cap fibroatheroma.

Conclusions: In late clinical event related lesions, atherosclerotic change such as TCFAs formation and calcification within neointima is often demonstrated in BMS and stent malapposition might be related in DES.

Assessment of coronary vascular response after first in man implantation of a novel thin strut low profile fixed wire stent

R. Diletti1, H.M. Garcia-Garcia1, V. Faroqq, P. Stella2, P. Agostini3, J. De Schepper4, M. Pomerantz4, P.W. Serruyts1, E. Erasmus Medical Center, Thoraxcenter, Department of Cardiology, Rotterdam, Netherlands; 2University Medical Center Utrecht, Utrecht, Netherlands; 3Svelte Medical Systems, New Providence, United States of America

Purpose: The Svelte Stent-On-A-Wire (SOAW) is a novel fixed wire thin struts cobalt chromium stent. This device was designed for a direct stenting use, to ensure reduction of fluoroscopy time and contrast usage that was observed to be clinically relevant in high-risk patients. In addition the very low lesion entry profile could provide additional advantages in challenging settings. The aim of the present study is to evaluate for the first time the vascular healing process after Svelte SOAW implantation in humans with optical coherence tomography (OCT).

Methods: The Svelte SOAW Coronary Stent Clinical First in Man Study is a multicenter, prospective, non-randomized, single-arm study aiming to evaluate the safety and performance of the novel Svelte SOAW for treatment of coronary de novo lesions. Out of the total population (46 patients) 19 subjects underwent OCT imaging at the index procedure and at 6-month follow-up.

Results: At 6-month follow-up a high percentage of struts were covered (97.6±15.00%) with variable thickness of neointimal tissue of 0.31±0.14 mm, no changes were observed in mean stent area (8.18±2.85 vs 7.68±3.06, p=0.14) and mean stent diameter (3.17±0.57 vs 3.07±0.61, p=0.07) over time. Post-implantation mean prolapse area (0.10±0.06 mm²), mean incomplete stent apposition (ISA) area (0.12±0.13 mm²) and mean intraluminal mass area (0.05±0.03 mm²) were minimal. Edge dissection was reported in 8 cases and was observed to be strongly associated with post-dilation at the index procedure.

Conclusions: Implantation of the Svelte SOAW was associated in the present report with a low acute vascular injury and a high percentage of strut coverage at 6-month follow-up with a mean neointimal thickness comparable with other bare metal stents.

Development of microporous covered stents for treating cerebral aneurysms without disturbing branching vascular flow

Y. Nakayama1, S. Nishii2, H. Ishihashi-Ueda3, M. Miyake4, A. Wada4, 1National Cardiovascular Center Research Institute, Osaka, Japan; 2Sapporo Higashi Tokushukai Hospital, Sapporo, Japan; 3National Cerebral and Cardiovascular Center Research Institute, Suita, Osaka, Japan; 4Japan Stroke Technology, Co., Okyama, Japan

Objective: Treatment of large (diameter ≥25 mm) or giant (diameter ≥25 mm) cerebral aneurysms with a broad neck in the crano-cervical area is difficult and carries relatively high risks, even with surgical and/or endovascular methods. To this end, we have been developing microporous covered stents.

Methods and Results: The covered stents were prepared using the specially...
Sex-related differences in percutaneous coronary interventions for chronic total occlusions

G. Ferrante¹, P. Garot², T. Harbi³, T. Untersee², H. Benamer¹, M.C. Monici³, T. Lefèvre⁴, Y. Louvard⁴, 1CPS - Institute Hospital Jacques Cartier, Massy, France; 2Institut Cardiovasculaire Paris Sud, Quincy, France

Purpose: The aim of this study was to assess sex-differences in percutaneous coronary intervention (PCI) for chronic total occlusions (CTO).

Methods: The study included all consecutive patients undergoing PCI for CTO at 3 tertiary PCI centres between January 2004 and December 2011. A multivariable mixed effect logistic regression for clustered data was used to assess the impact of female sex on PCI success after adjustment for clinical and procedural characteristics, CTO lesion difficulty, vessel site, and procedural techniques. CTO lesions were graded as easy (score of 0), intermediate (score of 1), difficult (score of 2), and ‘very difficult’ (score of ≥3), according to the J-CTO score on the basis of calcification, bending, blunt stump, occlusion length ≥20 mm, and previously failed lesion.

Results: Among 1261 patients, median age 63 yrs-old (25th-75th percentile, 55-72), undergoing PCI for 1418 CTO, 176 (13.9%) were women. Women, as compared to men, were significantly sicker (70.5 yrs-old (61-77) vs 62 (55-72), p<0.001), less frequently smoker (15.3% vs 28.8%, p<0.001), and had less frequently a previous coronary artery bypass graft surgery (2.8% vs 8.1%, p=0.01). In a lesion-based analysis, left anterior descending artery as the treated vessel, DM pts (insulin dependent 22%) that had been treated with 1st generation DES (Cypher 81%, Taxus 11%, combination 8%) were included. Five years clinical follow-up (FU) obtained in 576/598 (96%). Early and late (up to 12 months) stent thrombosis (EST) and very late stent thrombosis (VLST) were assessed according to ARC definition as Hard-end point (HENP) was considered the combination of all cause mortality (D), myocardial infarction (MI) and cerebrovascular accident (CVA).

Results: At 12 months (MO) 89% of pts were on DAPLT; the incidence of definite/probable EST (median time 6.5 MO) was 0.7% (one D, and 3 MI), and all pts were on DAPLT when the event occurred. The incidence of definite/probable VLST at 5 years (median time 34.5 MO) was 0.7% (2 D, 2 MI); two pts were on DAPLT and two on single (S) APTL when the event occurred. The incidence of HENP year according to APTL treatment is shown in the Table. In a Cox regression model (p<0.001) and EF (p<0.001) were predictors for HENP at 5 years. At 5 years 340 (65%) remained continuously on DAPLT and 187 (35%) on SAPLT. The comparison between these two groups regarding HENP and ST did not reveal significant differences.

Conclusions: In patients with distal LM bifurcation lesion undergoing PCI with DES, FKB group showed similar mid-term angiographic and one-year clinical outcomes as compared with those without FKB.
Germany) followed by bare-metal CoCr stent implantation (Prokinetic, Biotronik, Berlin, Germany) (PEB-CoCr-stent group) versus implantation of everolimus-eluting stent (Xience, Abbott Vascular, Redwood City, CA) (DES group) in the treatment of de novo stenosis in native coronary artery.

Methods: The study, randomized, single center, was planned to enroll 366 patients, 188 patients per arm, with stable angina, undergoing percutaneous coronary intervention of a de novo stenosis less than 15mm in length in a native coronary artery. Primary endpoint, in a non inferiority study design, was 9-month binary angiographic restenosis. Combined antilucapelet treatment was to be continued for 3 months in PEB-CoCr stent group and 12 months in DES group.

Results: The study was stopped after enrollment of 125 patients, 59 in the DEB group and 66 in the DES group, due to excess of Target Lesion Revascularization (TLR) in the PEB group (14% in the PEB vs 2% in DES; p=0.001). No significant differences in terms of clinical or angiographic characteristics were observed among the two study groups. No stent thrombosis occurred in both study groups.

Conclusion: In the treatment of de novo coronary stenosis, a strategy of predilatation with Elutax PEB prior to bare-metal CoCr stent implantation was significantly inferior to implantation of Xience stent in terms of 9-month target lesion revascularization.

P4767

Differential determinants of early stent thrombosis in drug-eluting and bare metal stents: ex vivo human autopsy study

M. Nakano1, F. Otuka1, S.K. Yazdani1, A.V. Finn2, R. Kuly3, E. Ladich1, F.D. Kolodev1, R. Virmani1. 1The international Registry of Pathology, CVPath, Gaithersburg, United States of America; 2Emary University School of Medicine, Atlanta, United States of America

Background: Early stent thrombosis (ST) in patients with acute coronary syndrome (ACS) remains an ongoing problem for both drug-eluting stents (DES) and bare metal stents (BMS) where potential mechanisms associated with stent placement relative to underlying lesion histo-morphology are not well addressed.

Methods and Results: Stented lesions (n=62) from 59 patients presenting with ACS and dying within 30 days were eligible for the histological assessment. Histologic cross-sections prepared at 3 mm intervals were evaluated for stent thrombosis, strut malapposition, and necrotic core prolapse in addition to other potential indicators of early ST such as the underlying plaque morphology and vessel/lesion area.

Early thrombosis was identified in 17 of 45 drug-eluting and 20 of 37 bare stents. There were no significant differences in the stented artery or relative location within the vessel with usage of DES versus BMS. In a “per section” analysis, 58 of 293 sections from DES showed evidence of luminal thrombosis compared with 62 of 287section from BMS. Stent malapposition was similarly seen for DES with or without early ST, respectively (29% vs 26%, p=0.60) while the incidence for BMS was significantly greater in those with early ST (37% vs 19%, p=0.004).

On the contrary, media disruption was more likely associated with thrombosis for DES (39% vs. 18%, p<0.002) while difference among BMS was of borderline significance (19% vs. 11%, p=0.08). Necrotic core prolapse was significantly higher for BMS exhibiting thrombosis (26% vs. 13%, p=0.018) while no significant difference was noted for DES (16% vs. 10%, p=0.25).

In morphological analysis, the percentage of struts with underlying medial disruption was noted for DES (16% vs. 10%, p=0.25). Strut malapposition was similarly seen for DES within the vessel with usage of DES versus bare BMS. In a “per section” analysis, there were no significant differences in the stented artery or relative location.

Conclusions: Autopsy data indicate divergent mechanisms of early ST between drug-eluting and bare metal stents: ex vivo human autopsy study.

P4771

Angiographic outcomes of everolimus-eluting stent as compared to sirolimus-eluting stent: a sub-study of the RESET trial

K. Kozuma1, N. Suzuki1, K. Tanabe2, S. Suwa3, M. Iwabuchi4, K. Igareshi5, Y. Morino5, K. Kimura2, K. Kadota2, T. Kimura2

on behalf of RESET study investigators. 1Tokyo University Hospital, Tokyo, Japan; 2Juntendo University, Japan; Shizuoka Hospital, Shizuoka, Japan; 3Kokura Memorial Hospital, Kitakyushu, Japan; 4Hokkaido Social Insurance Hospital, Sapporo, Japan; 5waste Medical University, School of Medicine, Kitakyushu, Japan; 6Tokohama City University Medical Center, Yokohama, Japan; 7Kurashiki Central Hospital, Kurashiki, Japan; 8Tokyo University Hospital, Kyoto, Japan

Objective: This study is aimed to clarify the difference in the angiographic findings of Everolimus-eluting stent (EES) as compared to the first generation Sirolimus-eluting stent (SES).

Methods: RESET is a prospective multicenter randomized open label trial comparing EES with SES in Japan. The trial was designed as “all-comers” trial. Out of 3197 patients of total cohort, 571 patients were enrolled in the angiographic sub-study. Angiograms were assessed qualitatively and quantitatively both at procedure and at 8-12month in the independent corelab.

Results: Baseline demographics were not different except for stent length, and follow-up results were not different between the 2 groups except for the late loss of proximal edge (table). Edge restenosis was mainly observed in EES group, whereas late thrombosis was dominant in SES group. Stent fracture was only observed in 1.2% of the SES cases (p=0.042), and peri-stent contrast staining (PSS) as a presentation of incomplete stent apposition during PCI was observed in 1.5% of EES cases and 3.6% of SES group (p=0.177).

Conclusions: Angiographic outcomes of EES and SES were similar. However, restenotic pattern and detrimental findings such as stent fracture and PSS were different between the 2 groups.

P4770

Thin-strut stent is favorable for severe calcified lesion needing rotational atherectomy in real world

Percutaneous Coronary Intervention


Background: Percutaneous coronary intervention (PCI) on severe calcified lesion is still challenging. There are a few studies about outcomes after PCI with drug-eluting stents (DES) on severe calcified lesion. The aim of this study is to clarify whether thin- or thick-strut stents are feasible thin- or thick-strut stents to calcified lesion after rotational atherectomy including hemodialysis patients and long lesion.

Methods: Sixty-six consecutive patients (115 stents) with DESs for severe calcified lesions which needed rotational atherectomy before stent implantation were enrolled. We divided them into the following two groups according to strut-thickness: thin-strut group (strut-thickness: ≤100μm) and thin-strut group (>100μm). Follow-up angiography was performed at 6 to 10 months after PCI. We compared late lumen loss by quantitative coronary angiography and target vessel revascularization (TVR) rate, in addition to incidence of hemodialysis, diabetes mellitus, hypertension and dyslipidemia, and stent size, length and number of stents, between the two groups.

Results: TVR rate was significantly lower in thin-strut group than in thick-strut group while there were no differences of the other parameters between two groups.

Conclusions: Thin strut DES has better clinical outcome than thick-strut DES for severe calcified lesion which needed rotational atherectomy.

P4772

Stent maximal expansion capacity with current DES: is platform a critical factor for left main stent selection?

N. Foin1, S. Sen2, C. Di Mario3, J. Davies2, 1Imperial College London, NHIL International Centre for Circulatory Health, London, United Kingdom; 2Royal Brompton and Harefield NHS Trust, London, United Kingdom

Coronary stents are usually manufactured in only 2 or 3 different “Workhorse”
Is there an advantage in using second vs. first generation drug eluting stents in acute coronary syndromes?

C. Machado1, L. Raposo2, S. Leal2, P. Gonçalves2, P. Gonçalves2, R. Mendes2, P. Macedo, H. Dore2, S. Leal2, P. Gonçalves2

1Hospital Divino Espírito Santo, Ponta Delgada, Portugal; 2Hospital de Santa Cruz, Lisbon, Portugal

Purpose: Registry series and RCTs show that DES have an overall better performance than BMS in patients treated in the clinical context of an acute coronary syndrome (ACS), both STEMI and NSTEMI/UA, mainly by reducing TLRE. Whether or not the use of 1st generation DES (DES1g) versus 2nd generation DES (DES2g) differs in this particular setting is largely unknown.

Methods and results: In a single center prospective registry, 3286 patients were submitted to PCI with at least 1 DES from January 2003 to December 2009. Of these, 1423 (43.6%) were treated in the setting of an ACS with either DES1g only (paclitaxel or sirolimus; n=923 [64.9%]) or DES2g only (n=500 [35.1%]). The primary outcome measure was the occurrence of death, myocardial infarction (MI) or target vessel failure (TVF), whichever came first: repeat revascularization of the index stented lesion (TLR) and the occurrence of definite stent thrombosis (according to the ARC definition) were assessed as secondary outcomes. At a median follow-up of 598 days (IQ range 453, 1206), the incidence of death was 8.8% (286), 220 pts (6.7%) had MI and TVF events occurred in 349 (10.7%). Disparity of follow-up duration was accounted for by considering only one year composite MACE (n=290; 8.9%). After adjusting for baseline characteristics (age, hypertension, diabetes, prior MI, and Synergy score), using a Cox proportional hazard model, we could not find a significant difference in the MACE rate between DES1g (8.9%) and DES2g (8.7%) patients (HR 1.1; 95% CI 0.82-1.56; p=0.46). Repeat target lesion revascularization was non-significantly inferior in DES2g (3.1% vs 3.3%; HR 0.98; 95% CI 0.63-1.57; p=0.85); in a per-patient analysis, at one year, ARC-definite stent thrombosis was documented in 1% of DES2g vs 2.8% of DES1g pts (corrected HR 0.37; 95% CI 0.14-0.97; p=0.0042), owing mostly to a higher difference in non-acute ST.

Conclusions: Our results suggest that in patients submitted to PCI with DES implantation in the setting of acute coronary syndromes, both 1st and 2nd generation devices seem to be similarly effective, despite a statistically higher incidence of ARC-definite stent thrombosis with 1st generation DES.

The anti-proliferative effect of atorvastatin is dependent on stent surface material

A. Strohbach1, B. Begunk2, H. Meyer Zu Schwabedissen3, S.A. Was3, M.C. Busch1, S.B. Felix1, R. Busch1,4, Ernst Moritz Arndt University of Greifswald, Department of Internal Medicine B, Greifswald, Germany; 3Ernst Moritz Arndt University of Greifswald, Institute of Pharmacology, Greifswald, Germany

Background: Percutaneous treatment (PCI) of distal left main bifurcation may involve stenting of the main branch including final kissing balloon of the side branch or single stenting of both branches. There is only limited data comparing single stenting including final kissing-dilatation versus T-stenting regarding the long term clinical follow-up.

Hypothesis: We tested the hypothesis that the lesions that were treated with the single stent have a lower target lesion revascularisation (TLR) 1 year after PCI than lesions treated with T-stenting.

Methods: We established a bifurcation registry of 394 consecutive patients undergoing percutaneous catheter intervention (PCI) for distal left main stenosis in our institution between January 2002 and december 2009. One stent approach was performed in 229 patients and T-stenting in 165 patients. The need for double stenting to achieve best angiographic result was 46%. Complete 1 year clinical follow-up of all patients is available for the analysis.

Results: Baseline clinical characteristics were well matched between 2 groups. Target lesion revascularisation (TLR) 1 year of EVG and SMC proliferation. At a concentration of 0.1 μM the proliferation of HCAEC remains unaffected whereas the proliferation of smooth muscle cells is significantly reduced. However, increasing Statin concentrations also affect endothelial cell proliferation. A similar effect on HCAEC was noted at concentrations above 1 μM. We suggest that the difference in response to Statins may be due to intrinsic differences in the endothelial cell and smooth muscle cell populations.

Conclusions: PCI of de-novo distal left main stenosis using simple approach (single stenting with final “kissing balloon”-dilatation) is associated with similar 1 year outcome as compared with T-stenting.
Drug eluting stents with microporous polymeric covering as a scaffold for acquisition of extremely thin neointimal lying without disturbing branching vascular flow

Y. Nakayama1, S. Nishii2, H. Ishibashi-Ueda1, 1National Cardiovascular Center Research Institute, Osaka, Japan; 2Sapporo Higashi Tokushuk Hospital, Sapporo, Japan

Objective: As new generation of drug eluting stents, we developed microporous polymeric-covered stents, whose design concept was utilization of covering for a scaffold for extremely thin neointimal lying. The effectiveness was demonstrated in this study for long-term animal experiments.

Methods and Results: Two types of covered stents based on different stent platforms of self-expandable stents (Luminexx from Bard Co.; 5 mm x 20 mm) and balloon-expandable stents (Momo from Japan Stent Technology Co.; 3 mm x 20 mm) were prepared in three steps, that is 1) dip-coating of polyurethane for covering, 2) laser-induced microporing, and 3) drug coating with argatroban. The stents had structural advantage with flat luminal surface impregnating strut completely into the cover film. The stents were placed at carotid or subclavian arteries of beagle dogs or rabbits. Even at 1 month of implantation (n=15), the covered stents could maintain the branching micro-vessel flow perfectly due to microporing of cover film. Argatroban had strong anti-thrombogenic and anti-inflammatory potentials.

Conclusion: Angiogram-loaded microporous covered stents developed here were effective for in short-term lying of extremely thin neointima with long-term highly reliability.

Comparison of 3-year clinical outcomes between classic crush and modified mini-crush technique in coronary bifurcation lesions

H.M. Yang, S.J. Tahk, S.Y. Choi, H.S. Lim, M.H. Yoon, B.J. Choi, G.W. Seo, J.W. Kim, G.S. Hwang, X. Jie. Ajou University Medical Center, Suwon, Korea, Republic of

Purpose: To compare long-term outcomes of modified mini-crush (modi-MC) technique with classic crush (Crush) technique for treating coronary bifurcation lesions. Modi-MC technique showed excellent procedural success immediately and good 9-months clinical outcomes. We compared 3-year clinical outcomes between 2 techniques.

Methods: From Jan 2000 to Nov 2009, we enrolled de novo bifurcation lesions treated with modi-MC (n=112 lesions in 111 patients) and crush technique (n=69 lesions in 67 patients). Primary end-point was major adverse cardiac events (MACE), composite of all-cause death, myocardial infarction (MI), target lesion revascularization (TLR) and stent thrombosis at 3 years.

Results: There were no significant differences in baseline characteristics. After 3 years, MACE was significantly lower in modi-MC group (25.4 vs 13.5%, p=0.046). The incidence of all-cause death was 7.5% vs. 2.7% (p=0.16), MI was 4.5% vs. 0.9% (p=0.15), TLR was 17.4% vs. 8.9% (p=0.09) and stent thrombosis was 3% vs. 1.8% (p=0.63) in Crush and modi-MC group, respectively. However, MACE of left main (LM) lesion was significantly higher than non-LM bifurcation (35.7% vs. 12.9%, p=0.001) in entire cohort. Cox regression analysis showed LM location(p=0.002, odds ratio[OR] 3.031, 95% confidence interval[Ci] 1.526-6.021), and crush technique (p=0.044, OR 2.035, 95% Ci:1.018-4.069) were independent predictors for MACE.

Conclusions: Modified mini-crush technique was more favorable 3-year clinical outcomes comparing with classic crush technique. However, both classic crush and modified mini-crush techniques are cautiously applied in LM bifurcation lesion.

Assessment of an asymmetrical coating stent with sirolimus released from abluminal matrix in porcine model

L. Shen1, Y. Wu1, F. Zhang1, A. Sun1, J. Gao1, W. Zhong2, J. Ge1, 1Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital-Fudan University, Shanghai, China, People’s Republic of; 2Shanghai Center for Biomedical Engineering, shanghai, China, People’s Republic of

Purpose: Delayed endothelialization contributes to stent thrombosis (ST) of current drug-eluting stents (DES). Asymmetrical coating technique is considered to perform antiproliferative effect as well as enhance surface endothelialization. We developed an asymmetrical coating stent with sirolimus released from abluminal matrix and assessed its efficacy in a porcine model.

Methods: Layer-by-layer self assembled chitosan/heparin (CH LBL) was ever proved to promote re-endothelialization. A novel stent system, CH/LBL coated luminally and sirolimus released abluminally(CH-LBL-SES), was fabricated. Bare metal stents (BMS), traditionally circumferential sirolimus-eluting stents(SES), and CH-LBL-SES were implanted into porcine coronary arteries. At 7, 14 and 28 days follow-up, angiography, intravascular ultrasound (IVUS), vasmotor function analysis, scanning-electron microscopy (SEM) and histopathology were performed. The study protocol followed the “Principles of laboratory animal care” (NIH Publication no. 85-23 revised 1985) and was approved by the Animal Care and Use Committee of Zhongshan Hospital Fudan University.

Results: 28 days after implantation, the diameter stenosis of CH/LBL-SES by quantitative coronary angiography was 18.76±2.48%, the area stenosis by histomorphometry was 24.17±2.94%, which were comparable to that of SES and superior to BMS. At 14 days, re-endothelialization of CH/LBL-SES almost completed while only around 50% of surface of SES was covered by endothelium. During 28 days follow-up, although CH/LBL-SES suffered a greater vascularization than BMS, it behaved better than SES. No sign of stent malposition was detected in all three groups by IVUS. Remodeling index was within the normal range. No acute or subacute thrombotic events occurred.

Conclusions: With pro-healing CH LBL membrane luminally coated on stent struts and sirolimus released from abluminal matrix, the asymmetrical designed CH/LBL-SES reduced in-stent stenosis as effectively as traditionally coated SES during 28 days follow-up. Comparing with circumferential coating of SES, the asymmetrical coating significantly promoted rapid re-endothelialization in the early stage of follow-up. No sign of LSM or paradoxical remodeling was detected by IVUS at the end of observation. No acute or subacute thrombotic events occurred. This finding highlighted asymmetrical designed DES may be a promising stent platform superior to traditionally DES.
Percutaneous coronary intervention outcomes 837

PERCUTANEOUS CORONARY INTERVENTION OUTCOMES

P4780 The impact of circadian variations on long-term clinical outcomes in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

J.B. Choi, K.S. Cha, M.J. Park, E.Y. Yun, H.W. Lee, J.H. Oh, J.H. Choi, H.G. Lee, T.J. Hong, S.G. An on behalf of the Korea Acute Myocardial Infarction Registry. Pusan National University Hospital, Busan, Korea, Republic of

Purpose: The circadian rhythm influences a number of cardiovascular physiological processes including the incidence of acute myocardial infarction. A circadian variation in infarct size has recently been shown in rodents, but there is no clinical evidence of its influence on long-term outcomes. The aim of this study was to investigate whether circadian rhythm could cause differences in long-term clinical outcomes in patients with STEMI.

Methods: A total of 3,581 STEMI patients with less than 12 hours of symptom onset were obtained from the Korea Acute Myocardial Infarction Registry and divided into 4 time groups based on time of symptom onset (period I: 00:00-05:59, period II: 06:00-11:59, period III: 12:00-17:59, and period IV: 18:00-23:59). The primary outcome was the composite of major adverse clinical events (MACE), defined as death, non-fatal myocardial infarction, and revascularization, at one-year follow-up.

Results: There was no difference between groups regarding baseline patient characteristics, angiographic findings, and procedural results. There was significant difference between groups regarding symptom-to-door time and door-to-balloon time with highest levels in patients with symptom onset of period I (251.7±182.1 min, p<0.001; 107.4±62.6 min, p=0.001, respectively). However, there was no significant difference between groups regarding maximum CK-MB and left ventricular ejection fraction. Total death and MACE were not different between groups during hospitalization (period I: 4.9%, period II: 5.1%, period III: 3.7%, period IV: 5.1%, p=0.410; period I: 5.9%, period II: 5.4%, period III: 4.4%, period IV: 5.2%, p=0.562, respectively) and at one-year (period I: 8.0%, period II: 8.6%, period III: 5.8%, period IV: 7.7%, p=0.103; period I: 14.6%, period II: 12.0%, period III: 12.0%, period IV: 7.7%, p=0.321, respectively).

Conclusions: This study showed that a circadian difference in symptom onset of STEMI did not influence in-hospital and long-term clinical outcomes. More data are needed to clarify the role of circadian variations on the long-term outcomes in patients with STEMI.

P4781 Impact of microalbuminuria on clinical cardiovascular outcomes in patients with mild renal dysfunction who underwent elective PCI

A. Kunimura1, T. Uetani1, K. Kitagawa1, Y. Shimbo1, H. Ando1, K. Harada1, T. Yoshida1, T. Matsubara1, T. Amano1, T. Murohara1
1Chubu Rosai Hospital, Nagoya, Japan; 2Aichi Gakuen University, School of Medicine, Nagoya, Japan; 3Aichi Medical University, Department of Cardiology, Nagoya, Japan

Background: Microalbuminuria (MIA) is considered an independent predictor of cardiovascular event. However, the impact of MIA on clinical cardiovascular outcomes in patients with mild renal dysfunction is unclear. The aim of this study was to investigate the association between elevated urinary albumin excretion rate and clinical cardiovascular outcomes in patients with mild renal dysfunction who underwent elective PCI.

Methods: In this study, 120 consecutive patients with early stage CKD (estimated GFR 60–90 ml/min/1.73 m²) who underwent elective PCI between November 2008 and April 2009 were enrolled. Urinary albumin to creatinin ratio (ACR; mg/gCr) was measured and population was divided into patients with MIA (ACR ≥30 mg/gCr, 39 patients) and those without MIA (ACR <30 mg/gCr, 81 patients). The endpoint of this study was defined as the composite of death, myocardial infarction (MI) and any revascularization.

Results: During the median follow-up of 1048 days, 45 total events occurred. Event-free survival was significantly higher in patients without MIA as compared to patients with MIA (74.1% vs 51.3%, p=0.012, log-rank test, Figure). There was no significant difference in the incidences of death or MI, target lesion revascularization between two groups. The incidence of revascularizations for new lesions was significantly higher in patients with MIA than those without MIA (13.6% vs 38.5%, p=0.019). Independent predictor of cardiac events identified by Cox proportional hazard model was MIA (hazard ratio 2.54; 95% CI: 1.20–5.35; p=0.014) after adjusted for age, gender, and conventional risk factors.

Conclusions: The elevated urinary albumin excretion rate is an independent predictor of adverse cardiovascular outcomes in patients with mild renal dysfunction who underwent coronary intervention.

P4782 High preprocedural total adiponectin levels are associated with poor long-term cardiovascular outcome after percutaneous coronary intervention

N. Krogbemabu1, D.C. Delhaye1, S.A. Sudre1, L.G. Lemestle1, M.T. Modine1, M.M. Mahmoud2, S.B. Steals1, L.G. Luc1, B.C. Bauters1, L.J.M. Lablanche1, J. B. Choi, K. S. Cha, J. H. Oh, J. H. Choi, H. G. Lee, T. J. Hong, S. G. An on behalf of the Korea Acute Myocardial Infarction Registry. Pusan National University Hospital, Busan, Korea, Republic of

Purpose: Adiponectin is considered to possess antiatherogenic and cardioprotective properties. In patients undergoing percutaneous coronary intervention (PCI), the prognostic value of preprocedural total adiponectin is unknown. The present study was designed to address this issue.

Methods: From March 2006 to September 2007, pre-procedural total adiponectin levels were measured in 477 consecutive patients who underwent PCI with a median follow-up of 3.7 years. Patients presenting with acute STElevation myocardial infarction (STEMI) were excluded. The primary endpoint was the composite of death, non-fatal MI or stroke. Target lesion revascularization (TLR) was also examined.

Results: Median adiponectin level was 17.4 µg/ml (25–75th percentile: 13.2–21.9 µg/ml). The primary endpoint occurred in 76 patients (15.9%). TLR was undertaken in 25 patients (5.2%). Female gender, high HDL cholesterol and BMI lower tertile levels and lack of pre-treatment with beta-blockers were independently associated with high adiponectin level. In univariate analysis, adiponectin had a significant positive relationship (p=0.002) with the primary endpoint. In multivariate analysis, diabetes mellitus, lower creatinine clearance, high CRP and high adiponectin levels (hazard ratio=1.05 [95% CI: 1.01–1.09; p=0.006]) were associated with the primary endpoint. When patients were divided into tertiles according to adiponectin levels, patients in the upper tertile (>20.2 µg/ml) had twice more risk of death, MI or stroke as compared to patients in the lowest tertile (<15.1 µg/ml) (Figure). No association was found between adiponectin levels and TLR (p=0.64).

Conclusions: In contrast to studies in the general population, high pre-procedural total adiponectin levels may be associated with increased risk of mortality, MI or stroke in patients undergoing PCI.

P4783 Prognostic significance of body mass index for in-hospital and long-term mortality in patients undergoing primary percutaneous coronary intervention

C.Y. Kanaan, V. Oduncu, A. Kalayci, A. Güler, S.M. Aung, R. Zehir, A. Elkilics, C. Gecmen, A. Kilicgedik, C. Kirma, Kartal Kasımpaşa Heart Education and Research Hospital, Department of Cardiology, Istanbul, Turkey

Purpose: Prognostic significance of body mass index for in-hospital and long-term mortality in overweight and obesity population with ST elevation myocardial infarction (STEMI) is well-defined. However, cause of this relation has not yet well understood. Method: 2007 patients in 36 months period admitted to our hospital emergency service within first 12 hours of chest pain and underwent primary percutaneous coronary intervention (p-PCI) were our study population. Patients were divided in four groups according to body mass index: <18.5 (n=182), 18.5 – 24.9 (n=732), 25 – 29.9 (n=768), >30 (n=325).

Results: Advanced age, anemia, renal functional impairment and nonspecific inflammation (baseline C-reactive protein) were more common in overweight group. Final TIMI 3 flow was lowest in overweight group and highest in over (82.9% vs 89.5%, vs 89.5%, vs 90.5%, p=0.038, respectively). In-hospital mortality was lowest in obese group (6.0% vs 5.3% vs 3.1% vs 2.5%, p=0.034, respectively) and one-year mortality was highest in overweight group (13.5% vs 9.5% vs 6.7% vs 7.8%, p<0.001, respectively). After adjusting for potential confounding variables by Cox proportional hazard model, BMI was not an independent predictor for one-year mortality (Hazard ratio 0.98, 95% confidence interval 0.92 – 1.06, p=0.76).

Conclusion: While overweight is associated with in-hospital and one year mortality in STEMI patients undergone p-PCI, body mass index is not a independent predictor for in-hospital and 1-year mortality. This can be explained by multiple comorbidities in overweight group and younger age, more aggressive treatment in overweight group.
Comparison on 1-Year MACE of everolimus-eluting stent Xience vs sirolimus-eluting stent cypher in diabetic patients

F. Listro, I. Porto, S. Gotti, P. Angioli, K. Ducu, R. Brandini, G. Falsini, L. Bolognesi. San Donato Hospital, Department of Cardiology, Arezzo, Italy

Background: To expand the paucity of data on the efficacy of sirolimus-eluting stents (Cypher, Cordis, Bridgewater, NJ) vs everolimus-eluting stent (Xience, Abbott Vascular, Redwood City, CA) in diabetic patients.

Methods: Due to Tuscany Region Medical Authority, Cypher stent was no more available after December 2008 and replaced by Xience stent. We collected the data of all consecutive type 2 diabetic patients presenting with de novo or in-stent restenosis lesions in native coronary arteries treated in our institution from January 2003 to November 2008 (Cypher period) and from December 2008 to May 2010 (Xience period). The primary end point was the 1-year composite of major adverse cardiac events (MACE), including cardiac death, myocardial infarction (MI), and clinically driven target vessel revascularization (TLR).

Results: During the study periods, 440 lesions in 256 patients were treated with Cypher stent and 420 lesions in 212 patients with Xience stent (p=0.2). There were no significant differences among the two study groups except for previous myocardial surgical revascularization (8.6% in Cypher group vs 4% in Xience group, p=0.03) and stent length (22.4±8.7 mm vs 30±8.7 mm respectively, p=0.004). MACE-free survival was 89% in the Cypher group and 88% in the Xience group (p=0.7). Cardiac death occurred in 3 (1.2%) Cypher vs 4 (1.9%) Xience patients (p=0.7). MI in 4 (1.9%) vs 4 (1.9%) respectively, TLR in 37 (4%) Cypher vs 25 (4.2%) Xience lesions (p=0.2). Stent Thrombosis (ST) confirmed by angiography occurred in 2 (0.8%) Cypher vs 1 (0.5%) Xience patients (p=0.7).

Conclusions: The present study suggests that in diabetic patients, the Cypher stent is associated with a similar 1-year MACE rate when compared with Xience stent. Longer follow-up will evaluate the impact of the two stent in the occurrence of TLR.

Effects of EPC capture stent and CD34+ mobilization in acute myocardial infarction

P. Scacciatella1, M. D’Amico1, M. Pennone1, F. Conrotto1, T. Usmani1, E. Meliga2, I. Meyert1, E. Pelloni1, G. Amato1, S. Marra1. 1University of Turin, San Giovanni Battista “Molinette” Hospital, Department of Transplantation Therapy and Oncology, Department of Cardiology, Turin, Italy; 2Mazzoni Hospital, Department of Cardiology, Turin, Italy

Background: Percutaneous revascularization is the gold standard for the treatment of acute myocardial infarction (AMI), with the main limitation of in-stent restenosis for BMS and late stent thrombosis (ST) for both BMS and DES. Endothelial progenitor cells (EPC) CD34+ capture stents, promoting vascular healing, may be advantageous in preventing ST. The role of EPC on restenosis and atheromasic disease progression is unclear. The aim of the study is to evaluate the outcomes of AMI patients treated with EPC CD34+ capture stent and describe the mobilization kinetics of CD34+ and their clinical correlation.

Methods: 50 AMI patients underwent primary PCI with EPC CD34+ capture stent. Serial assays of CD34+ were performed by flow-cytometric analysis. Primary outcome was occurrence of death, myocardial infarction (MI), target vessel revascularization (TVR), target lesion revascularization (TLR), stent thrombosis, and major adverse cardiac events (MACE).

Results: Procedural success rate was 100%. At six months follow-up cardiac death, MI, TVR and TLR occurred respectively in 2%, 4%, 10% and 12% of patients. No case of ST was observed. The MACE-free survival was 82%. The mean peak value of plasmatic CD34+ was 4.69±3.76 cells/ml. A positive correlation was found between CD34+ concentration, age and infarct area. No correlation was detected between CD34+ concentration and occurrence of TVR, TLR and MACE.

Conclusions: EPC capture stent implantation seems to be safe and effective in the clinical setting of AMI, representing a possible alternative to BMS and DES. CD34+ cells plasmatic concentration seems not to correlate to coronary restenosis and atheromasic disease progression.

Development in the last ten years - LHC and PCI

B. Levenson1, A. Albrecht1, S. Goehring1, W. Haerer2, N. Reifart1, G. Ringwald1, B. Tröger1 on behalf of QuIK Steering Committee. 1Kardiolische Gemeinschaftspraxis & Herzkatheterlabor am St. Gertraudenkrankenhaus, Berlin, Germany; 2Health Care Consulting, Berlin, Germany

Background: In 1996 German Cardiologists in Private Practice started to collect all their diagnostic procedures (LHC) and interventions (PCI) in a quality assurance registry. With only eight cath-labs in 1996 participants in the registry increased to 127 in 2010. We report changes since the beginning and compare the results of 2010 to the ones of the year 2000.

Methods: A quality based dataset is defined to enable a computer supported data collection. After each annual quarter a single center statistic and a benchmark comparison is reflected to the cath-labs. The registry allows conclusions about invasive cardiac care in Germany.

Results: The table shows the important values of the two compared years.

LHC and PCI in 2000 and in 2010

<table>
<thead>
<tr>
<th>Year</th>
<th>LHC (n)</th>
<th>PCI (n)</th>
<th>LHC (age, mean)</th>
<th>PCI (age, mean)</th>
<th>LHC (male sex)</th>
<th>PCI (male sex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>52,003</td>
<td>30,086</td>
<td>66.0</td>
<td>66.0</td>
<td>65.3</td>
<td>65.3</td>
</tr>
<tr>
<td>2010</td>
<td>75,630</td>
<td>50,086</td>
<td>66.9</td>
<td>66.9</td>
<td>69.1</td>
<td>69.1</td>
</tr>
</tbody>
</table>

Conclusions: More patients were diagnosed and treated in 2010, who were older and in worse condition (ACS). The PCI rate has increased and most of the procedures are performed ad hoc, there has been a trend in decision making from heart surgery to PCI.

Multivessel versus culprit lesion percutaneous coronary intervention in ST-elevation myocardial infarction: is more worse?

D. Radovanic1, B. Nallamothu2, O. Bertel3, F. Eiber4, G. Pedrazzini5, S. Windecker6, R. Jeger7, P. Erne8 on behalf of AMIS Plus Investigators. 1AMIS Plus Data Center, Institute of Social and Preventive Medicine, University of Zurich, Zurich, Switzerland; 2University of Michigan, Division of Cardiology, Michigan, United States of America; 3Klinikum der Universität München, Klinikum der Universität München, Berlin, Germany; 4Aegean Hospita, Kardiothorakaler, Hospita, Rege, 2011. Baseline characteristics of these groups were assessed using Student t-tests and chi-squared tests while multivariable logistic regression models were used to evaluate differences in in-hospital outcomes.

Results: From 11,099 STEMI patients who presented during this study period, we identified 4559 patients (41%) with multivessel disease (including 5.6% with main stem) who underwent PCI. Among these, 3541 patients (78%) were treated with culprit lesion PCI only who were enrolled in the national AMIS Plus registry of Switzerland from 2005 to 2011. Baseline characteristics of these groups were assessed using Student t-tests and chi-squared tests while multivariable logistic regression models were used to evaluate differences in in-hospital outcomes.

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Introduction: Existing data on the benefits of multivessel versus culprit lesion PCI during acute ST-segment elevation myocardial infarction (STEMI) is conflicting.

Methods: We compared outcomes between STEMI patients with multivessel disease treated with multivessel PCI versus those treated with culprit lesion only PCI who were enrolled in the national AMIS Plus registry of Switzerland from 2005 to 2011. Baseline characteristics of these groups were assessed using Student t-tests and chi-squared tests while multivariable logistic regression models were used to evaluate differences in in-hospital outcomes.

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Conclusion: More patients were diagnosed and treated in 2010, who were older and in worse condition (ACS). The PCI rate has increased and most of the procedures are performed ad hoc, there has been a trend in decision making from heart surgery to PCI.
Impact of successful thrombus retrieval during primary percutaneous coronary intervention with thrombus aspiration on the infarct size and microvascular obstruction: a magnetic resonance imaging study


Background: Thromboaspiration (TA) during primary percutaneous intervention (PPCI) is effective in opening the infarct-related artery in patients with ST-segment elevation myocardial infarction (STEMI), leading to better reperfusion and improved outcome. However, the effect of positive macroscopic efficiency of TA remains unknown. We aimed to evaluate the impact of positive thrombus retrieval during PPCI with manual TA on infarct size (IS) and microvascular obstrucion (MVO) as assessed by contrast-enhanced magnetic resonance imaging (CE-MRI) in a subset of patients with STEMI.

Methods: Inclusion criteria were patients aged <75 years, with first STEMI referred for PPCI within 12 hours of onset of symptoms, infarct-related artery ≥2.5 mm in diameter, thrombus score ≥3 and no prior history of coronary disease. All patients underwent TA before stenting and were categorized according to positive or negative TA. Clinical and procedural characteristics of the study population and CE-MRI was performed at 5 days and 6-months to evaluate MVO and IS.

Results: 88 patients were enrolled, mean age 55±10 years; 43.1% in the positive TA group. Main results are presented in the table. Clinical and procedural characteristics of the study population were recorded and CE-MRI was performed at days 5 and 6-months to evaluate MVO and IS.

<table>
<thead>
<tr>
<th></th>
<th>Negative TA (n=50)</th>
<th>Positive TA (n=38)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVO (%)</td>
<td>7.6±5.1</td>
<td>3.8±3.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Infarct size at 5 days (%)</td>
<td>28.2±20.8</td>
<td>14.9±8.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Final infarct size at 6 months (%)</td>
<td>22.3±19.3</td>
<td>12.0±8.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Conclusion: Positive thrombus retrieval during primary PPCI with manual TA in STEMI reduces MVO and IS at 5 days and 6 months and represents a powerful predictor of final infarct size.

MVO, microvascular obstruction. 

Intra-procedural stent thrombosis: a new risk factor for adverse percutaneous coronary intervention for acute coronary syndrome

S.J. Breret1, A.J. Kirtane2, M.B. Montez smooth1, E. Cristea1, K. Xu1, R. Mehran3, G.W. Stone4 on behalf of ACUITY and HORIZONS AMI.

1Cardiovascular Research Foundation, New York, United States of America; 2Columbia University Medical Center, New York, United States of America; 3Mount Sinai Medical Center, New York, United States of America

Background: Stent thrombosis (ST) is a rare complication of percutaneous coronary intervention (PCI). It is more common in the setting of acute coronary syndromes (ACS). It is not known whether intra-procedural ST (IPST) carries the same prognosis as post-procedural ST.

Objective: To examine the incidence, correlates and consequences of IPST.

Methods: We combined two large ACS studies – ACUITY and HORIZONS AMI. The angiograms were independently reviewed frame-by-frame for the occurrence of IPST. Patients with and without IPST were compared with respect to clinical and angiographic characteristics, and adjudicated events at 30 days and 1 year.

Results: Among 6,591 patients, there were 47 cases of IPST (49 lesions, 0.7%). There were no important differences in baseline characteristics between the two groups. Patients with IPST had significantly more often bifurcation lesions treated, PB-PES (0.53 vs. 0.51%, p=0.15) were inserted and control patients at 30 days (12.9% vs. 14.5%, p<0.0001) and 1 year (12.9% vs. 3.1%, p<0.0001) at a rate of 12.9% vs. 1.6% (p<0.0001). Table, ST occurred significantly more often among IPST patients at 30 days (17.4% vs. 8.1%, p=0.0001). The hazard ratio for IPST denotes intraprocedural stent thrombosis; MI, myocardial infarction; TVR, target vessel revascularization.

Incidence of MACE at 1 year

Table: IPST (N-47) No IPST (N=6544) HR p

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>MI or TVR</th>
<th>Definite/Probable ST</th>
<th>Death, MI or TVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>12.9%</td>
<td>3.1%</td>
<td>4.67 [2.07,10.52]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death or MI</td>
<td>30.1%</td>
<td>9.9%</td>
<td>3.79 [2.36,6.44]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Definite/Probable ST</td>
<td>19.9%</td>
<td>2.7%</td>
<td>9.19 [4.70,17.98]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death, MI or TVR</td>
<td>41.1%</td>
<td>14.5%</td>
<td>3.92 [2.56,6.19]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions: IPST is a rare complication of PCI in ACS, correlated with procedural factors. It is associated with an increased incidence of ST particularly in first 30 days and is an independent predictor of cardiac death at 1 year. IPST should be defined as a distinct category of ST.

Real-world use of the second-generation cobalt-chromium sirolimus-eluting stent: 12-month results from the prospective multicentre FOCUS registry

F. Zhang, J. Ge, J. Qian, L. Ge, J. Zhou on behalf of FOCUS registry investigators. Zhongshan hospital, Fudan university, Shanghai, China, People’s Republic of China.

Background: The second-generation Firebird-2 cobalt-chromium alloy sirolimus-eluting stent (CoCr-SES) has been widely used in the world. The FOCUS registry is a prospective, international, and web-based program designed to collect clinical outcome data from real-world patients receiving the CoCr-SES.

Methods: From March 2009 through February 2010, a total of 5,084 patients from 83 clinical centers in 3 Asian countries eligible to receive a Firebird-2 CoCr-SES were enrolled in the FOCUS registry. Baseline characteristics and procedure patterns were collected and clinical follow-up is available for 1 year. The primary endpoint was the major adverse cardiac events (MACE, defined as the composite of cardiac death, non-fatal myocardial infarction [MI], and target vessel revasculurization [TVR]) rate related to the CoCr-SES at 12-month follow-up.

Results: One year data were available for 5,013 (98.6%) of the 5,084 patients enrolled. The primary endpoint, MACE at 12 month follow-up, occurred in 174 (3.47%) of 5,013 patients, consisting of 43 (0.86%) cardiac death, 132 (2.63%) MI, and 46 (0.92%) TVR. According to the Academic Research Consortium definition, definite and probable stent thrombosis (ST) occurred in 528 (26.01%) of these patients, including 19 cases of early ST and 7 late ST. The 12-month MACE rates were 3.73% and 2.60% for extended- and standard-use patients, respectively (p = 0.006).

Conclusions: The second-generation CoCr-SES was associated with low rates of 12-month MACE and ST in a broad spectrum of patients, thereby confirming the clinical safety and efficacy of this stent in a real-world setting. (FOCUS Registry: NCT00868829)

Polymer-Free Sirolimus - versus Polymer-Based Paclitaxel-eluting stents. An individual patient data analysis of randomized trials

S. Cassese1, S. Desch2, T. Tada1, R.A. Byrne1, L. King1, J. Mehilli1, A. Schomig1, H. Thiele1, A. Kastrati1,2

1German Heart Center, Clinic for Heart and Circulaotory Diseases, Munich, Germany; 2University of Leipzig, Heart Center, Department of Internal Medicine and Cardiology, Leipzig, Germany

Aims: The efficacy of polymer-free sirolimus-eluting stents (PF-SES) and polymer-based paclitaxel-eluting stents (PF-PES) was recently debated, mainly in high-risk subsets. We investigate outcomes of PF-SES versus PB-PES with an individual patient data analysis of randomized trials.

Methods: Patient data of the randomised Clinical Sterting and Angiographic Restenosis - Test Evaluation Between 2 Drug-Eluting Stents (ISAR-TEST) and LIPSIA Yukon trials were pooled. Primary endpoint was in-stent late lumen loss (LLL) at 6-month angiography. Secondary endpoints were death or myocardial infarction (MI), cardiac death or MI, target lesion revascularization (TLR) and MI. Interaction of treatment effect with subgroups (gender, age, insulin/insulin treated diabetes, stable/unstable presentation and small/large vessels) was addressed.

Results: A total of 686 patients (PF-SES, n= 345 versus PB-PES, n= 341; diabetes 55.9% versus 51.0%, p= 0.19) and 751 lesions (PF-SES, n= 383 versus PB-PES, n= 368; B2/C-type 62.1% versus 67.1%, p= 0.15) were included. Control angiography (606 lesions) showed comparable in-stent LLL for PF-SES versus PB-PES (0.53±0.59 mm versus 0.46±0.57 mm, p= 0.15). Clinical follow-up (median 30.4 months) confirmed no significant differences between PF-SES versus PB-PES regarding death or MI (12.4% versus 12.6%, Relative Risk [RR] 95% Confidence intervals 0.79 [0.49-0.8] vs. 0.71, p= 0.049; cardiac death or MI (10.7% versus 9.0%, RR= 1.17 [0.72-1.89] vs. 0.95, p= 0.50), TLR (13.6% versus 13.7%, RR= 0.98 [0.65-1.47] vs. 0.93, p= 0.79) and MI (5.7% versus 3.2%, RR= 1.79 [0.85-3.76] vs. p= 0.12), without treatment-effect modification among subgroups.

Conclusions: Polymer-free SES is comparable to polymer-based PES with respect to angiographic and clinical efficacy. No difference exists among gender, age, clinical presentation, insulin/insulin treated diabetes and vessel diameter subgroups.
Lack of gender difference and improved in-hospital mortality rates in patients with cardiogenic shock following primary percutaneous coronary intervention: a UK tertiary cardiac centre registry study

V. Kuradian, M. Vreasurey, A. Zaman. Newcastle University.

Institute of Cellular Medicine, Newcastle upon Tyne, United Kingdom

Background: Despite substantial recent improvement in mortality from cardiovascular disease, due primarily to success of primary and secondary prevention strategies, it remains the leading cause of death in the developed world. Among those patients hospitalized with acute myocardial infarction (AMI), cardiogenic shock (CS) is the foremost cause of death complicating up to 10% of admissions. Introduction of early revascularisation strategies and mechanical ventricular support have been short-term mortality due to CS fall from 70-80% in the 1970s to around 50-60% in the 1990s. Previous studies suggest that women experience more CS than men (11.6% vs. 8.3%) in the setting of ST elevation MI. Whether primary percutaneous coronary intervention (PCI) for AMI has resulted in further reduction in in-hospital mortality and whether there are gender differences in outcomes due to CS is not known.

Aims: The aim of this study is to determine the rate of in-hospital mortality following primary PCI in the setting of CS and examine the gender differences in the incidence of CS and the rate of in-hospital mortality.

Methods: Data were collected prospectively among all patients presenting with AMI to a large UK tertiary cardiac centre and undergoing PCI during April 2009 and October 2011.

Results: In total 2866 patients (male: 2023 [70.6%] vs. female: 843 [29.4%]) underwent PCI. In total, 141/2866 (4.9%) had percutaneous coronary procedures (balloon angioplasty only or stenting) in the setting of cardiogenic shock. There were 81/2023 (4%) male patients and 60/843 (7.1%) female patients with CS undergoing PCI. There were no significant differences in the baseline characteristics between male and female patients except female patients were older than men (male: mean age 64.1 years vs. female: 69.9 years, p=0.004). The overall unadjusted in-hospital mortality rate was 35.4% with no difference in the genders (male: 35.8% vs. female: 35%, p=0.730).

Conclusion: The present analysis demonstrates that in the PCI era, there is reduction in the incidence of cardiogenic shock with reduced unadjusted in-hospital mortality rates following primary PCI. The unadjusted in-hospital mortality rates did not differ between the genders despite the fact that there were more women that had presented with cardiogenic shock.

In hospital clinical outcome of patients with definite stent thrombosis

M. Almalla, J. Schroeder, N. Marx, R. Hoffmann. University Hospital Aachen. RWTH, Internal Medicine I, Cardiology, Pulmonology & Vascular Medicine, Aachen, Germany

Background: The outcome of patients with angiographically proven stent thrombosis is only insufficiently known. We sought to evaluate presentation and outcome of patients with angiographically proven stent thrombosis.

Methods: 76 consecutive patients (mean age 69±15 years; 58 male) with 81 angiographically proven stent thrombosis between 2003 and 2010 were included in the analysis. The time interval between initial stent implantation, rate of dual antiplatelet therapy and clinical indication for repeat intervention were evaluated.

Results: 16 patients (21%) had early ST, 6 patients (8%) had late ST and 16 patients (21%) had very late ST. 59 patients (78%) were on dual antiplatelet therapy be available upon presentation. Target lesion revascularization (TLR) was performed in 81 patients (100%). There was no scaffold thrombosis. Clinical outcome after stent thrombosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>13 (17%)</td>
</tr>
<tr>
<td>ST-elevation myocardial infarction</td>
<td>60 (79%)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>20 (26%)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>28 (35%)</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>81 (100%)</td>
</tr>
<tr>
<td>Recurrence stent thrombosis</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>

Conclusion: Stent thrombosis is associated with a detrimental acute prognosis with severe systolic left ventricular dysfunction (EF <30%), cardiogenic shock and discontinuation of clopidogrel being predictors of death. Recurrent stent thrombosis is not infrequent.

Twelve-month safety and performance results of the paclitaxel-eluting bioabsorbable magnesium scaffold in the prospective, multicenter first-in-man trial - BIOFLOWE

M. Haude1, R. Erbe2, S. Verheyen3, R. Waksman4, H. Degen5, D. Boese6, P. Vermeersch6, P. Erne7, J. Koenen6 on behalf of BIOFLOWE-I Investigators. 1Städtische Klinik-Neuss, Lukaskrankenhaus GmbH, Neuss, Germany; 2West German Heart Center, Essen, Germany; 3ZNA Middelheim, Antwerpen, Belgium; 4Washington Hospital Center/Medstar Research Institute, Washington, United States of America; 5Luzerner Kantonzspital, Luzern, Switzerland; 6Catharina Hospital, Department of Cardiology, Eindhoven, Netherlands

Purpose: Absorbable metal scaffolds (AMS) are developed to overcome limitations of current permanent bare or drug-eluting coronary stents like stent thrombosis despite prolonged dual antiplatelet therapy (DAPT), caged vessel segment not allowing vasoconstriction and remodelling or chronic vessel wall inflammation. Magnesium is an essential element of the human body, thus Magnesium is considered as a potential alloy for absorption. To overcome the limitations associated with the first generation of a bare AMS a Drug (Paclitaxel) Eluting Absorbable Magnesium Scaffold was developed (DREAMS).

Methods: Between July and December 2010, 46 subjects were enrolled in the first-in-man BIOFLOWE-I study, and assigned to two different cohorts with different follow-up schedules. Clinical follow-up for both cohorts is scheduled at 1, 6, 12, 24 and 36 months, angiographic follow-up for cohort 1 at 6 months and for cohort 2 at 12 months. Angiographic assessment is performed by an independent core laboratory. The primary endpoint is Target Lesion Failure (TLF), defined as the composite of cardiac death, target vessel myocardial infarction and clinically driven target vessel reperfusion for cohort 1 and at 12 months for cohort 2.

Results: Of the 46 subjects 34 were male and 12 were female subjects with a mean age of 65.3±9.7 years ranging from 42 to 80 years. Hyperlipidaemia (89%), hypertension (87%) and history of myocardial infarction (33%) were the major medical risk factors. Type A (25.5%), Type B1 (6.2%) and Type B2 (8.6%) lesions were treated with a 3.25±0.16 mm (4.9%) or a 3.5±0.16 mm (51.1%) DREAMS. The target lesion failure rate at 12-month is 7.0% with no cardiac death, one peri-procedural target vessel non-occlusive myocardial infarction and two clinically driven target lesion revascularisations (TLR). There was no scaffold thrombosis. The angiographic results of 33 patients consenting for the 12-month follow-up will be available upon presentation.

Conclusion: DREAMS showed an excellent safety profile and a low TLF rate up to one year follow-up.

Cost-effectiveness of drug-coated balloon angioplasty and drug-eluting stent implantation for treatment of coronary in-stent restenosis

M. Dorekamp1, A. Leber2, G. Sehns3, L. Boldt4, M. Roser4, F. Kleber5, W. Haverkamp5, K. Bonaventura6, 1Charite - Campus Virchow-Klinikum, Department of Cardiology, Berlin, Germany; 2Municipal Hospital Munich-Lichtenhausen, Heart Center, Department of Cardiology, Munich, Germany; 3Universitatsmedizin Goettingen, Heart Center, Cardiology, Goettingen, Germany; 4Hospital Ernst von Bergmann, Department of Cardiology, Potsdam, Germany

Purpose: In-stent restenosis (ISR) is a persistent problem limiting the long-term success of percutaneous coronary intervention. Recent studies have demonstrated safety and efficacy of drug-coated balloon (DCB) angioplasty for the treatment of coronary ISR. The cost-effectiveness of this practice is unknown.

Methods: A Markov state-transition decision analytic model was used to assess the comparative cost-effectiveness of two common treatment strategies for BMS-ISR: stenting with paclitaxel-eluting DES versus paclitaxel-coated balloon angioplasty (SeQuent Please, B. Braun Melsungen AG, Berlin, Germany). The model accounted for varying procedural efficacy rates, complication rates, and cost estimators. Data on procedural outcomes associated with both treatment strategies were derived from the literature, and the cost analysis was conducted from a health care payer perspective. Effectiveness was expressed as life-years gained. Cost-effectiveness was calculated by dividing the difference in mean costs (costs – costs for DES implantation) by the difference in effectiveness (life expectancy in the DCB arm – life expectancy in the DES arm). All simulations were performed using Monte Carlo simulations with 100,000 random trials.

Results: In the base-case analysis, initial procedure costs for € 3,604.14 for DCB angioplasty and to € 3,309.66 for DES implantation. Over a 12-month time horizon, the DCB strategy was found to be less costly (€ 4,130.38 versus € 5,305.30) and slightly more effective in terms of life expectancy (0.983 versus 0.976) than the DES strategy. Extensive sensitivity analyses indicated that, in comparison with DES implantation, the cost advantage of the DCB strategy was robust to clinically plausible variations in the values of key input parameters. The variables with the greatest impact on base case results were the duration of dual antiplatelet therapy with acetylsalicylic acid and clopidogrel after DCB angioplasty, the use of generic clopidogrel, and variations in the costs associated with the DCB device.

Conclusion: DCB angioplasty is a cost-effective treatment option for coronary BMS-ISR. The higher initial costs of DCB are more than offset by later cost savings, predominantly as a result of reduced medication costs. Health care payers
would benefit from a wider adoption of this technology, as DCG angioplasty can be regarded as one of the rare innovative medical treatments that are cost-saving at equal or even increased effectiveness.

Differential of vascular response between everolimus- and paclitaxel-eluting stents for small coronary artery diseases: optical coherence tomography analysis

K. Nasu, Y. Oikawa, S. Shirai, H. Hozawa, S. Tohara, M. Kadotani, H. Abe, Y. Takeda, S. Usui, T. Serikawa on behalf of SACRA and PLUM registries investigators. 1Syohashi Heart Center, Toyohashi, Japan; 2The Cardiovascular Institute Hospital, Tokyo, Japan; 3Kokura Memorial Hospital, Kitakyushu, Japan; 4Ayase Heart Hospital, Adachi-ku, Japan; 5Kakusabke Chuo General Hospital, Kakusabke, Japan; 6Kakagawa East City Hospital, Kakagawa, Japan; 7Matsumoto Kyoutokan Hospital, Matsumoto, Japan; 8Rinku General Medical Center, Osaka, Japan; 9JR Tokyo General Hospital, Tokyo, Japan; 10Saiseikai Fukuoka Hospital, Fukuoka, Japan

Background: The aim of this study is to evaluate the differences of chronic vascular response following small coronary stenting between everolimus-eluting stent (EES) and paclitaxel-eluting stent (PES) evaluated by optical coherence tomography (OCT).

Methods: SACRA and PLUM registries are prospective, multicenter registry to assess the efficacy of single paclitaxel- (PES) or everolimus-eluting stents (EES) in patients with small coronary artery diseases. Inclusion criteria of both registries were: 1) significant stenosis in vessels <2.5 mm in reference diameter, 2) lesion length <30 mm from these two registries (506 patients with 533 lesions), non-restenotic 50 EESs and 50 PESs were imaged with OCT at 9-month follow-up and analyzed at interval of 1 mm.

Results: Average intimal hyperplasia thickness was not different between the two groups. Exposed struts and layered intima were observed more frequently in PES group than EES group.

OCT results

<table>
<thead>
<tr>
<th></th>
<th>EES</th>
<th>PES</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of stent</td>
<td>50</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>No. of observed cross-sections</td>
<td>859</td>
<td>825</td>
<td>-</td>
</tr>
<tr>
<td>Homogenous intima</td>
<td>80.9 (93%)</td>
<td>737 (79%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Heterogenous intima</td>
<td>38 (4.4%)</td>
<td>28 (3.4%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Layered intima</td>
<td>18 (2.1%)</td>
<td>60 (7.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peri-plant low signal</td>
<td>30 (3.5%)</td>
<td>103 (12.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peri stent ulcer like appearance</td>
<td>53 (6.2%)</td>
<td>106 (12.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. of analyzed strut</td>
<td>9706</td>
<td>7605</td>
<td>-</td>
</tr>
<tr>
<td>Exposed strut</td>
<td>26 (0.27%)</td>
<td>130 (1.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malapposed strut</td>
<td>9 (0.09%)</td>
<td>22.0 [10.7]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percent neointimal hyperplasia area, %</td>
<td>20.4±6.8</td>
<td>22.0±10.7</td>
<td>0.51</td>
</tr>
<tr>
<td>Average NIT, μm</td>
<td>0.14±0.06</td>
<td>0.15±0.08</td>
<td>0.44</td>
</tr>
<tr>
<td>Maximum NIT, μm</td>
<td>0.22±0.08</td>
<td>0.28±0.12</td>
<td>0.03</td>
</tr>
<tr>
<td>Minimum NIT, μm</td>
<td>0.07±0.04</td>
<td>0.07±0.05</td>
<td>0.75</td>
</tr>
<tr>
<td>Maximum NIT-Minimum NIT, μm</td>
<td>0.15±0.04</td>
<td>0.21±0.09</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions: This study suggested that characteristics of neointimal hyperplasia after EES implantation were more stable compared with PES although neointimal growth was similar between the two groups. After correcting for clinical differences and the Syntax Score, the use of 1a/GEN DES was associated with a significant 2.3 fold increase in the risk of definite ST (95% CI 1.02-5.12; p=0.046) and implantation of paclitaxel-DES only (but not sirolimus-DES) was an independent predictor of the occurrence of definite ST (corrected HR 1.8; 95% CI 1.01-3.34; p=0.047). Although slightly numerically superior in patients treated with 1a/GEN DES (3.5% vs. 3.4%), total mortality was not statistically different between groups (HR 1.1.6; 95 CI 0.77-1.74; p=0.48).

Conclusions: Our data suggests that in the real world clinical practice, the use of first generation DES should be restricted to very specific subsets of patients/lesions, and that newer devices actually appear to exhibit a better safety profile when broadly used for PCI with DES.

Impact of adjunctive post-dilatation after drug-eluting stent implantation on the clinical outcomes in patients with acute myocardial infarction: Sub-study of EVER-ZOTA multicenter trial

S.Y. Yoo1, J.K. Sung2, S.H. Lee, C.K. Lee, B.K. Lee, D.H. Yoon1, University of Ulsan College of Medicine, Gangneung Asan Hospital, Gangneung, 2Wonju College of Medicine, Yonsei University, Division of Cardiology, Department of Internal Medicine, Wonju, Kangweon National University Hospital, Chuncheon, 4Hallym University, Chuncheon Sacred Heart Hospital, Chuncheon, Korea, Republic of

Backgrounds: Although drug-eluting stents (DES) are more effective than bare-metal stents (BMS) in preventing coronary restenosis, stent underexpansion was known to be an important predictor of early stent thrombosis and restenosis in the DES era. Recently, a large retrospective study demonstrated that post-dilatation after DES implantation reduced the restenosis rate. However, the population of the study did not include patients with acute myocardial infarction (AMI). The aim of present sub-study of EVER-ZOTA multicenter trial was to evaluate the impact of an adjunctive post-dilatation after DES implantation on the clinical outcomes in patients with AMI.

Methods: We studied 474 (343 men, 65±12 years old) patients who underwent DES implantation for AMI including 358 with post dilatation (253 male, 66±12 years old) and 116 with un-post dilatation (90 male, 63±12 years old). Rate of cumulative 12-month events, such as cardiac death, target-vessel related MI, revascularization, or stent thrombosis was compared between groups.

Results: Compared with the postdilatation group, the un-post dilatation group had younger, less calcified lesion, and obtained postprocedural TIMI-3 flow. They had also significant benefit on composite events in 12 months (5.6% vs. 0.9%, p < 0.045) (Figure). However, Cox regression survival analysis showed the Killip Class ≥ 3 (odd ratio 17.27; 95% CI 5.43-54.906, p < 0.001) and age (odd ratio 1.061, 95% CI 1.005-1.119, p < 0.031) to be independent predictors of 12-month composite events rather than postdilatation itself.

Second vs. first generation DES are associated with a better safety profile in real world coronary percutaneous intervention: analysis of 3268 procedures from a single centre prospective registry

H. Dores, L. Raposo, S. Leal, C. Machado, P.A. Goncalves, R.C. Teles, H.M. Gabriel, M.S. Almeida, M. Mendes. Hospital West Lisbon, Hospital Santa Cruz, Department of Cardiology, Lisbon, Portugal

Background and Aims: When compared to their first generation counterparts, second generation DES have been associated with better clinical outcomes in recent RCTs, which, together with safety concerns (mostly stent thrombosis [ST]), led to a progressive abandon of the latter in most clinical settings. Our goal was to assess whether or not newer devices translate into higher safety in a real world population. For that purpose, our main outcome measure was the occurrence of definite ST.

Methods and Results: Between January 2003 and December 2009, 3268 patients (pts) were submitted to PCI with at least one DES. Of these, 2260 (69.2%) where treated with first generation (1stGEN) DES only [Sirolimus=1178 (36.1%) and Paclitaxel=929 (28.4%)], 153 pts both and 1006 (30.8%) with second generation (2ndGEN) DES only. Patient, angiographical and procedural characteristics were prospectively recorded in a dedicated data base; study groups differed in age (63 ±10.6y vs. 65.6 ±11.2y; p<0.001), prevalence of hypertension (72.6% vs. 77.1%; p<0.006), smoking (50.3% vs. 44.6%; p=0.003), prior ACS (17.1% vs. 12.4%; p<0.001), ACS presentation (40.8% vs. 49.7%; p<0.001) and Syntax score (14.10 ±3.2 vs. 13.38 ±2.0; p<0.04). ARCI-defined definite ST occurred in 75 (2.5%) pts during a median follow-up of 598 days (IQR range 453; 1206), 715 (IQR 463; 1546) for 1stGEN vs. 508 (IQR 440; 720) for 2ndGEN (p<0.001). In order to account for differences in follow-up duration, only adjudicated events occurring during the first year were included in the per-procedure analysis (n=44, 1.3%).

Conclusions: Postdilatation after DES implantation in patients with AMI does not seem to have a benefit on the 12-month clinical outcomes. Age and Killip Class rather than postdilatation itself would be more predictive of 12-month clinical outcomes.

Percutaneous coronary intervention outcomes

Bare-nitinol stent versus paclitaxel-coated balloon for femoro-popliteal revascularization. An adjusted indirect comparison meta-analysis of randomized trials

S. Cassese, R.A. Byrne, I. Okt, T. Ibrahim, T. Tada, L. King, A. Kastrati, M. Fusaro. German Heart Center, Clinic for Heart and Circulatory Diseases, Munich, Germany

Aims: In femoro-popliteal artery (FPA) disease, Bare-Nitinol Stent (BNS) and Paclitaxel-coated balloon (PCB) improved outcomes as compared to Uncoated-Balloon (UCB) angioplasty. Nevertheless, the relative efficacy of BNS vs. PCB remains unknown, due to the lack of head-to-head comparisons. We performed an adjusted indirect comparison meta-analysis of randomized trials to evaluate outcomes of BNS versus PCB in FPA disease.
Methods: A systematic literature search (PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, scientific session abstracts and relevant websites) through December 2011 was performed. Selected search words were: superficial-femoral artery, popliteal artery; angioplasty, self-expanding stent, nitinol-stent, bare-stent, drug-eluting balloon, paclitaxel-coated balloon, and randomized trial. Inclusion criteria were: randomized trial design, intention to treat analysis, ≥6-month follow-up (FU). Exclusion criteria were: other arterial segments treated than FPA, comparison other than BNS/PCB vs. UCB, irritable, duplicated or incomplete data. Odds ratio (OR [95% confidence intervals]) and z scores (z), with corresponding p values, were used as summary statistics. Main outcomes were target lesion revascularization (TLR), binary restenosis and all cause mortality.

Results: We identified 8 eligible trials, enrolling a total of 1,008 patients randomized to BNS/PCB or UCB angioplasty (BNS n= 342, PCB n= 196, UCB n= 480). Median FU was 11.5 months. Angioplasty with BNS was found inferior to PCB with respect to TLR (OR= 2.60 [1.27–5.32], z= 2.63, p= 0.008), with a trend toward higher binary restenosis (OR= 2.03 [0.99–4.18], z= 1.93, p= 0.052). No significance in mortality was evident among study groups (OR= 1.79 [0.37–8.55], z= 0.73, p= 0.46; BNS vs. PCB comparison).

Conclusions: In diseases of femoro-popliteal artery, PCB offers superior freedom from restenosis as compared to BNS. Both revascularization strategies appeared safe. Adequately powered, randomized, head-to-head comparisons are needed.

MANAGEMENT OF CORONARY ARTERY DISEASE AND PERCUTANEOUS CORONARY INTERVENTION COMPLICATIONS

P4801 Bivalirudin Vs Unfractionated Heparin during Percutaneous Coronary Intervention in High Risk Patients for Bleeding. AntiCoagulant Regimen In high risk Patients for Bleeding - ACRIPAB trial
A. Feldman, K. Suleiman, L. Bushari, E. Rozner, N.A. Freedberg, Y. Turgeman, Haaemek Medical Center, Afula, Israel

Introduction: In low to medium risk population undergoing PCI Bivalirudin (BIV) exhibited significantly lower rate of bleeding compared to unfractionated heparin (UFH). However, clinical outcome and bleeding complications in high risk population was not established yet.

Aim: Randomized double blinded prospective trial comparing efficacy and safety of BIV vs. UFH on top of dual antiplatelet therapy during PCI among patients with NSTE-ACS or acute aortic dissection with high risk for bleeding.

Methods: There were 100 consecutive patients (66.6±12.3 years old, 69% males) enrolled in our study with 1:1 distribution between BIV and UFH groups. With starting of PCI BIV or UFH were administered in acceptable doses. The study end points were: major, minor bleeding, post PCI complications, MACE in-hospital and after 30 days follow up.

Baseline characteristics: There were 87% patients with diabetes mellitus, 98% with hypertension, 22% with chronic renal failure, 30% older than 75 years, 21% with haemoglobin plasma level <10 mg/dl and 58% with systolic blood pressure >180 mm Hg. 24% of participants were catheterized due to NSTEMI. Femoral approach was used in 16% of patients. There were significantly more PCIs accomplished via radial approach in BIV group (90% vs. 78%, p=0.05). BIV group complication was not represented with higher male’s rate (78% vs. 60%, p=0.05).

Results: There were significantly more PCIs accomplished via radial approach in BIV group (90% vs. 78%, p=0.05). BIV group complication was not represented with higher male’s rate (78% vs. 60%, p=0.05). Comparison was not established yet.

Conclusions: In diseases of femoro-popliteal artery, PCB offers superior freedom from restenosis as compared to BNS. Both revascularization strategies appeared safe. Adequately powered, randomized, head-to-head comparisons are needed.

P4802 Triple over Dual anti-Platelet therapy was not mandatory in Acute Coronary Syndrome Patients with 2nd Generation Drug eluting Stent Implantation

Purpose: Triple antiplatelet therapy with clopidogrel has been known to be superior to dual antiplatelet therapy in the era of 1st generation DES in terms of clinical outcome. However, it remains to be cleared whether triple antiplatelet therapy also has the same efficacy after implantation as the era of 2nd generation DES even in patients with acute coronary syndrome (ACS) Methods: In CO-ACT registry, the study subjects were 644 patients who underwent PCI with Everolimus eluting or Zotarolimus eluting stent (Endeavor, Xience V or Promus) with ACS were analyzed retrospectively. The patients were divided into 2 groups after propensity score matching: those treated with triple antiplatelet drugs (aspirin, clopidogrel, and cilostazol; group 1, n=208, M±16 (55.7%), mean age=60.7±14.6 years) and those with dual antiplatelet therapy (aspirin and clopidogrel; group 2, n=636, M±407 (63.9%), mean age=67.8±11.3 years). The incidences of various clinical outcomes were compared between two groups.

Results: The mean follow-up duration of 17.6±8 month (median= 13.4). There was no significant difference in the incidence of major bleeding between two groups. Compared with group 1, group 2 showed no significant difference of cardiac death and MI (OR, 1.12; 95% CI, 0.78-1.379, p=0.43), MACE (cardiac death, MI and TLR) (OR, 1.55; 95% CI, 0.77-1.85, p=0.30). Kaplan-Meier curves for MACE did not show any survival benefits in triple anti-platelet therapy.

Conclusions: Triple antiplatelet therapy has no beneficial effect in clinical outcome compared to dual antiplatelet therapy in patients with 2nd generation DES even in ACS patients.

P4803 Brain natriuretic peptide during coronary intervention: prevents endothelial dysfunction post PCI via NP-cGMP activation
A. Peleg, D. Gharim, D. Darawany, Y. Hasin, Baruch Padler Medical Center, Poriya, Tiberias, Israel

Background: Percutaneous coronary intervention (PCI) is associated with endothelial dysfunction (ED) and systemic vascular injury induced by contrast media (CM). According to our previous study, brain natriuretic peptide (BNP) administration 24 hours post PCI decreases ED.

Aims: The purpose of this study: 1. To evaluate the ability of human BNP (hBNP) infusion during PCI, to prevent ED in patients with acute coronary syndrome (ACS) post the PCI. 2. To investigate the effect of contrast medium (CM) administration on human coronary microvascular endothelial cells (HCMEC).

Methods and Results (in vivo): Eleven hundred patients with non-ST elevation ACS who underwent PCI were randomized into 2 groups: a group who received hBNP infusion during the procedure (n=64), and another control group who received nitroglycerin (n=67) according to standard protocol. The endpoints were: the rate of decreased flow mediated dilatation (FMD) (by ≥2.5%), the increase in BNP corin, serum creatinine (sCr) and decrease of estimated Glomerular Filtration Rate (eGFR), 24 hr after, compared to pre operative value. There was no difference in baseline FMD. The post PCI FMD was significantly reduced in the control group (p=0.05) but increased non-significantly in the hBNP group (p=0.16). FMD was significantly higher in the hBNP group (p=0.04). BNP, corin and sCr increased significantly in the control group (p=0.001, 0.003, 0.0002 respectively) but not in hBNP group (p=0.09, 0.07, 0.18). eGFR decreased significantly in the control group (p=0.002), no change in the hBNP group (p=0.4).

Methods and Results (in vitro): HCMEC were treated with CM (10%) in the presence and absence of BNP, enos, corin and cGMP levels were measured by ELISA and the results were compared to untreated cells. In both treatments enos was significantly reduced (p=0.001) and corin was significantly increased (p=0.002), to the same levels. cGMP was not reduced by CM treatment (p=0.278), but was increased significantly (p=0.001) by BNP combination. Cgmp immuno-fluorescence staining of HCMEC showed distorted cellular cGMP appearance by CM treatment which was corrected in the combination with hBNP with accentuated subsarcomembranal staining.

Conclusions: These data show that CM reduces Enos in endothelial cells in a concentration dependent manner. Therefore, reduction of NO-cGMP pathway probably is the mechanism that induces ED in vivo. BNP treatment reduces FMD and kidney injury post PCI. A compensatory rise in corin that increases BNP as well the NO-cGMP pathway can compensate for NO-cGMP loss, which prevents ED.

P4804 Why is the posterior myocardial infarction the most frequent cause of acute mechanical complications?
S. Simek, J. Horak, T. Kovarik, J. Belohlavek, M. Aschermann, V. Mrázek, J. Humhal, A. Linhart, 2nd Med. Dep. of Cardiology, Charles University in Prague, First Faculty of Medicine, Prague, Czech Republic

Background: The prevalence of ramus circumflexus (LCX) and its branches as an infant related artery (IRA) in STEMI patient populations is low, around 10-15%. LCX is the most frequent IRA among patients with mechanical complica-

Objective: To estimate the reason for high involvement of LCX as IRA in patients with mechanical complication of AMI.

Methods: Registry of patients with acute coronary syndromes treated in the tertiary cardiac centre.

Results: In the group of 809 STEMI patients treated in period 2008-2011, the LCX, LAD, and RCA were detected as IRA in 133 (16%), 347 (43%) and 308 (38%) patients respectively. In the parallel group of 709 NSTE-ACS patients the proportion of LCX, LAD and RCA as IRA was 205 (31%), 322 (33%) and 209 (29.5%) respectively. The difference of LCX involvement in STEMI (16%) compared to NSTE-ACS patients (31%) was highly significant (p<0.001). From the group of 7 patients hospitalized for the acute mitral regurgitation due to rupture
Effect of high dose statin pretreatment on endothelial progenitor cells after percutaneous coronary intervention (Hypocrates study)

A. Eisen1, D. Leshem-Lev2, K. Orvin1, T. Ben Gal1, O. Daddu2, A. Battler1, E. I. Lev1, Rabin Medical Center, Bellinson Hospital, Petah Tikva, Israel; 2Felsenstein Medical Research Center, Tel-Aviv University School of Medicine, Rabin Medical Center, Petah Tikva, Israel

Purpose: Previous studies have not shown benefits of percutaneous coronary intervention (PCI). This could account for the beneficial effects of statins given prior to PCI.

Methods: Included were patients, either statin naïve or treated chronically with OMT (beta-blockers, statins, antiplatelets, ACE inhibitors) were included. In history (>2 months ago): acute coronary syndrome (ACS)–80.9%, PCI–14.9%, coronary bypass-12.7%, stroke-9.6%, diabetes-18.5%, 302 of pts underwent PCI (PCI group) and 179 of pts continued on conservative therapy (medical-therapy group). The mean follow-up period in PCI and medical-therapy groups was 5.3±1.8 yrs and 5.4±1.3 yrs respectively. The primary outcome was the occurrence of major adverse cardiac and cerebrovascular events (MACE):vascular death, ACS, stroke/transient ischemic attack. The composite endpoint included MACE and revascularization in any affected arterial area.

Results: Most of the demographic and clinical characteristics were similar in the two groups. PCI was performed for 1- and multivessel diseases in 57.3%, 30.5% and 9.3% respectively. 98% of PCI group received DES (Cypher and sirolimus-Eluting stents) and 98% of medical-therapy group received OMT (beta-blockers, statins, antiplatelets, ACE inhibitors) were included. In history (>2 months ago): acute coronary syndrome (ACS)–80.9%, PCI–14.9%, coronary bypass-12.7%, stroke-9.6%, diabetes-18.5%, 302 of pts underwent PCI (PCI group) and 179 of pts continued on conservative therapy (medical-therapy group). The mean follow-up period in PCI and medical-therapy groups was 5.3±1.8 yrs and 5.4±1.3 yrs respectively. The primary outcome was the occurrence of major adverse cardiac and cerebrovascular events (MACE):vascular death, ACS, stroke/transient ischemic attack. The composite endpoint included MACE and revascularization in any affected arterial area.

Conclusions: Most of the demographic and clinical characteristics were similar in the two groups. PCI was performed for 1- and multivessel diseases in 57.3%, 30.5% and 9.3% respectively.

Onset-to-needle times in patients with ST-segment elevation myocardial infarction: shortest referral route to a primary coronary intervention facility

H. Lees1, F. Capuano1, M. Ferrua1, G. Nitenberg2, E. Minivil81, F. Schiele2, 1Projet COMPAQ-HPST-INSERM U988, Institut Gustave Roussy, Villejuif, France; 2University Hospital of Besancon - Hospital Jean Minjoz, Besancon, France

Introduction: Primary percutaneous coronary intervention (PCI) is the preferred therapeutic strategy for patients with acute ST-elevation myocardial infarction (STEMI). However, several referral routes between onset of symptoms and PCI exist namely: Pre-hospital diagnosis and direct transfer to PCI, emergency room visit and on-site transfer to PCI, or emergency room visit and secondary transfer to PCI. We compared the delays between onset and PCI associated with each referral route.

Methods: Data was obtained in a retrospective analysis of randomly selectedSTEMI patients from 64 hospitals in France. For each patient, the referral route and onset-to-needle time was obtained. Onset-to-needle time was defined as time from onset of symptoms to time of arterial puncture for PCI. We used a Cox proportional-hazards model to compare delays between referral routes.

Results: In total, 1217 patients were included in the analysis. Median onset-to-needle time was 186 min (Q1:133; Q3:262) for the pre-hospital diagnosis route, 237 min (Q1:165; Q3:368) for the on-site transfer route and 305 min (Q1:230; Q3:570) for the secondary transfer route. There was no difference in median onset-to-needle times between hospital types or volume of activity. After adjusting for age, year of admission and history of cardiovascular disease, pre-hospital diagnosis was associated with the shortest delay as compared to on-site-transfer (Hazard ratio [HR] 0.71 [0.59 - 0.86]) and secondary transfer (HR 0.67 [0.52 - 0.86]).

Conclusions: Pre-hospital diagnosis with direct transfer to PCI leads to shorter delays in patient care. In France, this management pathway requires the presence of an emergency physician at first medical contact.
myocardial infarction (AMI). Implementation of national quality improvement program may have the potential to obviate the “weekend-effect” in patients with AMI.

Methods: Between November 2005 and December 2010, 25,233 patients (18.025 men; mean age = 63.3±12.8 year-old) were included from Korea AMI Registry. Exposure was defined as admission on a Saturday, Sunday, or a holiday. The study population was stratified according to exposure and three-time-periods: 2005.11.1 – 2006.12.31 (KAMIR I; n=7,077), 2007.11.1 – 2008.11.1 (KAMIR II; n=13,311) and 2008.11.1- 2010.12.31 (KorMI; n=4,605).

Results: The proportions of weekend-admissions were 27.4%, 27.9% and 28.2%, respectively. Patients admitted on weekend were younger and had more typical chest pain, inferior MI, ST-segment elevation MI, higher Killip class, and higher serum glucose, CK-MB, and triglyceride levels. Current smokers were more frequently observed in patients admitted on weekend. Cardiopulmonary re-suscitation were more frequently performed in patients admitted on weekend. From KAMIR II 6.5% of patients admitted on weekends compared to 5.2% of those admitted on weekdays (p<0.037). During the two following periods the apparent difference between weekends and weekdays decreased: KAMIR III (7.1% versus 7.8%, p=0.436) and KorMI (6.2% versus 5.8%, p=0.367). Accordingly, in the adjusted multivariate analysis an increased all-cause mortality in patients admitted on weekends was observed only in KAMIR I with a weekend-weekday hazard ratio (HR) of 1.320 (95% CI: 1.001-1.741, p=0.049) but was not found in KAMIR II (HR 1.945, 95% CI: 0.688-2.969, p=0.728) and KorMI (HR 0.904, 95% CI: 0.744-1.098, p=0.307).

Conclusions: We showed that a weekend-effect on mortality in patients with AMI has previously been present, but it has decreased over the past five years.

P4809 Syntax score predicts major bleeding after drug-eluting stent implantation


Purpose: The bleeding complication has been one of frequent complications in the drug-eluting stent (DES) era. Previous study reported that percutaneous coronary intervention (PCI) in complex lesion is an independent correlate of major bleeding. This finding may be explained by more complicated procedure and longer duration of dual anti-plalet therapy. The SYNTAX score is a current angiographic tool grading the complexity of coronary artery disease. The aim of this study was to assess the ability of the SYNTAX score to predict major bleeding after DES implantation.

Methods: We analyzed a consecutive 560 patients treated with DES in the all-comers population between January 2007 and January 2009. Endpoints were analyzed for major bleeding (defined according to the REPLACE-2 trial) and late stent thrombosis during 3 years. The SYNTAX score was assessed with angiogram before PCI by 2 cardiologists. Patients were stratified according to tertiles of the SYNTAX score: low score (0-12, n=170), intermediate score (13-24, n=202), and high score (>25, n=188).

Results: Incidence of the major bleeding was seen in 49 patients (8.8%) during the study period. The SYNTAX score had a predictive ability for patients at risk of major bleeding. The SYNTAX score was an accurate (area under the ROC curve (AUC) = 0.751, 95% CI 0.744-0.758, p<0.0001) predictor of major bleeding after PCI. In multivariate logistic regression including clinical factors showed in the table.

Predictive factors of Major Bleeding

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNTAX score (10-unit increase)</td>
<td>1.80</td>
<td>1.29-2.54</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>3.62</td>
<td>1.90-6.89</td>
</tr>
<tr>
<td>Age</td>
<td>1.68</td>
<td>1.09-2.57</td>
</tr>
</tbody>
</table>

Multivariate logistic regression model.

Conclusions: In the all-comers population undergoing DES implantation, the SYNTAX score has a predictive ability for patients at risk of major bleeding. The score may be useful for clinical decision making regarding optimal duration of dual anti-plalet therapy after DES.

P4810 Clinical risk scores for the prediction of CIN before primary PCI

G. Ando, G. Morabito, O. Tio, F. Saporito, C. De Gregorio, G. Oreti. Department of University of Messina, Department of Medicine and Pharmacology, Messina, Italy

Background: Several scores for risk stratification have been developed in candidates to percutaneous or surgical myocardial revascularization. These scores have been recently validated even in different settings than the ones where they were developed. We retrospectively assessed the relative accuracy of AGF score, EuroSCORE and Mehran Risk Score (MRS) as predictors of CIN, with the AUC as a measure of accuracy. The best cutoff value for each score was identified according to the Youden index.

Methods: We showed that a weekend-effect on mortality in patients with AMI has previously been present, but it has decreased over the past five years.

Methods: CIN was defined as an absolute increase in serum creatinine ≥0.5 mg/dl or an increase ≥25% from baseline within 72 hours after the administration of contrast medium. AGF score was calculated by adding 1 point to the age/EFR ratio if the eGFR was <60 mL/min per 1.73 m².

Logistic regression analysis, receiver-operating characteristic (ROC) curve analysis and Hosmer-Lemeshow χ2 statistic were performed to assess accuracy and calibration of AGF score. EuroSCORE and MRS as predictors of CIN, with the AUC as a measure of accuracy. The best cutoff value for each score was identified according to the Youden index.

Results: Overall, the incidence of CIN was 5.2%. AGF score was an accurate (OR 5.19, 95% CI 3.38-7.62, p<0.0001, AUC 0.08) and calibrated (Hosmer-Lemeshow χ2=2.66, p=0.62) predictor of CIN with a 100% sensitivity for AGF score >1.5 points; all patients developing CIN were in the highest tertile of AGF score (<0.0001). When considered linear, continuous variables MRS (OR1.27, 95% CI 1.28-1.79, p=0.0001, Hosmer-Lemeshow χ2=2.18, p=0.50) and Eur- roSCORE (OR1.65, 95% CI 1.36-2.1, p<0.0001, Hosmer-Lemeshow χ2=2.5, p=0.50) predicted the risk of CIN as well.

Both MRS (AUC 0.80, p=0.15 vs AGF score) and EuroSCORE (AUC 0.82, p=0.14 vs AGF score) were less accurate, though not significantly, than AGF score. The cutoff for MRS was 5, with 72% sensitivity and 73.5% specificity, and coincided with the upper boundary of the lowest risk category in the original Mehran study. The cutoff for EuroSCORE was 6, with 92% sensitivity and 92% specificity, and coincided with the lower boundary of the high risk category.

Conclusions: In patients undergoing primary PCI for STEMI, a linear risk score based on age, ejection fraction and eGFR can predict the risk of CIN at least as accurately as more complex non-linear risk scores. Simple models based on pre-procedural, readily obtainable objective variables, such as the AGF score, are well suited to the acute settings. Complex risk models may be over fitted, at least in populations with a low rate of events.

P4811 Comparison of the new Mayo Clinic risk scores and clinical SYNTAX Score in predicting adverse cardiovascular outcomes following percutaneous coronary intervention at our center

H.J. Brown, J. Ho Khe Sui, C. Tan. Philippine Heart Center, Quezon City, Philippines

Background: Risk stratification of patients who will undergo percutaneous coronary intervention (PCI) can help physicians and patients and their families understand the risks of the procedure, thus providing an objective basis for decision-making.

Objective: To compare the prognostic value of the Clinical SYNTAX Score (CSS) and New Mayo Clinic Risk Scores (NMCRS) for in-hospital and 30-day mortality and major adverse cardiovascular and cerebrovascular events (MACCE) following PCI

Study Design: Prospective Cohort Study

Methods and Results: The NMCRS for Predicting Mortality, NMCRS for Predicting MACCE and CSS of all patients who underwent PCI from April 1, 2011 to September 30, 2011 were computed. Of the 482 patients included in the study, 22 (4.6%) died while 37 (7.7%) had the composite endpoint (mortality, MI, emergency CABG, CVA) during hospitalization. 30 days after PCI, 9 (2.0%) died while 19 (3.9%) had the composite endpoint. The prognostic value of the NMCRS for Predicting Mortality, NMCRS for Predicting MACCE and CSS for in-hospital mortality, as measured, by the c-statistic, was 0.827, 0.813, and 0.816 (P < 0.05 for all), respectively and for in-hospital composite endpoints is 0.791, 0.751, and 0.755 (P < 0.05 for all), respectively and for composite endpoints is 0.736 (P < 0.05), 0.763 (P < 0.05), and 0.621 (P < 0.10), respectively.

Conclusion: The NMCRS for Predicting Mortality has better prognostic utility for in-hospital mortality and composite end-points while the NMCRS for Predicting MACCE better predicts 30-day mortality and composite end-points as compared to the CSS.

P4812 Protamine usage following implantation drug-eluting stents: is it safe?

B. Kremer Diniz Goncalves, A.L.T. Tedeschi, M.A.S. Sena, R.T.S.P. Peixoto. Proceds Hospital, Itaparica, Brazil

Background: Prompt reversal of heparin anticoagulation by protamine administration after coronary stent implantation could be an important therapeutic option. It could help the treatment of serious procedural complications such as vessel rupture or perforation or to allow immediate femoral artery sheath removal to avoid puncture site complications and decrease patient discomfort. However, this approach is rarely used after coronary drug eluting stent (DES) implantation because of the possible increased risk of stent thrombosis. ST is a rare event, so in order to be detected a large sample study is required.

Methods: We retrospectively analyzed the incidence of acute and subacute stent thrombosis in 6023 patients submitted to percutaneous coronary intervention who received 2456 drug eluting stent divided in 2 groups: GI with 2509 DES who
received protamine after procedure and GII with 436 DES who did not receive this drug.

**Results:** Six patients (0.24%) had subacute stent thrombosis in the group receiving protamine (290 DES) and only one patient (0.03%) in the group who did not receive this drug (436 DES) (p-value = 0.96; odds ratio: 0.96; 95% confidence limits).

**Conclusion:** Immediate reversal of heparin anticoagulation by protamine after coronary drug eluting stent implantation in our study was safe and did not predispose to stent thrombosis. This finding has important clinical consequences.

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**Table 1**

<table>
<thead>
<tr>
<th>Mehan risk score</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio (95% CI)</td>
<td>P-value</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Low</td>
<td>1.00 (reference)</td>
<td>0.00</td>
</tr>
<tr>
<td>Medium</td>
<td>1.18 [0.83-1.65]</td>
<td>0.394</td>
</tr>
<tr>
<td>High</td>
<td>1.91 [1.21-2.94]</td>
<td>0.004</td>
</tr>
<tr>
<td>Very High</td>
<td>7.75 [3.86-15.15]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Table 2**

<table>
<thead>
<tr>
<th>Summary of outcome events at discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACCE</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>8 (4.1%)</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
</tr>
<tr>
<td>Access site complications</td>
</tr>
</tbody>
</table>
| AAC = Additional anticoagulation; MACCE = major adverse cardiovascular and cerebrovascular events (death, MI, TIA, ST and stroke).
Functional syntax score improves stratification of risk in patients with left main coronary artery disease

OLV Hospital Aalst, Cardiovascular Center, Aalst, Belgium

The Functional Syntax Score (FSS) is obtained including in the computation of the Syntax Score (SS) only FFR positive lesions (i.e. FFR >0.80). FSS has demonstrated better prognostic value as compared with SS in patients with multivessel disease (lesions of left main excluded) treated with DES implantation.

The purpose of the present analysis is to assess whether FSS is able to better discriminate the potential PCI-related risk in patients with left main (LM) lesions compared with SS.

Methods and results: Patients (pts) with angiographically equivocal LM stenosis (n=209) undergoing FFR measurement were enrolled. Pts with (n=138) LM FFR > 0.80 with either deferred to optimal medical treatment or to PCI of other significantly stenotic vessels (n=75) with LM FFR < 0.80 underwent bypass surgery.

SS was calculated on all angiographies, FSS was calculated by excluding from the computation LM stenosis with FFR > 0.80. Based on the SS, patients were classified in the following tertiles: 68 pts in the low (<14 SS), 69 pts in the intermediate (15-21 SS), and 72 pts in the high (>22 SS). After calculation of FSS, 67 out of 209 patients (32%) were reclassified to lower SS tertile. More specifically, out of 69 patients with intermediate SS (15-21), 37 (54%) were reclassified to low tertile (<14). While out of 72 patients with high SS (22-42), 13 (18%) pts were reassigned to the intermediate tertile and 17 (24%) to the low tertile.

Conclusion: The present study demonstrates that FSS is particularly useful in the risk stratification of patients with equivocal LM stenosis, allowing to down-grade or up-grade contractile function severity in about one third of the cases. Further studies assessing the prognostic significance of FSS in LM disease are warranted.

Impact of real time 3D-echocardiography in the assessment of right ventricular volumes and function in patients with pulmonary hypertension

I. Fabiani, L.C. Conte, C. Giannini, V. Barletta, L.A. Leo, P. Pelloni, A. Palla, A. Balbarini, M. Mazzotti, P. Di Bello, Cisanello Hospital, Department of Cardio-Thoracic and Vascular, Pisa, Italy

Background: Right ventricular (RV) function is taking last years a higher relevance as a clinical and prognostic marker in many pathophysiological conditions. The aim of the study is to point out the incremental value of real time three dimensional echocardiography (RT3DE) and Tissue Doppler imaging (TDI) in the evaluation of patients affected by pulmonary hypertension (PH).

Methods: A total of 42 subjects affected by PH who underwent 2D and Doppler echocardiography, RT 3D Echocardiography and TDI evaluation of RV, and an healthy control group. PH can induce self decrease functional and structural abnormalities of RV, such as RV hypertrophy, right dilation, RV systolic and diastolic dysfunction.

Results: RV fractional area contraction (RV FAC) and tricuspid annular plane systolic excursion (TAPSE) showed marked alterations in patients with PH compared to control group (C); RV FAC: (PH) 30.0±0.06 vs (C) 50.0±0.05%, p <0.001; TAPSE (PH)15.4±3.1 vs (C) 21.0±2.5 mm, p <0.0001; 3D RV End Diastolic Volume was significantly higher in PH than in C (PH) 138.5±25.1 vs (C): 83±12.6 ml, p <0.0001 as well as 3D RV End Systolic Volume (PH) 97.7±25.4 vs (C) 39.4±9.6 ml, p <0.0001; 3D RV EF was significantly lower in pulmonary hypertension group than in healthy subjects (31.6±6.8 vs C) 52.7±4.6%, p <0.0001.

Discussion: RV diastolic, systolic volume and ejection fraction evaluated by RT3DE showed a higher discriminating power in comparison respectively with RV diastolic, systolic volume and ejection fraction evaluated by echocardiography. Early and late diastolic strain rate measurements were calculated on both a global (GSRa & GSRb) and segmental scale (SRSa & SRSb) using EchoPAC software. Statistical analysis was conducted using SPSS 19.0 using Pearson Correlation, ANOVA testing and Tukeys post hoc testing.

Results: 840 segments were successfully tracked creating a six segment model for the RV. Global strain rate results showed that with increasing age there existed a significant correlation for GSRa (r=0.45 p=0.001) but only a weak negative correlation with GSRb (r=−0.19 p=0.02). Tukeys testing revealed this difference existed between the increasing age groups when compared to the <30 group, with the trend displaying an increase in SRSa with age. The results were then analyzed based on a six segment model. This suggested that the significant increase in SRSa existed within the Apical (p=0.0001) Mid (p=0.001) and Basal (p=0.001) septal segments only.

Conclusion: Significant changes in RV late diastolic strain rate were found when related with age. Typically these enrolled those found within the RV with a trend towards an increase in the late diastolic phase. However these differences were located within the three septal segments of the RV only. The potential resistance that the RV lateral wall displays to the typical diastolic aging process could be due to the variation in fibre types found within the RV. Primarily consisting of longitudinal fibres compared to the multiple fibre types found in the LV, these fibres may maintain their contractile function for longer.

Right ventricular dP/dt in normal subjects: feasibility and normal values

E. Spitzer1, J. Moreno Uczategui1, N. Campos Jordan1, M. Quezada Fejoo1, E. Lopez Soberon1, L. Dominguez Perez1, J. Guineo Esquerdo1, G. Fuentes Fdez1, J. Pena Iruela1, C. Mateos1.
1Hospital Carlos III, Madrid, Spain; 2Hospital Clinic San Carlos, Department of Cardiology, Madrid, Spain

Recently published guidelines for the Echocardiographic Assessment of the Right Heart in Adults, point out that because of the limited data in both normal subjects and pathologic conditions, RV dP/dt cannot be recommended for routine uses. Our aim was to assess the feasibility of obtaining the dP/dt value in normal subjects with mild incidious regurgitation and to determine the normal values in this specific population.

Methods: Four hundred and thirty nine consecutive patients were enrolled. Patients were eligible if they were 18 years or older and their echocardiograms were performed as normal with the presence of mild incidious regurgitation. The highest tricuspid regurgitation (TR) velocity obtained from a sinus beat was measured to obtain the peak systolic RV-right atrial gradient. TR velocity-time integral (VTI) was manually tracked in order to obtain a high quality border to define the exact position of the pointer at 0.5 m/s, 1 m/s and 2 m/s. dP/dt measurements were repeated in 20 patients by the same investigator and by a second investigator.

Results: 49 patients had a normal echocardiogram with mild TR (11.2%) and RV dP/dt was measurable in 22 patients in this group (44.9%). The reasons for not calculating it in the remaining subjects were: 1) Peak TR velocity inferior to 2.3 m/s and 2) poor Doppler registry at the beginning of the TR slope. Intraclass correlation coefficient for the dP/dt measurement from 0.5 to 2 m/s was 0.197 (p = 0.196) for the intra-observer agreement and 0.173 (p = 0.027) for the inter-observer agreement. When the measurement was made from 1 to 2 m/s, the intraclass correlation coefficient was 0.140 (p = 0.272) for the intra-observer agreement and 0.123 (p = 0.298) for the inter-observer agreement.

Right chamber’s echo-Doppler variables

TAPSE (mm) 24.8±3.6
TR velocity-time integral of TR (m/s) 2.5±0.3
RV dP/dt from 0.5 to 2 m/s (mmHg/s) 586.1±237.8
RV dP/dt from 1 to 2 m/s (mmHg/s) 604.4±258.8

Conclusions: RV dP/dt measurement is feasible in a small proportion of normal subjects with mild tricuspid regurgitation (44.9%). Mean value from 0.5 to 2 m/s was 522.0 mmHg/s with a minimum of 0.7 mmHg/s. The methodology used offers only a poor intra and inter-observer agreement.

Management of coronary artery disease and PCI complications / Imaging of the right ventricle

846
**Impact of untreated obstructive sleep apnea on left and right ventricular myocardial function and effects of CPAP therapy**

R. Schueler, M. Wiesen, D. Momolovic, S. Pabst, G. Nickenig, D. Skowasch, C.H. Hammernstingl, University of Bonn, Medical Clinic II - Cardiology, Bonn, Germany

**Background:** Obstructive sleep apnea (OSA) has deteriorating effect on LV function, whereas its impact on RV function is controversial. We aimed to determine the effect of OSA and continuous positive airway pressure (CPAP) treatment on left and right ventricular (LV, RV) function using transthoracic echocardiography (TTE) and 2 dimensional speckle tracking (2D ST) analysis of RV deformation capability.

**Methods and results:** 82 patients with OSA and need for CPAP therapy were prospectively enrolled and underwent TTE at study inclusion and after 6 months of follow up. (FU). Multivariate regression analysis revealed an independent association between baseline apical RV-SI, BMI and the severity of OSA (apical RV-SI: P<0.0002, BMI: P<0.02). After CPAP therapy, LV functional parameters of OSA patients (LVEF: P<0.0001, LV performance index: P=0.03, stroke volume: P=0.042), and apical RV-SI (P<0.001) improved significantly. The effect of CPAP therapy was related to severity of OSA (LVEF: AHI 5-14, 66.4±8.8%, 68.5±10.6% [P=ns]; AHI 15-30: 59.6±7.7%, 68.6±9.3% [P<0.002]; AHI >30: 54.1±12.4%, 62.3±13.6%[P<0.001]; apical RV-SI: AHI 5-14: 17.3±10.8%, 16.0±10.8% [P=ns]; AHI 15-30: 9.8±6.0%, 7.5±4.10.9% [P<0.028]; AHI >30: -3.6±5.7%, -7.9±11.2% [P<0.001]).

Conclusions: OSA seems to have deteriorating effect on LV and RV function. We found a beneficial effect of CPAP on LV and RV functional parameters predominately in patients with severe OSA. 2D speckle tracking might be of value to determine early changes in global and regional right ventricular function.

**P4822** Biomarkers and imaging in early diagnosis of right ventricular dysfunction


1Medcenter, Bucharest, Romania; 2Clinical Emergency Central Military Hospital Dr. Carol Davila, Bucharest, Romania; 3University of Medicine and Pharmacy Carol Davila, Bucharest, Romania; 4Vector Babies National Institute, Department of Pathology, Bucharest, Romania

**Background:** While left ventricular dysfunction has been intensely studied, knowledge regarding the right ventricular dysfunction in diabetic patients is still incomplete.

**Aims:** To evaluate inflammatory biomarkers: high sensitivity C- reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-alfa), lipoprotein associated phospholipase A2 (Lp-PLA2) and their correlation with right ventricle strain and strain rate parameters in patients with diabetes mellitus type II.

**Methods:** We studied 51 patients with type 2 diabetes mellitus (DM), divided into two groups: group 1 DM with coexisting cardiovascular complications (coronary artery disease and high blood pressure (29 patients) and group 2 DM and controlled high blood pressure only, with no coexisting cardiovascular complications (22 patients).

We conducted the analysis of right ventricular (RV) function through Vector Velocity Imaging and determined the inflammatory profile (hsCRP, TNF-alfa, Lp-PLA2) for each patient.

**Results:** In group 1, patients with type 2 diabetes and cardiovascular disease, the Lp-PLA2 activities were significantly higher, with mean value 419.46 UI, compared to group 2, where Lp-PLA2 activity mean value was 207.22 UI. In addition, we identified significant differences between groups for hsCRP and HDL cholesterol (p<0.01). A higher impairment of right ventricular longitudinal systolic function was noticed within group 1, compared with group 2, being statistical significant for SbasalRV, SmidRV and SrandRV (p<0.01). Lp-PLA2 activity was statistically positive correlated with RV strain and strain rate (p<0.01). TNF-alfa and hsCRP did not correlate with any RV echocardiographic parameters.

**Conclusion:** By assessing the inflammatory profile of diabetic patients, it has been revealed that, even those asymptomatic for cardiovascular diseases, have a continuous inflammatory state, together with a decrease in RV systolic function, which should be screened as well in each diabetic patient. Lp-PLA2 was the best correlated marker with RV parameters, nevertheless due to the cross-sectional design, data collected could not provide prognostic value for the investigated inflammatory markers and it is necessary to extend the study with a follow-up period.

**P4825** Echo derived tricuspid dp/dt as a marker of right ventricular function

Y. Singhbal, L.T. Huynh, W. Vollbon, S. Ngai, W. Wang, A. Ng, S. Wahl. The Princess Alexandra Hospital, Brisbane, Australia

**Background:** Right ventricular (RV) systolic function assumes prognostic significance in various disease states. RV geometry is not readily amenable to volumetric assessment by 2-dimensional echocardiography. Intraventricular pressure rate of rise (dp/dt) predicts myocardial contractility and adjusting dp/dt for the maximal regurgitant velocity (Vmax) eliminates the effect of preload. We ex-
Aim: To evaluate the relationship of echo derived tricuspid dp/dt and dp/dt/Vmax with RV ejection fraction (EF) by cardiac magnetic resonance imaging (MRI) as a measure of RV systolic function.

Methods: Fifty cardiac MRI and echocardiograms performed within 30 days were included in the study cohort. The tricuspid regurgitation (TR) spectral doppler trace was analyzed offline. TR dp/dt calculated using simplified Bernoulli (dp/dt between 1m/s and 2m/s), dp/dt/Vmax was calculated as a ratio of dp/dt and TR Vmax. RV end diastolic and end systolic volumes obtained from contouring of steady state free precession axial stack MRI images; RVEF was calculated as [(RV end diastolic volume - RV end systolic volume)/ RV end diastolic volume] x 100. RV EF > 44% was considered normal.

Results: A majority (78%) of studies were adequate for measurement of dp/dt and included in the final analysis. Median age of the study population was 48 years (IQR: 36-63); 56.4% were female (n=22/39). There was moderate correlation between dp/dt and RVEF (r = 0.51, p < 0.01) which improved with dp/dt/Vmax (r = 0.59, p < 0.01). Using 400mmHg/s as the lower limit of normal for RV function, TR dp/dt had a positive predictive value of 91% and a sensitivity and specificity of 74% and 84% respectively. Interobserver agreement and repeatability analysis of dp/dt by Pitman’s variance ratio test showed no significant difference (ratio of standard deviation = 0.95, 95% CI 0.90-0.99, t = -1.9, p = 0.06).

Conclusion: Tricuspid dp/dt is a reproducible measure of RV function and correlates significantly with MRS RV EF. A dp/dt of more than 400mmHg strongly predicts normal RV EF. Adjusting for preload (dp/dt/Vmax) further improves this correlation.

Tricuspid annular plane systolic excursion obtained in the right ventricle modified apical four-chamber view shows strong correlation with right ventricular fractional area change

S. Uegawa, H. Oe, N. Tohi, Y. Kijima, R. Takenoto, N. Watanabe, Y. Tanabe, S. Sanz, H. Ito. 1Okayama University, Department of Cardiovascular Medicine, Okayama, Japan; 2Okayama University Hospital, Okayama, Japan; 3Okayama University, Department of Cardiovascular Surgery, Okayama, Japan

Purpose: Analysis of right ventricular (RV) function is considered to be difficult because of the complex structure. Tricuspid annulus plane systolic excursion (TAPSE) is easily obtainable method for assessment of RV function. However, conventional TAPSE obtained in apical four chamber view (cTAPSE) has a disadvantage of angle dependency. The purpose of this study is to evaluate the superiority of TAPSE obtained in RV modified apical four chamber view (mTAPSE) over cTAPSE as assessment of RV function.

Methods: This study consisted of 67 patients (39 females, 55±19 years) who underwent the standard transthoracic echocardiography. Our exclusion criteria is as follows: atrial fibrillation, device implantation, history of cardiac surgery and significant aortic or mitral valve disease. In apical and RV modified apical four chamber view, M-mode recording of long axis was taken from the lateral side of tricuspid annulus. In the RV modified apical view, we paid attention to take M-mode echo beam on the direction of tricuspid annulus motion. The maximum of tricuspid annulus. In the RV modified apical view, we paid attention to take M-mode echo beam on the direction of tricuspid annulus motion. The maximum of tricuspid annulus motion, which is regulated in response to the increase in loading conditions after MI. These results may indicate that RV dysfunction can progress as remote remodeling.

Conclusion: mTAPSE is a feasible and useful method for assessment of RV function, which shows better correlation with RVFAC.
Comparison of strain measurements with speckle tracking echocardiography and velocity vector imaging in detection of RV dysfunction in patients with ischemic cardiomyopathy: a validation study

J.H. Park, D.H. Kwon, T.H. Warwick, Cleveland Clinic, Cleveland, United States of America

Background: Though strain measurement has been introduced and used to measure LV function, it has been used to estimate RV function. However, variations in strain measurement by different vendors have limited the application of these techniques for assessment of RV dysfunction. We sought to compare two methods for the assessment of RV function, compared with cardiac magnetic resonance imaging (CMR).

Methods: We studied 25 patients (21 men, 66±12y) with ischemic cardiomyopathy who underwent both echocardiography and CMR. Global longitudinal strain of RV were measured on the same set of echo images. RV function was defined by RV ejection fraction (EF) = 50% by CMR.

Results: GLS-V and GLS-ST were correlated (r=0.76, P=0.001) and showed significant correlation with conventional echocardiographic parameters of RV (Table 1). RV strain correlated better with CMR-RVEF (r=0.75, P=0.001) than TAPSE (r=0.56, P=0.004). The best cutoff of GLS-V for detection of RV dysfunction was -16.9% (area under the curve = 0.89, P<0.001) with a sensitivity of 81.3% and specificity of 68%.

Conclusion: Although GLS-VI and GLS-STE show significant correlations with CMR-RVEF and other conventional echocardiographic parameters of RV function, GLS-VI appears superior to GLS-STE in the detection of RV dysfunction.

Evolution of classic parameters and deformation of right ventricular function 1 year after cardiac transplant


Right ventricular (RV) dysfunction causes more than 50% of all early cardiac complications in heart transplantation (HTx). However, few data on changes in RV in HTx and normal post-HTx time course have been published. We sought to describe the evolution of parameters of RV function during the first year after HTx.

Methods: We include 21 recipients since 2009. Mean age 50.3±14 years. For RV systolic functional assessment, the tricuspid annular systolic excursion (TAPSE), RV fractional area change (FAC), TDI systolic (S) velocity and Tei index were measured. RV longitudinal strain was measure in 6 RV segments (basal, mid, and apical segments of free wall and septum). We compared the first echocardiogram (7 days post-HTx) with the last one (year post-HTx). When EB showed ≥1R rejection echocardiogram was excluded.

Results: Evolution of echocardiographic parameters is shown in the table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GLS-V</th>
<th>GLS-STE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation Coefficient (r)</td>
<td>P-value</td>
<td>Correlation Coefficient (r)</td>
</tr>
<tr>
<td>CMR RVEF</td>
<td>-0.701</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV FAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAPSE</td>
<td>-0.574</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV Tei index</td>
<td>0.665</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Conclusion: Serial echocardiograms are useful and feasible to monitor the evolution of RV function after HTx. Most patients improve RV function 1 year after HTx. New techniques such as RV longitudinal strain offer an alternative to evaluate RV normalization.

Right ventricular regional systolic function and dyssynchrony in patients with pulmonary hypertension evaluated by three-dimensional echocardiography

D.H. Kong, X.H. Shu, C.Z. Pan, L.L. Cheng, D.X. Zhuo, J.B. Ge. Zhongshan Hospital of Fudan University, Shanghai, China, People’s Republic of China

Objective: Right ventricular (RV) function is of diagnostic and prognostic importance in patients with pulmonary hypertension (PH). The purpose of the present study was to evaluate RV regional systolic function and dyssynchrony in patients with PH using real-time three-dimensional echocardiography (RT3DE).

Methods: A total of 70 patients with PH and 26 age-matched controls were enrolled. RT3DE images were acquired and analyzed to obtain RV regional (inflow, body, outflow) function (EF) and to minimal systolic volume (Tmsv). The dyssynchrony index was calculated as the standard deviation of Tmsv in three RV segments corrected by heart rate (Tmsv-SD%). Conventional echocardiographic parameters including RV fractional area change (FAC), tricuspid annular peak systolic velocity (S), RV myocardial performance index (MPI) as well as echocardiography-estimated pulmonary artery systolic pressure (PASP) and pulmonary vascular resistance (PVR) were recorded. The patients with PH were divided into 3 groups as mild PH (PASP: 40mmHg<49mmHg), moderate PH (PASP: 50mmHg<69mmHg) and severe PH (PASP≥70mmHg). Results: Average RT3DE acquisition and analyze time was less than 10 minutes. RT3DE image quality was adequate to analyze in more than 95% of all the subjects. RV global and regional EF measured by RT3DE correlated with FAC, S and MPI in all PH patients. RV EF-inflow and EF-global was lower in all patients with PH (P<0.05), while EF-body was decreased in moderate and severe PH (P<0.05) and EF-outflow changed in severe PH (P<0.001). RV-SD% in mild/moderate PH was similar to that in the control group and was significantly lower in severe PH (P<0.05). RV-EF-inflow and RV-EF-global correlated with PASP (r=0.731, P<0.001) and EF-outflow changed in severe PH (P<0.001). RV-SD% in mild/moderate PH was similar to that in the control group and was significantly lower in severe PH (P<0.05). RV-EF-inflow and RV-EF-global correlated with PASP (r=0.731, P<0.001) and EF-outflow changed in severe PH (P<0.001). The relationship between other systolic parameters with PASP or PVR was weaker or not significant. The optimal cut-off value in determining PASP: 70 mmHg and PVR: 3-wood was 40.5% for EF-inflow 42.2% for RV-EF and sensitivity and specificity was 97% and 76%, 90% and 85% respectively.

Conclusions: In patients with PH, RV inflow and global systolic function was impaired in inverse relationship with PASP and PVR. RV systolic synchronicity was impaired in severe PH. Evaluation of RV regional systolic function using RT3DE method may play a potential role in the non-invasive assessment of the severity of PH.

A new morphological and quantitative approach of aortic atheroma: a preliminary 3D transesophageal echocardiography study

N. Hammoudi1, M. Ihaddaden2, L. Boubri3, C. Meuleman4, S. Edery5, P.L. Michel6, S. Alamowitch8, A. Cohen9, APHP - Hospital Pitie-Salpetriere, Department of Cardiology, Paris, France; 2AP-HP - University Hospital Ambroise Pare, Department of Cardiology, Boulogne-Billancourt, France; 3AP-HP - Hospital Pitie-Salpetriere, University Pierre & Marie Curie Paris VI, Dept of Cardiology, Paris, France; 4AP-HP - Hospital Saint Antoine, Paris, France; 5AP-HP - Hospital Tenon, University Pierre & Marie Curie Paris VI, Dept of Neurology, Paris, France; 6AP-HP - Hospital Tenon, University Pierre & Marie Curie Paris VI, Dept of Cardiology, Paris, France

Transoesophageal echocardiography (TEE) is the reference method for characterization of aortic atherosclerotic plaques (AAP) at risk of stroke. To evaluate the feasibility and contribution of 3D TEE in the evaluation of AAP, we prospectively included 82 patients referred for TEE. In addition to 2D, 3D study of AAP of the descending and horizontal thoracic aorta was performed. 308 AAP were identified in 2D. 98% of them were analyzed using 3D. We identified 3 morphological 3D types of plaques (figure). 2D characteristics of the 3D types were different: type I are thin and rarely calcified; type III are thicker and often calcified; type II have intermediate characteristics (Table). All AAP ulcerations seen in 2D were identified in 3D. Measurements from 3D correlated well with measurements performed on the 2D acquisitions (r=0.91; P<0.001). Area measurements of AAP were feasible in 58%, 14% and 23% of 3D types I, II and III respectively. The classification of AAP was not correlated with those of thickness in 2D.
3D types of plaques: 2D characteristics

<table>
<thead>
<tr>
<th>Type</th>
<th>I (n=115)</th>
<th>II (n=97)</th>
<th>III (n=89)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descending Aorta (n)</td>
<td>77</td>
<td>63</td>
<td>49</td>
<td>189</td>
</tr>
<tr>
<td>Horizontal Aorta (n)</td>
<td>38</td>
<td>34</td>
<td>40</td>
<td>112</td>
</tr>
<tr>
<td>Plaque thickness (π = 3.14159)</td>
<td>1.2±0.5</td>
<td>2.6±1.2</td>
<td>3.2±1.5</td>
<td>3.1-5.5, median with inter-quartile ranges</td>
</tr>
<tr>
<td>Net calcified plaques (%)</td>
<td>103 (80.5)</td>
<td>22 (17.2)</td>
<td>5 (2.3)</td>
<td>128</td>
</tr>
<tr>
<td>Vary calcified plaques (%)</td>
<td>3 (4.2)</td>
<td>13 (18.3)</td>
<td>55 (77.5)</td>
<td>71</td>
</tr>
</tbody>
</table>

Figure 1. 3D morphological types of plaques

In conclusion, 3D TEE is a feasible method and provides a new morphological and quantitative approach of AAP.

P4833
Assessment of the valvuloarterial impedance calculated with the use of 3-dimensional transosophageal echocardiography


Purpose: Valvuloarterial impedance (Zva), which represents combined valvular and vascular load opposing left ventricular ejection, has been investigated using 2-dimensional echocardiography. We sought to evaluate the difference of Zva between 2- and 3-dimensional echocardiography in patients with aortic stenosis (AS).

Methods: We analyzed 74 patients (62±10 years) with moderate to severe AS. Ellipticity of the left ventricular outflow tract (LVOT) and the sino-tubular junction (STJ) were calculated as the short axis dimension divided by the long axis one. The areas of LVOT and STJ were evaluated using circular formula (π x (x)^2) by 2-dimensional transthoracic echocardiography (2D-TTE) and using direct measurement by 3-dimensional transosophageal echocardiography (3D-TEE). Zva was calculated as the estimated left ventricular systolic pressure (systolic arterial pressure + the net mean pressure gradient taken into account post-stenotic pressure recovery) divided by the stroke volume index.

Results: Systolic blood pressure was 123±17 mmHg; peak EF 56±15%; and mean pressure gradient, 41±14 mmHg. The ellipticity of LVOT and STJ was 0.77±0.10 and 0.96±0.05. LVOT and STJ areas using 2D-TTE (3.6±1.1, 5.0±1.4 cm², respectively) was smaller than those using 3D-TEE (4.4±1.0, 5.4±1.3, respectively, p < 0.01); subsequently, energy loss index using 2D-TTE was smaller than that using 3D-TEE; consequently, Zva using 2D-TTE (4.2 mm Hg/m²/m², 31.5-55, median with inter-quartile ranges) was larger than that using 3D-TEE (3.4, 2.6-4.2, p < 0.01).

Conclusions: Two D-TTE overestimated the value of ELI relative to 3D-TEE due to the elliptical shape of the aortic root. It is desirable to use 3D TEE in the evaluation of Zva for risk stratification in patients with AS.

P4834
Transthoracic echocardiography to study the ascending aorta: in search of the best approach


Background and aim: Sequential transthoracic echocardiography (TTE) is used for a quantitative evaluation of the extent and severity of ascending aortic (AA) dilatation. The leading edge to leading edge has been recommended as the standard method to measure AA diameters, however other approaches have been proposed (inner to inner or outer to outer). Our aim was to analyze the accuracy of TEE by different methods in the evaluation of aortic dimensions in comparison with multidetector gated computed tomography (MSCT).

Methods: 80 patients with a severe aortic valvular disease (stenosis or regurgitation) were evaluated with a transthoracic echocardiography and MSCT to measure the thoracic aorta at different levels: sinuses of Valsalva, sino-tubular junction and ascending aorta. Three different echocardiographic methods were used: leading edge to leading edge, inner to inner and outer to outer and then compared to the ones obtained from MSCT. The interobserver and intraobserver variability was also performed.

Results: Transthoracic echocardiographic diameters were obtained in all patients but 3 (4%) because of poor acoustic window. The three methods showed an excellent interobserver and intraobserver variability, however, the inner to inner method presented the best reproducibility. Also, the inner to inner method showed the best correlation with MSCT for the assessment of thoracic aorta diameters (intrinsic correlation coefficient): sinuses of Valsalva 0.83, sinotubular junction: 0.87, and ascending aorta: 0.88. Mean difference between TTE and MSCT in measuring the ascending aorta were: inner to inner 0.25±0.6 mm, leading to leading -0.77±0.43, and outer to outer -3.2±1.23.

Conclusions: Transthoracic echocardiography is an accurate technique for the assessment and follow-up of thoracic aortic diameters in valvular patients. The inner to inner approach is the method that shows the best agreement with MSCT measurements of aortic root dimensions.

P4835
Incremental accuracy of transosophageal echocardiography over transthoracic approach for description of functional anatomy of aortic regurgitation


Background: Preoperative description of mechanisms of Aortic Regurgitation (AoR) is essential for planning valve sparing surgery (VSS). Either transosophageal (TEE) or transthoracic echocardiography (TTE) provide detailed anatomic view of aortic valve and ascending Aorta (AA) and information about dimensions and dynamic function of its components. Objective. To establish diagnostic value of multiplane TEE in comparison with TTE for definition of functional anatomy of AoR.

Methods: Using surgical observations as a reference, overall accuracy of TEE and TTE were calculated for both functional and anatomic classification of AoR in 51 patients operated on for AoR. Incremental accuracy of TEE over TTE was calculated as the ratio of the difference between their accurate diagnoses to the total number of cases examined and tested using McNemar’s test.

Results: Overall accuracy of TEE for functional classification was high (82%), but accuracy of TEE was higher (86%). Percentage of errors of TEE calculated by TEE was = 50% for all specific lesions of aortic valve and AA. Incremental accuracy of TEE was low (< 10%) except for diagnosis of aortic valve prolapse (AVP) associated with AA dilatation (16%) and for classification of AoR mechanisms (20.5%). Agreement between both modalities in AoR jet direction was good (kappa = 0.85). eccentric jet in 12/15 cases of AVP in TEE (p<0.0001) and in 11/15 in TEE (p<0.002).

Conclusions: Both TEE and TTE provide high degree of accuracy. Incremental accuracy of TEE for AVP and mechanisms of AoR is higher than VSS. Failure to identify pre-existing AVP may be responsible for unsuccessful operation. Therefore, preoperative TEE may help the surgeon to distinguish valves with high-repeal. In this setting it is advisable to repair from those that require replacement.

P4836
Gender difference in regression of myocardial hypertrophy after aortic valve replacement

E. Maruyama, K.H. Hirata, T. Yamano, K. Ishiibashi, T. Tanimoto, Y. Ino, T. Yamaguchi, T. Kubo, T. Imanishi, T. Akasaka. Wakayama Medical University, Wakayama, Japan

Background: In patients with aortic stenosis, pressure overload induces cardiac hypertrophy and fibrosis. Female sex influences cardiac remodeling and fibrosis in animal models. However, sex differences in hypertrophy regression after aortic valve replacement have not yet been studied.

Methods: We prospectively performed echocardiography before and 2 weeks, 3
and 6 months after operation in 47 patients, 28 women and 19 men, undergoing aortic valve replacement for isolated aortic stenosis.

**Results:** Preoperatively, women and men had similar ejection fraction (56 and 59%) and left ventricular mass (142 and 148 g/m²). Postoperatively, there was no difference in effective valvular orifice area index, mean transvalvular pressure gradient between men and women. Two weeks after operation, increased LV mass persisted in men (131 g/m²) although LV hypertrophy in women (119 g/m²) regressed to the similar level of 6 months (121 g/m²). LV mass in men was similar to those in women in 6 months after operation.

**Figure 1**

**Conclusion:** Women adapt to pressure overload quickly than men, while men caught up to women in 6 months after operation.

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**P4837**

**Age-related increase in aortic stiffness affects longitudinal myocardial function and ventricular-arterial coupling in both systolic and diastolic phase in normal subjects**

C. Palombo1, M. Kozakova1, C. Morazzo1, I. G. Fraser2.

1 Department of Internal Medicine, University of Pisa, Pisa, Italy; 2Wales Heart Research Institute and School of Medicine, Cardiff University, Cardiff, United Kingdom

**Background:** An increased arterial stiffness is an established mechanism contributing to LV dysfunction in hypertension and atherosclerotic disease. It is less clear whether an age-related increase in large artery stiffness affects LV performance even in young-to-middle-aged healthy subjects.

**The aim of this study was to evaluate the possible associations of aortic stiffness with LV longitudinal myocardial function and ventricular-arterial (V-A) coupling in normal subjects.**

**Methods:** A cohort of 134 subjects without clinical CV disease and atherosclerotic risk factors (69 males; mean age 39±13 years, range 18-61, LV EF ≥55%) was studied. Aortic stiffness was estimated by carotid-femoral pulse wave velocity (PWV) measured by Complior (Alam, Vincennes, France).

A CV ultrasound system (Alpha 10, Aloka, Tokyo, Japan) was used to measure LV mass (LVM) and LV longitudinal myocardial velocities (Vs, Ev, Av) by tissue velocimetry imaging (TVI) of the mitral annulus. The same US system was applied to estimate V-A coupling by means of a net wave intensity analysis (WI) algorithm implemented on carotid US. From simultaneous recordings of carotid diameter-derived and abdominal aorta blood pressure/diastolic blood pressure)/([Dmax-Dmin]/Dmin) where ln is natural logarithm, Dmax is maximum aortic lumen diameter, and Dmin is minimum aortic diameter. LV twist is the result of clockwise rotation of the LV base and counterclockwise rotation of the LV apex. It is well-known that stiffening of the aortic wall leads to changes in blood pressures compromising coronary perfusion and LV function. Three-dimensional (3D) speckle-tracking echocardiography (3DSTE) is a new clinical and with which LV rotational and twist parameters can be quantified non-invasively. The present study was designed to find a relationship between 3DSTE-derived LV rotation and twist and echocardiographic aortic elastic properties in healthy subjects.

**Conclusions:** The present study comprised 26 healthy volunteers (mean age: 36.0±11.3 years, 13 men). All subjects had undergone complete 2-dimensional Doppler echocardiographic study extended with aortic stiffness measurements and 3DSTE. From 3D datasets basal and apical LV rotation and LV twist were assessed. Echocardiographic aortic stiffness parameters were calculated from systolic and diastolic ascending aortic diameter and blood pressure data.

**Results:** Mean aortic area (0.131±0.094), aortic distensibility (3.61±2.54 cm²/dynes 10⁻⁶) and aortic stiffness index (ASI) (4.08±1.079) were in normal range, as well as basal (2.42±1.43 degrees) and apical LV rotation (8.56±1.43 degrees) and LV twist (11.01±5.19 degrees). Apical LV rotation correlated with aortic distensibility (r = -0.36, p < 0.05) and ASI (r = -0.41, p < 0.05), while LV twist showed similar correlation with ASI (r = -0.42, p < 0.05).

**Conclusions:** Aortic stiffness parameters are new clinical and with which LV rotational and twist parameters can be quantified non-invasively. The present study was designed to find a relationship between 3DSTE-derived LV rotation and twist and echo-cardiographic aortic elastic properties in healthy subjects.

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**P4840**

**A novel visualization of aortic arch stiffness using pulse wave tissue Doppler imaging: correlation with complicated aortic plaque**

K. Kurek1, T. Takahashi1, H. Saitou1, N. Kiriyasahi2, K. Ono1, T. Sasaki1, T. Niizeki1, S. Sugawara1, I. Kubota2, Nihonkai General Hospital, Sakata, Japan; 1Yamagata University School of Medicine, Yamagata, Japan

**Purpose:** Elevated aortic stiffness parameter (β) (A0D), defined as β = In (systolic blood pressure/diastolic blood pressure)/(Dmax/Dmin) [Dmax: maximum aortic lumen diameter, Dmin: minimum aortic lumen diameter by transesophageal echocardiography (TEE), and presence of complicated aortic arch plaque (CAP) provide prognostic information about cerebrovascular disease risk. However, this requires offline calculation and measurement of blood pressure during performance of TEE. Recently, ultrasound pulse wave tissue Doppler imaging (PWTDI) offers a new technique for assessing aortic wall pathology. The purpose of this study was to investigate whether this technique provides a new marker of aortic arch stiffness and correlates with CAP and atherosclerotic parameters.

**Methods:** We measured wall motion velocities in the aortic arch using PW-TDI in 198 consecutive cases that had undergone TEE with a 2.0mm sample volume placed at the lateral wall of the aortic arch. PW-TDI values for peak systolic expansion velocity (Vs) and peak systolic contraction velocity (Vd) were obtained from a long axis view of the aortic arch. CAP was defined as presence of atherosclerotic plaque ≥4mm or ulcerated plaque in aortic arch as assessed by TEE. We classified patients into two groups: those with CAP (n=80, 70±8years) and those without CAP (n=118, 59±13 years).

**Results:** Mean PWV was 7.8±1.7 m/s. PWV was directly related to β (r=0.71, p<0.0001) with age (r=0.71), systolic BP (r=0.47, p<0.0001) and diastolic BP (r=0.37) and negatively and inversely with age (r=-0.29, p<0.0002), Ev (r=-0.55, p<0.0001) and LVM (r=0.48, p<0.0001) and correlated with aortic distensibility (r = -0.36, p < 0.05) and ASI (r = -0.41, p < 0.05), while LV twist showed similar correlation with ASI (r = -0.42, p < 0.05).

**Conclusions:** Aortic stiffness parameters are new clinical and with which LV rotational and twist parameters can be quantified non-invasively. The present study was designed to find a relationship between 3DSTE-derived LV rotation and twist and echo-cardiographic aortic elastic properties in healthy subjects.

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**P4838**

**Significant recovery of left ventricular systolic function after transcatheter aortic valve implantation (TAVI) in aortic stenosis measured by longitudinal 2D strain echo after 1 year**

G. Baldenhohler, S. Spethmann, H. Dreges, M. Laule, V. Stangl, G. Baumann, K. Stangl, F. Knebel, Charité - University Medicine Berlin, Campus Mitte, Department of Cardiology and Angiology, Berlin, Germany

**Purpose:** Transcatheter aortic valve implantation (TAVI) is becoming an established treatment for patients with severe aortic stenosis (AS) and at high risk for conventional heart surgery. We aimed to measure left ventricular systolic function by a novel and sensitive method, the longitudinal 2D strain analysis, to detect even discrete changes after TAVI.

**Methods:** A total of 25 patients (9 male, 16 female) undergoing transfemoral TAVI (4 Edwards Sapien, 21 CoreValve prosthesis) were analysed. Echocardiography was performed at baseline, after 7days, 3 months and 1 year. The analysis included standard 2D and Doppler echocardiography, computed tomography stress test and global systolic and diastolic function as well as 2D Strain and Tissue Doppler echocardiography.

**Results:** The left ventricular ejection fraction (LVEF) was 51% (± 12%) at baseline, the mean pressure gradient was 44.4 (± 18.4) mmHg, and the valve area was 0.75 (± 0.24) cm². After 12 months global longitudinal peak systolic 2D strain increased significantly from -14.2±3.8 to -17.9±3.0%. This improvement of left ventricular function was seen in the apical four chamber (baseline -14.6±4.1% vs. -17.2±3.0% after 12 months), the apical three chamber (r=0.4±4.1% vs. -18.7±4.4%) and the apical two chamber view (r=13.9±4.2% vs. -18.2±3.7%). There was no significant difference in increased longitudinal function concerning particular left ventricular segments.

**Conclusions:** Our results show a significant improvement of the longitudinal systolic myocardial function as measured by 2D strain. The assessment of 2D strain appears to be a helpful and very sensitive novel technique to detect distinct improvement of myocardial function after TAVI.
without CAP (n=118, 63±13years). Vs and Vd were compared between groups and with conventional vessel parameters including cardio-ankle vascular index (CAVI, calculated from blood pressure and pulse wave velocity), ankle brachial pressure index (ABI), and carotid plaque score (PS, a composite index based on carotid artery plaque thicknesses).

**Results:** Comparing patients with vs. without CAP, Vs and ABI were significantly decreased (2.9±1.2 vs. 3.8±1.1 cm/sec, p<0.001; 1.6±0.5 vs. 2.0±0.8 cm/sec, p<0.001, 0.88±0.23 vs. 1.10±0.12, p=0.001), and Aoji and PS were significantly increased (17.4±12.5 vs. 12.3±6.8, p<0.01; 9.0±5.0 vs. 5.3±4.8, p<0.001, respectively). Furthermore, Vs and Vd were significantly correlated with Aoji (r=-0.381, p<0.001 and r=0.348, p<0.001, respectively), CAVI (r=-0.328, p<0.001) and Aoβ (r=-0.358, p<0.001, respectively), although there were no significant correlations with blood pressure, or heart rate.

**Conclusions:** Evaluation of Vs and Vd using PW-TDI in the aortic arch wall may be a novel and easily acquired indicator of aortic arch stiffness, and also correlates with several conventional vessel parameters.

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### High-resolution vascular ultrasound imaging for accurate measurement of carotid intima-media thickness

**Authors:** H. Taki1, T. Sakamoto1, K. Takii2, M. Yamakawa3, T. Shinra4, M. Kudo5, T. Sato5 on behalf of Kyoto University/Caron research project.

**Purpose:** Several clinical trials have used carotid intima-media thickness (CIMT) measured using the ultrasound B-mode image to monitor the progression of cardiovascular diseases. However, its accuracy and reliability is not enough to predict cardiovascular risk. In this study, we employ a non-invasive high-range-resolution ultrasound imaging method to improve the accuracy in ultrasound measurement of CIMT.

**Methods:** The imaging method used in this study is based on frequency domain interferometry (FDI), where optical coherence tomography also uses this technique in optics to acquire high-quality images of the human retina. We applied the FDI imaging method to both the simulation and experimental data. The experimental data were acquired by a commercial ultrasonographic device with a 7.5 MHz linear probe array. In vitro and in vivo experiments, we used a swine femoral artery and a living human carotid artery, respectively.

**Results:** The simulation study shows that CIMT value estimated using the conventional technique varies with the echo intensity returned from lumen-intima interface and that from media-endothelial interface. In contrast, the FDI imaging method succeeded to measure CIMT accurately. The FDI imaging method also depicted high-range-resolution images of a living human carotid artery in vivo and a fresh swine femoral artery in vitro, as shown in the figure. The in vitro results indicate that the FDI imaging method has the potential to estimate CIMT with an estimation error of less than 0.01 mm.

**Conclusions:** The simulation and in vitro results indicate that the FDI imaging method largely improves the accuracy in ultrasound measurement of CIMT. We believe that the FDI imaging method helps the appearance of a reliable indicator that predicts cardiovascular risk.

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### Real-time evaluation of the local carotid pulse wave velocity using ultrafast echo imaging in healthy population

**Authors:** M. Pernt1, M. Couade2, M. Frank2, T. Mirault4, A. Blanchard3, R. Niára3, M. Azizi4, J. Emmerich4, M. Tanner1, E. Messas1.

**Institute:** 1Institut Langevin, ESPCI ParisTech, Inserm, Paris, France; 2SuperSonic Imagine, Aix en Provence, France; 3AP-NP - European Hospital Georges Pompidou, Clinical Investigation Center, Paris Descartes University, Paris, France; 4AP-NP - Hospital Georges Pompidou, Vascular Medicine Unit, Paris Descartes University, Paris, France; 5AP-NP - European Hospital Georges Pompidou, Clinical Research Unit, URC HEGP, Paris, France.

**Background:** Pulse Wave Velocity (PWV) is widely used as an index of arterial stiffness and is recognized as a cardiovascular (CV) risk factor. Yet, its current assessment remains complex, limited to the systemic aortic stiffness evaluation, with a poor reproducibility. Ultrastar imaging (UF) with ultrasound newly emerged as a unique novel technique for tissue- imaging at ultra high frame rates (up to 10,000 images/s) which enables visualization of rapid events in the human body. By applying UF, and carotid on a healthy population for non-invasive, real-time local and direct measure of the carotid PWV, we aimed to establish normal values and to test its repeatability.

**Methods:** UF was performed on 102 healthy volunteers equally distributed for sex and age between 20 and 80 years old. 3 acquisitions of 1000 frames (1000 images/s frame rate) were performed on both common carotid arteries using conventional linear ultrasonic probe (IM3) connected to an ultrafast scanner (Aixplorer®). SuperSonic Imagine, France). Two pulse waves were identified: one at the ECG peak R wave (early-systole), the other at the ECG end T wave (end-systole). The two local carotid PWVs are derived from the tissue velocities (speckle tracking technique). The carotid-femoral PWV (cfPWV) was concomitantly measured by SphygmoCor®.

**Results:** The carotid PWVs, not differing from right to left side (p = NS), were 5.4±1.3 m/s in early-systole and 7.4±2.4 m/s in end-systole. Carotid PWVs measured by UF significantly increased with age (r=0.66, p<0.0001) similarly to cfPWV (r=0.60, p<0.0001). No difference between sexes was found in carotid PWVs in early-systole or cfPWV, but carotid PWVs in end-systole were higher in women than men (p = 0.015). Agreement between UF and SphygmoCor® was good; difference of 1.1±1.9 m/s (Bland-Altman analysis).

**Conclusion:** UF may be used as a novel non-invasive tool for the assessment of carotid PWV with a good repeatability on healthy volunteers. This technique has the advantages of measuring: (1) local PWV in early- and end-systole, and thus the variation of arterial stiffness during the cardiac cycle, (2) PWV with an ultrafast scanner without the need of external pressure sensor or dedicated device. This easy-to-use technique has a potential to spread PWV measurement in clinical practice, and to improve patient's CV risk evaluation consequently.

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### The relation between the CHADS2, CHA2DS2-VASc score and echocardiographic parameters of thromboembolism in patients with atrial fibrillation


**Institute:** 1Kyoto University Graduate School of Informatics, Kyoto, Japan; 2Kyoto University, Kyoto, Japan; 3Kyoto University Graduate School of Medicine, Osaka, Japan; 4Kyoto University, Kyoto, Japan; 5KYOTO University Graduate School of Medicine, Kyoto, Japan.

**Background:** CHADS2 score has been revised as CHA2DS2-VASc score for better embolic risk stratification in patients with AF. The aim of this study was to evaluate the relation between 2 clinical risk scores and echocardiographic parameters of embolism in AF patients.

**Methods:** 365 (M=305, mean age=55±10.4) patients with non-valvular AF who had trans-thoracic echocardiography and trans-esophageal echocardiography were enrolled. CHADS2 and CHA2DS2-VASc scores were calculated and correlated to echocardiographic findings. LA volume, LA emptying fraction (EF), LA annular velocity, LAA emptying velocity, LAA emptying fraction (E), the presence of dense SEC and thrombus in 2 patients. The patients with higher than 2 CHADS2 and CHA2DS2-VASc score was 65 and 182 respectively. Higher than 2 and CHADS2-VASc score only. The presence of SEC was related to echocardiographic parameters of thromboembolism.

**Results:** Increased LAV(LAVi)≥35(mL/m2) was found in 143 patients, impaired LAAEF(<30%) in 130 patients, decreased LAA emptying velocity(≤20cm/s) in 46 patients, decreased LAA EF(≤30%) in 136 patients, SECo in 100 patients and LA thrombus in 2 patients. The patients with higher than 2 CHADS2 and CHA2DS2-VASc score was 65 and 182 respectively. Higher than 2 CHADS2-VASc score only. The presence of SEC was related with increased LAV, low LAEF, the presence of SEC and thrombus. But the presence dense SEC and thrombus was associated with higher than 2 CHADS2-VASc score only (Table 1).

**Conclusion:** CHADS2 and CHA2DS2-VASc scores were correlated with echocardiographic markers of LA dysfunction. But LA dysfunction was associated with higher than 2 CHADS2-VASc score only. CHADS2-VASc score appears to be more sensitive than CHADS2 score in detecting high risk patients.
Assessment of left atrial deformation and dyssynchrony by three-dimensional speckle tracking imaging: comparative studies in healthy subjects and patients with atrial fibrillation

A. Mochizuki1, S. Yuda1, Y. Oh1, M. Kawakami1, J. Nishida1, A. Murakita2, S. Shimoshige1, K. Tsuchishii1, N. Watanabe2, T. Miura1.
1. Sapporo Medical University, 2nd Department of Internal Medicine, Sapporo, Japan; 2. Division of Laboratory Diagnosis, Sapporo Medical University Hospital, Sapporo, Japan; 3. Sapporo Medical University, Department of Clinical Laboratory Medicine, Sapporo, Japan

Background: Here we examined whether left atrial (LA) strains and synchrony are assessable by three-dimensional speckle tracking (3DS) and how the 3DS parameters are modified by atrial fibrillation (AF).

Methods: LA peak longitudinal, circumferential and area strains in systole (LSs, CSs, ASs) and those in late diastole (LSa, CSA, ASa) were determined by 3DS, and standard deviations (SD) of times to peaks of regional LA strains were calculated as indices of LA dyssynchrony. LA strain and synchrony in AF patients were compared with those in age-matched healthy subjects (controls).

Results: 3DS could measure LA strains in 75 (97%) of 77 healthy subjects and all 30 patients with AF (20 with paroxysmal AF (PAF) and 10 with permanent AF). The mean time of analysis was 3.5 ± 2.3 min for 3DS analysis, which was 18% shorter than for two-dimensional speckle tracking (2DS) analysis (4.0 ± 2.3 min, P < 0.05). In 3DS, inter-observer and intra-observer variabilities of LA strain were less than 10% and 12%, respectively. LSs (15.8 ± 6.9 vs 25.7 ± 12.2%, P < 0.05), CSs (19.2 ± 11.9 vs 27.1 ± 10.2%, P < 0.05), ASs (39.2 ± 23.0 vs 74.2 ± 20.2%, P < 0.05), and 2DS-LSs (22.3 ± 9.2 vs 32.6 ± 6.5%, P < 0.05) were significantly reduced in PAF than in age-matched controls (n=15), and further reduction of all of the parameters was observed in permanent AF. SDs of LSs, CSs, ASs were similar larger in PAF and permanent AF than in controls. LSa (6.6 ± 4.1 vs 12.0 ± 4.1%, P < 0.05), CSA (10.0 ± 8.0 vs 22.8 ± 8.1%, P < 0.05), and ASa (18.6 ± 24.2 ± 14.4%, P < 0.05) were also reduced in PAF than in controls. SDs of CSs and ASs were larger in PAF than in controls. Multivariate analysis, CSs (odds ratio [OR] 0.77, P=0.043), ASs (OR 0.90, P=0.011), SD of ASs (OR 1.15, P=0.039) and 2DS-LSs (OR 0.71, P=0.045) were independent factors for identifying PAF patients. ROC analysis indicated that optimal threshold to predict PAF was <32% for CSs, <57% for ASs, >22% for SD of ASs and <26% for 2DS-LSs. Using these thresholds, sensitivity and specificity of prediction of PAF was 80% and 95%, respectively. In the older more time consuming multiplane interpolation method by the Tomtec (Philips) with manual planimetry of 8 equidistant slices. These volumes were comparable with atrial volume determined by the QLAB 7.1 software (Philips) using a semiautomated border detection method. Results: Linear regression showed good correlation between volume and determined by Tomtec and QLAB software (r=0.97 and 0.89 respectively, P<0.001). Bland-Altman analysis of Tomtec versus QLAB volume determination showed rather narrow 95% limits of agreement (-12 to +16 cc for LA volume and -12 to +14 cc for RA volume) with a minimal slight bias of +1.8±7 cc and +0.8±6.5 cc respectively by the Tomtec method.

Conclusions: The QLAB 7.1 semiautomated border detection method shows good correlation for left and right atrial volume determination compared to the older more time consuming multiple interpolation method by the Tomtec software, with only slight underestimation. The results indicate that values of left and right atrial volume obtained by either algorithm can be compared, for example during follow-up examinations.
**Reference values of right atrial area and volume in healthy adults by two-dimensional echocardiography**

P. Herrn1, E. Grueining2, A. D’Andrea3, M. Claussens3, C. Nagel1, N. Ehlenke1, M. Faerler1, F. Prange1, E. Bossone4, C. Fischer1, N. Ehlken1, F. Maier1, F. Prange1, E. Bossone4, C. Fischer1, L. Thomas1

1University of Naples, Naples, Italy; 2Clinic Grosshansdorf, Grosshansdorf, Germany; 4University of Salerno, Salerno, Italy

**Background:** Right atrial (RA) size is important in several indications as for screening, diagnosis and follow-up assessment in patients with pulmonary hypertension. The objective of this paper was to define normal cut-off values for RA area by echocardiography in healthy subjects.

**Methods:** In this prospective study 880 healthy adult subjects (mean age 28 ± 5 years, 38% female, 395 top-level endurance athletes, 255 strength athletes and 230 non-athletes) were examined by echocardiography. For comparison we performed a meta-analysis of 9 previously published studies (1979-2010) describing RA area in healthy subjects (n=624). Statistical analysis included the calculation of 95% quantiles (for defining cut-off values) and the identification of possible confounding factors.

**Results:** Mean RA area was significantly larger in endurance athletes as in strength- and non-athletes (15.4 ± 2.0 cm² vs. 12.8 ± 1.6 cm² and 12.3 ± 2.0 cm², p<0.001). RA area correlated significantly with age, gender, body surface area and endurance exercise training and was similar in previously described 624 healthy adults (12.6 ± 3.8 cm²). 95% quantiles for RA area of all investigated non-endurance-trained subjects was 15.2 cm² (95% confidence interval 14.7-15.7 cm²) in females and 16.2 cm² (95% confidence interval 15.8-16.6 cm²) in males.

**Conclusion:** To our knowledge, this is the largest data set to describe RA size in adult healthy subjects (aged below 50 years). Cut-off values for RA area were significantly different in females (15 cm²) and males (16 cm²). This is clinically relevant.

**P4850**

**Evaluation of left atrial appendage dysfunction by strain imaging using transthoracic echocardiography**


**Background:** Left atrial appendage (LAA) thrombus is common cause of cardioembolic stroke. LAA dysfunction, which can induce thrombus formation, is usually evaluated by LAA peak flow velocity measured by transesophageal echocardiography (TEE), but it is an invasive procedure. Thereby we investigated whether LAA dysfunction can be evaluated by recently developed speckle tracking strain imaging using noninvasive transthoracic echocardiography (TTE).

**Methods:** Consecutive 55 patients, who underwent TEE to rule out thrombus or evaluate valvular disease, were enrolled. Immediately before TEE, we observed LAA by parasternal short-axis view using TTE. A following TTE parameter was evaluated as LAA dysfunction in this study: LAA shortening fraction which was defined as the difference between maximum and minimum longitudinal strain of LAA. We compared LAA shortening fraction with classical TEE parameter, LAA peak flow velocity and also analyzed the parameter in sinus or atrial fibrillation group separately.

**Results:** LAA shortening fraction was significantly correlated with LAA peak flow velocity measured by TEE (r=0.641, P<0.001). In addition, LAA shortening fraction was significantly worse in sinus rhythm group (35.6±15.3% vs 25.3±15.7%, P<0.001). LAA thrombi were found in three patients, whose rhythm were all atrial fibrillation and they were all on anti-platelet therapy. LAA shortening fraction of these three patients showed significantly worse value than the other patients in atrial fibrillation group (10.5±3.92% vs 26.7±15.7%, P<0.001).

**Conclusion:** LAA dysfunction including possible thrombus formation can be evaluated noninvasively by strain imaging using transthoracic echocardiography.
Prolonged atrial electromechanical conduction in hypertrophic cardiomyopathy and cardiac amyloidosis

Methods: We measured phasic LAV (max., min. and pre-atrial contraction (AC) volume) and emptying function (EF) (total, passive and active EF) and LA peak strain by 3-DSTE (Artida) which can provide time-LA volume curve with volume rates 3D-4KVs and by 2-DSTE from apical 2, 3 and 4-chamber views in 61 sub-
jects. Parameters were compared between 2-DSTE and 3-DSTE.

Results: LV and function were easily and rapidly obtained by 3-DSTE. There was a good correlation between LAV by 3-DSTE and LAV in 2, 3, and 4-chamber views and the average of the three views by 2-DSTE (r=0.76, 0.80, 0.78 and 0.84, p<0.001, respectively). LA total and passive EF in 4-chamber view by 2-
DSTE was underestimated compared to 3-DSTE despite no difference in LA peak strain. Phasic LAV in 3-chamber view by 2-DSTE was decreased and LA phasic function was increased compared to 3-DSTE (table).

Table 1. LA function and structure assessed by 3-D and 2-D speckle tracking

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3-DSTE</th>
<th>2-DSTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max. LAV, ml</td>
<td>52.2±13.4</td>
<td>53.3±18.4</td>
</tr>
<tr>
<td>Min. LAV, ml</td>
<td>28.0±9.4</td>
<td>28.2±11.9</td>
</tr>
<tr>
<td>LVAC LAV, ml</td>
<td>41.6±11.2</td>
<td>42.3±16.0</td>
</tr>
<tr>
<td>Total EF, %</td>
<td>46.5±9.1</td>
<td>47.3±14.0</td>
</tr>
<tr>
<td>Passive EF, %</td>
<td>30.8±5.1</td>
<td>19.5±11.6</td>
</tr>
<tr>
<td>Active EF, %</td>
<td>32.7±10.2</td>
<td>24.8±14.2</td>
</tr>
<tr>
<td>LA strain</td>
<td>19.7±5.7</td>
<td>22.9±9.6</td>
</tr>
<tr>
<td>LA global strain</td>
<td>17.6±7.5</td>
<td>19.5±3.8</td>
</tr>
</tbody>
</table>

*p<0.05 vs. 3-DSTE.

Conclusion: Although LA volume and function assessed in 3 and 4-chamber view by 2-DSTE was found to be over underestimated compared to 3-DSTE, those by 2-chamber view and the average of 3 views were comparable to 3-DSTE and revealed more reliable for the accurate diagnosis. This study demonstrated that 3-DSTE will be more promising method in assessing LA structure and function than 2-DSTE.

P4852

Prolonged atrial electromechanical conduction in hypertrophic cardiomyopathy and cardiac amyloidosis

C. Ito, K. Inoue, K. Nishimura, A. Fuji, T. Nagai, J. Suzuki, A. Ogiomo, J. Higaki. Division of Cardiology, Department of Integrated Medicine and Informatics, Ehime University Graduate, Toon, Japan

Left atrial (LA) remodeling is characterized by atrial dilatation, depressed contraction and interstitial fibrosis. Particularly, hypertrophic cardiomyopathy (HCM) and cardiac amyloidosis are representative disorders of left ventricular hypertrophy to progress LA remodeling. Recently, atrial electromechanical conduction time (EMT) measured by tissue Doppler method was reported as the useful parameter of recurrence of atrial fibrillation after cardioversion. However, this method has limitations having angle dependency and tethering effects by adjacent cardiac motion.

Methods: This study was aimed to clarify the impact of EMT measured by speckle tracking echocardiography on LA remodeling and outcomes in 38 patients with HCM and cardiac amyloidosis. LA EMT, but not LA volume index, was statistically different between amyloidosis and control groups, EMT was significantly related to LA volume index (R2=0.25, p<0.01) and LA global strain was not a predictor of CRT response (12.6±5.2 vs 11.3±5.1%, p=0.33). There were no significant correlation between LA longitudinal strain and left ventricular Yu index.

Conclusions: In our population LA longitudinal strain improved significantly with CRT.

P4854

The role of 3D echo in accurate measurement of the left atrial appendage size

S.Z. Ziekel1, H. Claussen2, J. Newton1. 1John Radcliffe Hospital, Department of Cardiology, Oxford, United Kingdom; 2Great Ormond Street Hospital for Children, London, United Kingdom

Purpose: Device occlusion of the left atrial appendage (LAA) in patients at high risk of thromboembolic stroke but unable to be anticoagulated has emerged as an established therapeutic option. 2D transesophageal echocardiography (TOE) is currently used to determine the appropriate size of an LAA occluder device. The LAA anatomy is highly variable and the orifice is oval shaped and 3D echocardiography may underestimate the LAA ostium even if a range of measurements are taken. This may result in subtotal occlusion of the ostium and residual flow into the LAA. Given the oval shape of the LAA ostium, the question of whether 3D TOE is more accurate at delineating the size and the shape of the LAA.

Method: Standard 2D LAA views from the mid-esophageal position from 30 – 130 degrees, and 3D zoom acquisitions using Philips iE33 platform with an X7-t probe were obtained in 74 patients. The LAA orifice, left upper pulmonary vein and lateral portion of the mitral annulus were included in the region of interest. 3D images were acquired and processed in Qlab7.1. Using multiplanar reconstruction (MPR) the en-face views LAA orifice was identified. The longest and shortest dimensions of the LAA ostium were measured. The LAA working depth was measured perpendicularly from the ostium to the back wall of the LAA. The data was further analyzed for differences in means between the 2D and 3D technique.

Results: All LAA orifices were oval in shape. The mean LAA orifice diameter on 2D imaging was significantly smaller at 17.3mm (4.3mm, 11.0–22.9mm) in comparison to 3D MPR diameter of 25.1mm (6.5mm, 11.7–46.8mm). The working LAA depth was similar using both methods: 2D 18.3mm (5.0mm, 7.8–36.0mm), MPR 18.8mm (6.3mm, 7.8–39.8mm).

Conclusion: Accurate LAA orifice measurement is important for successful implantation and complete occlusion of the LAA. The LAA orifice is oval in shape and 2D TOE may significantly underestimate the diameter of the LAA orifice by 30%. This has implications for full visualization and accurate measurement of the LAA orifice. Such improved measurement techniques facilitate accurate device selection during LAA occlusion.

P4855

Evaluation of right atrial dysfunction using 3D echocardiography in patients with pulmonary artery hypertension


Purpose: In patients with pulmonary artery hypertension (PAH), right ventricular pressure overload causes right heart failure (RHF). In these patients, right atrial pressure (RAP) increased, and cardiac index (CI) decreased. RAP CI, and serum brain natriuretic peptide (BNP) were independent predictors to evaluate the prognosis. We sought to investigate the degree of right atrial (RA) overload and the severity of RHF using 3-dimensional (3D) right atrial index by 3D echocardiography.

Methods: We performed 3D echocardiography and right heart catheterization in 53 PAH patients (age:41±15 years). We measured right atrial end-diastolic volume index (3DRAEVI), right atrial end-systolic volume index (3DRAESVI), and right atrial ejection fraction (3DRAEF) by 3D-echocardiography. Mean right atrial pressure (mRAP) and cardiac index (CI) by right heart catheterization, and serotonin were measured.

Results: mRAP was 8.7±6.0 mmHg (range 1 to 30mmHg), 3DRAEVI was 21.4±20.1 ml, 3DRAESVI was 37.2±26.4 ml, and 3DRAEF was 55.2±15.3%.
There were significant positive correlations between mRAP and 3DRAEDVI (r = 0.63, p < 0.001) and CI and 3DRAEFP (r = 0.39, p = 0.01). There were significant negative correlations between CI and 3DRAEDVI (r = 0.30, p = 0.02) and CI and 3DRAEFP (r = 0.35, p = 0.02). There were significant positive correlations between CI and 3DRAEDVI (r = 0.30, p = 0.01). There were significant positive correlations between BNP and 3DRAEDI (r = 0.58, p < 0.01), 3DRAESDI (r = 0.64, p < 0.01). There were significant negative correlations between BNP and 3DRAEF (r = 0.70, p < 0.01).

Conclusions: 3D echocardiography was useful for noninvasive evaluation of RA overload and severity of RHF in patients with PAH.

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**Detection of pulmonary congestion using the newly-developed pocket-sized transthoracic echocardiographic imaging device in patients with suspected heart failure**

H. Ge1, R. Takemoto1, N. Toh2, S. Uwagawa3, N. Watanabe3, Y. Tanabe4, S. Nagase4, S. Sano5, H. Ito3, Okayama University Hospital, Okayama, Japan; 2Okayama University, Department of Cardiovascular Medicine, Okayama, Japan; 3Okayama University, Department of Cardiovascular Surgery, Okayama, Japan

**Background:** Ultrasound lung comets (ULCs) assessment is simple, fast and clinically useful for the evaluation of pulmonary congestion in patients with heart failure (HF). Recently-developed pocket-sized transthoracic echocardiographic imaging device has allowed physicians to perform screening study in a variety of clinical settings. The aim of this study is to investigate the feasibility and usefulness of pTTE for the evaluation of ULCs in patients with HF.

**Methods:** This prospective study consisted of 51 consecutive patients (25 female, 66 ± 15 years) with known or suspected HF who underwent the standard TTE (sTTE) and pTTE. Exclusion criteria included the following: patients with hemodynamics, recent cardiac surgery, known pulmonary diseases. The examination of pTTE was performed with the VSCAN (GE Medical Systems). Immediately after pTTE study including the assessment of ULCs, all patients underwent sTTE and underwent another sonographer blinded to the results of pTTE study. We defined ULC score according to the number of ULCs observed in each 4 segments (right upper & lower, left upper & lower) of chest wall as follows; None: 0, Mild (the number of ULCs: 0-5); 1, Moderate (6-10); 2, Severe (11-3). The sum of these scores in each 4 segments is defined as total ULC score (0-12 points). Clinical diagnosis of congestive HF was based on the Framingham criteria, with all corroborative information reviewed by 2 cardiologists blinded to the information of ULCs and sTTE images.

**Results:** ULCs examinations by pTTE were successfully completed in all cases (feasibility 100%), the time needed for the ULCs assessment is about 5 minutes. ULCs were observed on pTTE in 34 patients (67%). There was a highly significant correlation between the total ULC score evaluated by pTTE and sTTE (r = 0.93; Spearman, p < 0.0001). The patients with ULCs had lower left ventricular (LV) ejection fraction and larger IVC diameter, left atrial volume index. BNP values were also well correlated with ULC score evaluated by pTTE (r = 0.60; Spearman, p < 0.0001). Receiver Operating Characteristic (ROC) curve analysis revealed the relationship between ULC score evaluated by pTTE and the diagnosis of HF (AUC: 0.93). The ULC score of 2 was found to maximize the diagnostic accuracy with a sensitivity of 88% and a specificity of 83%. The ULC score of 4 had a sensitivity of 60% and a specificity of 100%.

**Conclusion:** Detection of pulmonary congestion using the newly-developed pTTE imaging device in patients with HF is feasible and accurate.

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**Atrial fibrillation and atrial function / New ultrasound technology**

**Supranormal diastolic function in elite endurance-athletes is related to left atrial geometry and function**

M. Florescu1, C. A. Enescu1, D. Mihalcese1, R. Mincu1, R. C. Rimbas1, L. S. Magda1, M. Cinteza2, D. Vinereanu2, 1University of Medicine and Pharmacy Carol Davila, Bucharest, Romania; 2University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

**Endurance-training is associated with specific structural and functional cardiac changes. Supranormal diastolic function in athletes was demonstrated previously, but data on left atrial (LA) geometry and function are lacking. Our aim was to investigate complex changes in LA structure and deformation assessed by 2D strain (speckle imaging) and 3D strain (STI), and their relation with left ventricular (LV) diastolic properties in elite endurance-athletes.**

**Methods:** 64 subjects (21 ± 4 years, 44 male) were enrolled: 40 endurance athletes and control group of 24 age- and sex-matched sedentary subjects. LA geometry was assessed by volumes at the MVO (MV0, MVC, MVCV), and at the beginning of the P wave (PV), while LA function by passive EF (pEF) as MVCV/MV0, expansion index (Eix) as MV0/MVC-MVCV, and active EF (aEF) as PV-MV0/PV. LA deformation was measured by STI: contraction from peak negative strain (PNS) and strain rate (PNSR); relaxation from peak positive strain (PPS) and strain rate (PPSR), and global strain (GS). LV diastolic function was assessed by E/A ratio, flow propagation velocity (FPV), E/FPV, SD (from pulmonary vein flow), long-axis early diastolic velocity (E), and E/E'.

**Results:** Athletes had 'supranormal' LV diastolic function (EA=2±3.0±0.5 vs 1.5±0.2; PV=74±14 vs 37±9 cm/s; E/A=1.3±0.7 vs 1.8±1.1; SD=0.7±0.2 vs 1.3±0.1; E/E'=4.8±1.2 vs 5.9±2.1, all p<0.05). There were changes in LA geometry and optimized LA deformation in athletes (see table). Univariate analysis showed that GS was correlated with E', E/A and FPV (r=0.71; r=0.52; and r=0.58, all p<0.05) and with E/A and SD (r=0.64 and r=0.68, both p<0.01). By multiple stepwise regression analysis, best independent determinant of GS was E/E' ratio (r=0.62, r=0.48, p<0.01).

**Conclusions:** Elite endurance-athletes had a ‘supranormal’ LV diastolic function, rather than assessing intrinsic LA booster function, rather than assessing intrinsic LA reservoir and conduit function, because of its less dependence on corresponding LV S and SR during LA contraction.

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**Detection of pulmonary congestion using the newly-developed pocket-sized transthoracic echocardiographic imaging device in patients with suspected heart failure**

**Atrial fibrillation and atrial function / New ultrasound technology**

**Detection of pulmonary congestion using the newly-developed pocket-sized transthoracic echocardiographic imaging device in patients with suspected heart failure**

C. Prinz, J. Dohrmann, F. Van Buuren, T. Bitter, N. Bogunovic, D. Horstkotte, L. Faber. Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany

**Aims:** To investigate intra- and inter-rater variability of expert-users interpreting hand-held echocardiographic studies (HAND).

**Methods:** We scanned 330 consecutive patients both with HAND and high-end scanners (HIGH). Imaging studies were interpreted independently by two blinded level III echocardiographers. HIGH readings served as gold-standard. Segmental endocardial-border delineation was scored to describe image quality. Assessment
Effect of through plane motion for the accuracy of diagnostic accuracy of pocket-size handheld echocardiography

M. Takeuchi, K. Otori, M. Iwataki, H. Kurekai, K. Kaku, N. Haruki, H. Yoshitani, Y. Otsubu. University of Occupational and Environmental Health, School of Medicine, Kitakyushu, Japan

P4860

Purpose: Measurements of 2D circumferential strain (CS) is affected by loss of speckles due to through plane motion, raising the doubt regarding its accuracy. 2D speckle tracking echocardiography (STE) may eliminate this limitation. If through plane motion affects 2D speckle tracking analysis, we hypothesized worst correlation and largest mean difference of CS were observed at baseline level, and best correlation and least difference of CS were noted in the apical level between 2DSTE and 2DSTE measurements.

Methods: We obtained 2D basal, middle and apical short-axis images, and 3D full-volume datasets (GE, Vivid E9) in 44 patients with various cardiovascular disease (mean age 62±19 years, 23 men). Using 2D/3D speckle tracking software, segmental CS at end-systole was measured. Global CS and average CS at each of 3 LV short-axis levels were calculated in both modalities. Using anatomical M-mode, we measured mitral annular displacement (MAD) on apical 4-chamber view, and patients were divided into two groups according to the median value of MAD (9.4mm) for investigating the effect of through plane motion.

Results: Although a good correlation of global CS was noted between the two methods (r=0.80, p<0.01), mean values were significantly higher in 3DSTE compared to 2DSTE (-18.4±6.3 vs. -14.7±5.0, p<0.001). Correlation of averaged CS and their mean bias between the two methods were 0.66±0.61 at basal level, 0.78±0.17 at midwall level, and 0.60±0.23 at apical level, respectively. Correlation of global CS between the two methods was higher in group of patients who showed MAD less than 9.4mm (r=0.81) compared to group of patients with MAD >9.4mm (r=0.61).

Conclusions: Our results suggest that through plane motion affects CS measurements using 2DSTE, especially in subjects with normal longitudinal function.

Abstract P4862 – Table 1. Main results

<table>
<thead>
<tr>
<th>Parameter (scoring)</th>
<th>Vscan score</th>
<th>Vscan FS score</th>
<th>IE33 score</th>
<th>P Vscan vs IE33</th>
<th>P Vscan FS vs IE33</th>
<th>Kappa Vscan vs IE33</th>
<th>Kappa Vscan FS vs IE33</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV systolic function 1-5 (hyperdynamic/normal/mild/moderate/severe)</td>
<td>2.8±1.3</td>
<td>2.9±1.2</td>
<td>2.9±1.2</td>
<td>0.32</td>
<td>0.72</td>
<td>0.89</td>
<td>0.90</td>
</tr>
<tr>
<td>LV size 1-3 (small/normal/dilated)</td>
<td>2.2±0.5</td>
<td>2.1±0.4</td>
<td>2.1±0.5</td>
<td>0.06</td>
<td>0.23</td>
<td>0.59</td>
<td>0.59</td>
</tr>
<tr>
<td>RV systolic function 1-2 (normal/reduced)</td>
<td>1.1±0.3</td>
<td>1.1±0.3</td>
<td>1.2±0.4</td>
<td>0.06</td>
<td>0.12</td>
<td>0.69</td>
<td>0.69</td>
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<tr>
<td>RV size 1-3 (small/normal/dilated)</td>
<td>2.1±0.4</td>
<td>2.0±0.4</td>
<td>2.0±0.5</td>
<td>0.62</td>
<td>0.028</td>
<td>0.39</td>
<td>0.46</td>
</tr>
<tr>
<td>Aortic stenosis Absent/present</td>
<td>1.3±0.5</td>
<td>1.3±0.6</td>
<td>1.2±0.5</td>
<td>0.07</td>
<td>0.013</td>
<td>0.62</td>
<td>0.69</td>
</tr>
<tr>
<td>Mitral stenosis Absent/present</td>
<td>1.6±0.7</td>
<td>1.4±0.7</td>
<td>1.4±0.7</td>
<td>0.001</td>
<td>0.29</td>
<td>0.56</td>
<td>0.61</td>
</tr>
<tr>
<td>Tricuspid regurgitation 1-4 (NS/mild/moderate/severe)</td>
<td>1.7±0.7</td>
<td>1.5±0.7</td>
<td>1.4±0.7</td>
<td>0.003</td>
<td>0.70</td>
<td>0.55</td>
<td>0.69</td>
</tr>
<tr>
<td>LV size 1-3 (small/normal/dilated)</td>
<td>2.3±0.6</td>
<td>2.3±0.5</td>
<td>2.2±0.5</td>
<td>0.040</td>
<td>0.64</td>
<td>0.44</td>
<td>0.57</td>
</tr>
<tr>
<td>Pericardial effusion 1-4 (none/mild/moderate/severe)</td>
<td>1.2±0.5</td>
<td>1.3±0.7</td>
<td>1.3±0.6</td>
<td>0.41</td>
<td>0.53</td>
<td>0.81</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Mitrval and aortic stenosis = non-quantitative, so no mean ± SD values. Vscan FS = Vscan mpg images viewed on a computer in full-screen format; LV = left ventricle; RV = right ventricle; TV = inferior vena cava; NS = no or non-significant regurgitation. Kappa: <0.2 = poor; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = good; >0.80 = excellent agreement.
Results: A total of 104 patients were studied. There was excellent agreement between the Vscan and the high-end echocardiograph for left ventricular systolic function and pericardial effusion (Kappa 0.89 and 0.81 respectively), and agreement was good or moderate for evaluating aortic, mitral and tricuspid valve function and left ventricular size (Kappa 0.55-0.66). Visualization of the Vscan images in full-screen format on a PC did not in general confer added value.

Conclusion: The Vscan used by a trained cardiologist has good diagnostic accuracy in the emergency setting compared to a high-end echocardiograph, despite small screen size and lack of pulse-wave and continuous Doppler.

P4863 Inter-vendor variability for measurements of left ventricular strain using two-dimensional speckle tracking analysis: a study of Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE)

K. Takigiku1, M. Takeuchi2, S. Nakatani2, C. Izumi3, S. Yuda4, K. Sakata5, N. Hitoe6, K. Tanabe7, Nagano Children’s Hospital, Nagano, Japan; 6Kyorin University, School of Medicine, Tokyo, Japan; 7Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan; 8Shimane University, Faculty of Medicine, Izumo, Japan

Purpose: Two-dimensional speckle tracking analysis of the left ventricular (LV) strain has been widely used for the evaluation of the LV mechanics. However, controversy exists regarding the inter-vendor agreement of 2D strain. We aimed to determine inter-vendor variability of LV 2D strain in healthy subjects.

Methods: Among 817 healthy subjects enrolled in JUSTICE, inter-vendor variability was determined by analyzing echocardiographic images in 193 subjects using systems from 2 of 3 different vendors (V1 vs. V2, n=47; V1 vs. V3, n=96; V2 vs. V3, n=50). The acquired images included 3 short axis views and 3 apical views. With the 2D speckle tracking software from each vendor, radial, circumferential and longitudinal strain were measured using an 18-segment model, and global 2D strain values were determined. Agreement was assessed using intraclass correlation coefficients (ICCs) with its limit of agreement (LOA) and Bland-Altman analysis.

Results: Global 2D strains were significantly different between the two vendors in majority of comparisons. In each two-vendor comparison, the ICCs of global strain were poor to fair (Table). The ICC was the worst for the global radial strain, and the best for the global longitudinal strain.

Table 1. Inter-vendor variability

<table>
<thead>
<tr>
<th></th>
<th>V1</th>
<th>V2</th>
<th>Bias (95% LOA)</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRS</td>
<td>53.7±10.7</td>
<td>37.4±9.11</td>
<td>16.3 (–4.7 to 37.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>GLS</td>
<td>27.1±2.33</td>
<td>19.7±2.71</td>
<td>–1.5 (–15.1 to 11.1)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Conclusions: 2DSTE-derived LV strain measurements are highly vendor-dependent. Due to a low inter-vendor agreement, 2D strain data are not interchangeable when conducting a longitudinal follow-up or across-sectional assessment of the LV myocardial deformation.

P4864 Usefulness of automated function imaging to detect myocardial ischemia during dipyridamole stress echocardiography

C. Zito, M. Cusma-Piccione, S. Tripesi, M. Mohammad, G. Di Bella, G. Oronte, P. Crea, A. Masadifati, G. Falanga, S. Carerj

Clinical-Experimental Department of Medicine and Pharmacology, University of Messina, Messina, Italy

Purpose: Dipyridamole stress echo (DSE) is currently used as an alternative to dobutamine stress echo in detecting coronary artery disease (CAD). However, the lower sensitivity, especially in single-vessel disease and the high inter-observer variability of wall motion (WM) analysis are two major drawbacks of DSE. We aimed to investigate the usefulness of global longitudinal strain (GLS) by automated function imaging (AFL, Echopac GE Horten, Norway) to improve diagnostic accuracy and reproducibility of DSE in detecting myocardial ischemia.

Methods: 37 patients (16 men, 67±9 years), with intermediate/high pre-test CAD probability, underwent DSE followed by coronary angiography within one week. Diagnostic accuracy in the identification of CAD, evaluated through sensitivity, specificity and positive/negative predictive values (PPV/NPV), was analyzed for wall motion score index (WMSI) and GLS. Optimal cutoff value to define normal

GLS was -20%. Concordance between each diagnostic method and the reference standard, represented by coronary angiography, was evaluated by kappa score and Kendall’s tau coefficient. Furthermore, the agreement between two observers with different experience in DSE was assessed by using Cohen’s k coefficient.

Results: Prevalence of significant CAD (more than 50% of luminal narrowing) was 70% and prevalence of single vessel disease was 60%. Mean GLS significantly decreased from rest (-17±4.5%) to peak DSE (-15±4.4%, p<0.001). Sensitivity, specificity, PPV and NPV for WMSI were respectively: 50%, 67%, 83% and 29%. However, combination GLS and WMSI had the highest sensitivity (70%), specificity (70%), PPV (87.5%) and NPV (40%). Furthermore GLS showed higher concordance with coronary angiography (k = 0.75; Kendall’s tau = 0.78) than WMSI (k = 0.11; Kendall’s tau = 0.14). In addition, there was a good agreement between a trainee and an expert observer by using GLS in comparison with WM analysis for images interpretation at rest (k = 0.61 for WM, k = 0.57 for GLS) whereas the agreement significantly improved for images interpretation at peak stress (k = 0.50 for WM, k = 0.70 for GLS).

Conclusions: Combination of GLS and WMSI resulted in significant increase in the accuracy of DSE to detect myocardial ischemia, especially with regard to the test sensitivity. Besides, GLS analysis provides an increase of the agreement for images interpretations between experienced and non-experienced observer, especially at peak stress. Hence, adding routinely GLS analysis during DSE could probably be helpful for more accurate patient risk stratification.

P4865 Changes in left ventricular strain during exercise stress echocardiography in healthy subjects: a speckle tracking echocardiography study

M. Camelii, F.M. Righini, M. Lisi, S. Benincasa, S. Mondillo. University of Siena, Department of Cardiovascular Diseases, Siena, Italy

Background: Stress echocardiography is widely used but its major limitation is the subjective interpretation of wall motion changes. Speckle tracking echocardiography (STE) offers a quantitative method with the semiautomatic evaluation of the different components of myocardial deformation. The aim of our study was to evaluate changes in left ventricular (LV) systolic performance during the different steps of exercise stress echocardiography (ESE) in a population of healthy subjects.

Methods: ESE was performed in 25 healthy subjects (mean age 26.2±3.1) in the semi-supine position on a tilting ergocycloergometer: the workload was increased every 2 minutes by 25W, up to the achievement of 100W. Echo was performed at each stage of the physical exercise and during the recovery phase. LV global longitudinal strain was calculated averaging values of all myocardial segments in apical 2-, 3- and 4-chamber views; radial, circumferential strain and LV twisting were obtained from the parasternal short-axis views at basal and apical levels.

Results: Mean heart rate of 164±21 bpm was reached. All LV parameters explored increased significantly, reaching the maximum value at peak exercise. Subjects showed a relative increase of strain values respect to baseline of 48.2±14.1% for LV global radial strain (baseline: 23.9±8.6, peak value: 35.4±10.1%), 43.8±12.2% for LV twisting baseline: 10.5±3.6, peak value: 15.5±4.7%, 34.9±8.6% for global circumferential strain (baseline: 24.3±6.6, peak value: 32.8±9.6%) and 13.4±4.9% for global longitudinal strain (baseline: 20.1±2.9, peak value: 22.8±2.8%).

Conclusions: This is the first study that reported the normal range values and the percentages of increment of LV strain that physiologically occurs during ESE, fixing a reference point to better interpret pathological studies.

Figure 1. Normal exercise cardiac performance
Hypertrophic cardiomyopathy in Iceland: MYBPC3

B. Adalsteinsdottir, P. Teekakirikul, J.-G. Seidman, C.E. Seidman, B.J. Maron, R. Danislen, G.T. Gunnarsdottir

The aim of this study was to investigate Hypertrophic Cardiomyopathy (HCM) in Iceland, identify sarcomeric mutations causing HCM and understand the phenotype-consequence of these mutations. Iceland, an island with the population of 300,000 offers a great opportunity to investigate this heterogeneous disease in a whole population.

Methods: The study cohort consisted of all patients having clinical diagnosis of HCM in Iceland from 1997-2010. Patients were searched through medical records and echocardiographic database at the main hospitals and cardiologists private clinics. All HCM patients were invited to have genetic testing and an interview. Samples were screened for the MYBPC3 c.927-2A>G mutation previously described in two Icelandic families. If negative, targeted sequencing of 8 HCM genes and the GLA gene was performed. Information on phenotype and clinical parameters was obtained from patient medical records and interviews.

Results: 17 patients with HCM diagnosis were identified, 156 were still alive. 12 had already been genotyped and 119 accepted to participate in the study. 72 (55%) had the c.927-2A>G mutation in MYBPC3. 4 had other variants in MYBPC3, one was diagnosed with a variant in MYH7. 5 were diagnosed with variants in the GLA gene. Fabry disease has been confirmed in three of them. Clinical data on patients with c.927-2A>G mutation in MYBPC3 are shown in the table 1.

<table>
<thead>
<tr>
<th>Age at diagnosis (range)</th>
<th>Average LV thickness (mm)</th>
<th>Age at first adverse event</th>
<th>Atrial Fib 4KHz</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.4 (9-72)</td>
<td>21.7</td>
<td>51 (17-72)</td>
<td>12 (16.7%)</td>
</tr>
</tbody>
</table>

Sudden cardiac death (SCD), ICD implant, myectomy, alcohol septal ablation.

Atrial Fibrillation 12 (16.7%)

Conclusion: The c.927-2A>G mutation in MYBPC3 is the leading cause of HCM in Iceland, accounting for 55 of cases. The c.927-2A>G mutation causes serious disease with an average age of onset of 40 yrs. We hypothesize that all 72 individuals with the c.927-2A>G mutation are offspring of a common ancestor. At present, we cannot estimate when this common ancestor lived in Iceland, but we expect from inheritance studies, that he/she lived more than 5 generations ago.

Hypertrophic cardiomyopathy in muscular dystrophy: genetically caused structural weakness vs. acquired myocarditis? Answers based on a siblings study


Background: Muscular dystrophy type Duchenne (DMD) and type Becker (BMD) represent the most common X-linked genetic diseases. Apart from progressive proximal skeletal muscle weakness, DMD and BMD are characterised by cardiac muscle involvement with a characteristic pattern of myocardial damage affecting the subepicardium of the left ventricular (LV) free wall. The molecular pathomechanism leading to cardiomyopathy is still unclear: the fragility of the cell membrane caused by deficient sarcolemmal dystrophin may predispose cardiomyocytes to cell death in response to mechanical stress. However, it is also argued that DMD/BMD patients are more susceptible to myocarditis which in turn may also cause subepicardial damage in the LV free wall. In order to further elucidate the pathogenic mechanisms underlying cardiomyopathy, we evaluated myocardial magnetic resonance (CMR) studies of DMD/BMD siblings of the same age group.

Methods: Since 2007, we have performed cardiac examinations comprising (amongst others) comprehensive CMR studies in more than 120 patients with DMD and BMD. The CMR studies comprised (amongst others) cine-CMR and T1-weighted late-gadolinium-enhancement (LGE) imaging in order to assess functional and structural parameters. In order to enable a meaningful comparison of CMR study results, we selected only those DMD/BMD siblings who were at least 12yrs (DMD) or 20yrs (BMD) old and in whom the difference of age was less than 10yrs.

Results: Four pairs of siblings were identified (with each sibling having the same dystrophic gene mutation) fulfilling the inclusion criteria. The age of sibling pair no.1 (BMD) was 21yrs and 24yrs, left ventricular ejection fraction (LVEF) was 48% and 38%, and the extent of LGE was 2.8% and 2.6%, respectively. The age of sibling pair no.2 (BMD) was 36yrs and 38yrs, LVEF was 36% and 42%, and the extent of LGE was 4.1% and 3.3%, respectively. The age of sibling pair no.3 (BMD) was 29yrs for both (monozygous siblings), LVEF was 65% and 66%, and the extent of LGE was 0.5% and 1.1%, respectively. The age of sibling pair no.4 (BMD) was 40yrs and 43yrs, LVEF was 58% and 63%, and the extent of LGE was 3.7% and 5.1%, respectively. All siblings demonstrated the same localization of LV free wall (i.e.: septal wall).

Conclusions: The similar results in LVEF, extent of LGE and localization of LGE in siblings with the same dystrophin gene mutation clearly suggest that the fragility of the cell membrane caused by genetically deficient dystrophin – but not by acquired myocarditis(!) is the cause of the characteristic cardiomyopathy in DMD/BMD patients.

Phenotype-genotype correlation in patients with mutations in the beta-myosin converter domain

D.A. Garcia-Giustiniani1, X. Fernandez2, M. Ortiz-Gonzalez1, R. Barrias-Villa1, A. Mazzarelli1, I. Rodriguez1, L. Cazon1, M. Perez-Barbeito1, E. Maneiro1, L. Monserrat-Iglesias1,1

Institute of Biomedical Investigation (Research). A Coruña, Spain; 2Network of Operative Research in Cardiovascular Diseases (RECAVA). A Coruña, Spain; 2University Hospital Complex A Coruña, A Coruña, Spain

Purpose: Our main purpose was to evaluate the genotype-phenotype correlation of mutations located in the beta-myosin converter domain. This region, located between aminoacids 299 and 777, is responsible for the elastic properties of the protein which allows strain to develop within the motor before the cargo is actually moved. Several mutations affecting this important and highly conserved region have already been genetically described.

Methods: Identification of mutations in the converter domain of MYH7 was performed in a cohort of more than 800 cases diagnosed either with Hypertrophic Cardiomyopathy (HCM) or Dilated Cardiomyopathy (HCM). Additionally, a search was conducted to identify any affected person from unaffected families. We also reviewed the published data about all missense mutations located within this domain.

Results: In our centre, mutations were identified in 11 families comprising 59 relatives and 30 carriers, all diagnosed with HCM except 1 family (LVNC and DCM). These mutations were G716R (2 families), G741R (1 family), G768R (1 family), 1730N (1 family, novel mutation), 7367C (5 families) and R719Q (1 family).

Taking into account our data and data from literature, a total of 21 pathogenic mutations have been identified within this domain. They were distributed in 143 families comprising 470 relatives (in half of those families more than 1 member was described). Of these relatives, 424 were affected or possibly affected (11 of them diagnosed with DCM and the rest with HCM) and 382 were mutation carriers. We observed an early onset of disease with a mean age at the diagnosis of 27±18 years (range 1 to 77, 56% males). Thirteen of 21 mutations were associated with a severe adverse event affecting at least one member in 52/143 families (36%). These serious events occurred in 151 affected or possible affected relatives (36%), distributed as follow: sudden death occurred in 96 patients (22, 6%) and at least 54 of them were younger than 45 years old, heart failure death in 35 (8,2%), cardiac transplantation in 18 (4,2%) and fatal stroke in 6 (1,4%). Finally, 61 patients (16%) presented an impairment in the left ventricular systolic function.

Conclusions: Data from our families and from the extensively reviewed publications indicated that mutations located within the beta-myosin converter domain presented an early onset of disease. A significant proportion of mutations were associated with the occurrence of a severe adverse event and also left ventricular dysfunction, in a high proportion of families.

Is the gene MYOM2 encoding myomesin 2 involved in the pathogenesis of hypertrophic cardiomyopathy?

A. Perrot1, A. Barton1, B. Kherad2, L.H. Boldt2, W. Haverkamp2, S. Rickert-Sperling1, 1Charité - Experimental & Clinical Research Center/Cardiovascular Genetics, Berlin, Germany; 2Charité - Campus Virchow-Klinikum, Department of Cardiology, Berlin, Germany

Background: Hypertrophic cardiomyopathy (HCM) is the most frequent genetic cardiomyopathy with a prevalence of 1:500. Although twenty mostly sarcomeric genes have been shown to cause HCM, it is anticipated that additional so far unknown disease genes exist. In a candidate gene approach, we did a genetic screening of myomesin 2 (MYOM2), a M-band protein expressed in cardiac sarcomeres.

Methods: We clinically evaluated a cohort of fifty-eight HCM patients on the basis of medical history, physical examination, echocardiography, and 12-lead ECG, after obtaining informed consent. Using PCR and direct automated Sanger sequencing, the thirty-six coding exons of MYOM2 were analyzed. The study was approved by the institutional review board of the Charité.

Results: As expected, a number of known mutations were found. Furthermore, they are not registered in the SNP database, although more than 200 variations are known in MYOM2. The mutations affect different domains of the protein. Whereas the affected residue of codon 468 is highly conserved in different species from chimp to fish, the codon 269 is conserved only in mammals. While M097T and S466R are missense mutations affecting one residue, the mutation R1079X created a premature stop and is predicted to lead to a truncated protein from immunoglobulin-like domain 10. The two most common HCM disease genes, MYH7 and MYBPC3, as
well as a number of other disease genes (MYL2, MYL3, ACTG, TNNT2, TNN3, TPM1, TNNC1, CSRP3) showed no mutation in this HCM cohort. Notably, the phenotype of the three identified patients was characterized by left ventricular outflow tract obstruction and arrhythmias which lead in one of them to an ICD implantation. The examination of the families is underway.

Conclusions: According to Mendelian inheritance in man, MYOM2 was not considered to cause disease so far. We could detect the first three novel mutations in that gene in HCM patients. Our data suggest that MYOM2 may be involved in the pathogenesis of hypertrophic cardiomyopathy.

**P4870** Unravelling mutation effects from secondary adaptations in cardiomyocytes of Familial Hypertrophic Cardiomyopathy patients

T. Krafl1, E.R. Paalberends2, N.M. Booten2, S. Tripathi1, J. Montag1, A. Francion1, F. Navarro-Lopez, B. Brenner1, G.J.M. Stienen1, J. Van Der Velden4, 1Medical School, Hannover, Germany; 2VU University Medical Center, Amsterdam, Netherlands; 3Hospital Clinic Provincial, Barcelona, Spain

**Purpose:** About 1/3 of genotyped FHC patients carry missense mutations in the β-cardiac myosin heavy chain (β-MHC). Yet, at the sarcolemma level of cardiomyocytes, the primary functional effects of these mutations are still largely unknown. We aimed to characterize the effects of the highly malignant β-mysin heavy chain (β-MHC) missense mutation R722G in myocardial tissue and to compare the data with previous findings in M. soleus fibres with the same mutation. This allows to differentiate (1) the primary functional effects of the mutation and (2) adaptational processes in the myocardium.

**Methods:** In left ventricular cardiomyocytes from explanted hearts of patients with the β-mysin mutation R722G and in donor cardiomyocytes we determined force generation, force-calcium relations, and cross-bridge kinetics. We also determined the relative expression of mutated vs. wildtype β-MHC at the RNA- and protein level and analyzed the phosphorylation of sarcomeric proteins. To assess cardiomyocyte structural properties, histology and electron microscopy was also performed.

**Results:** Measurements revealed reduced maximum force generation but unchanged calcium-sensitivity of the myocytes. Yet, previous studies on slow skeletal muscle fibers with the same mutation showed reduced calcium-sensitivity and increased maximum force. Expression of mutated β-MHC-mRNA and β-myosin in LV tissue was found to be 68% and 64% of total β-MHC-mRNA and β-myosin, respectively, which is the same fraction as in M. soleus. Gel electrophoresis of the HCM cardiac tissue showed reduced phosphorylation of troponins I and T, myosin binding protein C and myosin light chain 2 compared to donor tissue, which is similar to previous findings for failing human heart. Treatment with protein kinase A (PKA) to adjust phosphorylation of Titin and MyBP-C in donor and HCM myocytes, however, uncovered reduced calcium-sensitivity, similar to what was observed previously in M. soleus, while maximum force was not affected by PKA. Electron microscopy showed lower myofibrillar density and disorganization of myofilaments in the cardiac tissue samples which most likely accounts for the reduced force.

**Conclusions:** (1) The primary effects of HCM related mutations might obscure typical adaptations commonly seen in end stage heart failure like increased calcium-sensitivity due to changes in protein phosphorylation. (2) To identify primary functional effects of a mutation in myocardial tissue at an advanced stage of the disease, posttranscriptional modifications like protein phosphorylation and ultrastructural alterations must be taken into account.

**P4871** Lamin A/C mutation is independently associated with an increased risk of arterial and venous thromboembolic complications

I.A.W. Van Rijsingen1, A.L. Van Der Kooi1, J.P. Van Tintelen2, M.P. Van Den Berg2, L. Christiaans1, A.A.M. Wilde1, J.C.M. Meijers1, R. Nieuwland1, Y.M. Pinto1, S.J. Pinto-Sietsma1, 1Academic Medical Center, Amsterdam, Netherlands; 2University Medical Center Groningen, Groningen, Netherlands

**Purpose:** Lamin A/C (LMNA) mutation carriers suffer from a variety of clinical phenotypes, including dilated cardiomyopathy (DCM). Although it has been suggested that carriers are at risk for thromboembolic complications, it is unknown whether this risk is higher than can be expected from the underlying cardiac abnormalities.

**Methods:** We compared a cohort of 76 LMNA mutation carriers with a cohort of 1127 DCM patients without a LMNA mutation, with respect to the prevalence of arterial and venous thromboembolic complications. Furthermore, we carried out a case-control study to explore whether a prothrombotic phenotype was present in LMNA mutation carriers without DCM or atrial tachyarrhythmias (n=14) and compared this with mutation negative relatives (n=13).

**Results:** The prevalence of thromboembolic complications was higher in the cohort of LMNA mutation carriers than in DCM patients (22 vs 11%; p<0.05), after adjustment for mean follow-up of 42±12 and 49±12 years. After adjustment for possible confounders, including atrial tachyarrhythmies and left ventricular ejection fraction, LMNA mutation carriership was independently associated with an increased risk of thromboembolic complications (HR 4.8, 95% CI: 2.2-10.6). The results of the case-control study suggested a prothrombotic phenotype in LMNA mutation carriers, as reflected by an altered platelet function and increased thrombin generation.

**Conclusions:** LMNA mutation is independently associated with an increased risk of arterial and venous thromboembolic complications. Laboratory research in LMNA mutation carriers without severe cardiac abnormalities suggests a prothrombotic phenotype.

**P4872** New genetic determinants of disease phenotype in hypertrophic cardiomyopathy: high-throughput sequencing reveals unexpected complexity

L. Rocha Lopes1, P. Syris1, M. Hubank2, C. Giambartolomei3, P.M. Elliott1, 1University College London, Institute of Cardiovascular Science, London, United Kingdom; 2UCL Genomics, London, United Kingdom; 3UCL Genetics Institute, London, United Kingdom; 4University College London, London, United Kingdom

**Background:** Hypertrophic cardiomyopathy (HCM) is an important cause of sudden death and heart failure and has a prevalence of 1/500. In 50% of adolescents and adults, it is an autosomal dominant trait caused by mutations in sarcome genes, but 50% of all cases remain unexplained. Also, genotype-phenotype relationships remain elusive. Next-generation sequencing (NGS) potentially increases the yield of variant detection and facilitates the study of large cohorts. Its impact on genetic testing strategies in HCM is to be determined.

**Purpose:** Our aims were to establish a methodology for the clinical use of NGS in HCM and to further characterize the genetic determinants of the phenotype.

**Methods:** Unconsecrated and consecrated NGS patients were clinically evaluated. DNA was isolated from blood lymphocytes. Targeted sequencing in the Illinima Genome Analyzer IIx platform, using paired-end multiplexing, covered 20 genes associated with HCM and dilated cardiomyopathy and 20 genes implicated in other cardiac diseases and channelopathies. Insertion-deletions and single-nucleotide polymorphisms were called and then filtered, selecting for non-synonymous exonic or splice-site sequence variants (SVs) with a frequency >0.5%.

**Results:** Two-hundred-and-twenty-two patients (45±15-years old at diagnosis, 74% males) were studied. Genotype calling resulted in a total of 21912 exonic and splice-site SVs (1743 distinct SVs). After exclusion of synonymous substitutions, 9153 exonic and splice-site SVs (976 distinct SVs) and were selected and further filtered by frequency, resulting in 462 unique SU candidates. In total, 204 patients (92%) carried at least one candidate SV and 164 (74%) carried multiple. Excluding the highly variable titin gene, 112 distinct rare sarcomeric and 35 rare Z-disc and calcium-handling SVs were present in 141 patients (64%), including 60 known pathogenic mutations and 22 novel nonsense, frameshift/insertion-deletion or splice-site SVs predicted to cause loss-of-function. Eighty-six SVs (64 novel) in 91 patients (41%) were present in genes implicated in arrhythmogenic cardiomyopathy and channelopathies.

**Conclusions:** We analyzed the clinical application of NGS in a large cohort of unrelated HCM patients. A majority of patients carried multiple rare variants, questioning our understanding of the genetic basis of HCM and suggesting a role for extra-sarcomeric variants as possible modifiers.

**P4873** Missense mutations in titin-associated proteins identified in patients with dilated cardiomyopathy

V. Ruppert1, T. Meyer2, S. Ackermann1, A. Perro1, M. Posch3, A. Richter1, B. Maasch1, S. Parkewi4, on behalf of German Competence Network of Heart Failure, 1Philips University of Marburg, Marburg, Germany; 2University of Göttingen, Department of Psychosomatic Medicine, Göttingen, Germany; 3Experimental & Clinical Research Center (ECRC) at the MDC for Molecular Med. & Charite-Med. Faculty, Berlin, Germany

**Introduction:** Mutations in sarcomere proteins expressed in the heart have been reported to cause dilated cardiomyopathy (DCM). Recently, missense mutations in the giant protein titin and its associated cytoskeletal proteins have been linked to the pathogenesis of DCM, suggesting that the structural organization of the sarcomere and the cardiomyocytes’s stretch sensor. In this study we have searched for novel disease-associated mutations in the human titin-binding proteins, myopalladin and CARP (cardiac ankyrin repeat protein) in DCM patients.

**Methods:** In a heterogeneous study population of 255 independent cases we have screened the entire coding regions and all flanking intron sequences in the myopalladin-encoding MYPN and CARP-encoding ANKRD1 gene. From each patient genomic DNA was extracted and exon sequences were amplified by PCR. Base exchanges were detected by means of denaturing gradient gel electrophoresis (DGGE) or single strand conformation polymorphism (SSCP). All mutations were confirmed by direct sequencing and missense mutations were additionally checked by restriction fragment length polymorphism (RFLP). As controls, 50 healthy blood donors were tested for the presence of the identified mutations.

**Results:** In the coding sequence of the myopalladin gene we detected two novel heterozygous missense mutations in exon 13 (p.R955W and p.P961L), both of which were located in the third immunoglobulin-like domain of the protein. None of
these mutations were found in healthy subjects. Immunohistochemical analysis of endomyocardial biopsy demonstrated an abnormal distribution of myofibrillin in cardiac myocytes from the p.P961L mutation carrier, while the periodic localization of myofibrillin in sarcomeres was unchanged in the p.R565W carrier and four other DCM patients used as controls. Interestingly, in cardiac myocytes from the p.P961L patient we also observed a disturbed localization of α-actinin, which is a known binding partner for myofibrillin. In the ANKR01 gene we identified only one novel synonymous mutation in a DCM patient, which was a mononucleotide substitution in exon 2 (c.108C>T), but failed to detect non-synonymous mutations.

Conclusions: Taken together, we have identified novel point mutations in the third immunoglobulin-like domain of myofibrillin. One of these missense mutations, a substitution of a highly conserved prolyl residue in position 961, was associated with structural alterations in the sarcomere organization. These findings point to the role of myofibrillin in myofibrillarlogenesis with impact on the pathogenesis of dilated cardiomyopathy.

![Image](https://example.com/figure1.jpg)

**Figure 1.** NT-proBNP increases with age in men and women.

**P4874**

**Tei index, a useful indicator for right ventricular involvement in fabry disease**

H.A.C.M. Bruin De Bon1, B.E. Smid2, B.J. Bouma1, R.B.A. Van Der Brink1, H.M. Eedemann1, D.A. Samson1, J. Vliegels1, C.E. Hollak2, M. Zerres1

1Academic medical center, Amsterdam, Netherlands; 2Department of Internal Medicine, Division of Endocrinology and Metabolism, Amsterdam, Netherlands

**Aim:** Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency of α-galactosidase A. Besides renal failure and strokes, cardiomyopathy and cardiac arrhythmias are frequent complications of the disease. The cardiomyopathy can be characterized by left and right ventricular hypertrophy and cardiac fibrosis. The Tei index, a marker for combined diastolic and systolic function, has been investigated in Fabry disease to assess left ventricular dysfunction and correlates with left ventricular hypertrophy. Whether right ventricular involvement is accompanied by systolic and diastolic dysfunction in Fabry patients is as yet unknown. The aim of this study was to investigate if right ventricular hypertrophy is accompanied by right ventricular dysfunction, using Tei index.

**Methods:** A total of 83 (30 males, mean age 43 years) genetically confirmed consecutive Fabry patients and 21 (9 males, mean age 43 years) healthy controls were included in this study. Standard echocardiography was performed in all patients, including Tei-index of the lateral annulus off the right ventricular, left ventricular mass index (LVMI), tricuspid annular plane systolic excursion (TAPSE) and tricuspid lateral annular systolic velocity (Sa). 49 Patients receiving enzyme replacement therapy (ERT) and 34 patients had natural history.

**Results:** TAPSE (22.6±0.8) and Sa (12.4±0.4) were significant lower in the Fabry patients compared controls (TAPSE 24.8±1.63, p=0.001, Sa 13.6±0.8, p=0.001). The Tei-index was significantly higher in the Fabry patients (0.51±0.03) compared to the controls (0.28±0.03, p<0.001). The LVMI was significantly higher in the Fabry patients (124.8±11) compared to the controls (94.2±17, p<0.001). The Tei-index of the right ventricle correlated significantly with LVMI and the Tei-index (r 0.542, p<0.001).

**Conclusion:** In comparison to healthy controls, Fabry patients display right ventricular dysfunction as measured by Tei-index. The right ventricular dysfunction correlates to the degree of left ventricular hypertrophy.

**P4876**

**Advanced left heart disease in cystic fibrosis: a distinct form of cardiomyopathy**

R. Ruiz Baustista1, J. Segovia2, C. Salazar1, C. Prado2, L. Maza2, R. Gorosti2, M. T. Martinez2, S. Mingol1, J. Miriel1, L.A. Alonso Pulpon1, 1University Hospital Puerta de Hierro Majadahonda, Department of Cardiology, Madrid, 2University Hospital Puerta de Hierro Majadahonda, Department of Pathology, Madrid, 3University Hospital La Paz, Madrid, 4University Hospital Ramon y Cajal, Madrid, 5University Hospital La Princesa, Madrid, 6University Hospital 12 de Octubre, Madrid, Spain

During decades, occasional cases of cardiomyopathy (CMP) have been described in patients with cystic fibrosis (CF). Necropsies of children with CF who died of sudden death showed dilated left ventricle with patchy fibrosis. Currently, patients with CF usually reach adulthood, and the incidence and features of CMP in them are unknown.

**Methods:** We describe cardiologic findings of 9 adult patients with CF and left ventricular (LV) systolic dysfunction, 3 of them referred to our centre for cardiopulmonary transplantation and 6 found in a study of 120 CF patients without known cardiac disease (5% prevalence). We report data of clinical evaluation, blood tests, ultrasound and magnetic resonance (MRI) studies. Histological findings of the three explanted hearts are described. The remaining 114 patients without CMP served as control group.

**Results:** The mean age of the 9 CMP patients was 31±7 years and 6 were male. Four of them had def508 mutation and 2 had a rare mutation of other CF-related genes. Their mean LV ejection fraction was 36% (vs 66±8% in controls, p<0.01); 55% had also diastolic dysfunction (vs 5% in controls, p<0.01). Four patients (44%) showed moderate mitral regurgitation. Right ventricle was affected in 1 patient (11%) and was normal in all control patients. Mean NT-proBNP in CF patients with CMP was 1498±3219 pg/ml (vs 58±45 pg/ml in controls, p<0.001). MRI showed a patchy delayed myocardial gadolinium uptake in 43% of CMP patients, vs 0.04 among controls, p<0.05. Pathology of the 3 hearts explanted at transplantation showed patchy myocardial fibrosis in all cases, a finding similar to the autopsies of Keshan syndrome (CMP due to selenium deficiency). Eight patients (89%) with CMP had pancreatic exocrine deficiency, needing high-dose pancreatic enzyme supplements (vs 30% in the control group, p=0.05); and 69 (67%) had a body mass index <20 kg/m² (vs 53 among controls, p=0.07). From the pulmonary standpoint, the mean FEV1 for the 9 patients was 45±16% (vs 60±20% for controls, p=0.08). All of them had a permanent airway colonization by Pseudomonas (vs 58% among controls, p=0.04). In fact, 49 (44%) patients with cardiac involvement required lung transplantation (vs 1% in controls, p<0.05).

**Conclusions:** A small percentage of adult CF patients show a distinct CMP with a characteristic patchy myocardial fibrosis, a finding similar to the autopsies of children with CF and other malnourishment syndromes. CMP should be suspected in CF patients with significant malnutrition and more severe pulmonary involvement. NT-proBNP levels could serve as a screening tool for this form of CMP.

**P4877**

**Role of serum NT-proBNP measurement in the diagnosis of early cardiac involvement in patients with anderson-fabry disease**

C.J. Coats1, V. Pares2, M. Ramos2, K. Janagarajan3, C. O’Mawho4, A. Dawny5, A. Mela6, D. Hughes7, P.M. Elliott1

1University College London, Institute of Cardiovascular Science, London, United Kingdom; 2The Heart Hospital, University College London Hospital Trust, London, United Kingdom; 3University College Hospitals London NHS Trust, London, United Kingdom; 4Royal Free & University College London Medical School, London, United Kingdom

**Purpose:** NT-proBNP has an established role in the diagnostic and prognostic assessment of heart failure. Cardiac involvement in AFD is common, however detection of early disease is challenging. The aim of this study was to determine the relation between serum NT-proBNP concentration and cardiac abnormalities in patients with Anderson Fabry disease (AFD).

**Methods:** NT-proBNP was measured under resting conditions in 117 patients with AFD (48±15 years old, 46.2% male). All patients underwent clinical evaluation including ECG and echocardiogram.

**Results:** NT-proBNP concentrations ranged from 5pmol/L to 6059pmol/L. Eighty six (74%) patients had cardiac involvement (defined as an abnormal ECG or echocardiogram). A cut off of >200pmol/L had a 69% sensitivity and 94% specificity for detecting cardiac involvement in AFD in area under a receiver operator characteristics curve of 0.85 (95% CI 0.79-0.92). In multiple regression analysis the following were independently associated with logNT-proBNP levels: age, creatinine, LV aortic volume index, E/Ea and the presence of an abnormal ECG (R2 = 0.67, p <0.05).

**Conclusion:** NT-proBNP concentrations are raised in patients with Anderson-Fabry disease and cardiac involvement and correlate with non-invasive markers of diastolic dysfunction. These findings suggest that measurement of NT-pro-BNP may assist in decisions on the timing of enzyme replacement therapy.

**P4878**

**Cardiac autonomic nervous system dysfunction in a cardiomyopathy mouse experimental model**

N. Athanasiadis, M. Mavroidis, M. Katsiboulas, S. Nikolopoulos, I. Kostavassili, C. Dimitriou, Y. Capetanaki, C.H. Davos. Biomedical Research Foundation, Athens, Greece

**Purpose:** Desmin is the major muscle specific intermediate filament protein.
Desmin null mice (des–/–) develop dilated cardiomyopathy with myocardial de-generation, extensive calcification and fibrosis which leads to arrhythmias and sudden cardiac death. Our aim was to investigate the cardiac autonomic nervous system function in the des–/– mouse by measuring heart rate variability (HRV) indices.

Methods: We generated des–/– mice by gene targeting via homologous recombination in 129Sv genetic background. Twenty four hours EGCG recordings were obtained from 6m old des–/– and wild type (WT) mice, using a telemetry system (DST) and all RR intervals were recorded. The following linear and non-linear HRV indices were calculated: Approximate Entropy (ApEn) modified to avoid self-occurrences, Detrended Fluctuation Analysis (DFA) and the beta-spectral Exponent. Poincare map measures were used to extract 3D measures of spread and maximum and the 2D distances axis sd1 and sd2. Time domain (SDNN, SDNNi, RMSSD, pNN50) and frequency domain (LV, HF) indices were also calculated.

Results: Results are presented in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>WT (n=15)</th>
<th>des–/– (n=15)</th>
<th>P</th>
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<tbody>
<tr>
<td>ApEn</td>
<td>0.75±0.10</td>
<td>0.56±0.12</td>
<td>0.2</td>
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<tr>
<td>Beta-SE</td>
<td>0.94±0.08</td>
<td>0.61±0.08</td>
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<tr>
<td>DFA_a2</td>
<td>0.89±0.06</td>
<td>0.72±0.05</td>
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<tr>
<td>3Dmax</td>
<td>216.96±31.27</td>
<td>349.12±57.56</td>
<td>0.04</td>
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<tr>
<td>sd1</td>
<td>3.79±0.74</td>
<td>8.48±1.88</td>
<td>0.02</td>
</tr>
<tr>
<td>LF</td>
<td>0.002±0.0007</td>
<td>0.001±0.0004</td>
<td>0.02</td>
</tr>
<tr>
<td>HF</td>
<td>0.004±0.0001</td>
<td>0.003±0.0001</td>
<td>0.03</td>
</tr>
<tr>
<td>SDNN</td>
<td>0.012±0.001</td>
<td>0.016±0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>SDNNi</td>
<td>0.004±0.001</td>
<td>0.011±0.002</td>
<td>0.02</td>
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<tr>
<td>RMSSD</td>
<td>0.005±0.001</td>
<td>0.012±0.003</td>
<td>0.02</td>
</tr>
<tr>
<td>pNN50</td>
<td>0.31±0.12</td>
<td>1.58±0.56</td>
<td>0.02</td>
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</table>

Conclusion: Desmin null mice show a global autonomic nervous system dysfunction which affects both the sympathetic and the parasympathetic components. This may explain the presence of arrhythmias and sudden cardiac death in these mice. Further investigation is needed so as to clarify whether this dysfunction is a result of the extended myocardial fibrosis and calcification caused by the absence of desmin.

P4879

Adiponectin promotes coxsackievirus B3 myocarditis by controlling viral infection within the heart

A. Jenke1, J. Stehr2, S. Wlik3, A. Weissheuer1, K. Klingel1, H.P. Schulteis1, C. Scheltenbogen1, C. Struk1, J. Charite - Campus Benjamin Franklin, Cardiology & Pneumology, Charité - University Medicine Berlin, 11th Cardiovaculatry Medicine, Berlin, Germany; 2Charite - Campus Virchow - Klinikum (CVK), Medical Immunology and BCR1, Berlin, Germany; 3University of Tübingen, Department of Molecular Pathology, Tübingen, Germany

Purpose: Adiponectin (APN) is an adipokine that is expressed in cardiac cells and mediates immunomodulatory and cardioprotective effects. High APN expression promotes favorable outcome in patients with virus-negative inflammatory cardiomypathy and in mice with autoimmune myocarditis. Interestingly, APN also controls antigen-specific T cell responses and viral replication during hepatitis. Coxsackievirus B3 (CVB3) is cytopathic for cardiac myocytes and causes severe myocarditis, which might progress to dilated cardiomyopathy. Here, we investigated whether APN mediates cardiac inflammation and injury in CVB3 myocarditis.

Methods: Myocarditis was induced by infection of APN-/- and WT mice with CVB3. Viral load was determined by qRT-PCR, plaque assay and in situ hybridization. H&E stained heart sections were used for histological analysis. Gene expression was analysed by qRT-PCR. Matrix metalloproteinase (MMP) activity was measured by zymography. The areas of enhancement were measured by commercial software and expressed in arbitrary units (a.u.)

Results: APN-/- mice displayed significantly reduced CVB3 load in the myocardium. This was accompanied by decreased myocarditis severity designated by reduced number and size of inflammatory infiltrates and diminished expression levels of immune cell markers NKp46, CD3, CD4, CD11b and CD45. Correspondingly, APN-/- mice displayed significantly decreased cardiac expression levels of IFNγ, INFgamma, TNFα, TNF-NFκB, IL-1α, IL-6, and IL-12. However, in APN-/- mice cardiac resident macrophages exhibited an increased M1/M2 phenotype ratio. Histological analysis of the heart revealed less severe necrotic lesions in APN-/- mice after CVB3 infection. Accordingly, CVB3 induced cardiac remodeling was significantly increased in APN-/- mice. The expression levels of Collagen type I, Collagen type III and MMP-13 as well as activities of MMP-2 and MMP-9 were attenuated. In contrast, APN-/- mice displayed unchanged expression levels of Coxsackie-Adenovirus receptor, TRPV3 and TRIF. In cell culture APN treatment resulted in significantly increased CVB3 replication in cardiac myocytes accompanied by enhanced TNFα expression.

Conclusions: Our observations indicate that APN promotes myocardial inflammation and injury in CVB3 myocarditis by facilitating viral infection of cardiac myocytes. Increased viral replication might be enhanced by APN mediated differentiation of cardiac resident macrophages towards an immunosuppressive M2 phenotype. Thus, in contrast to other models of inflammatory heart disease the immunomodulatory effects of APN result in increased myocardial damage following CVB3 infection.

P4880

Clinical presenting patterns and CMR features of acute myocarditis predicting outcome

O.E. Rimoldi1, D. Lanza2, P. Pedrotti3, A. Milazz2, S. Pedretti3, A. Roghi3, I.Institute for Biomedical Technologies ITB - CNR, Milan, Italy; 2University of Verona, Verona, Italy; 3Niguarda Ca' Granda Hospital, Department of Cardiovascular Medicine, Milano, Italy

Background: Acute myocarditis (AM) clinical onset can span from subclinical disease to acute heart failure (AHF) ventricular fibrillation (VF) or sudden cardiac death in young adults. Myocarditis may cause arrhythmias both in the acute stage of the infection and as a consequence of myocarditis based on clinical, laboratory and CMR findings and 50 healthy aged-matched controls. All patients had chest pain, abnormal ECGs and preserved EF (>45%) whereas coronary artery disease was angiographically excluded.

Results: In comparison with controls, global longitudinal strain values in myocarditis group (<17.35±3.08% vs. >20.08±2.63%, p< NS) were not statistically different, reflecting the preserved longitudinal contractility. On the contrary, myocarditis patients showed decreased LV torsion (10.30±3.85 degrees, vs 14.28±4.30 degrees, respectivly, p<0.01), apical rotation values (4.74±3.77 vs 8.73±2.83 degrees, respectivly, p<0.003) and circumferential strain in the mid posterior (7.1±5.6% vs 18.3±7.4%, p<0.001), mid lateral (7.1±7.3% vs 16.4±11%, p<0.001) and mid inferior wall (11.5±6.9% vs 20.5±4.7%, p<0.001) compared to controls. Tropinon elevation was found in 25 patients (50%) with mean values 14.83±23.79 ng/ml and was correlated with both LV torsion (r=-0.584, P =0.001) and the number of affected segments in CMR (r=0.57, p=0.04). A circumferential strain cut off below -12.5% for mid lateral and below -10.5% for mid interalsteral segment yielded a sensitivity of 75% & 87.5% and a specificity of 60% & 60% respectively, in predicting late enhancement (LGE) at CMR in these segments.

Conclusion: STI assessment revealed abnormal LV torsion and circumferential strain in acute myocarditis. Torsion impairment was strongly correlated to the level of tropinin release. On the contrary, longitudinal strain and conventional echocardiographic parameters were not significantly affected. Circumferential strain yielded modest specificity in predicting the segments with LGE at CMRI.

P4880

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In vivo delivery of adenoviral vector containing Interleukin-17 receptor A reduces cardiac remodeling and improves myocardial function in CVB-3-induced chronic myocarditis

R. Chen1, Y.G. Xie1, P. Chen1, X. Zhang1, M.H. Li1, X.G. Wang1, T.Q. Peng2, Y.Z. Zou2, H.Z. Chen1, J.B. Ge2, 1Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital-Fudan University, Shanghai, China. 2People’s Republic of: Johns Hopkins University School of Medicine, Baltimore, United States of America; 3Lawson Health Research Institute, University of Western Ontario, London, Canada.

Purpose: Th17 cells have been implicated in the pathogenesis of myocarditis. Interleukin (IL)-17A-17A-induced chronic myocarditis, delivery of adenovirus containing IL-17 receptor A (Ad-IL17R:Fc) reduced IL-17A production and decreased the mortality compared with control treated mice. The aim of the present study was to investigate the therapeutic effect of IL-17R:Fc in chronic viral myocarditis. Methods and Results: A mouse model of Coxsackievirus B3 (CVB3)-induced chronic myocarditis, delivery of adenovirus containing IL-17 receptor A (Ad-IL17R:Fc) reduced IL-17A production and the mortality compared with control treated mice, which was accompanied by down-regulation of ADAMTS-1, MMP-2, collagen subtypes I and III, and a reduction in fibroblasts in the heart, suggesting an important role of IL-17A in fibrosis. These effects of Ad-IL17R:Fc correlated with a decrease of Th17 cells in the spleen and heart, and a reduction of systemic TNFα and IL-6 productions. In cultured cardiac fibroblasts, IL-17A induced expressions of ADAMTS-1, MMP-2, collagen subtypes I and III, and increased the proliferation of fibroblasts.

Conclusion: Th17 cell and IL-17A induces cardiac fibrosis through mediating extracellular matrix remodeling and fibroblast proliferation in chronic viral myocarditis and DCM. Thus, blockade of IL-17A by adenoviral transfer of IL-17 receptor A may represent an alternative therapy for chronic viral myocarditis and its progression to DCM.

Relationship between cardiac magnetic resonance criteria for acute myocarditis and biomarkers of inflammation and myocardial damage

G. Nucifora1, A. Di Chiara1, D. Miani1, G. Piccillo1, M. Puppato1, G. Slavich1, D. Gasparini1, A. Proclemer1. 1Cardiothoracic Department, University Hospital “Santa Maria della Misericordia”, Udine, A.S.S. n.3 Alto Friuli, Department of Cardiology, Tolmezzo, 2Division of Interventional Radiology, University Hospital “Santa Maria della Misericordia”, Udine, Italy.

Purpose: Diagnostic cardiac magnetic resonance (CMR) criteria for acute myocarditis ("Lake Louise" criteria) have been recently proposed. In the setting of clinically suspected myocarditis, CMR findings are consistent with myocardial inflammation, if at least 2 of the following features are present: 1) regional or global myocardial thickening, 2) hyperaemia and 3) extent of late gadolinium enhancement (LGE) in focal lesion of myocardial necrosis; with non-ischemic regional distribution. Scarc data are however available regarding the relationship between these criteria and biochemical markers of inflammatory activity and myocardial injury.

Methods: A total of 26 consecutive patients (20 males, mean age 38±14 years) with diagnosis of acute myocarditis on the basis of clinical presentation (chest pain, dyspnea or palpitations, associated with recent gastrointestinal or respiratory infection) and CMR "Lake Louise" criteria were included. For each patient, peak values of C-reactive protein (CRP) and cardiac troponin I (cTnI) were determined. In addition, the following CMR features were determined: 1) global myocardial signal intensity (SI) in T2W images, quantified by a SI ratio of myocardium over skeletal muscle (expression of myocardial edema); 2) global myocardial early gadolinium enhancement (EGE) ratio between myocardium and skeletal muscle; 3) early gadolinium enhancement (EGE) ratio in hyperaemic areas (expression of myocardial hyperaemia) and 3) extent of late gadolinium enhancement (LGE) in inversion recovery-prepared gadolinium-enhanced T1-weighted images (expression of myocardial necrosis). The extent of LGE was expressed as percentage of the left ventricular (LV) mass (%LV LGE). Univariate and multivariate linear regression analysis was performed to investigate the relationship between biochemical markers of inflammatory activity and myocardial injury.

Results: The correlations between peak CRP and cTnI and SI-T2, EGE ratio and %LV LGE were 0.94±0.94, 6.40±2.0 and 0.86±0.72, respectively. At multivariate analysis, peak value of CRP was significantly and independently related only to T2 ratio (β=0.64, p<0.001) and EGE ratio (β=0.33, p=0.030). Conversely, peak value of cTnI was significantly and independently related only to %LV LGE (β=0.93, p<0.001).

Conclusion: In patients with acute myocarditis, T2 ratio and EGE ratio are expression of inflammatory activity, while LV LGE is expression of irreversible myocardial injury.

Immunoglobulin suppressed autoimmune myocarditis in severe combined immunoodeficient (SCID) mice by inducing T cell unresponsiveness

C. Kishimoto1, K. Shioj1, Z. Yuan1, 2Kyoto University Graduate School of Medicine, Department of Cardiovascular Medicine, Kyoto, Japan; 2First Hospital of Medical College of Xi’an Jiaotong University, Department of Cardiology, Xi’an, China. People’s Republic of

Purpose: Suppressive effects of immunoglobulin against myocarditis were already demonstrated. However, the precise mechanisms are still unknown. Accordingly, we investigated the suppressive effects of immunoglobulin (Ig) upon effector T cells in autoimmune myocarditis.

Methods and Results: Treatment with Ig reduced the production of the so-called Th1 cytokines stimulated by concanavalin A or cardiac myosin in cultured lymph node (LN) cells from rats with myocarditis. The cytoktic activities of LN cells from rats immunized with myosin and treated with Ig were reduced against cardiomyocytes and IF-2 cells, compared with those treated without Ig. The adoptive transfer of myocarditis from LN cells of Lewis rats with myocarditis into severe combined immunoodeficient (SCID) mice was successfully achieved. Treatment with Ig, but not with Flab-2 fragments of Ig, reduced the mortality and the severity of myocarditis in SCID mice. Decreased ability of LN cells of Ig-treated rats, but not of Flab-2 fragments-treated rats, to transfer autoimmune myocarditis was also demonstrated.

Conclusion: Treatment with Ig ameliorated autoimmune myocarditis with inducing myosin unresponsiveness via the Fc portion, resulting in suppression the Th1 cytokine production and the cytoktic activities of LN cells, which operated together in the development of autoimmune myocarditis.

Injectable collagen implant improves survival and early cardiac remodeling after fulminant myocarditis in rats

S. Rinkевич-Szep1, N. Landa-Rouben1, R. Holbová1, F.H. Epstein2, T. Ben Mordechai1, M.S. Feinberg1, O. Golein1, T. Kushnir3, E. Konen3, J. Lear1. 1Cardiovascular Research Institute, Tel-Aviv University, Sheba Medical Center, Tel Hashomer, Israel; 2Departments of Radiology and Biomedical Engineering, University of Virginia, United States of America; 3Diagnostic Imaging Department, Sheba Medical Center, Tel Hashomer, Israel.

Purpose: Acute myocarditis can lead to massive cell death, destruction of extracellular matrix, left ventricle (LV) dilatation, dysfunction and death. We sought to test the hypothesis that injection of collagen-based implant into the inflamed myocardium would stabilize LV and prevent adverse remodeling and dysfunction.

Methods and Results: Autoimmune myocarditis was induced in 42 male Lewis rats. Fourteen days after immunization, sick animals were randomized into either injectable-collagen implant or saline injection, into anterior inflamed myocardium. LV remodeling and function were assessed by serial echocardiography and cardiac magnetic resonance (CMR) scans; before immunization, before collagen implantation and 17 days after immunization. Thirty one days after immunization rats were euthanized and subsequently underwent histopathological examination. Notably, 30 day survival rate was significantly higher in collagen-treated group compared with control (87.5% vs. 50%; p<0.003). CMR imaging of control animals showed epicardial late gadolinium enhancement, as marker of fibrosis, LV wall motion abnormalities, and in some cases pericardial effusion. The injectable collagen implant increased systolic and diastolic wall thickness, 10 days after treatment, compared with control (p=0.07, p=0.05). Furthermore, while injectable collagen implant attenuated the LV systolic and diastolic dilatation and preserved LV ejection fraction, control animals developed significant LV dilatation (p=0.02, p=0.04) and dysfunction (p=0.01). However, these favorable effects disappeared within 17 days after treatment.

Conclusions: Injectable collagen implant improves survival in a rat model of fulminant myocarditis. However, while the effect on survival was sustained, the early protective effect on remodeling was limited to the early period after treatment.

Matrix Metalloproteinase-13 is beneficial in viral myocarditis not only by preventing cardiac inflammation but also reducing cardiac inflammation due to regulating chemokines

D. Westermann, D. Lindner, H.P. Schuhleiss, C. Tschoepe. Chantle - University Medicine, Campus Benjamin Franklin, Berlin, Germany.

Myocarditis is an important cause for cardiac failure especially in younger patients followed by the development of cardiac dysfunction and death. The present study investigated whether gene deletion of matrix metalloproteinase-13, an important collagenase in the heart, influences cardiac inflammation and remodeling in murine coxsackievirus-B3 (CVB3) induced myocarditis.

Methods and Results: MMP-13 knockout mice (MMP-13-/-) and their controls (WT) were infected with CVB3 to induce myocarditis and 7 days later LV function was analyzed invasively. CVB3 induced significant cardiac inflammation (increased CD3 (+18 fold) and CD68 (+25 fold) cells) as well as cardiac dysfunction (decreased cardiac output (-24%)) in WT CVB3 animals. Interestingly, deletion of MMP-13 increased the protein level of the chemokine MCP-1 (4 fold). This increa
ment of a potent chemokine due to MMP13 KOagrivated cardiac inflammation (3 fold) as well as cytokine levels (increased TNF-alpha 6 fold and IL1 beta 3 fold) compared to infected WT animals. Moreover, this excessive cardiac inflammation was associated with an increased transmigration of fibrinoids to pathological activated myofibroblasts (10 fold), which are known to be induced by inflammatory cells. This was associated with detrimental cardiac remodeling leading to severe cardiac dysfunction when MMP-13−/− were compared to WT animals after CBV3 infection. Interestingly, also viral load was increased in MMP-13−/− mice with significantly more cardiac apoptosis being present in the infected myocardium.

Conclusions: Loss of MMP-13 increased the inflammatory response after CBV3 infection, which impaired cardiac remodeling, apoptosis and function during CBV3 induced myocarditis due to an increment of the chemokine MCP-1. MMP-13, similar to other MMPs like MMP-2 might be more than just a degradation system for cardiac collagen but may modulate inflammation by processing chemokines as MCP-1 and therefore being one negative feedback loop in cardiac inflammation.

No evidence of adenoviral genome in endomyocardial biopsy specimens in patients with new-onset unexplained dilated cardiomyopathy

T. Palecek, P. Kuchynka, E. Nemecek, J. Horak, T. Kavarnik, I. Vlkova, A. Linkhart. Charles University Prague, 1st Faculty of Medicine, Prague, Czech Republic

Background and aim of the study: Dilated cardiomyopathy (DCM) may represent a sequela of acute or chronic myocarditis, either due to persistence of infectious agent (mostly virus) or to a secondary autoimmune myocardial injury. Some studies reported adenovirus as an important causative agent in the pathogenesis of myocarditis and DCM in children and adults. Therefore, we aimed to prospectively evaluate the presence of genomes of several cardiotropic pathogens including adenovirus and Borrelia burgdorferi (Bb) in myocardium of patients with new-onset unexplained DCM.

Methods: In 58 consecutive patients (53±11 years, 42 men) with new-onset unexplained DCM (left ventricular ejection fraction 30±8%), endomyocardial biopsy (EMB) specimens were studied by immunohistochemistry (HLA expression) and polymerase chain reaction (PCR) techniques.

Results: The genome of cardiotropic infectious agent was found in EMB specimens of 21 patients (35%). Namely, Bb genome was present in 13 subjects (22%), adenovirus B19 in 6 (10%), enterovirus in 5 (9%), human herpes virus 6 in 5 (9%), cytomegalovirus in 3 (5%) and Epstein-Barr virus in 2 (3%) patients. Adenovirus and herpes simplex virus 1 genomes were not detected in any subjects. Myocardial inflammation was found in 18 patients (31%), of whom in 7 subjects (12%) the presence of viral or Bb genome was also revealed.

Conclusions: The genome of cardiotropic infectious agent, viral or Bb, is present in the myocardium of more than half of the patients with new-onset unexplained DCM. Notably, Bb genome can be detected in almost one quarter of these subjects, which may have important therapeutic consequences. However, adenovirus infection does not seem to play an important role in the pathogenesis of new-onset unexplained DCM. Therefore, it is not necessary to perform adenovirus PCR assay of EMB specimens in patients with new-onset unexplained DCM.

Clinical, ECG and echocardiographic criteria are inadequate to reach a definite diagnosis in patients with myocardial injury and normal coronary angiogram: insights from magnetic resonance-based imaging


Purpose: Some patients (p) with troponin-positive chest pain have no coronary obstruction on angiography, leading to diagnostic uncertainty. Cardiac magnetic resonance (CMR) is able to determine causative aetiology in most p. The aim of this study was to analyse whether clinical, ECG or echocardiographic criteria could be useful for diagnostic assessment using CMR as gold standard.

Method: 59 consecutive p referred for CMR after admission in our institution for acute or subacute chest pain and normal coronary arteries or non-flow-limiting CAD in coronary angiography were analysed. CMR studies were performed with a 1.5 T Philips Intera and included SSFP sequences, T2-weighted black-blood, first pass perfusion and late enhancement. P were classified as AMI, myocarditis, a 1.5 T Philips Intera and included SSFP sequences, T2-weighted black-blood, first pass perfusion and late enhancement. P were classified as AMI, myocarditis, aortic valve disease, and coronary artery disease.

Results: Mean age was 45±15 years and 43% were female. P with AMI showed a non-significant trend towards more frequent non-significant stenosis in coronary angiography (3 p, 27%) compared to myocarditis (2 p, 9%) or apical ballooning (0 p). All with apical ballooning recalled a previous stressing event and showed a typical distribution of wall motion abnormalities. 17 p (50%) with myocarditis had evidence of a recent infection, whereas no p from the other groups had (p=0.001). Characteristics of different subgroups are displayed in table 1.

Conclusions: In p admitted for troponin-positive chest and no coronary obstruction on angiography which do not recall a recent infection, clinical, ECG and echocardiographic data are unreliable to differentiate AMI and myocarditis.

Conclusions:

Table 1. Characteristics of different subgroups

| Subgroup | CMR | AMI | Myocarditis | Apical ballooning | Inconclusive | p
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<td>(n=11)</td>
<td>(n=8)</td>
<td>(n=4)</td>
<td>(n=8)</td>
</tr>
<tr>
<td>Typical chest pain</td>
<td>25 (72%)</td>
<td>9 (81%)</td>
<td>3 (27%)</td>
<td>4 (50%)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>ST segment elevation</td>
<td>24 (75%)</td>
<td>6 (54%)</td>
<td>7 (64%)</td>
<td>2 (25%)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Wall motion index (mean ± SD)</td>
<td>18.6 ± 3.1</td>
<td>25.3 ± 1.1</td>
<td>11.1 ± 3.1</td>
<td>0.3 ± 0.4</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>LVEF (mean ± SD)</td>
<td>55.6 ± 7.6</td>
<td>65.0 ± 13</td>
<td>50.0 ± 10</td>
<td>60.7 ± 7</td>
<td>0.1</td>
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</table>

Omesartan, an angiotensin II type 1 receptor antagonist, suppresses cytotoxic myocardial injury in autoimmune heart failure

C. Kishimoto1, K. Shimada1, Z. Yuan1,2, Kyoto University Graduate School of Medicine, Department of Cardiovascular Medicine, Kyoto, Japan; 1First Hospital of Medical College of Xi’an Jiaotong University, Department of Cardiology, Xi’an, China; People’s Republic of China

Background: Some angiotensin II receptor type 1 (AT1) antagonists are reported to inhibit proinflammatory cytokine production. However, the effects of the drugs on autoimmune diseases are unknown.

Aims of the study: We tested the hypothesis that olmesartan, an AT1 antagonist, ameliorates experimental autoimmune myocarditis (EAM) in rats attributed to the suppression of inflammatory cytokines.

Methods and Results: We tested the effect of a 50 mg/kg/day dose of olmesartan orally at doses of 1, 3, and 10 mg/kg/day to rats with EAM for 3 weeks. The results showed that olmesartan decreased blood pressure significantly compared with the untreated group and markedly reduced the severity of myocarditis associated with the decrease of myocardial macrophage, CD4+, and CD8+ T lymphocyte infiltration and serum cytokines. Numbers of myocardial interleukin-1 (IL-1) positive-staining cells (obtained by immunohistochemistry) and quantities of IL-1 expression (obtained by Western blotting) were significantly lower in rats with EAM given olmesartan treatment compared with rats given vehicle. In vitro study showed that both olmesartan and its active metabolite RNH-6270 suppressed IL-1 production in U-937 cells and cultured myocytes.

Conclusions: Olmesartan ameliorates acute EAM in rats. The cardioprotection of olmesartan may be due to suppression of inflammatory cytokines as well as to suppressive effects of cytotoxic myocardial injury in addition to hemodynamic modifications.

Secretome from mononuclear cells confers immunosuppression in a murine autoimmune myocarditis model

K. Hoetzenecker1, M. Zimmermann1, T. Schweiger1, D. Kollmann1, M. Milder2, A. Mitterbauer1, P. Birner1, M. Lichtenauer1, H. Ankersmit1,1 Christian Doppler Laboratory for the Diagnosis and Regeneration of Cardiac and Thoracic Cells, University of Vienna, Department of Cardiology, Austria; 1Christian Doppler Laboratory for the Diagnosis and Regeneration of Cardiac and Thoracic Cells, University of Vienna, Department of Pathology, Austria; 4Medical University of Vienna, Institute of Pathophysiology, Vienna, Austria; 2Medical University of Vienna, Department of Dermatology, Vienna, Austria; 3Medical University of Vienna, Department of Pathology, Vienna, Austria.

Although auto-immunity is thought to play a major role in the pathogenesis of myocarditis, “classical” clinical immunosuppression has not been effective in treating patients suffering a post-infectious viral myocarditis. However, a modification of the autoimmune response could possibly lead to better results. We have recently shown that a high dose application of parasite factors obtained from mononuclear cells (MNC) modulates the inflammatory response following myocardial ischaemia. In this subsequent study, we sought to determine immunosuppressive features of MNC secretome in a CD4+ cell dependent model of murine myocarditis (EAM model).

Cell culture supernatants derived from murine MNC were injected intraperitoneally after induction of autoimmune myocarditis with a cardiac myosin peptide homologue. The inflammatory response was determined by histopathological evaluations and by ELISAs. Impact of MNC secretome on proliferation and cell viability of T cells was measured by FACS and histone release assays. Treatment of EAM mice with a single high dose of MNC secretome resulted in an attenuation of myocardial infiltrate (myocarditis score 2.7±0.4 vs 0.01±0.01; p<0.002). We further enpowered the effect of MNC secretome on JURKAT cell line and purified human CD4+ cells. Coinubcation of MNC secretome with T-cells led to a caspase-9 dependent induction of apoptosis.

Our data give first p to play that secretome obtained from MNC possess immunosuppressive features in an autoimmune myocarditis model.
**P4890**

**Etenrecept treatment improves acute chagas disease and regional repolarization parameters**

H.O. Rodríguez Angulo, J.E. Castillo, E.J. Cárdenas, J.A. Marquez, A.J. Ramírez, J.Venezuela Institute of Scientific Research (IVIC), Caracas, Venezuela; 2Lisandro Alvarado Center-West University, UCLAN, Barquisimeto, Venezuela; 3Institute of Tropical Medicines (IMT UCV), Caracas, Venezuela.

**Background:** Chagas disease affects 8 million people in Latin America. Even some decrease in transmission has been achieved, recently acute cases especially by oral transmission has been reported. The Tumoral Necrosis Factor (TNF-α) plays a key role in the immune response against the Trypanosoma cruzi, but is not clear their beneficial or deleterious effects on disease outcome. In this sense, the aim of this work is to determine the effects of the TNF blocker etanrecept on infarction parameters, ECG recordings and survival in an acute infection with a wild T. cruzi virulent strain.

**Methods:** NMRI male mice (30 g) were infected with 1000 trypomastigotes per gram and treated subcutaneously with 0.38 mg/kg of etanrecept at 7 day post infection (dpi). Levels of TNF and C reactive protein (CRP) were determined in blood by semi-quantitative RT-PCR and ELISA respectively at day 0, 7, 14 and 21 dpi. Vertical, Horizontal motility and mechanical allodynia were recorded with an automated activity cage and a dynamic plantar aesthesiometer during the last and second post infection. ECG was taken weekly with surface electrodes coupled to a Blip amplifier.

**Results:** The survival of treated animals was increased significantly with respect to infected untreated animals (20 vs 24 days, p = 0.0048). The peak of CRP was at 7 dpi and decreased until 21 dpi in all groups, but the levels were significantly lower in treated animals. TNF relative levels peak occurred at 7dpi and there was not differences between treated and untreated animals. Vertical and Horizontal motility reduction and hyperalgesia in infected animals was reversed by etanrecept treatment. Finally, the infected animals showed T-wave height and repolarization slope reduction associated with histological changes (myocarditis).

**Conclusion:** TNF blocking was able to improve acute Chagas outcome increasing survival and reducing inflammation and sickness behavior parameters in acutely infected mice. However, was observed an alteration of ECG parameters that could be associated with arrhythmogenesis and progression to chronic cardiomyopathy, which suggest an role of TNF-α in cardiac regional response.

**P4891**

**Diagnostic and prognostic value of biomarkers in suspected myocarditis**

C. Ukena, F. Mahlouf, M. Kindermann, J. Poessle, P. Lepper, R. Kandolf, M. Boeheim, I. Kindermann, 1Saarland University Hospital, Department of Internal Medicine III, Cardiology, Homburg, Germany; 2Caritasstift St. Andrae, Saarbrücken, Germany; 3Department of Internal Medicine V, Homburg, Germany; 4Eberhard-Karls University Tübingen, Medical Clinic, Pathology, Tübingen, Germany.

**Background:** Myocarditis can be associated with increased markers of myocardial injury. However, data on novel biomarkers as high-sensitive Troponin (hs-TnT) or Copeptin or proadrenomedullin (MR-proADM) should be evaluated.

**Methods:** Seventy patients with suspected myocarditis (age 43.4 ± 20.3 years, 76% male) were included in this study. LV myocardial biopsy (EMB) and were follow-up for 7.5 (± 2.0) months. At the time of EMB, concentrations of hs-TnT, Copeptin, NT-proBNP and proadrenomedullin (MR-proADM) were measured. Values are given as mean ± standard deviation or median (interquartile range).

**Results:** According to EMB 6 patients were diagnosed with acute myocarditis (AMI) and 36 patients with chronic myocarditis (CM). In 28 patients, EMB revealed no myocardial infarction (NM). Acute myocarditis was associated with high concentrations of hs-TnT compared to other groups (AM 262.9 pg/ml (61.4-196.3), CM 12.2 pg/ml (3.0-40.6), p<0.0001). During the last and second post infection, ECG was taken weekly with surface electrodes coupled to a Blip amplifier. TNT was significantly higher in viral myocarditis compared to non-viral myocarditis (p=0.011). Concerning the concentrations of Copeptin, NT-proBNP and MR-proADM, no significant differences existed between the groups. The concentration of hs-TnT was significantly higher in viral myocarditis compared to non-viral myocarditis (37.4 pg/ml (21.9-76.6) vs 29 heart failure (39.9-296.6), p=0.042). During the last and second post infection, ECG was taken weekly with surface electrodes coupled to a Blip amplifier. TNT was significantly higher in viral myocarditis compared to non-viral myocarditis (p=0.011).

**Conclusions:** Acute and viral myocarditis are characterized by elevated concentrations of hs-TnT. However, these biomarkers do not replace EMB for diagnosis of myocardial infarction.

**P4892**

**Measurement of interatrial dysynchrony using tissue doppler imaging predicts functional capacity and heart involvement in systemic sclerosis**


**1Department of Cardiology, University Hospital, Dijon, France; 2Department of Internal Medicine and Clinical Immunology, Dijon, France.

**Background:** Heart involvement in systemic sclerosis (SSc) is associated with poor prognosis, and early detection is crucial. SSc may affect all heart structures, including conduction pathways: interatrial block is considered common and may reflect atrial involvement, but has been so far poorly evaluated. Echocardiography may detect interatrial dysynchrony, using either M-mode or strain modalities.

**Methods:** Results: Patients with SSc were selected if there were in sinus rhythm and were able to walk. The following data were collected: NYHA functional class and distance walked in 6 minutes (6’WD), P wave duration on ECG, serum creatinine and NT proBNP levels. Echo-Doppler study comprised: left ventricular (LV) mass, LV systolic and diastolic function, right ventricular (RV) function, pulmonary artery pressure (PAP), left atrial (LA) volumes and function; IAD was assessed using colour TDI study, by measuring the delay between annular tricuspid and mitral ala waves. A cut off value of 35 ms was chosen to define the presence of IAD.

**Results:** Forty patients were studied. Forty% of patients were found to have IAD. These patients were significantly older. Using age-adjusted analysis, patients with IAD had more severe symptoms, lower 6’WD, higher NT proBNP and creatinine levels, and longer P wave duration than patients without IAD. No difference was found regarding LV dimension and EF. IAD was more prevalent in female and IAD was more prevalent in female. At 6 months of follow-up, 5 patients died or had severe events: all of them were in the dysynchrony group.

**Discussion:** The prevalence of interatrial dysynchrony among SSc patients is high (40%). IAD was found to be associated with lower exercise capacities, altered LV diastolic function, decreased LA and RV function, increased pulmonary pressure, and increased natriuretic peptides. This finding suggests that IAD may represent a marker of myocardial involvement and may indicate a poorly compli- ant left atrium.

**Conclusion:** IAD is a simple parameter showing good correlations with all other usual indexes of heart involvement. We believe that it should be added to the routine echocardiographic evaluation of SSc patients, and that its prognostic value should be evaluated.

**P4893**

**Myocardial mechanics for the early detection of cardiac sarcoidosis**

C. Aggeli, I. Felekos, E. Giolafos, E. Pouliakos, A. Katsaros, E. Venieri, A. Rapiti, C. Stefanidis, Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece.

**Purpose:** Speckle tracking has emerged as valuable tool for a more comprehensive assessment of regional myocardial function, providing angle-independent measurements of strain. The aim of this study was to evaluate left ventricular (LV) function in patients with newly diagnosed sarcoidosis, utilizing the novel method of 2D speckle tracking.

**Methods:** Patients with newly-diagnosed sarcoidosis and with unremarkable medical history of cardiovascular disease, as well as 29 healthy age- and gender-matched controls underwent echocardiographic study. Apical 4-, 2-, and 3-chamber as well as short axis acquisitions were made. In addition to conventional 2D, Doppler and TDI measurements, speckle tracking echocardiography was applied and LV global longitudinal strain was derived from the obtained images. Moreover, LV base and apex rotation angles were assessed from which LV twist was derived.

**Results:** The mean age of patients (26 men) was 43±6.1 years old. Compared with controls, patients had similar conventional 2D and Doppler measurements. TDI revealed increased E/E’ in the patient group vs control group (8.9±1.45 vs 4.7±1.29, p<0.05). Strain analysis demonstrated reduced global longitudinal strain values in the patient vs control group (18.98±1.89 vs 22.93±2.28%, p<0.05). Furthermore, twist was increased in the patient group as compared to the healthy individuals (35.1±2.3° vs 10.7±1.7°, p<0.05).

**Conclusions:** Speckle tracking echocardiography revealed alterations in strain and rotational indices, implying elevated filling pressures of the left ventricle. This could represent an early sign of myocardial involvement in patients with newly-
Echocardiographic abnormalities and their relation to exercise capacity in young unselected survivors of Hodgkin's lymphoma late after mediastinal irradiation

M.G. Poltavskaya, V.V. Budnov, I.V. Kuprina, S.B. Shornikov, A.L. Svirid, I.M. Sekoven First Moscow State Medical University, Moscow, Russian Federation

Purpose: To assess the prevalence of cardiac abnormalities and their relation to exercise capacity in young unselected survivors of Hodgkin's lymphoma late after mediastinal irradiation.

Methods: We performed echocardiography, multispll CT and cardipulmonary exercise test (CPET) in 60 patients without known cardiac disease (38 male and 22 female, mean age 28.8±6.5 years) 5-16 years after mediastinal irradiation for Hodgkin's disease. Mean age at the time of treatment was 19.6±6.0 years, mean mediastinal irradiation dose =36.5±5.9Gy, anthracyclines in 83.3% patients. Echocardiographic measurements above or below ±2SD age specific normal mean were considered abnormal.

Results: 26 patients were asymptomatic, 34 had mild nonspecific symptoms (cardiovascular). Any cardiac abnormality was found in 50 (83.3%) patients. 2 had mitral regurgitation grade 2, 3- aortic regurgitation grade 1, 1- tricuspid regurgitation grade 2. Pericardial impairment was found in 6 cases (1 patient had pericardial effusion). 10 patients had increased LV and RV Doppler velocities, left atrium was leftward shift with mean EDV/BSA=42.3±10.7mm²/m2 and reduced EVDV/BSA in 15 (25%) patients. Mild and moderate diastolic dysfunction was present in 12 (20%) patients, severe in 4 patients. RV longitudinal diastolic function was impaired in 9 (15%) patients. Peak exercise VO² and aerobic threshold correlated with EVDV/BSA (Spearman correlation coefficient R=0.75, p<0.001) and septal and aortic annular (R=0.53-0.74) lateral wall tissue Doppler early diastolic annular velocity (e') was reduced in 31 (51.7%) and septal e' in 9 (15%) patients. Peak exercise VO² and aerobic threshold correlated with EVDV/BSA (Spearman correlation coefficient R=0.75, p<0.001) and septal and aortic annular (R=0.53-0.74) lateral wall tissue Doppler early diastolic annular velocity (e') was reduced in 31 (51.7%) and septal e' in 9 (15%) patients. "R=0.60, p<0.05 for all cases).

Conclusion: Echocardiography with tissue Doppler anular measurements detected the abnormalities in 83.3% of young asymptomatic or oligosymptomatic survivors of Hodgkin’s lymphoma ≥5 years after mediastinal irradiation. Early signs of restrictive/constrictive impairment were prevalent and correlated with exercise limitations.

Prevalence of cardiomyopathy in an unselected population of adult patients with cystic fibrosis

L. Ruiz Bautista1, J. Segovia1, C. Prados2, L. Maiz3, R. Girón4, M.T. Martínez1, M. González Esteche1, S. Mingó1, M. Pastrana1, L.A. Alonso Pulpon1, 1University Hospital Puerta de Hierro Majadahonda, Department of Cardiology, Madrid, Spain; 2University Hospital La Paz, Madrid, Spain; 3University Hospital Ramón y Cajal, Madrid, Spain; 4University Hospital La Princesa, Madrid, Spain; 5University Hospital 12 de Octubre, Madrid, Spain; 6Hospital Clinic San Carlos, Madrid, Spain; 7University Hospital Puerta de Hierro Majadahonda, Madrid, Spain

Purpose: Cystic fibrosis (CF) is characterized by an obstructive pulmonary pattern and a pancreatic exocrine deficiency, frequently associated with malabsorption and enteropathies. Cardiomyopathy (CMP) has been described in children with CF since the 1950's, with histologic features similar to those seen in malnourishment-related CMP, such as Keshan’s disease. Our aim in this study was to describe the prevalence and features of CMP in a population of unselected adult CF patients.

Methods: As part of an investigation of the prevalence and causes of CMP in CF, we studied a series of unselected adult CF patients without known cardiac disease. After obtaining clinical and genetic information, we performed a blood test, a proBNP, and an echocardiographic study. We defined systolic dysfunction as left ventricular ejection fraction less than 55% (Simpson’s method). Diastolic dysfunction was defined by pathological patterns in mitral flow as classically obtained by doppler ultrasound. Patients with data of CMP were also studied with magnetic resonance (MR).

Results: Study population included 120 adult CF patients recruited from 4 specialized outpatient clinics. Mean age at study was 31±8.9 years, and 52% were male. Pancreatic disease was present in 80% of them, and low levels of vitamins and trace elements were common in spite of receiving dietary supplements. Left heart disease was present in 12 patients, with a prevalence of 10%; systolic dysfunction was evident in 6 patients (5%), and diastolic dysfunction in 9 patients (7.5%). There was a 2.5% that had both systolic and diastolic dysfunctions. Systolic dysfunction was significantly associated with a patchy myocardial enhancement pattern on MR (P<0.05), as well as with a higher frequency of Pseudomonas aeruginosa airway colonization (p=0.04) and a trend to having a lower body mass index (22±4.9kg/m² vs 20.6±4.1kg/m²; p=0.07). Median value for proBNP in systolic dysfunction was 53 pg/ml (range 22 - 8000 pg/ml).

Conclusions: The prevalence of CMP in an unselected group of adults with CF was 10%. The subgroup with left ventricular systolic dysfunction showed patchy fibrosis, similar to that described in malnourishment-related CMP. This form of heart disease should be included in the spectrum of organic involvement in CF patients and should be ruled out, especially in those with severe malabsorption or under evaluation for pulmonary transplant.
arteries in PXE patients independently of the presence of cardiovascular risk factors. In heterozygous carriers, diastolic ventricular function is also abnormal, indicating cardiovascular involvement and the need for cardiovascular assessment in this specific group.

**P4998** Differential effect of antiretroviral drug regimens on aortic elastic properties in HIV infected individuals

A. Synodinos1, C. Vlachopoulos1, P. Xaplanteris1, H. Sambatakou2, E. Maroillis2, N. Isakidis1, D. Terentes-Prezios1, D. Pektasidis2, C. Stefanadis2. 1Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece; 2Hippokration Hospital, University of Athens, Department of Medicine, Athens, Greece

**Purpose:** Aortic elastic properties mediate cardiovascular performance. Pulse wave velocity (PWV), an index of aortic stiffness, is an independent predictor of future outcomes. HIV infection is linked to higher cardiovascular risk and certain classes of antiretroviral therapy (ART) drugs, i.e. protease inhibitors, increase this risk disproportionally. The aim of the study was to assess the interplay of ART and arterial stiffness. Moreover, we sought to investigate how different ART regimens are linked to arterial stiffness.

**Methods:** 51 HIV infected patients were studied (50 men, age 40±10 y.o.). 12 were naïve to treatment, 39 were on ART. Among the ART treated, 22 were on a combination of nucleoside reverse transcriptase inhibitor plus non-nucleoside reverse transcriptase inhibitor (NRTI/NNRTI) and 17 were on a combination of nucleoside reverse transcriptase inhibitor plus protease inhibitor (NRTI/PI). Carotid-femoral PWV was measured non-invasively with a validated device (Complior).

**Results:** Naïve patients had lower values of PWV compared to patients on ART (7.45 m/sec vs. 7.15 m/sec, P=0.05). Regarding drug regimens, those on NRTI/PIs had higher levels of PWV compared to those on NRTI/NNRTIs and to naïve to treatment patients (7.98±1.83 m/sec vs 7.04±1.21 m/sec vs 6.68±0.98 m/sec respectively, P=0.037 for overall ANOVA) (Figure).

**Conclusions:** PWV treatment according to their physician’s criteria.

**P4999** Study of heart involvement in Kawasaki disease: a multicenter study

Z.M. Amirmoghadam, Shahid Beheshti University of Medical Sciences, Imam Hossein Medical Center Department of Cardiology. Tehran, Iran (Islamic Republic of)

**Introduction:** Kawasaki disease happens mostly in children less than 5 years of age and presents itself as an acute and self limiting disease with worldwide spread. One of the important aspects of this disease is the serious heart morbidity it can cause if undetected. Coronary vessels are the most common site of heart involvement. The aim of this study was to determine demographic of heart involvement in Kawasaki patients. We also studied age and sex and their relation with heart findings in patients suffering from Kawasaki disease.

**Methods:** A prospective study of patients suffering from Kawasaki disease in two hospitals from year 2000 to year 2005 was performed. Findings: 97 patient had Kawasaki disease, 65 (67%) were male and 32 (33%) were female. 75 (77%) were below five years of age and 22 (22.7%) above 32 (32.9%) had one or more heart involvement. From patients with heart involvement 20 (62.5%) were male and 12 (37.5%) were female. 22 (67%) of patients with heart involvement were under 5 years of age and 7 (12%) were from 6 to 10 years old and 3 (9%) over 10 years old. The highest age among patients was 11/5 years. The distribution of heart involvement was 23 (23%) pericardial effusion (the highest heart involvement), Coroner dilation and Aortic stenosis each with 2 (2%) patients were the rarest heart findings.

**Conclusion:** CV performance as measured by S significantly improves during follow-up in PH patients who are under PV treatment. Further investigation is needed to find out whether this improvement is secondary to a functional recovery of the RV or to a decrease in RV afterload. We suggest routine measurement of RV S to follow up the disease progression.

**P5000** Right ventricular 2D-strain: a new tool to follow up pulmonary hypertension patients under vasodilator therapy


In patients with pulmonary hypertension (PH), progression of the disease and survival are related to the capability of the right ventricle (RV) to adapt to the chronically elevated pulmonary artery pressure (sPAP). Recent studies have successfully applied speckle-tracking derived strain (S) to quantify RV dysfunction in PH. Little is known about RV deformation evolution under pulmonary vasodilator (PV) treatment.

**Methods:** We performed echocardiographic follow-up of 17 patients with PH (Groups I and IV of the Dana Point classification) during 13±5.8 months and measured RV longitudinal systolic S from 6 RV segments. All cases were under PV treatment according to their physician’s criteria.

**Results:** We found a significant improvement in most conventional echocardiographic measurements as well as global and regional S during follow-up (table 1, figure 1).

**Conclusion:** Our patients compared to 2/3% mortality in other studies which might be due to adequate treatment or incomplete patient follow up.
Echocardiographic prognostic factors for mortality in pulmonary hypertension: way beyond tricuspid annular displacement


Right ventricular (RV) function is the main determinant of morbidity and mortality in pulmonary hypertension (PH), and echo-derived tricuspid annular plane systolic excursion (TAPSE) has a well-recognized prognostic importance in this setting. Recently, RV deformation parameters have shown to accurately quantify RV function in PH. The aim of our study was to find out whether RV speckle-derived strain (S) may have an additional prognostic role for PH patients when added to classic RV function measurements such as TAPSE.

Methods: We prospectively studied 55 patients with PH of varied etiology and 22 controls. RV longitudinal systolic S was evaluated by echocardiography for 6 RV segments (from the 4-chamber apical view).

Results: We found a significant reduction of global and regional S in PH patients when compared to controls: -15.5±5.9 vs -25.9±3.9 (p<0.005). During a mean follow-up of 9.2±7.1 months, 8 cardiovascular (CV) events (death and cardiac or pulmonary transplant) occurred. We identified two variables significantly associated with CV events: TAPSE (r=0.005) and S (p=0.002). Global S was found to improve the Area Under the ROC Curve (AUC) for the prediction of adverse CV events when added to TAPSE (from 0.841 (p=0.001) to 0.907 (p=0.005), figure 1a). Kaplan-Meier survival analysis showed that the subgroup of patients with low TAPSE and low S had a marked predisposition to clinical deterioration and death when compared to the groups with either low TAPSE or low S alone (figure 1b).

Conclusion: In our study global S has shown an additional value for the prediction of CV events when added to TAPSE. Therefore we suggest the routine assessment of deformation parameters for the follow-up of PH patients.

Echocardiography of pulmonary vascular function in asymptomatic carriers of the bone morphogenetic protein receptor type 2 mutation

A.T. Pavelscu,1 R. Vanderpol,1 J.L. Vachier,2 E. Gruning1, R. Naeije1. 1Free University of Brussels (ULB), Department of Pathophysiology, Brussels, Belgium; 2ULB Erasme University Hospital, Department of Cardiology, Brussels, Belgium; 1University Hospital of Heidelberg, Internal Medicine III, Dept Cardiology, Angiology & Pneumology, Heidelberg, Germany

Purpose: Relatives of patients with idiopathic pulmonary arterial hypertension (IPAH) tend to present with enhanced pulmonary vascular responses to exercise or hypoxia as measured by the maximum velocity of tricuspid regurgitation (TRV), this may be driven by carriers of a mutation of the bone morphogenetic protein receptor type 2 (BMPR-2). We wondered if this potentially important risk factor might better defined by more extensive study of pulmonary vascular function.

Methods: Echocardiographic measurements were performed during an incremental exercise test and during 2 hours of hypoxic breathing in 35 relatives (of whom 5 were carriers of a BMPR-2 gene mutation) of IPAH patients, and in 38 healthy controls. Pulmonary artery pressures (PAP) were estimated from TRV, total pulmonary vascular resistance (PVR) was calculated from the right ventricular outflow time-velocity integral and TRV, and cardiac output (Q) from left ventricular outflow tract velocity. Multipoint PAP-Q relationships and a distensibility coefficient, alpha were also derived.

Results: In BMPR-2 carriers, no carrier relatives and controls, PAP at an average workload of 100 watts and after 120 min of hypoxia, and the P-Q slopes were not different. However, alpha was markedly decreased in BMPR-2 carriers, at rest (0.018±0.005 vs 0.034±0.004 vs 0.029±0.004/mmHg, p<0.05) and exercise (0.012±0.004 vs 0.021±0.002 vs 0.015±0.009/mmHg, p<0.05). The hypoxia induced increase in PVR was greater in the relatives with BMPR-2 compared to relatives without mutations.

Conclusion: Asymptomatic carriers of the BMPR-2 mutation present with decreased pulmonary vascular distensibility and increased hypoxic pulmonary vasoconstriction which are identifiable at echocardiographic examination.

Survival in pre-capillary pulmonary hypertension: does echocardiography make the difference?


Purpose: The aim of this study was to assess pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertensive (CTEPH) patients’ survival in relation to a prospective, protocol-based collection of echocardiographic data in pre-capillary pulmonary hypertensive patients referred to the National Pulmonary Hypertension Centre in London. All patients received the guideline-indicated best medical therapy.

Methods: All patients referred to the National Pulmonary Hypertension Service from 2002 until 2010 were included in the study. The patient cohort was solely focused in pre-capillary pulmonary hypertensive patients and consisted of 777 consecutive patients. The data was analysed using a univariate and multivariable time-dependent Cox model. The survival outcome was determined by death. Of 777 patients, 195 (25.1%) died. Median follow up of patients was 4.75±2.1 years. Echocardiographic indices were inserted into univariate and multivariable analysis according to the cause (pulmonary arterial hypertension vs. chronic thromboembolic pulmonary hypertension) and trends cut-off values were used for the overall population as well as for the establishment of a prognostic index. Heagerty time-dependent ROC curves were employed for the predictive value of each parameter.

Results: The overall survival was best determined by the severity of tricuspid regurgitation (p=0.005, HR=10.98), the presence of pericardial effusion (p=0.0003, HR=1.714) and the composite score of RV systolic function (p=0.0002, HR=1.37), followed by left atrial diameter (p=0.0349, HR=1.04), the diameter of inferior vena cava (p=0.001, HR=0.896) and the echocardiographic measurement of pulmonary vascular resistance (p=0.0002, HR=0.822) that were the strongest predictors of mortality.

A greater than moderate tricuspid regurgitation, pericardial effusion, a greater than moderate impaired RV systolic function, pulmonary end-diastolic pressure more than 20.9 mmHg, a diameter of inferior vena cava ≥ 21.8 mm, a pulmonary vascular resistance > 8.9 Wood units and a RV cardiac output ≤ 3.45 l/min, on initial echocardiographic assessment indicate a poor survival.

Conclusion: In a large group of consecutive pre-capillary pulmonary hypertensive patients, the severity of tricuspid regurgitation, RV systolic function and the presence of pericardial effusion may indicate poor survival. Inoperable CTEPH patients had worse survival when compared to patients with pulmonary arterial hypertension.
Improving echocardiography estimation of right atrial pressure: comparison among several models and a new one based on right atrial evaluation

C. Magrini1, P. Omedea2, W. Grosso Mairad2, M. Chiara3, D. Presutti3, G. Bucca2, C. Moretti2, F. Gaia2, F. Veglio3, A. Milani1, 1Univ. of Turin, Dpt. of Medicine & Experimental Oncology, Div. of Internal Med. & Hypertension Unil. Turin, Italy; 2University of Turin, San Giovanni Battista Molinette Hospital, Cardiology Department 1, Turin, Italy; 3University of Turin, Department of Clinical Pathophysiology, turin, Italy.

Purpose: The estimation of right atrial pressure (RAP) has a great impact on the non-invasive evaluation of pulmonary hemodynamics. Several models have been developed to estimate RAP based on the inferior vena cava (IVC) diameter and collapsibility. However, IVC evaluation is not reliable for intermediate RAP values, young adolescents, patients on ventilators or bad subcostal window. The aim of this study was to compare several known models of RAP estimation against the invasive RAP (iRAP) and develop a new one to overcome the limitations of IVC analysis.

Methods: Echocardiography was performed on 75 patients within 60 minutes from cardiac catheterization. IVC was evaluated in long and short-axis view. Images of right chambers, tricuspid Pulsed Tissue Doppler, and hepatic vein flow were acquired. RAP was estimated using 5 different known models based on IVC evaluation and a new one based on right atrial analysis. All RAP models were compared to iRAP by Bland-Altman analysis.

Results: A population of 75 patients was evaluated (age: 62±14 years; iRAP: 9.5 mmHg [7-12], range 1 - 22 mmHg). IVC measured by MMode in long-axis view showed better correlation with iRAP. Among the 5 models based on IVC, the most recent one performed better (r=0.29; p=0.04), but had a wide confidence interval. Right atrial total ejection fraction (ToEF) and systolic volume (sVol) showed a strong positive (sVol) and inverse (ToEF) linear association with iRAP (p<0.0001). Our model based on these parameters performed significantly better (r=0.48; p<0.001) and had a narrower confidence interval (8.9±8.4 mmHg).

Conclusion: RHC remains the gold standard for the diagnosis of PH. Nevertheless, an easy and integrated echo score allows pathophysiologic insight along a hemodynamic spectrum in a mixed PH cohort providing a good pre-test probability of having a pre-capillary rather than post-capillary PH.

An echocardiographic score for evaluating the pre-test probability of having a pre-capillary rather than a post-capillary pulmonary hypertension

M. D’Alto, E. Romeo, P. Argentino, A. Correra, B. Sarubbi, N. Grimaldi, M. Pignatello, A. Caronna, R. Calabro’, M.G. Russo. Second University of Naples - Monaldi Hospital, Department of Cardiology, Naples, Italy.

Aim: To provide an easy and integrated echo-score for evaluating the pre-test probability of having a pre-capillary (pre-PH) rather than post-capillary (post-PH) pulmonary hypertension (PH).

Methods: One hundred thirty-five consecutive patients referred to our PH center from January to December 2011 underwent standard Doppler echocardiography (DE) within 1 hour of a clinically indicated right heart catheterization (RHC). The DE was scored on the basis of features suggesting pre-PH: right atrium (RA) > left atrium (LA), right ventricle (RV) > left ventricle (LV), apex forming RV, LV eccentricity index (EI) >0.9, pericardial effusion (PE), systolic notch at right ventricular outflow tract (RVOT) pulse wave Doppler, dilated and fixed inferior cava vein (ICV) (score for yes = 1, no = 0), or post-PH: LV ejection fraction (EF) >40%, moderate to severe aortic and/or mitral disease (score for yes = 1, no = 0). The echo range scored from -2 to 7. Patients were arbitrarily divided in 3 groups: low score (-2 to 0), medium score (1 to 2) and high score (3 to 7) probability of having pre-capillary PH.

Results: Twelve/135 patients did not have pulmonary hypertension at RHC. 84 patients showed pre-capillary PH (34 group 1, 22 group 3 and 39 post-capillary PH (group 2) at RHC. The probability of having pre-PH was 37% in presence of low, 86% in presence of medium and 95% in presence of high echo score. No patient with LV-EF <40% had pre-PH (specificity for post-PH 100%). The majority of echo features showed a high specificity but a low sensitivity for pre-PH.

Figure 1. Comparison of RAP models

Conclusions: The adoption of a new model based on RA morphology and function can provide a better estimation of RAP helping to improve non-invasive pulmonary pressure estimations.

Pulmonary artery trunk dilation in symptomatic subjects referred for coronary artery calcium scoring by means of a 64-slice cardiac computed tomography

M. Sosnowski1, A. Czekaj1, B. Korzeniowski1, R. Mlynarski2, Z. Gasior1, M. Tendera4, 1Medical University of Silesia, Unit of Noninvasive Cardiovascular Diagnostics, Katowice, Poland; 2Silesian Heart Centre, Unit of Noninvasive Cardiovascular Diagnostics, Katowice, Poland; 3Silesian Medical University, Department of Cardiology, Katowice, Poland; 4Medical University of Silesia, 3rd Chair and Department of Cardiology, Katowice, Poland.

Non-contrast cardiac computed tomography is as established method for coronary artery calcium determination in both asymptomatic and symptomatic subgroups. We aimed at assessment of the prevalence of ancillary findings, including pulmonary artery dilation. 1075 females and 484 males examined between March 2010 and January 2012 were examined for CAC scoring by means of cardiac MDCT (64-slice Aquilion). A retrospective analysis of the data for evaluation of pulmonary artery trunk diameter (PAD, mm) was performed. Gender-dependent upper normal limits were established in 74 women and 50 men with normal CT scanning, zero CAC score, who were never smokers, non-obese, non-diabetic and non-hypertensive. Proportion of subjects with abnormal PAD was determined separately in men and women. Abnormal PAD was detected in 209 women (19%), while increased PAD:AAD ratio in 57 women (5%). In total, the PA dilation was found in 219 women (20.3%) including 172 with one measure abnormal, and 47 with both measures abnormal. Among men, abnormal PAD was detected in 89 subjects (18%), while abnormal PAD:AAD ratio in 9 men (2%). In total, any PAD increase was found in 82 men (17%), while both measures abnormal was found in 8 subjects (2%). Logistic regression analysis revealed that independent predictors of PAD increase in females were a positive CACS (OR 2.78) and obesity (1.83). Similar determinants were recognized in men (a positive CAC OR 3.0, OR 2.84, respectively).

Conclusions: Pulmonary artery trunk dilation is relatively frequently observed in subjects referred for coronary artery calcium determination. Presence of coronary atherosclerosis and obesity were found as independent predictors of PAD enlargement. Detection of PAD abnormality might help to optimize diagnostic and therapeutic approaches in symptomatic subjects referred for CAC scoring.

Pulmonary vasculopathy assessed by intravascular ultrasound in patients with severe chronic respiratory failure evaluated for lung transplantation: comparison to pulmonary arterial hypertension


Purpose: The aim of the study is to assess pulmonary vasculopathy (wall fibrosis, pulmonary arterial pulsatility and elastic modulus) in patients with chronic respiratory failure evaluated for lung transplantation, by means of intravascular ultrasound (IVUS) in medium sized pulmonary arteries, and to compare it to pulmonary arterial hypertension (PAH) and healthy controls.

Methods: We studied 37 patients, 9 Group 1 (pre-lung transplantation, COPD, pulmonary fibrosis, NYHA 3-4), 18 Group 2 (PAH, NYHA 2-3) and 10 in Group 3 (healthy controls). Group 1: 2 females, 59±8 years. Group 2: 14 females, 53±14 years and Group 3: 6 females, 51±5 years. All patients were submitted to left and right heart catheterization, and IVUS in medium sized elastic PA (2-3 mm diameter) of the inferior lobes.
Egr-1 expression is specific for neointimal pulmonary neointimal lesions in PAH. A female model of severe neointimal pulmonary hypertension was established by exposing adult female rats to monocrotaline (MCT) and increasing flow (MCT+Flow). Animals were sacrificed 1 day before increased flow and at day 10 after MCT. Using micro-array analysis, we recently identified that transcription factor Egr-1 was upregulated in experimental PAH-associated end-stage PAH. Its role in neointimal development in PAH is unknown. Here, we aimed to assess in both human and rats apicaloloporexpression of Egr-1 in neointimal (flow-associated) PH compared to non-neointimal Pulmonary Hypertension (PH).

Methods: In rats, flow-associated PAH was created by combining monocrotaline with an aortalocal shunt (MCT+Flow); and compared with a non-neointimal PH model (MCT-only). Animals were sacrificed 1 day before increased flow and at multiple time points after flow addition (1 day, 1 week, 4 weeks). Egr-1 expression was spatiotemporally assessed using laser-dissection, qRT-PCR and immunohistochemistry. In humans, apicaloloporexpression of Egr-1 mRNA expression of the pro-inflammatory cytokine MCP-1 increased during disease development in both human and experimental PAH.

Conclusions: Patients with severe chronic respiratory failure, even in the absence of severe pulmonary hypertension, suffered from a severe pulmonary arte- riosclerotic pulmonary hypertension with a high degree of stenosis and functional PA wall remodeling similar to that of PAH patients.

PULMONARY HYPERTENSION: MECHANISMS

Egr-1 expression is specific for neointimal development in both human and experimental PAH

M.G. Dickinson1, B. Bartelds1, M.A.J. Borgdorff1, G. Molenaar1, J. Sijtsma2, R.M.F. Berger1, J. Center for Congenital Heart Diseases, Beatrix Children's Hospital, Univ. Medical Center Groningen, Groningen, Netherlands; 2University Medical Center Groningen, Groningen, Netherlands

Objectives: In Pulmonary Arterial Hypertension (PAH) due to congenital heart disease, increased pulmonary blood flow is an essential trigger for neointimal formation. Using micro-array analysis, we recently identified that transcription factor Egr-1 is upregulated in experimental PAH-associated end-stage PAH. Its role in neointimal development in PAH is unknown. Here, we aimed to assess in both human and rats apicaloportunexpression of Egr-1 in neointimal (flow-associated) PH compared to non-neointimal Pulmonary Hypertension (PH).

Methods: In rats, flow-associated PAH was created by combining monocrotaline with an aortalocal shunt (MCT+Flow); and compared with a non-neointimal PH model (MCT-only). Animals were sacrificed 1 day before increased flow and at multiple time points after flow addition (1 day, 1 week, 4 weeks). Egr-1 expression was spatiotemporally assessed using laser-dissection, qRT-PCR and immunohistochemistry. In humans, apicaloloporexpression of Egr-1 expression was studied in lung biopsy samples of 27 end stage PAH patients (associating with congenital shunt (flow) PH, n=12; IPAH, n=15) and compared with non-neointimal PH (hypoxic PH; n=4) and healthy controls (n=11).

Results: In rats, MCT+Flow rats developed, within 4-5 weeks, severe PAH (pSVRP 64±12 mmHg, Fulton index 0.57±0.03) and complex neointimal lesions (vessel occlusion 49.3%; compared to MCT-only; pSVRP 50±14 mmHg; Fulton index 0.32±0.03, no neointimal lesions) and control (pSVRP 25±4 mmHg, Fulton index; 0.29±0.04). In MCT-flow rats Egr-1 mRNA was upregulated 1 day after flow addition and in end-stage PAH. Increased flow directly induced Egr-1 expression in pulmonary endothelial cells; during disease development, Egr-1 expression migrated throughout the vascular medial layer. In contrast, Egr-1 mRNA was not upregulated in MCT-only rats and Egr-1 expression was observed only sporadically in the non-neointimal vessel remodeling. In both flow PH and IPAH patients, Egr-1 expression was upregulated compared to hypoxic PH (P<0.001) and controls (P>0.001). The strongest expression was seen in the in-earina vessels of flow-PH (P=0.05 vs IPAH; P<0.001 vs hypoxic PH and control) and in plexiform lesions. In flow-PH, endothelial Egr-1 expression in the in-earina-cal vessels correlated with increase in pulmonary artery pressure (mPAP).

Conclusions: We show that in both experimental human and PAH, but not in non-neointimal PH, Egr-1 is upregulated and associated with neointimal development. This suggests that Egr-1 is an important regulator in the development of pulmonary neointimal lesions in PAH.

A female model of severe neointimal pulmonary hypertension: evidence for increased susceptibility in a female rat following pneumonectomy and monocrotaline

R.J. White1, D.F. Meck1, D. Haight1, W. O’Dea2, F. Ahmad3
1University of Rochester Medical Center, Rochester, United States of America; 2University of Florida, Gainesville, United States of America; 3University of Pittsburgh, Pittsburgh, United States of America

Pulmonary arterial hypertension (PAH) is an enigmatic, fatal disease with few treatment options. Decades of important animal studies in pulmonary hypertension have utilized male rats, exposed either to chronic hypoxia or monocrotaline (MCT), to define disease mechanisms and test novel treatment strategies. However, females represent 70-80% of the afflicted human population, and a female rat model with the key features of human disease would be useful for testing hypotheses about sex and the susceptibility to PAH. Previous studies exposing female rats to MCT did not demonstrate significant pulmonary hypertension.

We sought to establish a female rat model of PAH with neointimal formation and right ventricular (RV) failure. 7 days after left pneumonectomy, we administered 40-60 mg/kg MCT to young rats (male or female); early signs of RV dysfunction were present day 10 after MCT using a Visusonics 2100 echo. In some animals, echo measures were made at day 21 after MCT before the rats were sacrificed for lung micro-CT and histology; other rats were allowed to progress to death.

At 60 mg/kg, female rats experienced mortality at least as severe as males, perhaps worse. In contrast to previous findings, micro-CT illustrated more severe vascular pruning in female rats receiving 40 mg/kg MCT as compared to male rats receiving 50 mg/kg suggesting that female rats in this model are more sensitive to MCT. Male and female rats had severe RV dilation and loss of fractional shortening at day 21 after MCT. In a separate group, RV gene expression profiling in rats (n=4 each) sacrificed at day 10 illustrated greater magnitude RNA differences for females as compared to males in functional clusters controlling cellular hypertrophy, sarcomere contraction, cell-cell adherence, cytokine regulation, and calcium signaling. There was no apparent renal or liver disease in males or females as assayed by urine, blood chemistry, and tissue histology on days 7, 14, and 21 after MCT. We will also present exciting quantitative data from the micro CT which details length, radius, and branching of the individual vessels in the micro CT images.

Young female rats treated with relatively low dose MCT following left pneumonectomy develop a severe, neointimal pulmonary vasculopathy with vascular pruning and RV failure. This model offers a unique opportunity to explore hormonal or sex chromosomal influences on the susceptibility to PAH. It also affords the opportunity to examine sex-specific differences in the response to an experimental PAH therapy and the potential to analyze sex-specific RV adaptation to increased afterload.

Increased pulmonary blood flow causes perivascular macropassage inflowation in experimental PAH

M.G. Dickinson, B. Bartelds, M.A.J. Borgdorff, R.M.F. Berger, J. Center for Congenital Heart Diseases, Beatrix Children's Hospital, Univ. Medical Center Groningen, Groningen, Netherlands

Background: In Pulmonary Arterial Hypertension (PAH) due to congenital heart disease, increased pulmonary blood flow is an essential trigger for neointimal formation. Inflammatory processes have been suggested to play a role in the development of these lesions.

Objectives: Here, we aimed to investigate the role inflammation, specifically macropassage inflowation, during neointimal development due to increased blood flow in experimental PAH.

Methods: Flow-associated PAH (with neointimal formation) was created in Sprague-Dawley rats by combining monocrotaline (MCT) with an aortalocal shunt (MCT+Flow). Rats that received monocrotaline MCT-only (non-flow, non-neointimal Pulmonary Hypertension) and sham operated rats (Con) served as control. After invasive hemodynamic measurements, animals were sacrificed 1 day before flow addition and 1 day, 1 week, 4-5 weeks after flow addition for biomolecular analysis.

Results: In MCT+Flow rats developed neointimal lesions with perivascular pro-inflowation with severe PAH. The strongest expression was seen in the in-earina arteries of flow-PH (P<0.005 vs MCT-only). In MCT+Flow rats strong perivasalocal macrophage infiltration was seen around neointimal lesions. In MCT+Flow rats mRNA expression of the pro-inflammatory cytokine MCP-1 increased during disease development in both human and experimental PAH.

Conclusions: We show that in both experimental human and PAH, but not in non-neointimal PH, Egr-1 is upregulated and associated with neointimal development. This suggests that Egr-1 is an important regulator in the development of pulmonary neointimal lesions in PAH.

Nitrated fatty acids attenuate right ventricular dysfunction in hypoxia-induced pulmonary hypertension in mice

T.K. Rudolph, A. Kline, A. Moeller, T. Ravekes, K. Friedrichs, S. Blankenberg, V. Rudolph, S. Baldus, University Medical Center Hamburg-Eppendorf, Center for Cardiology and Cardiovascular Surgery, Hamburg, Germany

Background: The pathophysiological hallmarks of pulmonary arterial hypertension (PAH) are centered around vasoconstriction, vascular hypertrophy and fibrosis. So far, the molecular mechanisms underlying consecutive righthalf failure re-
Right ventricular hypertrophy and failure abolish cardioprotection by ischemic preconditioning

A. Andersen, J.A. Povlsen, H.E. Boeker, J.E. Nielsen-Kudsk. Aarhus University Hospital, Skejby, Aarhus, Denmark

Purpose: To investigate whether hypertrophy and failure of the right ventricle changes the response to ischemia and ischemic preconditioning.

Materials and Methods: Male Wistar rats were subjected to moderate pulmonary trunk banding (mPTB), severe PTB (sPTB) or SHAM operation. The degree of RV caused an increase in infarct size in hearts from mPTB and sPTB animals. This translated in significantly reduced right heart failure as determined by BNP (<0.05). Leucocyte infiltration as well as oxidative stress superoxide bioavailability in the right ventricle were significantly reduced following OA-NO2 treatment. In addition, picrocumarol red staining revealed attenuated ventricular fibrosis in response to OA-NO2 (1.2±0.43 vs. 2.3±0.31 in vehicle treated animals, p=0.03).

Conclusions: The current findings not only underscore the significance of inflammation and oxidative stress in the pathophysiology of right ventricular dysfunction in pulmonary hypertension, but reveal that nitrated fatty acids may provide a novel therapeutic option in pulmonary arterial hypertension.


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Low-frequency intermediate penetrance variants in the ROCK1 gene predispose to congenital heart disease

J. Palomino Doza1, A. Topf2, J. Bentham1, S. Bhattacharya1, C. Cosgrove1, J. Granados-Riveran1, J. Godship2, D. Henderson2, J. O’Sullivan1, B.D. Keavney1,1Clinical University Hospital of Valladolid, ICIROC, Valladolid, Spain; 2Newcastle University, Institute of Genetic Medicine, Newcastle upon Tyne, United Kingdom; 3University of Oxford, Department of Cardiovascular Medicine, Oxford, United Kingdom; 4Nottingham University, Institute of Genetics, Nottingham, United Kingdom; 5Newcastle upon Tyne Hospitals NHS foundation trust, Newcastle upon Tyne, United Kingdom

Background: Epidemiological studies indicate a substantial excess familial recurrence followed by non-syndromic Tetralogy of Fallot (TOF), implicating genetic factors that remain largely unknown. The Rho induced kinase 1 gene (ROCK1) is a key component of the planar cell polarity signaling pathway, which plays an important role in cardiac development. The aim of this study was to investigate the role of genetic variation in ROCK1 on the risk of TOF.

Methods: ROCK1 was sequenced in a discovery cohort of 93 non-syndromic TOF patients to identify rare variants. TagSNPs were selected to capture common variation in ROCK1. Novel variants and TagSNPs were genotyped in 458 TOF cases and 1920 healthy controls.

Results: A novel rare SNP (c.807C>T) was associated with TOF risk (OR 4.29 [95% CI 1.91-9.60]; p=0.0002). The minor allele frequency of c.807C>T in the controls was 0.003, and the variant accounted for 2% of the population attributable risk (PAR) of TOF. There was also significant association with TOF for an uncommon SNP in ROCK1, rs288979 (OR 1.64 [95% CI 1.15-2.30]; p=1.5x10^-4). The minor allele frequency of rs288979 in the controls was 0.043, and the variant had a significant PAR of TOF. These association signals were independent of each other.

Conclusions: We conclude that low frequency intermediate penetrance (LFIP) variants in the ROCK1 gene predispose to the risk of TOF.

Influence of genetic polymorphisms of alpha-adrenergic receptors, endothelial nitric oxide synthase and Bradykinin receptor B2 on treadmill exercise test responses

R.A. Belo Nunes1, L.P. Barrosso2, R.T. Schmidt2, D.D. Barreto2, H.F. Freitas4, A.C. Pereira3, J.E. Krieger1, A.J. Mansur1, 1Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paulo, Brazil; 2Institute of Mathematical and Statictic, University of Sao Paulo, Sao Paulo, Brazil

Purpose: Treadmill exercise testing responses have been associated with cardiovascular prognosis in individuals without overt heart disease. Neurohumoral and nitric oxide responses may influence cardiovascular performance during exercise. The aim of this study was evaluate associations between genetic polymorphisms of alpha-adrenergic receptors (ADRA1A, ADRA2A and ADRA2B), endothelial nitric oxide synthase (eNOS) and bradykinin receptor B2 (BKGR) on treadmill exercise test responses in individuals without overt heart disease.

Method: We enrolled 766 (417 women and 349 men) asymptomatic subjects. We selected the following variables during a maximal-symptom-limited treadmill exercise test: exercise capacity, chronotropic reserve, maximum heart-rate and blood pressure recovery. Genotypes for the ADRA1A Arg347Cys (rs1048101), ADRA2A C1780T (rs553668), ADRA2B Del 301-303 polymorphisms were assessed by polymerase chain reaction (PCR) followed by high resolution melting analysis. Laboratory and demographic levels and cardiovascular risk factors. Such finding supports the hypothesis of a possible causal relationship between the variant and left ventricular mass warranting further investigation.

Systematic testing of literature reported genetic variation associated with restenosis after percutaneous coronary intervention: results of the genetic determinants of restenosis study


Purpose: Despite all medical advances, coronary restenosis after percutaneous coronary intervention still is a significant problem. Unraveling the mechanisms leading to restenosis development remains challenging. Although many studies have identified genetic markers associated with restenosis, consistent replication of the reported markers is scarce, mainly due to small sample sizes, heterogeneity of the phenotype and lack of proper replication cohorts. The aim of the current study was to analyze the joined effect of previously in literature reported candidate genes for restenosis using the gene-set analysis of GENetic DEterminants of Restenosis (GENDER) databank.

Methods: Candidate genes were selected using a search on MEDLINE including the terms ‘genetic polymorphism’ and ‘coronary restenosis’. The final set included 36 genes. All single nucleotide polymorphisms in the genomic region of each gene, including a 10kb window, were analyzed using set-based analysis in PLINK in the GENDER databank, containing genotypic data of 2,575,000 SNPs of 295 patients who developed restenosis (cases) and 571 matched controls.

Results: The set including all candidate genes was significantly associated with
restenosis, p=0.041. Subsequent analyses of the individual genotypes demonstrated that the observed association of the complete set was determined by 7 of the 36 genes. Removing these 7 genes from the complete set and subsequent analysis of the subset of the other 29 genes did not demonstrate a remaining jointed effect, p=1.0 (subset1).

Conclusion: Despite the overt inconsistencies of individual candidate gene studies, this study demonstrates that the joint effect of all these genes together, indeed is associated with clinical restenosis.

**Synergistic effects of genetic variants of the apolipoprotein A-V gene and the butyrophilin, subfamily 2, member A1 gene on dyslipidemia in east Asian populations**

M. Oguri, Y. Shibata, H. Kamiya, M. Hiramatsu, H. Horibe, K. Kato, T. Murakata, J.H. Lee, Y. Jang, Y. Yamada, Japanese Red Cross Nagoya First Hospital, Department of Cardiology, Nagoya, Japan; 2Nagoya Central Hospital, Department of Cardiology, Nagoya, Japan; 3Gifu Prefectural Tajimi Hospital, Department of Cardiovascular Medicine, Tajimi, Japan; 4Meito Hospital, Nagoya, Japan; 5Nagoya University Graduate School of Medicine, Heart Center, Department of Cardiology, Nagoya, Japan; 6Vesalius University, Department of Food and Nutrition, College of Human Ecology, Seoul, Korea, Republic of; 7Vesalius University College of Medicine, School of Medicine, Belgium; 8Life Science Research Center, Mie University, Tsu, Japan

**Purpose:** The genes that underlie genetic susceptibility to dyslipidemia in Asian populations remain to be identified definitively. We previously showed that the rs662799 of the apolipoprotein A-V gene (APOA5) and the C polymorphism (rs662799) of the butyrophilin, subfamily 2, member A1 gene (BTN2A1) were significantly associated with an increased serum concentration of triglycerides (TG) and a decreased serum concentration of HDL-cholesterol in Japanese individuals. The purpose of our study was to examine whether these polymorphisms synergistically affect serum lipid profiles and the prevalence of dyslipidemia in East Asian populations.

**Methods:** The study comprised 7471 Japanese and 3529 Korean individuals. Bonferroni's correction was applied for statistical significance of association.

**Results:** The rs662799 of APOA5 was significantly (P < 0.004) associated with serum concentrations of TG and HDL-cholesterol, but not LDL-cholesterol, in Japanese and Korean individuals, whereas the rs6929846 of BTN2A1 was significantly associated with serum concentrations of TG and HDL-cholesterol, but not LDL-cholesterol, in Japanese individuals. There was no relation between rs6929846 of BTN2A1 and serum concentrations of TG, HDL-cholesterol, or LDL-cholesterol in Korean individuals. Analysis of combined genotypes for rs662799 of APOA5 and the C polymorphism of BTN2A1 revealed that the CC genotype of APOA5 and the CC genotype of BTN2A1 were associated with an increased serum concentration of triglycerides (TG) and a decreased serum concentration of HDL-cholesterol in Japanese individuals. Furthermore, there was no relation detected between rs6929846 of BTN2A1 and serum concentrations of TG, HDL-cholesterol, or LDL-cholesterol in Korean individuals. Analysis of combined genotypes revealed that Japanese or Korean individuals with the C allele of APOA5 and the C allele of BTN2A1 had a 2.05- or 1.92-fold increased risk for hypertriglyceridemia, respectively, whereas a 1.21- or 1.56-fold increased risk for hyper-HDL-cholesterolemia, respectively, compared to those with the TT genotype of APOA5 and the CC genotype of BTN2A1.

**Conclusions:** Genetic variants of APOA5 and BTN2A1 may synergistically affect the prevalence of dyslipidemia in East Asian populations.
Results: After conditional analysis, among 34 variants exceeding significance threshold and located all near the adrenomedullin gene, GWAS identified 2 variants, rs9257692 (p=1.5 x 10-13) and rs2957717 (p=4.2 x 10-10) independently associated with MRproADM levels. Together the 2 SNPs of the epithelial sodium channel (ENaC), encoding the alpha, beta, and gamma subunits, respectively. These 2 SNPs accounted for 1.4% [0.7-2.2] of the variability before and after adjustment for non-genetic correlates.

Purpose: Genetic polymorphisms of CYP2C19 and effect of clopidogrel.

Methods: 45 healthy Malaysian volunteers were given 300-mg of clopidogrel and their platelet reactivity were assessed. Subsequently, 45 of these volunteers (18 Malays, 25 Chinese) were genotyped for CYP2C19*2 and CYP2C19*3 alleles using polymerase chain amplification followed by gel electrophoresis. The CYP2C19*2 allele was detected in all 3 ethnic groups. The prevalence of CYP2C19*2 allele appeared to be high in Chinese volunteers (67.3%).

Conclusions: We investigated the relation between A–173G polymorphism in SCNN1G and longitudinal changes in blood pressure (BP) and renin function in general population. The study group included 527 subjects, members of two-generation families, recruited from the general population. At baseline and after 6-8±1.4 years of follow-up, we used the same methods for phenotyping.

Methods: The study group consisted of 1008 individuals: 728 consecutive coronary patients with ACS diagnosis (mean age 8.0 years; 79.3% male) and 280 controls without coronary events (mean age 8.0 years; 75.7% male). The second study consisted of a total of 1018 individuals: 202 patients with stable angina (mean age 56.0±8.0 years; 73.9% male) and 816 controls without coronary disease.

Objective: The aim of this study was to evaluate whether the SNP rs1333049 of 9p21 locus influences the development of the acute coronary syndrome (ACS) or more complex coronary lesions.

Methods: Two case-control studies were performed. The first one included 1655 individuals: 728 consecutive coronary patients with ACS diagnosis (mean age 8.0 years; 79.3% male) and 927 controls without coronary events (mean age 53.3±7.9 years; 75.7% male). The second study consisted of a total of 1018 individuals: 202 patients with stable angina (mean age 56.0±6.9 years, 70.8% male) submitted to coronary angiography, and 816 controls without coronary disease.
Influence of rs5065 atrial natriuretic peptide gene variant on coronary artery disease.

E. Barbato1, S.A. Sciarretta2, J. Bartunek3, F. Mangiacapra4, D. Lambrecht5, P. Sinnaeve5, F. Van De Werf6, K.A.A. Fox7, M. Volot8, S.A. Rubatul2, OLV Hospital Aalst, Cardiovascular Center, Aalst, Belgium;2 Sapienza University of Rome, Sant’Andrea Hospital, 2nd Faculty of Medicine, Division of Cardiology, Rome, Italy;3 Catholic University of Leuven/Vesalius Research Center, Leuven, Belgium;4 Catholic University of Leuven, Department of Cardiology, Leuven, Belgium;5 University of Edinburgh, Centre for Cardiovascular Science, Edinburgh, United Kingdom;6 IRCCS, Mediterranean Neurological Neuromed Institute, Pozzilli, Italy

Either modified ANP plasma levels or peptide structural alterations have been involved in development of cardiovascular events. To investigate the impact of rs5065 atrial natriuretic peptide (ANP) gene variant on coronary artery disease (CAD) and its outcomes and to gain potential mechanistic insights on the association with CAD.

Methods: Controls and 1004 patients undergoing coronary angiography for suspected CAD [432 stable angina (SA), 572 acute coronary syndrome (ACS)] were genotyped for rs5065 ANP gene variant. Data in SA and ACS groups were replicated in an independent population of 482 SA patients (rSA) and of 675 ACS patients (rACS), respectively. Clinical follow-up was available for both SA and rSA patients. Plasma NT-proANP, myeloperoxidase (MPO), lipoprotein-associated phospholipase A2 (Lp-PLA2), oxidized low density lipoprotein (OxLDL) were assessed in a subgroup of rSA patients.

Results: rs5065 minor allele (MA) was an independent predictor of ACS (OR=1.19; 95% CI: 1.00-2.38; P=0.001). At follow-up, rs5065 MA was indepen-
dently associated with significantly higher rate of major adverse cardiovascular events (MACE) in SA group, p<0.001. Data were replicated in rSA group at follow-up (p=0.008). Cox proportional hazard analysis tested by 4 models confirmed higher MACE risk in rSA patients carriers of rs5065 MA compared to SA and rSA cohorts. Signifi-
cantly higher MPO levels were detected in rSA MA carriers (rs579345-832 vs. 488[353-612], p=0.038). No association of rs5065 was observed with NT-proANP levels.

Conclusions: The MA of rs5065 ANP gene variant associates with increased susceptibility to ACS and has unfavorable prognostic value in CAD.

Coronary artery disease risk polymorphisms in Latvian patients and population controls.

R. Peculis1, G. Latkovskis1, I. Kalnina2, A. Erglis3, J. Klovins1,1 Latvian Biomedical Research and Study Centre, Riga, Latvia;2 Paul Stradins Clinical University Hospital, Department of Cardiology, Riga, Latvia

Purpose: Genome-wide association studies (GWAS) have discovered multiple single nucleotide polymorphisms (SNP) associated with coronary artery disease (CAD). These results are generally based on populations of Northern and Western European ancestry and importance and informativeness of the results may be limited for researchers studying patients of other ethnic backgrounds. Our aim was to validate findings of European CAD GWAS in Latvian population which is of Eastern European ancestry. We focused on six loci: 1p13.3, 2q28.3, 6q25.1, 9p21, 10q11.21 and 15q25.23 characterized by SNPs r599839, rs2943634, rs692269, rs1333049, rs501120 and rs17728212 respectively.

Methods: All six SNPs were genotyped in a case-control study consisting of 1100 clinically ascertained CAD cases and 452 population controls with no history of cardiovascular manifestations. Written informed consent was obtained from all participants of this study. Genomic DNA was extracted from white blood cells by chloroform-phenol method and genotyped using fluoroscence labeled hydrolysis probes in a real-time PCR system.

Results: Two of the investigated polymorphisms rs2943634 and rs1333049 were significantly associated with CAD. Allele C of the rs1333049 had frequency 0.522 and 0.437 in controls and cases respectively (CAD OR=1.40; 95% CI: 1.20-1.64; P=2.12e-5). None of other four SNPs reached significance level of P=0.05 even before correction of results.

Conclusions: Our findings suggest that rs1333049 is strongly associated with CAD risk in Latvian population and that rs2943634 also increases risk of CAD. Further we found evidence that MAF difference of SNPs among regions within Europe is significant, therefore making interpretations based on other population samples challenging.

Secretoneurin gene therapy reverses the impairment of hindlimb post-ischemic recovery in Apo E−/− mice.

M. Theurl1, K. Albrecht-Schroger, W. Schroger, I. Tanczewski, M. J. Oliva2, P. Pascual4, I. Gomez1, I. Perez1, I. Tovar5, M. Valdes5,1 University Hospital Virgen de la Arrixaca, Department of Clinical Analysis, Murcia, Spain;2: University Hospital Virgen de la Arrixaca, Department of Cardiology, Murcia, Spain

Introduction: Genetic diagnosis in inherited cardiomyopathies is still limited and reimbursement policies are lacking. There is need to evidence the cost of genetic testing and know their profitability in order to establish criteria for priorizing access to genetic testing for these diseases.

Methods: We determined the cost per positive genotyping (CPG) in 234 index cases with diagnosis of HCM, ARVC, LQTS, and Brugada Set (BS). The genetic test of the most prevalent genes were included (MYH7 and MYBPC3 for HCM; PKP2, DSP, DSC2, DSG2, PKG for ARVC; KCNQ1, KCN2, SCN5A, KCN1, KCN2, KCNJ2 for LQTS; and SCN5A for BS). Genetic studies expenses were HCM 1300 €; ARVC 2050 €; BS 725 €; LQTS 1755 €. Estimation of the cost of periodical screening in wildtype relatives (WT) was calculated from 10-60 yrs (ECG 20 €, echocardiogram 60 €, cardiac consultation 40 €). Frequency of the clinical screening of relatives was assessed from the genetic information.

Results: Mutations in HCM-related genes were identified in 92 of 115 patients (80%); leading to a CPG of 1650 € in HCM group. Mutations in ARVC-related genes were identified in 14 of 18 (78%) and CPG was 2363 €. The yield of genetic test in LQTS was 65%(11 of 17) and CPG was 2434 €. Genetic screening of BS identified a mutation in 16 of 18 (90%), with a CPG of 3806 € . A high pick up rate of HCM and ARVC was probably due to bias towards the high risk (sudden death) or high penetrance cases, and a founder effect of some of the mutations. A total of 738 individuals from 234 probands (917 HCM (293 carriers of mutation (CM)), 76 ARVC (36 CM), 71 LQTS (35 CM) and 74 BS (33 CM)) were genotyped.

Conclusion: Based on our findings we suggest that individuals with conclusive diagnostic of HCM should have a priority to access genetic testing. The benefits from periodical tests saved in WT that can be discharged exceed the expenses of genetic testing. The yield of genotyping is substantially high in ARVC and LOTS patients suggesting these two groups should be genetically studied too, although less cost-effective.
Early AAV9-mediated over-expression of S100A1 ameliorates myocardial hypertrophy in dystrophin-deficient mice

University Hospital of Heidelberg, Department of Cardiology, Heidelberg, Germany

Mutations of dystrophin leading to a complete loss of the protein cause x-chromosomal Duchenne muscular dystrophy (DMD), frequently associated to severe cardiomyopathy (CMP). However, although cardiac complications increase to near-term death of these patients, strategies to efficiently treat the CMP are not well established. It has been suggested that the loss of cardiomyocyte calcium (Ca2+) cycling integrity plays a key role in the development and progression of CMPs, although so far its role in dystrophin-associated CMPs is unclear. In this context, the cardiomyocyte EF-hand Ca2+-sensor protein S100A1 plays a critical role in regulating Ca2+-cycling integrity and has been considered for therapeutic approaches to treat CMP.

We have investigated the efficiency of Adeno-associated virus serotype 9 (AAV9) -mediated cardiac over-expression of S100A1 to prevent the development of CMP in dystrophin-deficient (mdx) mice. Therefore, AAV9 vectors containing S100A1 CDNA under transcriptional control of a CMV-MLC promoter (AAV9/S100A1) were created. 1012 AAV9/S100A1 vector particles were intravenously injected into 8 week-old mdx mice before the onset of CMP. AAV9 harboring an enhanced green fluorescent protein reporter (AAV9/EGFP) was used as a control vector. At the age of 1 year histological examinations, echocardiography and PV-loops were performed to assess myocardial morphology and contractility (cardiomyocyte cross-sectional areas (csa; μm²), enddiastolic posterior wall thickness (PWTd; mm), fractional shortening (FS;%) and left ventricular maximum rate of pressure change (dp/dtmax; mmHg/sec).

Conclusion: Our data suggest therapeutic potential of SN under hypercholesterolemic conditions and open up new therapeutic options for the treatment of PAD.

Adenovirus-mediated gene transfer of a luciferase reporter gene by a cardiac-specific promoter through direct injection into the left ventricular wall

Z. Xu, Z.X.T. Tao, Z.J.Y. Yang. The First Affiliated Hospital of Nanjing Medical University, Department of Cardiovascular Medicine, Nanjing, China, People's Republic of China

Purpose: Localized administration of a highly efficient gene transfer system in combination with a cardiac-specific promoter may provide a biologically safe strategy in the cure of ischemic cardiac disease. We hypothesized that such expression could be restricted to the heart after local direct injection by packaging an adenovirus carrying the luciferase CDNA driven by the cardiac troponin I promoter.

Methods: Adenoviral vectors carrying the firefly luciferase gene under the control of the cardiac troponin I (Ad-TnI-Luc) or CMV promoter (Ad-CMV-Luc) packaged into adenovirus serotype 6 were directly injected into the left ventricular wall of SD rats via thoracotomy. Luciferase expression was monitored for 28 days through in vivo bioluminescence imaging system (IVIS, Xenogen) and in vitro luciferase assays. Myocardial infarction was induced immediately before direct injection.

Results: Luciferase expression was evident within 12 h after Ad-TnI or Ad-CMV- luciferase injection. At 24 h post-infection, levels were similar to vascular endonuclease growth factor.

Conclusions: Ad serotype 6 in combination with a cardiac specific promoter (cardiac troponin I) is highly efficient for cardiac gene transfer, as evident by high-level expression for 28 days and more cardiac specific, especially under the myocardial infarction condition.

Identification of AAV6 as most efficient vector for transvascular gene transfer into porcine myocardium based on an in vitro model for prediction of the cardiac gene transfer performance

University Hospital of Heidelberg, Internal Medicine III, Dept Cardiology, Angiology & Pneumology, Heidelberg, Germany

Background: Adeno-associated virus (AAV) mediated gene transfer into diseased myocardium holds high promises for numerous gene therapy applications. While high transfer efficiencies are achieved in small rodents, gene transfer to the hearts of larger animals appears to be limited. Aim of our work was the development of an efficient gene transfer system for large animal models using an adeno-associated virus serotype 6 (AAV6) as a candidate for gene transfer into myocardium.

Methods: AAV6-mediated gene transfer into porcine myocardium was performed with AAV6 vectors carrying the firefly luciferase gene (AAV6-Luc) under the control of the CMV promoter. Myocardial infarction was induced in pigs by coronary artery ligation and reperfusion. Luciferase expression was monitored for 28 days through in vivo bioluminescence imaging system (IVIS, Xenogen) and in vitro luciferase assays. Myocardial infarction was induced immediately before direct injection.

Results: Luciferase expression was evident within 12 h after Ad-TnI or Ad-CMV- luciferase injection. At 24 h post-infection, levels were similar to vascular endonuclease growth factor.

Conclusions: Ad serotype 6 in combination with a cardiac specific promoter (cardiac troponin I) is highly efficient for cardiac gene transfer, as evident by high-level expression for 28 days and more cardiac specific, especially under the myocardial infarction condition.
Penetration study in SCN5A-mutations in brugada syndrome

E. Garcia-Molina1, J. Lacunza2, M. Sabater1, P. Pascal1, I. Gomez1, J. Lopez-Cuenca1, F. Ruiz-Espejo1, J. Gimeno2, I. Tovar1, M. Valdes3. 1Genetic Diagnostic Laboratory, University Hospital Virgen de la Arrixaca, Murcia, Spain; 2University Hospital Virgen de la Arrixaca, Department of Cardiology, Murcia, Spain; 3University of Murcia, School of Medicine, Department of Cardiology, Murcia, Spain

Introduction: Brugada syndrome (BS) is an inherited channelopathy associated with mutations in SCN5A gene and up to 7 genes more. The disease is inherited in autosomal dominant manner, although with variable penetrance.

Aim: To evaluate the penetrance of the disease in a unselected population.

Material and Methods: Seventy six non-related patients with BS were studied. Clinical characteristics and family risk profile were recorded. Direct sequencing of the SCN5A gene for identification of mutations and familial genetic study of parents was performed.

Results: Eight patients (10.5%) had point mutations (R27H, E901K, G1743R, V728I, N1443S, G1195D, A1197E, E1230D) and 19 additional carriers (10 male and 9 female) could be identified. Index patients with mutations had more frequently spontaneous type I Brugada pattern (87.5% vs 52.9%, p = 0.06) and evidence of familial disease (62.5%, vs 23.5%, p = 0.03). Symptoms and risk profile of the proband carriers 144 years later was similar to ours. The prevalence of spontaneous type I ECG varied according to sex in carriers, with 8 cases among 18 men (44.4%) and no cases among 9 female (p=0.2). However, after the flecainide test, the rate of type II ECG was doubled between men (66.7% vs 62.5%, p=0.9). Flecainide test unmasked a higher proportion of females (66.7% vs 25.0%, p=0.4).

The penetrance of spontaneous type I ECG in carriers was 29.6%, and rise to 63.2% after drug challenge test. Percentage of carriers who expressed type I ECG varied among different mutations (figure 1). A 36.8% of carriers who underwent a complete study, had normal ECG despite the drug challenge test.

R4938

Age-related penetrance in genetic carriers of hypertrophic cardiomyopathy

I. Perez, A. Romero-Puche, M. Sabater-Molina, E. Garcia-Molina, I. Gomez-Milanes, D. Lopez-Cuenca, F. Ruiz-Espejo, J.R. Gimeno Jr, M. Valdes M.University Hospital Virgen de la Arrixaca, Department of Cardiology, Murcia, Spain

Introduction and Purpose: Hypertrophic cardiomyopathy (HCM) was initially considered to have an early onset in the life. The last advances in genetic area have showed new carriers without clinical diagnosis. The aim is study the age-related penetrance of HCM in patients with different MYBPC3, MYH7 and TNN2 mutations to determinate whether the age at diagnostic depends on genetic background.

Methods: We included 195 HCM causal mutation carriers (55% males, age 40±16 years); 64.8% had clinical manifestations of the disease. All patients were diagnosed in inheritance cardiomyopathy consultation, in a reference hospital. Seventy six patients were carriers of at least one mutation in MYBPC3 (IVS23+1G→A (72), Arg891fs (37), A107fsX116 (26), A216T (11), V696M (4)), 21 were carriers of a mutation in MYH7 (T1377M (21), D928N (4), E1348Q (8), E1356Q (4), 138SO (4)) and 8 patients were carriers of R557H in TNN2. IVS23+1G→A, the most prevalent mutation, was present in 18 unrelated families. We performed time-to-diagnosis analysis according to the affected gene and the most prevalent mutations.

Results: No differences in time to diagnosis were detected between the most prevalent mutations. Median age at diagnosis was 46±2 years old for IVS23+1G→A; 44±3 years old (Arg891fs), 44±7 years old (T1377M) and 51±9 years old (A216T); log rank p=0.963 (figure 1). Similarly, there were no differences according to the 3 analyzed genes (log rank p=0.35). Median age at diagnosis for the whole was 47±2 years.

Conclusions: Mutations in MYBPC3 encoding myosin binding protein C could be considered more benign form of HCM than initially was considered. Now, genetic diagnosis reveals that HCM-phenotype can appear later in life, reaching near full penetrance in the elderly.
Association of a matrix metallopeptidase 1 gene polymorphism with long-term outcome of thoracic aortic aneurysm

K. Kato1, N. Inagaki2, T. Fujimaki3, M. Ogura1, T. Hibi2, K. Yokoi2, Y. Yamada4 - 1Department of Human Functional Genomics, Life Science Research Center, Mie University, Tsu, Japan; 2Gifu Prefectural Tajimi Hospital, Department of Cardiovascular Medicine, Tajimi, Japan; 3Department of General Hospital, Department of Cardiology, Inaba, Japan; 4Nagoya First Red Cross Hospital, Department of Cardiology, Nagoya, Japan; 5Nagoya University Graduate School of Medicine, Department of Cardiology, Nagoya, Japan

Objective: Although genetic variants are thought to contribute to the development of thoracic aortic aneurysm including dissection (TAA), it remains unclear whether gene polymorphisms are associated with the long-term outcome of TAA. The identification of genetic variants related to the long-term outcome of medically treated TAA may lead to a better understanding of the factors relevant to the progression or rupture of TAA, and consequently may better inform the selection of patients as candidates for surgical therapy because of a higher risk of rupture. The purpose of the present study was to identify genetic variants associated with the long-term outcome of medically treated patients with TAA.

Methods: A total of 103 medically treated patients with TAA [age, 63.3±11.9 (range: 30-78 years; 13 aneurysms and 90 dissections)] were retrospectively studied for their outcomes (mean follow-up period, 24 months). An unfavorable outcome was defined as: (1) death from cardiovascular causes or aneurysm rupture, (2) ascending aortic aneurysm, (3) need to undergo surgical repair, or (4) the occurrence of cardiovascular events after initial hospitalization. The genotypes for 95 polymorphisms of 89 candidate genes were determined by a method that combines polymerase chain reaction and sequence-specific oligonucleotide probes with suspension array technology.

Results: The prevalence of Stanford A, hypertension, prior cardiac surgery, shock, and a maximum aneurysm diameter were greater in subjects with the unfa-

Conclusion: Determination of genotypes for this polymorphism may prove informative for assessment of the long-term outcome of TAA.

NO from neuronal NO synthase increases after beta-adrenergic stimulation but does not control mitochondrial respiration

S. Bergem1, M. Kohlhaas1, A. Nickel1, M. Meiser1, M. Hohl1, B. Carrer1, U. Lauf1, M. Boehm1, B. Casadesus1, C. Maack1
1Saarland University Hospital, Department of Internal Medicine III, Homburg/Saar, Germany; 2University of Oxford, Department of Cardiovascular Medicine, Oxford, United Kingdom

Background: During β-adrenergic stimulation, the amplitude and frequency of myocardial Ca2+ transients and contraction increase as does the demand for ATP supply. This latter is matched by an increase in mitochondrial Ca2+ uptake, which stimulates Krebs cycle dehydrogenases to accelerate the regeneration of ATP supply. The latter is matched by an increase in mitochondrial Ca2+ uptake, which stimulates Krebs cycle dehydrogenases to accelerate the regeneration of ATP supply. The latter is matched by an increase in mitochondrial Ca2+ uptake, which stimulates Krebs cycle dehydrogenases to accelerate the regeneration of ATP supply. The latter is matched by an increase in mitochondrial Ca2+ uptake, which stimulates Krebs cycle dehydrogenases to accelerate the regeneration of ATP supply. 

Methods and Results: Experiments were performed in isolated mitochondria and field-stimulated left ventricular (LV) myocytes from mice and guinea-pigs. In mitochondria, the NO donor spermine-NONOate inhibited ADP-induced O2 consumption and NADH oxidation. In LV myocytes, isoproterenol (30 nM) and an increase in stimulation frequency from 0.5 to 5 Hz augmented intracellular NO production by ~12% within 3 minutes (as evaluated by the L-NAMe-inhibitable DAF-AM fluorescence). eNOS inhibition with L-NIO (1 μM) led to a 10-fold increase in mitochondrial NO production (Un). Dialyzing myocytes with a DAF-free pipette solution eliminated >50% of DAF fluorescence, with the remaining DAF signals deriving from mitochondria. In response to isoproterenol, the resi-
in SHR-ob than in SHR-lean when compared to Ctr (4.3±1.1mmHg and 8.8±0.62mmHg, respectively; p<0.0001 for all). Increased LV-fibrosis, collagen I and TGF-β gene expression together with increased myocyte diameters and ANF gene expression in SHR-ob was associated with increased GLUT1 and GLUT1/TGF-β gene expression in SHR-ob suggestive for an upregulation of the GLUT1/ANF- and GLUT1/TGF-β axis. Serca2a protein levels were decreased in SHR-lean but not altered in SHR-ob compared to Ctr, while PLB-phosphorylation was not modified.

Conclusion: In addition to hypertension alone, metabolic syndrome and obesity adds to the myocardial phenotype by aggravating diastolic dysfunction. Upregulation of the GLUT1/ANF- and GLUT1/TGF-β axis may lead to metabolic disarrangements to structural cardiac remodeling in the state of insulin resistance and obesity on the background of hypertension.

**P4943** Subclinical hyperthyroidism and cardiovascular mortality

C. Selmer1, J.B. Olesen2, J.C. Madsen2, U. Schmidt3, J. Faben2, F.R. Hansen1, O.D. Pedersen1, M.L. Hansen1, C. Torp-Pedersen1, 1Gentofte Hospital - Copenhagen University Hospital, Department of Cardiology, Hellerup, Denmark;2Copenhagen General Practitioners Laboratory, Copenhagen, Denmark;3Herlev Hospital - Copenhagen University Hospital, Department of Endocrinology, Herlev, Denmark;4Roskilde Hospital - Copenhagen University Hospital, Department of Cardiology, Roskilde, Denmark

Background: It is still uncertain if subclinical hyperthyroidism and “high-normal” thyroid function is a risk-factor for cardiovascular mortality.

Objectives: To examine the risk of cardiovascular mortality in relation to subclinical hyperthyroidism.

Methods: Patients consulting their general practitioner from 2000–2009 in Copenhagen, Denmark, who went through thyroid blood tests, were identified by individual-level linkage of nationwide registries. Patients with a history of thyroid disease or related medication were excluded. Risk of cardiovascular mortality was analyzed using Kaplan-Meier curves and Poisson regression models to estimate Incidence Rate Ratios (IRR).

Results: Of 525,100 individuals in the study population (mean age 51.7 years [SD ±18.0]; 39.5% males) 504,113 (96.0%) were euthyroid, 1,474 (0.3%) had clinical hyperthyroidism (TSH <0.05 mU/L) and 18,484 (3.5%) had subclinical hyperthyroidism (0.05 mU/L < TSH ≤ 0.4 mU/L). After adjusting for confounders, individuals with clinical hyperthyroidism had an increased cardiovascular mortality (IRR 1.16 [1.09–1.25]). IRR 1.20 [1.05–1.37] and in “high-normal” levels of euthyroidism (TSH 0.2–0.4 mU/L): IRR 1.16 [1.09–1.25].

Conclusion: Subclinical hyperthyroidism and “high-normal” thyroid function is a significant risk-factor for cardiovascular mortality.

**P4944** Endothelial Microparticles derived under high Glucose concentrations increase monocyte adhesion on endothelial cells through upregulation of adhesion proteins in a p38 dependent way

X. Yang1, F. Jansen1, B. Franklin2, T. Schmitz1, H. Slomka1, G. Niemling1, N. Werner1, 1University Hospital of Bonn, Medical Clinic II, Bonn, Germany;2Institute of innate immunity, Bonn, Germany

Background: Circulating endothelial microparticles (EMP) are increased in diabetic patients, but their role in the progression of atherosclerosis is unclear. We tested the hypothesis if EMP isolated from glucose treated human coronary endothelial cells (HCAC) influence adhesion protein expression in target endothelial cells and thereby increase adhesion of monocytes to the endothelium, an important step in the development of atherosclerosis.

Methods and results: We created a hyperglycemic condition by treating HCAC for 72h with 30mM glucose and generated EMP after 24h starvation. These modified EMP were defined as “injured” EMP (IEMP). Confocal microscopy, flow cytometry and electron microscope were used to characterize size (~1μm) and cellular origin of IEMP. The effects of IEMP were compared with EMP generated from untreated HCAEC. IEMP, but not EMP, induced upregulation of ICAM-1 and VCAM-1 in target HCAEC demonstrated by Western Blot and real-time RTPCR. Moreover, Western Blot experiments revealed that IEMP treated with IEMP enhanced ICAM-1 and VCAM-1 in a time- and dose-dependent way. Following experiments showed increased monocyte adhesion on IEMP-treated HCAEC compared to EMP-treatment and control (47.3% vs. 26.9% vs. 8.4%, p<0.05). We next investigated how EMP activate endothelial cells and found that pro-inflammatory cytokines IL-8, IL-6, TGF-β and MCP-1 were detectable in IEMP. IEMP contain higher level of TGF-β (807 ng/μL) vs. 1647 ng/μL, p<0.05) and IL-8 (115 pg/μL vs. 33 pg/μL, p<0.05) than EMP. As cytokines mentioned above activate p38 into phospho-p38 (p38-phospho), expression of p38 activity was analyzed in HCAEC after IEMP stimulation. Time dependent experiments revealed that IEMP induced activation of p38 into phospho-p38 in HCAEC within 30min. Inhibition of p38 blocked IEMP-dependent induction of adhesion proteins on HCAEC and promotion of monocyte adhesion on target cells.

Conclusion: Endothelial Microparticles from glucose treated cells increase monocyte adhesion by altering adhesion protein expression in endothelial cells. Activation of p38 through proinflammatory cytokines containing MP might be a possible pathway.
Pathophysiological implications in cardiovascular pathology. The aim of our study was to evaluate the prognostic value of AGEs and its soluble receptor (sRAGE) in the context of acute coronary syndrome (ACS), both in-hospital phase and follow-up period.

**Methods:** AGE and sRAGE were analyzed by fluorescence spectroscopy and competitive ELISA (respectively) in 215 consecutive ACS patients admitted to coronary care unit (62.7 ± 13.0 years, 24.2% female). 47.4% had a diagnosis of ST segment elevation myocardial infarction. The end-points were the development of cardiac events (cardiac deaths, reinfarctions and new-onset heart failure) during in-hospital phase and follow-up period (366 days, interquartile range: 273-519 days).

**Results:** The mean fluorescent AGEs and sRAGE levels were 57.7 ± 4.5 AU and 1045.4 ± 850.0 pg/mL, respectively. 15 patients presented cardiac events during in-hospital phase and 29 during the follow-up. In-hospital cardiac events were significantly associated with higher sRAGE levels (P < 0.001), but not long-term cardiac events (P = 0.36). Regarding fluorescent AGE the opposite was happened. After multivariate analysis correcting for sex, left ventricular ejection fraction, glucose levels, hemoglobin, GRACE and SYNTAX scores, sRAGE was significantly associated with in-hospital prognosis whereas fluorescent AGEs was significantly associated with long-term prognosis (figure 1: by quartiles of fluorescent AGE).

**Conclusion:** We conclude that elevated values of sRAGE are associated with worse in-hospital prognosis, whereas high AGE levels are associated with more follow-up events.

**P4947**

**Acute cardiac ryanodine receptor loss-of-function leads to bradycardia, arrhythmia, heart failure and transcriptional metabolic reprogramming**

M.J. Brouard1, R. Wambolt1, P. Asghari1, D.S. Luciani1, F. Taghizadeh1, J. Kulpa1, K.R. Boehler1, E.D.W. Moore1, M.F. Alland1, J.D. Johnson1

Canadian Institute of Aging, Laboratory of Cardiovascular Science, 1Baltimore, United States of America

**Rationale:** The cardiac ryanodine receptor Ca²⁺ channel (RyR2) plays a central role in excitation-contraction coupling. RyR2-mediated Ca²⁺ flux into mitochondria also controls metabolism, stimulates TCA cycle flux and aerobic metabolism, and atypical cell death in other cell types. Cardiac RyR2 levels can be reduced up to 50% with age and in disease states such as heart failure, ischemia and diabetes. Objective: We tested whether a similar, controlled depletion of cardiac RyR2 proteins sufficient to recapitulate the pleiotropic events associated with heart failure.

**Methods and Results:** Wapert that conditional RyR2 knockout mice (cryr2NOKO) rapidly exhibit bradycardia, arrhythmia and transcriptional metabolic changes. RyR2 levels can be reduced up to 50% with age and in disease states such as heart failure, ischemia and diabetes. Objective: We tested whether a similar, controlled depletion of cardiac RyR2 levels can be sufficient to recapitulate the pleiotropic events associated with heart failure.

**Conclusions:** Our data show that RyR2 loss is sufficient to rapidly induce a complex heart failure-like phenotype, placing RyR2 and its associated energy-stimulating Ca²⁺ fluxes above hierarchical cascade of core transcription factors controlling cardiomyocyte metabolism, function, and survival.

**P4948**

**Genetic deficiency of corticotropin releasing hormone influences cardiac function through fatty acid metabolism**

T. Tanzawi1, A. Varela1, S. Theodoris1, C. Panton2, D. Cokkinos1, K.P. Karalis1, 1Academy of Athens (SAntiBiological Research Foundation, Athens, Greece; 2University of Athens Medical School, Athens, Greece; 1st Cardiology Department GCSC - Biomedical Research Foundation Academy of Athens, Athens, Greece

**Purpose:** We have previously shown that Corticotropin Releasing Hormone (CRH)−null (Crh−/−) mice have compromised cardiac capacity, demonstrated by their reduced FS (%) and EF (%) values compared to wild-type (Crh+/+) mice; this effect is exaggerated by acute administration of LPS in non-lethal doses. We investigated whether this effect is due to changes in fatty acid (FA) metabolism, since the heart relies mostly on FA to fulfill its energy needs.

**Methods:** Endotoxemia was induced by i.p. LPS administration (120ug/g animal). Cardiac function was assessed by 2D M-mode echocardiography, basally and 20hrs after LPS. Fatty acid metabolism related gene expression was studied by real time PCR.

**Results:** At basal state, significantly reduced mRNA levels of PPARα, PPARγ, FAS and CD36 by 37% (P < 0.05), 62% (P < 0.05), 40% (P < 0.05) and 70% (P < 0.05) were found in the myocardium of Crh−/− compared to the Crh+/+ mice. LPS administration resulted in downregulation of myocardial peroxisome proliferator activator receptor (PPAR) α, PPARγ, PPARγ coactivator (PGC)-1α and AMPKα2 mRNA levels by 66% (P < 0.01), 44% (P < 0.05), 50% (P < 0.05) and 58% (P < 0.05) respectively. In Crh−/− mice LPS administration caused further reduction of PPARα, PPARγ, AMPKα2 as well as carnitine palmityl-transferase (CPT)-1b levels. As we have previously reported, Crh−/− mice demonstrate significantly compromised ability to survive the above LPS challenge. To assess whether support of PPARs function via administration of PPAR ligands would rescue the detrimental effects of LPS administration in Crh−/− mice, we i.p. injected both Crh+/+ and Crh−/− mice with the PPARα ligands pioglitazone and rosiglitazone (3mg/kg/day), or the non-specific PPAR antagonist bezafibrate (50mg/kg/day) for 7 days prior to LPS administration. Neither pioglitazone nor rosiglitazone treatment had any effect on the reduced myocardial survival or capacity of Crh−/− given LPS. However, indices of cardiac function were improved in all bezafibrate-treated Crh−/− mice and their survival rate 24 hours after LPS administration was indistinguishable from that of the Crh+/+ mice.

**Conclusion:** We have shown that genetic Crh deficiency is characterized by impaired myocardial FA metabolism, most likely through inhibition of the PPARα effects.
Stress-induced adipose inflammation promotes a procoagulant state and impairs insulin sensitivity by adipocyte-derived monocyte chemotactic protein-1

Y. Uchida, K. Takeshita, R. Kikuchi, T. Murohara. Nagoya University Graduate School of Medicine, Nagoya, Japan

Objective: Stressors contribute to thrombosis and perturbation in glucose metabolism. Since adipose inflammation is also involved in obesity-induced insulin resistance and thrombosis disease, we tested the hypothesis that stress correlates with adipose inflammation.

Research Design and Methods: Male mice were subjected to daily restraint stress for 2 weeks. Inguinal white adipose tissue (WAT) was collected from control and stressed mice to examine CD11b-positive cells and expression of macrophage markers (C6D8 and F4/80), proinflammatory cytokines (MCP-1, TNF-α, and IL-6), adiponectin, and coagulation factors (PAI-1 and tissue factor [TF]) using immunohistochemistry and RT-PCR, respectively. Glucose metabolism was assessed by glucose (GTT) and insulin tolerance tests, and expression of IRS-1 and GLUT4 in WAT. To examine the effects of MCP-1 blockade, animals were intraperitoneally transplanted with control- or 7ND (dominant negative form of MCP-1)-overexpressing adipose-derived stromal cells (ADSCs). Plasma free fatty acid (FFA), mouse MCP-1, TNF-α, and IL-6 levels were measured.

Results: Stress increased accumulation of CD11b-positive cells and expression of CD68 and F4/80 in WAT. The stressed mice also showed a higher frequency of smaller adipocytes in the inguinal adipose tissue compared to the control mice. Chronic stress also induced proinflammatory cytokine expression including MCP-1, TNF-α, and IL-6 and reduced adiponectin. Furthermore, stressed mice showed increase in FFA, MCP-1, TNF-α, and IL-6 concentration. The stress-induced adipose inflammation worsened the prothrombotic state through induction of PAI-1 and TF. Without any changes in GTT, stress worsened insulin sensitivity and decreased IRS-1 and GLUT4 in WAT. 7ND-ADSCs reversed the stress-induced adipose inflammation with reduction of CD11b-positive cells, macrophage markers, and proinflammatory cytokines. Moreover, 7ND-ADSC treatment rescues the stress-induced decline in insulin sensitivity and the prothrombotic state.

Conclusions: Restraint stress over a 2-week period evoked the expression of MCP-1 and other inflammatory adipokines in adipose tissue and a low-grade chronic state of adipose inflammation that exacerbated insulin resistance and induced the procoagulant factors through the expression of MCP-1, MCP-1 inhibition with 7ND-ADSCs reversed adipose inflammation and these pathological consequences. Increased lipolysis and FFA would be also involved in stress-induced adipose inflammation.

P9452

Significant association of the CYP27A1 polymorphism with adipokynes, cholesterol profiles and metabolic syndrome in middle-aged male patients

K.-H. Cheng, C.-C. Liu, C.-N. Huang, Y.-C. Lee, C.-S. Chu, E. Hsi, W.-T. Lai, S.-P. Huang. Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Purpose: Significant association of vitamin D deficiency with metabolic syndrome (MetS) and cardiovascular risk has been reported. Vitamin D[3-25 hydroxyvitamin D[3 (1,25(OH)2D3)] and 25-hydroxyvitamin D[3 (25OHD3)] are two key enzymes of vitamin D3 metabolism. Although CYP27B1 has been reported to be associated with type 1 diabetes, little is known of the associations of CYP27A1 with MetS. The aim of the study was to examine the role of vitamin D CYP27A1 single nucleotide polymorphisms (SNPs) in components of MetS and adipokynes in middle-aged male subjects.

Methods: Cross-sectional data and DNA samples were collected from male volunteers (n=649, aged 55.7±4.7) reenrolled for health screening. Demographic characteristics and biochemical variables, including E2, 1,25(OH)2D3, adiponectin and leptin were analyzed. Two tagging SNPs were selected in CYP27A1 rs4674344 and CYP27B1 rs10877012 genes. SNPs were determined by using TaqMan 5′ allelic discrimination assay.

Results: CYP27A1 rs4674344 was significantly associated with MetS (odds ratio 1.47, 95% CI 1.01-2.10, p=0.036). The two ratios of adiponectin (3.7±0.1 vs. 5.1±0.6, p=0.001) and 1,25(OH)2D3 (4.3±1.0 vs. 4.1±1.0, p=0.006) were the most significant non-MetS parameters in AT/TT genotype than in AA subjects. The significant association of CYP27A1 rs4674344 with MetS was abolished by adjusting for TG (1.33, 0.89-2.00), HDL (1.43, 0.98-2.09) and WC (1.46, 0.96-2.22) of MetS components, Chol(T)/HDL (1.22, 0.84-1.79) of lipid profile, and adipin 1.32, 0.89-1.89; leptin 1.74, adiponectin/leptin 1.06, 0.71-1.60). However, CYP27B1 rs4674344 was not significantly associated with MetS after adjusting for all the other significant non-MetS components (1.12, 0.69-1.81).

Conclusion: The vitamin D metabolism gene CYP27A1 rs4674344 is significantly associated with both cholesterol and adipokynes homeostasis and may contribute to the development of MetS.

P9453

The heme oxygenase system reduces pericardial adiposity and improves diabetic cardiomyopathy in zucker diabetic fatty rats

J.F. Nsindou, University of Saskatchewan, College of Medicine, Department of Physiology, Saskatoon, Canada

Visceral adiposity adversely affects many vital organs including the heart. We investigated the effects of the heme oxygenase (HO) inducer, hemin on pericardial adiposity and diabetic cardiopathy in Zucker diabetic fatty rats, and age/sex-matched Zucker-lean controls.

Hemin administration normalised glycemic levels in ZDF rats and suppressed pericardial adiposity with the reduction of pro-inflammatory/oxydative mediators including, NF-kB, c-Jun-N-terminal kinase (cJNK), endothelin (ET-1), TNF-α, interleukin (IL)-6, IL-1β and 8-isoprostane. Similarly, hemin reduced the pro-inflammatory macrophage-M1 phenotype, but increased the M2-phenotype that dampens inflammation in the heart, and improved cardiac hemodynamics by enhancing ejection fraction, stroke volume, cardiac output, while reducing total peripheral resistance. Hemin improved glucose metabolism by potentiating insulin-signalling agents like the insulin-receptor substrate-1 (IRS-1), phosphatidylinositol-3-kinase (PI3K), glucose-transporter-2 (GLUT2) and glycogen-kinase (PKB). The hemin effects were accompanied by increased HO-activity, whereas the HO-blocker, stannous-mesoporphyrin (SnMP) nullified the effects. Interestingly, the hemin effects were less pronounced in Zucker-lean controls with healthy status, suggesting greater selectivity in ZDF with disease. Since NF-kB activates TNF-α IL-6 and IL-1β, while TNF-α and JNK impair insulin-signalling, the high levels of these cytokines in obesity/diabetes would create a vicious cycle that together with 8-isoprostane and ET-1 exacerbates tissue injury, compromising its function. Therefore, the concomitant reduction of proinflamatory cytokines and macrophage infiltration coupled to increased levels of IRS-1, GLUT2, PI3K, PKB and cardiac hemodynamics may account for enhanced glucostasis, and improved cardiac performance and diabetic cardiopathy.

We conclude that HO-inducers may be explored against the co-morbidity of impaired insulin-signalling, visceral adiposity and diabetic cardiopathy.

P9454

Synergistic effect of human immunodeficiency virus and the metabolic syndrome on arterial stiffness

M. Asaad, O.J. Rider, N. Ntusi, R. Banerjee, G. Hancock, G. Clutton-Brock, J.F. Ndising, E. Wainwright, L. Dorrell, K. Clarke, C. Holloway. Centre for Clinical Magnetic Resonance Research, Department of Cardiovascular Medicine, Oxford, United Kingdom

Purpose: Patients with Human Immunodeficiency Virus (HIV) on combination antiretroviral therapy have a high incidence of the metabolic syndrome (MS) and cardiovascular (CV) disease. To determine the contribution of HIV infection and the MS to vascular disease, we investigated aortic stiffness using aortic pulse wave velocity (PWV) in HIV patients with and without the MS.
The metabolic syndrome significantly affects the association between resting heart rate and all cause as well as cardiovascular mortality

A. Vonbank¹, F. Schmidt¹, P. Rein¹, C.H. Saéz², H. Drexel²
¹Academic Teaching Hospital, Department of Internal Medicine, Feldkirch, Austria, ²Cantonal Hospital St. Gallen, Department of Cardiology, St. Gallen, Switzerland; ³Drexel University College of Medicine, Philadelphia, United States of America

Purpose: Epidemiological studies suggest that the resting heart rate (RHR) is an independent predictor of cardiovascular and all cause mortality. However, the predictive power of the RHR to predict cardiovascular events in patients with the metabolic syndrome (MetS) is not known.

Methods: We prospectively investigated the relationship between RHR and cardiovascular events in 766 consecutive patients undergoing coronary angiography for the evaluation of coronary artery disease (CAD) over a follow-up period of 7.1±0.1 years. The MetS was defined according to NCEP-ATPIII criteria.

Results: In the total study population, both all cause and cardiovascular mortality were increased with an increasing RHR (standardised adjusted HRs 1.03 [1.01-1.04]; p = 0.001 and 1.15 [1.03-1.17]; p = 0.001, respectively). From our patients, 357 (47.2%) had the MetS and 399 did not have the MetS. Among patients without the MetS, a higher baseline RHR indicated a significantly higher risk of total mortality (HR = 1.14 [1.11 - 1.16], p = 0.001) after multivariate adjustment. However, the RHR did not significantly affect total mortality (p = 0.120) or cardiovascular mortality (p = 0.244) in patients with the MetS. Interaction terms RHR×MetS were significant for both total cardiovascular mortality (p = 0.027 and p = 0.037, respectively), indicating that the respective risks conferred by a high RHR were significantly higher in patients without the MetS than in patients with MetS.

Conclusions: We conclude that among angiographically characterized coronary patients, the metabolic syndrome status significantly affects the association of the RHR with total and cardiovascular mortality: RHR is a strong predictor of both total and cardiovascular mortality among subjects without the MetS, but not among MetS patients.
Multi compartment body composition analysis in chronic heart failure: air displacement plethysmography, body impedance analysis, dual-energy X-ray absorptiometry, and 3D-and-white light analysis

T. D. Tippel1, A. Stahn2, V. Tschoßl2, S. Inkerl1, W. Döhner2, S. Von Haehling2, E. Tahirovic1, W. Haverkamp3, H. D. Quenglen1, D. Obradovic1,1Charité Campus Virchow Klinikum, Competence Network Heart Failure, Department of Cardiology, Berlin, Germany; 2Charite - University Medicine, Campus Benjamin Franklin, Institute of Physiology, Berlin, Germany; 3Charite - Campus Virchow-Klinikum, Department of Internal Medicine-Cardiology, Berlin, Germany.

Concordance Correlation Coefficient (CCC) for FM in DEXA vs ADP was 0.76 (95% CI 0.64-0.89) and for FM in 3DBS vs ADP was 0.78 (95% CI 0.6-0.88). The mean percentage of extracellular fluid measured by BIA was 45.0% (CI 41.7-48.4) and 44.3% (CI 41.4-47.2) in MIBI, which differed significantly (p<0.003); consequently percentage of intracellular body fluid was increased (56.4% CI 53.9-58.9) in MIBI as compared to ADP and even significantly different (p<0.001). In HFrEF MIBI 53% (CI 51.9-54.6) and 49% in MIBI 54.3% (CI 52.5-56.1) in HFrEF and 56% (CI 54.6-58) in HFrEF. Concordance Correlation Coefficient (CCC) for FM in HFrEF vs HFrEF was 0.88 (95% CI 0.86-0.91) and for FM in HFrEF vs HFrEF was 0.66 (95% CI 0.6-0.7) and for FM in HFrEF vs HFrEF was 0.66 (95% CI 0.6-0.7).

These results show that OF induces metabolic, oxidative and functional disturbances but also a higher susceptibility to cardiac functional damage after ischemia ex vivo. Complementary data are required to understand the cellular pathways involved in these cardiovascular and metabolic modifications.

Longitudinal study of Advanced Glycation End product plasma levels in patients undergoing coronary artery bypass grafting surgery: effects of statin treatment, gender and type 2 diabetes

V. Salpeas1, J.N. Tosporinis1, G. Proteau2, S. Izhar1, E. Sakadakis1, T.G. Parker1, I.A. Ricos1, M. Anastasiou-Nana1,1Attikon University Hospital, Athens, Greece; 2St. Michael's Hospital, Toronto, Canada.

The accumulation of advanced glycation end products is thought to be a key factor in the initiation and progression of type 2 diabetes. Despite studies demonstrating a beneficial role of statins in reducing cardiovascular morbidity/mortality risk with type 2 diabetes, statins may also raise the risk of type 2 diabetes in the elderly. We aimed to show an association between plasma AGE levels and statin therapy in 17 diabetic patients (11 male, 6 female) mean age 63.59 years ± 5.79 (SD) and 10 non-diabetic patients (8 male, 2 female) mean age 65.60 years ± 6.39 (SD) all in sinus rhythm undergoing coronary artery bypass grafting (CABG) surgery with a mean follow-up 7.3 years.

Our longitudinal model (pre- and post-CABG) was adjusted for cross – clamp time (non-significant) and for differences in diabetes status, gender and treatment with statin (lipid plasma was taken before aortic occlusion and after reperfusion. Plasma AGE (μg/mL) was assayed by enzyme-linked immunosorbent assay (ELISA).AGE levels were higher in non diabetic compared to diabetic patients pre- (64.1±26.2 vs 47.6±21.1 μg/mL, p<0.05) and post- (33.1±12.6 vs 14.7±5.1 μg/mL, p<0.05) CABG. Taking into account gender differences, non diabetic females vs males had increased AGE plasma levels pre- (108±7.08 vs 79.5±12.4 μg/mL, p<0.01) and post- (57±3.9 vs 21.9±1.2 μg/mL, p<0.05) whereas, diabetic males had higher AGE plasma levels pre- (54.8±27.4 vs 22.4±21.6) and post- (16.6±6 vs 10.1±4.3 μg/mL, p<0.05).

CABG induced a drop in AGE plasma levels independent of diabetes or gender. Non diabetic and diabetic pts on statin therapy vs no therapy had higher AGE levels pre- and post-CABG. Female diabetics experienced a significant drop in plasma AGE 4 weeks after CABG. Similar significant drop happens after CABG in female patients not treated with statin. In pts not under statin treatment the post CABG drop in AGE plasma concentrations was significantly higher in non diabetics vs diabetic patients, a reduction 3- to 4- fold higher than the significant reduction for pts treated with statins (diabetic and non-diabetic). AGE plasma levels significant reduction post-CABG in patients with statins was on average almost 50-fold the post-CABG reduction in patients not submitted to statin treatment. The significant mean reduction of post-CABG AGE plasma levels was not different in magnitude between diabetic and non diabetic pts. Statin treatment and diabetes may contribute to gender differences in AGE plasma levels pre- and post-CABG and may have a similar effect in limiting the post CABG drop of AGE plasma levels in female patients.

Early-induced overweight causes rapid changes in heart genomic expression and long-term cardiovascular, metabolic and oxidative alteration

A. Habbout1, J. Lorin1, E. Rigal1, C. Fassot2, L. Rochette1, C. Vergely1. 1Inserm UMR866, Equipe LPPCM, Dijon, 2Inserm UMR1083, Biologie neurovasculaire et mitochondriale Intégrée, Angers, France.

Several studies in rodents have shown that postnatal overfeeding (OF) induces permanent moderate increase of body weight in the adult; however, cardiovascular and oxidative repercussions of postnatal OF are less known. Immediately after birth, litters of C57BL/6 mice were either maintained at 10 animals per chip at early and late stages of development.

Purpose: To assess the influence of OF on heart and both SOD and catalase activities were measured. Cardiac function was assessed by echocardiography and the susceptibility to myocardial global ischemia ex vivo. Complementary data are required to understand the cellular path-ways involved in these cardio-metabolic and oxidative modifications.
Detection of subclinical left ventricular dysfunction in asymptomatic young adults with type-2 diabetes: a cardiac magnetic resonance study

J.N. Khan1, E. Wilmot1, M. Davies1, T. Gorely1, K. Khunti1, M. Leggate2, M. Nimmo2, A. Singh1, T. Yates1, G.P. Mccann1.
1University of Leicester, Departments of Cardiovascular and Health Sciences, Leicester, United Kingdom; 2School of Sport Sciences, University of Loughborough, Loughborough, United Kingdom

Introduction: There is an epidemic of obesity and Type 2 diabetes (T2DM) in the developed world. Although diabetic cardiomyopathy is well documented in older adults with T2DM there is very little data on younger adults and no published CMR data.

Objective: To use CMR to assess whether asymptomatic young adults with T2DM have subclinical left ventricular (LV) dysfunction compared to healthy lean and obese controls.

Methods: 40 asymptomatic subjects (20 T2DM, 10 obese non-diabetic controls, 10 lean non-diabetic controls) underwent CMR assessment of the LV on a Siemens Avanto 1.5T system. LV function and volumes were assessed using SSFP. Circumferential strain was assessed using a multi breath-hold CSPAMM tagging sequence at 3 slices (basal, mid-cavity, apical). Perfusion was assessed on first-pass contrast imaging during adenosine stress.

Results: Subjects were matched for age, height, and blood pressure. Global peak early diastolic strain rate (PESDR) was significantly lower in T2DM, compared to lean and obese controls. There was a significant trend towards reduced global peak systolic strain (PSS) in T2DM, compared to lean and obese controls (Table 1). There was no evidence of coronary artery disease on perfusion testing.

Conclusions: This is the first CMR study demonstrating subclinical diastolic dysfunction in young adults with T2DM. The significant difference between the T2DM and obese groups suggest that T2DM in early adulthood has detrimental effects on cardiac function, additional to those associated with obesity.

Heart rate variability, postprandial responses of glucose and insulin and beta-cell function: the NEO study

S. Hillebrand1, K.B. Gast1, C.A. Swenne1, J.W. Jukema1, J.W.A. Smit1, F.R. Rosendaal1, M. den Heijer2, R. DeMutsert1, on behalf of NEO Study Investigators.
1Leiden University Medical Center, Department of Clinical Epidemiology, Leiden, Netherlands; 2VU University Medical Center, Amsterdam, Netherlands

Introduction: Low heart rate variability (HRV) is associated with diabetes mellitus (DM). We hypothesize a negative association of HRV with insulin resistance in fasting state (IR) and postprandial responses of glucose and insulin and a positive association with beta-cell function.

Methods: Baseline analysis of the Netherlands Epidemiology of Obesity (NEO) study, including 6000 individuals aged 45-65y with a BMI ≥ 24 kg/m2. HRV was calculated as SDNN (ms), RMSSD (ms), LF (ms²) and HF (ms²). Blood was sampled fasting, 30min and 150min after a mixed meal (400 ml, 600 kcal). We calculated Homeostasis Model Assessment of insulin resistance (HOMA2-IR) as a measure IR. Area under the curve (AUC) for glucose and insulin were used as measures of the postprandial responses. Beta-cell function was calculated with the insulineogenic index (IGI): Δinsulin/(30-150 min)/glucose(30-150) and AUC/IACG. Linear regression analysis was used to assess the association of HRV with IR, postprandial responses and beta-cell function, stratified by day/night and adjusted for sex, age, BMI, waist circumference, ethnicity, education, smoking, medication, hypertension, beats per minute and physical activity.

Results: Of 4562 included participants, 639 had HRV measurements. Participants with recordings<72h (n=75), CVD (n=43) or DM (n=47) were excluded, resulting in 489 participants (46% men, mean age (SD): 56 (6) years, BMI: 31.4 (kg/m²), fasting glucose: 5.6 (0.78) mmol/L. We found no association of lnSDNN (ms) during daytime with lnHOMA2-IR (p=0.15, 95%CI: -0.32, 0.03).

Full appraisal of glycemic risk

Abstract P4963 – Table 1. CMR results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lean control (LC)</th>
<th>Obese control (OC)</th>
<th>Type 2 diabetes (T2DM)</th>
<th>T2DM + B C (p)</th>
<th>T2DM vs LC (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.0±6.6</td>
<td>30.9±5.6</td>
<td>31.8±6.6</td>
<td>0.871</td>
<td>0.862</td>
</tr>
<tr>
<td>Sex (men, %)</td>
<td>64</td>
<td>91</td>
<td>5.5</td>
<td>0.804</td>
<td>0.456</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.9±1.71</td>
<td>33.2±2.55</td>
<td>33.6±5.80</td>
<td>0.001</td>
<td>0.240</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131.20±13.74</td>
<td>130.33±14.82</td>
<td>136.55±14.74</td>
<td>0.239</td>
<td>0.255</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79.90±12.31</td>
<td>84.33±16.66</td>
<td>83.75±8.88</td>
<td>0.101</td>
<td>0.417</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>10.46±4.51</td>
<td>0.54 (±4.86)</td>
<td>0.54 (±0.45)</td>
<td>0.052</td>
<td>0.816</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55.00±3.53</td>
<td>53.64±3.46</td>
<td>54.80±5.95</td>
<td>0.727</td>
<td>0.481</td>
</tr>
<tr>
<td>PSS (%) (for analysis)</td>
<td>-20.35±2.43</td>
<td>-20.50±2.8 (n=9)</td>
<td>-18.41±1.69 (n=16)</td>
<td>0.028</td>
<td>0.054</td>
</tr>
<tr>
<td>PEDSR (%) (for analysis)</td>
<td>1.80±0.47 (n=9)</td>
<td>1.59±0.32 (n=9)</td>
<td>1.27±0.34 (n=16)</td>
<td>0.006</td>
<td>0.026</td>
</tr>
</tbody>
</table>

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Mean±SD, or median (IQR) where non-parametric data (normalised using log10). Data corrected for sex and ethnicity (ANCOVA).

Figure 1: Detection of subclinical left ventricular dysfunction in asymptomatic young adults with type-2 diabetes: a cardiac magnetic resonance study

Figure 1a) while AIRg was 1909 and 1043 pmol l-1 min-1 (p<0.0001; Figure 1b).

Conclusion: Sitagliptin, prescribed soon after the event, improved beta-cell function and glucose perturbations in patients with ACS and newly diagnosed glucose intolerance.
Diabetes is related to higher central blood pressure  

D. Debička-Dąbrowska, P. Jarzkowski, M. Kloch-Badelek, J. Wilinski, M. Brozowska-Ksiazka, K. Kawecka-Jaszcz, D. Czarnecka.  
Jagiellonian University Medical College, 1st Department of Cardiology and Hypertension, Krakow, Poland

Background: Central blood pressure (BP) is directly related to LV overload as well as blood supply to the heart and brain. It may also directly damage coronary and cerebrovascular beds being one of the most important causes of atherosclerotic cardiovascular disease. Several studies have shown closer correlation between end-organ damage and central than peripheral BP. Central BP was also shown to better predict cardiovascular risk. Diabetes is related to at least two-fold increased in CV risk. The influence of diabetes on central BP values is unknown.

Aim: To assess the independent influence of diabetes on the ascending aortic BP.

Methods: BP in the aorta was measured using fluid-filled filter in 400 patients (200 with type 2 DM and 200 without DM matched for age and gender) undergoing emergency coronary angiography. Brachial BP was measured using a sphygmomanometer. Both groups did not differ in respect of age and sex. General regression model (age, sex, mean BP, risk factors, LVFE, creatinine level, and drugs were included into the model) was used to assess the independent influence of diabetes on BP.

Results: Systolic, diastolic, and mean brachial BP did not differ between the study groups (138.6±21.3 vs. 133.7±20.3 mmHg; p=0.06; 83.4±12.0 vs. 82.6±10.7 mmHg; p=0.11; 109.1±16.0 vs. 99.6±13.0 mmHg; p=0.27 in diabetics and non-diabetics, resp.) but brachial pulse pressure was higher in diabetics (55.4±15.3 vs. 51.1±14.2; p=0.02). Central BP values are shown in the table. In multivariable analysis diabetes was related to higher ascending aortic systolic BP by 2.9% (95% confidence intervals: 1.7-3.8) mmHg and pulse pressure by 4.1 (2.5-5.7) mmHg vs. 51.1

Conclusions: Diabetes is independently related to higher values of systolic and pulse pressure in the ascending aorta. This may partly explain the higher CV risk in diabetics.

# P4968

Impaired glucose homeostasis in non-diabetic hypertensives with family history of diabetes  

C. Liakos1, G. Vyssoulis2, E. Karpouzis3, A. Michaelides1, C. Stefanadis1, 1 1st Department of Cardiology, University of Athens Medical School, Hippokration Hospital, 11527, Athens, Greece; 21st Department of Cardiology, Antihypertension Center, Onassis Cardiac Surgery Center, 1764, Athens, Greece

Purpose: Arterial hypertension (AH) and diabetes mellitus (DM) are established cardiovascular risk factors. Impaired glucose homeostasis (IGH, i.e. impaired fasting glucose and impaired glucose tolerance), obesity and family history of diabetes identify individuals at risk for DM in whom preventive interventions should be required. The aim of this study was to determine the glycemic profile of non-diabetic hypertensive patients according to the presence of diabetes family history in the obese status.

Methods: Diabetes family history, obesity markers (waist to hip circumference ratio - WHR, body mass index - BMI), glycemic parameters (fasting glucose, glycated haemoglobin, insulin resistance indices (homeostasis model assessment - HOMA, quantitative insulin sensitivity check index - QUICKI, McAuley) and the prevalence of IGH were all determined in a large cohort of 11540 hypertensives (mean age 56.8 years, 57.7% males, mean office blood pressure 164.0±98.8 mmHg) who were referred to the hypertensive units of our institutions.

Results: Positive DM family history was associated with elevated glucose (9.9±1.7 vs. 9.3±1.7 mmol/L; p=0.003), fasting insulin (21.3 vs. 133.7 ng/mL; p=0.025 vs 0.345; 0.46%), insulin resistance (HOMA, 5.68±0.49 vs 5.03±0.46%, 0.08, 95%CI: -0.05, 0.04) or lnAUCinsulin (β=-0.002, 95%CI: -0.05, 0.001) even higher than in non-diabetics. Excluding 21% of patients with DM, the prevalence of IGH was 24% in those with DM family history vs. 19% in those without DM family history (p=0.025)

Conclusions: Non-diabetic hypertensives with positive diabetes family history present with higher prevalence of impaired glucose homeostasis and worse glycemic indices levels compared to those with negative family history.

Omentin-concentrations predict 10-year incidence of diabetes in Thai: the EGAT study, 1998-2008  

D. Wardomwich, W. Chaiyaratana, N. Thongmuang, M. Vanichapuntu, P. Sirita. Faculty of Medicine Ramathibodi Hospital of Mahidol University, Bangkok, Thailand

Background: Obesity has reached epidemic proportions and is an established risk factor for insulin resistance, type 2 diabetes (T2D) and cardiovascular disease. Alterations in the secretion of adipokines in obesity are believed to contribute to the undesirable changes in glucose metabolism that ultimately result in the development of T2D. Omentin-1 is a novel adipokine preferentially produced by visceral adipose tissue with insulin-sensitizing effects, where the circulating concentrations are significantly lower in obese compared to lean subjects, thus contributing to the insulin resistance. The current study was conducted to determine: 1) the baseline and 10-year serum concentration of omentin-1 concentrations were measured by ELISA method.

Results: Baseline socioeconomic status, educational background BMI, and wa -sit and hip circumferences were significantly higher in incident cases compared with controls. Omentin-1 concentrations were significantly negatively correlated with BMI (r=-0.196, p<0.0001) and waist circumference (r=-0.168, p=0.002) newly diagnosed diabetes at 10-year follow up in a cohort of initially healthy middle-aged Thais and the observed association was independent of obesity.

Figure 1. IGH prevalence, obesity & DM fam. History.

Conclusions: No dietetic hypertensives with positive diabetes family history present with higher prevalence of impaired glucose homeostasis and worse glycemic indices levels compared to those with negative family history.

Current smoking and pre-diabetes in young and healthy adults  

S. Aeschbacher1, T. Schoen1, M. Risch2, L. Risch2, D. Conan1, 1University Hospital Basel, Department of Internal Medicine, Basel, Switzerland; 2Labormedicinisches Zentrum Dr Risch, Schaan, Liechtenstein

Purpose: Several studies have shown a strong relationship between smoking and type 2 diabetes. However, it is unclear whether smoking is related to changes in glucose homeostasis in young adults without prevalent type 2 diabetes and with a relatively short smoking history. We therefore aimed to assess the association between smoking and pre-diabetes in young and healthy adults.

Method: The Genetic and Phenotypic Determinants of Blood Pressure and Other Cardiovascular Risk Factors (GAPP) study is a population based cohort of healthy adults aged 25-40 years in the Principality of Liechtenstein. Smoking was defined as smoking at least one cigarette per day and pre-diabetes was defined as HbA1c ≥5.7 and ≤6.4.

Results: Baseline smoking behaviour was assessed by self-report. Smoking at 10 years follow up in a cohort of initially healthy middle-aged Thais and the observed association was independent of obesity.
Results: Of 857 patients, 231 (27%) had prediabetes. Compared to normoglycemic subjects, prediabetics were significantly older (40 vs 38 years, p<0.0002), more often male (57 vs 43%, p=0.001), and they had a higher body mass index (24.9 vs 23.9 kg/m², p=0.0001). The prevalence of active smokers among prediabetic and normoglycemic subjects was 29% and 19%, respectively (p=0.0003), with a median (interquartile range) number of pack years among current smokers of 11.3 (5.8-18.8) and 5.9 (3.8-13.5), respectively (p=0.003). In age- and sex-adjusted logistic regression models using prediabetes as the outcome variable, current smoking was significantly associated with prediabetes (Odds ratio (OR) 1.79 (95% confidence interval 1.24-2.59), p=0.004). Former smoking was not significantly related to prediabetes (OR 0.76 (95% CI 0.51-1.13), p=0.18). Compared to never and past smokers, current smokers with 5, 5 to 10 and >10 pack years had an OR (95% CI) of 1.07 (0.53-2.13), p=0.86; 2.09 (1.08-4.07), p=0.03; and 2.22 (1.34-3.68), p=0.002, respectively.

Conclusion: Accumulating as few as 5-10 pack years of smoking carries a more than 2-fold increased risk of having prediabetes in healthy young adults. Thus, our data reinforce the importance of smoking cessation in the general population.

### P4971

**Prognostic impact of coexistence of metabolic syndrome and chronic kidney disease in patients undergoing coronary artery revascularization**

A. Kunimura1, T. Amano2, K. Kitagawa2, Y. Shimbo1, H. Ando1, K. Harada1, T. Yoshiida1, T. Uetani1, M. Matsubara3, T. Murakara4, Chujo Rosai Hospital, Nagoya, Japan; 1Aichi Medical University, Department of Cardiology, Nagoya, Japan; 2Aichi Gakuen University, School of Dentistry, Department of Internal Medicine, Nagoya, Japan; 3Nagoya University Graduate School of Medicine, Department of Cardiology, Nagoya, Japan

**Background:** Both metabolic syndrome (MetS) and chronic kidney disease (CKD) have been reported to be risk factors of cardiovascular events. Objective: The aim of this study was to assess the synergistic effect of MetS and CKD on atherosclerotic plaque and cardiovascular outcomes.

**Methods and Results:** A total of 204 consecutive patients who underwent percutaneous coronary intervention (PCI) were enrolled. They were divided into four groups according to the presence or absence of MetS and CKD. MetS was defined by following criteria of the National Cholesterol Education Program in Adult Treatment Panel III. CKD was defined as an estimated GFR < 60 ml/min/1.73 m². We analyzed the incidence of major adverse cardiac events (MACE) including cardiovascular death, nonfatal myocardial infarction, target lesion revascularization, and revascularization for new lesion as well as coronary plaque characteristics using integrated backscatter intravascular ultrasound (IB-US). Major adverse cardiac events occurred more frequently in patients with both MetS and CKD (46.2%) as compared to the other three groups during follow-up period (Log rank p=0.029). In the IB-US analyses, patients with both MetS and CKD showed a greater plaque burden (p<0.001) with larger lipid contents (p=0.048) as compared to the other three groups. In cox analyses, patients with both MetS and CKD proved to be an independent predictor of MACE even after adjustment of confounding factors (hazard ratio 1.79; 95% confidence interval 1.011-2.991; p=0.046).

**Conclusion:** Administration of alagliptin significantly improved postprandial endothelial dysfunction and increase in triglyceride, suggesting alagliptin that may be a promising anti-atherogenic agent.

### P4973

**7-year exercise test early heart rate predicts new onset diabetes**

K. Engeseth1, P.T. Skretteberg1, I. Grundvold1, K. Liestøl1, G. Erikssen1, J. Erikssen1, S.E. Kjeldsen1, J. Bodegard1 on behalf of Oslo Ischaemia Study Group. 1Oslo University Hospital, Oslo, Norway; 2University of Oslo, Department of Informatics, Oslo, Norway; 3University of Oslo, Faculty of Medicine, Oslo, Norway

**Purpose:** An elevated resting heart rate has previously been reported to predict new onset diabetes (NOD). Pre-diabetic autonomic nervous system dysfunction
Full appraisal of glycemic risk

P4974 Metabolic syndrome in the Czech population. Current status and trends

J. Brhata, R. Ciklová, Z. Slodova, Z. Adamkova, M. Jozifova, P. Wohtlharth, M. Galovcova, V. Lanska. Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Purpose: The prevalence of the metabolic syndrome is perceived as high and increasing among Czech adults. Our objective was to determine its exact prevalence and trends among men. Our aim was to assess the control and treatment of the metabolic syndrome in the Czech population.

Methods: A total of 3196, 3249 and 3537 men and women aged 25-64 years from 1997/8, 2000/1 and 2006-9 Czech post MONICA cross-sectional population surveys (1% random representative population sample of nine districts of the Czech Republic) were included in the analyses. We used the definition of the metabolic syndrome developed by the Joint Interim Statement of several major scientific organizations (Circulation 2009;120:1640-1645).

Results: The prevalence of the metabolic syndrome was 37.1% in 1997/8 and 32% in 2006-9 among women (P=0.002, a significant decrease) and 55.5 and 48.2%, respectively, among men (P=0.218). The prevalence of the metabolic syndrome increased with the age in all surveys. In 2006-9 survey in men 25-34 years old the prevalence was 20.1%, in 35-44 years old 33.4%, 45-54 years old 56.1% and 55-64 years old 67.1%; among women the prevalence was 5.8%, 13%, 36.5% and 58% respectively. The prevalence decreased with the level of achieved educational status, differences more pronounced among women. Of the metabolic syndrome component factors central obesity was the most frequent; in men with metabolic syndrome, 2006-9 survey, 93.1%, in women 97.8%, followed by raised blood pressure (89.7 and 84.5%) and by raised triglycerides (81.3 and 69.8%). In both genders, prevalence of central obesity and of raised blood pressure in the period 1997/8-2006/9 increased, but prevalence of raised fasting glucose decreased. Compared to the lifestyle interventions and drug therapies of major cardiovascular risk factors (arterial hypertension, hypercholesterolemia, smoking), the components of the metabolic syndrome were less targeted by comprehensive preventive and therapeutic means.

Conclusions: Contrary to the earlier data and some foreign (US) trends, the prevalence of the metabolic syndrome among adult Czech men did not increase and it even decreased among adult Czech women. However, it remains high, especially among elderly and among persons with basic and lower education. The metabolic syndrome and its components, compared to the "classical" cardiovascular risk factors, was less targeted by preventive and therapeutic means. As far as uncertainty about the effect of drug interventions persists, lifestyle interventions should be further encouraged.

P4975 Autonomic neuropathy is independently associated with new heart failure and atrial fibrillation in diabetic patients with preserved ejection fraction: prognostic significance of heart rate recovery

N. Negishi, S. Seikawa, T. Negishi, Yingcharoen, C. Gibby, T. Marwick. Cleveland Clinic, Department of Cardiovascular Medicine, Cleveland, United States of America

Purpose: Atrial fibrillation (AF) and heart failure (HF) are important and interacting complications of type 2 diabetes mellitus (T2DM), and may be predicted by left atrial volume index (LAWI). Diabetic autonomic neuropathy may be an important contributor to AF, and may be evidenced by attenuated heart rate recovery (HRR). We sought whether HRR had an association with HF and AF in T2DM, independent of LA size.

Methods: We enrolled 814 consecutive uncomplicated patients with T2DM (56±11yrs, 508 men) who had negative stress echocardiography from 2004 to 2007. Patients with prior cardiac surgery, AF, ≤ mild valvular disease, HF, ejection fraction <50% or any cancer at enrollment were excluded. Demographics, clinical assessment, standards of diabetes care, co-morbidities, and treatment with insulin, diuretics, beta-blockers, statins, ace-inhibitors and aspirin were collected prospectively. Associations of echo indices and HRR with a composite of new onset HF and AF were sought using a Cox proportional hazard model.

Results: There were 47 events (22 HF and 25 AF) during 7.8 yrs follow up. HbA1c of patients with and without outcome were 7.6±1.5 and 7.4±1.7 (p=NS). The composite endpoint showed univariate associations with age, exercise capacity (maximal metabolic equivalent [Max Mets]), HRR and LAVI, but not with ventricular mass index, diastolic functional stage, E/A ratio or deceleration time. HRR and LAVI were independently associated with outcomes (Table).

Conclusion: HRR is associated with new onset HF and AF in T2DM, independent of LAVI. This association may reflect the contribution of autonomic neuropathy to both HRR and HF.

P4976 Tight glycemic control after cardiac surgery reduces the incidence of post-surgical atrial fibrillation regardless of existence of diabetes mellitus


Purpose: Atrial fibrillation is a common occurrence after cardiac surgery. However, there remains some uncertainty surrounding the relationship between onset of atrial fibrillation and pre-existing diabetes mellitus as well as the role of tight glycemic control after cardiac surgery. The purpose of this study was to clarify the relationship between incidence of atrial fibrillation after cardiac surgery and diabetes mellitus, and the effect of tight glycemic control.

Methods: Consecutive 60 subjects after cardiac surgery were divided into two groups, tight glycemic control group (Group T, n=30) and usual control group (Group C, n=30, 62±13y.o.). In Group T, glycemic status was aimed to be be between 80-150mg/dL. Incidence of atrial fibrillation was compared between two groups, as well the effect of diabetes status on occurrence of atrial fibrillation was investigated.

Results: Atrial fibrillation occurred in 24 patients. There was no significant difference in the occurrence of atrial fibrillation between patients with or without diabetes mellitus (Hazard ratio 0.65, 95%CI 0.41, 1.04). However, the incidence of atrial fibrillation was significantly lower in the tight glycemic control group (Hazard ratio 0.47, 95%CI 0.26, 0.85). In a multivariate analysis, the incidence of atrial fibrillation was not significantly lower in patients with diabetes mellitus (P=0.29). In both groups, the incidence of atrial fibrillation was 30% and 29%, respectively (p=NS).

Conclusion: It is revealed that tight glycemic control after cardiac surgery reduces the incidence of post-surgical atrial fibrillation regardless of the diabetic status.

P4977 Low levels of IgM antibodies against phosphorylcholine are not associated with glucometabolic disturbances in patients with acute ST-elevation myocardial infarction

E.C. Kruiderink1, I. Seljelid1, C. Muller2, G.B. Andersen1.

1Department of Cardiology, Center for Clinical Heart Research, Oslo University Hospital, Ullevål, Oslo, Norway; 2Department of Nuclear Medicine, Oslo University Hospital Ullevål, Oslo, Norway

Purpose: Phosphorylcholine (PC) is an important epitope on oxidized low-density lipoproteins and might contribute to atherosclerosis and cardiovascular disease. The association between low levels of IgM antibodies against PC and glucometabolic disturbances in patients with acute ST-elevation myocardial infarction (STEMI) is unknown. The aim of the present study was to evaluate whether low levels of IgM antibodies against PC were associated with glucometabolic disturbances in a cohort of patients with STEMI.

Methods: Plasma samples were collected from 100 patients with STEMI during hospital stay. Levels of IgM antibodies against PC were measured using an ELISA. Glucometabolic disturbances were assessed by the HbA1c, fasting plasma glucose and insulin, and an oral glucose tolerance test was performed. Presence of cardiovascular risk factors and the use of anti-diabetic and cardiovascular drugs were also recorded.

Results: The mean age of the patients was 64 years (range 29-83) and 59% were men. The mean HbA1c was 5.8% (range 3.8-10.8), fasting plasma glucose was 5.2 mmol/L (range 3.0-11.6), and the mean oral glucose tolerance test area under the curve was 1319 (range 202-4591). The mean level of IgM antibodies against PC was 9.7 ng/ml (range 0.6-37.0). No significant associations were found between low levels of IgM antibodies against PC and glucometabolic disturbances (HbA1c: r=0.06, p=0.55; fasting plasma glucose: r=0.03, p=0.73; oral glucose tolerance test area under the curve: r=0.07, p=0.47).

Conclusion: Low levels of IgM antibodies against phosphorylcholine are not associated with glucometabolic disturbances in patients with acute STEMI.
lipoprotein (oxLDL), and IgM antibodies against PC (anti-PC) are present as nat-
ural antibodies in humans. Low levels of IgM anti-PC have been shown to be asso-
ciated with an increased risk of myocardial infarction, indicating that PC may play
an important role in the atherosclerotic process via oxLDL. oxLDL has proin-
flammatory properties and inflammation is important in the development of both
cardiovascular diseases and diabetes.

The aim of the present study was therefore to elucidate a possible association
between IgM anti-PC measured in-hospital and undiagnosed abnormal glucose
regulation in patients with acute ST-elevation myocardial infarction (STEMI).

Methods: Patients (n=200, median age 58 (St. 68) years) with a primary coro-

nary intervention (PCI) treated STEMI without known diabetes were
included. Serum levels of IgM anti-PC were measured in-hospital and a stan-

dardised 75g OGTT (venous plasma glucose measurements at 0 and 120 min)
was performed at three-month follow-up. Based on the OGTT results, the
patients were categorised according to the WHO criteria, and the term abnormal glucose
regulation was defined as the sum of impaired fasting glucose, impaired glucose
tolerance, and type 2 diabetes.

Results: A total of 50 patients were classified with abnormal glucose regulation
at three-month follow-up. Median (25th, 75th percentiles) levels of IgM anti-PC in
patients with abnormal vs. normal glucose regulation were 32.9 (23.7, 51.7) U/ml
vs. 41.5 (24.7, 59.7) U/ml (p=0.55). Low levels of IgM anti-PC (≤ 24.6 U/ml (25th
percentile) were not associated with abnormal glucose regulation (OR 1.2 (95%
CI 0.6-2.5, p=0.5)).

No significant correlations were found between IgM anti-PC and different glucose
parameters (admission glucose, HbA1c, fasting glucose and 2-h glucose).

Conclusions: Low levels of IgM anti-PC were not associated with newly de-
tected abnormal glucose regulation in patients with acute STEMI without previ-
ously known diabetes. The previously reported association between low levels of
IgM anti-PC and mycardial infarction seems to be independent of glucometabolic
disturbances.

Chemerin is associated with the metabolic syndrome but is not linked to angiographically determined coronary artery disease


In the present study we have investigated if the administration of pioglitazone or perindopril could be proved beneficial with respect to angiogene-

sis and in re-endotheliazation of injured blood vessels. Endothelial progenitor cells (EPCs) play a significant role in neovascu-

larization of ischemic tissues and in re-endotheliazation of injured blood vessels. The purpose of this study was to investigate if the administration of pioglitazone or perindopril in diabetic patients can modify the number of EPCs in the peripheral blood and alter the endothelial function and inflammatory status of these patients. Methods: Fifty type 2 diabetic patients were recruited and were randomly as-
grained to receive either pioglitazone (15mg/day) or perindopril (4mg/day) for a one-month period. Blood samples were obtained in order to count EPCs and inflammation markers such as C-reactive protein (hsCRP), vascular endothelial growth factor (VEGF) and asymmetric dimethilarginine (ADMA). Circulating EPCs were defined by the surface markers CD34+/KDR (CD34 and VEGF-R2 expressing
cells) and analyzed by flow-cytometry. Moreover the endothelial function of the patients was evaluated both on admission and after treatment with flow mediated dilatation (FMD).

Results: We have found that neither pioglitazone (p=0.09), nor perindopril (p=0.55) affected the number of EPCs. Importantly, we have shown that pioglitazone re-
duced CRP (2.5±2.4 vs. 1.8±1.5 mg/dL, p=0.04) and ADMA levels (0.8±0.5 vs 0.7±0.5 mmol/L, p=0.02), both at admission, pioglitazone improved FMD (0.05±0.02 vs 0.07±0.04, p=0.04) and increased plasma concentrations of VEGF (102.7±70.6 vs 169.3±120.7 pg/mL, p=0.001). On the contrary, perindopril had no significant effect on CRP levels (p=0.57), FMD (p=0.27) as well as on ADMA levels (p=0.24). However, perindopril administration increased significantly plasma levels of VEGF (126.3±100.0 vs 163.2±121.5 pg/mL, p=0.03). Moreover, both agents did not differ regarding to their effect on ADMA levels (p=0.54), FMD (p=0.70), VEGF (p=0.27) and CRP (p=0.85). Interestingly, we have found that perindopril had a superior effect than that of pioglitazone considering ADMA levels (0.16±0.15 vs 1.5±0.01), despite the non significant effect on ADMA levels resulting solely.

Reduction of glucose consumption can be a beneficial tool to improve blood pressure and reduce the risk of cardiovascular disease in patients with diabetes. However, the most effective anti-diabetic treatment is still a matter of debate. The purpose of this study was to investigate if the administration of pioglitazone or perindopril could be proved beneficial with respect to angiogen-
esis as well as on ADMA levels. Moreover, perindopril administration increased significantly plasma levels of VEGF (126.3±100.0 vs 163.2±121.5 pg/mL, p=0.03). However, both agents did not differ regarding to their effect on ADMA levels (p=0.54), FMD (p=0.70), VEGF (p=0.27) and CRP (p=0.85).

Conclusions: Our results support the beneficial role of pioglitazone in terms of inflammation and oxidative stress. In addition, the combined administration of pi-
oglitazone and perindopril could be proved beneficial with respect to angiogene-
sis as well as on ADMA levels.
fraction (MI), adrenomedullin as a marker for congestive heart failure (CHF). Both hormones may be involved in the pathophysiology of metabolic syndrome.

**Methods:** Sera of 920 patients (pts) were eligible for this analysis, 777 pts had undergone elective coronary angiography (CA), 143 pts CA in acute coronary syndrome. All pts underwent an oral glucose tolerance test (OGTT), pts with previously known diabetes mellitus were excluded from the study. Definition of glucometabolic state (OGTT): NGT = normal glucose tolerance; IFG = isolated impaired fasting glycemia; IGT = impaired glucose tolerance; DM = diabetes mellitus. Definition of coronary anatomy: no CAD = normal; minor CAD = lesions < 50%; 1VD, 2VD, 3VD = 1-, 2- or 3-vessel disease. In pts with elective CA 59 pts had no coronary artery disease (no CAD), 152 pts only lesions ≤50% (minor CAD), 164 pts 1-vessel disease (1VD), 172 pts 2-vessel disease (2VD), and 230 pts 3-vessel disease (3VD). In OGTT 930 pts had normal glucose tolerance (NGT), 279 pts impaired glucose tolerance (IGT), and 105 pts diabetes mellitus (DM). Copeptin and MR-pro-adrenomedullin (ADM) were measured by ELISA (Germany) (non-invasive testing, Germany). Statistical analyses were performed by ANOVA and Kruskal-Wallis methods.

**Results:** Pts with no CAD had significantly lower copeptin levels compared to pts with beginning CAD (p = 0.023), 1VD (p = 0.03), 2VD (p = 0.012) or 3VD (p = 0.001). Concerning ADM, only pts with 3VD (p = 0.0002) and beginning CAD (p = 0.009) had higher ADM levels compared to no CAD pts. Interestingly, both pts with DM (p = 0.0001) and IGT (p = 0.0003) had higher copeptin levels compared to pts with NGT; there was no significant difference (p = 0.08) between pts with DM and IGT. Similarly, pts with NGT had lower ADM levels compared to pts with IGT (p = 0.001) or pts with DM (p = 0.005). And again there was no difference in ADM levels with DM and IGT (p = 0.85).

**Conclusions:** Copeptin was elevated in pts with CAD compared to those with no CAD, but there was no grading based on severity of CAD. Similarly, ADM was elevated primarily in pts with advanced CAD (3VD), but also in pts with minor CAD compared to no CAD pts. Both markers were elevated in pts with IGT and previously unknown DM. The fact that both hormones were already elevated in newly diagnosed IGT may be an argument for their early involvement in the pathophysiology of the metabolic-vascular syndrome.

**Impact of exercise training on waist circumference, glucose metabolism and endothelial function in pre-diabetic, adipose patients with severe coronary heart disease**

**E.B. Beck1, F.J. Wolke1, S. Erbs2, R. Hoeltinge1, V. Adams1, M. Blueter2, M. Stummvoll3, F.W. Mohr4, G. Schuler1, A. Linke1. 1University of Leipzig, Heart Center, Department of Internal Medicine and Cardiology, Leipzig, Germany; 2University of Leipzig, Heart Center, Department of Internal Medicine, Leipzig, Germany; 3University of Leipzig, Heart Center, Department of Cardiac Surgery, Leipzig, Germany.

**Purpose:** Certain fat-tissue-derived adipokines are thought to contribute to impaired glucose metabolism and endothelial dysfunction, which is a predictor of future cardiovascular events. The aim of our study was to elucidate the association between obesity and endothelial function of the left internal mammary artery (LIMA) in pre-diabetic patients with severe coronary heart disease (CHD), who were scheduled for elective coronary bypass grafting (CABG), and to investigate the influence of 4 weeks of regular physical exercise training (ET) in these patients.

**Methods:** 29 patients with CHD (age ≤ 75 years), obesity (BMI ≥26 kg/m²) and impaired glucose tolerance were randomized to 4 weeks of ET (in-hospital basis, 6 times a day for 20 min on a bicycle and rowing ergometer) (n=15) or sedentary lifestyle (n=14). One week before and after 4 weeks of ET, blood pressure, heart rate, waist circumference, oral glucose tolerance, LDL- and HDL-cholesterol levels, maximum oxygen uptake (VO₂max) and average peak velocity (APV) in response to LIMA selective intraarterial infusion of increasing doses of acetylcholine (0.072, 0.72 and 7.2 μg per minute) and nitroglycerin (200 μg as bolus) were assessed by Doppler velocimetry (Cardiomedics, USA).

**Results:** Compared to C exercise training was associated with a reduction in waist circumference by 4.4±0.1 cm (p < 0.01), Blood glucose levels two hours after oral glucose load decreased from 10.2±2.4 to 7.7±0.5 mmol/l (p < 0.01), LDL-cholesterol level declined from 2.87±0.7 to 2.36±0.17 mmol/l (p < 0.05), whereas HDL-cholesterol increased by 1.11±0.05 to 1.20±0.04 mmol/l (p < 0.05). VO₂max during cardiopulmonary exercise testing improved from 20.2±2.1 to 23.9±1.4 ml/min/kg body weight (p < 0.01). Additionally, four weeks of ET resulted in an increase in APV response to acetylcholine compared to intraarterial saline infusion by 87%, 50% and 25%, respectively (p < 0.05). In contrast, endothelium-independent inhibition of APV in response to nitroglycerin remained unchanged.

**Conclusion:** Four weeks of exercise training lead to a reduction in body weight, waist circumference and LDL-cholesterol and an increase in HDL-cholesterol in obese patients with severe coronary artery disease. This is associated with a normalization of glucose tolerance and improved endothelial function of the left internal mammary artery. Further analysis will link these findings with adipokine expression patterns in peripheral subcutaneous fat and peri-arterial fat from the chest wall (LIMA) and the pericardium (coronaries), which was harvested during CABG.

**Higher incidence of hypoglycaemia under oral anti-diabetic therapy in patients with type 2 diabetes and manifest vascular disease: 12-months follow-up study**

**A.K. Giltl1, P. Bramlage2, E. Deeg1, C. Brinzel3, M. Krekler4, D. Tischhoe1 on behalf of DiaRegis-Study-Group. 1Herzzentrum Ludwigshafen, Institut f. Herzinfarktforschung Ludwigshafen an der Unv. Heidelberg, Ludwigshafen am Rhein, Germany; 2Institute for Cardiovascular Pharmacology & Epidemiology, Mauthol, Germany; 3Institut für Herzinfarktforschung Ludwigshafen an der Universität Heidelberg, Ludwigshafen, Germany; 4Bristol-Myers Squibb GmbH & KGaA, Munich, Germany; 5Heart and Diabetes Center NRW, Bad Oeynhausen, Germany.

**Background:** Patients with type 2 diabetes and manifest vascular disease (VD) were at higher risk for hypoglycemic complications in a 12-months retrospective analysis of DiaRegis. We examined if the incidence of hypoglycemic events in diabetics with manifest vascular disease did change after adjustment of anti-diabetic therapy in clinical practice.

**Methods:** In the ongoing DiaRegis registry, 3,740 consecutive outpatients with type 2 diabetes and insufficient glycemic control under chronic oral antidiabetic monotherapy or dual combination therapy were enrolled to document patient characteristics, medical treatment as well as the prevalence of hypoglycemia. We examined differences between diabetics with and without vascular disease (VD), defined as known coronary artery disease (CAD) or prior stroke or peripheral artery disease (PAD) in the prevalence of hypoglycemia during a 12 months prospective follow-up.

**Results:** A total of 909 patients had known VD (17.9%CAD, 4.7% prior stroke, 6.0% VD). Type 2 diabetes outpatients with manifest VD were older, less often female and longer duration of diabetes as compared to patients without manifest VD. No difference was found in baseline HbA1c as indicator of long-term glycemic control, but patients with VD more often suffered from hypoglycemia during the 12 months prior to enrolment. The retrospective data collection even underestimated the incidence of hypoglycemias, as in the prospective 12 months follow-up the rate of hypoglycemia increased to 22.8% in VD patients. Independent predictors of hypoglycemia in VD were the treatment with sulfonylureas as well as with insulin.

**Comparison between the effects of ibradinidine and atenolol on heart rate variability in type II diabetic patients**

**R. Neria1, M. Milo1, G. Careini1, P. Tarza1, G. Scavone2, F. Zaccardi2, D. Pitocco2, G. Ghirlanda2, G. A. Lancia1, F. Creap.1 Catholic University of the Sacred Heart, Department of Cardiovacular Medicine, Rome, Italy; 2Catholic University of the Sacred Heart, Department of Internal Medicine, Rome, Italy.

**Purpose:** Beta-blockers improve cardiac autonomic function in patients with type II diabetes, but data on the effects of these drugs on heart rate variability (HRV) are limited. The aim of the study was to compare the effects of atenolol (atenolol 25 mg b.i.d.) with ibradinidine (ibradinidine 5 mg b.i.d.) on HRV in patients with type II diabetes and manifest vascular disease (80%).

**Methods:** We enrolled 56 type II diabetic patients (age 60±5, 54 without overt cardiovascular disease with a previous history of CABG and stroke). Patients were randomized to receive atenolol 25 mg b.i.d. (n=17), ibradinidine 5 mg b.i.d. (n=20) or placebo b.i.d. (n=19) for 1 month. Cardiac autonomic function was assessed by measuring time-domain and frequency-domain heart rate variability (HRV) on 24-hour ECG Holter monitoring both at baseline and at 1-month follow-up.

**Results:** HRV results are summarized in the table. Basal clinical variables were similar in the 3 groups. Most HRV variables improved significantly at follow-up in the atenolol group, compared to placebo. Ibradinidine significantly improved HF
Hyperglycaemia-induced oxidative stress mediates monocyte dysfunction in diabetes mellitus


University of Munich, Department of Cardiology and Angiology, Munich, Germany; Institut für Molekular Cell Biology at the Hospital of the Friedrich-Schiller-Universitaet Jena, Jena, Germany

Purpose: Monocytes play a very vital role in the biological process which increases the diameter of the existing arterial vessels. This process, also known as arteriogenesisis essential for maintaining vascular integrity. Circulating monocytes are recruited to the sites of collagenal growth where arteriogenesis is mediated through VEGF1 signaling pathways, among others. The impaired monocyte function in hyperglycaemia, due to the reduced ability of monocytes to respond to VEGF stimulation, has been implicated in reduced arteriogenesis in diabetes patients. Molecular mechanisms leading to this VEGF-specific signal transduction defect in monocytes is incompletely understood.

Methods: Human monocytes were isolated from peripheral blood through gradient centrifugation and subsequent negative immunological magnet isolation. THP-1 was used as the model monocyctic cell line. Expression of relevant molecules was detected by RT-qPCR and confirmed by Western blotting. Re- active oxygen species (ROS) was detected using Amplex Red and H2DCFDA dye. Protein tyrosine phosphatase (PTP) activity was measured using nPnNOS substrate. VEGF-A-induced monocyte chemotaxis was assessed in the modified Boyden chamber assay.

Results: The monocyte cell line THP-1 and primary monocytes isolated from healthy donors were subjected to normoglycaemia (5.5 mmol glucose) or hyperglycaemia (25 mmol glucose) for 7 days and 72 hours, respectively. Hyperglycaemia induced reactive oxygen species in the cells leading to a reduction in total PTP activity. Induced oxidative stress resulted in reduced VEGF-A-induced chemotaxis. RT-qPCR analysis indicated that NADPH oxidase 2 (NOX2) is upregulated in hyperglycaemic conditions which could be blocked by inhibiting pyridoline dithiocarbamate (PDTC) and by a general NOX inhibitor diphenyleneiodonium chloride (DPI).

Conclusions: Our results reveal oxidative stress as a negative regulator of human monocyte function. Our results suggest that the hyperglycaemia-induced ROS in monocytes is mediated through NF-kB mediated NOX2 expression. Quenching of ROS generation can have positive effects on monocyte function.

P4986

Low rate of LDL-cholesterol target achievement in patients with type 2 diabetes with and without manifest vascular disease in Germany: results of DiaRegis

A.K. Gitt, P. Bramlage, E. Deeg, C. Birn, M.G. Krekeler, D. Tacke

DiaRegis-Registry-Group, Herzcentrum Ludwigsﬁn, Institut für Herzinfarktforschung, Ludwigshafen an der Universi Hamburg, Ludwigshafen at the Rhein, Germany; Institute for Cardiovascular Pharmacology & Epidemiology, Mahlow, Germany; Institut für Herzinfarktforschung Ludwigshafen an der Universi Heidelberg, Ludwigshafen, Germany; Bisk-Meyers Squibb GmbH & KGAa, Munich, Germany; Heart and Diabetes Center NRW, Bad Oeynhausen, Germany

Background: Patients with type 2 diabetes are at high risk for cardiovascular events. The new ESC/EAS guidelines for the management of dyslipidemias recommend LDL-cholesterol (LDL) not only <100 mg/dl but even <70 mg/dl. Little is known about the current lipid target achievement in diabetics in clinical practice in Germany.

Methods: In the DiaRegis registry, 3,740 consecutive outpatients with type 2 diabetes and insufficient glycemic control under chronic oral antidiabetic mono- or dual combination therapy were enrolled to document patient characteristics, medical treatment and prevalence of hypoglycemia. We examined differences between diabetics with and without vascular disease (VD), deﬁned as known coronary artery disease (CAD) or prior stroke or peripheral artery disease (PAD) in the achievement of LDL targets.

Results: A total of 890 patients had known VD (17.9%, CAD, 4.7% prior stroke, 6.0% PVD). Type 2 diabetes outpatients with manifest VD were older, less often female and already had a signiﬁcantly longer duration of diabetes. No difference was found in baseline HbA1c. Only 42.0% of the overall population were on statin treatment, 66.1% of diabetics with manifest VD and 34.3% of diabetics without known VD. Mean LDL was lower in diabetics with VD as compared to diabetics without known VD. The newly defined LDL target of <70mg/dl was reached in only 12.1% of diabetics with manifest VD and in only 5.2% of diabetics without VD.

Conclusions: Despite the high risk of subsequent cardiovascular events in type 2 diabetes less than half of the patients were treated with a statin. In very high risk diabetics with already manifest VD only 12.1% did reach the recommended target values of LDL <70 mg/dl in clinical practice.

P4987

Can we predict the risk of glucose metabolism abnormalities in patients with previous percutaneous coronary intervention?


Hospital Fernando Fonseca, Amadora, Portugal

Background: Oral glucose tolerance test (OGTT) is recommended in all patients who underwent coronary artery disease, since glucose metabolism abnormalities (GMA) adversely impact their prognosis. However, there are no risk models developed for the assessment of GMA in CAD patients. These models would be useful to identify patients with higher risk and to obviate the need of an OGTT in lower risk patients.

Purpose: To identify CAD related risk factors for GMA in patients with previous percutaneous coronary intervention (PCI).

Methods: 294 patients (mean age 60.9±10.9 years, 222 males), with previous PCI and without known diabetes were included. OGTT was performed according to WHO protocol and patients were classified, according to ADA criteria in normal (N), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM). The relation between main epidemiological and CAD related factors was than evaluated.

Results: The OGTT identified 63 patients (21.4%) with IFG, 61 patients (20.7%) with IGT and 48 (16.3%) with DM, leaving only 122 (41.5%) patients with a normal glycemic risk. The OGTT identified 63 patients (21.4%) with IFG, 61 patients (20.7%) with IGT and 48 (16.3%) with DM, leaving only 122 (41.5%) patients with a normal glycemic risk.

Conclusions: In patients previously submitted to PCI and without known DM, GMA are very frequent (58.5% of patients, Age, previous hypertension, dislipidemia and BMI (all included in most risk models for the prediction of diabetes in non-CAD populations) were not useful in this CAD population. These results suggest that all patients with CAD should have an OGTT, since it’s not possible to identify lower risk groups.

P4988

The impact of diabetes mellitus according to gender difference on acetylcholine induced coronary artery spasm

S.W. Rha, J.Y. Park, S.K. Ryu, J.W. Choi, B.G. Choi, A. Elmagaz, S.J.B. Im, S.W. Kim, C.U. Choi, D.J. Oh, Korea University Guro Hospital, Seoul, Korea, Republic; EJui University, Seoul EJui Hospital, Seoul, Korea, Republic

Background: The gender difference is known to be a strong predictor of coronary artery spasm (CAS). Diabetes mellitus (DM) is also a well known risk factor of atherosclerosis and endothelial dysfunction. However, the impact of DM according gender difference on CAS during acetylcholine (ACh) provocation test has not been defined.

Methods: A total of 2504 consecutive patients without significant coronary artery disease who underwent the ACh provocation test were enrolled between Novem-
bber 2004 and October 2010. The patients were divided into two groups according to the gender difference (male group: n=1158, female group: n=1346) and each gender group were divided into two groups according to the DM (male group with DM: n=146, female group with DM: n=145).

Results: At baseline, in both gender groups, diabetes group had higher incidence of hypertension, dyslipidemia, current alcohol and old age, as well as the higher body mass index. At angiographic characteristics, male patients with DM had higher incidence of significant CAVS and diffuse CAS than male patients without DM. But, in female group, there were no difference of CAS between with or without DM. Multivariate analysis showed that in male group, DM was associated with ACh induced CAS (odds ratio: 1.618, 95% confidence interval: 1.051-2.488, p<0.028), but, in female group, DM was not associated with ACh induced CAS.

Conclusion: In this study, in male patients, DM was an independent predictor of ACh induced CAS. But, in female patients, DM was not associated with ACh induced CAS. Therefore, gender difference must be considered in evaluating the predictor of ACh induced CAS, and more intensive antithrombolytic treatment would be required in male patients with DM.

P4989

Girls and boys with type 1 diabetes mellitus show different pathophysiology in premature atherosclerosis assessed by carotid-intima media thickness


Cardiovascular disease (CVD) shows a substantial sex-difference, with men having a 3 times higher risk. Diabetes mellitus increases the risk strongly both in men and women. In premature atherosclerosis, DM and glycemia dependent parameters in girls but not in boys. Our pilot study differed between the two sexes: Whereas cIMT in girls was associated with Body Mass Index (r=0.441; p=0.009), Insulin Units/kg (r= –0.346; p=0.045) and HbA1c (r=0.32; p=0.016), in boys only correlated with T1D duration (years) at a p-value of <0.05). In linear regression analysis sex remained the only significant independent predictor of cIMT (beta=0.459; p=0.001).

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
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<tr>
<td>White Blood Cell</td>
<td>0.065</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean Blood Glucose (mg/dl)</td>
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<td>0.000</td>
</tr>
<tr>
<td>HDL/C (mg/dl)</td>
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<td>0.003</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
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</tr>
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<td>Glycated Hb (%)</td>
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</tr>
<tr>
<td>BMI</td>
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<td>0.002</td>
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<tr>
<td>Glucose (mg/dl)</td>
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<td>0.000</td>
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</table>

Boys with T1D had higher cIMT than girls; moreover cIMT correlated with weight and glycemia dependent parameters in girls but not in boys. Our pilot study suggests an important sex-dependent difference from the very beginning of atherosclerosis in patients with type 1 diabetes.

P4990

Prognostic impact of diabetes mellitus and hypertension for mid-term outcome of patients with Acute Myocardial Infarction in the era of Percutaneous Coronary Intervention

M.G. Lee1, M.H. Jeong1, M.J. Kim2, K.H. Lee1, K.H. Park1, D.S. Sim1, Y.J. Hong1, J.H. Kim1, Y. Ahn1, 1The heart center of chonnam national university hospital, Gwangju, Korea, Republic of; 2The internal medicine of chonnam national university hospital, Gwangju, Korea, Republic of

Aims: The synergistic effect of diabetes mellitus (DM) and hypertension on mid-term outcome among acute myocardial infarction (MI) patients underwent percutaneous coronary intervention (PCI) is still controversial era. The aim of the present study was to assess the mid-term clinical outcomes among acute MI patients underwent PCI in relation to a history of hypertension or DM alone or a combination of the two.

Materials and Methods: A total of 2,438 patients with acute MI underwent PCI who were included from January 2007 to November 2010 were studied. Patients were stratified to four groups according to the presence of DM or hypertension and followed up during 12 months period. The influence of cardiac risk factors, medications, angiographic findings, and interventional procedures were analyzed, and Cox proportional hazard analysis was used to determine the influence of hypertension and DM on major adverse cardiac events (MACE: death, recurrent MI, revascularization, PCI). No known history of hypertension, and no known history of diabetes, were included in each group. The study population was divided into 5 groups with different GA: diabetes mellitus (DM, n=146), female group with DM (n=145), male group with DM, new onset DM (23%, n=69); IGT (18%, n=68); IFG (16%, n=92), and control group (n=616). Anemia was defined using WHO criteria—hemoglobin level less than 13 g/dl for men and less than 12 g/dl for women. Cox regression was used to identify independent mortality predictors.

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<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.002</td>
<td>0.026</td>
</tr>
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</table>

Conclusion: The incidence of anemia on long-term prognosis of patients with acute myocardial infarction and concomitant glucose abnormalities

M. Mazurek1, J. Kowalczyk1, R. Lenarczyk1, T. Kurek1, A. Swiatkowski1, E. Jedrzejczyk-Patej1, J. Gumprecht2, K. Strojek3, L. Polonski4, Z. Kalusura1, 1Medical University of Silesia, Silesian Heart Diseases & Electrotherapy, Zabrze, Poland; 2Medical University of Silesia, Department of Internal Medicine/Diabetology & Nephrology, Zabrze, Poland; 3Medical University of Silesia, Dept of Internal Medicine, Diabetology and Cardiometabolic Diseases, Zabrze, Poland; 4Medical University of Silesia, Silesian Center for Heart Diseases, 3rd Department of Cardiology, Zabrze, Poland

Background: Anemia deteriorates the prognosis in patients (pts) with myocardial infarction. However, the prognostic value of anemia in subjects with different glucose abnormalities (GA) and acute myocardial infarction (AMI) treated invasively remains unclear.

Aim: To assess the incidence and impact of anemia on clinical outcomes in subjects with different GA and AMI treated with percutaneous coronary intervention (PCI).

Methods: A prospective registry of 2154 consecutive AMI subjects treated with PCI was analyzed. In all hospital discharges interpreted according to WHO criteria. This made it possible to divide the study population into 5 groups with different GA: diabetes mellitus (DM, n=360), new onset DM (n=298), impaired glucose tolerance (IGT, n=434), impaired fasting glycaemia (IFG, n=340), and control group (n=616). Anemia was defined using WHO criteria—hemoglobin level less than 13 g/dl for men and less than 12 g/dl for women. Cox regression was used to identify independent mortality predictors.

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<tr>
<td>CRP (mg/dl)</td>
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Conclusion: The incidence of anemia in different glucose abnormalities was as follows: in DM (27.5%, n=99); new onset DM (23%, n=69); IGT (18%, n=68); IFG (16%, n=68); and in control group (14.7%, n=91). The long-term mortality in all AMI in-hospital survivors with anemia was significantly higher than in subjects without anemia (11.4 vs 5.6%, P<0.05). Further analysis with 15 and 30 days follow-up demonstrated that DM patients with anemia did not influence the remote outcomes in subjects with DM, new onset DM and IGT (P=NS). However, during the long-term follow-up, death rate events for anemic pts with IGT as well as control group were significantly more frequent than in pts without anemia (16.0 and 10.9 vs. 2.8 and 4.0%, respectively, P<0.05).

What is more, anemia along with incomplete revascularization (HR 4.8), previous stroke/TIA (HR 4.3) and ejection fraction (HR 0.94) appeared to be one of the strongest independent predictors of death in IFG and control group (HR 4.13 and 2.2 respectively, all P<0.05).

Conclusions: Anemia is significantly more frequent in pts with AMI and concomitant glucose abnormalities. However, the remote prognosis of anemic AMI subjects differs substantially and seems to be significantly worse in the absence of glucose disturbances.
A. Milrou1, C. Antoniades1, C. Bakogiannis1, D. Tousoulis1, A.S. Antonopoulous1, M. Demosthenous1, M. Margaritis1, K. Marinou2, C. Psarros1, C. Stefanadis1. 1Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece; 2University of Athens Medical School, Department of Physiology, Athens, Greece

**Purpose:** Soluble CD40 ligand (sCD40L) is an inflammatory marker released by activated platelets and inflamed adhesion tissue. Recent evidence suggests that sCD40L levels are higher in patients with metabolic syndrome. We sought to examine the relationship between chronically elevated sCD40L levels and insulin resistance by using the functional single nucleotide polymorphism (SNP) A3459G of the sCD40L gene.

**Methods:** The study population consisted of 265 individuals. After an overnight fast, a sample of blood was collected and used for biochemical measurements and genotyping. Plasma sCD40L levels were determined by ELISA. Plasma insulin levels were used to calculate insulin resistance by means of the Homeostatic Model Assessment (HOMA-IR). DNA was extracted from whole blood by using a commercially available kit and genotyping for the A3459G SNP of the sCD40L gene was performed by restriction fragment length polymorphism PCR method.

**Results:** In the study population, 188 individuals were carriers of the AA genotype, 44 of the AG and 33 of the GG genotype. Subjects exhibiting the GG genotype had significantly higher sCD40L levels when compared to AA and AG individuals. A significant difference in the mean plasma levels of the GG genotype was not significantly associated with fasting glucose levels (B), it was associated with higher insulin resistance, as calculated by HOMA-IR (C).

**Conclusions:** Our data show that chronically increased activation of platelets and the related inflammation of the adipose tissue releasing sCD40L, are associated with increased insulin resistance. Therefore, our study shows novel links between the CD40/CD40L axis and insulin resistance, providing novel insights into the pathophysiology of diabetes mellitus.

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**Gene expression of diabetes mellitus (DM) is associated with an increased incidence of coronary artery disease (CAD). However, factors predicting the presence and extent of coronary atherosclerosis in patients with DM have been suggested to be different than those for non-DN patients. The aim of the present study was to determine predictors of the presence and extent of CAD in patients with or without DM undergoing coronary angiography.**

Methods: One thousand and seventy consecutive patients without previous history of CAD who underwent coronary angiography for suspected stable CAD were included in the study. Demographic, clinical, and metabolic parameters were recorded. Significant angiographic CAD was defined as the presence of stenosis >50% in at least one epicardial coronary artery or >30% in left main coronary artery. Diabetes was diagnosed based on a fasting glucose ≥126 mg/dl and/or use of antidiabetic medications. Logistic regression analysis was used to identify predictors of the presence and extent of CAD in the two groups.

Results: The prevalence of CAD was 60% and 45% in DM and non-DM patients respectively (OR 1.80, p < 0.001). The association of DM with CAD presence remained significant (OR 1.70, p < 0.001) even after adjustment for differences in risk factors between DM and non-DM patients; DM patients were older, proportionally less smokers, more hypertensives, had higher body mass index and triglycerides and lower estimated glomerular filtration rate and HDL cholesterol compared to non-DM patients. In DM patients (n=413), independent predictors of CAD presence were fasting glucose levels (OR 1.008, p < 0.001), male gender (OR 2.03, p < 0.002) and hypertension (OR 2.01, p < 0.017). In non-DM patients (n=657), independent predictors of CAD were age (OR 1.05, p < 0.001), smoking (OR 2.21, p < 0.001), male gender (OR 2.26, p < 0.001), hypercholesterolemia (OR 2.69, p < 0.001) and body mass index (OR 2.03, p < 0.002).

Conclusions: DM is an independent predictor of the presence of angiographic CAD in patients with suspected stable CAD undergoing coronary angiography.
Predictors of long-term cardiovascular outcomes in patients with type 2 diabetes mellitus

H. Bianco1, T. Hellsten1, M.C. Izar1, H.A. Fonseca1, S.C. Fischer1, C.E. Ferreira1, H.T. Xavier1, R.M. Povoa1, A.F. Fonseca1
1Federal University of São Paulo (UNIFESP), Department of Medicine, Cardiology, São Paulo, Brazil; 2Santa Casa de Misericórdia of Santos, Santos, Brazil

Introduction: Type 2 Diabetes mellitus (T2DM) is a public health problem associated with various morbidities, such as hypertension, dyslipidemia and obesity. Prevalence of cardiovascular events in T2DM is twice the observed in non-diabetic subjects, even after adjustment for classic risk factors. Early detection of predictors of hard outcomes are needed to try to avert this scenario. Objectives: To identify biomarkers associated with higher rates of clinically relevant events in a prospective cohort of patients with T2DM.

Materials and Sampling: We retrospectively evaluated a cohort of 323 individuals with T2DM followed by 10 years. Blood samples were collected at baseline. We examined biomarkers with potential risk of events in this population. Troponin, homocysteine, creatinine, fasting glucose, high-sensitivity C-reactive protein (hsCRP), and lipid profile. Fatal and nonfatal acute coronary syndromes and stroke were evaluated. ECG and clinical information were obtained from all patients. Cumulative survival curves were analyzed by Log-rank/Mantel-Cox.

Results: The study population comprised of individuals of both genders, 59% males, aging 59y, with mean time of diagnosis of 8y, obese (39%), mostly with hypertension and dyslipidemia. The presence of prior myocardial infarction (MI) was detected in 9% of patients. Mean value of CRP (hsCRP) were 3.7 mg/l (CI 1.7 to 4.7). Sub analyses 0.015 mg/dl, homocysteine 10.86 umol/l, creatinine 0.89 mg/dl and estimated glomerular filtration rate (Cockroft-Gault) was 70.56 ml/min. Left ventricular hypertrophy (LVH, Perugia score) was present in 28% of patients. There were associations between higher event rates in males (HR 2.95 CI 1.6 to 4.1), with previous MI (HR 1.5 CI 1.4 to 1.6), reduced creatinine clearance (HR 1.6 CI 1.1 to 2.5) and elevated levels of serum creatinine (-1.3 mg/dl for men and -1.1 mg/dl for women) (HR 2.3 CI 1.2 to 4.3).

Conclusion: Male gender, previous MI and renal function impairment were associated with higher rates of cardiovascular events, thus highlighting the importance of risk factors and comorbidities in this high-risk population.

The association of the A3872G polymorphism with hs-c-reactive protein levels and peripheral arterial disease in patients with type 2 diabetes mellitus

S. Papaoikonomou1, D. Toussou1, N. Tentiouris1, G. Aplia1, A. Miliu2, G. Hatzis1, N. Papageorgiou2, C. Stefanidou2, C. D. Ivan2
1Lakso General Hospital, The Diabetes Center, Athens, Greece; 2Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece

Purpose: The aim of this study was to examine the impact of A3872G polymorphism on C-reactive protein (CRP) gene on high sensitivity CRP (hs-cRP) levels and peripheral arterial disease (PAD) in patients with type 2 diabetes mellitus (T2DM).

Methods: The study population consisted of 431 patients with T2DM (documented for PAD or not). The A3872G polymorphism was detected by polymerase chain reaction and appropriate restriction enzyme digestion (HpyCH48I). Carotid intima-media thickness was assessed by particle-enhanced immunonephelometry and peripheral arterial arterial disease was evaluated based on history of intermittent claudication, reduced or absent foot pulses, interventional procedure of revascularization or amputation. Hs-cRP was measured by nephelometry by doppler ultrasonography in lower leg arteries or ankle brachial pressure index (ABPI) <0.9.

Results: The genotype distribution was 52, 27.2, 20.8 for the G/G, AG, AA genotypes respectively; [mean age 66.55±1.953, males n=218 (50.6), females n=421 (49.2)] with significant gender difference males/females GG (46.4%/53.6%), AG (60%/50%), AA (61.2%/38.8%), [p=0.019]. Hs-cRP levels were higher in GG homozygotes (GG: 0.61±0.257) compared with carriers of ‘A’ allele (AG+AA: 0.56±0.188, p=0.021). The presence/absence of PAD was not significantly different among the GG (34.2%/63.5%), the AG (39.7%/60.3%) and AA (61.8%/38.2%), (p=0.019). Hs-CRP levels were significantly lower in patients with PAD compared to those without PAD (38.4±1.4 vs 27.5±3.8 kg/m², p=0.001), waist circumference (102.7±10.3 vs 93.7±11.2 cm, p=0.001) and office systolic BP (144±17 vs 141±16 mmHg, p=0.008), while did not differ regarding gender, serum creatinine and LVMI (p=NS for all). By multivariate Cox regression analysis, MS (hazard ratio=2.386, p=0.022), apart from male gender (hazard ratio=2.823, p=0.019), turned out to be an independent prognosticator of CAD but not of stroke.

Conclusion: In essential hypertensive patients, MS constitutes a strong predictor of future CAD but exhibits no prognostic value regarding stroke. These findings further support the use of MS for global risk assessment and suggest differential effects of the MS related atherosclerotic mechanisms on the coronary tree and the cerebrovascular.

One-third of patients with diabetes mellitus do not have subclinical coronary atherosclerosis

M.L. Toffler1, O. Gerke1, K. Egstrup1, N.P.R. Sand1, H. Munkholm5, H. Mickle1, A.C. Diedrichsen1
1Odense University Hospital, Department of Cardiology, Odense, Denmark; 2Odense University Hospital, Department of Nuclear Medicine, Odense, Denmark; 3Svendborg Hospital, Department of Cardiology, Svendborg, Denmark; 4Sydvestykket Hospital, Department of Cardiology, Esbjerg, Denmark; 5Vejle Hospital, Department of Cardiology, Vejle, Denmark

Purpose: All patients with diabetes mellitus (DM) are recommended lipid lowering treatment, although not all are at similar risk. Measuring coronary artery calcification (CAC) enables to further the cardiovascular risk, also in diabetics. The prevalence of CAC among random selected patients with DM is uncertain. For this purpose we set out to examine the occurrence of CAC in patients with DM, and compared with non-diabetic subjects.

Method: A random selected cohort of 1825 men and women, 50 or 60 years old were invited to the screening study. DM was defined as the use of anti-diabetic medication or fasting plasma blood glucose level ≥7.0 mmol/l on two different days. Traditional risk factors were obtained and for the non-diabetics HeartScore was calculated. A non-contrast CT-scan was performed to assess the CAC score (Agatston score ≥400 was considered as high).

Results: A total of 1226 subjects without previous cardiovascular disease participated. Five % (59 subjects) had DM while 92% (1167 subjects) were non-diabetics. Among patients with DM the prevalence of males, 60 years old, smokers, hypertension and statin treatment were 49%, 58%, 32% and 55% respectively, while 47%, 50%, 25% and 10% for the non-diabetics. Also CAC was more frequent in diabetics (63% versus 44%; p=0.006), as well as severe calcification (9% versus 5%; p=0.022). However, adjusting for covariates in multivariate logistic regression results only in a non-significant increased risk for calcification in diabetic patients (OR=1.3; p=0.04).

Conclusion: We found that one-third of patients with DM did not have any coronary calcification and thus a better prognosis, while few had severely calcified coronary arteries. These data suggest that also in diabetics preventive therapy should be individualised based on CAC.
Arterial elastic wall properties are similarly impaired in first degree relatives and diabetic patients on the grounds of significant insulin resistance

Evaluation of the relationship between aortic elasticity and insulin sensitivity in healthy subjects with a normal carbohydrate metabolism

Type 2 diabetes and the progression of visualized atherosclerosis to clinical cardiovascular events

Suboptimal LDL-cholesterol control by atorvastatin monotherapy in high-risk patients with coronary heart disease or atherosclerotic vascular disease in the UK

Full appraisal of glycemic risk

Purpose: Presence of coronary heart disease (CHD) or atherosclerotic vascular disease (AVD) places a patient at high risk for a cardiovascular (CV) event. Lowering LDL-cholesterol (LDL-C) is associated with improved clinical outcome in high-risk patients. LDL-C goals recommended by European guidelines are dependent upon pre-existing CV risk factors. Since statins are widely recommended and approval of generic atorvastatin (ATORVA) will increase its use, this analysis examined LDL-C goal attainment in high-risk patients treated with ATORVA monotherapy.

Methods: Using a UK general practice database, patients who received a prescription for ATORVA monotherapy (the index Rx) between 01/01/08 and 11/30/10 were identified. Additional inclusion criteria were: an ICD-10 diagnosis of CHD or AVD, <1 LDL-C measurement between 3 mo and 1 yr post index Rx, an ATORVA Rx claim within 60 days of LDL-C measurement, and use of medical records for 1 yr prior to and following index Rx. Endpoints were the proportion of patients achieving an LDL-C <1.8 mmol/L (very high-risk goal in 2011 ESC guidelines), <2.0 mmol/L (high-risk goal and 2007 ESC guidelines), or <2.5 mmol/L (optimal LDL goal, optional ESC guidelines). Results: Of 2,403 high-risk patients (65% males, mean age 69 yrs [SD 10]) who met selection criteria, 24, 27, and 14% received Rx for 10-, 20-, 40-, and 80-mg dose of ATORVA, respectively. 24% of patients were newly initiated on ATORVA monotherapy at the index date. Mean follow-up LDL-C was 2.14 mmol/L (SD 0.68). Overall, 27% of patients had an LDL-C <1.8 mmol/L, 41% had an LDL-C <2.0 mmol/L, and 75% had an LDL-C <2.5 mmol/L. Greater goal attainment was observed with the highest ATORVA dose (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Atorvastatin dose</th>
<th>Follow-up LDL-C (mmol/L)</th>
<th>&lt;1.8 mmol/L</th>
<th>&lt;2.0 mmol/L</th>
<th>&lt;2.5 mmol/L</th>
<th>Mean ± SD</th>
</tr>
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<tbody>
<tr>
<td>10 mg</td>
<td>567</td>
<td>23%</td>
<td>37%</td>
<td>77%</td>
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<tr>
<td>20 mg</td>
<td>655</td>
<td>22%</td>
<td>37%</td>
<td>69%</td>
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<tr>
<td>40 mg</td>
<td>841</td>
<td>21%</td>
<td>42%</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>80 mg</td>
<td>380</td>
<td>19%</td>
<td>37%</td>
<td>62%</td>
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</table>
Whole body periodic acceleration (WBPA) system is recently developed as a passive exercise device by providing increased pulsatile shear stress for improvement of peripheral and coronary endothelial function (Figure left). This study aimed to investigate the acute effects of WBPA on coronary microcirculation and glucose tolerance in patients with type 2 diabetes (T2D).

Methods: The study subjects were 8 patients with T2D who underwent transthoracic Doppler echocardiography (TTE) for the assessment of coronary flow reserve (CFR) before and immediately after a 45-min session of WBPA. The flow velocity in the distal portion of the left anterior descending coronary artery was measured at baseline and during adenosine infusion. The CFR represented the ratio of hyperemic to basal mean diastolic flow velocity.

Results: WBPA was completed and well-tolerated in all patients, and no significant hemodynamic or mechanical complications were observed during the procedure or follow-up. WBPA increased CFR from 2.3±0.3 to 2.6±0.4 (p=0.02) (Figure right). WBPA decreased serum insulin level from 26±19 μIU/ml to 19±15 μIU/ml (p=0.01) and increased total adiponectin from 11.6±7.3 μg/ml to 12.5±8.0 μg/ml (p=0.02). High-molecular weight adiponectin from 4.9±3.6 μg/ml to 5.3±3.9 μg/ml (p=0.03), whereas the serum glucose level was stable from 207±66 mg/dl to 203±56 mg/dl (p=0.8).

Conclusions: This study demonstrates that a single session of WBPA treatment simultaneously improved coronary microcirculation and glucose tolerance in patients with T2D, providing the mechanical insights into the relationship between exercise and adiponectin.

A novel anti-inflammatory adipokine, secreted frizzled-related protein 5, is associated with coronary artery disease in non-elderly population

Background: Secreted frizzled-related protein 5 (Sfrp5) has been reported to be a novel anti-inflammatory adipokine. Sfrp5 deficient mice fed a high-calorie diet showed severe glucose intolerance and hepatic steatosis, leading to the inflammation in adipose tissue. These evidences suggest that Sfrp5 would be involved in the development of atherosclerosis; however, the clinical relevance of sfrap5 remains unknown. We investigated whether reduced serum sfrp5 level can be associated with the presence of coronary artery disease (CAD) in human subjects.

Methods: The consecutive 185 patients (68±11 years, 79% male) were enrolled from inpatients who underwent coronary angiography (CAG). The subjects were divided into two groups on the basis of the CAG findings: patients with significant coronary artery disease (CAD) and without significant coronary artery disease (non-CAD). Serum sfrp5 levels were measured by ELISA.

Results: In all subjects, serum sfrp5 levels in CAD patients tended to be lower than those in non-CAD patients (48.9±26.9 vs. 52.4±31.5 ng/ml, median ± IQR, p=0.08 by Mann-Whitney test). There were no significant difference in serum sfrp5 between two groups according to gender, the presence of diabetes, hypertension and dyslipidemia. Serum sfrp5 levels were significantly associated with body mass index (r = -0.15, p = 0.03) and HDL-cholesterol (r = 0.15, p = 0.03), but the associations of other biochemical parameters with sfrp5 levels were not significant. In sub-analysis of subjects aged < 65 years (n=75), serum sfrp5 levels in CAD patients were significantly lower than those in (45.6±24.8 vs. 52.4±24.5 ng/ml, p = 0.03); however in subjects aged ≥ 65 years (n=110), serum sfrp5 did not differ between CAD and non-CAD patients. In subjects aged < 65 years, serum sfrp5 levels were significantly correlated with body mass index (r = -0.35, p < 0.01), HDL-cholesterol (r = 0.32, p < 0.01) and tended to be correlated with LDL-cholesterol (r = -0.21, p=0.08), HOMA-R (r = -0.21, p = 0.08) and eicosapentaenoic acid/ arachidonic acid (r = -0.19, p = 0.11). Multiple logistic regression analysis in subjects aged < 65 years revealed that serum sfrp5 level was independently associated with the presence of CAD (odds ratio 0.69, 95% confidential interval 0.49 to 0.97, p=0.03) even after adjustment of gender, diabetes, hypertension, dyslipidemia, smoking, and body mass index and medications.

Conclusion: Serum sfrp5 levels are significantly associated with coronary artery disease in subjects aged < 65 years. Low sfrp5 levels may contribute to coronary atherosclerosis.

Predictors of Hypoglycaemia in patients with Type-2 Diabetes - an Analysis of the Prospective DiaRegis Registry

Methods: A cross-sectional study was carried out on 75 normotensive subjects with type 2 DM (Group 1), and 70 age-gender matched normotensive healthy volunteers (Group 2). Treadmill exercise test, 24 hours ambulatory BP monitoring (ABPM) were performed for each patients and healthy volunteers.

Results: There were 67 patients (mean age 52.9 and 42% male) in group 1 and 68 healthy volunteers (mean age 51.7 and 43% male) in group 2. Eight patients from group 1 and 2 subjects from group 2 were excluded because of high blood pressure response to exercise is exaggerated in normotensive diabetic patients

Objective: The aim of this study was to investigate the blood pressure (BP) response to exercise in normotensive patients with type II diabetes mellitus (DM). Methods: A cross-sectional study was carried out on 75 normotensive subjects with type 2 DM (Group 1), and 70 age-gender matched normotensive healthy volunteers (Group 2). Treadmill exercise test, 24 hours ambulatory BP monitoring (ABPM) were performed for each patients and healthy volunteers.

Results: There were 67 patients (mean age 52.9 and 42% male) in group 1 and 68 healthy volunteers (mean age 51.7 and 43% male) in group 2. Eight patients from group 1 and 2 subjects from group 2 were excluded because of high blood pressure response to exercise.
Serum adiponectin is a negative predictor of incident metabolic syndrome: a population-based follow-up study

S.V. Ahn, J.Y. Kim, J.K. Park, S.B. Koh. Wonju College of Medicine, Yonsei University, Wonju, Korea, Republic of

Objective: Growing evidence suggests that increased adiponectin levels may play a role in the development of metabolic abnormalities, but prospective studies of adiponectin levels and incident metabolic syndrome are lacking. We investigated whether serum adiponectin predicts incident metabolic syndrome and its components in a population-based longitudinal study.

Methods: We analyzed data from 2,068 adults (838 men and 1,230 women) without metabolic syndrome, aged 40 to 70 years, who participated in a health survey in 2000-2011. Baseline serum adiponectin concentrations were measured by radioimmunoassay. Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III report.

Results: During an average of 2.6 years of follow-up, 154 men (16.4%) and 206 women (16.5%) developed metabolic syndrome. Median baseline adiponectin levels in subjects who developed metabolic syndrome were significantly lower than in those who did not, both in men (7.09 vs. 8.63 μg/mL, p < 0.001) and women (10.96 vs. 12.64 μg/mL, p = 0.001). In multivariable adjusted models, the odds ratio (95% confidence interval) for incident metabolic syndrome comparing women with the lowest tertile of adiponectin levels with the highest tertile was 0.57 (0.42-0.77) in men and 0.70 (0.52-0.95) in women. Serum adiponectin levels were also inversely associated with the number of metabolic syndrome components developed by study participants over follow-up (P trend < 0.001 in both men and women).

Conclusion: Our findings suggest that increased serum adiponectin could be a negative predictor of incident MetS and its components.

Impact of a cardiac diabetic nurse in reducing the incidence of hypoglycaemic events in cardiac patients with type 2 diabetes mellitus

H. Eid, M.B. Bedir, A. Fataho, M. Ghidan, T. Conboy. King Abdullah Medical City, Riyadh, Saudi Arabia

Introduction: Hypoglycaemia is a potential lethal complication of hypoglycaemic medications for patients with diabetes mellitus (DM), as was demonstrated in the Diabetes Control and Complication Trial (DCCT), United Kingdom Prospective Diabetes Study (UKPDS) reported an annual incidence of major hypoglycaemic events of 2.3% in that receiving insulin therapy.

Objective: To evaluate the effectiveness of the Cardiac Diabetic Nurse in Reducing the Incidence of Hypoglycaemic Events in Cardiac Patients with Type 2 DM at KACC.

Methodology: In this prospective study, we implemented two interventions. The first focused on an intensive educational strategy for 140 cardiac nurses, and all patients were instructed about the latest evidence based guidelines over a six week period. A pre-test evaluation was carried out for cardiac nurses on hypoglycaemia management and repeated after the education intervention was completed (post-test).

Results: In September and October, 2010 in KACC, 401/1163 (3.4%) patients had documented hypoglycaemic events. In December 2010 and Jan 2011 after the intervention phase only 5/1408 (0.4%) patient had documented hypoglycaemic events, P value <0.0001.

Conclusion: Focused educational interventions by cardiac diabetic nurses are effective in reducing the incidence of hypoglycaemic events in cardiac patients with Type 2 DM.

Non-dipping heart rate and microalbuminuria in a type 2 diabetic population

C.J. Magri, R.G. Xuereb, S. Fava. Mater Dei Hospital, Msida, Malta

Purpose: There is increasing interest in the association between non-dipping heart rate and target organ damage. However, this has not been adequately studied in diabetic patients. The aim of the study is to identify factors that are independent predictors of non-dipping heart rate in a type 2 diabetic population who is at high risk of cardiovascular disease.

Methods: One hundred eighty six type 2 diabetic subjects with mean diabetes duration of 18.3 (± 9.5) years were recruited. All participants had proliferative retinopathy, thus enabling analysis of factors independent of glycaemic control. All underwent 24-hour BP and heart rate monitoring, and were assessed for markers of inflammation (erythrocyte sedimentation rate and high-sensitivity C-reactive protein), insulin resistance as well as albuminuria, presence of peripheral neuropathy (as assessed using vibration perception thresholds) and peripheral vascular disease. Data were analyzed using SPSS version 20.0. Analysis of the right-time heart rate did not decrease > 10% as compared to day-time readings were classified as non-dippers. Independent samples t-test and Mann-Whitney U test were performed for parametric and non-parametric variables respectively, while categorical variables were analysed using chi-squared test. Multivariate regression analysis ensued to identify independent predictors of non-dipping heart rate.

Cost-effectiveness of cardiac resynchronization therapy in combination with an implantable cardioverter defibrillator in mild heart failure based on Markov modeling using UK cost approach in MADIT CRT

V. Kutyifa, 1 P. Aidelbersburger 2, S. Schauer 3, B. Merkely 4, H. Klein 5, M. Kuniss 6, A. Kloppe 7, T. Kayser 8, R. Peppa 9, A. M. Moss 10 on behalf of the MADIT CRT Investigators. 1 Heart Center, Budapest, Hungary; 2 CAREM GmbH, Sauerlach, Germany; 3 University of Rochester Medical Center, Cardiology Division, Rochester, United States of America; 4 Kerckhoff Clinic, Bad Nauheim, Germany; 5 Aekisches Kliniken GmbH, Klinikum Luedenscheid, Luedenscheid, Germany; 6 Boston Scientific Corp., Brussels, Belgium

Purpose: To evaluate the cost-effectiveness of CRT-D in mild heart failure LBBB or female patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT).

Method: A decision analytic Markov model was created to evaluate the costs, gained life-years and quality-adjusted life years (QALYs) associated with CRT-D compared to ICD treatment. Analysis was performed in 1281 LBBB patients and in 453 CRT-D treated females from the perspective of the United Kingdom National Health Service. Costs and utilities were discounted at 3.5% per year. Base-case analysis and multiple one-way sensitivity analyses were performed.

Results: Compared with ICD treatment, CRT-D gained 1.51 QALYs having a cost of £19,855 in LBBB patients, resulting in an incremental cost-effectiveness ratio (ICER) of £13.147 per QALY gained when using a life-time horizon of 35 years. The female population gained 3.81 QALYs at an additional cost of £30.088 resulting in an ICER of £7.898. ICER implemented for a 10-year time-period was £14,262 for LBBB patients, £8,313 for female patients, respectively. One-way sensitivity analyses revealed the discount rate and the utility per cycle without heart failure events to be the most sensitive variables for cost-effectiveness.

Conclusions: CRT-D treatment is cost-effective in mild heart failure LBBB or female patients with severely depressed left ventricular ejection fraction and wide QRS when compared to ICD only, for a 10-year and 35-year time horizon.

Cost-effectiveness of the molecular autopsy in sudden unexplained death in the young

J. Ingles, C. Semarian. University of Sydney, Sydney Medical School, Sydney, Australia

Purpose: Sudden unexplained death (SUD) accounts for 30% of young sudden cardiac deaths under the age of 35 years. The underlying cause is suspected primary arrhythmogenic disease in such cases, including long QT syndrome (LQTS). The “molecular autopsy” (genetic testing of postmortem DNA) can clarify both the cause of death, and the genetic status of asymptomatic family members. This study sought to determine the incremental cost-effectiveness of a family management strategy including the “molecular autopsy” in addition to conventional clinical screening, compared to clinical screening alone.
Economic analysis of the randomised assessment of Discharge status of atrial fibrillation patients

Sheffield, Sheffield, United Kingdom
to become even more cost saving as newer genetic technologies facilitate testing saving benefit in predictive genetic testing of the surviving family members, par-
ticularly for those who test gene negative. The “molecular autopsy” is expected to become even more cost saving as newer genetic technologies facilitate testing more genes, at lower cost, with higher mutation detection rates.

Economic analysis of the randomised assessment of treatment using panel assay of cardiac markers - contemporary biomarker evaluation study (RATPAC CBE)
P. Collinson1, D. Gaze1, P. Hokalla2, S. Goodacre3, 1St George’s Healthcare NHS Trust, London, United Kingdom; 2The University of Sheffield, Sheffield, United Kingdom

Objective: To estimate the potential cost-effectiveness of using highly sensitive troponin assays (at presentation alone or presentation and 90 minutes later) and new cardiac biomarkers instead of 10-12 hour troponin measurement.

Methods: A decision tree model was developed to explore the costs and health outcomes associated with different diagnostic strategies. The model took an eco-
nomic perspective of the NHS in England and Wales and a lifetime horizon with mean life expectancy based on UK interim life tables and applied different testing scenarios, where the ICER for ten hour troponin, compared to high sensitivity tro-
nin at presentation and 90 minutes: Discharge if both tests were negative or admit to hospital for troponin testing at 10-12 hours if either test is positive.

Standard troponin testing at 10-12 hours.

It was assumed blood tests performed at presentation were undertaken in the emergency department (ED) and that results would be available and a decision made within 120 minutes of presentation. Standard troponin measurement at 10-12 hours was the reference standard for MI.

Results: At the £20,000/QALY threshold, ten hour troponin testing is cost-
effectiveness compared to the next most effective alternative using a £20,000/QALY threshold.

Conclusion: The results showed that, as expected, effectiveness (QALYs) in-
creased with increasing sensitivity and costs increased with decreasing spec-
ificity. At £20,000/QALY threshold, in all but one scenario a strategy of measuring high sensitivity troponin T and HFABP at presentation (admission for a ten hour troponin if positive and discharge home if negative) was the optimal strategy.

Discharge status of atrial fibrillation patients hospitalized for ischemic or hemorrhagic stroke in the United States

T. Simon1, K. Patel1, A. Kuznik2, 1Bristol-Myers Squibb, Princeton, New Jersey, USA

Purpose: Limited information is available on the proportion of patients with atrial fibrillation (AF) that continue to require follow-up care post-stroke. Our aim was to describe the clinical characteristics and discharge status in AF patients hospital-
ized post-stroke.

Methods: A retrospective cohort study was conducted in the Premier Hospital-
ization database between January 2006 and June 2011. The Premier database includes data on 200 hospital and healthcare systems accounting for 37 million hospitalizations per year. Patients were included if they had a diagnosis of either ischemic stroke (ICD-9: 433.xx, 434.xx) or hemorrhagic stroke (HS) (ICD-9: 430.xx, 431.xx, 432.xx) and a secondary listed diagnosis of AF (ICD-9: 427.3x). Demographic information, Charlson morbidity index (CCI), comorbid conditions and discharge status stratified by stroke type were evaluated.

Results: In sum, 107,818 hospitalizations met the inclusion criteria. IS accounted for 83% and HS for 17% of hospitalizations. The sample had a mean age of 78 years, 55.5% were female, and the mean CCI was 5.7. The most frequently identified individual comorbidities were hypertension (63%), diabetes (30%), and congestive heart failure (29%). The mean hospital mortality rate was 6.6% for IS and 24.0% for HS; for both stroke types the mortality rate was positively correlated with the CCI. A minority of all admitted patients were discharged home (IS: 28.1%; HS: 13.6%). Most patients were discharged to a center requiring additional care and resources (IS: 61.4%; HS: 59.7%); more specifically, a skilled nursing facility (IS: 22.9%; HS: 19.5%), another rehabilitation facility (IS: 15.7%; HS: 15.3%), home health organization (IS: 10.9%; HS: 7.1%), home care services (IS: 7.1%; HS: 6.5%), or any other center providing additional follow-up care (IS: 6.0%; HS: 11.7%). Unknown discharge status was reported for IS: 1.9% and HS: 0.7%.

Conclusion: Among patients with AF, one in twelve experiencing an IS and one in four experiencing a HS did not survive the index hospitalization. Patient care was extended beyond the initial hospitalization in more than half of all patients. To what extent post-discharge care actually increases the direct medical cost associated with stroke events in AF patients could be evaluated in further research.

USA or Northern European countries. Little is known, however, on the evolution of the incidence of AMI in countries with a low prevalence of the disease, such as France. In addition, whether the trends are uniform according to gender and age groups is not known.

Aim: To assess the trends in the annual incidence of hospitalisations for AMI in France from 2002 to 2008 in men and women, according to age groups.

Methods: Data were extracted from the French national administrative databases of pa-
ients admitted for acute hospital stays from 2002 to 2008 in France. Hospital stays for AMI were selected on the basis of principal diagnosis codes from the ICD 10 (I21 to I23). Only first hospital stays each year were retained. Annual rates were standardized on the European population and annual trends in subgroups (according to age and sex) were analysed using Poisson regression.

Results: On a nationwide scale, the absolute number of patients admitted for AMI decreased by 7.4% and the standardised rate decreased by 15.3%. This global trend to a decreased incidence, however, differed according to gender and age groups. In men, there was an homogeneous decrease in the incidence of AMI whatever the age group. In women, the incidence of AMI decreased in the >65-year age group and paralleled that observed in men in the same age group (standardized rates decreased -22.5% in men and -23.4% in women), while in women aged 35 to 54 years, the incidence of AMI significantly increased during this time period (age 25-34 years: +8.3%; 35-44 years: +14.6%; 45-54 years: +17.9%).

Conclusion: In a country with comparatively low rates of coronary artery dis-
ease, the overall incidence of hospitalized AMI has consistently decreased over the past decade. These results are in keeping with results from the French MON-
ICA centres. The increase in the incidence of AMI in younger women, however, appears highly perplexing and will deserve further study.

Evidence-based medicine in the clinical practice guidelines of the European Society of Cardiology

A. Ciszewski, M. Kosek, K. Lech, L. Malek, C. Kepka. Institute of Cardiology, Warsaw, Poland

Purpose: Guidelines, to be accepted and commonly used by practi-
tioners, should be short, clear, and non-controversial. The aim of the study was to evaluate how frequently different levels of evidence and classes of recommen-
dations are used in currently published Guidelines of the European Society of Cardiology (ESC) in comparison to the first ESC guidelines.

Methods: 5 latest Clinical Practice Guidelines of the ESC published on their web-
site in 2010-11 were analyzed and compared with 5 first ESC guidelines published in 2001-04 using a grading of recommendations. We evaluated the proportion of different levels of evidence (A, B and C) and classes of recommendations (I, II and III).

Results: Differences in levels of evidence and classes of recommendations be-
tween latest and first ESC guidelines are presented in Table 1.

Taking into account the economic crisis in cardiology / The use of statistics to improve cardiovascular care

THE USE OF STATISTICS TO IMPROVE CARDIOVASCULAR CARE

Evolution of the incidence of myocardial infarction in France 2002-2008: the "younger women paradox"

C. De Peretti1, F. Chin1, P. Tuppin1, N. Danchin2, 1INVS, St Maurice, CBE

Purpose: To estimate the potential cost-effectiveness of using highly sensitive troponin assays (at presentation alone or presentation and 90 minutes later) and new cardiac biomarkers instead of 10-12 hour troponin measurement.

Methods: A decision tree model was developed to explore the costs and health outcomes associated with different diagnostic strategies. The model took an eco-
nomic perspective of the NHS in England and Wales and a lifetime horizon with mean life expectancy based on UK interim life tables and applied different testing scenarios, where the ICER for ten hour troponin, compared to high sensitivity tro-
nin at presentation and 90 minutes: Discharge if both tests were negative or admit to hospital for troponin testing at 10-12 hours if either test is positive.

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It was assumed blood tests performed at presentation were undertaken in the emergency department (ED) and that results would be available and a decision made within 120 minutes of presentation. Standard troponin measurement at 10-12 hours was the reference standard for MI.

Results: At the £20,000/QALY threshold, ten hour troponin testing is cost-
effectiveness compared to the next most effective alternative using a £20,000/QALY threshold.

Conclusion: The results showed that, as expected, effectiveness (QALYs) in-
creased with increasing sensitivity and costs increased with decreasing spec-
ificity. At £20,000/QALY threshold, in all but one scenario a strategy of measuring high sensitivity troponin T and HFABP at presentation (admission for a ten hour troponin if positive and discharge home if negative) was the optimal strategy.
A retrospective cohort of long term all-cause mortality and recurrent cardiovascular events in patients with acute coronary syndrome in Thailand

V. Thirawuth, T. Tangcharoen, P. Vathesatogkit, S. Yamwong, T. Erdogan1, Y. Cicek1, M. Erdogan, A. Temiz2, A. Canga1, Rize University Medical Faculty, Department of Cardiology, Rize, Turkey; 2 Rize Education and Research Hospital, Department of Cardiology, Rize, Turkey

Objective: To assess the long-term outcome of patients presenting with acute coronary syndrome (ACS); ST-segment elevation myocardial infarction (STEMI), non-STEMI and unstable angina (UA) in Thailand.

Methods: This is a retrospective cohort study. The data of admission and the vital status were obtained from the records of ICD 10 and ICD 9CM systems of central office for healthcare information and bureau of policy and strategy of Thailand. All patients admitted to the hospitals using 2 health security services of Thailand; national health security (UC) and civil servant (CS) due to ACS, in 2005 (from January 1st-December 31st) were collected and followed through 2010. Primary outcome was 5 years all-cause mortality.

Results: A total of 31,087 patients with ACS in 2005 were collected. In-hospital death rate was 14%. A total of 26,722 patients (86%) survived at discharge (UA 51.6%, MI 48.4%). The post-discharge overall all-cause mortality was 11.3% and 40.6% at 1 and 5 years, respectively. At 5 years, post-discharge all-cause mortality of patients presenting with MI was significantly higher than that of UA (43% vs 38.4%, HR 1.18; 95%CI 1.14-1.23, P < 0.0001). Among the patients with MI, those with NSTEMI died after hospital discharge more than those with STEMI (48.7% vs 37.5%, HR 1.12; 95%CI 1.04-1.20, P < 0.0001). Independent predictors of death were age, gender, BP, diabetes mellitus, smoking, C-reactive protein (CRP), and urinary albumin/creatinine ratios were analysed.

Conclusion: Our results suggest that diminished nocturnal decline in BP is independently associated with WNNBP and nocturnal BP rather than daytime BP. Non-dipper pattern, mainly related to increased pulse wave velocity and impaired modulation of vascular smooth muscle tone during the night, may justify an increased cardiovascular risk in these patients.

AMBULATORY BLOOD PRESSURE MONITORING: FOCUS ON NOCTURNAL BLOOD PRESSURE

Non-dipping pattern in untreated hypertensive patients is related to increased pulse wave velocity independent of raised nocturnal blood pressure

T. Erdogan1, Y. Cicek1, M.E. Durakoglugil1, M. Cetin1, A. Temiz2, V. Katsi, G. Souretis, C. Stefanadis, L. Kalikazaros, Athens, Greece

Background: Non-dipper pattern, characterized by diminished nocturnal decline in blood pressure (BP), is associated with increased cardiovascular events. In this study, we investigated the association between pulse wave velocity as the surrogate of arterial stiffness and non-dipper pattern in untreated hypertensive patients.

Methods: Eighty-four hypertensive patients, consulted for initial evaluation of hypertension, were enrolled. CF-PWV as the indicator of arterial stiffness was measured by a validated tonometry system (Sphygmocor). Patients with the history of any cardiovascular disease were excluded from study.

Results: Fifty-six patients had non-dipper pattern and 28 patients had dipper pattern in the study. Baseline characteristics were not significantly different between the two groups, except the carotid-femoral pulse wave velocity (Non-dipper vs. dipper: 9.85 ± 5.29 vs. 7.66 ± 1.08 m/s, p=0.002), female gender (55% vs. 32%, p=0.045) and nocturnal BP measurements (for mean BP: 106±11 vs. 92±8 mmHg, p<0.001). Multiple logistic regression analysis including age, gender, BP and PWV measurements, revealed female gender (OR: 5.112, immuocord, 1.23-20.4, p=0.021), nocturnal mean BP (OR: 1.243, 95%CI: 1.107-1.396, p<0.001) and CF-PWV (OR: 1.992, 95%CI: 1.240-3.198, p=0.004) as the independent predictors of non-dipper hypertensive pattern.

Conclusion: Our results suggest that diminished nocturnal decline in BP is independently associated with nocturnal BP and WNNBP rather than daytime BP. Non-dipper pattern, mainly related to increased pulse wave velocity and impaired modulation of vascular smooth muscle tone during the night, may justify an increased cardiovascular risk in these patients.

The relation between serotonin levels and insufficient blood pressure decrease during night-time in hypertensive patients

M.G. Kaya, R. Topakal, N. Kaya, E. Gunturk, A. Dogan, M.T. Inanc, M. Varygloules, A. Ergin, Erciyes University School of Medicine, Department of Cardiology, Kayseri, Turkey

Aim: The serotonin levels in thrombocytes are decreased in hypertensive patients. The aim of our study was to investigate the relationship between serotonin levels and insufficient nocturnal blood pressure (BP) decrease (non-dipper) in hypertensive patients.

Patients and methods: Fifty-six hypertensive patients and 27 healthy control subjects were included in the study. Of the hypertensive patients, 28 were classified as dippers and 28 as non-dippers based on nocturnal BP drops of <10 mmHg and <10 mmHg, respectively. Thrombocyte serotonin levels, serum uric acid, and C-reactive protein (CRP), and urinary albumin/creatinine ratios were analysed. After giving an informed consent, the patients were randomized into two groups (Groups A, n=40, or group B, n=48). Repeated measurements of blood pressure were registered with non-invasive automatic blood pressure monitors (SpaceLabs 90207, Welch Allyn 6100S devices) every 20 min. Self-reported data regarding the quality of sleep, numbers and duration of arousals were obtained via standardized questionnaire.

Results: Group A compared to group B demonstrated a small but significant increase in the number of nocturnal awakenings (2.8±1.2 vs. 1.8±1.2, p=0.045), although their duration did not significantly differ (p=NS). However, the two groups exhibited similar mean values of nocturnal blood pressure and heart rate (121±73 vs. 119±71 mmHg, 67±65 beats/min, p=NS in both cases). The reported sleep quality did not differ between the two groups but both sleep quality and higher number of awakenings (25%) were associated with non-dipping status (p<0.05, in both cases).

Conclusion: Our findings indicate that even though ambulatory blood pressure monitoring induces modest sleep disturbances, it can accurately evaluate night-time blood pressure profile and heart rate, without affecting sleep efficiency and quality. Sleep evaluation may be particularly useful in essential hypertension, as poor quality of nocturnal sleep was associated with non-dipping status.
group were significantly lower than in the dipper group. Serotonin levels negatively correlated with blood pressure (r = -0.6, p = 0.001). CRP concentration in the non-dipper group was higher than in the dipper (4.8 ± 1.4 vs 3.6 ± 1.6, p = 0.01) and control (2.4 ± 0.9, p = 0.001) groups, and microalbuminuria was significantly higher in the non-dipper group compared with dipper (24.9 ± 8.6 vs 13.4 ± 8.8, p < 0.001) and control (9.6 ± 4.8, p < 0.001) groups. Serotonin level was negatively correlated with microalbuminuria (p < 0.001, r = -0.3), uric acid (p = 0.01, r = -0.3), and CRP (p = 0.01, r = -0.35).

Conclusion: In non-dipper hypertensive patients, thrombocyte serotonin levels were significantly lower than in dipper and control groups. Serotonin levels may be characterized by increased benzodiazepine's administration, impaired arterial elasticity and more pronounced activation of proatherogenic mechanisms.

P5024

Inverse dose-response association between urinary melatonin excretion and nocturnal systolic blood pressure in the elderly

K. Obayashi1, K. Saeki1, J. Iwamoto2, N. Okamoto1, K. Tomioka1, S. Nczi1, Y. Ikeda1, N. Kurumata1, N. Nara Medical University School of Medicine, Nara, Japan; 2 Kokichi Nursing and Medical Care University, Miy, Japan

Purpose: Oral melatonin administration decreases nocturnal systolic blood pressure (SBP); however, it remains unclear whether endogenous melatonin, considered lower than pharmacological levels, is associated with nocturnal SBP. The purpose of this study was to evaluate the association between urinary melatonin excretion (UME), an index of endogenous melatonin, and nocturnal SBP.

Methods: This cross-sectional study included 109 elderly individuals aged 60 years or older (50 males, 69.1 ± 6.1 years), not taking antihypertensive medication, and completed two 48-h monitoring sessions consecutively selected from 217 subjects (HELO-KYO cohort). We simultaneously measured overnight UME (detailed in Section 2) and nocturnal SBP. The final model was based on 216 BP data (the average in 48 h) from 109 participants.

Results: The median UME was 7.6 µg (interquartile range 4.7–11.5) and mean nocturnal SBP was 114.8 ± 17.8 mmHg. Univariate mixed linear regression analysis showed significant associations between nocturnal SBP and age, gender, current smoking status, diabetes, log-transformed UME, daytime physical activity, and diurnal BP.
The majority of these subjects were self-referred. The ECVDRS consists of 10 non-invasive tests: large (C1) and small (C2) artery stiffness, BP at rest and PME according to a pre-specified protocol, carotid and abdominal aorta ultrasound, retinal photography, Microalbuminuria, ECG, LV ultrasound, and pre-BNP. We defined HTN according to JNC VII.

**Results:** Among the subjects screened 1277 were not receiving any CV medications, 198 of them met criteria for HTN: 90 female (45.5%) and 108 male (54.5%). Among the 198 subjects 36 females (40%) and 40 males (37%) had no other comorbidities. Detailed results are outlined on table 1.

**Conclusion:** An inverse dose–response association exists observed between UME and nocturnal SBP among elderly individuals.

**P5027**

**Does blood pressure variability influence the left ventricle mass index in patients with primary arterial hypertension?**

M. Kurpessa, M. Zajec, E. Tirisz, B. Uznanska-Loch, U. Cieslik-Gocu, T. Rechcinski, J.D. Kasprzak. Medical University of Lodz, Department of Cardiology, Lodz, Poland.

**Background:** Arterial hypertension (HA) leads to left ventricular (LV) hypertrophy which is a potent independent risk factor. Blood pressure (BP) variability has shown a significant relationship to end organ damage. Ambulatory blood pressure monitoring (ABPM) allows to observe a BP variability as well as short-term (beat to beat) as long term (diurnal variations). The aim of this study was to assess whether the BP variations influence the LV mass index (LVMi) in patients with primary HA.

**Materials and methods:** 97 pts (45 women and 52 men) with primary HA, aged 60.1±10.9 years underwent 24-h ABPM and ECHO measurements. The LV mass was calculated using the Penn formula and the result was corrected to body surface to obtain the LVMi. For the purpose of estimating the long-term variability of BP the dipping status was assessed. Additionally the following parameters of short-term variability of BP were determined:

- Standard deviation (SD) between values of the consecutive BP measurements.
- Rate of BP changes calculating separately for systolic BP (SBP) and diastolic BP (DBP) using the formula: \( \frac{B P_{(n+1)} - B P_n}{t_{(n+1)} - t_n} \) (BP, value of BP; t, time of BP measurement; n, measurement; n+1, next measurement after measurement n).

**Results:** In the study group LVMi ranged from 114 to 289 g/m². There were 52 non-dippers (without nocturnal fall in BP), 27 dippers (with preserved circadian pattern of BP), and 18 reverse dippers (with nocturnal increase in BP). There were no differences in LVMi between dippers, non-dippers and reverse dippers. We also did not find a correlations between LVMi and SD. The rate of BP changes (RSBP) ranged from -0.37 to 0.16 mmHg/min, the rate of DBP changes (RDBP) ranged from -0.7 to 0.12 mmHg/min. No correlation was found between RSBP or RDBP and LVMi. However, the significant correlations with LV mass index revealed: 24-hour mean SBP and mean daily SBP \((r=0.51, p<0.0001)\), mean nocturnal SBP \((r=0.41, p<0.001)\), 24-hour mean DBP and mean daily DBP \((r=0.48, p<0.001)\), minimal SBP and DBP during the day \((r=0.56, p<0.048; r<0.0001)\), minimal nocturnal SBP and DBP \((r=0.47, p<0.001)\), maximal SBP during the day and the night \((r=0.35, p<0.032, p<0.01)\), max DBP during the day \((r=0.41, p<0.001)\) and the night \((r=0.46, p<0.01)\).

**Conclusions:** 1. There is lack of relationship between the dipping status or the short-time variation of BP and the magnitude of LV mass index in primary HA. 2. From among several parameters obtained during ABPM only values of BP presented the most significant correlation with the LV mass index.
Combined effects of blood pressure and aldosterone on cardiac left ventricular mass - ethnic differences between Han, Kazakh and Uygur subjects

M. Ota1, Y. Kasamaki, Y. Ozawa, A. Hirayama, T. Nakayama1, S. Matsuura, A. Fukuda, M. Azano, Y. Izumi

1Niigata University School of Medicine, Department of Medicine, Division of Cardiology, Tokyo, Japan; 2Niigata University School of Medicine, Tokyo, Japan; 3Nippon Dental University, Department of Medicine, Tokyo, Japan; 4Department of Science and Research, Xinjiang Medical University, Urumqi, China, Urumqi, China, People’s Republic of; 5Kanazawa Medical University Hospital, Kanazawa, Japan

Purpose: Hemodynamic factors such as blood pressure have been established to be major determinants of cardiac left ventricular structure. However, factors other than blood pressure have also been shown to influence cardiac mass. We performed a medical survey and found that cardiac left ventricular mass index (LVMI) in an ethnic group of China with higher blood pressure was smaller than in another ethnic group with lower blood pressure. Here, such contradictions were analyzed with regard to blood pressure, LVMI and chemical parameters of blood and urine.

Methods: In a medical survey conducted in Xinjiang, China, 303 subjects (age, 65-70 years) from 3 ethnic groups (Han, Kazakh and Uygur) from two separate regions provided blood and urine samples, and underwent 24-h ambulatory blood pressure monitoring (AB-PM). The Ethics Committee of Xinjiang Medical University approved all study protocols. All subjects provided informed consent. Plasma aldosterone (PA) and plasma renin activity (PRA) were significantly lowest in Kazakh. Values for LVMI in all ethnic groups were positively correlated with both blood pressure and PA. An inverse correlation was observed between PA and urinary sodium excretion values.

Results: Systolic and diastolic blood pressure obtained by AB-PM were significantly higher in the Kazakh than Han and Uygur groups. However, LVMI in Kazakh was lower than in the other 2 groups. Plasma aldosterone (PA) and plasma renin activity (PRA) were significantly lowest in Kazakh. Values for LVMI in all ethnic groups were positively correlated with both blood pressure and PA. An inverse correlation was observed between PA and urinary sodium excretion values.

Conclusion: These results suggest that blood pressure is not always a determinant of LVMI value. It is possible that relatively low PA resulting from higher sodium intake suppressed the increase in LVMI caused by higher blood pressure in Kazakh subjects.

Ambulatory blood pressure monitoring in hypertensive patients with chronic kidney disease

M. Derevyanenko, M.E. Statsenko. Volgograd State Medical University, Volgograd, Russian Federation

Chronic kidney disease (CKD) is predictor of cardiovascular (CV) events in hypertensive patients. But the parameters of ambulatory blood pressure monitoring (ABPM) in hypertensive patients with CKD have not been fully examined. We investigated ABPM in a group of non-diabetic hypertensive patients with CKD. Patients with diabetes, a body mass index (BMI) of more than 35 kg/m2, and a creatinine clearance less than 60 ml/min per 1.73 m2 were excluded. 120 patients were included into the research. According to the classification of the European cardiac society (2007), all of them suffered from stage I and II arterial hypertension (AH). Of these, 60 patients suffered from AH and CKD who underwent surgery of the upper urinary tract. They made up the first (basic) group in which there were 31 males and 29 females, the mean age was 54.5±1.2 years and duration of AH was 11.7±1.2 years. The other 60 patients suffered from AH without CKD and they made up the second (control) group in which there were 27 males and 33 females, the mean age was 55.2±1.2 year and duration of AH was 11.1±0.9 years. The patients in both groups were similar in sex, age, duration of AH. The analysis of the results of the 24-hour ABPM revealed that systolic and diastolic pressure time indices were more significant in hypertensive patients with CKD than in patients without CKD (69.0±3.1% vs 53.2±3.2 and 63.8±3.6% vs 51.1±3.8%, respectively, p < 0.05). The number of patients with increased 24-hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) variability was more among hypertensive patients with CKD (59.3±23.2% vs 42.0±30.8%, respectively, p < 0.05). It was more significant differences in pulse rate, though the mean values of pulse rate in both groups exceeded the normal one (75.4±10.9 mm Hg in hypertensive patients with CKD versus 55.3±11.9 mm Hg in hypertensive patients without CKD). The analysis of distribution of patients according to daily SBP values showed that the amount of non-dipper and night-peaker patients was significantly higher in the basic group than in the control one (48.8% vs 25.4%, respectively, p < 0.05). It was established that the number of patients with DBP daily value <10 was more significant in hypertensive patients with CKD versus hypertensive patients without CKD. Moreover, the patients with CKD who underwent surgery of the upper urinary tract in comparison with patients suffering from AH without CKD have significantly more pronounced changes of a daily BP profile.

The association of mean platelet volume levels with subclinical target organ damage in asymptomatic hypertensives

M.G. Kayara, M. Yarlagadda, E. Gunturk, M. Akpek, R. Topkaya. Erciyes University School of Medicine, Department of Cardiology, Kayseri, Turkey

Significant numbers of asymptomatic hypertensives are attacked by subclinical target organ damages (TOD) such as proteinuria, increased left ventricular mass (LVM) and carotid atherosclerosis because of inadequate treatments. There is increasing evidence that platelets get activated in uncontrolled hypertension and have a crucial role in the increased thrombotic tendency. Mean platelet volume (MPV) is one of the markers that correlate closely with platelet activity. In our study we aimed to investigate relationship between MPV levels and subclinical early period of TOD in asymptomatic hypertension patients.

Methods and Results: Between 1995-2002, 112 subjects (46 male, mean age: 51±8) with primary hypertension attending the outpatient clinic of our institution were included to the study. 24-hour ambulatory blood pressure monitoring, Echocardiography, carotid ultrasonography was performed to all patients. MPV was measured from triipotassium EDTA-based anticoagulated blood samples and urine albumin/creatinine ratio (UACR) was measured from spot urine samples. The average value of MPV levels, UACR, LVMI, and carotid intima-media thickness (cIMT) was 9.6±0.42 fl, 2.3±0.8, and 0.9±0.13 mm, respectively. MPV is significantly correlated with 24-hour systolic and diastolic blood pressure (r=0.51, p<0.001) and cIMT (r=0.50, p<0.001). Multivariate stepwise linear regression analyses identified that MPV levels independently associated with severity of proteinuria (r=0.45, p=0.001) and LVMI (r=0.46, p<0.001).

Conclusion: These results call to mind that MPV levels could be used as a simple and cheap marker tointerrogate adequacy of anti-hypertensive therapy during 24-hour, to anticipate early period of TOD and intensity therapy to prevent TOD development.

Diastolic but not systolic blood pressure was more significantly affected by the gender in newly diagnosed hypertensive patients with obesity

H.J. Yoon1, Y.K. Ahn1, K.H. Kim1, J.C. Park1, J.H. Bae3, J.J. Rim3, H.J. Yoon5, J.K. Woo1, S.W. Park7. 1The Heart center of Chonnam National University Hospital, Gwangju, Korea, Republic of; 2Kwangdong University, Cheil General Hospital, Seoul, Korea, Republic of; 3Koryang University Hospital, Daejeon, Korea, Republic of; 4Yonsei University, Severance Hospital, Seoul, Korea, Republic of; 5Cardiovascular Hospital, Seoul, Korea, Republic of; 6Inha University Hospital, Incheon, Korea, Republic of; 7Samsung Medical Center, Cardiovascular Center, Seoul, Korea, Republic of

Background: Obesity is associated with an increased risk of cardiovascular morbidity and mortality as well as quality of life. Body mass index (BMI) provided the most useful parameter of obesity. The aim of this study was to search the differences in certain well-defined blood pressure pattern according to gender between obese and non-obese patients with hypertension. We analyzed with regard to obesity and non-obese group difference in BP pattern between obese and non-obese group.

Methods: Total 773 hypertensive patients (442 male, 481±11 year) enrolled from Korea Hypertension Network II were evaluated in this study. The patients were no history of hypertensive medication. BP was checked by nurse or doctor in office, home and ambulatory blood pressure monitoring, Echocardiography, carotid ultrasonography and urine. The Ethics Committee of Chonnam National University Hospital approved all study protocols. All patients provided informed consent.

Results: In female, there was no significant difference of systolic and diastolic BP measured in office, home and ambulatory monitoring between groups. In male gender, there was no significant BP difference measured in office, home and ambulatory monitoring between groups. Mean diastolic BP in office (97.1±12 vs. 94.1±11mmHg, p=0.016), average diastolic BP in AH at home (92.4±14 vs. 90.1±11mmHg, p=0.017), average diastolic BP in PM at home (92.4±14 vs. 88.6±11mmHg, p=0.010) and mean diastolic BP in home (91.1±12 vs. 87.7±11mmHg, p=0.005) were significantly higher in obese group than non-obese group. There was no significant difference in BP pattern between obese and non-obese group obtained from ambulatory monitoring. Although there was no clinical significance, diastolic mean BP from all measurement included office, home and ambulatory monitoring was more significantly affected by the gender in newly diagnosed hypertensive patients with obesity.
Antihypertensive treatment less efficacious when evaluated by Ambulatory Blood Pressure Monitoring

V. Gjini, G. Gjini. Internal Medicine Clinic, Hospital of Fier, Fier, Albania

Ambulatory blood pressure monitoring (ABPM) is now widely used not only for a better diagnosis of hypertension, but also for considering of antihypertensive treatment.

Purpose: We aimed to study the efficacy of antihypertensive drug treatment by ambulatory office and ABPM recorded values.

Methods: From a database of more than 1000 ABPM recordings we have selected 146 pts whose BP was monitored twice, first without and then 2 weeks after beginning of standard antihypertensive treatment. Office measured, peak and mean (systolic/diastolic) values were selected for comparison. Treatment was considered efficacious when BP values (either systolic or diastolic) were reduced >10 mm Hg, or when were returned to normal (<130/80 mm Hg).

Results: At first evaluation Office (sys/dia) BP values (mean±SD) were 145±18 and 96±14 mm Hg. Peak 171±20 and 113±15 mm Hg and Mean 136±14 mm Hg, 83±10 mm Hg respectively.

After a 2-week treatment the Office BP values were significantly reduced to 138±16 (<0.001) and 91±11 mm Hg (<0.001), Peak BP values to 167±19 (<0.001) and 107±15 (<0.001) mm Hg and Mean BP values to 133±14 (p=0.07), 78±9 mm Hg (p=0.06), respectively. Office-measured BP values (sys or dia) were reduced >10 mm Hg in 121/146 pts (83%) and were found normal in 82/146 pts (56%). Peak BP values were reduced >10 mm Hg in 101/146 pts (69%) and were within normal limits in only 40/146 pts (27%).

Mean BP values were returned to normal in 110/146 (75%) pts.

Conclusion: These data indicate that when evaluated by ABPM antihypertensive treatment results less efficacious then when traditionally evaluated.

AMBULATORY BLOOD PRESSURE MONITORING

Masked hypertension and atherogenesis: the impact of nocturnal continuous positive airway pressure on blood pressure variability in patients with obstructive sleep apnea and prehypertension

D. Papadopoulou1, O. Papazachou2, I. Mourouzis1, A. Kotrothou1, M. Daskalaki2, C. Thomopoulos2, E. Sanidas1, D. Perrea3, E. Tsouranis4, T. Makris2, 1Laiko General Hospital, Department of Cardiology, Athens, Greece; 2General Maternity Distric Hospital Elena Venizelou, Department of Cardiology, Athens, Greece; 3Laboratory of experimental surgery, Medical School, Athens, Greece.

Purpose: Recent evidence demonstrates that masked hypertension (MH) is a significant predictor of cardiovascular disease, while hypo-albuminemia and hypoperoxidase may contribute to vascular damage accelerating atherogenesis.

Aim of our study was to examine the apelin and relaxin plasma levels in patients with MH and compare the findings to those of healthy normotensives matched for age, sex, body mass index and the rest of risk factors.

Methods: One hundred-thirty (60 M, 70 F) healthy subjects mean age 45±10 years who had clinic blood pressure >140/90 mmHg were included. The whole study population underwent 24 hour ambulatory blood pressure monitoring (ABPM). According to the ABPM recordings, 18 individuals (7M, 11 F) had MH (daytime systolic blood pressure >135 mmHg or daytime diastolic blood pressure >85 mmHg - group A) and the remainder 112 subjects (53 M, 59 F) had normal ABPM recordings, group B. Apelin and relaxin plasma levels were determined in both groups (ELISA method).

Results: Our findings and the comparisons between the two groups are shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Group A (n=18)</th>
<th>Group B (n=112)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apelin (ng/ml)</td>
<td>220±121</td>
<td>315±147</td>
</tr>
<tr>
<td>Relaxin (ng/ml)</td>
<td>35±2.8</td>
<td>53±28</td>
</tr>
</tbody>
</table>

Conclusions: Our findings suggest that subjects with masked hypertension have significantly lower apelin and relaxin levels compared to healthy individuals. This observation may have prognostic significance for future cardiovascular events in subjects with masked hypertension and needs further investigation.

The prevalence of masked hypertension and blood pressure variability in patients with renal transplantation

M. Kayrak1, E.E. Guı1, C. Kaya2, K. Turken3, Y. Solak1, R. Yaziçi3, I. Guı, L. Altıntepe4, S. Turk5, K. Ozdemir1, 1Selcuk University Meram, Faculty of Medicine, Konya, Turkey; 219 Mayıs University Medical School, Konya, Turkey; 3Meram Research and Training Hospital, Konya, Konya, Turkey

Purpose: Arterial hypertension is a risk factor affecting graft function in renal transplants (Rtx). In pediatric Rtx, high prevalence of masked and nocturnal hypertension was reported. Most of the Rtx had a history of hypertension and some of them are nonresponsive in outpatient control, however home blood pressure levels are higher. Masked hypertension (MHT) is defined as a normal office blood pressure but an elevated ambulatory blood pressure. Use of ambulatory-blood pressure monitoring (ABPM) enables the identification of MHT. Previous reports have demonstrated the role of MHT in the outcome of hypertensive patients. However, the true prevalence of MHT in Rtx is still unknown.

Methods: The study enrolled Rtx with normal office blood pressure level (SBP/DDBP <140/90mmHg) admitted to the outpatient clinic of Nephrology and Transplantation over a year. ABPM was performed in all patients during 24-h period. MHT was defined as normal office BP associated with daytime ambulatory hypertension (SBP/DBP >135/85).

Results: The prevalence of MHT and nocturnal hypertension in our group were 49% and 61%, respectively. Fifty-four (54%) patients had a history of HT. Fifty-eight (58%) patients were being treated with antihypertensive medications. Non-dipping was present in 81.5% of patients. There were no significant differences in demographic and clinical features between patients with and without MHT (Table).

Table 1

<table>
<thead>
<tr>
<th>With MHT (n=50)</th>
<th>Without MHT (n=50)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>40±11</td>
<td>42±11</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>123±12</td>
<td>122±11</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>79±9</td>
<td>77±8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±5</td>
<td>26±4</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>72±24</td>
<td>70±20</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>CCB, n</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>BB, n</td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

Conclusion: We demonstrated an increased prevalence of MHT and BP variability in Rtx population. These results may explain high cardiovascular events in Rtx patients. Therefore routine recommendation of ABPM in Rtx patients may be reasonable.

Impact of nocturnal continuous positive airway pressure therapy on ambulatory blood pressure monitoring in patients with obstructive sleep apnea and prehypertension

H. Yorgun1, G. Kabako2, E. Kirmizigil1, U. Canpolat1, A.H. Ates1, E.B. Kaya1, K. Aytemri1, A.U. Demir1, L. Tokgozoglu1, A. Oto1, 1Hacettepe University, Faculty of Medicine, Ankara, Turkey; 2Hacettepe University, Faculty of Medicine, Department of Cardiology, Ankara, Turkey

Background: We aimed to investigate the short term effects of CPAP treatment on blood pressure (BP) and non-dipper or dipper status in OSAS patients without a prior diagnosis of hypertension (HT).

Methods: We included a total of 24 patients (19 male, mean age: 48.7±10.4 years). The study group was divided into 2 groups; group 1 with mild-moderate OSAS (AHI≤30) and group 2 with severe OSAS (AHI>30). Patients with OSAS were assigned treatment with CPAP. An overnight polysomnography was performed by a computerized system. A 24-h ambulatory monitor was used to record BPs in all patients.

Results: Mean ambulatory 24 hour systolic and diastolic BPs were 126±6±9.4 mm Hg and 79.5±10.2 mm Hg respectively.CPAP treatment significantly decreased 24 hour mean BP after 12 weeks irrespective of AHI (89±8.4 mm Hg baseline vs. 82±7.3 mm Hg after 12 weeks, p<0.001). After 6 weeks CPAP treatment, non-dippers reduced to 16.6% and at the end of 12 week CPAP treatment 12.5% of the patients were non-dipper (p=0.008). Multiple linear regression analysis revealed that male gender, Epworth sleepiness scale, apnea-hypopnea index, smoking and mean 24 hour BP were the predictors of BP reduction in patients between baseline and after 12 week CPAP (p<0.05)

Multiple linear regression analysis for the predictors of BP reduction after CPAP therapy

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>-5.76</td>
<td>-8.2 to -3.34</td>
</tr>
<tr>
<td>Baseline AHI score</td>
<td>-0.35</td>
<td>-0.57 to -0.197</td>
</tr>
<tr>
<td>AHI</td>
<td>-0.14</td>
<td>-0.191 to -0.097</td>
</tr>
<tr>
<td>Baseline BMI (kg/m²)</td>
<td>-0.09</td>
<td>-0.004 to -0.52</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.66</td>
<td>0.75 to 4.5</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>5.59</td>
<td>2.96 to 8.23</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-4.7</td>
<td>-7.6 to -1.8</td>
</tr>
</tbody>
</table>

Baseline 24h MBP (mmHg) | -0.70 | -0.32 to 0.84 | <0.0001 |

Conclusion: Effective CPAP therapy reduces BP levels in OSAS patients without hypertension and improves dipper-non-dipper status.
Metabolic syndrome increases morning blood pressure surge

E. Chatzistamatiou1, G. Moustakas1, E. Androulakis1, D. Tousoulis2, A. Avgeropoulou1, N. Kalovidouris1, M. Divani1, D. Liakos2, C. Stefanadis1, I. Kalikazaros1, 1Hippokration General Hospital, Cardiology Department, Athens, Greece; 2Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece

Purpose: Large scale studies suggest that systolic blood pressure morning surge is an independent predictor of target organ damage. Aim of our study was to investigate associations between 24hr ambulatory blood pressure monitoring (ABPM) levels and morning surge in never-treated essential hypertensive (EH) patients with and without metabolic syndrome (MS).

Methods: We studied 366 consecutively newly diagnosed EH patients stage I-III (age 51±12 years, 60% males) without prevalent cardiovascular disease. In all participants anthropometric data were recorded. Also, all subjects underwent a 24-hour ambulatory blood pressure monitoring (ABPM) and morning surge index was calculated as: the mean systolic blood pressure (SBP) during the 2 hours after awakening minus mean SBP during the 1 hour that included the lowest sleep BP. Heart rate variability was calculated as the ratio of day-night mean heart rate difference normalized to mean day heart rate. According to ATPIII criteria, the study cohort was divided in two groups: group A (n=210, MS-) and group B (n=156, MS+).

Results: The two groups did not differ regarding age, sex, smoking and snoring status, alcohol and coffee consumption, serum cholesterol, office systolic and diastolic blood pressure and 24-h ABPM blood pressure levels. Group B compared to A exhibited increased BMI (31±7 vs. 26±3, p<0.001), 24-hour average (74±9 vs. 72±8, p=0.019) and night (66±8 vs. 63±8, p=0.002) heart rate, heart rate variability (12±7 vs. 15±7, p=0.037) and morning surge index (23±13 vs. 19±12, p=0.009).

Conclusion: In never-treated EH patients, the presence of metabolic syndrome unfavourably affects autonomic function as expressed not only by decreased HR variability, but also by increased blood pressure morning surge. These autonomic disturbances may be the link between MS, subclinical target organ damages and prevalent CVD.

A novel non-invasive continuous system for estimating arterial blood pressure: first-in-man clinical results

S. Bras1, D. Ribeiro1, J.P. Silva Cunha2, R. Fontes-Carvalho2.
1Institute of Electronics and Telematics Engineering of Aveiro (IEETA), Universidade de Aveiro, Aveiro, Portugal; 2Hospital Center of Vila Nova de Gaia/Espinho, Department of Cardiology, Vila Nova de Gaia, Portugal

Purpose: There was growing interest on noninvasive technologies for arterial blood pressure (BP) measurement on beat-to-beat basis. Our aim was to clinically evaluate the accuracy of a novel device for estimating real-time BP using an algorithm based on pulse-wave transit time (PTT).

Methodology: This device measures PTT between ECG R wave and the onset of photoplethysmography (PPG) and is estimated using an improved technique first reported by Heath. BP estimation involves the delay between Rwave and the inflection point of positive slope of PPG and the instantaneous heart rate. PPG sensor was attached to the right index finger. Rwave was registered using lead I. Values obtained with this method were compared with a validated oscilometric device (Omron M6 Comfort) measured in the left arm. Duration of study was 49.38±0.38±0.50±0.45min (healthy volunteers/hypertensive patients). Results are presented as mean±SD.

Results: 10 subjects (3healthy/7patients) were evaluated, 5 female. Baseline systolic BP (SBP) was 121.0±0.8/128.0±2.5mmHg, diastolic BP (DBP) was 66.0±0.5/77.0±2.0mmHg and heart rate was 60.0±3.0/56.0±2.5bpm in healthy/patients.

The median absolute error was 2.94±1.12/2.97±3.38 (SBP), 1.67±0.51/5.59±1.79 (DBP), in healthy/patients. Relative low error was 2.75±0.01%/9.13±0.04% (SBP) and 2.53±0.01%/17.0±0.02% (DBP) in healthy/patients. Figure 1 shows estimated BP in a healthy volunteer.

Conclusion: The obtained results with this new system are within the acceptable error margin. Future work will focus on motion artifacts reduction introduced by PPG sensor since one of the aims of our system is to continuously monitor ambulatory BP. Following these results new studies are now underway to compare with BP data obtained from subjects with interarterial catheterization.
### Results

Fifty patients were included, 72% were males, mean age was 63 years, mean BMI was 29.7 kg/m² and 64% had hypertension. The mean baseline clinic BP was 118/75 mm Hg. Fifty two percent were treated with ACE/ARB, 90% beta-blocker, 68% calcium antagonist, 92% long acting NTG and 42% with diuretics. The CCS class improved from mean 2.6 to 1.5. No significant change was found in medication. The mean daytime and night time ABP did not change significantly during the study period (p<0.05), see table. Further, when controlling for quartiles of baseline ABP level no interaction was found between ABP and baseline level.

### Conclusion

EECP treatment has no lasting effect on blood pressure.

### Effect of atmospheric pressure on blood pressure

#### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of investigation</th>
<th>Age (years)</th>
<th>24-hour SBP</th>
<th>24-hour DBP</th>
<th>Day SBP</th>
<th>Day DBP</th>
<th>Night SBP</th>
<th>Night DBP</th>
<th>Morning Peak SBP</th>
<th>Morning Peak DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipper</td>
<td>163</td>
<td>55.9 ± 10.4</td>
<td>130.7 ± 18.9</td>
<td>77.3 ± 11.9</td>
<td>125.0 ± 11.8</td>
<td>74.6 ± 8.8</td>
<td>127.5 ± 11.6</td>
<td>76.4 ± 7.1</td>
<td>130.0 ± 17.2</td>
<td>79.2 ± 10.6</td>
</tr>
<tr>
<td>Non-Dipper</td>
<td>109</td>
<td>61.3 ± 13.8</td>
<td>123.0 ± 11.7</td>
<td>73.7 ± 7.4</td>
<td>125.3 ± 11.4</td>
<td>73.6 ± 8.6</td>
<td>125.3 ± 11.4</td>
<td>73.6 ± 8.6</td>
<td>128.9 ± 16.0</td>
<td>76.4 ± 10.6</td>
</tr>
<tr>
<td>All</td>
<td>272</td>
<td>59.6 ± 10.5</td>
<td>126.2 ± 11.8</td>
<td>75.9 ± 7.4</td>
<td>125.0 ± 12.1</td>
<td>75.8 ± 8.6</td>
<td>125.0 ± 12.1</td>
<td>75.8 ± 8.6</td>
<td>128.9 ± 16.0</td>
<td>76.4 ± 10.6</td>
</tr>
</tbody>
</table>

### Conclusion

In conclusion our data confirm that the reproducibility of the circadian blood pressure pattern in 24 h recordings in patients with CHD is significantly reliable.

### Reproducibility of ambulatory blood pressure monitoring in patients with coronary heart disease

#### Figure 1

**Figure 1. ROC curves**

### Conclusion

The CRUSADE and ACUITY-HORIZONS risk scores showed an excellent predictive value for in-hospital bleeding in our cohort of STEMI patients. The CRUSADE risk score seemed to perform better than the ACUITY-HORIZONS risk model for bleeding prediction.
**Real-world primary PCI with bivalirudin: a report from the prospective, multi-centric EUROVISION registry**

U. Limbruno¹, A. Pichii¹, S. Hassanii, S. Galli², B. Cortese³, K. Huber², J. Lipiecki⁴, F. Pagani³, M. Sangioni⁴, M. Hamon⁴ on behalf of EUROVISION investigators. ¹Milan Cordis Hospital, ASL 9, Grosseto, Italy; ²Nîort Hospital, Nîort, France; ³Cardiology Center Monzino (IRCCS), Milan, Italy; ⁴Clinical Institute Humanitas Gavazzeni, Bergamo, Italy; ⁵Wilhelminen Hospital, 3rd Department of Internal Medicine, Cardiology and Emergency Medicine, Vienna, Austria; ⁶University Hospital of Clermont-Ferrand, Clermont-Ferrand, France; ⁷University of Marseille, Marseille, France; ⁸University of Rome, Polytechnic “Tor Vergata”, Department of Cardiology, Rome, Italy; ⁹University Hospital of Caen, Department of Cardiology, Caen, France

**Purpose:** In primary PCI, bivalirudin (BIVA) is superior to heparin. GPI/llb/lla inhibitors (GPI) as shown in the HORZOND-AMI trial (HOR) due to significant reduction in bleedings and improved survival. However, a higher incidence of acute stent thrombosis was observed in BIVA-treated patients. The purpose of this analysis was to evaluate 30-day outcomes from a real-world STEMI population from the EUROVISION (EUR) registry treated with a BIVA alone strategy.

**Methods:** Among the 2018 EUR BIVA-treated patients, 663 underwent primary PCI for STEMI. Outcomes measures were 30-day death, re-inflation (MI), stroke, stent thrombosis, urgent revascularization (URV), bleedings, and thrombocytopenia. The net adverse cardiovascular events (NACE) rate combining death, MI, URV, and major bleeding was also calculated.

**Results:** Patients from EUR in EUR patients BIVA infusion was frequently continued post-PCI (62%, median 122 min, 60-296 IQR). Pre-PCI thienopyridine loading was performed in 95%, GPI used in 5%, and radial approach performed in 30% of cases. STEMI patients in EUR were older (p<0.001), but with similar 30-day mortality rate to HOR BIVA-treated patients. Thirty-day outcomes (MI, URV or bleedings) were lower in EUR resulting in lower NACE rates compared with HOR (Table 1). In EUR patients there were no acute (<24 hrs) stent thrombosis cases and no cases of thrombocytopenia.

**Table 1**

<table>
<thead>
<tr>
<th>EUROVISION-STEMI</th>
<th>HORZOND-AMI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>663</td>
<td>1800</td>
</tr>
<tr>
<td>Death (%)</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Re-infection (%)</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Thrombocytopenia (%)</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Stent Thrombosis (%)</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Thrombocytopenia (%)</td>
<td>0.0</td>
<td>0.6</td>
</tr>
<tr>
<td>NACE (%)</td>
<td>4.4</td>
<td>9.3</td>
</tr>
</tbody>
</table>

**Conclusion:** Real world data from EUR confirm the HOR trial results with a favorable impact of BIVA alone strategy on STEMI patients’ outcome. Prolongation of BIVA infusion after the end of PCI seems a safe strategy that may further contribute to improve patient’s outcome.

**Impact of one versus multiple heparin administration on clinical outcome after primary PCI for STEMI: a prespecified analysis of the ATOLL trial**

J.-P. Cotlet¹, U.Z. Zeynam², C.P. Pollack³, M. Cohen⁴, K. Huber⁵, J. Stolden⁶, J. Silvern¹, M. Aouf⁴, E. Vicaulet⁷, G. Montalescot⁸ on behalf of ACTION. ¹AP-HP - Hospital Pitie-Salpetriere, Paris, France; ²Research Institute for Heart Attack Ludwigshafen (IHP), Ludwigshafen, Germany; ³Hospital of the University of Pennsylvania, Philadelphia, United States of America; ⁴Newark Beth Israel Medical Center, Newark, United States of America; ⁵Wilhelminen Hospital, 3rd Department of Internal Medicine, Cardiology and Emergency Medicine, Vienna, Austria; ⁶Hospital Regional University of Lille, SAMU, Lille, France; ⁷AP-HP - Hospital Fieraud Widal, University of Medicine Paris 7, Paris, France

**Background:** The ATOLL trial evaluated the efficacy and safety of IV enoxaparin versus UFH in primary PCI. Patients who had received any anticoagulation before randomization were not allowed. Cross over to a different anticoagulant after randomization was not allowed.

**Objective:** To evaluate the impact of anticoagulant cross over on clinical outcome. The baseline clinical characteristics, duration of administration, clinical outcome as defined in the original ATOLL trial were first compared between patients who received more than one (n=100) versus only one anticoagulant (n=800). Patients who did not receive any anticoagulation were excluded (n=10).

**Results:** Patients who were administered more than one heparin were more frequently older, female, treated with long-term insulin therapy than patients that stayed on one heparin as allocated by randomization. They also presented more frequently with acute heart failure or cardiacogenic shock. They were treated for a longer duration (7.9±9.1 vs. 3.9±3.2 days, p<0.001). A significant interaction was measured between “one” versus “multiple” heparins for the primary EP (p for interaction=0.05) and main secondary EP (p for interaction=0.001). The primary endpoint was reduced by 11% after anticoagulation with one versus more than one anticoagulant administration as well all its individual components. Conversely, major and minor bleed was significantly reduced.

**Table 1**

<table>
<thead>
<tr>
<th>TIMI flow grade</th>
<th>MLVD (mm)</th>
<th>D5 (%)</th>
<th>Lumen (mm3)</th>
<th>P+M (mm3)</th>
<th>EEM (mm3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.4±0.7</td>
<td>0.58±0.39</td>
<td>82±11</td>
<td>143±58</td>
<td>233±79</td>
</tr>
<tr>
<td>After TA</td>
<td>2.7±0.5</td>
<td>1.09±0.44</td>
<td>71±17</td>
<td>165±97</td>
<td>206±66</td>
</tr>
<tr>
<td>After Stent</td>
<td>3±0.5</td>
<td>3.08±0.66</td>
<td>5±12</td>
<td>9±428</td>
<td>157±56</td>
</tr>
</tbody>
</table>

**Conclusion:** TA reduces the “mobilizable” atherothrombotic plaque burden and may be safely performed before S-PCI in high-risk NSTEMI pts as an alternative to balloon predilatation. These data are encouraging for a beneficial role of TA in reducing peri-procedural myocardial damage also in S-PCI in the setting of NSTEMI-ACS.

**Evidence of ischemic post-conditioning in optimally treated patients with myocardial infarction**

H. Thibault¹, G. Souer², C. Berger³, L. Ermou², M. Altman¹, P. Croisille², M. Ovize³, G. Derumeaux³ on behalf of EUROVISION-STEMI HORIZONS-AMI P5043

**Purpose:** Ischemic post-conditioning (PCI) has been shown to reduce myocardial

**Table 1**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Only One</th>
<th>More than One</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>TIMI flow grade</td>
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<td>82±11</td>
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</tr>
<tr>
<td>After Stent</td>
<td>3±0.5</td>
<td>3.08±0.66</td>
<td>5±12</td>
</tr>
</tbody>
</table>

**Conclusion:** In primary PCI for STEMI, c crossover to the other anticoagulant showed significant higher rates of both ischemic and bleeding events and should be discouraged.
Coronary revascularization in patients that become stable

Methods: Patients presenting, within 12h of the onset of chest pain, with a first STEMI, and for whom the clinical decision was made to perform revascularization by percutaneous coronary intervention, were eligible for enrolment. After reperfusion by direct stenting, 47 patients were randomly assigned to either a control (no intervention; n=23) or a post-conditioned group (repeated inflation and deflation of the angioplasty balloon; n=24). MI size was assessed by cardiac enzyme release during 72h after reperfusion. At 3 days and 6 months after MI, LV size and function was evaluated by echocardiography.

Results: The 2 groups had similar ischemic duration, area at risk and medical treatment during and after reperfusion. PC significantly reduced MI size (~34% compared to controls). At Day3 after MI, no difference was observed on LV size and function (LV ejection fraction (EF): 55.8±4% in Controls, 54.1±10% in PC, p=0.7). At 6 months, controls displayed LV end-diastolic volume enlargement compared to initial echocardiography (91.2±29 vs. 100±30 ml, respectively; p<0.02) and no significant improvement on LVEF or wall motion score index (Figure 1). In contrast, PC patients displayed no LV enlargement (90.2±28 vs. 95±35 ml, respectively, p=0.27) and improved both their LVEF and wall motion score index compared to the initial echocardiography (Figure 1, *p<0.05 vs baseline).

Conclusions: Ischemic PC on top of optimal therapy reduces MI size in patients with acute MI and improves remodeling at 6 months compared to controls.

Enoxaparin is superior to unfractionated heparin in primary PCI for STEMI: results of the prespecified per-protocol analysis of the ATOLL trial

Objective and methods: To present the results of the pre-specified per-protocol analysis excluding patients that received more than one heparin (protocol violation). A total of 850 patients (87.8%) were treated according to the protocol with consistent anticoagulation using enoxaparin (n=403) or UFH (n=487). The per-protocol analyses as for the intent-to-treat analysis were performed in this cohort of patients.

Results: Enoxaparin resulted in significantly reduced rates of the primary endpoint and main secondary endpoint (table). The net clinical benefit of death was also reduced with enoxaparin (table). There were favorable trends for enoxaparin on bleeding complications and blood transfusion as well.

Conclusions: The per-protocol analysis of the ATOLL trial confirms and reinforces the main findings of the study. Intravenous enoxaparin was superior to UFH on both the primary and secondary endpoints. Most of the benefit is observed on ischemic endpoints. However, in a study with predominant radial access, bleedings tended also to be less frequent on enoxaparin than on UFH. The net clinical benefit was significantly improved with enoxaparin.
IS reduction in the postconditioning group (29.1±15 vs. 37.1±19; P= 0.16), but there was a significant IS reduction in infarcts of the anterior territory (35.4±14 vs. 48.1±8; P=0.05). No significant difference in LVEF was found between groups but there was a significant dilation of the LV end-diastolic volume in the control group (P=0.02). Thrombus aspiration did not have any significant effect on IS or MVO (P=0.34 and P=0.42).

Conclusion: Mechanical postconditioning reduces MVO in patients with acute STEMI treated with PCI. The impact of postconditioning seems to be independent of thrombus aspiration and our data suggest that it does not increase distal embolization.

Addition of ivabradine during beta-blockers titration improves systolic and diastolic LV function in patients with recent Q-wave myocardial infarction

Y.A. Lutay, A.N. Parkhomenko, O.I. Irkin, A.A. Stepura. National Scientific Center M.D. Strazhkevici Institute of Cardiology, MAS of Ukraine", Kiev, Ukraine

Heart rate (HR) is a powerful predictor of mortality and heart failure (HF) in pts with acute myocardial infarction (AMI). β-blockers are the first line treatment for these pts but time is needed for their titration and side effects can limit their use in an appropriate dose. Ivabradine may be a good alternative for HR reduction during β-blockers titration.

80 pts with recent (36-72 h after symptoms onset) Q-wave AMI and HR >80 bpm were studied: β-blockers were initiated in all the pts. 40 pts were randomized for ivabradine 5mg bid in addition to standard treatment and 40 pts were controls. Dosage of ivabradine was increased to 7.5 mg if HR remained > 70 bpm after 24 hrs of treatment. 69 (86.3%) pts had anterior AMI and 55 (68.8%) pts had symptoms of acute heart failure (Killip II). Study and control groups did not differ in regards of baseline, clinical characteristics, reperfusion and initial treatment. Standard two-dimensional, M-mode, spectral, color and tissue Doppler were performed at baseline and day 7.

Ivabradine significantly decreased HR after the first 24 hrs of treatment and increased EF (without any changes of EDI) and improved LV diastolic function. At treatment. Standard two-dimensional, M-mode, spectral, color and tissue Doppler were performed at baseline and day 7.

In patients with recent Q wave AMI and HR >80 bpm ivabradine can be used during β-blockers uptitration for LV systolic and diastolic function improvement.

Table 1

| Ivasbradine (40 pts) | Control (40 pts) | p | p
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Day 7</td>
<td>Baseline</td>
<td>Day 7</td>
</tr>
<tr>
<td>EDI, mm²</td>
<td>58.8±1.6</td>
<td>59.3±1.4</td>
<td>ns</td>
</tr>
<tr>
<td>EF %</td>
<td>39.5±0.8</td>
<td>44.4±1.0</td>
<td>p=0.008</td>
</tr>
<tr>
<td>LA, mm</td>
<td>36.2±0.5</td>
<td>37.5±0.6</td>
<td>ns</td>
</tr>
<tr>
<td>E/A</td>
<td>1.09±0.1</td>
<td>0.98±0.1</td>
<td>ns</td>
</tr>
<tr>
<td>DT, ms</td>
<td>152.2±7.8</td>
<td>169.3±7.9</td>
<td>ns</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>89.7±3.9</td>
<td>94.3±5.4</td>
<td>ns</td>
</tr>
<tr>
<td>E’_c RES</td>
<td>6.8±0.4</td>
<td>8.1±0.5</td>
<td>p=0.036</td>
</tr>
<tr>
<td>E/E’</td>
<td>10.9±0.6</td>
<td>9.0±0.4</td>
<td>p=0.002</td>
</tr>
</tbody>
</table>

In patients with recent Q wave AMI and HR >80 bpm ivabradine can be used during β-blockers uptitration for LV systolic and diastolic function improvement.

The utility of thrombectomy and distal protection in patients with ST-segment elevation myocardial infarction showing poor coronary artery flow prior to primary percutaneous coronary intervention

N. Suzuki1, K. Kozuma1, K. Tanabe2, T. Muramatsu3, Y. Ikarai4, T. Isshiki1. 1T eikyo University Hospital, Division of Cardiology, T okyo, Japan; 2Center, Department of Cardiology, Rotterdam, Netherlands; 3Department of Cardiology and Radiology, Rotterdam, Netherlands; 4Department of Cardiology, Dokkyo University, Tochigi, Japan

Introduction: Previous studies had shown that poor coronary artery flow prior to primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) is associated with exacerbated clinical outcomes, although the positive clinical results of the facilitated percutaneous coronary intervention have not been shown. The aim of this study was to evaluate the efficacy of thrombectomy and/or distal protection device in PCI for STEMI patients showing poor pre TIMI grade.

Methods: Out of 696 STEMI patients enrolled either in the two multicenter randomized trials (VAMPIRE trial: tested the efficacy of thrombectomy or ASPARAGUS trial: tested the efficacy of distal protection device), 185 lesions in 185 patients who underwent the primary PCI for proximal or mid left anterior descending coronary artery lesion and have complete sets of angiographic data (Ejection fraction [EF] evaluated by left ventriculography, myocardial blush grade [MBG] and TIMI grade) at baseline and 6-months follow-up were evaluated. Delta EF was calculated by [follow-up - baseline].

Conclusion: In the present study cohort, poor pre TIMI grade seemed to result to the late exacerbated microcirculation. In patients with STEMI showing poor pre PCI TIMI grade, thrombectomy and distal protection may be promising remedies for the myocardial salvage with lower risk of bleeding complication.

Chronic intermittent pacing therapy amends infarct geometry and composition

A. Uitterlinden1, T. Springeling2, V.J. De Beer1, E. Mokelek3, W.M. Blankesteijn4, E.P. Doskalopoulos4, F.W. Prinzen5, R.J. Van Geuns2, W.J. Van Der Giessen1, D.J. Dunker1, E. Erasmus Medical Center, Department of Cardiology, Rotterdam, Netherlands; 2Erasmus Medical Center, Department of Cardiology and Radiology, Rotterdam, Netherlands; 3Boston Scientific Corporation, St. Paul, MN, United States of America; 4Department of Pharmacology, Maastricht, Netherlands; 5Department of Physiology, Maastricht, Netherlands

Purpose: Despite early revascularization strategies, left ventricular (LV) remodeling and dysfunction after myocardial infarction (MI) remain of clinical significance. Intermittent pacing therapy (IPT) has been shown to limit infarct size and subsequent LV remodeling when applied during early reperfusion. Here we investigated the effects of chronic IPT on global and regional LV function and infarct composition in a preclinical porcine model of reperfused infarction.

Methods: Fourteen pigs underwent proximal LCx ligation for 2h followed by reperfusion to induce a transmural infarction, and were instrumented with a pacemaker connected to an epicardial LV lead positioned in the anterior peri-infarct zone. Three days later, LV function and infarct-size were assessed with 3.0-Tesla cardiac MRI and animals were stratified into Control therapy and IPT groups (after which all pigs survived). IPT consisted of LV pacing twice daily for 3 x 5 min separated by 5 min of normal sinus rhythm until 5 wk post-implantation, after which follow-up cardiac MRI was obtained and myofibroblasts were quantified in the infarct zone, using a co-labeled muscle actin staining.

Results: Although IPT had no significant effect on global LV remodeling or function (data not shown), or infarct mass, it markedly influenced infarct geometry (Table). Thus, in IPT pigs the reduction in infarct mass over time was principally due to infarct thinning. In contrast, in the IPT pigs it was principally due to decreases in circumference and longitudinal length (both p<0.05) with no significant change in infarct thickness. Subsequently, histological scoring of myofibroblasts in the infarct zone revealed an increase in myofibroblasts in IPT animals (10.9±2.1%) compared to controls (5.4±1.6%, p<0.05).

Conclusions: IPT favorably modified infarct remodeling, likely by enhancing myofibroblast numbers in the infarct zone.
Gender differences in major bleeding with bivalirudin versus heparin during primary PCI in Acute Myocardial Infarction: results from the HORIZONS-AMI trial

J. Yu, R. Mehran1, L. Grinfeld2, K. Xu4, M. Fahy3, E. Nikolsky6, B.R. Brode4, A.J. Lansky3, G.D. Dangas4, G.W. Stone3,1, Mount Sinai Medical Center, New York, United States of America;2Mount Sinai Medical Center and the Cardiovascular Research Foundation, New York, New York, United States of America;3Italian Hospital of Buenos Aires, Buenos Aires, Argentina;4Cardiovascular Research Foundation, New York, United States of America;5Rambam Medical Center, Haifa, Israel;6LeBauer Cardiovascular Research Foundation, Greensboro, United States of America;7Yale University School of Medicine, New Haven, United States of America;8Columbia University Medical Center and the Cardiovascular Research Foundation, New York, United States of America

Purpose: Previous studies have shown that women are at increased bleeding risk post AMI and primary PCI. Bivalirudin (BIV) has been shown to reduce bleeding complications compared with heparin plus glycoprotein IIb/IIIa inhibitor (HEP + GPI). The purpose of this study was to examine the differential impact of BIV on short- and long-term outcomes (>1 year) in women vs. men.

Methods: We examined 3-year outcomes from the HORIZONS-AMI trial according to sex and assignment to BIV vs. HEP + GPI. We used Cox proportional-hazards methods with stepwise selection using entry and exit criteria of p < 0.1 to determine the independent predictors of major bleeding among women. Candidate variables tested were assignment to BIV vs. HEP + GPI, age, gender, hypertension, history of smoking, prior MI, prior PCI, CABG, Killip class >1, baseline creatinine, creatinine, radial vs. femoral access, and symptom onset to balloon time.

Results: Women (n=842), as compared with men (n=2760), were significantly older and had higher prevalence of hypertension and hyperlipidemia but were less likely to have a prior history of MI, PCI, CABG or smoking (all p < 0.05). BIV was associated with reduced in-hospital and 30-day major bleeding in both men and women (all p < 0.05). At 3 years, men receiving BIV compared with HEP + GPI had reduced major bleeding (5.3% vs. 9.1%, p=0.0002), however the difference among women did not reach statistical significance (12.3% vs. 15.1%, p=0.16). After multivariable analysis, randomization to BIV vs. HEP + GPI showed a trend towards reduced major bleeding among women (Figure 1).

Conclusions: In the HORIZONS-AMI trial, BIV significantly reduced short-term and long-term bleeding in men and 3-year bleeding in men. Among women, BIV was associated with a trend toward reduced 3-year bleeding.

ADVANCES IN NON-ST ELEVATION MYOCARDIAL INFARCTION ACUTE CORONARY SYNDROMES – DIAGNOSTICS AND TREATMENT

Prospective evaluation of the diagnostic accuracy of the novel ESC 2011 guidelines for rapid rule-out of NSTEMI using high sensitive cardiac troponin T


Purpose: High-sensitive cardiac troponin (hs-cTn) assays have been shown to significantly improve the early diagnosis of acute myocardial infarction. The novel 2011 ESC guidelines for the management of acute coronary syndromes in patients with persistent ST-segment elevation contain for the first time a new fast track rule-out protocol including hs-cTn. We intended to verify the safety of this fast track protocol in our prospective study setting.

Methods: Out of our ongoing prospective international multicenter study 1871 consecutive patients who presented with symptoms suggestive of acute myocardial infarction and absence of significant ST-elevations in the ECG were included. The final diagnosis was adjudicated by two independent cardiologists using all available informations including high sensitive cardiac Troponin T (Roche). We examined the diagnostic accuracy of the novel ESC rapid rule-out protocol using the Roche high sensitive cardiac troponin T (Roche) 99th percentile defined as 0.014 μg/L performed on blood samples obtained in the emergency department and after 3 hours according to the novel guidelines. All patients were divided in line with the ESC algorithm into the subgroups of late presenters with chest pain onset/maximum (CPM) ≥ 6 hours and early presenters with CPM < 6 hours. In the former group rapid rule-out was based on a single measurement using hs-cTnT, and in the latter group on two hs-cTnT values, at presentation and at 3 hours.

Results: Of all late presenters (n=169), 19% (n=117) received the final diagnosis of NSTEMI, compared to 17% (n=214) of early presenters (n=1526). Six late presenters and two early presenters with the final diagnosis of NSTEMI had hs-cTnT levels below the cutoff of 0.014 μg/L. The overall negative predictive value (NPV) applying only the hs-cTnT cut points was for CPM < 6h: 98.4% (95% CI 96.6 to 99.4%) and for CPM ≤ 6h: 99.4% (95% CI 97.9 to 99.9%). As one of late presenters had a GRADE score = 140 and two other were not found as NSTEMI when the troponin became available after one hour, the NPV increased to 99.2% in this subgroup.

Conclusions: Using a high sensitive assay for troponin T, the novel ESC guidelines provide an effective way of rapid rule-out of NSTEMI with a very high however not perfect negative predictive value. These results indicate some room for improvement of the algorithm.

ClinicalTrials.gov number: NCT00740878.
recommendations on secondary prevention (9 studies) and pharmacological interventions (29 studies) were based on the largest amount of non-gov't/industry sponsorship (100% and 93%), compared with bleeding complications (9 studies) and revascularization interventions (29 studies) were based on the largest amount of non-gov't/industry sponsorship (100% and 93%), compared with bleeding complications (9 studies). The study of the incidence and prevalence of non-ST elevation myocardial infarction (NSTEMI) in the elderly patients presenting to our hospital emergency department with an age ≥70 years. Patients with STElevation acute coronary syndrome (STEMI), hospital admission for acute coronary syndrome (ACS), heart surgery or percutaneous coronary intervention within 3 months prior to the index hospital stay were excluded. Measurement of hs-cTnT ([Elecsys Troponin T high-sensitive, Mannheim, Germany]) was performed in a blinded fashion on admission and after 3 hours. Echocardiography was used to rule in or rule out differential diagnosis in all patients. The final diagnosis was adjudicated by two independent cardiologists after reviewing all available medical records.

Results: Among 307 recruited patients (mean age 81±6 years), 206 (67%) patients had elevated hs-cTnT levels (≤0.014 μg/L). 45 (15%) of all patients had a history of non-ACS-condition. The median time from symptom onset to admission was not significantly different between both groups (4.1 vs. 4.7 h, p≥0.06). 36% of non-ACS-patients had heart failure, 20% rhythm disorders, 19% severe renal insufficiency, 11% hypertensive heart disease, 6% valve disease, 4% endo-mycardiac and 4% sepsis. Using hs-cTnT levels obtained at 3 hours after admission, the sensitivity was 93.6% and the negative predictive value was 97.1% to rule-out NSTEMI. The diagnostic performance for the absolute hs-cTnT concentration - as quantified by the area under receiver operating characteristic curve (AUC) - significantly improved for serial measurements from 3 hours after admission (AUC 0.80 vs. 0.84, p<0.007). The diagnostic delta-changes detection was better than relatives changes in the entire study population (AUC 0.58 vs. 0.53, p=0.054).

Conclusions: Many elderly patients presenting to the emergency department revealed elevated hs-cTnT mainly due to non-ACS conditions. In elderly patients, a serial measurement in hs-cTnT from admission to 3 hours after admission was beneficial for an early diagnosis of NSTEMI.

P5060 Direct comparison of absolute and relative changes in high-sensitive cardiac troponin I in the early diagnosis of AMI


Background: The current guidelines for the diagnosis of acute myocardial infarction (AMI) require, especially in non-ST-elevation infarction, a rise and/or fall in the levels of cardiac troponin (cTn). We evaluated whether absolute or relative changes in high-sensitive cTn have a higher diagnostic accuracy.

Methods: In a prospective, observational, multicenter study, we analysed the diagnostic performance of absolute and relative changes in high-sensitive cTn as measured with a novel precommercial prototype assay (Siemens: LioT 0.5ng/L, 99th percentile 9ng/L and <10% CV at 3ng/L) in 1127 patients presenting to the emergency department with symptoms suggestive of AMI. Blood samples were collected at presentation and after 1, 2, 3 and 6 hours in a blinded fashion. The final diagnosis was adjudicated by two independent cardiologists using all available information including hs-cTnT (Roche) levels.

Results: Baseline high-sensitive cTn levels were higher in patients with AMI (16.4% of the cohort) than in patients with other diagnosis of chest pain (p<0.001).
The area under the receiver operating characteristic curve for diagnosing AMI was significantly higher for 1-, 2-, and 6-hour absolute changes versus relative changes in hs-TnT (Delta abs: AUC 0.840 [95% CI 0.790-0.900], 0.863 [0.834-0.932], 0.844 [0.809-0.878], and 0.866 [0.802-0.930]; Delta rel: AUC 0.711 [95% CI 0.667-0.754], 0.759 [0.709-0.809], 0.732 [0.672-0.792] and 0.744 [0.676-0.812]; p.<0.001 for the comparison). The receiver operating characteristic curve-derived cutoff values for 1-, 2-, and 6-hour absolute changes were 8.5, 7.7, and 6.9 ng/l, all near the 95th percentile of the hs-TnT assay. Absolute changes at 2 hours were superior to relative changes in patients with both low and elevated baseline troponin levels. Combining the baseline troponin I levels with absolute and relative changes in a logistic regression performed even better in diagnosing AMI for absolute changes (1h: AUC 0.921 vs 0.864, 2h: 0.919 vs 0.866, 3h: 0.923 vs 0.858, 6h: 0.922 vs 0.860; p.<0.001 for all comparisons).

Conclusions: Absolute changes of high-sensitive cTnT levels showed a significantly higher diagnostic accuracy for AMI than relative changes, and seem therefore superior in the interpretation of the changes of elevated troponin levels regarding AMI.

Complementary intravenous Enoxaparin during percutaneous coronary interventions and NSTE-ACS. Is it necessary?


Objectives: To assess the incidence of thrombotic complications during percutaneous coronary intervention (PCI) in patients (n) with non ST elevation acute coronary syndrome (NSTEACS) pretreated with subcutaneous (sc) enoxaparin (ENX) with two different anticoagulation strategies.

Methods and Results: We analyzed two retrospective cohorts of patients with NSTEACS pretreated with sc ENX 1mg/kg and PCI performed within 8 hours after the last dose of ENX. Cohort 1 (C1) includes 48 patients with additional doses of ENX during PCI from 05/2009 to 12/2010. Cohort 2 (C2) includes 41 patients with additional doses of ENX after PCI from 01/2011 to 01/2012. We evaluated baseline, 10 minutes and 2 hours after iv ENX activated clotting time (ACT) and antiXa levels (antiXa). Thrombosis was defined as the detection of angiographically visible thrombus not present previously or macroscopic thrombus observed in the material in contact with the blood (guiding catheter or angioplasty guidewires) during the procedure that required specific treatment. The primary endpoint was the incidence of thrombosis (including catheters). Secondary endpoints: incidence of bleeding complications, in-hospital and 30 days death and non fatal acute myocardial infarction (AMI). Both groups had comparable baseline characteristics. The proportion of patients with no differences in basal levels of ACT or antiXa. The incidence of thrombosis was 37.5% (18/48) in C1 versus 2.4% (1/41) in C2 (p=0.007; OR 0.058). There were no bleeding complications in either group nor any differences in mortality (3.2% C1 vs 2.4% C2) or AMI (2.2% C1 vs 0% C2) at 30 days. There was a greater need for additional doses of unfractonated heparin and/or ENX during PCI in C1 (31% C1 versus 2.4%,C2). In C2 antXa level 10 minutes after bolus administration was 1.45±0.05 and 2 hours after was 1.13±0.40. In C2 ACT level 10 minutes after bolus administration was 189±49 sec. In the multivariate analysis, the administration of bolus of ENX (p=0.011; OR 0.019) showed a protective effect while the total duration of the procedure (p=0.014; OR 1.034) was related to thrombotic complications and 7 complications.

Conclusions: A high incidence of thrombotic complications occurs during PCI performed within 8 hours after the last dose of sc ENX in patients with NSTEACS. The intravenous administration of an additional ENX bolus of 0.75mg/kg at the beginning of the PCI significantly reduces the incidence of such complications while AntiXa levels observed after this extra bolus are within the safety range reported in previous studies.

Early diagnosis of acute myocardial infarction in patients with kidney disease using more sensitive cardiac troponin assays

R. Twernbold1, T. Reichen2, M. Reiter1, P.H. Haaf1, K. Wildi1, M. Potocki1, S. Oswald1, C.H. Mueller1,2, University Hospital Basel, Basel, Switzerland;3Brigham and Women’s Hospital, Department of Medicine, Cardiovascular Division, Boston, United States of America

Purpose: The rapid and reliable diagnosis of acute myocardial infarction (AMI) is a major unmet clinical need, particularly in patients with kidney disease (KD), who are known to have elevated levels of cardiac troponins (cTn) already in the absence of AMI, which may lead to a lower diagnostic value of cTn in this high-risk subgroup.

Methods: We conducted an international multicenter study to examine the diagnostic accuracy of new, more sensitive cTn assays in 1291 consecutive patients presenting to the ED with symptoms suggestive of AMI, of whom 186 (14%) were enrolled in the study to determine how to (MDRD GFR <60ml/min/1.73m2). cTn levels were determined in a blinded fashion using three sensitive assays (Roche high-sensitive Troponin I (hs-TnI), Siemens Troponin I Ultra (Tn Ultra), Abbott-Architect Troponin I (Tn Abbotti)) and a standard assay (Roche Troponin T (TnT)). The final diagnosis was adjudicated by two independent cardiologists based on hs-TnT.

Results: AMI was the final diagnosis in 33% (n=61) of all KD-patients as compared to 17% in patients with normal kidney function (p.<0.001). Among KD-patients, hs-TnI levels were significantly higher in AMI compared to non-AMI patients (p<0.001). When using hs-TnI cutoffs with 99th percentile with hs-TnI in 67%, with Tn Ultra in 16% and Tn Abbotti in 12%. In patients with KD the diagnostic accuracy at presentation, quantified by the area under the receiver-operator-characteristic curve (AUC), was significantly

910 Advances in non-ST elevation myocardial infarction acute coronary syndromes – diagnostics and treatment

Cardiac magnetic resonance tissue characterization in the acute and chronic phase of reperfused Non-ST elevation myocardial infarction

M. Mariyadas, T. Walcher, W. Rottbauer, P. Bernhardt. University of Ulm, Faculty of Medicine, Department of Internal Medicine II, Cardiology, Ulm, Germany

Background: In ST elevation myocardial infarction cardiac magnetic resonance (CMR) tissue characterization has been described in details. However, little is known about acute infarct area, microvascular obstruction (MVO), area at risk and papillary muscle involvement in the acute and chronic phase in non-ST elevation myocardial infarction (NSTEMI). Aim of our prospective study was to evaluate and compare tissue characteristics in the acute and chronic NSTEMI.

Methods: Forty NSTEMI patients who were revascularized within 48 hours after symptom onset were enrolled into the study. CMR at 1.5T (Philips Medical Systems) was performed within 3-5 days and 3 months after symptom start. Left ventricular volumes were calculated using a short axis cine stack. Area at risk was visualized in a 3D T2-weighted sequence in the same contiguous short axis orientation. Ten minutes after application of 0.2 mmol/kg gadolinium-based contrast agent (Dotarem, Guerbet) a 3D late gadolinium enhancement (LGE) sequence in the same orientation for evaluation of infarct size, MVO and papillary muscle involvement.

Results: Median age of the patients was 62.5±12.9 years, N=9 (22.5%) were female. The area at risk as determined using a 2-standard deviation threshold was 29.1±20.4 g. LGE revealed a significantly larger infarct size in the acute in comparison to the chronic phase (22.5±17.7 vs. 15.9±13.9 g, p=0.0003). In 6 (15%) patients presence of papillary muscle involvement was detected which was associated with larger infarct size in comparison to patients without papillary muscle involvement (45.3±21.8 g vs. 16.5±13.7 g, p=0.003). MVO could be visualized in 16 (40%) patients in the acute phase and 7 (17.5%) after 3 months. MVO was significantly reduced at follow-up in comparison to baseline (0.2±0.6 g vs. 1.2±3.2 g, p=0.05) and was associated with larger infarct size (30.1±22.1 g vs. 17.5±12.5 g, p=0.025). Infarct size negative correlated with increase of ejection fraction at follow-up (r=-0.56, p=0.0002).

Conclusion: CMR provides a lot of information about myocardial tissue characteristics in NSTEMI patients. MVO and papillary muscle involvement correlate with infarct size. Further studies are warranted to prove clinical significance of described characteristics.
greater for the sensitive cTn-assays compared to the standard assay (AUC for hs-TnT, 0.88; Tnt Ultra, 0.89; and Tni Abbott, 0.89 vs. AUC for the standard assay, 0.83, p<0.05 for all comparisons). In patients presenting within three hours after the onset of chest pain, Tnt Ultra (AUC 0.90) and Tni Abbott (AUC 0.93) were superior to hs-TnT (AUC 0.82, p<0.05 and p=0.015 for comparisons, respectively) and TnT4 (AUC 0.73, p<0.01 for both comparisons), whereas hs-TnT no longer performed superior to TnT4 (p=0.07). Using the predefined 99th-percentile cutoff of the sensitive cTn-assays, specificity and diagnostic accuracy was significantly reduced in KD-patients compared to the subgroup with normal kidney function, whereas sensitivity remained similar.

Conclusions: Sensitive cTn-assays have high diagnostic accuracy also in KD and are superior to conventional cTn-assays. In addition, there seems to be a difference among the sensitive assays in the early presenters with a higher diagnostic accuracy of TnT Ultra and Tni Abbott as compared to hs-TnT. Mid elevations are common in non-AI-MI patients and test-specific optimal cut-off levels tend to be higher in KD-patients than in patients with normal kidney function.

P5065 Use of troponin testing in internal emergency medicine

J. Searle1, A. Slagman2, J.O. Vollert1, H. Storchmann3, P. Oestereich3, R. Muller4, R. Koch5, R. Somasundaram5, M. Mockett6 on behalf of Biomarkers in Cardiology. 1Charité - Department of Cardiology CVK and Emergency Medicine CVK, CCM, Berlin, Germany; 2Charité - Campus Virchow-Klinikum, Department of Cardiology, Berlin, Germany; 3Charité - University Medicine Berlin, Department of IT, Berlin, Germany; 4James Cook University, Townsville, Australia; 5Charité - University Medicine, Campus Benjamin Franklin, Emergency Medicine, Berlin, Germany

Purpose: Troponin is recommended as the preferred biomarker for the diagnosis and risk stratification of non-ST myocardial infarction (NSTEMI). Per definition, the diagnosis AMI requires not only a positive test result but also corresponding signs and symptoms. We analyzed the association of chief complaint, cardiac main hospital diagnoses and troponin testing in two large EDs over a one-year period to evaluate its use in Emergency Medicine.

Methods: Data of all 34,333 patients who presented to either one of the two EDs were retrieved from the hospital information system. The patient’s chief complaint was documented in the electronic ED form by the treating physician.

Results: Troponin testing was performed in 38.1% (n=13,071) of all patients. Of these, 23.3% presented with chest pain, 10.4% with dyspnoea, 5.8% with abdominal pain, 3.3% with headache. The vast majority (57.1%) presented without one of these pre-defined chief complaints.

Of all patient tested, 10.4% had a positive test result at admission, of these 24.6% with chest pain, 22.1% with dyspnoea, 2.5% with abdominal pain, 0.6% with headache and 50.2% without any of these symptoms. Even though 52.3% had a cardiac main hospital diagnosis, only 4.6% were diagnosed with a NSTEMI and 2.5% with a STEMI.

Conclusion: Troponin was tested in almost 40% of the patients at admission to the ED, a quarter of those tested presented with chest pain. A total of 10% of patients tested had a positive troponin result at admission and only 7% were finally diagnosed with acute myocardial infarction. Troponin testing requires a clear indication and should not be used as a screening test in patients with a well justifiable reason to suspect ACS.
Abstract P5068: Reduction of medical consumption in low risk chest pain patients

A. E. C. Kingma1, A. J. Six2, B. E. Backus1, M. J. M.ramer1, G. A. De Wit1, A. Mosterd3, P. J. Smedevaar1, P. A. Doevendans1
1Netherlands Red Cross Blood Transfusion Service, Amsterdam, Netherlands; 2Hague Medical Center, Department of Cardiology, Utrecht, the Netherlands; 3Zwolle Hoofdpolikliniek, Zwolle, the Netherlands.

Background: Patients with chest pain are often admitted for clinical observation, and treated as ACS awaiting final diagnosis. Consequently, unnecessary diagnostics and treatment are common. The HEART score serves the making of a quick diagnosis and consists of five elements: History, ECG, Age, Risk factors and Troponin.

Methods: This study was performed in 260 patients in three hospitals in the Netherlands. These patients were participating in a prospective validation study of the HEART score in 238 chest pain patients in the ED of ten hospitals. Numbers of hospitalization days, exercise tests, echocardiography and various other diagnostic and therapeutic evaluations were counted.

Results: Chest pain patients visiting the ED were classified as low-risk, based on the HEART score, in 100/260 (36.5%) of the cases. MACE did not occur in these 102 patients; the risk of MACE was 15/870 (1.7%) in the low HEART score group of the entire prospective study. Eighteen patients (17.6%) were hospitalized for a total of 28 days and additional cardiology work-up was done in 52 patients (51%). Numbers of examinations were: 27 (26.5%) exercise tests, 16 (15.7%) echocardiograms, 5 (5%) CT scans and 6 (5.9%) SPECT.

Conclusion: When a policy would be made to withhold redundant medicine in low-risk chest pain patients, with a HEART score ≤3, hospitalizations would be saved in one fifth and various examinations in half of the patients. Improved risk stratification in chest pain patients may result in a reduction of medical consumption.

Table 1

<table>
<thead>
<tr>
<th>Group A (N=216)</th>
<th>Group B (N=40)</th>
<th>Group C (N=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>61.1 ± 12.4</td>
<td>58.8 ± 12.4</td>
</tr>
<tr>
<td>RCA (n, %)</td>
<td>103 (47.7)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>Non-Proximal LAD (n, %)</td>
<td>60 (28.2)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td>Proximal LAD (n, %)</td>
<td>25 (11.6)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Ca (n, %)</td>
<td>25 (11.6)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>7.3 (2%)</td>
<td>3 (7.5%)</td>
</tr>
</tbody>
</table>

ST elevation measuring 2mm or more in two contiguous chest or limb leads respectively. **TW inversion/ST depression in two or more contiguous leads. Calculated with one way analysis of variance for age. Other values calculated by Rxy distribution.

Abstract P5069: A significant proportion of patients with acute coronary occlusion lack ST-elevation: implications for diagnosis and provision of primary angioplasty services

A. Appa1, A. Mahotra2, C. Alli1, R. Smith1, R. Lane1, T. Kabb1, M. Mason1, M. Whitbread3, C. Ilsley1, M. Dalby1, Narefield Hospital, London, United Kingdom; 2London Ambulance Service, London, United Kingdom

Purpose: Primary percutaneous coronary intervention (PCIPI) programmes vary in admission criteria from autonomous diagnosis with open access, to strict acceptance of ECG protocol positive (ST elevation or LBBB) cases. Rigid referral criteria may result in patients with acute coronary occlusions not receiving reperfusion therapy. We compared rates of coronary occlusion between ECG protocol positive and protocol positive cases in a cohort taken from our open access PCIPI service.

Methods: Presenting ECG, baseline characteristics, TIMI flow grades, peak creatine kinase levels, and mortality from 308 consecutive PPCI cases performed from 2004 to 2008 were reviewed. Patients were categorised according to the presenting ECG: group A with positive ECG protocol (ST elevation or LBBB), group B with echocardiographic evidence of acute MI, group C: minor changes/within normal limits.

Results: 216 (70%) cases were in group A, with 46 (15%) in group B, and 46 (15%) in group C. Prevalence of TIMI 0/1 flow was 75% for group A patients vs. 74% for group B (P=0.93), and 63% for group C (P=0.11). Median Peak CK rise was higher in group A than group C (9400 U/L vs 571 U/L, P<0.01), but was similar to group B (940 U/L vs 925 U/L, P=0.28). Age, vessel treated, and mortality are shown in the table. Cardiovascular risk factor prevalence did not differ between groups.

Conclusion: A significant minority of ECG protocol negative cases were found to have an acute vessel occlusion with comparable biomarker rises to the protocol positive group suggesting significant myocardial infarction.

Abstract P5070: Mitral annular excursion in patients with suspected non-ST-elevation acute coronary syndrome: an identify coronary occlusion and predict mortality

W. Zahid1, J. Johnson2, C. Westholm3, C. Eek1, R. Skulstad1, E. Fosse4, R. Winter1, T. Edvardsson1, 1Oslo University Hospital, Department of Cardiology, Oslo, Norway; 2Royal Institute of Technology, School of Technology and Health, Stockholm, Sweden; 3Karolinska University Hospital, Department of Clinical Physiological, Stockholm, Sweden; 4Oslo University Hospital, The Interventional Centre, Oslo, Norway; 5Karolinska Institute, Department of Medicine, Cardiology Unit, Stockholm, Sweden

Background: Many non-ST-elevation acute coronary syndrome (NSTE-ACS) patients have coronary occlusions but do not receive acute reperfusion therapy as the occlusion is not readily identified. Identification and closer follow up of high risk patients may reduce mortality. Mitral annular excursion (MAE) reflects the global longitudinal shortening deformation of the left ventricle (LV). We therefore hypothesized that MAE may differentiate between coronary occlusion and non-occlusion in NSTE-ACS patients, and predict mortality.

Methods: 167 patients were examined in relation to NSTE-ACS at two Scandinavian centers. 47 healthy individuals were used as controls. Tissue Doppler by echocardiography was done at the mitral level of the LV in three apical planes and a mean MAE value was acquired from a newly developed software (Gripping Heart AB, Stockholm, Sweden). Mortality data was collected over a mean period of 1477 days.

Results: MAE was significantly reduced in NSTE-ACS patients as compared to healthy individuals (9.5±2.1mm vs. 13.1±2.0mm, p<0.001), and at 10.9 mm identified the NSTE-ACS diagnosis with a sensitivity and specificity of 89% and 71%, respectively, area under curve (AUC) 0.89. In the NSTE-ACS population, 56 of 167 (34%) patients had coronary occlusions. MAE could differentiate between coronary occlusion artery (9.9±2.2mm and non-occlusion (10.0±2.0mm, p=0.003), and MAE of 9.2 mm yielded sensitivity and specificity levels of 68% and 61% respectively, AUC 0.65. During follow up, 22 patients died. Cox regression model gave a hazard ratio for MAE of 1.52 (95% CI 1.24-1.92), p<0.001.

Conclusion: MAE assessed by tissue Doppler echocardiography might be helpful in identifying NSTE-ACS patients at risk. MAE identified coronary occlusion and could predict mortality in patients with NSTE-ACS.

Abstract P5071: Risk stratification in non-ST-elevation Acute Coronary Syndromes: utility of both GRACE and CRUSADE models

J. Ferreira Santos, S. Goncalves, P. Amador, F. Seixo on behalf of Portuguese Registry of Acute Coronary Syndromes Investigators. Hospital Sao Bernardo, Setubal, Portugal

Background: According to ESC guidelines, patients (pts) presenting with non-ST-elevation acute coronary syndromes (NSTE-ACS) should have their prognosis and bleeding risk determined using established risk scores (RS), namely GRACE for in-hospital mortality and ischaemic events and CRUSADE RS for bleeding. However, the clinical implications and utility of combining both risk scores is less well established.

Aim: Evaluate how risk stratification combining GRACE and CRUSADE performs in pts with NSTE-ACS.

Methods: Analysed 1425 pts (66±13 years, 72% male) with NSTE-ACS, exclusively included in a nationwide registry. GRACE RS and CRUSADE RS at hospital admission were calculated for each patient and tested, respectively, for
predicting in-hospital death and major bleeding (defined using CRUSADE crite-
ria). Pts were divided according to low, intermediate or high risk of fatal events,
using GRACE RS (≤ 108, 109-140 or > 140, respectively) and then sub-stratified
into low, intermediate or high risk of major bleeding, according to CRUSADE RS
(≤31, 31-40 or >40, respectively). In-hospital pharmacological treatment, proce-
dures and events were compared between groups.
Results: GRACE and CRUSADE had a good performance in predicting in-
hospital death (AUC 0.880, p<0.001) and major bleeding (AUC 0.755, p<0.001).
respectively. Only 53% of pts had a concordant risk by both RS (table). Sub-
stratification using CRUSADE was useful for identifying major bleeding risk across
all categories of GRACE RS. Use of ib/Ilia inhibitors, fondaparinux and radial ac-
cess for catheterization diminished with increasing bleeding risk (p<0.001).
Conclusion: Both GRACE and CRUSADE RS have good performance for pre-
dicting in-hospital death and major bleeding, respectively. Half of NSTE-ACS pts
have a discordant fatal and bleeding risk. CRUSADE RS can be used for identi-
fying pts at risk of bleeding events, independently of risk estimated with GRACE
RS.

**P5072** Rapid rule-out of NSTEMI by using a high sensitive
prototype assay for troponin I: a prospective evaluation of the safety of the novel ESC 2011
guidelines

B. Moehring, R. Twenbohl, K. Widi, N. Arena, T. Mosimann, C. Zellweger, T. Reichlin, M. Reiter, P. Haal, C. Mueller. University Hospital Basel, Department of Cardiology, Basel, Switzerland

Purpose: High-sensitive cardiac troponin (hs-cTn) assays have been shown to signifi-
cantly improve the early diagnosis of acute myocardial infarction. The novel 2011
ESC guidelines for the management of acute coronary syndromes in pa-

entients without persistent ST-segment elevation contain for the first time a new fast
track rule-out protocol including hs-cTn. We intended to verify the safety of this
fast track protocol in our prospective study setting.

Methods: Out of our ongoing prospective international multicenter study 1102
consecutive patients who presented with symptoms suggestive of acute myocar-
dial infarction and absence of significant ST-elevations in the ECG were included.
The final diagnosis was adjudicated by two independent cardiologists using all
available informations including high sensitive cardiac Troponin T (Roche). We
examined the diagnostic accuracy of the novel ESC rapid rule-out protocol using
the pre-commercial Beckman Coulter high sensitive cardiac troponin I assay (hs-
cTnl, 99th percentile defined as 9.2 ng/l) performed on blood samples obtained
in the emergency department at presentation and after 3 hours according to the
novel guidelines. All patients were divided in line with the ESC algorithm into the
subgroups of late presenters with chest pain onset/maximum (CPM) ≤ 6 hours and early presenters with CPM > 6 hours. In the former group, rapid rule-out was
based on a single measurement using hs-cTnI and in the latter group, on two
hs-cTnI values, at presentation and at 3 hours.

Results: Of all late presenters (n=393), 17% (n=67) received the final diagnosis
of NSTEMI, compared to 15% (n=104) of early presenters (n=709). Three late
presenters and three early presenters with the final diagnosis of NSTEMI had hs-cTnl levels below the cutoff of 9.2 ng/l. The overall negative predictive value
(NPV) approached only the hs-cTnl criteria was found for CPM ≤ 99.7% (95% CI 96.3 to
99.7%) and for CPM > 6h 98.7% (95% CI 96.3 to 99.7%). All missed patients had
a GRACE Score below 140. As two late and two early presenters were not free of
symptoms at the point of time when the decisive troponin became available, the
NPV increased to 99.6% in both subgroups.

Conclusions: Using a novel high sensitive prototype assay for troponin I, the 2nd
hour rule-out provides an effective way of rapid rule-out of NSTEMI with a
very high however not perfect negative predictive value. (ClinicalTrials.gov num-
ber, NCT00470587)

**P5073** The nature and clinical outcomes of total occlusion in
non-ST elevation myocardial infarction; is it bad or good?

B.-H. Hwang, K.Y. Chang, K.B. Seung, Y.S. Koh, L.J. Choi, S.M. Lim, J.J. Kim, M.O. Chang, M.G. Kang, J.E. Lee. The Catholic University of Korea, St. Mary’s Hospital, Seoul, Korea, Republic of

Background and Objectives: Non-ST-elevation MI is a different disease entity from ST-elevation MI. But while undergoing coronary angiography, there are les-
ions in NSTEMI with TIMI grade 0, showing near total occlusion. Our objectives
are to get a knowledge in these situations.

Subjects and Methods: In 2011, 5694 patients were registered in COREA-AMI (COnvergent REgistry of aTholic and chonnAm university for AMI) registry. 2324
patients were NSTEMI, and we divided these patients into two groups, based on
TIMI grade 0. Occluded lesion was defined as a lesion with > 100% stenosis, or
TIMI flow 0. 1009 patients had occluded lesion, and 1315 patients had non-
occluded lesion. We compared baseline characteristics, ECG findings, in-hospital

treatment, and long-term outcomes between patients with and without occluded
culprit arteries.

Results: In baseline characteristics, initial creatine level, peak troponin before
PCI, initial ejection fraction in echocardiography, total stent length, follow-
up hsCRP showed significant difference between two groups. Also former as-

pin, statin, metformin use was different between two groups. Total occlusion in
NSTEMI was frequent in left circumflex artery. Using multivariate cox-regression
analysis, the hazard ratio for occluded infarct artery was 1.67 (95% confidence
interval 1.30-2.10, p<0.001). Kaplan-Meier curve for median follow-up of 6 months
showed a significant difference between occluded and non-occluded lesion group.

Conclusion: In NSTEMI, occluded lesion showed poor outcome than non-
occluded lesion. The early diagnosis of am I is still a ques-
tion to solve, and the comparison between totally occluded NSTEMI and STEMI
will be studied soon.

**NEW INSIGHTS IN POST-MYOCARDIAL INFARCTION FOLLOW-UP**

**P5074** One-year risk of stroke following acute myocardial infarction

A. Ulvenstam, U. Kajermo, A. Modica, T. Mooe. Ostersund Hospital, Ostersund, Sweden

**Background:** Ischaemic stroke following acute myocardial infarction (AMI) is an important complication. It is unknown whether the risk has changed as

the treatment of AMI has improved during the last decade, particularly in terms of
antithrombotic, lipid lowering and reperfusion treatment. There is also conflicting
data about predictors of stroke risk.

**Objectives:** To obtain the one-year incidence of stroke following AMI, the Register
of Information and Knowledge about Swedish Heart Intensive Care Admissions
(RIKS-HIA) database for the years 1998 to 2008 was merged with the Swedish
National Patient Register (PAMR). The time period was studied by dividing the entire
time period into five separate periods. Independent predictors were identified using a
multivariable Cox proportional hazards regression model.

**Results:** Between 1998 and 2008, 7108 out of 172353 patients with AMI suffered
an ischaemic stroke within one year (4.1%). The years 2007/2008 were associated with a 21% relative risk reduction, com-
pared to the years 1998-2000, relative risk (RR) 0.79 (95% CI 0.73-0.85), p<0.001.

A reduced risk of stroke was also found for the years 2003/2004 and 2005-2006,
compared to 1998-2000, RR 0.86 (95% CI 0.80-0.93), p<0.001 and 0.81 (95% CI 0.75-0.88), p<0.001, respectively.

Independent predictors of stroke were age, female sex, STEMI, prior stroke, prior
diabetes mellitus, heart failure at admission and atrial fibrillation. Reperfusion
treatment with fibrinolysis and PCI and treatment with aspirin, P2Y12-inhibitors
and statins predicted a reduced risk of stroke.

**Conclusions:** The risk of ischaemic stroke within a year following myocardial
infarction is substantial but has clearly been reduced during the studied time period.
The predictive factors found correlate well with previous investigations. Reperfu-
sion treatment, thrombocyte aggregation inhibition and lipid lowering are the main
contributors to the observed risk reduction.

**P5075** Improving quality of care in the elderly after acute
myocardial infarction? The Myocardial Ischaemia
National Audit Project (MINAP) 2004 - 2009

C.P. Gale1, A.D. Simms2, B.A. Cattle2, P.D. Baxter1, D.R. Greenwood1, J. Dearfield2, L.R. Pearson1, K.A.A. Fox2, A.S. Hall1, R.M. West2. 1-Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; 2-University of Leeds, Leeds, United Kingdom; 3-University of Edinburg, Centre for Cardiovascular Science, Edinburgh, United Kingdom

**Purpose:** Recent evidence suggests improvements in provider care for acute my-

ocardial infarction (AMI) and significant reductions in in-hospital mortality across
all age groups. We investigate whether the impact of temporal advances in card-
diac care for the elderly with AMI extend beyond the hospital stay.

Methods: A mixed-effects regression analysis of the Myocardial Ischaemia Na-
tional Audit Project (MINAP) was performed stratified by STEMI/NSTEMI, sex, and age group on 30-day mortality and opportunity-based composite scores (OBCS) for aspirin, ACE-inhibitor, statin, β-blocker, and referral for cardiac reha-
bilition for 47542 patients with AMI between 2004 and 2009 from 215 hospitals in England and Wales.

Results: From 2004 to 2009 30-day mortality rates (95% CI) decreased: STEMI: 2004/5: 12.0% (11.7 to 12.3%); 2006/7: 10.8 (10.6 to 11.1); 2008/9: 9.6 (9.4 to 9.9); NSTEMI: 2004/5:10.1 (9.9 to 10.3); 2006/7: 8.8% (8.6 to 9.0%); 2009: 7.8% (7.7 to 8.0%). The proportion of patients with AMI achieving an OBCS >80% increased over time. 2004/5: 84.0%, 2006/7: 90.0%, 2009: 93.2%, P<0.001. The proportion of patients achieving an OBCS >80% was lower in females than males (P<0.001), and decreased with increasing age group for STEMI (P<0.001) and NSTEMI (P<0.001). Of patients ≥80 years, only females with STEMI did not show a significant reduction in 30-day mortality risk. Male STEMI and NSTEMI demonstrated significant reductions in 30-day mortality risk, except STEMI aged <65 years. For females, the only group to demonstrate a significant reduction in 30-day mortality risk were those aged ≥80 years with NSTEMI.

Conclusions: In England and Wales, for patients hospitalized with AMI there are sex- and age-dependent differences in temporal improvements in 30-day mortality risk. The proportion of patients with an OBCS >80% compared with inhospital mortality, equivalent temporal improvements in mortality do not appear to extend beyond the hospital stay for all groups of patients.

The rs12526453 polymorphism in intron of the PHACTR1 gene is associated with 5-year mortality of patients with ST-elevation myocardial infarction

A. Kozieradzka1, W. Pepiksi2, E. Waszkiewicz1, D. Maciorowska1, M. Olszewski1, M. Skawronska2, A. Niemcunowicz-Janica2, S. Dobrzycki2, W.J. Musial3, K.A. Kamiński1, M. Medical University of Białystok, Department of Cardiology, Białystok, Poland; 2Medical University of Białystok, Department of Forensic Medicine, Białystok, Poland; 3Medical University of Białystok, Department of Invasive Cardiology, Białystok, Poland

Purpose: The rs12526453 (C/G) is a single nucleotide polymorphism in intron of the PHACTR1 gene (phosphatase and actin regulator 1). It was shown to be associ-
ated with early-onset myocardial infarction in a genome-wide association study with cytosome as a risk allele (1). The mechanism, however, remains unknown. The aim of our study was to investigate the association of the polymorphism with 5-year overall mortality in patients with ST-elevation myocardial infarction (STEMI) treated invasively.

Methods: We included in our registry consecutive patients with STEMI treated with primary PCI who survived 48 hours from hospital admission. Genotyping was performed with a TaqMan SNP Genotyping Assay using the ABI 7500 Real Time PCR System (Applied Biosystems). The analyzed end-point was all-cause mortality with a mean follow-up of 3 years.

Results: The study group comprised 629 patients (mean age 62.6±12 years; 25% of females, n=157; TIMI 3 obtained in 93.1% of patients, n=586). The per-
centages of CC, CG and GG genotypes were: 10% (n=63), 44.7% (n=281) and 45.3% (n=285), respectively. No significant differences in clinical characteristics were found between the genotypes. The 5-year total mortality was 16.2% (n=105). Of 285 (n=16) of CC high-risk homoyzogotes, 16.4% (n=44) of heterozygotes and 13.3% (n=38) of GG homozygotes (Figure 1). The difference was statistically significant (p<0.009, log-rank test).

Conclusions: The CC genotype of the rs12526453 polymorphism in intron of the PHACTR1 gene is associated with increased 5-year mortality in patients with STEMI treated invasively.

New insights in post-myocardial infarction follow-up

M. Olszewska1, M. Skawronska2, A. Niemcunowicz-Janica2, S. Dobrzycki2, W.J. Musial3, K.A. Kamiński1, M. Medical University of Białystok, Department of Cardiology, Białystok, Poland; 2Medical University of Białystok, Department of Forensic Medicine, Białystok, Poland; 3Medical University of Białystok, Department of Invasive Cardiology, Białystok, Poland

Age (years) 71 64 <0.01
PriOR (%) 13.0 18.8 <0.01
PriOR CABG (%) 6.3 7.7 <0.02
PriOR stroke (%) 5.7 5.8 <0.96
Primary PCI in STEMI (%) 95.9 96.6 ns
Primary PCI in NSTEMI (%) 65.6 68.1 ns
Known diabetes mellitus (%) 30.2 23.1 <0.01
Duration of known diabetes (years) 10 7 <0.01
Hospital mortality (%) 2.6 2.2 <0.02
Results of OGGT
Newly diagnosed diabetes (%) 19.7 15.3 <0.01
Newly diagnosed IGT/IFG (%) 18.1 23.1 <0.01
Diabetes IGT/IFG (%) 68.0 60.5 <0.01
3-year mortality (%) 30.0 35.4 <0.05
– newly diagnosed 30.5 21.8 <0.05
– IGT/IFG 13.2 11.3 ns
– no diabetes 10.8 11.2 ns

Conclusion: Although the prevalence of known diabetes was already much higher in females, the rate of newly diagnosed diabetes was significantly in-
creased in females as compared to males. Females with newly diagnosed di-
babetes had the same 3-year mortality as those high risk patients with MI and already known diabetes.

The clinical significance of right ventricular dysfunction with or without pulmonary hypertension after acute myocardial infarction

D. Aronson, K. Shahar, H. Hammerman, R. Dragu, Rambam Health Care Campus, Haifa, Israel

Background: Right ventricular (RV) dysfunction may accompany inferior wall in-
farction and is not uncommon in patients with acute anterior infarction. Pulmonary hypertension (PH) may exacerbate RV dysfunction (RVD). However, with severe RVD, pulmonary arterial pressure may decrease as a consequence of low RV output. We sought to determine the prognostic implications of RVD in relation to PH in acute myocardial infarction (AMI).

Methods: Echocardiography was performed in 1054 patients with AMI. RV func-
tion was assessed both visually and by measuring the RV fractional area change (RV-FAC). Patients were classified into 4 groups according to the presence or ab-
ence of pulmonary hypertension (estimated pulmonary artery systolic pressure >35 mmHg by echocardiography) and RVD (RV-FAC<35%). The primary end-
point was all-cause mortality with a mean follow-up of 3 years.

Results: RVD was present in 141 patients, with 91 (6.6%) and 50 (4.7%) patients with and without PH, respectively. Compared with patients with RVD without PH, patients with RVD and PH presented with higher Killip class (Killip class II or III: 48% vs. 14%; P<0.01) and were more likely to have reduced left ven-
tricular (LV) systolic function (LV ejection fraction<45%: 71% vs. 44%; P<0.01).


High 3-year-mortality rates in females with newly diagnosed diabetes after acute STEMI and NSTEMI in clinical practice in Germany: results of the Sweetheart-registry

A.K. Gitt1, F. Towa2, E. Deeg3, A. Papp2, U. Zeymer1, J. Senges1, R. Zahm1 on behalf of SWEETHEART-Study-Group. 1Herzzentrum Ludwigshafen, Institut f. Herzinfarktkrankenheiten der Univ. Heidelberg, Ludwigshafen am Rhein, Germany; 2Herzzentrum Ludwigshafen, Ludwigshafen, Germany; 3Institut f. Herzinfarktkrankenheiten der Univ. Heidelberg, Ludwigshafen, Germany

Background: Many patients with coronary artery disease suffer from diabetes and/or its pre-states. Joint guidelines of the ESC and the EASO recommend testing for diabetes using OGTT in patients with established CAD and without previously known diabetes.

Methods: Since 2007, 2,767 consecutive patients with STEMI or NSTEMI were enrolled into the Mi-registry SWEETHEART to identify abnormal glucose metabolism and to document acute treatment and outcome. In patients with pre-
viously unknown diabetes, oral glucose tolerance test (OGTT) was performed at day 4 after acute MI. We examined gender differences in the prevalence of abnormal glucose metabolism and the impact of newly diagnosed diabetes on 3-year-mortality of MI.

Results: Female patients with MI were older, less often had prior MI and prior PCI as compared to males. Female patients had a higher rate of known diabetes as well as a longer duration of diabetes at the time of MI. The prevalence of newly diagnosed impaired glucose metabolism was much higher in females than in males. In females, OGTT identified another 19.8% with manifest diabetes and 18.1% with impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) as compared to 15.3% and 23.3% in males respectively. After 3 years of follow up, female patients with newly diagnosed diabetes had a 30.5% mortality similar to that of females with already known diabetes (30.0%).
The results of a multivariable Cox regression model are shown in the Figure. Patients with RVD and normal pulmonary pressures had the highest adjusted risk for mortality.

Conclusion: Patients with RVD without PH are at a particularly high risk for mortality despite better LV systolic function. These results emphasize the importance of interpreting RV function in combination with pulmonary pressures data.

One year outcome in HIV-infected patients with myocardial infarction

G. Molins1, J. Cottenet2, M. Zeller1, L. Lorgis1, C. Touzery1, H. Aube2, Y. Cottin1, C. Quraini1, 1University Hospital Center, Department of Cardiology, Dijon, France; 2University Hospital Center, Department of Medical Informatics, Dijon, France

Background: Risk of myocardial infarction (MI) in HIV infected patients is increased and short term prognosis is good. One year outcome remain to be determined in large scale study.

Methods: From the French nationwide hospital medical information database, all the consecutive patients hospitalized in the 1546 French hospital/clinics for myocardial infarction from 1st January 2005 to 31st December 2009 were included. We compared one year outcome between patients infected or not by HIV.

Results: Among the 628454 patients included, 1286 (0.2%) was infected by HIV. At one year of follow-up, we observed an increased rate of recurrent MI in HIV-infected patients than non-infected patients (14.9% vs 12.9%; p=0.02) and respectively 14.9% vs 11.3% (p<0.01) in a sub-group of patients matched for age, sex and type of MI (ratio 1:2).

Conclusion: From our large scale nationwide study, HIV patients have an increased risk of recurrent MI during follow-up, thus emphasizing the benefit of secondary prevention in such patients.

Accuracy of high-sensitive cardiac troponins for long-term mortality

P. Haas1, K. Wild1, M. Reiter1, C. Zellweger1, R. Twereh1, R. Hoeller1, T. Reichlin1, M. Rubini Gimenez2, B. Moehring1, C. Mueller1, 1University Hospital Basel, Department of Cardiology, Basel, Switzerland; 2University Hospital Basel, Department of Internal Medicine, Basel, Switzerland

Background: Several high-sensitive cardiac troponins (hs-cTn) have recently been introduced. It is unknown which hs-cTn is most accurate for long-term prognosis and whether early changes improve prognostic accuracy.

Methods: In a prospective, international multicenter study, hs-cTn was measured with three assays (hs-cTnT, Roche Diagnostics; hs-cTnI, Beckman-Coulter; hs-cTnI, Siemens) in a blinded fashion at presentation and 1 hour later in 849 unselected patients with acute chest pain. Patients were followed-up 2 years regarding mortality.

Results: Acute myocardial infarction was the adjudicated final diagnosis in 150 (17.7%) patients. 62 (7.3%) patients died during the first 2 years. The prognostic accuracy of hs-cTnT (Roche Diagnostics) at presentation for mortality in the first 2 years as quantified by the area under the ROC curve (AUC) was 0.756 (95% CI 0.726-0.785) and outperformed both hs-cTnI (Beckmann-Coulter) 0.704 (95% CI 0.672-0.734; p=0.029 for comparison) and hs-cTnI (Siemens) 0.687 (95% CI 0.653-0.718; p=0.010 for comparison) (Figure 1). Absolute changes in the first hour of hs-cTnT were more accurate than relative changes (AUC 0.660; 95% CI 0.627-0.692 vs. 0.512; 95% CI 0.477-0.548; p=0.035 for comparison) (Figure 2).

Conclusion: Hs-cTnT seems to be more accurate than hs-cTnI in the prediction of long-term mortality. Absolute changes outperformed relative changes in the first hour as to long-term mortality in all three hs-cTn assays but were inferior to respective presentation values.

Large differences between patients with acute myocardial infarction included in two Swedish health registers

S. Aspberg1, T. Kahan1, M. Koster2, U. Stenestrand1, 1Karolinska Institute, Danderyd Hospital, Department of Clinical Sciences, Stockholm, Sweden; 2National board of Health and Welfare, Unit for Statistics on Public Health and Social Care, Stockholm, Sweden; 3Deceased, former Department of Medical and Health Sciences, Div. of Cardiology, University Hospital, Linkoping, Sweden

Background: Acute myocardial infarction (MI) is a leading cause for morbidity and mortality in Sweden. We aimed to compare patients with an acute MI included in the Register of information and knowledge about Swedish heart intensive care admissions (RIKS-HIA, now included in the register Swedeheart), and the Swedish statistics of acute myocardial infarctions (S-AMI).

Methods: Population based register study including RIKS-HIA, S-AMI, the National patient register and the Cause of death register. Odds ratios were determined by logistic regression analysis.

Results: From 2001 to 2007, 114 311 cases in RIKS-HIA and 198 693 cases in S-AMI were included with a discharge diagnosis of an acute MI. Linkage was possible for 110 958 cases. These cases were younger, more often males, had less concomitant diseases and were more often treated with invasive coronary artery procedures than patients included in S-AMI only. There were substantial regional differences in proportions of patients reported to RIKS-HIA.

Conclusion: Approximately half of all patients with an acute MI are included in RIKS-HIA. They represent a relatively more healthy population than patients included in S-AMI only. These limitations are important to know about since the register has become increasingly important in international research. S-AMI covers almost all patients with an acute MI but has limited information about the patients. Used in combination these two registers can give better prerequisites for improved quality of care of all patients with acute coronary syndromes.
Non-ST-segment elevation acute coronary syndrome caused by the left main stem stenosis - impact of multivessel diseases on treatment strategy and 12-month. Analysis from the PL-ACS Registry

M. Gielerka1, M. Gasior1, M. Hawranek1, M. Tapi1, P. Buszman2, J. Kubic1, A. Lekston1, M. Zembal1, G. Opolski1, L. Polonski1 on behalf of PL-ACS investigators.1 Medical University of Silesia, Silesian Center for Heart Disease (SCHD), Zabrze, Poland; 2-American Heart of Poland, Katowice, Poland; 3-Nicolaus Copernicus University, Collegium Medicum, Department of Cardiology, Bydgoszcz, Poland; 4-Medical University of Warsaw, Warsaw, Poland

The aim was to analyze the impact of multivessel disease on 12-month mortality in patients with NSTE-ACS caused by LM stenosis.

Methods: All patients with NSTE-ACS caused by LM stenosis registered in the PL-ACS between 10.2003 and 11.2009 were included. Patients were divided into 4 groups according to the number of significantly stenosed vessels.

Results (table): In PL-ACS Registry 1654 (2.5%) pts from 65767 had NSTE-ACS caused by LM stenosis. As the number of stenosed vessels increased the percentage of pts treated by PCI decreased and by CABG raised. In-hospital and 12-month mortalities increased together with the number of stenosed vessels. After adjustment the number of significantly stenosed vessels remains significantly associated with higher 12-month mortality (relative risk = 1.14, 95% CI = 1.01-1.29, p=0.036).

Conclusion: The implementation of this universal health plan in Chile was associated with an increase in 1-year survival in AMI patients. This has been achieved through a better use of evidence based medicine and repurification strategies. This effort has contributed to improving inequity in the health care attention of AMI patients.

Prognostic factors in chest pain patients: a quantitative analysis of the HEART score

B.E. Backus1, A.J. Six2, P.A. Doevendans1, J.C. Kelder3, E.W. Steyerberg1, Y. Vergouwe4.1 University Medical Center Utrecht, Department of Cardiology, Utrecht, Netherlands; 2 Zuwe Holpoot Hospital, Woerden, Netherlands; 3 St Antonius Hospital, Department of Cardiology, Nieuwegein, Netherlands; 4 Erasmus Medical Center, Rotterdam, Netherlands

Purpose: Risk stratification for chest pain patients at the emergency department is recommended in several guidelines. The HEART score is based on medical literature and expert opinion and calculates the risk of a major adverse cardiac event (MACE). We aimed to assess the predictive effects of the five HEART components and to compare performance of the original HEART score with a model based on regression analysis.

Results and discussion: We analyzed prospectively collected data from 2388 patients, of whom 407 (17%) had a MACE within 6 weeks (AMI, PCI, CABG, significant stenosis with conservative treatment and death due to any cause). Univariate regression analysis showed the same set of predictors as used in the HEART score. An adjusted score was based on multivariable logistic regression analysis (HEART-adj), which showed slightly better calibration and discrimination than the HEART score (c-statistic HEART 0.83, HEART-adj 0.85). HEART-adj proved in a decision curve analysis to be clinically more useful than HEART for decision thresholds over 25% (figure 1). Nevertheless, the original HEART classified patients better than HEART-adj, when the predefined thresholds of 2.5% and 40% were applied (NRI=14.1%).

Occurrence of major bleeding during long-term follow up of unselected patients with STE vs NSTE Acute Coronary Syndromes

F. Vagnarelli, G. Malandi, N. Taglieri, F. Sempri, L. Cinti, G. Noscrini, P. Ortolani, S. Nanni, C. Raperazi, A. Branzi. University of Bologna, Institute of Cardiology, Bologna, Italy

Background: The occurrence of bleeding following ACS has been well described in clinical trials but little is known in the real world, especially in the long-term. Purpose: To evaluate bleeding rates during long-term follow-up of a large, unselected ACS population with particular reference to comparison between STE and NSTE.

Methods and results: We analyzed data from 2046 consecutive patients hospitalized in 2004-2005 were followed up for 5 years after discharge. In-hospital bleeding was classified as major or minor according to TIMI classification. Major bleeding (MB) occurred as defined as follows: requiring transfusion or surgery or hospitalization, reduction in haemoglobin of more than 5 g/dl or intracranial haemorrhage. Events were adjudicated by the Endpoint Committee and disagreements resolved by consensus.

Results: The mean age was 71.6 years. Patients with NSTE-ACS were older and had a higher prevalence of AF, Killip class III-IV and comorbidities compared to patients with STE-ACS. Patients in the latter group were more likely to be treated with Gp IIb-IIIa Inhibitors and to receive both aspirin and P2Y12 inhibitor (82% vs 64%, p<0.001). PPCI was performed in 84% of STE-ACS and 70% of NSTE-ACS were managed invasively. Overall, during the 5 years of follow-up there were 135 MB with no significant difference between STE and NSTE-ACS in any time period (figure). Of these, only 30 took place during the index hospitalization, whereas 105 occurred after discharge, raising from 1.5% in-hospital to 3.5% at 1 year and 7.9% at 5 years.
Purpose: To compare 5-year outcome of unselected patients with STE versus NSTE ACS in a real-world context of contemporary acute treatment and secondary prevention.

Methods: All consecutive patients with ACS admitted in 2004-2005 were enrolled. The main study endpoint was 5-year mortality. The Kaplan-Meyer method was used to analyze the occurrence of death. A landmark analysis was performed: 0-30 days, 30 days-1 year and from 1 year to 5 years.

Results: 2046 patients were enrolled (896 STE, 1150 NSTE). Patients in the former group were younger, had fewer comorbidities and more often received antithrombotic drugs/PCI. Of note, almost 70% of NSTE patients were managed invasively and given dual antiplatelet therapy at discharge. In the whole population 5-year all-cause mortality rate increased from 5.7% (in-h) to 9.6% (30d), reaching 21.1% at 1 year and 43.2% at 5 years. Figure 1 shows the Kaplan-Meyer curves up to 5 years. In the first 30 days the mortality is higher for STE but curves intersect at 1 year and 5-year mortality tends to be higher for NSTE without statistical significance. Landmark analysis displays a greater risk for NSTE after the first year (STE vs NSTE HR=0.67 95% CI 0.51-0.84, p=0.001).

Conclusion: Despite the extensive use of antithrombotic therapies and PCI, the rates of in-hospital MB are acceptably low in the real world and similar to those reported for trials of ACS. On the contrary occurrence of MB is still high in the long run and greater than shown in trials.

Conclusion: Despite increased use of PCI and medications, the late mortality of ACS has vastly declined thanks to interventional and pharmacological therapy. However there is growing evidence of high events in the long run, but data are mainly derived from large clinical trials. Studies addressing long term follow up of unselected patients with ACS are few and led to conflicting results.

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Results: In total 107 individuals developed non-surgery or surgery related bleeding (26.6%; n=402). Forty two (10.4%) developed in-hospital non-surgery related bleeding and forty two (10.4%) developed non-surgery related bleeding within 1 year after discharge. There were 7 (2.5%) TIMI major bleedings, 38 (9.5%) TIMI minor and 61 (15.2%) TIMI minimal non-surgery related bleedings. Most bleedings were due to gastrointestinal (GI) bleeding, 45.2% of the in-hospital bleedings and 54.8% of the follow up bleedings. Significantly more women developed GI bleedings (9.8% vs. 3.7%; P=0.013) during follow up. Otherwise no gender differences in bleeding incidence were found. No increased risk of mortality or ischemic events during follow up was found in patients who developed bleeding complications.

Conclusion: In a Swedish real life ACS population we found a substantial amount of bleeding complications during one year follow up. The majority of the non-surgery related bleedings were gastrointestinal and potentially preventable. In this relatively small cohort we could not verify earlier reported mortality risk associated with bleeding complications.

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Background: The criteria for pathological Q-waves after acute myocardial infarction (MI) have changed in recent years. Also, there is limited data regarding correlation of Q-wave regression and preservation of left ventricular fraction (LVEF) in patients with an initial Q-wave MI.

Methods: Standard 12 lead electrocardiogram (ECC) was recorded in 200 ST-elevated myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention. ECCs were recorded before and following PCI, as well as at 1, 4, 12 and 24 months of follow-up. Cardiac magnetic resonance imaging (CMR) examination was performed at 4±2 days after reperfusion and repeated after 4 and 24 months.

Results: The incidence of Q-wave MI according to the 2007 criteria was 58%, 1 hour after PCI. At 24 months of follow-up, 22% of patients with initial Q-wave MI displayed Q-wave regression. The “classic” ECG criteria showed strongest correlation with infarct size as measured by CMR. Patients with Q-wave MI had larger infarct size and lower LVEF on baseline CMR respectively (24±10% LV mass and 37±8% compared to patients with non-Q-wave MI (17±9% LV mass, p<0.01 and 45±6%, p<0.001). Patients with Q-wave regression displayed significantly larger LVEF improvement in 24 months (9±11%) as compared to both Q-wave MI (2±8%) as well as non-Q-wave MI (3±8%, p<0.04 for both comparisons).

Conclusion: Association of Q-waves with infarct size and LVEF is strongest when using the “classic” Q-wave criteria. Q-wave regression is associated with the largest improvement of LVEF over a 2 year follow-up.

Long-term prognosis estimation after acute coronary syndrome: is there a role for angiographic scores?

Background: Scoring systems are useful tools to assess the severity of coronary lesions and can provide prognostic information. We aimed to explore the association of Leaman Score (LS) and Duke Jeopardy Score (DJS) with 10-year mortality in univariate analysis revealed an independent association of LS with 10-year mortality (HR 1.06, 95% CI 1.01-1.12; p=0.018), not shown by the DJS (HR 1.03, 95%CI 0.92-1.14; p=0.06).

Conclusions: In this population of patients with ACS submitted to coronary angiography, both scores were associated with 10-year mortality in univariate analysis but only the Leaman score was an independent predictor of long-term mortality.

Table 1. Incidence of severe bleeding during hospital stay

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bleeding</td>
<td>98.3%</td>
<td>97.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.3%</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>Non-major bleed</td>
<td>1.4%</td>
<td>2.3%</td>
<td></td>
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</table>

Non-bleeding women had significantly higher mortality than non-bleeding men, both short- and long-term mortality, 7.7 vs 5.2% (p<0.001) in 4 d and 19.9 vs 13.9% (p<0.001) in one y. Major bleeding had a high impact on outcome in both women and men regarding mortality at 14d (36.6 vs 42.9%, p=0.211) and 1y (46.2 vs 53.9%, p=0.021) but without difference between the genders. In patients with a bleeding complication requiring transfusion or surgery there was an indication of higher mortality in men at 14 d (11.4 vs 8.2, p=0.03) and at 1y (28.5 vs 24.6 p=0.08).
Angiotensin receptor blockers as the first choice in patients with preserved left ventricular systolic function after acute myocardial infarction from the Korean Acute Myocardial Infarction Registry

J.H. Lee¹, J.K. Kang¹, S.Y. Jiang¹, M.H. Bae¹, D.H. Yang¹, H.S. Park¹, Y. Cho¹, S.C. Chae¹, M.H. Jeong¹, Y.J. Kim² on behalf of the Korean Acute Myocardial Infarction Registry. ¹Kyungpook National University Hospital, Daegu, Korea. Republic of; ²Chonnam National University Hospital, Gwangju, Korea, Republic of; ³Yeungnam University Hospital, Daegu, Korea, Republic of.

Purpose: It has not been known that the prognostic impact of angiotensin II receptor blockers (ARBs) compared with angiotensin-converting enzyme inhibitors (ACEIs) in reducing major adverse cardiovascular events (MACE) in patients with preserved left ventricular systolic function (LVFSF) after acute myocardial infarction (AMI).

Methods: Between November 2005 and January 2008, 5,012 ACEI- or ARB-naive patients with preserved LVFSF (LV ejection fraction more than 40% by 2D echocardiogram) after AMI were included from the Korea AMI Registry. Patients who had already received ACEIs or ARBs before hospitalization were excluded from this study. The 12-month MACEs were defined as death and non-fatal MI.

Results: The prescription rate of ARBs among these ACEI- or ARB-naive patients was 14% (10.6% for ACEIs). Before propensity score (PS) matching, there were no significant differences in the 12-month MACEs (3.9% versus 3.6%; p = 0.664) and mortality (3.2% versus 3.0%; p = 0.810) between ACEIs use and ARBs use. For each patient, a PS indicating the likelihood of using ARBs during hospitalization or at discharge was calculated using a non-parsimonious multivariable logistic regression model, and was used to 1:3 match the patients on ARBs with the patients on ACEIs, leaving 594 ARBs users versus 1,782 ACEIs users. The 12-month MACEs and mortality were assessed using matched logistic and Cox regression models. Compared with ACEIs, the ARBs significantly reduced 12-month MACEs (2.7% versus 4.9%; hazard ratio [HR] 0.540, 95% confidence interval [CI] 0.317–0.930; p = 0.023) and mortality (2.0% versus 3.8%; HR 0.525, 95%CI 0.284–0.969; p = 0.039).

Conclusions: In real-world practice, the 12-month MACEs and mortality were significantly higher in ACEIs users as compared with ARBs users in patients with preserved LVFSF after AMI.

Copeptin predicts long-term mortality in patients with non-st-elevation myocardial infarction

C. Liebertra¹, O. Doeri², S. Szardien³, C. Trodel³, C. Horstmann³, J. Rixe¹, D. Sedding², H. Moellmann¹, C. Hamm¹, H. Neef³.
¹Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany; ²Justus-Liebig University Giessen, Medical Clinic I, Cardiology, Giessen, Germany; ³Franz-Groedel Institute of the Kerckhoff Clinic Heart & Thorax Center, Bad Nauheim, Germany

Purpose: Copeptin has been shown to improve diagnostic sensitivity when used in combination with conventional measured cardiac troponin T (cTnT) in patients with suspected acute coronary syndrome (ACS). However, less is known about the predictive value of differences in patients with and without acute myocardial infarction. Therefore, in the present study we aimed to analyse the possible predictive value of copeptin in patients with Non-ST-Elevation myocardial infarction (NSTEMI) and unstable angina (UA).

Methods: 321 patients with suspected Non-ST-Elevation ACS (NSTE-ACS) were included in the study. Final diagnosis of NSTEMI was made in 201 patients (62.6%), 47 patients (14.7%) had unstable angina pectoris (UA). The remaining 33 patients (10.3%) were without coronary artery disease (CAD) documented by coronary angiography. Copeptin was measured on admission. Blood was taken immediately after admission and was sent to the laboratory for centrifugation and frozen stored at –80°C until assayed.

Results: Copeptin plasma levels were higher in patients with NSTEMI compared to patients with UA (16.6 pmol/ml IQR [10.7-35.6] vs. 13.2 pmol/ml IQR [7.8-30.8]; P=0.019). There was no difference in copeptin plasma concentrations in patients with UA compared to patients without documented CAD (17.2 pmol/ml IQR [10.7-34.4] vs. 13.7 pmol/ml IQR [8.6-31.7]; P=0.038). During 5-year follow-up 29 (14.4%) patients with NSTEMI, 6 (18.9%) patients with UA and 3 (9.0%) patients without CAD died. The mortality rate among patients with NSTEMI and copeptin plasma concentration ≥ 14.0 pmol/ml was higher during 5-year follow-up (LogRank 12.1; P=0.01, multivariable Cox-Ross (1.003-1.023; P=0.01). Excluding patients with NSTEMI from the analyses mortality did not differ in patients with copeptin plasma concentration ≥ 14.0 pmol/ml compared to patients with copeptin levels < 14.0 pmol/ml.

Conclusion: Copeptin has a predictive value for long-term mortality in patients with NSTE-ACS. However, this difference is restricted to patients with NSTEMI.

Prognostic implications of sleep duration in first months after ST-elevation myocardial infarction

F.M. Szymanski¹, G. Karpiński¹, A. Hrynkwiecz-Szymanska¹, A. Platek¹, M. Grabowska¹, F. Majstrak¹, K.J. Filipiak¹, G. Opolski¹, G. Opolski¹. ¹Medical University of Warsaw, 1st Department of Cardiology, Warsaw, Poland; ²Department of Cardiology, Hypertension and Internal Diseases, Medical University of Warsaw, Warsaw, Poland; ³Department of Cardiac Surgery, Medical University of Warsaw, Warsaw, Poland

Purpose: Too little or too much sleep are associated with adverse health outcomes including: hypertension, type 2 diabetes, obesity and poor self-rated health. The aim of this study was to assess the relationship between duration of sleep and all-cause mortality in ST-elevation myocardial infarction (STEMI) patients.

Methods: 407 consecutive patients (271 males), aged 36 to 79 years (mean age, 62.5 ±10.6 years), admitted to our department with diagnosis of STEMI, were enrolled in the study within 12 hours from the onset of symptoms. All patients were asked by telephone for sleep duration in first 3 months after discharged from the hospital. The primary endpoint was all-cause mortality. Response to follow-up was carried out as close to 2 years from the baseline interview. 28 patients were lost of follow-up and were not analyzed. Sleep duration was assessed by asking the study participants to give the habitual night sleep time: How many hours do you sleep usually each night? Patient response: |__|__| hours per night. According to the division we, divided patients into 3 groups: group A) the reference category was defined as 6-8 sleep hours per night, group B) short sleep was defined as < 6 hours per night and group C) long sleep was defined as > 8 hours per night.

Results: Out of total of 379 patients, 35 (9.2%) patients slept less than 6 hours and (6.9%) patients slept > 8 hours per night. Patients with long sleep disturbances were older (62.5±10.2 vs. 58.8±10.6 years; p=0.01), had significant higher death rates (18±1.9%; p<0.0001), often history of diabetes mellitus (27.3% vs. 11%; p=0.04) and higher mean body mass index (28.4 kg/m² vs. 26.6 kg/m²; p=0.02) compared to the patients without. There was a statistically significant increase in 2 years all-cause mortality: 1.9% for reference category, 11.4% for patients who slept less than 6 hours, and 26.9% for patients who slept more than 8 hours per night; p value for trend =<0.0001.

Conclusions: Sleep disturbances were highly prevalent in STEMI patients. Physicians should routinely screen and evaluate myocardial infarction patients for sleep duration. Our findings suggest that short and long duration of sleep in first months after STEMI are associated with a greater risk of death.
were significantly predictive of future MACE. Only Mon2 counts were an independent predictor of MACE after adjusting for age and sex (Table 1).

### Table 1. Predictive value of monocytes in MACE

<table>
<thead>
<tr>
<th>Monocyte</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocytopeny (relflush)</td>
<td>1.002 (1.104)</td>
<td>0.032</td>
</tr>
<tr>
<td>Mon1</td>
<td>1.001 (0.998-1.003)</td>
<td>0.111</td>
</tr>
<tr>
<td>Mon2</td>
<td>1.008 (1.003-1.013)</td>
<td>0.047</td>
</tr>
<tr>
<td>Mon3</td>
<td>1.01 (0.999-1.02)</td>
<td>0.388</td>
</tr>
</tbody>
</table>

**Conclusion:** Increased total monocyte and Mon 2 counts in the first 24 hours post-infarction are predictive of MACE in STEMI patients. Mon 3, despite an assumed role in reparation and fibroblast deposition, was not predictive of MACE in post-STEMI patients. This suggests a specific role for Mon2 monocyte subset in post-infarction in STEMI, and a potential role of this subset as a future therapeutic target. Remodelling data from cardiac magnetic resonance is awaited.

### P5096 Prediction of late mortality after myocardial infarction by means of the GRACE Score in contemporarily treated patients

**Background:** The GRACE Score (GS) was proposed for prediction of early and late mortality risk in acute coronary syndrome (ACS) patients. The GS includes age, history of congestive heart failure and previous myocardial infarction, these rate, systolic blood pressure and presence of ST-segment depression at admission, and serum creatinine, cardiac enzymes and percutaneous coronary inter- vention (PCI) during hospitalization. GS was developed and validated in patient with ACS collected in a multinational registry between 1999 and 2003. Less than one third of the registry patients were treated with PCI. Aim of this study was to investigate the predictive power of the GS in contemporarily treated post-infarction patients.

**Methods:** 941 consecutive AMI patients aged >81 yrs were included. 93% underwent a PCI, 95% received beta-blockers, 94% ACE inhibitors and 95% statins. The GS was calculated according to the published protocol. Uni- and multivariable analyses were performed with traditional risk stratifiers like LVEF <35%, and diabetes mellitus. Follow-up was up to 5 years. Primary endpoint was total mortality. Follow-up was up to 5 years. Primary endpoint was total mortality.

**Results:** During follow-up, 72 patients (7.7%) died. The GS shows the strongest association with mortality in the univariate analysis follow by reduced LVEF and diabetes mellitus (see table). By analyzing the different components of the GS in a multivariable analysis, only age, serum creatinine and history of previous myocardial infarction were independent and significantly associated with mortality (HR CI 1.09 (1.06-1.12); 1.82 (1.42-2.34); 2.01 (1.12-3.63)).

**Conclusion:** The GS is a strong risk predictor of 5-year mortality after acute myocardial infarction in a contemporary treated patient population and independent of reduced LVEF and diabetes mellitus. Age, serum creatinine and history of prior myocardial infarction carried the most predictive information of the GRACE score.

### P5097 Clinical outcomes after percutaneous or surgical revascularization of unprotected left main coronary artery related myocardial infarction: a single-center experience

**Purpose:** Unprotected left main coronary artery (ULMCA) related acute myocardial infarctions (AMI) are clinically catastrophic events. Due to the rarity of these events, only limited clinical data is available. Therefore, we evaluated 30-day and 1-year clinical outcomes after percutaneous or surgical coronary revascularization in these patients.

**Methods:** Between January 1998 and December 2008, 87 patients with ULMCA related AMI have undergone revascularization treatment in our institution (57 with PCI, 30 with CABG). Clinical follow-up was obtained retrospectively by means of in- and outpatients medical charts. Patient’s vital status was verified with the national population registry. Cumulative event rates were estimated using the Kaplan–Meier method. Multivariate regression analyses were performed to identify predictors for 30-day mortality and PCI as revascularization treatment.

**Results:** 30-day mortality rate was 51%; 64% in the PCI group and 24% in the CABG group. One-year mortality rate was 54% (69 PCI; 24 CABG, figure 1). Major adverse cardiac and cerebrovascular event (MACCE) rates were 58% (30-day) and 84% (1-year). Diabetes mellitus (HR 2.9, 95% CI 1.3-6.3, p:0.009) and TIMI 0 flow (HR 3.1, 95% CI 1.2-8.3, p:0.017) were independent predictors for 30-day mortality. Angiographic characteristics were independent predictors for revascularization treatment: TIMI 0 flow strongly predicted performing PCI, and distal (balkration) LM lesion predicted performing CABG.

**Conclusions:** This is the first study to report ULMCA related AMI data including both PCI and CABG treated patients. Clinical results are worse in PCI treated patients, most likely due to selection bias. This is demonstrated by TIMI 0 flow and distal LM disease to be independent predictors for treatment choice.
**P5099**

**Probable effects of obstructive sleep apnea on plaque vulnerability and progression of coronary atherosclerosis in patients with acute myocardial infarction**

H. Nakashima, T. Henmi, Y. Uchida, Y. Shirai, T. Nunohiro, K. Maemura. 1. Nagasaki Citizen's Hospital, Nagasaki, Japan; 2. Nagasaki University, Graduate School of Biomedical Sciences, Department of Cardiovascular Medicine, Nagasaki, Japan

**Aims:** Impact of OSA on the clinical and angiographic follow-up outcomes in patients undergoing primary percutaneous coronary intervention (PPCI). PPGI was not been fully elucidated. We hypothesized that OSA may contribute to plaque vulnerability and cause adverse cardiovascular outcomes in patients who experienced acute myocardial infarction (AMI).

**Methods:** This study included a total of 272 patients with AMI who underwent PPCI. Polysomnography at first admission determined 124 patients with OSA defined as apnea-hypopnea index ≥ 15 events/h. Clinical outcomes measured were cardiac death, recurrence of acute coronary syndrome (ACS), and re-admission for heart failure. Major adverse cardiac events (MACE) were defined as composite end points of individual clinical outcomes. Follow-up angiography was performed in 222 patients. Intervention measures were target lesion revascularization (TLR) and newly necessitated PCI (new PCI) owing to disease progression.

**Results:** Mean follow-up duration was 4.0±1.7 years. Patients with OSA had more experienced the recurrence of ACS and MACE than control patients (17.6% vs. 6.6%, P=0.010; 21.8% vs. 10.8%, P=0.014). TLR was not different between the groups. In contrast, new PCI was significantly higher in OSA patients than in controls (28.4% vs. 14.8%, P=0.012). Cox regression hazard model showed that the OSA was an independent predictor for recurrence of ACS and MACE (hazard ratio=1.98, P=0.027). Logistic regression analysis adjusting for OSA and other known risk factors identified that only OSA was positively correlated with new PCI (odds ratio=2.23, P=0.021). Treatment with continuous positive airway pressure could not improve the outcomes.

**Conclusions:** OSA may be related to plaque vulnerability and a risk factor for progression of coronary atherosclerosis.

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**P5101**

**Chest pain patients with false positive hs-TnT in emergency department have the same one year risk of MACE as those who were hospitalized for acute coronary syndromes**

M.T. Cardillo, L.M. Biaussce, M. Zaninotto, N. Gentilioni Silveri, G. Biasillo, M. Monir, G. Niccoli, M. Gustapane, M. Plebani, F. Crea. 1. Catholic University of the Sacred Heart, Rome, Italy; 2. University Hospital of Padua, Department of Laboratory Medicine, Padua, Italy

**Background:** The introduction in clinical practice of high sensitivity troponin (hs-TnT) assays has led to an increased diagnostic accuracy for Acute Coronary Syndrome (ACS) characterized by a higher sensitivity at the cost of a lower specificity leading to more false positive (FP) cases. The prognostic value of hs-TnT in false positive subjects has not been reported yet.

**Methods:** Four hundred and fifty-two (452) pts, admitted to ED because of chest pain, were enrolled. Serum levels of Roche hs-TnT were measured from baseline samples. All pts received a telephonic follow up (FU) contact at 30 and 360 days. The endpoint was the composite of MACE. Prognostic accuracy was evaluated by Kaplan-Meier curves.

**Results:** 60 pts were discharged with a diagnosis of ACS (13% of overall population) according to current guidelines. At follow up 412 patients were in good health, 8 had died (5 for cardiac causes and 3 of cancer) and 16 had experienced an episode of ACS (16 pts were lost to follow up). Among patients with negative hs-TnT at ED admission MACE were 3%, but were 8.5% in the group of FP and 12% in the true positive. Kaplan-Meier curves showed a significant difference in event-free survival between pts negative to hs-TnT versus FP (p=0.03) and versus true positive pts (p=0.004). However the last two group had a similar event free survival (p=0.5).

**Conclusions:** In pts admitted to ED for chest pain, a positive value beyond the hs-TnT cut-off (14 pg/ml) is associated with a similar prognostic value in true and false positive patients, suggesting that the latter group should receive an accurate work-out in ED and a careful follow-up after discharge.

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**P5102**

**Acute coronary syndromes in the elderly**

P.C. Amador, S. Gonzalves, F. Seixo, J. Ferreira Santos on behalf of Portuguese Registry of Acute Coronary Syndromes Investigators. Centro Hospitalar de Setúbal EPE, Setúbal, Portugal

**Background:** Elderly patients (pts) with acute coronary syndromes (ACS) are frequently underrepresented in clinical trials which serve as source of evidence-based data used for practice guidelines. Aim: Characterize and evaluate the compliance to guideline-oriented therapies and clinical outcomes in elderly patients with ACS in community practice.

**Methods:** Analyzed 30161 patients with ACS consecutively included in a nationwide registry. We clustered pts into four age groups: <65, 65 to 74, 75 to 84, and ≥85 years old; in our analysis, young pts refer to those <65 years of age. We compared pts' baseline demographics, clinical characteristics, care patterns, and in-hospital outcomes. Early medication compliance score was created, attributing one point for each of the following: aspirin and clopidogrel (1 point), any heparin (1 point), beta-blockers (1 point), angiotensin-converting enzyme (ACE) inhibitors (1 point), lipid-lowering agents (1 point), Discharge medication compliance score was also created, attributing one point for each of the following: aspirin and clopido- grel (1 point), beta-blockers (1 point), ACE inhibitors (1 point), lipid-lowering agents (1 point). In-hospital clinical outcomes of interest included all cause in-hospital mortality, major adverse cardiac events, hospital death, re-infarction and stroke.

**Results:** Fifty seven percent of the population was 65 years or older. During their hospitalization, elderly pts were less likely to use guidelines-recommended therapies evaluated by the compliance score. Escalation of care or to undergo coronary angiography or revascularization procedures. With advancing age, elderly pts had a higher incidence of in-hospital events (Table 1).

**Conclusion:** Age has a negative impact on the use of guidelines-recommended

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**P5103**

**Prognostic impact of plasma aldosterone levels on long term outcome after myocardial infarction**

K. Inoue, T. Tangaki, Y. Tsubakimoto, T. Sabatari, S. Kimura, A. Matsuo, H. Fujiita, M. Kitamura, Kyoto Second Red Cross Hospital, Kyoto, Japan

**Background:** It was reported higher aldosterone (ALD) levels were predictors of mortality risk in patients with heart failure or myocardial infarction (MI). The prognostic significance of ALD in the Japanese patients with acute myocardial infarction remains unknown.

**Methods:** Baseline plasma ALD levels were quantified in a prospective cohort study of 214 consecutive Japanese patients with acute MI (170 men, 44 women, age 67.8±12.6) to determine if there was an association of ALD levels and long term cardiac events. The subjects were divided into two groups of elevated ALD group (group H) and non-elevated ALD group (group L) according to the median value of baseline plasma ALD for data analysis. The primary end point of the study was cardiac death. The secondary end point was left ventricular ejection fraction (LVEF) at 6-month follow-up. heart failure required hospitalization and all cause death.

**Results:** The median value of baseline ALD was 104.5 pg/ml in all patients. During a median follow-up of 1194 days, cardiac death occurred in 15 patients (7%). Twenty-two patients (11.7%) had worsened heart failure. All cause mortality was 9.8%. Patients of group H (N=107) with higher ALD had a significantly higher incidence of cardiac death, as compared to those of group L (N=107) with lower ALD (12.2% vs. 1.9%, P=0.0489). The LVEF at 6-month follow-up of group H was significantly lower than those of group L (55.2% vs. 64.3%, P<0.0001). The incidence of hospitalization due to heart failure tended to be higher in the group H than in the group L (18.7% vs. 4.7%, P=0.0034). Patients of group H were likely to die more frequently than patients of group L (15.0% vs. 4.7%, P=0.3537). Higher ALD were independent predictors of increased cardiac mortality in Cox regression analysis adjusted for age, sex, body mass index, LVEF, brain natriuretic peptide and medication at acute phase (adjusted hazard ratio=1.133[95%CI 1.071-1.193]; P=0.0009).

**Conclusion:** Among Japanese patients with MI, higher ALD were associated with long term left ventricular remodeling. Elevated ALD levels at acute phase were independent predictor of cardiac mortality.
Baseline hypercalcaemia in acute coronary syndrome patients: a five-year outcome study

Background: Serum calcium level has been associated with ischaemic myocardial infarction but its role as a predictor of outcome in patients with acute coronary syndromes (ACS) was not determined.

The aim of this study was to assess the role of admission calciumaemia in predicting also long-term outcome, among ACS patients.

Methods: Serum calcium was measured at admission in 365 patients with ACS. Data on sociodemographic and clinical characteristics were evaluated. The occurrence of a composite outcome (all-cause mortality and hospitalization for congestive heart failure (CHF) or ACS) was assessed at 60 month follow-up.

Results: Among all, 71% patients were male and the mean age was 64±13 years. Mean serum calcium was 2.38±0.33 mmol/L and 20% of patients had hypercalcaemia (>2.60 mmol/L). Patients with hypercalcaemia were more frequently women (45% vs 25%; p=0.001), diabetic (43% vs 24%; p=0.001), hypertension (74% vs 60%; p=0.021) and presented more kidney disease (KD) (49% vs 21%; p=0.001) as well as left ventricular (LV) systolic dysfunction (45% vs 28%; p=0.010).

At 5-year follow-up, composite outcome occurred in 92 (25%) patients and occurred more frequently in patients with hypercalcaemia (41% vs 22%; p=0.001). Furthermore, this patient group presented a significant preponderance of adverse outcomes, among ACS patients. At 5-year follow-up, comorbid death, major adverse cardiac events (MACE), major adverse vascular events (MAVE), hospitalization for congestive heart failure (CHF) and hospitalization for ACS were more frequent in patients with hypercalcaemia (95% CI) (95% CI) (95% CI) (95% CI) (95% CI).

For ACS patients: a five-year outcome study

Background: Serum uric acid (UA) has been shown as an independent predictor of all-cause mortality in patients with acute coronary syndromes (ACS), but its role as a predictor of outcome in patients with acute coronary syndromes (ACS) was not determined.

The aim of this study was to assess the role of admission uric acid (UA) in predicting also long-term outcome, among ACS patients.

Methods: Serum UA was measured at admission in 365 patients with ACS. Data on sociodemographic and clinical characteristics were evaluated. The occurrence of a composite outcome (all-cause mortality and hospitalization for congestive heart failure (CHF) or ACS) was assessed at 60 month follow-up.

Results: Among all, 71% patients were male and the mean age was 64±13 years. Mean serum UA was 3.84±1.20 mg/dL and 20% of patients had hyperuricaemia (>4.20 mg/dL). Patients with hyperuricaemia were more frequently women (45% vs 25%; p=0.001), diabetic (43% vs 24%; p=0.001), hypertension (74% vs 60%; p=0.021) and presented more kidney disease (KD) (49% vs 21%; p=0.001) as well as left ventricular (LV) systolic dysfunction (45% vs 28%; p=0.010).

At 5-year follow-up, composite outcome occurred in 92 (25%) patients and occurred more frequently in patients with hyperuricaemia (41% vs 22%; p=0.001). Furthermore, this patient group presented a significant preponderance of adverse outcomes, among ACS patients. At 5-year follow-up, comorbid death, major adverse cardiac events (MACE), major adverse vascular events (MAVE), hospitalization for congestive heart failure (CHF) and hospitalization for ACS were more frequent in patients with hyperuricaemia (95% CI) (95% CI) (95% CI) (95% CI) (95% CI).

Table 1. Outcomes by age

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>&lt;65 yrs</th>
<th>65–74 yrs</th>
<th>75–84 yrs</th>
<th>&gt;84 yrs</th>
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<tbody>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>In-hospital</td>
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<td>4.9</td>
<td>21.0</td>
<td>31.0</td>
</tr>
<tr>
<td>IH death</td>
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<td>3.8</td>
<td>5.8</td>
<td>7.1</td>
</tr>
<tr>
<td>IH MACE</td>
<td>2.8</td>
<td>6.4</td>
<td>2.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.6</td>
<td>1.4</td>
<td>2.4</td>
<td>3.3</td>
</tr>
<tr>
<td>FMD at 5 months</td>
<td>2.2</td>
<td>2.8</td>
<td>2.7</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Conclusions: Hyperuricaemia is an independent predictor of all-cause mortality in ACS patients. It is essential to improve the compliance with these therapies in elderly pts in order to improve outcomes.

Conclusion: Endothelial function is markedly impaired in the acute phase of NSTE-ACS patients, but achieves values comparable to those of stable CAD patients over 3 months of follow-up. Both FMD on admission and at 3 months from the acute event independently predicted cardiac outcome in NSTE-ACS patients.
Mitrval regurgitation in postmyocardial infarction

Independent contribution of additional risk factors to variables (HR 8.282, 95% CI 5.821 to 11.784, p < 0.001), together with NT-proBNP and the infarction extension (measured by the troponin I peak), were predictors of the development of post-infarction HF. AGE levels over the median multiplied by 5 the risk of developing HF during the follow-up.

Conclusions: High levels of advanced glycation end products (AGE) are an independent predictor for the development of post-infarction HF.

P5107 Mitral regurgitation in postmyocardial infarction patients

V.A. Kuznetsova, E.I. Yaroslavskaya, G.S. Puskharev, M.G. Shakhova. Tyumen Cardiology Center, Tyumen, Russian Federation

Background: The association between mitral regurgitation (MR) and localization of previous myocardial infarction (MI) remains debatable. Results of studies are contradictory, and one opinion is that association in another opinion.

Purpose: To determine the relationship of moderate or severe MR with the clinical and functional characteristics in postmyocardial infarction patients.

Methods: We selected patients with previous myocardial infarction who had no acute myocardial infarction, congenital heart disease or valvular disease. There were 1,167 patients with no MR and 403 patients with moderate or severe MR.

Results: The patients with MR were significantly older (55.5 ± 8.4 vs 50.7 ± 7.6 year) with more severe New York Heart Association (NYHA) functional class (II-V) (35.5 ± 11.2%). Echocardiographic indices of left atrium (23.5 ± 2.9 vs 20.3 ± 2.1 mm) and extent of left ventricular (LV) wall motion abnormalities (32.8 ± 14.9 vs 23.6 ± 12.7%) were higher in patients with MR as well as reduced LV systolic function (LV ejection fraction < 50% - 63.7 ± 25.6%) and LV dilation (66.5 ± 21.3 mm) compared to patients without MR.

Conclusions: LV dilation, NYHA class of congestive heart failure, index of the left atrial size, and extent of LV wall motion abnormalities in patients without MR (5.5 ± 1.2 vs 5.2 ± 1.3 mm) were higher in patients with MR compared to patients without MR. According to results of multivariate analysis, MR was independently associated with LV dilatation, NYHA class of congestive heart failure, index of the left atrial size, and extent of LV wall motion abnormalities.

P5108 Risk stratification by kllip class and left ventricular systolic function in patients with acute myocardial infarction in modern era from Korean acute myocardial infarction registry

J.H. Lee1, J.K. Kang1, S.Y. Jang1, W.S. Choi1, D.H. Yang1, H.S. Park2, Y. Cho3, S.C. Chae1, M.H. Jeong4, Y.J. Kim5. On behalf of Korean Acute Myocardial Infarction Registry: 1Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, 2Chonnam National University Hospital, Gwangju, Korea, Republic of Korea, 3Yeungnam University Hospital, Daegu, Korea, Republic of Korea, 4Seoul National University Hospital, Seoul, Korea, Republic of Korea

Purpose: The aims of this study were to determine the interactive effect of Killip class and left ventricular systolic function on 12-month mortality in patients with acute myocardial infarction (AMI) in modern era.

Methods: Between November 2005 and January 2008, 8,418 eligible patients (5,842 men; mean age = 62.7 ± 12.5 years-old) were analyzed from the Korean AMI Registry. Patients were stratified into 4 groups based on Killip class (1 versus ≥2) and left ventricular ejection fraction (LVEF; <50% versus ≥50%); group 1 (Killip class 1 and LVEF ≥50%; n = 4,394), group 2 (Killip class 1 and LVEF <50%; n = 851), group 3 (Killip class ≥2 and LVEF ≥50%; n = 1,344), and group 4 (Killip class ≥2 and LVEF <50%; n = 851). The LVEF were measured by two-D echocardiography.

Results: The 12-month mortality was 2.0% in group 1, 7.3% in group 2, 10.6% in group 3, and 22.5% in group 4, respectively. Kaplan-Meier survival showed there was significant difference in 12-month mortality among 4 groups (log-rank p < 0.001). Patients in group 2 had significantly higher 12-month mortality compared with patients in group 1 (hazard ratio [HR] 3.9.12; 95% confidence interval [CI] 2.728 to 5.610, p < 0.001), as did patients in group 3 (HR 3.991, 95% CI 2.592 to 6.152, p < 0.001) after adjustment for clinical variables and angiographic variables in Cox proportional hazards model. In fully adjusted model including also medications during hospitalization and discharge, patients in group 2 had significantly higher 12-month mortality compared with patients in group 1 (HR 4.341; 95% CI 2.716 to 6.732, p < 0.001), as did patients in group 3 (HR 3.359, 95% CI 2.125 to 5.310, p < 0.001). The patients in group 4 had the highest 12-month mortality compared to patients in group 1 after adjustment for clinical and angiographic variables (HR 8.262, 95% CI 5.821 to 11.764, p < 0.001), and after adjustment for clinical, angiographic, and discharge medications (HR 7.748, 95% CI 5.372 to 11.176, p < 0.001).

Conclusions: Despite technical improvement and new treatment modality in modern era, the traditional risk stratification by Killip class alone still could provide prognostic implication on 12-month mortality in post-MI patients.

P5109 Early effects of ivabradine in combination with beta-blockers compared to beta-blockers up titration on systolic and diastolic function, NT-proANP and exercise capacity in pts after Q-MI with EF <45%

K. Amosova, I.U. Rudenko, I. Prudky, Y. Xu, A. Bezdrizhny. National O.O. Bohomolots Medical University, Kiev, Ukraine

Purpose: To compare the early impact of heart rate (HR) control with ivabradine plus metoprolol and metoprolol up titration on left ventricular (LV) systolic and diastolic function, serum NT-proANP and exercise capacity in anterior Q-MI pts with EF <45%.

Methods: In single-blind parallel-group study 62 pts with a first Q-MI, EF 30-45%, sinus rhythm > 80 bpm, Killip class I-II were randomized 1:1 into ivabradine plus beta-blockers (BB) and BB up titration groups. Pts with anterior MI (24 and 18 respectively) were included in this analysis. Pts in Group 1 from day (D) 1 took oral metoprolol tartrate up titrated till D 4 to 50mg bid (66.8 ± 19.9 mg pd) on top of which from D 4-6 ivabradine 2.5 mg bid was up titrated to 7.5 mg bid. Pts in Group 2 were up titrated to 75 mg metoprolol bid (117.6 ± 4 mg pd). Besides, EF, survival and NT-proANP at D 1 and 25 early mitral inflow velocity (E) was filling velocity (E') by TDI at D 5 and 25 were estimated. Symptom-limited treadmill test (Bruce protocol) was performed at D 25.

Results: Resting HR was similar in both groups at D 1 (86.7 ± 17.2 vs 87.5 ± 16.1 bpm), D 5 (68.4 ± 15.2 vs 68.1 ± 14.4 bpm) and D 25 (60.7 ± 17.4 vs 61.6 ± 8.1 bpm, p > 0.05). Echo-Doppler and NT-proANP data (M ± s.e.m) see in the Table. In Group 1 compared to Group 2 higher exercise capacity (4.9 ± 0.73 vs 4.4 ± 0.25 MET) and duration (206 ± 112 vs 168.2 ± 12.3 s, p < 0.05) were attained in spite of higher HR at peak load (105 ± 21.2 vs 99 ± 23.2 bpm, p > 0.05).

Conclusions: In pts after anterior MI with EF <45% LV systolic dysfunction, addition of ivabradine to metoprolol, in comparison with up titration of metoprolol was associated with decrease of serum NT-proANP level, improvement of systolic and diastolic function and exercise capacity in spite of larger increase of HR at peak workload by D 25.

P5110 Independent contribution of additional risk factors to GRACE score in after-discharge, long-term prognosis

M. Grabowski, K.J. Filipiak, R. Glowczynska, G. Opolski, Medical University of Warsaw, Warsaw, Poland

Introduction: There is a limited data for long-term prognosis of patients discharged from the hospital after acute coronary syndrome (ACS).

Aim: A prospective, long-term follow-up of unscheduled ACS patients treated at the 24-hour invasive cardiology on-site and discharged from referral hospital. The GRACE score was used to evaluate the independent contribution of risk factors primarily not included in the GRACE risk score. The primary endpoint was all-cause mortality during 6 years.

Methods: Study included 672 patients discharged after ACS: ST segment elevation (STEMI, n=417 [62%]), non-ST segment elevation (UA/STEMI, n=255 [38%]). All patients underwent coronary angiography and if indicated primary angioplasty (417 [100%] with STEMI and 157 [62%] with UA/STEMI). Cox proportional hazards regression model was used to evaluate the independent contribution of risk factors primarily not included in the GRACE risk score. The primary endpoint was all-cause mortality during 6 years.

Results: Survival in STEMI and UA/STEMI was: 82% vs 81%, p=0.7852. The 6-year overall mortality was comparable in STEMI vs UA/STEMI patients (82% vs. 81.2%, p=0.785). The GRACE score for the post-discharge risk assessment was the tool with good prognostic value (area under ROC curve was 0.7 for the independent factors additional to GRACE.

New insights in post-myocardial infarction follow-up
end of observation; cut-off point of 105 points displayed 58.5% sensitivity and 70.7% specificity). Multivariate analysis identified additional independent risk factors for long-term mortality (table).

Conclusions: There are some risk factors obtained both from the medical history and during the hospitalization that could increase the power of the risk stratification model. This suggests need for particular risk stratification performed to discharge in context of long-term period.

P5111 Prognostic importance of absence of angina in non-ST elevation myocardial infarction

J.Y. Takada, R.B. Ramos, S.D. Avakian, J.A.F. Ramires, A.P. Mansur. Heart Institute (InCor) - University of Sao Paulo Faculty of Medicine Clinics Hospital (HC-FMUSP), Sao Paulo, Brazil

Purpose: Cardiac troponins increased myocardial infarction diagnosis in patients without specific electrocardiographic changes. Absence of angina has become common and prognostic significance remains unclear.

Methods: We followed 204 consecutive patients after myocardial infarction non-ST elevation (NSTEMI) at emergency department. Outcomes were in-hospital death and follow-up death or cardiac readmission.

Results: No-angina (NAG) group (n = 27, 13.2%) had more women (p = 0.001), higher blood glucose (p = 0.011) and B-type natriuretic factor (p < 0.001). In-hospital (14.8% vs 4.5%, p = 0.035) and 20-months follow-up mortality (43.5% vs 12.9%, p < 0.001) were higher in NAG. Combination of death and cardiac readmissions was similar (70.4% vs 53.1%, p = 0.093). Age (HR = 1.038, 95% CI 1.006 to 1.071), absence of angina at admission (HR 2.554, 95% CI 1.037 to 6.289), male gender (HR 2.706, 95% CI 1.099 to 6.667) and dyspnea (HR 3.113, 95% CI 1.417 to 6.842) were independent predictors of long-term mortality.

Conclusion: The absence of chest pain in NSTEMI implies in higher in-hospital and long-term mortality.

P5112 Is female gender a real independent predictor of mortality after acute coronary syndrome?

A.T. Timoteo, J. Labandeiro, J.A. Oliveira, M.L. Ferreira, R. Cruz Ferreira. Hospital Santa Marta, CHLC, Lisbon, Portugal

Background: Female gender has been described as an important predictor of outcome after elective coronary interventions. Is this ominous impact of female gender also present in the context of acute coronary syndromes (ACS)?

Methods: Study of consecutive patients admitted for an ACS at a single-centre coronary care unit. Kaplan-Meier analysis and Cox regression analysis regarding the primary end-point of all-cause mortality at 30-day and one-year follow-up were performed to investigate the influence of gender on outcome.

Results: The study included 1423 patients, with a mean age of 64±3 years, 31% females. Thirty-day and one-year mortality were 6.7% and 8.5% respectively. ST-segment elevation acute myocardial infarction (STEMI) was present in 60.2% of the patients. Females were more elderly (70.1±12 vs. 61±12 years, p<0.001), had more hypertension and diabetes and were less smokers. Heart rate and GRACE risk score were higher in females and estimated glomerular filtration rate lower. Females presented more often in Killip class ≥ 2, but had similar left ventricular ejection fraction. STEMI was more frequent in males (64.6% vs. 50.6%, p<0.001). Kaplan-Meier analysis in the entire population, showed a significant increase in the incidence of the primary endpoint in females in comparison to males (Log–rank, p=0.030, HR 1.49, 95% CI 1.04 – 2.15). However, analysing different age strata, females had identical mortality compared to males of the same age group (Table 1). On the other hand, 69% of women had an age ≥ 65 years, suggesting an important effect of age. After adjustment for age, female gender was no longer a predictor of mortality (HR 0.85, 95% CI 0.58 – 1.24, p = 0.404).

Conclusions: Female gender is not a predictor of all-cause mortality after ACS. In fact, age is a major confounder in the influence of gender on outcome and must be taken into account, since women admitted with an ACS are significantly older than men.

P5113 Peak Systolic Velocity (PSV) using colour-coded Tissue Doppler Imaging (TDI) is a strong and independent predictor of outcome in acute coronary syndrome patients

C. Westholm1, J. Johnson1, T. Jernberg1, R. Winter1, 1Karolinska Institute, Department of Medicine, Stockholm, Sweden, 2Royal Institute of Technology, School of Technology and Health, Stockholm, Sweden

Background: Traditional echocardiographic methods like left ventricular ejection fraction (EF) and wall motion scoring (WMS) and new methods like speckle tracking (ST) based peak strain and strain rate carry important prognostic information in acute coronary syndrome (ACS) patients. Parameters from tissue Doppler imaging (TDI), with its high time resolution, may further increase the prognostic value. Peak systolic velocity (PSV) of the basal segments of the left ventricle from TDI is a robust and user independent parameter. The aim was to investigate the prognostic value of PSV compared to EF, WMS, 2D strain and strain rate.

Methods: Echocardiographic images were collected and post processed in 227 ACS patients. Additional clinical data was prospectively gathered and patients were followed for 3-5 years regarding the combined endpoint of death or admission due to ACS or heart failure.

Results: The combined endpoint occurred in 84 (37%) patients. Those with an event had lower median PSV than those without (4.4cm/s vs. 5.3cm/s), (p=0.001). In a ROC analysis, the AUC was larger for PSV (0.74) than for EF (0.68), WMS (0.65), 2D strain (0.71) and strain rate (0.69). The combined end-point increased with decreasing PSV (figure). When adjusting for differences in baseline characteristics in a COX-regression model, PSV remained independently associated with outcome where the others did not. PSV was also less sensitive to image quality with fewer values missing or unacceptable for analysis.

P5114 Left atrial volume and dynamics in chronic kidney disease

K. Kadappu1, L. Hee2, A. Aravindan2, S.T. Spicer1, G. Suryanarayanan4, J.K. French1, L. Thomas1, Liverpool Hospital and University of New South Wales, Liverpool, Sydney, Australia; 2Liverpool Hospital, Liverpool, Sydney, Australia

Background: Left ventricular changes in end stage renal failure are well recognized; however, little is known about the same in early stages of chronic kidney disease (CKD) and associated changes in left atrial function.

Methods: 50 CKD patients (eGFR 30-60 ml/min/1.73m2), underwent a transthoracic echocardiogram and were compared with 49 normal subjects as well as 30 hypertensive subjects. LV ejection fraction and LV mass indexed to body surface area (LVMi) were measured. Biplane LA volume indexed to body surface area (LAVi), LA global and segmental function was measured using 2-dimensional strain imaging in the apical four and two chamber views from the septal and lateral walls using 2D speckle tracking. Systolic (S-GR), early (E-GR) and late (A-GR) peak velocities were measured.

Table 1. All-cause mortality by age strata

<table>
<thead>
<tr>
<th>Age Strata</th>
<th>Overall</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=240</td>
<td>n=50</td>
<td>n=190</td>
</tr>
<tr>
<td>60-64 years</td>
<td>6.1%</td>
<td>4.6%</td>
<td>7.4%</td>
</tr>
<tr>
<td>65-74 years</td>
<td>7.9%</td>
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</tr>
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<td>≥ 75 years</td>
<td>12.3%</td>
<td>18.9%</td>
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</tr>
</tbody>
</table>

Conclusion: Peak systolic velocity (PSV) using colour-coded TDI is a robust and independent predictor of outcome in acute coronary syndrome patients.

**PATHOPHYSIOLOGY – BASIC MECHANISMS AND ATRIAL FUNCTION**

K. Kadappu1, L. Hee2, A. Aravindan2, S.T. Spicer1, G. Suryanarayanan4, J.K. French1, L. Thomas1, Liverpool Hospital and University of New South Wales, Liverpool, Sydney, Australia; 2Liverpool Hospital, Liverpool, Sydney, Australia

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Methods: 50 CKD patients (eGFR 30-60 ml/min/1.73m2), underwent a transthoracic echocardiogram and were compared with 49 normal subjects as well as 30 hypertensive subjects. LV ejection fraction and LV mass indexed to body surface area (LVMi) were measured. Biplane LA volume indexed to body surface area (LAVi), LA global and segmental function was measured using 2-dimensional strain imaging in the apical four and two chamber views from the septal and lateral walls using 2D speckle tracking. Systolic (S-GR), early (E-GR) and late (A-GR) peak velocities were measured.

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</tr>
</tbody>
</table>

Conclusion: Peak systolic velocity (PSV) using colour-coded TDI is a robust and independent predictor of outcome in acute coronary syndrome patients.
SR) diastolic strain rate were also measured. One-way ANOVA with Bonferroni correction used to examine the differences between the groups.

**Results:** LVMI was increased significantly in the hypertensive group (P<0.03). LAV was increased in the CKD group compared with both the normal and hypertensive group (Table 1). There was an associated reduction in global strain compared to normal and hypertensives (Table 1). LA reservoir function (S-SR), and conduit function (E-SR) were significantly reduced in the CKD group compared with normals and hypertensive group. However, there was no significant difference in atrial contractile function as A-SR was similar in all 3 groups.

Table 1. Differences in LA volume, strain and strain rate in CKD group vs HT group vs controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=35)</th>
<th>Narrow QRS (n=35)</th>
<th>Wide QRS (n=35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAV (mL/m²)</td>
<td>30.5±6.2</td>
<td>39.9±10.6*</td>
<td>27.1±7.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Global strain (%)</td>
<td>19.96±6.2</td>
<td>24.4±8.6*</td>
<td>18.6±5.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S-SR (±)</td>
<td>1.1±0.3</td>
<td>1.1±0.3*</td>
<td>1.5±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E-SR (±)</td>
<td>1.4±0.5</td>
<td>1.4±0.6*</td>
<td>1.4±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A-SR (±)</td>
<td>1.7±0.4</td>
<td>1.5±0.4</td>
<td>1.7±0.5</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*p<0.05 compared to normal; †p<0.05 compared to HT group.

**Conclusion:** LV diastolic dysfunction starts in early stages of CKD with consequent atrial changes as demonstrated by LA enlargement and reduced global as well as phasic functions. The severity of LA changes in CKD appears to exceed that due to the presence of LV hypertrophy as LAV was significantly greater and LA function parameters significantly lower even compared to a cohort with hypertension with preserved kidney function.

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**P5115**

**Next generation sequencing approach for the diagnosis of heart disease patients using a panel of 72 genes**


**Purpose:** Genetic characterization of heart disease patients in a fast, comprehensive, and cost-effective manner using a 72 gene NGS approach, coupled with a robust bioinformatics pipeline.

**Methods:** We developed a methodology for resequencing 72 genes (44 genes associated with cardiomyopathy, arrhythmogenic right ventricular dysplasia, Marfan syndrome, aortic aneurysm, and 28 genes associated with Brugada syndrome, long QT syndrome, 1 case with dilated cardiomyopathy, 2 cases with familial cardiomyopathy, 6 cases with long QT syndrome, 1 case with arrhythmic right ventricular dysplasia, 7 cases with hypertrophic cardiomyopathy, 1 case with dilated cardiomyopathy, 2 cases with familial cardiomyopathy, 6 cases with long QT syndrome, 1 case with Brugada syndrome, 3 cases with familial arrhythmia, and 5 cases with familial history of sudden death).

**Results:** We found 91 relevant nucleotide changes; 14 pathogenic mutations; 77 small indels, as well as their involvement at the transcriptional level.

**Conclusion:** Targeted resequencing enables the efficient high throughput analysis of genes associated with heterogeneous congenital heart diseases.

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**P5116**

**Relation between QRS duration and atrial synchronicity in systolic heart failure: a color tissue Doppler imaging study**


We investigate atrial dysynchrony in HF by tissue Doppler. Study included 35 narrow, 25 wide QRS HF and 35 controls. The atrial contraction was measured as distance between P-wave on ECG and A-wave on TDI and measured at atriums (P-RA, P-LA) and (P-RAS, P-LAS). Atrial dysynchrony was defined as differences between P-RA and P-LA (RA dysynchrony), P-LA and P-RAS (LA dysynchrony) and P-RA and P-LAS (Interatrial dysynchrony). Wide QRS is associated with impaired atrial dysynchrony.

**Abstract P5116 – Table 1. Patient characteristics, atrial conduction times and atrial dysynchrony**

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Control (n=35)</th>
<th>Narrow QRS (n=35)</th>
<th>Wide QRS (n=35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>18 (%54)</td>
<td>15 (%43)</td>
<td>25 (%71)</td>
<td>0.001</td>
</tr>
<tr>
<td>LV Ejection Fraction (%)</td>
<td>64±3</td>
<td>64±3</td>
<td>26±8±4</td>
<td>0.012</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>22 (±62.9)</td>
<td>22 (±62.9)</td>
<td>22 (±62.9)</td>
<td>0.768</td>
</tr>
<tr>
<td>Non ischemic heart disease, n (%)</td>
<td>13 (±37)</td>
<td>13 (±37)</td>
<td>13 (±37)</td>
<td>0.748</td>
</tr>
<tr>
<td>LA dyssynchrony (ms)</td>
<td>14±3</td>
<td>14±3</td>
<td>14±3</td>
<td>0.001</td>
</tr>
<tr>
<td>RA dyssynchrony (ms)</td>
<td>14±3</td>
<td>14±3</td>
<td>14±3</td>
<td>0.001</td>
</tr>
<tr>
<td>Interaltrial dyssynchrony (ms)</td>
<td>29±4</td>
<td>29±4</td>
<td>29±4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Conclusion:** The combination of ALP and 6MWT would improve the prediction of the AF development in CHF patients.

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**P5117**

**Prediction of the development of atrial fibrillation in patients With chronic heart failure: a comparative study of atrial late potential, 6 minute-walk test and Seattle Heart Failure Model**


**Background:** The prediction of atrial fibrillation (AF) is clinically important for the management of patients with chronic heart failure (CHF). Atrial late potentials (ALP) is useful for the prediction of the AF development in CHF patients. On the other hand, 6-minute walk test (6MWT) and Seattle Heart Failure Model (SHFM) provide prognostic information in CHF patients. However, it remains unclear whether the combination of ALP, 6MWT and SHFM could improve the prediction of AF development.

**Methods:** We prospectively studied 103 CHF pts not having AF with Left ventricular ejection fraction < 40%. At the entry, ALP was measured on 12 lead signal-averaged ECG. Furthermore, abnormal 6MWT distance was defined as less than 300 m. SHFM score was also calculated by using commonly obtained clinical, laboratory, medication, and device variables.

**Results:** During a mean follow-up period of 6.3±5.5 yrs, 21 of 103 CHF pts had the AF development. At multivariate Cox analysis, ALP (p<0.04) and abnormal 6MWT (p<0.002) were independently significantly associated with the AF development, although SHFM (p<0.02) had the significant association with the AF development at univariate analysis. Patients with both ALP and abnormal 6MWT had the AF development significantly more frequently than those with either ALP or abnormal 6MWT, or those without them (p<0.0001). The hazard ratio of ALP and abnormal 6MWT for the AF development was 10.9 (95%CI 3.1-37.7), which was greater than that of ALP (2,8, 95%CI 1.2-6.7) or 6MWT (3.2, 95%CI 1.3-7.5).
Nicorandil improved electrical and structural remodeling and prevented ventricular tachyarrhythmias in a mouse model of desmin-related cardiomyopathy

M. Hirose, A. Sanbe, N. Matsushita, E. Taira. Iwate Medical University, Shizu-gun Yahabacho, Japan

Introduction: It is well known that cardiac arrhythmias were observed in patients with desmin-related cardiomyopathy. Transgenic (HSBPS R120G-TG) mice with insertion of an arg1320g (R120G) missense mutation in HSBPS display desmin-related cardiomyopathy. Recently, cardioprotective effect of nicorandil, a KATP-sensitive potassium channel opener and NO donor, prolongs survival in HSBPS R120G-TG mice. However, whether the TG mice induce ventricular arrhythmias and nicorandil can inhibit the arrhythmias remains unknown. Therefore, we examined the effects of chronic administration of nicorandil on ventricular electrical and structural remodeling and arrhythmias in HSBPS R120G-TG mice.

Methods and Results: Nicorandil (15mg/kg/day) was orally administered in HSBPS R120G-TG mice from 5 weeks to 30 weeks of age. Ventricular function was investigated at the age of 30 weeks using two-dimensionally-directed M-mode echocardiography. Electrocardiogram (ECG) lead II and optical action potentials were recorded from HSBPS R120G-TG mice and the epicardial surface of the Langendorff-perfused TG mouse hearts, respectively at the age of 30 weeks. We also examined the expression of ventricular gap junction proteins (connexin43) in the TG mouse hearts using western blots. Nicorandil improved ventricular dysfunction, determined by reduction of LV fractional shortening in HSBPS R120G-TG mice. Nicorandil also improved the prolonged P, PQ, and QT intervals at the ventricle induced tachyarrhythmias (VT) in 6 of 8 vehicle-treated HSBPS R120G –TG mouse hearts but in none of 8 nicorandil-treated HSBPS R120G –TG mouse hearts (p<0.05).

Conclusion: These findings suggest that nicorandil can inhibit ventricular electrical and structural remodeling and prevent VT induction in a mouse model of desmin-related cardiomyopathy.

Right atrial stretching does not induce fluid intake with myocardial infarction

M. Roscani1, A.C.M. Omoto2, L. Zernof2, L.S. Matsubara1, B.B. Matsubara1, J.F. Gobbi1, S. Sao Paulo State University, Botucatu Medical School, Department of Internal Medicine, Botucatu, 1Univ. Estadual Paulista (UNESP), Biosciences Institute, Botucatu, Brazil

Purpose: Low-pressure cardiopulmonary receptors are important in maintaining body fluid balance. One set of these receptors is located in the superior vena cava-right atrium junction (SVC-RAJ). Heart failure following myocardial infarction (MI) presents increased body fluid and may have an impairment of the mechano receptors receptors at SVC-RAJ function. The aim of this study was to investigate the effect of SVC-RAJ stretching on water and sodium intake in rats after MI.

Methods: Male Wistar rats (BW: 280-300g) underwent surgical left coronary artery ligation (n=9) or sham operation (n=5). Four weeks later an echocardiogram (SVC-RAJ measurement) was performed followed by the introduction of a balloon close to the SVC-RAJ. Two days later, the balloon was stretched and the rats received furosemide (10mg/kg) plus captopril (5 mg/kg), in accordance to the FUROCAP protocol, to induce diuresis and inhibits sodium reabsorption. Comparisons were done using Student’s t test or two-way ANOVA, using time and treatment as factors (p<0.05).

Results: MI caused increase of left ventricular sphericity index (0.88±0.03 vs. 0.64±0.03, P < 0.01) and systolic dimension (0.87±0.09 vs. 0.62±0.03 cm2, P < 0.01). MI rats and controls presented similar ingestion of NaCl 0.3M or water. SVC-RAJ stretching induced decreased intake of NaCl 0.3M only in the controls at 60 min monitoring (7.6±2.0 vs 2.9±1.0 ml/min).

Conclusion: Left ventricular dilation after MI is associated with lack of reduced salt intake following SVC-RAJ stretching. This suggests an impairment of cardiac low-pressure receptors.

Characterization of cyclophilin A in coxsackievirus B3-induced myocarditis

P. Sezler1, K. Klingel2, M. Sauter2, T. Schonberger1, C. Ochmann1, R. Kandolf2, M. Gawaz2, A.E. May1, 1Kardiologie und Kreislaufkrankungen, Tübingen, Germany; 2Institut für Molekular Pathologie, Tübingen, Germany

Background: The Extracellular Matrix Metalloprotease Inducer (EMMPRIN, CD147) and its ligand Cyclophilin A (CyPA) modulate MMP activity and appear to modulate inflammatory processes. To our knowledge the functional role of this receptor/ligand pair has not been characterized in inflammatory cardiomyopathy. Therefore we investigated the role of CD147 and CyPA in mouse models of acute and chronic coxsackievirus CVB3-myocarditis.

Methods and Results: CyPA+/+ (SV129) and CyPA−/− mice were infected with CVB3. EMMPRIN and CyPA were upregulated at 8 days (western blot, immuno-histochemistry). Myocardial tissue of CyPA+/+ mice showed a significantly reduced number of infiltrated T-cells and macrophages at day 8 (macrophages: 75.6±10.35% vs. 100±7.01%, p<0.05; T cells: 58.3±14.5% vs. 100±9.4%, p<0.01). Consistently, in ABY/Snu mice, which are susceptible to chronic CVB3-myocarditis, treatment with the CyPA-inhibitor NIM811 starting at the day of infection significantly reduced macrophage and T-cell recruitment at day 8 (p<0.05), which was associated by impaired virus elimination. Interestingly, NIM811-treatment of CVB3-infected A.BY/Snu mice starting at day 12 p.i. significantly reduced the myocardial amount of collagen in myocardial lesions.

Conclusion: In summary, our data suggest that CyPA is critically involved in the pathophysiology of virus-induced myocarditis. CyPA may represent a target to modulate myocardial remodeling in myocarditis.
P5124 Olmesartan inhibits ventricular remodeling and arrhythmias in a mouse model of chronic heart failure
N. Matsushita1, M. Hirose2, Y. Takeishi1, H. Shimopo3, T. Kashihara3, T. Nakada1, E. Taira1, U. Mende4, M. Yamada1. 1Iwate Medical University, Shio-gun Yahabacho, Japan; 2Fukushima Medical University, Department of Cardiology and Hematology, Fukushima, Japan; 3Shinshu University, Matsumoto, Japan; 4Brown University, Providence, United States of America

Introduction: While beneficial effects of olmesartan, an angiotensin II type 1 receptor blocker, on chronic heart failure (CHF) have been demonstrated, whether it has inhibitory effects on ventricular arrhythmias induced by CHF is still unclear. Recently, we demonstrated that a transgenic mouse with transient cardiac expression of activated G protein αq (Gq-TG) develops CHF and frequent ventricular arrhythmias. We examined the effects of chronic administration of olmesartan on ventricular function, the number of premature ventricular contractions (PVC), and ventricular remodeling in Gq-TG mice.

Methods and Results: A lower dose of olmesartan (LDG, 1mg/kg/day) or vehicle was orally administered to 30 Gq-TG mice from 6 weeks to 32 weeks of age. At the age of 32 weeks, systemic blood pressure (SBP) and electrocardiogram (EKG) were measured and ventricular function was investigated using echocardiography. The degree of fibrosis was changed. A pronounced decrease of end-diastolic LV compliance may occur in mice with MFM.

Conclusion: These findings demonstrated that lower but not higher doses of olmesartan inhibit ventricular arrhythmias and decreased heart-to-body weight ratio. We found that pitavastatin treatment inhibited the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and STAT4 in the heart, and suppressed production of Th1 and Th17-type cytokines (interleukin(IL)-17, IL-23, and IL-1L) by CD4+ T cells. Pitavastatin inhibited the differentiation of Th1 cells into Th1 and Th17 in vitro experiments. Plasma lipid levels did not differ between the groups.

Conclusions: Pitavastatin ameliorated EAM by inhibiting T cell responses and suppressing Th1 and Th17-type cytokine production. Statins may be beneficial for myocarditis and other Th1- and Th17-mediated diseases.

P5125 Enhancement of cardiac histone deacetylase 6 (HDAC6) activity protects against cardiac disease in alpha-B-crystallin arg120gly transgenic mouse
A. Sanbe1, T. Marunouchi2, M. Hirose1, S. Akoli3, Y. Tada1, K. Tanonaka2, H. Nishigori2, A. Tanoue3. 1Iwate Medical University, Shio-gun Yahabacho, Japan; 2Tokyo University of Pharmacy and Life Science, Hachioji, Japan; 3National Research Institute for Child Health and Development, Tokyo, Japan

Background: An Arg120Gly (R120G) missense mutation in crystallin, alpha B (CRYAB), a member of the small heat shock protein family, causes myofibrillar myopathy (MFM), which is characterized by the formation of aggresomes containing CRYAB and desmin. It is known that these aggresomes are formed around nuclei by the retrograde transportation of small aggregates. Besides, they are associated with aggregated mutant CRYAB. We investigated whether they are associated with cardiac disease in MFM and that alpha-tubulin, a component of microtubules, is acetylated at amino acid lysine, position 14. Although acetylation of tubulin is associated with aggregation of microtubules, as well as cellular function, the mechanisms underlying the aggregosomal formation remain unclear.

Methods and Results: Cardiac disease in MFM can be recapitated in transgenic (TG) mice by expressing the mutant CRYAB R120G protein specifically in the cardiomyocytes, which causes perinuclear formation of aggresomes. Overexpression of mutant CRYAB increased acetylated tubulin levels and reduced HDAC6 activity in the heart, suggesting that CRYAB R120G impairs the tubulin deacetylation ability of HDAC6. These results may imply that a reduction in HDAC6 activity may be involved in the progression of aggresomal formation and cardiac disease in MFM. To analyze the role of HDAC6 in MFM, a specific HDAC6 TG mice with overexpressed dominant negative HDAC6 (H216A, H611A) or wildtype HDAC6 were generated. The mice with dominant negative HDAC6 showed increased acetylated tubulin levels concomitantly with higher numbers of CRYAB-positive aggresomes and enhancement of heart weight/body weight ratio, while overexpression of wild-type HDAC6 was protective in CRYAB R120G TG mice hearts. These results indicate that HDAC6 inhibition exacerbates cardiac disease in mice with MFM.

Conclusion: Impairment of HDAC6 activity may be a critical factor involved in both aggresom formation and cardiac disease in MFM, and enhancement of HDAC6 activity may offer a new therapeutic approach in MFM treatment.

P5126 Nicorandil protects cardiomyocytes against alpha-B-crystallin arg120gly-induced apoptosis
A. Sanbe1, T. Marunouchi2, M. Hirose1, E. Koizumi1, K. Tanonaka2, H. Nishigori2, A. Tanoue3. 1Iwate Medical University, Shio-gun Yahabacho, Japan; 2Tokyo University of Pharmacy and Life Science, Hachioji, Japan; 3National Research Institute for Child Health and Development, Tokyo, Japan

Background: An Arg120Gly missense mutation in crystallin, alpha B (CRYAB) causes myofibrillar myopathy (MFM), characterized by the formation of aggregates containing CRYAB and desmin. The mutation leads to reduced cardiac function and heart failure. We examined the protective effects of nicorandil, an opener of the mitochondrial ATP-sensitive potassium channel (mitoK(ATP)) in the hearts of CRYAB R120G TG mice.

Methods and Results: Apoptotic cell death induced by CRYAB R120G in disease progression, however, remains uncertain.

Methods and Results: Apoptotic cell death induced by overexpression of CRYAB R120G was analyzed in neonatal rat cardiomyocytes using an adenoviral vector. Overexpression of the mutant CRYAB led to cardiomyopathic changes in MFM, which are known to be associated with cardiomyocyte death.

Conclusions: Nicorandil treatment appeared to reduce apoptotic cell death by opening the mitoK(ATP) channel and maintaining the BCL2 protein level.
**The mitochondrial translocator protein ligands, Soluble vascular endothelial growth factor receptor-2, Adrenomedullin, ghrelin and leptin as potential markers of heart failure.**

**Introduction:** There is a wide evidence of the existence of clinical and environmental factors that predispose individuals to developing cardiovascular disease. Thus, ischemic heart disease and hypertensive heart disease have been described as the main causes of heart failure. However, there are fewer data on genetic events and signaling involved. The VAV3 guanine nucleotide exchange factor is a protein that in humans is encoded by the VAV3 gene. This gene is a member of the VAV genes family (proto-oncogenes). VAV3 is a GDP-GTP-dependent factor that stimulates Rho and Rac GTPases.

**Aim:** To investigate if VAV3 Ser298Thr polymorphism (rs7528153) genotypes are correlated with the heart failure development.

**Patients and Methods:** We analyzed VAV3 Ser298Thr polymorphism in 219 patients diagnosed with heart failure (HF) to determine whether it is associated with the occurrence of different genotypes of VAV3 Ser298Thr polymorphism in HF. We show that subjects carrying the A/A genotype are more represented in the group with non-hypertensive heart failure whereas subjects carrying the heterozygous A/T genotype are more represented in the group with hypertensive heart failure (Table).

**Conclusion:** Our results are statistically significant (p<0.006) after comparing hypertensive heart disease and non-hypertensive one with the frequency of occurrence of different genotypes of Ser298Thr polymorphism in HF. These results indicate that VAV3 Ser298Thr polymorphism is associated with the occurrence of heart failure.

**Etiology and genotype**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Genotype</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Hypertensive Heart Failure</td>
<td>A/A</td>
<td>88 (57.5%)</td>
</tr>
<tr>
<td></td>
<td>A/T</td>
<td>33 (21.6%)</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>17 (10.8%)</td>
</tr>
<tr>
<td>Hypertensive Heart Failure</td>
<td>A/A</td>
<td>34 (6.4%)</td>
</tr>
<tr>
<td></td>
<td>A/T</td>
<td>36 (5.7%)</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>66 (100%)</td>
</tr>
</tbody>
</table>

**Conclusion:** Our results suggest that VAV3 could be involved in predisposition to heart failure, as recent studies performed on mice indicate.

**Study of vav3 ser298thr polymorphism in patients with heart failure**

**A. Andres Llamas1, C. Ciez Borrella1, M.J. Ruiz Olagado2, J.A. Perez Rivera1, P. Pabon Oszma2, C. Martin Luengo2**

1. Hospital Erasme, Brussels, Belgium; 2. University Hospital “Virgen del Rocio,” Seville, Spain

**Introduction:** Vascular endothelial growth factor (VEGF) plays a key role in angiogenesis and is required for preventing the transition from compensatory left ventricular hypertrophy (LVH) to heart failure (HF). Soluble VEGF receptor-2 (sVEGF-R2), which retains an affinity for VEGF but is unable to activate its signal transduction, acts as an endogenous inhibitor of VEGF. Recently, we demonstrated that serum sVEGF-R2 levels are increased in subjects with metabolic syndrome. However, the possible role of sVEGF-R2 in LVH or HF in human is unknown.

**Methods and Results:** We recruited 434 consecutive outpatients with or without HF, whose NIHYA classes were stable for at least 3 months. Among them, 19 had LVH (LV mass index [LVMI]; male = 116 g/m² and systolic dysfunction (LV ejection fraction [LVEF] <50%) (LVH+HF+). From leaving 415 patients, we selected patients with the presence of LVH or LVH+HF+ and divided them into LVH+HF+ and LVH+HF-. The results showed that serum sVEGF-R2 levels were increased in sera from patients with left ventricular hypertrophy and systolic dysfunction.

**Conclusion:** Our results suggest that sVEGF-R2 levels are increased in sera from patients with left ventricular hypertrophy and systolic dysfunction.

**Soluble vascular endothelial growth factor receptor-2, but not vascular endothelial growth factor, is decreased in sera from patients with left ventricular hypertrophy and systolic dysfunction**

**H. Wada, S. Ura, M. Akao, N. Masunaga, M. Abe, M. Ishii, T. Unoki, G. Osakada, A. Shimatsu, K. Hasegawa, National Hospital Organization Kyoto Medical Center, Kyoto, Japan**

**Background:** Vascular endothelial growth factor (VEGF) plays a key role in angiogenesis and is required for preventing the transition from compensatory left ventricular hypertrophy (LVH) to heart failure (HF). Soluble VEGF receptor-2 (sVEGF-R2), which retains an affinity for VEGF but is unable to activate its signal transduction, acts as an endogenous inhibitor of VEGF. Recently, we demonstrated that serum sVEGF-R2 levels are increased in subjects with metabolic syndrome. However, the possible role of sVEGF-R2 in LVH or HF in human is unknown.

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**Conclusion:** Our results suggest that sVEGF-R2 levels are increased in sera from patients with left ventricular hypertrophy and systolic dysfunction.
Conclusions: Serum levels of sVEGFR-2, but not those of VEGF or SVEGFR-1, are decreased in HF patients with LVH. sVEGFR-2 might play a role in modulation of angiogenesis in hypertrophied LV with systolic dysfunction in human.

Matrix metalloproteinase level can predict left ventricular remodeling and systolic dysfunction after myocardial infarction

M. Abdelhamid1, A. El Faramawy1, H. Gabr2, W. Ammar1, F. Al Enezi1. 1Cardiology Department, Cairo University, Cairo, Egypt; 2Department of Clinical Pathology, Cairo University, Cairo, Egypt

Purpose: Assessment of serum biomarker evidence of the early course of the cardiac type I collagen degradation (matrix metalloproteinase, MMP type-2) after myocardial infarction (MI) and relationship to left ventricular (LV) remodeling. Methods: Our study included 28 patients (14 males & 14 females with a mean age of 57.8 yrs) with acute anterior STEMI (group1) and 12 healthy volunteers (7 males & 5 females with a mean age of 59 yrs) as a control group (group2). All patients were subjected to clinical evaluation, 12-lead ECG, echo-doppler study and laboratory work-up which included formation of plasma activity level of MMP-2 within 24 h and 2 months post infarction. Echocardiography was performed within 48 h and 2 months after MI for assessment of LV volumes and ejection fraction (EF) by Simpson's method.

Results: The mean level of MMP was higher in group I than group II (20.74 vs 1.27 mg/mL, p< 0.001). The mean EF in group I was 47.8 and 37.0 within 48 hr and 2 months post MI respectively (p< 0.017). ANOVA test was conducted to evaluate the relationship between LV systolic function and MMP level both at baseline and 2 months after MI. The mean baseline MMP was 3.19, 18.6, 24.4 mg/mL in patients with normal (EF>54%), moderate (EF= 45-54%), and severe (EF< 45%) LV systolic dysfunction. ROC analysis revealed a cut off level of MMP > 3 mg/ml can predict the development of LV systolic dysfunction with a sensitivity and specificity of 89% and 84% respectively.

Conclusions: MMP increase after MI. The increase of MMP is associated with deterioration of LV systolic function both at baseline and 2 months later. A level > 3 mg/ml can predict the development of LV systolic dysfunction with a sensitivity and specificity of 89% and 84% respectively.

Activation of agonistic proteins for toll-like receptor 4 in patients with dilated cardiomyopathy

A. Riad1, J. Witte1, M. Doeri1, L. Herda1, K. Weitmann1, M. Busch1, W. Hofmann1, S.B. Félix1. 1Ernst Moritz Arndt University Greifswald, Department of Internal Medicine B, Greifswald, Germany; 2Ernst Moritz Arndt University of Greifswald, Institute of Community Medicine, Greifswald, Germany

Background: Although there is a growing body of evidence for a potential role of the innate immune receptor Toll-like receptor 4 (TLR4) in heart failure and pharmacological antagonists are currently under investigation in clinical trials regarding inflammatory diseases, the activation cascade of this receptor in cardiac diseases is still unknown. Therefore we investigated agonistic proteins of TLR4 in blood from patients with dilated cardiomyopathy (DCM).

Methods: Classical agonistic proteins of TLR4 in blood from patients with dilated cardiomyopathy (DCM) were measured: toll-like receptor 4 (TLR4), namely lipopolysaccharide binding protein (LBP), soluble CD14 (sCD14), lipopolysaccharide (LPS) and MD-2, were quantified in serum from 158 patients with early stage of DCM (disease duration <1 year, LV-EF< 50%, LV end-diastolic diameter > 60 mm) by ELISA. Other reasons for heart failure were excluded by coronary angiography, myocardial biopsy and echocardiography. Healthy blood donors served as controls (n=13). Protein contents of LPS were significantly reduced in patients with DCM (50%; P< 0.05) when compared to healthy controls. In contrast, protein level of LBP (+78%; P< 0.05) and sCD14(+19%; P< 0.001) were significantly decreased in DCM patients when compared to controls. MD-2 serum protein level were in- creased in direction in DCM patients when compared to healthy controls, but it did not reach a statistically significant value (P=0.06).

Conclusion: In a carefully characterised cohort of DCM patients, we showed for the first time a systemic regulation of TLR4 agonists on protein level suggesting a potential role of TLR4 in DCM. Our findings might give a basis of further therapeutic approaches.

Oxidative stress, inflammation and low levels of adiponectin in risk factors of left ventricular hypertrophy in type 2 diabetics with renal disease


Introduction: The pathophysiology of left ventricular hypertrophy is multifactorial and not completely understood. Recent studies have demonstrated the role of oxidative stress, inflammation and adiponectin in cardiovascular morbidity and mortality.

Purpose: The aim of this study was to evaluate factors associated with the left ventricular hypertrophy (LVH) in a population of type 2 diabetics with mild and moderate kidney disease.

Methods: In this cross-sectional study we included 78 type 2 diabetic patients (f = 30, m = 48), with a mean age of 61 years and a mean estimated glomerular filtration rate (MDRD) of 43.5 ml/min, followed in our outpatient nephrology clinic. We analyzed several laboratory parameters, such as: interleukin 6 (IL6), adiponectin (visfatin, resistin, apelin-36), oxidative stress (xSLOD), as well as the left ventricular mass index (LVMI) in our patients.

Results: In a simple regression model, the LVMI was positively correlated with age (r=0.322 p=0.004), IL6 (r=0.722 p=0.0001), resistin (r=0.705 p=0.0001), vis- fatin (r= 0.706 p= 0.0001), xSLOD (r= 0.752 p= 0.0001) and inversely with apelin-36 (r= -0.901 p<0.0001) and the glomerular filtration rate (r= -0.381 p<0.0001). In a multiple regression model, only IL6 (r=0.148 p=0.049), xSLOD (r=0.257 p=0.024) and apelin-36 (r=-0.736 p=0.001), independently influenced the LVMI. ROC curve analysis showed that oxSLOD (AUC= 0.852 p< 0.0001) and IL6 (AUC= 0.931 p<0.0001) are predictors of left ventricular hypertrophy.

Conclusion: Our study showed that in type 2 diabetic patients with nephropathy, the oxidative stress, the inflammation and the adiponectins are determinants of left ventricular hypertrophy. Surely they also contribute to the complexity of CKD associated cardiovascular risk.

Cardiomyocyte structural deterioration and metabolic response in human DCM hearts

E. Czarnecka1, L. Ziolkowska2, M. Kaleta1, M. Syczewskawi, W. Kawaalic, E. Flejchman-Warmusz3, R. Wojniczi4. 1The Children’s Memorial Health Institute, Department of Cardiology, Warsaw, Poland; 2The Children’s Memorial Health Institute, Department of Pediatric Rehabilitation, Warsaw, Poland; 3Silesian Medical University, Department of Histology and Embryology, Zabrze, Poland

Dilated cardiomyopathy (DCM) is associated with cardiac dysfunction and various histopathological characteristic and poorly known metabolic deterioration during structural and functional remodelling. The aim of this study was the expression pattern of structural deterioration and metabolic responses in human DCM hearts. The archive tissue samples of left ventricle originated from DCM hearts divided in respect to ≤EF on three groups: (1) 45-55% (n=13), (2) 30-40% (n=6) and (3) <30% (n=10) were investigated histopathologically, ultrastructurally and immunohistochemically in DCM hearts from patients with dilated cardiomyopathy (DCM). The collective findings reveal a close relationship between functional, structural and metabolic remodeling of cardiac myocytes in group 2 and 3, and cumulative ultrastructural pathology as loss of contractile filaments, increased size and number of mitochondria or mitochondria matrix and cristae deterioration. Increased cardiomyocytes diameter and fibrosis were significant in all 3 vs 1 and 2 groups and both ctrl. The decrease of PAS(+) material, and expression of fetal phenotype in about 12% cardiomyocytes and PPARalpha in predominant number of nuclei was observed in group 1. Contrary, in group 2 further advanced cellular pathology followed by minor number of nuclei PPARalpha(+) cytoplasm, increased PAS(+) material, and expression of fetal phenotype in about 1% cardiomyocytes. The decrease of PAS(+) material and expression of fetal phenotype in about 1% cardiomyocytes. The decrease of PAS(+) material and expression of fetal phenotype in about 1% cardiomyocytes were characteristic features. Either glucogen nor SMAlpha and apoptosis were not detected in tissue sections in group 3. In this group PPARalpha expression was present in various number of nuclei (from 0 to 50%). The PPARY in scarce nuclei, and presence of PAS(+) material and re-expression of fetal phenotype in many cardiomyocytes were characteristic features of ctrl. There was a significant correlation between PPARalpha and %EF (R=0.684, p<0.001) and %EF (R=0.768, p<0.001) and %PAS(+) cardiomyocytes (R<0.544, p<0.001).

The collective findings reveal a close relationship between functional, structural and metabolic remodeling of cardiomyocytes and PPARalpha expression. Disturbance in glucogen presence and PPARalpha expression in biopsies of DCM hearts seem to be markers of cardiomyocytes metabolic shift.

Abrogation of S100B expression in S100A1 deficient mice improves survival post myocardial infarction

J. Tosporisi, J-F. Desjardins1, S. Ithazi1, F. Mohammadiadeh1, G. Proteau1, J. Baudler2, T.G. Parker1, 1St. Michael’s Hospital, Toronto, Canada; 2Universite Joseph Fourier, Grenoble, France

Post-myocardial infarction (MI) ventricular remodeling involves ventricular dilatation, hypertrophy of non-infarcted myocardium, myocyte apoptosis, the induction of S100B and the downregulation of S100A1. Whereas S100A1 defends results in cardiac functional impairment and high early mortality post-MI. Abrogation of S100B preserves cardiac function in the setting of augmented hypertrophy post-MI. To assess the consequences of S100B expression in S100A1 knock out (KO) mice, wild-type (WT), S100A1 KO, S100B KO and S100A1-B KO mice. After 8 week-old mice were subjected to 35 days after left anterior descending coronary artery ligation with similar age-matched sham-operated controls. S100A1-B KO mice demonstrated better survival as compared to S100A1 KO and WT mice.
Impact of the PPARGC1A Gly482Ser polymorphism on left ventricular structural and functional abnormalities in patients with cardiovascular risk factors

W. Kosmala, M. Ciecieja-Prynda, L. Laczmannski, A. Orda, B. Karolko, A. Mysiak, M. Przewlocka-Kosmala. Wroclaw Medical University, Wroclaw, Poland

The Gly482Ser polymorphism in peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PPARGC1A) has been demonstrated to be involved in some pathophysiological aspects of metabolic and hemodynamic regulation, however the exact data linking these genomic variations with cardiac remodelling is incomplete. We sought to investigate the association between the PPARGC1A Gly482Ser polymorphism and left ventricular (LV) structural and functional abnormalities in patients with cardiovascular risk factors: hypertension, diabetes and obesity.

Methods: Each of 150 enrollees (age 59±8 yrs) underwent echo study with assessment of LV systolic (strain and strain rate, s′E) and diastolic function (mitral inflow E/A ratio, tissue E velocity, Em) and myocardial reflectivity (calibrated integrated backscatter, iIB), and evaluation of the PPARGC1A Gly482Ser polymorphism.

Results: Patients with the Ser allele (Ser/Ser or Ser/Gly) showed a greater extent of LV hypertrophy and LV diastolic function impairment compared to C/G and mitral E/a ratio compared with subjects with the Gly homoygote. No differences between these groups in metabolic control parameters (fasting glucose, HOMA IR and HbA1c), as well as in blood pressure were noted. In a multivariable analysis, the independent correlates of LV mass index were hypertension (β=0.31; p<0.001), Ser allele (β=0.32; p<0.001), HbA1c (β=0.25; p<0.001), BMI (β=0.25; p<0.001) and patient age (β=0.22; p<0.001). Em velocity was independently associated with age (β=0.22; p<0.001), HbA1c (β=0.25; p<0.001), CIB (β=0.26; p<0.001), hypertension (β=0.21; p<0.001) and Ser allele (β=0.19; p<0.02).

Conclusions: In patients with cardiovascular risk factors, the PPARGC1A Gly482Ser polymorphism contributes to LV hypertrophy and diastolic dysfunction with the Ser allele promoting these abnormalities.

Circulating myeloid dendritic cells and interleukin-6 are predictors of heart failure in dilated and ischemic cardiomyopathy


Background: We previously reported significant decreases of circulating myeloid dendritic cells (mDCs) in peripheral blood of patients with dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (ICM). Presently, we investigated the release of proinflammatory cytokines, their correlation to circulating mDCs, as well as their predictive value for heart failure (HF) in DCM and ICM.

Methods: Plasma levels of interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-10 (IL-10), and interleukin-12 (IL-12), and tumor necrosis factor alpha (TNF-α) were analyzed using a cytokine bead array kit in 62 patients with DCM, 48 patients with ICM and 42 healthy age-matched individuals as controls. In the same groups, circulating mDCs were flow cytometrically analyzed. The predictive value for HF (EF < 55%) was investigated for inflammatory cytokines, circulating mDCs, as well as for different clinical factors, such as hypertension, age, diabetes, gender, and dyslipidemia using univariate analysis. Factors showing a statistical significance were further entered in a multivariate analysis using stepwise logistic regression in order to identify independent predictors for HF.

Results: From the analyzed cytokines in the ICM group, only serum levels of IL-6 were significantly elevated (1.8 fold, p = 0.005) compared to controls. No significant changes regarding inflammatory cytokines were found for the DCM group. Circulating mDCs were significantly reduced in patients with DCM (0.14% vs. 0.20%, p = 0.01) as well as in ICM (0.15% vs. 0.20%, p = 0.039) compared to healthy controls. There was a significant inverse correlation between IL-6 levels and circulating mDCs in DCM (r = -0.49, p<0.001); in ICM a similar but less significant correlation (r = -0.25, p = 0.05) was observed. In univariate analysis, we found mDCs, male gender, hypertension, diabetes, and dyslipidemia to be predictive for HF for the DCM group; while mDCs, male gender and hypertension remained as independent predictors for HF. In contrast, for ICM, independent predictors were IL-6, male gender and dyslipidemia.

Conclusions: We show different results in plasma levels of IL-6 and circulating mDCs in our patient collectives with respect to their etiology of HF (ischemic vs. dilated cardiomyopathy). Circulating mDCs and IL-6 could therefore be useful as differentiation markers in the diagnosis of cardiomyopathies and they appear to be independent predictors of HF in DCM and ICM respectively.

The bone morphogenic protein-antagonist Gremlin-1 serves as a new biomarker for structural heart disease and predicts clinical outcome

K.A.L. Mueller1, C.S. Zuen1, U. Kramer2, R. Kandolf3, M. Gawaz1, I.J. Mueller1. Universitätsklinikum Tübingen, Kardiologie, Tübingen, Germany; 2Universitätsklinikum Tübingen, Radiologie, Tübingen, Germany; 3Universitätsklinikum Tübingen, Pathologie, Tübingen, Germany

Background: Gremlin-1 is involved in inflammatory and fibrotic processes. Aim of the present study was to assess the diagnostic and prognostic value of Gremlin-1 expression in endomyocardial tissue of patients with structural myocardial diseases.

Methods: 214 unselected patients undergoing endomyocardial biopsies were enrolled. Endomyocardial tissue sections were evaluated according to standard histological and immunohistological criteria (CD68, MHC II, CD3, virus genome detection) along with Gremlin-1 staining. The primary combined endpoint was still not known. In the present study, we have hypothesized alteration in Tregs is associated with deterioration of cardiac function in the patients with reduced EF.

Methods: Total 52 patients were enrolled in this study. The study population consisted of thirty three chronic heart failure (HF) patients with low ejection fraction (less than 50%), who were hospitalized for acute decompensated HF, and nineteen non-HF patients as control. Peripheral proportion of Tregs was evaluated by flow cytometric analysis (FCM), plasma cytokine levels were measured. Furthermore, HF patients were followed by 1 year for evaluation of clinical outcome.

Results: The proportion of Tregs was significantly decreased (5.9±1.4% vs 8.0±2.2%, p<0.01) as well as in ICM (0.175% vs 0.20%, p=0.039) compared to healthy controls. There was a significant inverse correlation between IL-6 levels and circulating mDCs in DCM (r = -0.49, p<0.001); in ICM a similar but less significant correlation (r = -0.25, p = 0.05) was observed. In univariate analysis, we found mDCs, male gender, hypertension, diabetes, and dyslipidemia to be predictive for HF for the DCM group; while mDCs, male gender and hypertension remained as independent predictors for HF. In contrast, for ICM, independent predictors were IL-6, male gender and dyslipidemia.

Conclusions: We show different results in plasma levels of IL-6 and circulating mDCs in our patient collectives with respect to their etiology of HF (ischemic vs. dilated cardiomyopathy). Circulating mDCs and IL-6 could therefore be useful as differentiation markers in the diagnosis of cardiomyopathies and they appear to be independent predictors of HF in DCM and ICM respectively.
Lung ultrasound for the evaluation of pulmonary congestion in pre-transplantation heart failure outpatients: clinical comparison with natriuretic peptides

M.H. Miglioranza1, L. Gargani2, R.T. Sant’Anna1, M. Roveri1, M. Martinelli1, C.J. Feldman1, R.A. Kall1, R. Sicari2, T.L. Leilha1.
1 Institute of Cardiology of Rio Grande do Sul - University Foundation of Cardiology, Porto Alegre, Brazil; 2Institute of Clinical Physiology of CNR, Pisa, Italy

Purpose: Evaluation of pulmonary congestion is a frequent diagnostic challenge even by highly skilled clinicians. Recently, lung ultrasound (LUS) has been proposed for a reliable, easy evaluation of pulmonary congestion, by assessment of B-lines (also called ultrasound lung comets). Our aim was to define the relationship between B-lines and natriuretic peptides (NT-proBNP) as part of the evaluation of pre-transplant heart failure (HF) patient in an outpatient clinic.

Methods: Fifty-eight patients admitted to a pre-transplantation clinic due to advanced systolic HF (65.5% men, mean age 49±11 yns, 47.2% with idiopathic and 29.3% with post-ischemic cardiomyopathy) were enrolled. Clinical assessment, NT-proBNP analysis and LUS evaluation were independently performed.

Results: Feasibility was 100%. Mean time toperform LUS was 9.9±2.45 minutes. Significant pulmonary congestion was present in 57.9% by LUS (total B-lines number ≥15). B-lines number was significantly correlated to NT-proBNP values (r=0.74, p<0.0001). Assuming NT-proBNP > 1000ng/mL as a reference for decompensated HF, ROC analysis showed a C statistic of 0.88 (95% CI: 0.72-0.92, p<0.0001) for LUS, providing the best accuracy with a cut-off of 14 B-lines (sensitivity 96.2, specificity 71.9%).

Conclusion: In a pre-transplantation heart failure outpatient clinic, B-lines evaluated by LUS are significantly correlated to NT-proBNP values. Given its accuracy, low cost and portability, LUS may be considered as a reliable tool for a quick and easy evaluation of pulmonary congestion in decompensated HF patients.

Depressed midwall fractional shortening is a powerful prognostic determinant in cardiac AL amyloidosis

S. Perlini1, F. Salinaro1, F. Muscarà1, R. Mussinelli1, M. Boldrini1, A. Raimondi1, A. Alogna1, P. Pesce1, G. Merlini1, C. Rapezzi1.
1 Foundation IRCCS Policlinico San Matteo, Medical Clinic II - University of Pavia, Pavia, Italy; 2Niguarda Ca Granda Hospital, Department of Cardiology, Milan, Italy; 3Center for Amyloidosis, Biotechnology Laboratories IRCSS San Matteo, Pavia, Italy; 4Sant’Orsola-Malpighi Polyclinic, Department of Cardiology, Bologna, Italy

Background: Systemic amyloidoses are characterized by extracellular deposition of insoluble fibrils in various tissues. Clinical presentation is variable, depending on the extension of deposits and on the extent of organ dysfunction. In AL amyloidosis, the amyloidogenic protein is an immunoglobulin light chain or a fragment of an Ig light chain that is synthesized by clonal plasma cells in bone marrow. Cardiac involvement is not only frequent, but it is also the most common potential cause of death. Cardiac amyloidosis represents an archetypal form of restrictive heart disease, characterized by profound diastolic dysfunction. Since ejection fraction is preserved until the late stage of the disease, the majority of patients with cardiac AL amyloidosis do fulfill the definition of diastolic heart failure, i.e. heart failure with preserved ejection fraction. In another clinical model of diastolic heart failure, i.e. pressure-overload left ventricular hypertrophy, depressed midwall fractional shortening (i.e. a marker of myocardial contractile dysfunction) has been shown to be a powerful prognostic factor.

Method: To assess a potential prognostic role of midwall fractional shortening in cardiac AL amyloidosis patients, we enrolled 261 consecutive patients with cardiac AL amyloidosis, in whom a cardiac involvement had been shown to be a powerful prognostic factor.

Results: When compared with AL patients without myocardial involvement, cardiac AL was characterized by increased wall thickness (p<0.001) and reduced end-diastolic LV volumes (p<0.001). As expected, diastolic dysfunction was evident in all cardiac AL patients, as evident by increased E/E' ratio (p<0.001). Midwall fractional shortening was markedly depressed (11.2±4.3 vs 22.1±4.4%, p<0.001), despite preserved ejection fraction. At multivariable analysis, midwall fractional shortening (p<0.0003) and NT-proBNP (p<0.0002) were the only significant prognostic determinants, whereas other indices of diastolic (E/E' ratio, transmural and pulmonary vein flow velocities) and systolic function (tissue-Doppler systolic indices, ejection fraction) did not enter the model.

Conclusions: In cardiac AL amyloidosis with normal ejection fraction, depressed midwall fractional shortening, a marker of myocardial contractile dysfunction, is a powerful predictor of survival.

The electrocardiographic/echocardiographic mass ratio in the diagnosis of cardiac amyloidosis

S. Perlini1, F. Salinaro1, F. Muscarà1, R. Mussinelli1, M. Boldrini1, A. Alogna1, C. Quarta1, G. Palladini1, G. Merlini1, C. Rapezzi1.
1 Foundation IRCCS Policlinico San Matteo, Medical Clinic II - University of Pavia, Pavia, Italy; 2Niguarda Ca Granda Hospital, Department of Cardiology, Milan, Italy; 3Sant’Orsola-Malpighi Polyclinic, Department of Cardiology, Bologna, Italy; 4Center for Amyloidosis, Biotechnology Laboratories IRCSS San Matteo, Pavia, Italy

Background and Aim: In cardiac AL amyloidosis the increase in wall thickness caused by extracellular amyloid deposition leads to marked increases in left ventricular (LV) mass. At variance with other forms of cardiac hypertrophy, this is often associated with abnormally low electrocardiographic (ECG) voltages, due to amyloid negative effects on intracardiac electrical conduction. Although such a discrepancy (low ECG “electrical” LV mass/high echo-derived LV mass) might be a helpful diagnostic clue, this is often missed since almost 40% of cardiac AL patients do not strictly fulfil the definition of “EKG low voltages” (≤5 mV in all peripheral leads).

Methods: To evaluate its possible clinical relevance, an index of the ECG/echocardiographic mass ratio was compared in 1000 consecutive patients with cardiac AL (n=315), hypertrophic cardiomyopathy (n=207), hypertension with different degrees of LV hypertrophy (n=478). Echo-derived LV mass was indexed for body-surface area (g/m²), whereas peripheral QRS score (sum of QRS voltage in the peripheral leads, mV) was used as an index of “electrical” LV mass. ECG/Echo ratio was expressed as [mV]/[g/m²]). Also total QRS score and Sokolow-Lyon index were computed and divided by echo-derived LV mass in order to estimate potential causes of low QRS voltages (large pericardial effusions, obesity, chronic obstructive lung disease, and severe peripheral edema) were excluded.

Results: In a preliminary evaluation of NT-proBNP values. Given its accuracy, a 91.43% sensitivity and a 74.53% specificity in identifying the presence of cardiac involvement in 145 out of 200 consecutive AL patients. When compared to both hypertrophic cardiomyopathy [0.37 (0.30-0.53) mV/g/m²] and hypertensive [0.33 (0.27-0.40) mV/g/m²] subjects, the ECG/Echo ratio was markedly depressed in patients with cardiac AL [0.14 (0.10-0.20) mV/g/m²], p<0.001 vs. all the other groups. The area under the ROC curve for the detection of cardiac AL involvement was high: 0.970 (95% CI 0.956 to 0.980; p<0.0001)},
Evidence of subclinical perimyocardial involvement in patients with systemic lupus erythematosus: late gadolinium enhancement study

King's College London, Division of Imaging Sciences, London, United Kingdom

Purpose: Increased inflammation has been linked to myocardial dysfunction and heart failure. We investigated whether patients with systemic inflammatory diseases, such as systemic lupus erythematosus (SLE), free of cardiac symptoms, have evidence of subclinical inflammatory myocardial involvement.

Methods and results: A total of 27 SLE patients (male=6, mean age 41±11 years) with no previous cardiac history underwent cardiovascular magnetic resonance imaging for assessment of function and late gadolinium enhancement on a 3 Tesla scanner. In these patients, the presence of significant coronary artery disease was excluded by virtue of negative adenosine myocardial perfusion or normal high-resolution magnetic resonance coronary angiography. Fifteen age-matched subjects with a low pre-test probability acted as a control group. In SLE group, there was deceased global systolic function (SLE vs. controls: 47±7% vs. 60±5%, p<0.05) and increased LV mass index (68.2 g/m² vs. 43.4 g/m², p<0.001). Late enhancement was visualized in 20 SLE subjects: 14 patchy areas of intramyocardial enhancement and 6 subjects showed intramyocardial stria. Myocardial enhancement was invariably affecting the basal segments of inferior septum, inferior and inferolateral walls and right-ventricular insertion points. The mean thickness of the pericardial space along the free LV wall was present in 4 patients. Pericardial enhancement was present in 17 patients.

Conclusions: We demonstrate that in SLE patients free of significant coronary artery disease there is evidence of subclinical perimyocardial involvement.

Cardiac myosin binding protein C gene polymorphisms and diastolic heart failure

C. Wu1, J. Lee2, C. Tsai1, F. Chiang3, National Taiwan University Hospital, Taipei, Taiwan; 4Far Easter Memorial Hospital, New Taipei City, Taiwan

Objective: Myosin binding protein C (MYBPC3) gene polymorphisms and diastolic heart failure (DHF) in a human case-control study.

Methods: A total of 352 participants of 1752 consecutive patients from the National University Hospital and its affiliated hospital were enrolled. 176 patients diagnosed with DHF confirmed by echocardiography were recruited. Controls were matched 1:1 by age, sex, hypertension, diabetes, renal function and medication use. We genotyped 12 single nucleotide polymorphisms (SNPs) according to HapMap Han Chinese databank across a 40 kb genetic region containing the MYBPC3 gene and the neighboring DNA sequences to capture 100% of haplotype variance in all SNPs with minor allele frequencies ≥5%. We also analyzed associations of SNPs and haplotypes with DHF and linkage disequilibrium (LD) structure of the MYBPC3 gene.

Results: In a single locus analysis, SNP rs2290149 was associated with DHF (allele-specific p = 0.004; permuted p = 0.031). The SNP with a minor allele frequency of 9.4%, had an odds ratio 2.14 (95% CI 1.25-3.66; p = 0.004) for the additive model and 2.06 for the autosomal dominant model (GG+Ga, 95% CI 1.17-3.63; p = 0.013), corresponding to a population attributable risk fraction of 12.02%. The haplotypes in a LD block of rs2290149 (C-C-G-G) was also significantly associated with DHF (odds ratio 2.10 (1.53 - 2.89); permuted p = 0.029).

Conclusions: We identified risk-conferring genetic variants of MYBPC3 gene for DHF in a Chinese population.

Subclinical abnormalities of the arterial tree and left ventricular myocardial deformation, relaxation and twist in chronic kidney disease

V. Panoulas, S. Sulemane, A. Bratas, P. Nihoyannopoulos.
Hammersmith Hospital, London, United Kingdom

Purpose: Chronic kidney disease (CKD) associates with adverse cardiovascular outcomes. However, the disadvantageous effects of renal dysfunction on left ventricular systolic and diastolic function remain unclear. The objective of this study was to look at the effect of CKD on (i) left ventricular (LV) systolic and diastolic strain patterns and LV twist with the use of conventional and 2D speckle tracking echocardiography, and (ii) arterial stiffness as measured by pulse wave velocity (PWV).

Methods: Seventy-four consecutive CKD patients were assessed using conventional, 2D speckle tracking echocardiography (EchoPAC-GE) and applanation tonometry (Sphygmocor). Patients with (i) LV systolic dysfunction or regional wall motion abnormalities, (ii) moderate to severe valvular disease or (iii) heart rhythm other than sinus were excluded (N=5). Global systolic strain (GS) and strain rate (GSRs), early (GSe) and late (GSRa) diastolic longitudinal strain rate, LV twist and twist rate, mitral inflow, tissue PW-Doppler velocities and PWV were recorded.

Results: The mean age of CKD patients was 54±15.4 years and 34 (49.3%) were female. Femoral bioimpedance (EF) was 62.2±5.4%. Six (8.7%) patients were stage 1 CKD, 17 (24.6%) stage 2, 29 (42%) stage 3, 12 (17.4%) stage 4 and 5 (7.2%) stage 5. Estimated Glomerular Filtration Rate (eGFR) correlated significantly with PWV (r=-0.27, p=0.001), GSRs (r=-0.26, p=0.028), LV twist rate (r=-0.27, p=0.026) and E/E' (r=-0.37, p=0.002). There was a trend of a correlation between eGFR and LV twist (r=-0.216, p=0.083), isovolumic relaxation time (IVRT) (r=-0.232, p=0.058) and E/A ratio (r=0.217, p=0.073). There was no correlation between eGFR and GS, GSRa or biomarker parameters in eGFR and GSRa in diastolic ejection fraction. When including the echocardiographic parameters in a linear regression model with dependent variable eGFR, E/E' (beta -1.75, p=0.007) and LV twist rate (beta -0.17, p=0.021) were independent significant predictors. Amongst CKD stages 1-2 patients there were 6 (33.3%) with diastolic dysfunction, in stage 3 the figure increased to 17 (75%) and in stages 4,5 further to 14 (82.4%) (Chi-Square 13.7, p=0.03).

Conclusions: Arterial stiffness and LV relaxation demonstrate progressive deterioration with worsening eGFR whereas LV filling pressure and twist rate appear to increase, compensating for the impaired diastolic filling. Outcome studies may be required to identify the association of these early markers of cardiovascular disease in CKD patients.

Peak cardiac power output: a new hemodynamic tool to aid the diagnosis of heart failure with preserved ejection fraction? A pilot study

1Department of Cardiology, Witten/Herdecke University, HELIOS Klinikum Wuppertal, Wuppertal, Germany; 2Core Vital, Institute for Cardiovascular Medicine and Wupper, Germany; 3Bayer Schering Pharma, Global Biomarker Research, Wuppertal, Germany; 4Augusta Krankenhaus Düsseldorf, Düsseldorf, Germany; 5Institute for Cardiology and Sports Medicine, German Sport University Cologne, Germany

Purpose: By coupling both the pressure and flow generating capacities of the heart, the peak cardiac power output peak (CPO) is a direct measure of cardiac function during exercise and a major determinant of exercise capacity. Furthermore, in patients with systolic heart failure (SHF), peak CPO x 1.5 W is an independent and powerful predictor of prognosis that can be measured non-invasively using cardio-pulmonary exercise testing. This is the first study to investigate the diagnostic value of the CPO in patients with heart failure with preserved ejection fraction (HFpEF).

Methods: Among the 45 patients (age 66 [53-73] years) included into the study, 10 subjects were classified as HFpEF, 24 patients had SHF (EF < 35%) and 11 subjects served as a control group. All subjects underwent symptom limited bicycle exercise with noninvasive quantification of cardiac output (CO) using an inert gas rebreathing method. CPO was calculated as the product of CO and mean arterial blood pressure/451 as described previously.

Results: The peak CPO was significantly different among the groups: 2.42 (1.88-3.32) W in controls vs. 1.67 (1.17-2.09) W in SHF vs. 1.44 (1.22-1.69) W in HFpEF (p=0.018). There was a significant correlation between the peak CPO and the peak oxygen uptake (VO2peak; n=40, p=0.002) and NT-proBNP levels (n=56, p=0.001).

Conclusions: The present study is the first to evaluate peak CPO as a direct measurement of hemodynamic response to exercise in patients with HFpEF. The peak CPO of patients with HFpEF and SHF was similar reduced. Therefore, peak CPO can identify abnormalities in cardiovascular function consistent with those
predicting mortality in HFpEF and may enhance the ability to accurately identify patients at greatest risk for heart failure related complications.

Relationship of pro-collagen biomarkers of myocardial fibrosis with myocardial dysfunction and metabolic derangement in type 2 diabetes

C. Jelli1, J. Sacre1, J. Jenkins1, B. Haluska2, J. Martin1, T. Marwick2
1University of Queensland, Brisbane, Australia; 2Cleveland Clinic, Department of Cardiovascular Medicine, Cleveland, United States of America

Purpose: Myocardial fibrosis is a potential contributor to non-ischemic diastolic dysfunction (DD) in type 2 diabetes (T2DM). We sought the relationship between fibrosis markers, myocardial dysfunction and metabolic derangement.

Methods: Clinical, imaging and biochemical data were measured in 390 asymptomatic subjects (216 men, 58±10 yrs) with T2DM. Myocardial function was examined with standard 2D echo, early diastolic [em] and systolic velocity, strain, strain rate, and backscatter (cIB). Amino-terminal propeptides of pro-collagen type I (PINP) and type III (PNIINP) were measured by radio-immunoassay, and the carboxy-terminal propeptide of type I pro-collagen (PICP) was measured by enzyme linked immunosorbent assay.

Results: Patients were stratified by metabolic derangement; 53 (14%) had isolated T2DM, 67 (17%) had T2DM with isolated hypertension, 178 (45%) had T2DM with both metabolic syndrome and 92 (24%) had T2DM with metabolic syndrome and end-organ involvement (microalbuminuria). Progressive metabolic derangement was mirrored by worse DD (em p=0.001), increased cIB (p=0.016), greater insulin resistance (log HOMA-IR p<0.001) and worse exercise capacity (VO2 max p<0.001) but only a trend towards proportionally higher PNIINP levels. PNIINP (3.9±1.9 μg/L) was associated with insulin resistance (log HOMA-IR r=0.208, p=0.008) independent of age (r=0.186, p=0.017) and renal function (creatinine r=0.227, p=0.004). PINP (42.2±28.4 μg/L) and PICP (275.2±80.4 ng/ml) were not associated with metabolic parameters or myocardial properties.

Conclusions: Metabolic derangement in T2DM is proportionally associated with worsening DD and increased myocardial signal intensity (cIB). The association with PNIINP levels is weak, suggesting a limited role of type III collagen turnover in subclinical, non-ischemic diabetic heart disease.

Acute improvement of left atrial mechanics and left ventricular diastolic function after Transcatheter Aortic Valve Implantation

Charité - University Medicine Berlin, Campus Mitte, Department of Cardiology and Angiology, Berlin, Germany

Purpose: Aortic stenosis leads to remodelling of the left ventricle and atrium that causes systolic and diastolic dysfunction. Transcatheter aortic valve implantation (TAVI) is a rapidly evolving therapy for severe aortic stenosis in high-risk patients. Two-dimensional speckle tracking echocardiography (STE)-derived strain measurements enable the regional assessment of left atrial (LA) mechanics. The goal of this study was to describe the acute effects on myocardial deformation of the LA and left ventricle (LV) diastolic function after TAVI.

Methods: 32 consecutive patients (17 female, mean age 76 years, mean Euroscore 18.7%, mean LVEF 52±5.17%) with severe aortic stenosis (0.73±0.19 cm²) were enrolled into our study. We performed transhosphoric echocardiography including STE of the basal septal segment of the left atrium to determine peak positive strain (LAps), strain during early diastole (eLAD) and, if feasible, strain during atrial contraction (LAA) representing LA reservoir, conduit, and contractile function, respectively. In addition, the corresponding strain rate values such as peak positive strain rate (LApsr), strain rate during early diastole (eLARD) and, if feasible, strain rate during atrial contraction (LAAr) were calculated. Aortic regurgitation was quantified according to visual estimate (median annulus, the best TDE parameter, and 0.867, 0.851, 0.812, 0.813, 0.854, and 0.825 for E/E', P1, P2, PA, Ap, and Pb, respectively (Figure)). Multivariable logistic regression models proved that measures of pul- satile arterial function provided independent and additive diagnostic information.

Conclusion: Measures of arterial stiffness, central pressures and wave reflections complement TDE for the diagnosis of DHF.

Perhexiline corrects energy deficiency and improves symptoms in chronic heart failure

1University of Aberdeen, Aberdeen, United Kingdom; 2Toronto General Hospital, Toronto, Canada; 3University of Birmingham, Birmingham, United Kingdom; 4University of Wales College, Cardiff, United Kingdom

Background: We hypothesized that the metabolic modulator perhexiline would ameliorate myocardial energy deficiency and improve symptoms in dilated cardiomyopathy.

Methods and Results: 50 patients with heart failure (NYHA II - IV; LVEF <40%) were randomised to 100mg bd (n=25) or placebo (n=25) for 1 month in a double blind fashion. Myocardial ratio of phosphocreatine to adenosine triphosphate was established marker of cardiac energetic status, as measured by 31P magnetic resonance spectroscopy, echocardiography, symptoms and quality of life scores were assessed at baseline and at study end. Perhexiline improved the primary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Perhexiline Group</th>
<th>Placebo Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCr/ATP</td>
<td>1.16±0.08</td>
<td>1.51±0.11</td>
<td>0.005</td>
</tr>
<tr>
<td>NYHA Class</td>
<td>2 (I: 10 (8)); 2 (I: 10 (8)); 2 (I: 10 (8)); 2 (I: 10 (8))</td>
<td>1 (IV)</td>
<td>0.005</td>
</tr>
<tr>
<td>dT</td>
<td>20 (9-46)</td>
<td>30 (11-49)</td>
<td>0.02</td>
</tr>
<tr>
<td>NTProBNP, pg/ml</td>
<td>1325 (763-1890)</td>
<td>454 (248-659)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Effect of perhexiline and placebo on PCr/ATP ratio, NYHA class, dT and NTProBNP levels.
We hypothesised that levosimendan will improve myocardial regional contractility without harmful side effects in acute PCI treated STEMI patients complicated by decompensated heart failure.

**Method:** Patients developing clinical signs of heart failure (including cardiogenic shock) within 48 hours after a primary PCI treated STEMI with decreased wall-motion in ≥ 5 of 16 segments evaluated by echocardiography, were randomised to a 216 hours levosimendan infusion or matching placebo in a double blind design. Primary endpoint was change in wall-motion score index (WMSI) from baseline to day 5. Infarct size was measured by single photon emission computed tomography (gated SPECT) at 6 weeks.

**Results:** (mean ±SD): A total of 61 patients were included. Age (64±13 years), peak cardiac troponin T (1300±6996 ng/l), BP (104/66 mmHg) and left ventricular EF (46±9%) at inclusion, were not significantly different between groups. Infarct size at 6 weeks (42±16%) was similar in both groups. There was significantly larger improvement in WMSI from baseline to day 5 in the levosimendan group compared to placebo (from 1.94±0.20 to 1.66±0.31 vs. 2.02±0.26 to 1.83±0.26 respectively, p=0.03). There were no significant between-group-differences from baseline to day 5 in changes in NT-proBNP levels, a clinical composite score, frequency of atrial fibrillation or ventricular arrhythmia, new ischemic episodes or use of inotropy as rescue therapy. There were significantly more episodes of hypotension during study drug infusion in the levosimendan group (63% vs 36%, p=0.03), but no difference in blood pressure at the end of infusion or in use of vasopressors. One patient died in the levosimendan group and 4 patients in the placebo group during 6 months follow-up. No significant between-group-differences at 6 months in MACE (death, nonfatal myocardial infarction or revascularisation of the infarct related artery) or in rehospitalisation for heart failure, were present.

**Conclusions:** Levosimendan treatment improved regional contractility measured by WMSI in patients with acute PCI treated STEMI complicated by heart failure, but did not affect NT-proBNP levels or clinical symptom score. The treatment was well tolerated without any increase in atrial fibrillation or ventricular arrhythmias.

**P5153**

The effect of aldosterone-antagonist therapy on aortic elastic properties in patients with moderate heart failure

E. Vizzardi, A. D’Alapia, D. Pella Pina, C. Lombardi, I. Bonadei, R. Piovelli, M. Metra, L. Del Cas. Civil Hospital of Brescia, Department of Cardiology, Brescia, Italy

**Purpose:** Many studies proved the prognostic importance of aortic stiffness as an independent predictor of cardiovascular predictor of cardiovascular mortality and all – cause mortality. The decrease of arterial compliance presents an high prevalence in heart failure patients affecting haemodynamics and prognosis. Aortic stiffness is partially caused by excessive activation of renin – angiotensin – aldosterone system (RAAS) and aldosterone – antagonist like Spironolactone seems decrease aortic stiffness and fibrosis in experimental models. Nevertheless there are few studies that describe the effects of aldosterone – antagonist on aortic stiffness in patient with dilated cardiomyopathy.

**Aims of study:** To evaluate the effect of a therapy with aldosterone – antagonist Spironolactone aortic stiffness in Patients with idiopathic dilated cardiomyopathy.

**Methods:** We randomized (1:1) 102 patients with idiopathic dilated cardiomyopathy and New York Heart Association class I – II to receive Spironolactone 25 mg/die or placebo, in addition to recommended therapy. The end points were aortic stiffness index, systolic and aortic strains. All measures were obtained with echocardiography M – mode at 3 cm above the aortic valve on parasternal long axis view and simultaneous brachial arterial pressure with sphygmomanometer.

**Results:** Ascending aorta measures, aortic stiffness index, aortic distensibility and aortic strain were similar at randomization in the two groups. After 6 month of therapy in the treated group we found a statistically significant reduction of aortic strain index (7.2±3.5 cm² dyn⁻¹ 10⁻⁶ vs 9.6±4.8 cm² dyn⁻¹ 10⁻⁶; p=0.03) and a significant increase of aortic distensibility (3.77±1.0 cm³ dyn⁻¹ 10⁻⁶ vs 2.92±0.55 cm³ dyn⁻¹ 10⁻⁶; p=0.01) and systolic aortic strain (10.0±5.0% vs 8.0±2.1%; p=0.01). The therapy with Spironolactone has not significantly modified systolic arterial pressure, diastolic arterial pressure and differential pressure in the two groups.

**Conclusions:** The therapy with aldosterone – antagonist Spironolactone reduced aortic stiffness in patients with idiopathic dilated cardiomyopathy. This effect could improve haemodynamics suggesting the use of aldosterone – antagonist in patients with low NYHA class (III)

**P5154**

The treatment in patients with chronic heart failure with erythropoietin failure

K. Zhaidova. The Azerbaijan State Advanced Training Institute for Doctors, Baku, Azerbaijan

**Purpose:** Anaemia although common in chronic heart failure (CHF) patients reduces functional status quality of life and is an independent risk factor for hospital admission and mortality. Erythropoiesis stimulating agents (ESA) are frequently used for its treatment. The effects of ESA treatment in patients CHF with anaemia remain largely unknown.

Therefore, our aim was to perform the study to determine the effect of continuous erythropoietin reseptor activator C.E.R.A-
methoxy polyethylene glycol-epoietin (Mircera) treatment on mortality, hospitalization and adverse events in patients with CHF.

Methods: Randomised clinical trials comparing the effect of Mircera treatment with placebo or usual care in patients CHF NYHA functional class II-VLVHEF <40% with anaemia (Hb 10.0–11.0 g/dL) were included. 128 patients with anaemic CHF were obtained of whom 70 patients were treated with Mircera and 56 patients with placebo. Percutaneous Mircera in dose 50 IU in day in one month in follow-up 6 months.Echocardiographic indices of LV systolic and diastolic function and RV function, plasma N terminal B-type natriuretic peptide (NT pro BNP) and 6 minute walked distance were assessed at baseline and posttreatment.

Results: Mircera treatment had a significantly lower risk CHF hospitalization (risk ratio (RR)=0.55, 95% CI 0.43 to 2.28, p=0.5). No differences were observed in the occurrence of hypotension or venous thrombosis.The treatment patients with anaemic CHF with erythropoietin failure of Mircera there was a significant increase Hb from 10.9±0.8 g/dL to 13.4±0.7 g/dL (p<0.01), a significant improvement NYHA functional class from 3.6±0.5 to 2.6±0.4 (p<0.05), a longer endurance on exercise testing from 5.2±1.2 to 8.9±1.9 minutes (p<0.05), a greater distance walked on exercise testing from 280±43 to 375±81 meters (p=0.01).There was also a significant fail in serum NT pro BNP levels from 63.8±11.2 to 228±146pg/ml (p=0.05).Mircera treatment significant reduction in plasma creatinine (p<0.01) and an increase in estimated creatinine clearance (p<0.05).

Conclusions: Anaemia is a common and multifactorial condition associated with poor outcome in CHF patients. One of the main causes of anaemia is erythropoietin failure. Erythropoietin failure can be detected by laboratory tests. Percutaneous Mircera in dose 50 IU in day in one month in follow-up 6 months has emerged as a well tolerated and effective therapy to improve symptoms and quality of life in anaemic CHF patients with erythropoietin failure.

Acute heart failure patients with high initial blood pressure shows paradoxical hemococoncentration on admission

Yokohama City University Medical Center, Yokohama, Japan; Yokohama City University, Yokohama, Japan

Introduction: As volume overload is a major profile of acute heart failure syndrome (AHFS), diuretics, as well as oxygen, nitrites, and morphine, are a mainstay of therapeutic strategy for those patients. Though decongestion/diuretic therapy are started immediately after admission in most of patients, changes in concentration of blood components in this period remain to be investigated.

Method: We studied 135 patients admitted to our hospital with symptoms of AHFS between January and December 2010. Changes in hemoglobin levels between on admission and 24±12 hours postadmission were evaluated. Patients with cardiogenic shock, hemodialysis, blood transfusion, and/or urgent coronary angiography were excluded.

Results: In spite of decongestion/diuretic therapy started immediately after admission, hemoglobin level on admission was paradoxically higher than the level of 24±12 hours postadmission in 95 patients (70%). Patients in the top tertile of baseline-to-24h decrease of hemoglobin (ΔHb) were defined to have an evidence of admission hemococoncentration. The ΔHb in patients with admission hemococoncentration was 1.8±0.7 g/dL (12.9±2.5 on admission and 11.1±2.4 g/dL at 24h, p<0.001) whereas 0.0±0.7 g/dL (11.6±2.1 on admission and 11.5±2.1 g/dL at 24h, p=0.71) in those without admission hemococoncentration, and it showed significant difference between two groups (p=0.001). Admission hemococoncentration was more frequently present in patients with higher initial systolic blood pressure (SBP; >140 mmHg) than lower SBP (45% vs. 16%, p<0.001). Furthermore, ΔHb was positively and significantly correlated not only with initial SBP (r=0.43, p<0.001) but also initial heart rate (r=0.28, p=0.001), suggesting sympathetic effect on the pathophysiology of admission hemococoncentration. Patients with admission hemococoncentration had significantly lower ejection fraction (31±12 vs. 39±14% p=0.003), higher presence of New York Heart Association class IV (45% vs. 17%, p=0.02), and night time admission (32% vs. 30%, p=0.03) than those without admission hemococoncentration. Age, sex, renal function, history of hypertension, diabetes, and dyslipidemia, presence of ischemic heart disease are comparable between two groups.

Conclusion: AHFS with high initial SBP shows paradoxical hemococoncentration on admission. Sympathetically mediated fluid shifts between extracellular and circulating volume may underlie the development of AHFS.

Myocardial and vascular dysfunction in young subjects, are related to dyslipidaemia and abdominal obesity but not to glycaemia

Cardiff University, School of Medicine, Wales Heart Research Institute, Cardiff, United Kingdom; University Hospital of Wales, Cardiff, United Kingdom; University Hospital Llandough, Cardiff, United Kingdom

Purpose: To investigate the relationships between cardiovascular risk factors and subclinical myocardial and vascular dysfunction in young adults.

Methods: We recruited 53 young subjects under 30 years of age including 34 healthy volunteers (mean age 24.6±2.9 years) and 19 subjects with type 1 diabetes mellitus (mean age of 21.1±3.6 years, mean duration of diabetes 9.0±7.5 years; mean HbA1c 8.8±1.6%). All subjects had detailed echocardiography; all type 1 diabetics and 21 controls had myocardial velocity measurements of LV long-axis function (at the mitral annulus). Applanation tonometry was used to measure augmentation index and carotid-femoral pulse wave velocity. Local arterial stiffness parameters (beta and epsilon) and carotid intima media thickness (cIMT) were assessed using high-resolution B-mode ultrasound of the common carotid artery. Fasting blood samples were taken at baseline and posttreatment.

Results: Conduit arterial stiffness was related to body weight (beta, r=0.32, p=0.023) and epsilon r=0.41, p=0.003. Pearson correlations). The stiffness parameter epsilon correlated with the waist-hip ratio (r=0.37, p=0.008). Early diastolic myocardial function was inversely related to fashi-hip ratio (p=0.034). It was positively correlated with serum HDL cholesterol (p=0.034) and medi al myocardial annular velocities r=0.38, p=0.02 and r=0.37, p=0.02, respectively.

All measurements of vascular and myocardial function were unrelated to blood glucose, glycaemic control, and haCRP.

Conclusions: In young adults, abdominal obesity and dyslipidaemia may be more important risk factors for early myocardial and vascular dysfunction than is glycaemia.
Sonographic pulmonary comet sign in diagnosis and monitoring of pulmonary congestion in HF

M. Tsvareva, D. Tsvareva. Khechinashvili University hospital, Tbilisi, Georgia, Republic of

Background and Aim: Pulmonary congestion is useful marker of decompensated HF. The aim was to study the importance of Lung "Comet tail" artefact in diagnosis and monitoring of Pulmonary Congestion in patients with different types Heart Failure.

Methods: We studied 430 patients with II-IV NYHA class HF. 338 Patients have Systolic HF (SHF), 92 patient – HF with preserved systolic function (DHF), and 155 patients with heart diseases but without HF (control). Sonographic evaluation of a lung was done in horizontal or vertical positions of patient, from 10 points of thoracic wall which corresponded to the projection lung lobes.

Results: In patients with CHF we significantly often found the "Comet Tail" artefact (CTa) There was good correlation between the count of CTa registrations point from the thoracic wall and the heart failure NYHA class (r=0.57), left ventricular systolic (r=0.43) and diastolic (r=0.34) diameters and negative correlation with EF% (r= -0.44). In the HF gr. CTa was registered from 3 or more points of thoracic wall in 89.6%, in SHF -91.4%, in HF -82.6%, in COPD -9.1% and in control -7.1% of patients. If we take 4 points and more as a reference value the sensitivity of sign in diagnosis of pulmonary congestion was 83.5% an specify - 97.6%. In CHF group CTph was prominent, protracted and multiple while in the II gr it was single and short-lasting. After use of diuretics CTa disappears or was less prominent then before treatment.

Conclusion: Thoracic US is accurate method for evaluation and monitoring of pulmonary congestion in patients with systolic and diastolic HF. The US sign of pulmonary congestion is a CTa, which is multiple and registered from larger area of thoracic wall (3 points or more). The intensity of CTi is reduced if the dehydration is successful.

Circadian variation of the occurrence of acute heart failure syndromes contributes to long-term prognosis in patients with non-ischemic cardiomyopathy

H. Yasui, T. Hiyoshi, A. Funada, M. Amaki, T. Ohara, T. Hasegawa, M. Asakura, H. Kanzaki, T. Arzai, M. Kitakaze, National Cerebral and Cardiovascular Center Hospital, Department of Cardiovascular Medicine, Suita, Osaka, Japan

Background: Although previous studies reported that the occurrence of acute myocardial infarction peaked in the morning, little is known for the clinical significance of circadian variation in the occurrence of acute heart failure syndromes (AHFS) in patients with non-ischemic cardiomyopathy (NICM). We aimed to investigate the clinical significance of the occurrence of AHFS during the morning in NICM patients.

Methods: We have retrospectively studied consecutive 201 NICM patients admitted for AHFS. We defined the patients of AHFS, who developed their symptoms from the midnight until 8 a.m. as the morning-HF group, and the others as the control-HF group.

Results: Twenty seven patients with the occurrence of AHFS during the morning were recognized in the present study, whose characteristics were significantly higher in age, increased systolic blood pressure (BP) than in the control-HF group (72±13 vs 66±16 y.o., 156±154 vs 124±28 mmHg, p<0.05). Although in- and out-of hospital mortality did not differ between the morning-HF and control-HF groups, but the rate of re-hospitalization for heart failure in the morning-HF group was significantly higher than the control-HF group. Sub-analysis using polysomnography revealed that the prevalence of sleep apnea was significantly higher in the morning-HF group compared with in the control-HF group (100% vs. 74%, p=0.03).

Conclusion: The occurrence of acute heart failure syndromes in the morning itself predicts poor clinical prognosis in association with higher age and sleep apnea, suggesting that increased sympathetic nerve activity (SNA) in the morning may play a significant role in deteriorating HF. Management to control SNA by treating sleep apnea or BP control in chronic phase would be the key to reduce the re-hospitalization for the worsening heart failure.
Predictors of augmented peripheral chemosensitivity in patients with systolic heart failure

P. Niewokulski1, Z. J. Engelmann1, M. Fudim2, S. Tubek3, E. A. Jankowska1, W. Banasiak1, P. Ponikowski1, 1Centre for Heart Disease - Clinical Military Hospital - Department of Cardiology, Wroclaw, Poland; 2Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand; 3Heinrich-Heine University, Duesseldorf, Germany

Background: Augmented peripheral chemosensitivity is typical feature of chronic heart failure (CHF), associated with poor prognosis, however its clinical predictors remain poorly understood.

Purpose: We investigated clinical predictors of peripheral chemosensitivity in contemporary CHF patients receiving optimal medical treatment.

Methods: Thirty CHF patients were studied (NYHA class II, mean LVEF 27.1±7.11%, who were treated with beta-blocker (100%), angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker (98%) and aldosterone antagonist (87%). Peripheral chemosensitivity was assessed with the transient hyperpnoea test by using nitrogen gas administration and expressed by a linear regression slope between SaO2 (%) and minute ventilation (l/min). Based on previous experience, high peripheral chemosensitivity was defined as a response ≥ 0.7 l/min%. Statistical significance was defined at p < 0.05.

Results: Thirteen (43%) CHF patients showed high chemosensitivity. The following clinical parameters differentiated those with high vs normal chemosensitivity: elevated NTproBNP (4534±2195 vs 2051±2232 pg/ml), lower peakVO2 (14.1±1.8 vs 18.6±6.3 ml/kg/min), shorter pulmonary acceleration time (84.2±18.8 vs. 103.±16.7 ms), greater right ventricle end-diastolic diameter (37.1±10.8 vs 27.0±5.46 mm) and more frequent incidence of atrial fibrillation (65% vs 24%), (high vs normal chemosensitivity, respectively, p < 0.05 in all comparisons). Controlling for all these factors, NTproBNP alone significantly predicts chemosensitivity.

Conclusions: High peripheral chemosensitivity is common in contemporary CHF patients despite optimal neurohumoral blockage. Correlation of NTproBNP, peakVO2, pulmonary acceleration time and AF with chemosensitivity suggests 1) an association between peripheral chemosensitivity and 2) that common clinical measurements might be used to screen patients for peripheral chemosensitivity. Assessment of these parameters may therefore be useful for selection of patients for novel therapies targeting peripheral chemoreceptors.

P5162

A classical clinical signs revised in 2012: echocardiographic assessment of jugular vein. A report from SICA-HF study

P. Pellicori, J. Warden, A. Bennett, T. Mabote, S. Smith, E. Wright, P. Costanzo, A.L. Clark, J.G.F. Eliander, University of Hull, Department of Academic Cardiology, Hull, United Kingdom

Background: Jugular vein (JV) distension reflects the pressure in the right atrium. Clinical assessment of JV distension in patients with heart failure is a fundamental tool. Moreover the JV distension could be used as a predictor of the congestive heart failure exacerbations.

Methods: Altogether 111 patients in 12 institutes were included. The median age of patients enrolled was 70 years and their average EF was 43%. The mid-tercile range of values for NT-proBNP was from 588ng/L to 1868ng/L. JV diameter (median and interquartile range, IQR) at rest was 0.20 (0.16 – 0.23) cm in controls and 0.21 (0.17 – 0.24), 0.23 (0.18 – 0.29) and 0.29 (0.18 – 0.37) cm for each tercile of increasing NT-proBNP respectively (P=0.016). The ratio between JV diameter during Valsalva and at rest (JVD ratio) was 5.2 (3.8 – 6.5) in controls and 5.1 (3.5 – 3.6), 3.9 (2.7 – 4.9) and 3.2 (2.2 – 4.8) in patients (p=0.005). JVD ratio correlated with log (NT-proBNP) (r = 0.29, p=0.003), ejection fraction (EF, r= 0.20, p=0.04) and trans-tricuspid systolic gradient (r = 0.39, p=0.001). However, a multiple regression model suggested only mitral E/E' and trans-tricuspid gradient were independently associated with JVD ratio (R²=0.27). When the analysis was restricted to patients with EF < 40% (n= 45), only higher trans-tricuspid gradient, and lower BMI were independently associated with a lower JVD ratio (R²= 0.56).

Conclusions: A decreased capacity of distension of the jugular veins during Valsalva manoeuvre is a reliable sign of severe heart failure.

P5163

Artificial neural network in early identification of heart failure progression in OptiVol telemonitoring management of chronic heart failure

T. Heinz1, A. Polzer1, M. Von Lowis2, C. Sprenger3, M. Oelf3
1Fontane-Projekt, Hasso-Plattner-Institute, Potsdam, Germany; 2Hasso-Plattner-Institute, Potsdam, Germany; 3Hospital Brandenburg, Brandenburg an der Havel, Germany

Daily acquisition and analysis of vital sign data and clinical symptoms in chronic heart failure patients allow for early recognition of an emerging decompensation. Artificial Neural Networks (ANN) are a statistical model, which is able to learn probability distributions of a dataset by inductive example training. Here, the capability of a personalized ANN was tested to predict the progression of chronic heart failure in the individual patient.

Methods: In 169 patients hospitalized due to chronic heart failure decompensation, a multiparameter telemonitoring was performed after discharge for up to 3.5 years with 150,000 patient days in total. Daily recording of vital signs (ECG, body weight, blood pressure, O2-saturation, thoracic impedance, symptoms, drug adherence, request of contact) generated 1.5 million telemonitoring datapoints, which were used to predict the primary endpoint 'new heart failure hospitalization' by ANN. An ANN to predict the probability of a health state change was trained based on recent vital measurements. Therefore, 80% randomly chosen datapoints of all patients were used to train the ANN (group1). The remaining 20% were used to test the predictive value of the trained model (group2). Doing that, the last 7 measure-
Abnormal acetylcholine-induced vasoreactivity in Takotsubo cardiomyopathy, novel pathophysiology insights on Takotsubo cardiomyopathy

G. Crimi1, M. Previsi2, D. Bartolini1, A. Iannone1, S. Bellotti1, A. Valbusa3, P. Rubarleti3, ASL Genovesi, Villa Scassi Hospital, Genova-Sampierdarena, Italy;1 Policlinico San Matteo, Pavia, Italy;3 San Martino Hospital, Department of Cardiology, Genoa, Italy

More than 10 years has passed since the first report of Takotsubo Cardiomyopathy (TTC). While the pathophysiology of this syndrome is believed to be linked to stress, the mechanisms underlying TTC have not been fully elucidated. A recent study aimed to assess the role of acetylcholine in TTC, a common clinical condition that can mimic acute cardiac events.

Methods: TTC patients were enrolled in the Registry. A Subgroup of 11 patients underwent intracoronary acetylcholine (ACh) test. Positive test was defined as coronary spasm, stable TTC pts were tested with intracoronary administration of acetylcholine (bo-

Results: TTC patients were enrolled in the Registry. A Subgroup of 11 patients underwent ACh test. The symptoms analyzed were naptime, nocturnal dyspnea and nocturia. These data are quite similar to those reported in the CASPAR study that tested intracoronary ACh in patients with acute coronary syndromes and nonsignificant CAD. In our population prevalence of abnormal coronary vasomotor response to acetylcholine is high and comparable with that reported in acute coronary syndromes with no CAD. Our findings suggest that abnormal coronary artery vasomotion related to endothelial dysfunction could play a significant pathogenetic role in TTC.

Heart failure symptoms and sleep-disordered breathing in patients with chronic heart failure - results from the SchlaHF-registration

O. Oldenburg1, M. Arzt1, E. Erdmann1, H. Teschler1, A. Grafl1, K. Wegscheider1, H. Wehrl1.1 Medical University of Regensburg, Department of Internal Medicine II, Regensburg, Germany.

Objective: In patients with stable chronic heart failure (CHF) we investigated the clinical value of different heart failure symptoms and its relationship to the presence of sleep-disordered breathing (SDB). These data are quite similar to those reported in the CASPAR study that tested intracoronary ACh in patients with acute coronary syndromes and nonsignificant CAD. In our population prevalence of abnormal coronary vasomotor response to acetylcholine is high and comparable with that reported in acute coronary syndromes with no CAD. Our findings suggest that abnormal coronary artery vasomotion related to endothelial dysfunction could play a significant pathogenetic role in TTC.

Heart rate control is important even in heart failure patients - an interim analysis of the CHART-2 study

M. Miura1, N. Shibata1, J. Takahashi1, K. Nochioka1, T. Takada2, H. Shimokawa1.1 Tohoku University Graduate School of Medicine, Department of Cardiovascular Medicine, Sendai, Japan;2 International University of Health and Welfare Hospital, Nasu, Tochigi, Japan

Purpose: Elevated heart rate (HR) is an independent risk factor for mortality in heart failure (HF) patients. However, the medications for the management of HR often lower systolic blood pressure (SBP) that may worsen the prognosis of HF patients. We examined the importance of HR control in terms of SBP in patients of our Chronic Heart Failure Analysis and Registry in the Tohoku district 2 (CHART-2) Study.

Methods: The CHART-2 Study (N=10,219) is a multicenter prospective cohort study enrolling Stage B/C/D patients. The study subjects were 2,761 overt HF patients with sinus rhythm and divided them into 6 groups based on the tertiles of SBP and the median HR as follows; G1 (SBP >135 and HR>70, N=490), G2 (SBP >135 and HR>70, N=469), G3 (SBP >120, ≤135 and HR>70, N=444), G4 (SBP >120, ≤135 and HR≤70, N=410), G5 (SBP ≤120, ≤135 and HR≤70, N=490), G6 (SBP ≤120, HR≤70, N=490).

Results: G5 had the lowest NYHA class and brain natriuretic peptide (BNP) level. On the other hand, G6 were characterized by lower beta-blocker use, lower left ventricular ejection fraction, and the highest BNP level. During a mean follow-up of 3.1 years, non-adjusted Kaplan-Meier curves for all-cause death and cardiovascular death showed that G3 had better prognosis and G6 had poorer prognosis (Figure). In multivariable Cox model including covariates that might influence HR and SBP, Groups with elevated HR showed 165% increased hazard ratios for all-cause death as compared to G3 (reference). Furthermore, G4 and G6 had significant higher cardiovascular mortality.

Conclusions: Regardless of SBP, elevated HR was associated with higher mortality. In view these results and well-known importance of increased HR for mortality, HR control (>70/min) should be given higher priority even in the HF patients with relatively low SBP.
Incident heart failure with preserved ejection fraction in the general population

F.P.J. Brouwers1, R.A. De Boer1, P. Van Der Harst1, R.T. Gansevoort2, S.J.L. Bakker2, H.L. Hillege1, D.J. Van Veldhuisen1, W.H. Van Gilst1. 1University Medical Center Groningen, Department of Cardiology, Groningen, Netherlands; 2University Medical Center Groningen, Department of Nephrology, Groningen, Netherlands

Purpose: The incidence of heart failure (HF) with preserved ejection fraction (HF-PEF) is increasing, compared to HF with reduced ejection fraction (HF-REF). Data on distinctive epidemiology and prediction of incident HF-PEF and HF-REF in a general population have not been described.

Methods: In 8569 HF-free subjects of a general population based cohort study (PREVEND), we studied the performance of established cardiovascular risk factors on incident HF, their hazard ratios given per 1-SD increment and 95% confidence interval (CI), and the additive value of N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP) and high-sensitive troponin T (hs-TnT) by c-statistics and net reclassification improvement (NRI). Incident HF was diagnosed by record linkage with databases of regional hospitals. All cases were reviewed and scored as HF-PEF or HF-REF by an independent adjudication committee.

Results: During median follow-up for 10 years, 135 individuals were diagnosed with HF-PEF and 239 with HF-REF. When adjusted for age, sex and body mass index, development of HF-PEF showed strongest associations with hypertension (HR: 2.08, 95% CI: 1.02-4.27, p=0.045), cystatin-C (HR: 1.49, 95% CI: 1.05-2.11, p=0.024) and urinary albumin excretion (HR: 1.37, 95% CI: 1.14-1.65, p=0.001). In similar analyses, development of HF-REF showed strongest associations with history of myocardial infarction (HR: 2.45, 95% CI: 1.53-3.93, p=0.001), smoking (HR: 1.69, 95% CI: 1.07-2.68, p=0.025) and hypercholesterolemia (HR: 1.55, 95% CI: 1.03-2.34, p=0.037). NT-proBNP was independently associated with both incident HF-REF and incident HF-PEF (HR: 1.55, 95% CI: 1.21-1.97, p=0.001 and HR: 1.36, 95% CI: 1.03-1.80, p=0.030, respectively). Hs-TnT was independently associated with incident HF-REF (HR: 1.39, 95% CI: 1.22-1.60, p<0.001), but not with HF-PEF. CRP was not associated with either type of incident HF. For HF-PEF, NT-proBNP, hs-TnT and CRP significantly improved the model c-statistic from 0.85 to 0.86 (p=0.015) and enhanced risk reclassification (NRI=0.06, p=0.048). For HF-REF, the model c-statistic improved from 0.84 to 0.88 (p<0.001) and also enhanced risk reclassification (NRI=0.26, p<0.001).

Conclusions: HF-PEF shows a clear distinctive baseline profile compared to HF-REF, with a blood pressure and renal function pressure-load driven profile for the former and an ischemic driven profile for the latter. The incremental value of biomarkers seems to be less strong for predicting HF-PEF than for HF-REF.