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Vorträge

V-1

NOAC vs Warfarin – Asymptomatic cerebral lesions during left atrial ablation of atrial fibrillation

M. Derndorfer, S. Chen, E. Sigmund, G. Kollias, W. Jauker, M. Gschwendtner, J. Aichinger, H. Pürerfellner, M. Martinek

Kardiologie 1, Krankenhaus Elisabethinen Linz, Linz, Austria

Background: Performing left atrial radiofrequency ablation in treating atrial fibrillation (AF) has been associated with an increased risk of asymptomatic cerebral lesions (ACL). ACL's clinical consequences are unclear but some studies suggest that it can result in later cognitive decline. Uninterrupted oral anticoagulation (OAC) during AF ablation is recommended by recent guidelines to prevent thromboembolism. Non-vitamin-K novel oral anticoagulants (NOACs) were introduced for stroke prevention in AF and their efficacy and safety have been shown in several studies. Our aim was to compare the incidence of ACLs during AF ablation using either uninterrupted Vitamin-K-Antagonists (VKAs) or NOACs (1 dosage before ablation omitted). Pre- and post-procedural cerebral magnetic resonance imaging (MRI) was used to assess ACLs.

Methods and Results: A total of 408 consecutive patients with paroxysmal or persistent atrial fibrillation (VKA $n=304$; NOAC $n=104$) scheduled for catheter ablation were included in the study. Baseline parameter as female sex, age and BMI as well as presence of paroxysmal AF showed no significant difference (Tab. 1). AF duration before procedure was similar. Patients in both groups were with normal LVEF. During all procedures targeted activated clotting time (ACT), maintained by a continuous i. v. heparin infusion or additional boluses as needed, was between 300 and 400 seconds (s) in both groups, but a significantly lower ACT in NOAC-procedures could be observed ($p<0.0001$, Fig. 2|V-1). Left atrial procedure time and distribution of PVI-only-procedures (pulmonary vein isolation) were comparable.

29 (9.6%) patients in the VKA group and 18 (17.3%) patients on NOACs showed new ACLs in post-procedural cerebral MRI ($p=0.049$, Fig. 1|V-1). All-cause mortality, rate of stroke or need for cardiac surgery intervention did not occur in both groups.

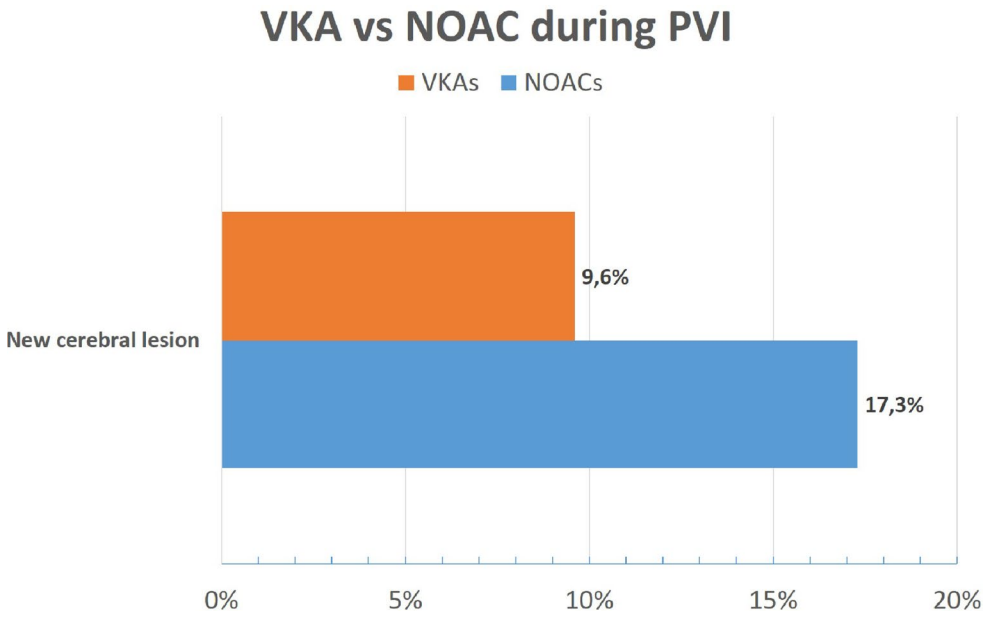


Fig. 1|V-1

	VKAs	NOACs	p
Paroxysmal AF, n (%)	61 (62.9%)	189 (66.1%)	0.622
Female, n (%)	31 (29.8%)	78 (25.7%)	0.442
Age (years)	63.0 ± 8.0	61.4 ± 10.2	0.135
BMI	29.0 ± 4.9	28.3 ± 5	0.188
LA diameter (mm)	41.5 ± 5.5	39.7 ± 5.4	0.01
LA procedure time (min)	156.2 ± 48.2	166.4 ± 48.8	0.213
PVI only, n (%)	73 (70.9%)	197 (66.6%)	0.464
ACT (sec)	345.1 ± 31.1	301.3 ± 50.7	<0.0001

Fig. 2|V-1

Significant risk factors associated with higher incidence of ACLs were higher CHADS and CHADSVASc score and a greater LA diameter at baseline as well as a lower ACT during procedures.

Conclusions: The use of VKAs during AF-ablation was associated with a lower risk of post-ablation ACLs as compared to NOACs. Higher CHADS and CHADSVASc score, a greater LA diameter at baseline as well as a lower ACT during procedures seem to be the clinical predictors of such events.

V-2

Predictors of radial artery occlusion after transradial catheterization: Prospective single centre registry with 1000 consecutive patients

P. Madreiter, A. Podczeck-Schweighofer, G. Christ, RAO Evaluation Group

5. Medizinische Abteilung, Kardiologie, SMZ-Süd/Kaiser Franz Josef Spital, Vienna, Austria

Background: The incidence of radial artery occlusion (RAO) after transradial access (TRA) for coronary angiography (CA) and percutaneous coronary intervention (PCI) ranges from 1% to 33%. Besides higher heparin dosage and lower sheath size, patent hemostasis (i. e. documented radial patency during hemostatic compression) is reported to decrease the occurrence of RAO. We were interested to evaluate the incidence of patent hemostasis under standard local compression technique and the incidence and predictors of RAO in our patient cohort with a high rate of preloading with ADP receptor blocker and aspirin.

Methods: Single-centre registry of consecutive TRA patients with a standard deflation protocol of the compression devices over 4 hours. Patent hemostasis was assessed by pulse oximetry under ipsilateral ulnar artery occlusion. Radial artery patency was evaluated the following day (within 24 hours) by pulse palpation. In case of clinical uncertainty or occlusion, vascular ultrasound was performed. TRA was performed with 5F- (Glidesheath slender, Terumo; Prelude, Merit) or 6F-sheaths (Prelude, Merit) and routine application of 2.5 mg Verapamil and 5000 IU heparin for CA, and 100 IU/kg heparin for PCI. The type of compression device was at the discretion of the angiographer [TR-band (TR; Terumo), IO-band (IO; Comed) or Safeguard (SG; Merit)].

Results: Between December 2015 and September 2016, 1000 consecutive patients with 1190 TRAs were included. Primary reasons for repeated TRA were staged PCI (60%) and control CA (22%). Sheath size was 5F in 19% and 6F in 81% of patients. The cohort included 34% female patients, 32% diabetics and 40% PCI patients. Preloading with ADP receptor blocker and/or aspirin was present in 93% and 96% of patients, respectively. Patent hemostasis was observed in 10% of TRA with significant differences between compression devices (TR-band 14%; SG 19%; IO-band 4%; $p<0.001$). RAO occurred in 10 patients (1.0% of patients; 0.8% of TRAs) without differences between compression devices ($p=0.5$). Multivariate logistic regression analysis revealed peripheral artery disease (PAD) [adjusted odds ratio (OR), 4.80; 95% confidence interval (CI), 1.14–20.2; $p=0.03$] and repeated TRA (adjusted OR, 2.00; 95% CI, 1.07–3.76; $p=0.03$) as independent predictors of RAO. Statin medication (adjusted OR, 0.17; 95% CI, 0.04–0.65; $p=0.01$), but not patent hemostasis (adjusted OR, 0.58 95% CI, 0.06–5.68; $p=0.6$), showed a significant inverse relation to RAO.

Conclusions: In our real world registry, we observed a lower incidence of RAO (0.8%) than reported in meta-analyses of published studies (median 8%). Patent hemostasis showed no significant association with RAO in our patient cohort, in contrast to statin medication, which seems to reduce the risk of RAO. Independent predictors for the occurrence of RAO at 24 hours were presence of PAD and repeated TRA. We hypothesize, that besides unknown confounders, the high percentage of preloading with ADP receptor blocker and aspirin might be responsible for the very favorable low percentage of RAO in our single-centre registry.

V-3

Increased arrhythmia stability in hypertensive heart disease is not associated with increased rotational activity in porcine model of atrial fibrillation

M. Manninger, D. Zweiker, A. van Hunnik, B. Zirngast, A. Alogna, S. Zeemering, V. Herbst, U. Schotten, H. Brussee, B. M. Pieske, F. R. Heinzel, H. Post, D. Scherr

Universitätsklinik für Innere Medizin, Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Austria
Department of Physiology, University Maastricht, Maastricht, Netherlands
Abteilung für Herzchirurgie, Medizinische Universität Graz, Graz, Austria
Abteilung für Kardiologie, Charité Berlin Campus Virchow, Berlin, Germany

Background: Arterial hypertension (HT) is the most important risk factor for the progression of atrial fibrillation (AF) while the underlying mechanisms remain unknown. Localized rotors have been proposed as a dominant activation pattern during AF underlying stabilisation and maintenance of the arrhythmia, but ablation in these regions show ambiguous results.

We previously established an animal model of rapid atrial pacing (RAP) induced AF combined with DOCA (desoxycorticosterone acetate) induced HT to investigate how HT affects the progression of AF.

Methods: 17 landrace pigs were implanted with pacemakers to induce AF. DOCA pellets were subcutaneously implanted in a subgroup of 9 animals (AF+HT). Final experiments including electrophysiologic studies, high density endo- and epicardial multielectrode mapping as well as histological stereological analyses were conducted after two weeks of RAP.

Results: Both groups had comparable body weight and cardiac output. Animals in the AF+HT group had significant HT (mean aortic pressure 109.9 (100.137) vs. 82.8 (79.96) mmHg, $p<0.05$), concentric left ventricular hypertrophy, atrial dilatation and increased left (33.5 ± 8 vs. 24.9 ± 6 g, $p<0.05$) and right (23.7 ± 3 vs. 19.4 ± 3 g, $p<0.05$) atrial weights.

AF duration was significantly higher in AF+HT animals (AF duration >60 min after PM deactivation: 56% vs. 13%, $p<0.05$), while left and right AERPs (mean at clycle lengths 400/350/300/250/200 ms; LA: 170 ± 23 vs. 157 ± 27ms, RA: 185 ± 25 vs. 187 ± 34ms, $p=$n.s.), action potential durations (mean APD90 at cycle length 350 ms; LA: 121 ± 23 vs. 95 ± 5 ms, RA: 176 ± 23 vs. 173 ± 16ms; $p=$n.s.) and AF complexity (AF cycle length, waves/cycle length, epicardial breakthroughs, conduction velocity during AF) were unaltered. Epicardial mapping reavealed that number of rotations were comparable in both groups (phase singularities per cycle length; LA: 2.67 ± 0.6 vs. 2.56 ± 0.8, RA: 1.37 ± 0.8 vs. 1.23 ± 0.5; $p=$n.s., Fig. 1|V3).

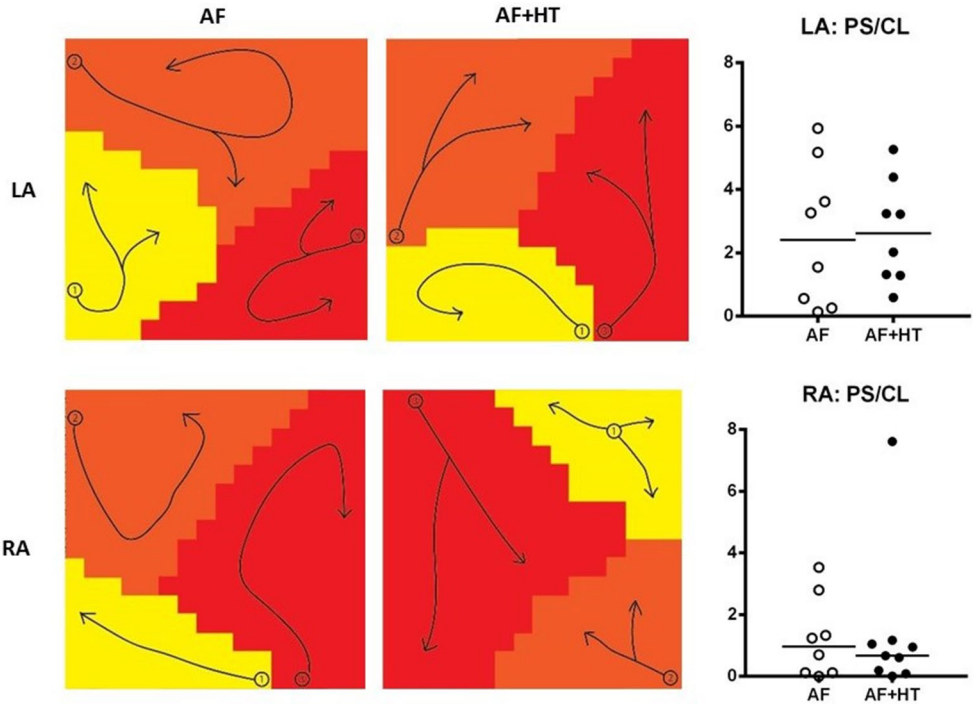


Fig. 1 | V3 Representative epicardial activation maps during AF and graphs demonstrating rotational activity in the LA and RA (PS/CL = phase singularities per cycle length during AF)

HT was associated with structural remodeling. Stereologic evaluation showed increased total left atrial collagen content (1.95 ± 0.5 vs. 1.18 ± 0.3 g, $p < 0.05$) while cardiomyocyte volume and distribution of Cx43 remained unchanged in the AF+HT group.

Conclusions: In this model of secondary hypertension, higher AF stability after two weeks of RAP is not caused by rotors but is mainly driven by ultrastructural remodelling. Since rotors do not seem to be the driving mechanism in this substrate, ablation in these regions are unlikely to increase arrhythmia-free survival in patients with hypertensive heart disease.

V-4

Effects of timed physical exercise on arterial stiffness in night shift workers

C. Schäfer, B. Mayr, E. E. Müller, R. H. Böger, M. Schönfelder, J. Niebauer

Research Institute of Molecular Sports Medicine and Rehabilitation, Paracelsus Medical University, Salzburg, Austria
Department of Clinical Pharmacology and Toxicology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Faculty of Sport and Health Sciences, Exercise Biology, Technical University of Munich, Munich, Germany

Background: Night shift workers have a higher incidence of cardiovascular and cardiometabolic diseases. Indeed, frequent to chronic disruption of the circadian rhythm promotes arterial stiffening, which is associated with cardiovascular diseases and negatively influenced by lack of physical activity, smoking, a proatherogenic diet and aging. Since regular physical activity is generally cardioprotective it was the aim of this study to assess whether physical exercise training before each night shift exerts comparable effects on markers of cardiovascular risk. This trial is part of the European wide study, called EuRhythDia, analyzing the influence of different kinds of interventions on the circadian rhythm in night shift workers (EU-project, study coordination University Medical Center Hamburg-Eppendorf).

Methods: Normotensive night shift workers from Salzburg ($n = 57$; median age 35 (21–57) years) were enrolled and randomized into an intervention (IG, $n = 47$) or a control (CG, $n = 10$) group. Subjects in the intervention group but not in the control group performed 35 minutes of high intensity interval training on cycle ergometers not longer than 2 hours before each night shift (≥4/month) for 12 weeks. All subjects were followed for further 12 weeks without structured exercise training. At baseline, 12 and 24 weeks arterial stiffness parameters, e. g. central systolic blood pressure (cSBP), central pulse pressure (cPP), augmentation index corrected for heart rate of 75 bpm (AIx@75), reflection coefficient, amplitude of the backward- (Pb) and of the forward pressure wave (Pf) as well as the pulse wave velocity (PWV) were measured non-invasively by oscillometry.

Results: After 12 weeks of exercise training, all parameters of arterial stiffness but the reflection coefficient were significantly improved ($p < .05$). No significant effects were examined in the control group. Gender correlated with the reflection coefficient in both groups (IG, r = 0.455, $p < .01$, CG, r = 0.922, $p < .001$), where values in women (-3.1%) but not men (+3.1%) decreased. Furthermore, in the intervention group there was a negative correlation between age, cPP and Pf. Within the control group, smoking correlated negatively with cPP, Pf and PWV (all $p < .05$).

Conclusions: High intensity interval training no longer than 2 hours before night shift work improves arterial stiffness already after 12 weeks of training. Greater responses correlated with the number of exercise training sessions. Our data demonstrate for the first time that exercise training before night shift work can lead to an improvement in cardiovascular risk.

V-5

Toll-like receptor 3 mediates the onset of calcific aortic valve disease

C. Tepeköylü, M. Graber, L. Pölzl, J. Hirsch, E. Kirchmair, G. Degenhart, E. Demetz, D. Lobenwein, C. Fuchs, G. Feuchtner, M. Grimm, J. Holfeld

Universitätsklinik für Herzchirurgie, Medizinische Universität Innsbruck, Innsbruck, Austria
Universitätsklinik für Radiologie, Medizinische Universität Innsbruck, Innsbruck, Austria
Universitätsklinik für Innere Medizin III, Medizinische Universität Innsbruck, Innsbruck, Austria
FH Technikum Wien, Institut für Biochemical Engineering, Vienna, Austria

Background: Calcific aortic valve disease (CAVD) is caused by an osteoblastic phenotype switch of valvular interstitial cells (VICs), the predominant cell type in heart valves. However, the trigger for the phenotype switch remains unknown. Toll-like receptor 3 (TLR3) is part of the innate immune system activated by viral and endogenous RNA released from dying cells. We hypothesized that mechanical strain leads to TLR3 activation leading to an osteoblastic phenotype switch of VICs with subsequent initiation of CAVD.

Methods: Aortic valves were obtained from patients undergoing aortic valve replacement or from explanted hearts. VICs were isolated and treated with TLR3 agonist poly (I:C) or a TLR3/dsRNA complex inhibitor. Osteoblastic gene expression was evaluated via RT-PCR. Cells were challenged with osteoblastic medium and analyzed for alkaline phosphatase activity and calcific nodule formation. A Flexcell system was used to apply mechanical strain to VICs. Aortic valve morphology and function of aged wild-type (WT) and TLR3-/- mice were analyzed via transthoracic echocardiography, microCT and histological evaluation. To confirm results in a second model, experiments were repeated in ApoE-/- and ApoE-/-/TLR3-/- mice.

Results: Aortic valves and VICs showed abundant TLR3 expression. Mechanical stimulation of VICs resulted in TLR3 activation. Stimulation of TLR3 lead to expression of TNF-a, IL-6, IFN-y, IL-10, Runx2 and BMP2 and significantly enhanced osteoblastic activity of treated cells. Mice showed age-dependent TLR3 expression. Aortic valves as well as VICs derived from CAVD patients showed increased TLR3 expression compared to healthy control valves and VICs. TLR3 Inihibition resulted in prevention of osteogenic phenotype switch in conditioned VICs. Aged WT mice showed significantly increased mean gradients (mmHg: 3.140.64 vs. 1.160.22, $p=0.025$) and mean velocity (mm/s: 79.677 vs. 52.755, $p=0.029$) in transthoracic echocardiographies. MicroCT and histological analyses revealed thickened valve leaflets and commissural atherosclerotic plaques. These changes were missing completely in age-matched TLR3-/- mice. ApoE-/- mice under high fat diet exhibited clear signs of CAVD with decreased aortic valve opening diameters (mm: 1.070.046 vs. 1.220.41, $p=0.023$) and increased valve leaflet thickness (mm: 0.110.01 vs. 0.080.001, $p=0.018$) in the echocardiographical assessment. However, these findings were completely missing in ApoE-/-/TLR3-/- mice.

Conclusions: TLR3 stimulation leads to an osteoblastic phenotype switch of VICs, whereas inhibition of TLR3 prevents from osteoblastic activity. TLR3 expression is increased in aortic valves from CAVD patients. TLR3-/- mice show no phenotype of CAVD. TLR3 could become an effective target for the pharmacological prevention of CAVD.

V-6

Prognostic value of fractional flow reserve, measured immediately after drug eluting stent implantation

G. Toth-Gayor, Z. Piroth, P. Tonino, E. Barbato, S. Aghlmandi, N. Pijls, W. Fearon, B. De Bruyne

Abteilung für Kardiologie, Medizinische Universität Graz
National Institute of Cardiology, Budapest, Hungary
Catharina Hospital, Eindhoven, Netherland
OLV Aalst, Aalst, Belgium
University of Bern, Bern, Switzerland
Stanford University, Stanford, USA

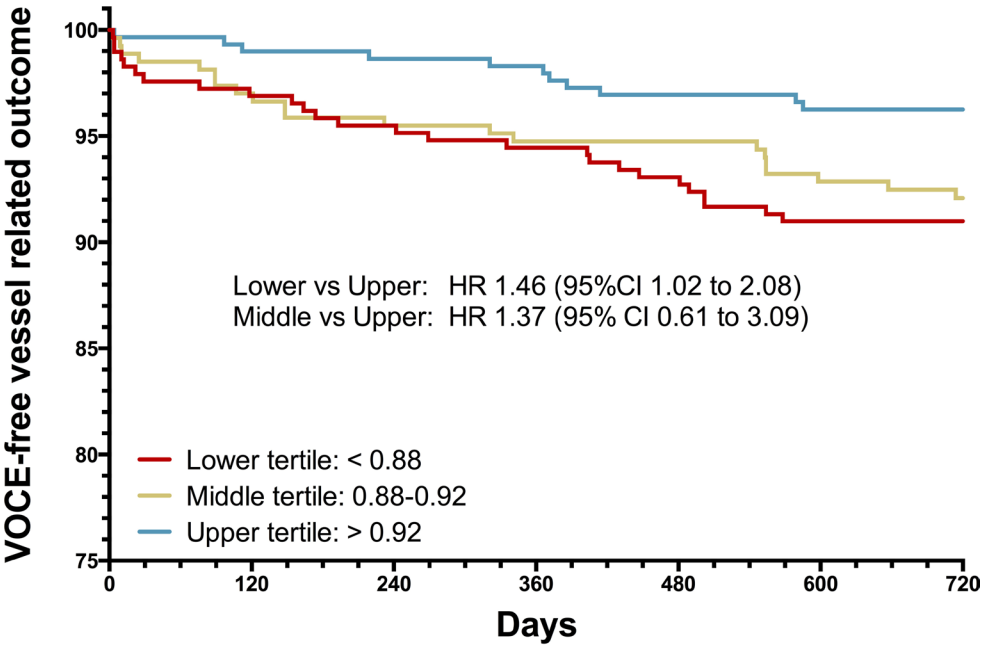


Fig. 1 | V6

Background: Fractional Flow Reserve (FFR) is the standard of reference for decision making about percutaneous coronary intervention (PCI). The predictive value of FFR measured immediately after PCI with drug eluting stent (DES) placement has not been prospectively investigated.

Objectives: We investigated the potential of post-PCI FFR measurements to predict clinical outcome in patients enrolled in the FAME 1 and FAME 2 trials.

Methods: All patients of FAME 1 and FAME 2 who had post-PCI FFR measurement were included. The primary outcome was vessel-oriented composite end-point (VOCE) at 2 years, defined as the composite of vessel-related cardiovascular death, vessel-related spontaneous myocardial infarction, and ischaemia driven target vessel revascularization (TVR, both urgent and non-urgent) and adjudicated by a blinded event committee.

Results: 838 vessels in 639 patients were analyzed. Pre-PCI FFR values did not differ between vessels with versus without VOCE (0.66 ± 0.11 vs. 0.63 ± 0.14, respectively; $p = 0.207$). Post-PCI FFR was significantly lower in vessels with VOCE during follow-up (0.88 ± 0.06 vs. 0.90 ± 0.06, respectively; $p = 0.019$). Comparing the 2-year outcome of Lower and Upper tertiles of post-PCI FFR a significant difference was found favoring the upper tertile in terms of overall VOCE (9.2% vs 3.8%, respectively; HR 1.46, 95% CI 1.02 to 2.08; $p = 0.037$) and TVR (7.0% vs 2.4%, respectively; HR 1.59, 95% CI 1.03 to 2.46; $p = 0.037$) (Fig. 1 | V-6). No statistical difference was found either in spontaneous MI or in vessel-related death.

Post-PCI FFR of 0.92 was found to have the highest diagnostic accuracy, however the positive likelihood ratio of post-PCI FFR values in predicting clinical events remained low (<1.4).

Conclusions: A higher post-PCI FFR value is associated with a better vessel-related outcome. However, the predictive value of post-PCI FFR is too low to advocate its use of as a surrogate clinical end-point.

Featured Poster Session 1

FP 1-1

Spontaneous stable transfection of PET-reporter gene for in vivo tracking of xenogeneic mesenchymal stem cells

K. Zlabinger, D. Lukovic, A. Gugerell, J. Winkler, A. Spannbauer, M. Emmert, S. P. Hoerstrup, M. Pavone-Gyöngyösi

Universitätsklinik für Innere Medizin II/Kardiologieforschung, Medizinische Universität Wien, Vienna, Austria
Universitätsspital Zürich, Zurich, Switzerland

Background: Replication deficient virus, such as human adeno-associated virus (AAV) as a plasmid vector, is commonly used for treatment of diverse human diseases, such as eye, nerve and kidney disease. Principally, transient transfection of cells with plasmid vector does not carry the risk of introducing foreign genetic material into the genome of eukaryotic cells, therefore this method is frequently used in human gene

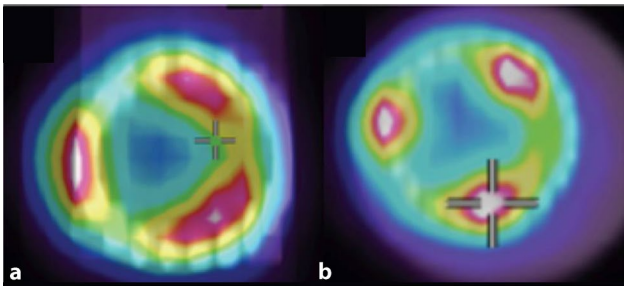


Fig. 1 | FP 1-1

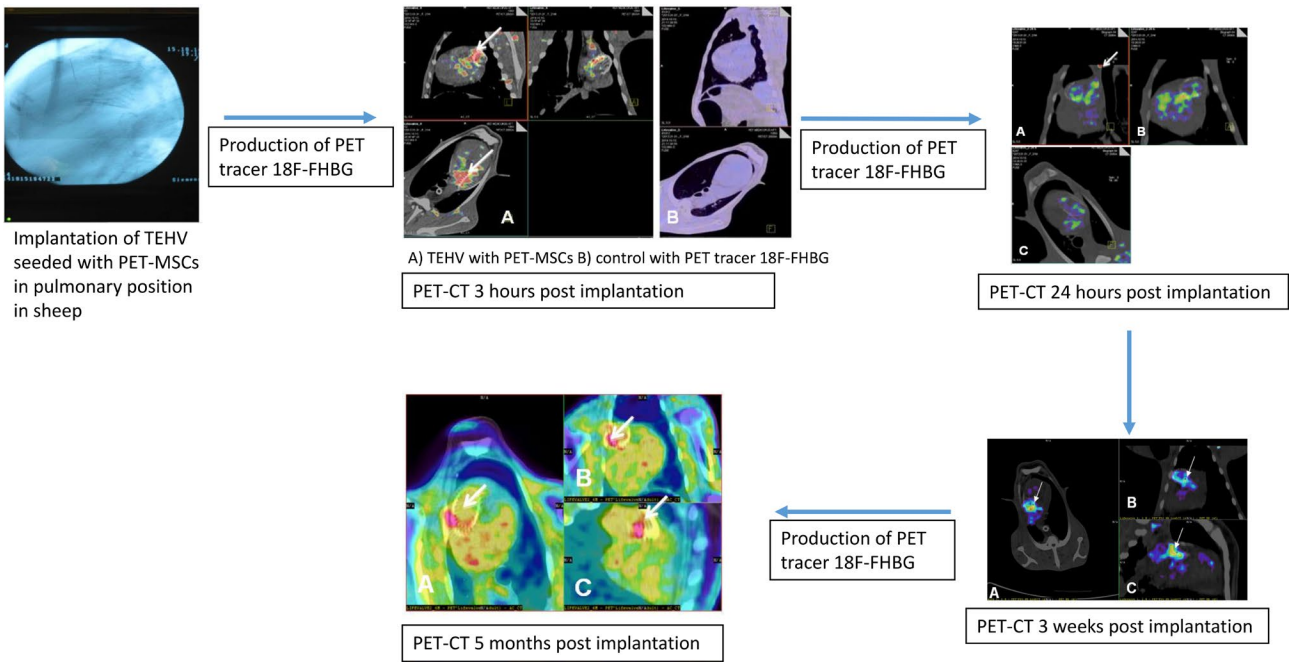


Fig. 2 | FP 1-1

therapies. The aim of the present sub-study of the LifeValve EU project was to seed tissue engineered heart valves (TEHV) with xenogeneic (porcine) mesenchymal stem cells (MSCs) transfected transiently with PET-reporter gene, implant them into sheep, and track the fate of the seeded stem cells via serial in vivo non-invasive positron emission tomography-computer tomography (PET-CT).

Methods: Porcine MSCs were cultured one week before seeding and transfected transiently with PET-reporter gene using Lipofectamine, resulting in a transfection efficiency of 40,1%. The transfected cells were seeded carefully onto the valve scaffolds. Static cultivation of TEHV scaffolds led to successful ingrowth of the MSCs into the TEHV scaffolds, resulting in an average cell number of 7×10^6 in each TEHV. The TEHVs were then implanted percutaneously into the pulmonary position of sheep under general anaesthesia ($n=8$), while an additional sheep with no valve implantation served as a control. Then mCi [18F]-FHBG PET tracer was produced for each procedure and serial PET-CT imaging of the sheep was performed 3 h, 6 h, 24 h, 3 weeks and 5 months after valve implantation. For quantitative assessment of the number of cells survived in the TEHV scaffold after in vivo implantation, vials containing 5×10^4, 2×10^5 and 4×10^5 transfected cells were mixed with the PET tracer for one hour, then the non-bound tracer was washed out and the vials were in vitro PET-CT imaged.

Results: PET-CT of control vials containing transient transfected cells showed dose-dependent tracer uptake. In vitro PET-CT images of the TEHVs displayed an accumulation of seeded cells at the base of the leaflets (Fig. 1|FP 1-1). PET-CT images of the sheep 3 h after implantation of the TEHV showed a clear signal of transfected cells, with a mean estimated number of living cells of 4.95×10^6. No meaningful decrease of the amount of living cells occurred at 6 h or 24 h. Three weeks after valve implantation, living MSCs could be found in the TEHV (estimated cell number 4.67×10^6) in one sheep. Interestingly, 6-month PET-CT images showed clear PET signal (estimated 3.16×10^6 cells) on the valves, indicating a spontaneous stable transfection of the cells with the introduction of PET-reporter plasmid into donor cell genome (Fig. 2|FP 1-1).

Conclusions: This is the first report on serial non-invasive in vivo tracking of long-term survival of xenogeneic MSCs seeded onto tissue engineered heart valves (TEHVs) and percutaneous implanted into the pulmonary position of sheep. Long-time follow-up revealed spontaneous stable transfection of the PET-reporter gene, which suggests the risk of genomic mutation induced by plasmids. The study was supported by the LifeValve EU project

FP 1-2

Maladaptive mitral valve changes after myocardial infarction can be therapeutically modulated

P. Bartko, L. Guerrero, C. Szymanski, M. Handschumacher, S. Sullivan, M. Garcia, J. Wylie-Sears, W. Irvin, A. Carpentier, J. Dal-Bianco, E. Aikawa, J. Bischoff, R. Levine

Innere Medizin 2/Kardiologie, Medizinische Universität Wien
Massachusetts General Hospital, Boston, USA
Hôpital Européen Georges Pompidou, Paris, France
Boston Children's Hospital, Boston, USA
Brigham and Women's Hospital, Boston, USA

Background: In patients after myocardial infarction (MI), mitral valve (MV) tethering stimulates adaptive leaflet growth but also MV fibrosis that augments MV regurgitation (MR), doubling heart failure and mortality. Post MI MV fibrosis is associated with excessive endothelial to mesenchymal transition (EMT) and overexpression of TGFβ, which drives EMT and

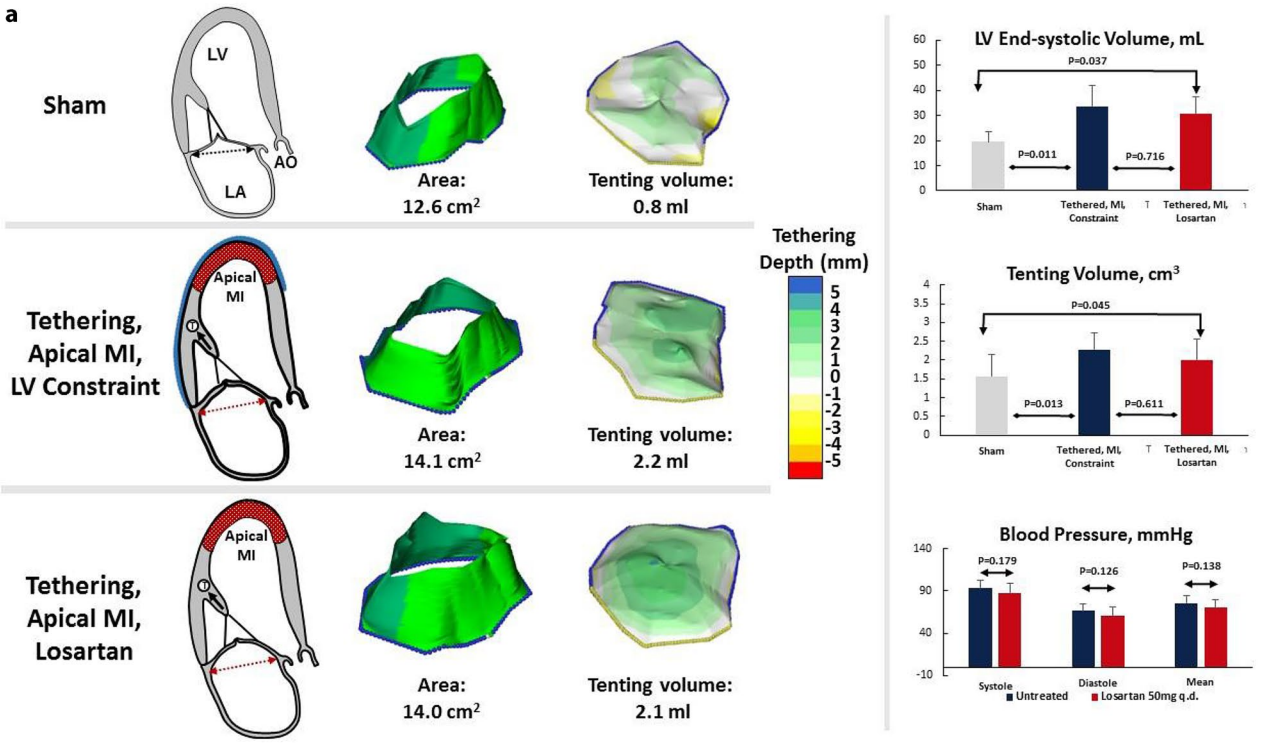


Fig. 1|FP 1-2

b	Sham	Tethered MI LV constraint	Tethered MI Losartan
LVESV, mL	19.57 ± 3.89	33.67 ± 8.11*	30.58 ± 6.63*
Tenting Volume (late systole),cm3	0.90 ± 0.48	1.73 ± 0.65*	1.71 ± 0.36*
Leaflet area increase, %	–0.93 ± 4.14	17.83 ± 8.07*	16.73 ± 5.38*
Leaflet thickness, mm	0.42 ± 0.05	1.57 ± 0.22*	0.85 ± 0.23*‡
VECs coexpressing α-SMA, %	7.17 ± 3.45	51.64 ± 11.66*	27.18 ± 12.04‡
CD45-positive Cells/HPF	3.34 ± 1.21	21.89 ± 3.51*	10.73 ± 1.26*‡
Ki67-positive cells/HPF	4.72 ± 1.03	32.52 ± 13.96*	4.28 ± 1.19‡
Microvessels/HPF	0.93 ± 1.62	4.95 ± 1.9*	0.33 ± 0.81‡

* $p < 0.05$ Sham vs LV Constraint vs Losartan ‡ $p < 0.05$ Tethered plus MI LV constraint versus Tethered plus MI Losartan.

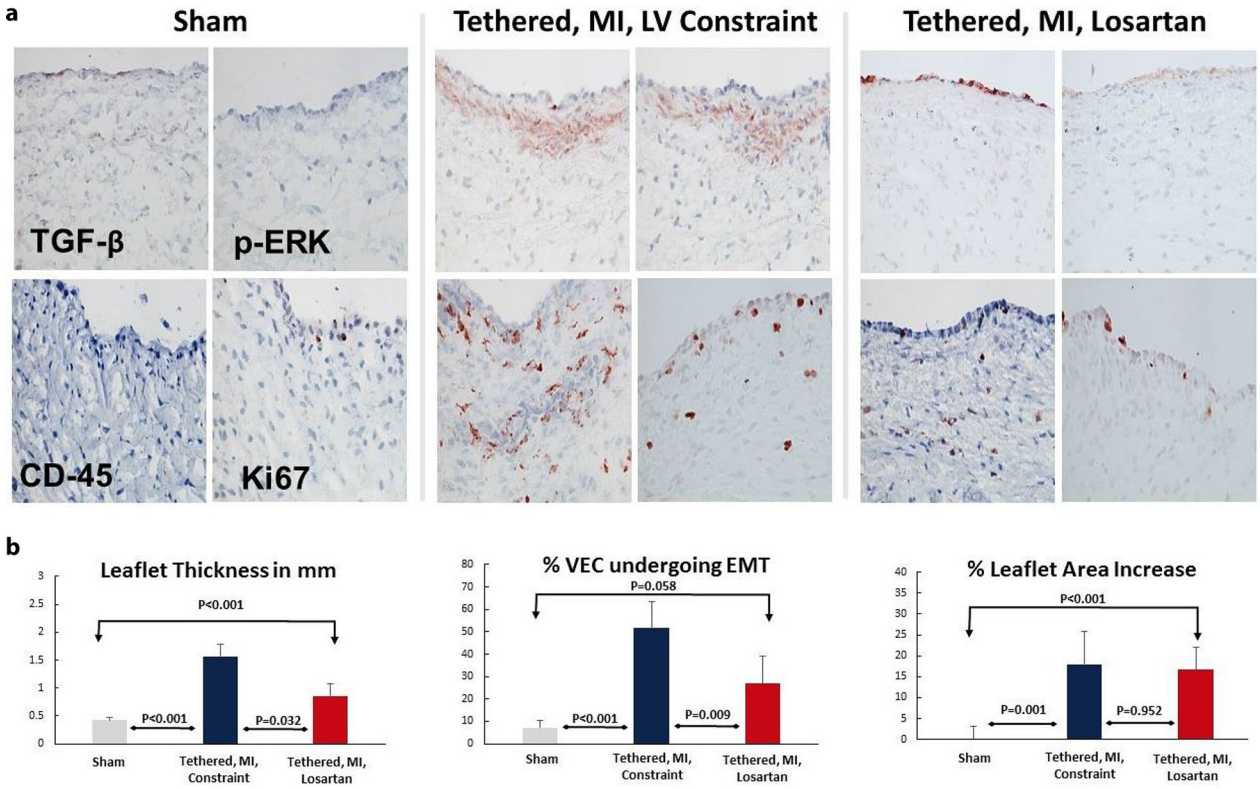


Fig. 2|FP 1-2

matrix turnover. In vitro, TGFβ inhibition with Losartan reduces MV endothelial cells EMT.

Hypothesis: To test whether profibrotic post MI MV changes are therapeutically accessible, and can be modulated by Losartan TGFβ inhibition.

Methods: 17 sheep were examined. Papillary muscles of 11 sheep were retracted, short of producing MR, followed by an apical MI. 6 were treated with daily Losartan, 5 with an epicardially sutured mesh to comparably limit left ventricular (LV) remodeling (LV constraint). 6 sheep were controls. (Fig. 1|FP 1-2a) LV volumes, tethering measures and MV area were quantified by 3D echo, followed by MV histopathology and flow cytometry.

Results: Post MI LV dilatation was similar in the Losartan and LV constraint sheep, with similar leaflet tethering and tenting. Blood pressure (BP) monitoring to control for BP effects showed no changes with Losartan in 6 normotensive sheep. (Fig. 1|FP 1-2a and b)

Losartan MVs showed resolution of endothelial cell activation with vascular adhesion molecule expression seen post MI, and significantly reduced matrix metalloproteinase expression, neovascularization, and CD45-positive cells. (Fig. 1|FP 1-2b, Fig. 2|FP 1-2a) Leaflet area increased to a comparable degree (17%) in the Losartan and LV constraint sheep (Fig. 1|FP 1-2a and Fig. 1|FP 1-2b, Fig. 2|FP 1-2b).

Conclusions: Profibrotic MV changes post MI, including excessive EMT, cellular hyperproliferation, endothelial cell activation, and matrix turnover, can be modulated using Losartan without eliminating the capacity for adaptive leaflet growth. Understanding cellular and molecular mechanisms could provide new opportunities to reduce ischemic MR.

FP 1-3

Gender differences in heart failure with preserved ejection fraction – insights from a prospective registry

F. Duca, C. Zotter-Tufaro, A. Kammerlander, S. Aschauer, C. Binder, B. Köll, J. Mascherbauer, D. Bonderman

Innere Medizin II, Abteilung für Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Approximately half of all heart failure (HF) patients present with a near normal left ventricular ejection fraction (LVEF). This condition has been termed HF with preserved ejection fraction (HFpEF). One of the most robust findings across HFpEF studies is that patients are predominantly female, with a gender ratio of approximately 2:1. However, even though gender is thought to play an important role in this disease, studies elucidating gender-differences are scarce.

Methods: Between December 2010 and November 2016, 260 consecutive patients with HFpEF were included in our study. Patients underwent clinical assessment including 6-minute walk test (6-MWT), left and right heart catheterization and cardiac magnetic resonance imaging. Prospective follow-up of study participants via outpatient visits or telephone calls was performed. The primary outcome was a composite endpoint of HF hospitalization or cardiac death.

Results: Median age of the total cohort was 73.0 years (IQR: 76.0–77.0), 181 (69.6%) were female, median N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was 1169 pg/mL (IQR: 557–2072) and 170 (65.4%) study participants were in NYHA class ≥III.

Men had lower percentages of their predicted 6-MWT distance (66.7% versus 78.1%, $p=0.036$), lower LV (58.0 versus 66.0, $p=0.005$) as well as right ventricular EF (50.0 versus 55.0, $p=0.006$), and higher a diastolic pressure gradient (3.0 versus 1.0, $p=0.010$). With regards to co-morbidities, prevalences of atrial fibrillation (69.6% versus 54.7%, $p=0.024$), anemia (73.4% versus 60.8%, $p=0.050$), sleep apnea (20.3% versus 5.0%, $p<0.001$), COPD (46.8% versus 27.1%, $p=0.002$) and smoking history (46.8% versus 27.1%, $p=0.009$) were higher in the male cohort. Concomitant medications were equally distributed between the two genders.

During follow-up, 87 events, which included 24 cardiac deaths, occurred. Men had a worse event-free survival, both for the combined endpoint (Fig. 1|FP 1-3a, $p=0.031$) and cardiac death (Fig. 1|FP 1-3b, $p=0.011$). No difference could be detected for all-cause death (Fig. 1|FP 1-3c, $p=0.629$). Also, men were more likely to die from cardiac death as compared to women (16.5% versus 6.1%, $p=0.008$) and less likely to die from non-cardiac death (2.5% versus 10.5%, $p=0.030$). NT-proBNP, mean pulmonary artery pressure and exercise capacity were predictors of outcome in both genders. However, right ventricular function and co-morbidities such as atrial fibrillation, diabetes mellitus or COPD only predicted event-free survival in female HFpEF patients.

Conclusions: Among a well-characterized typical HFpEF study population, marked gender-differences could be detected. Men had worse exercise capacity, worse hemodynamics, and a higher burden of co-morbidities, which was accompanied by a shorter cardiac event-free survival in comparison to female HFpEF patients. Interestingly, the clearly higher burden of co-morbidities hardly affected outcome in the male cohort, but strongly did so in the female cohort.

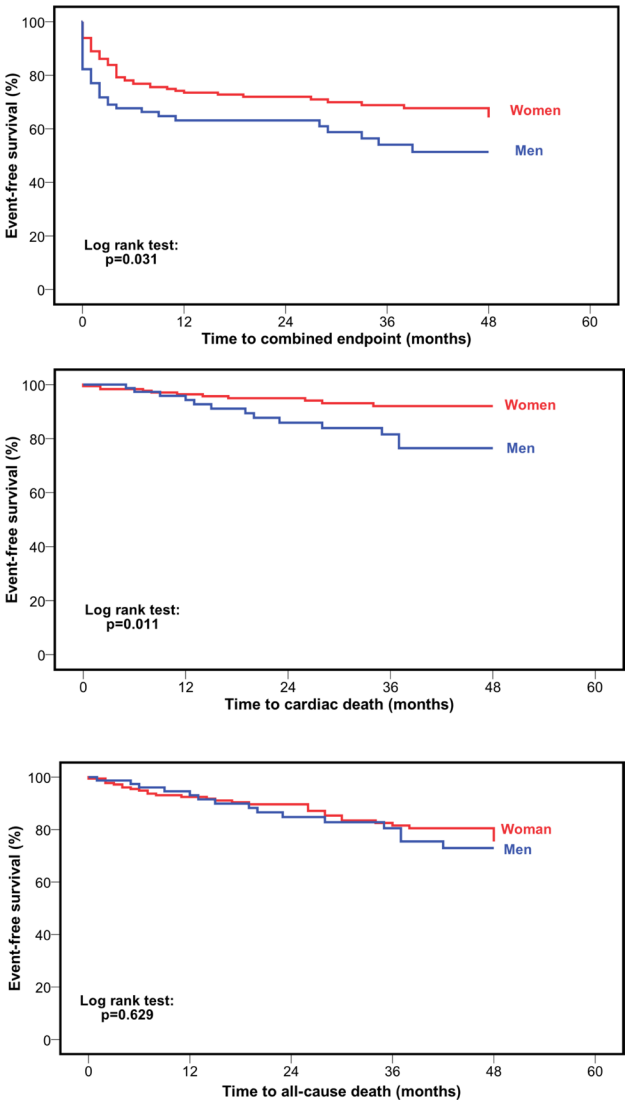


Fig. 1 | FP 1-3

FP 1-4

Validation of cardiac magnetic resonance T1 mapping in cardiac amyloidosis

F. Duca, C. Zotter-Tufaro, A. Kammerlander, A. Panzenböck, S. Aschauer, B. Börries, H. Agis, R. Kain, D. Bonderman, J. Mascherbauer

Innere Medizin II, Abteilung für Kardiologie, Medizinische Universität Wien, Vienna, Austria
Klinik für Innere Medizin I, Onkologie, Medizinische Universität Wien, Vienna, Austria
Klinisches Institut für Pathologie, Medizinische Universität Wien, Vienna, Austria

Background: Cardiac amyloidosis (CA) is caused by extracellular deposition of amyloid fibrils within the myocardium, thus expanding the extracellular volume (ECV). The gold standard for ECV quantification is the histological assessment of

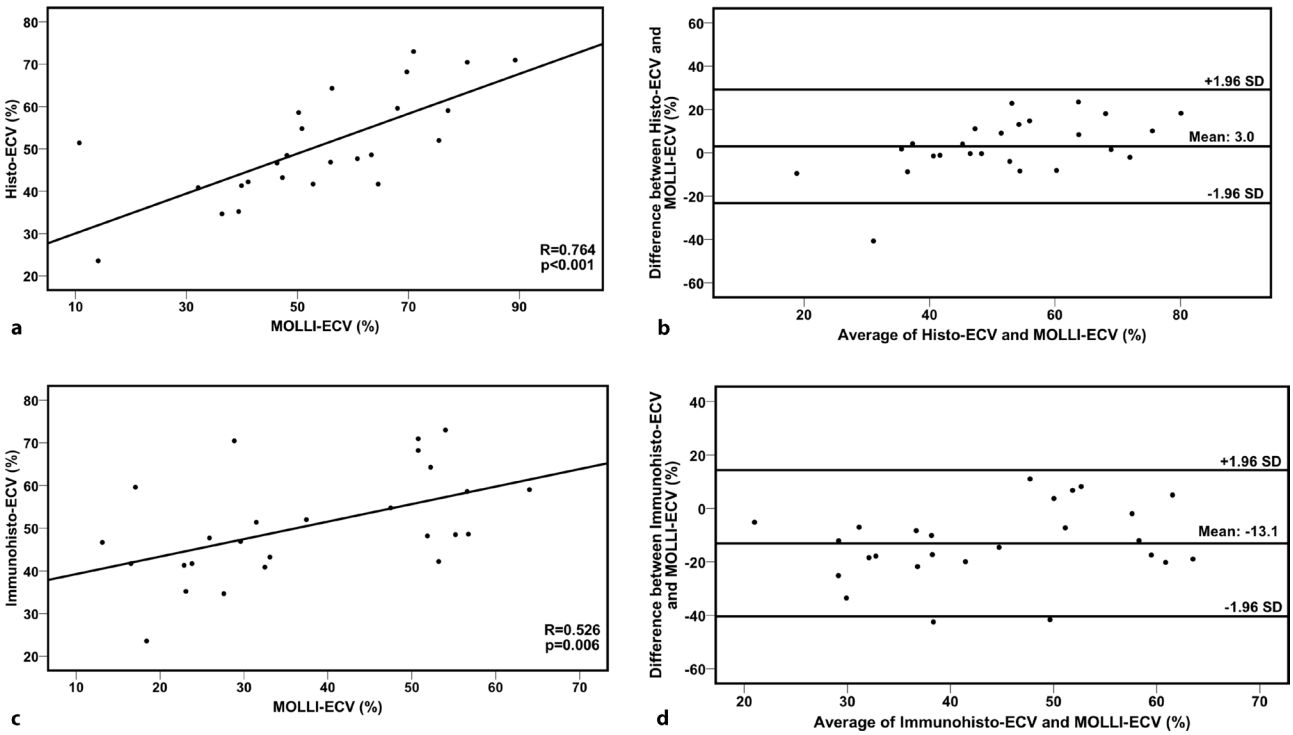


Fig. 1 | FP 1-4 a. Correlation between Histo-ECV and MOLLI-ECV. b. Bland–Altman plot showing good agreement of Histo-ECV and MOLLI-ECV. c. Correlation between Immunohisto-ECV and MOLLI-ECV. d. Bland–Altman plot showing good agreement of Immunohisto-ECV and MOLLI-ECV. Histo-ECV indicates extracellular volume quantified via TissueFAXS in Trichrome stained biopsy samples. Immuohisto-ECV, extracellular volume quantified via TissueFAXS in immunohistochemically stained biopsy samples; MOLLI-ECV, extracellular volume quantified via cardiac magnetic resonance T1 mapping

endomyocardial biopsies (EMB). However, this method is limited by procedural risk and therefore not ideal for the monitoring of response to treatment. Cardiac magnetic resonance (CMR) T1 mapping has recently been shown to allow accurate ECV measurement in various cardiac diseases. Thus far it has not been investigated weather CMR-ECV accurately measures ECV in CA.

Methods: Between July 2011 and December 2016, 26 CA patients were enrolled in our study. All patients underwent EMB and CMR for invasive and non-invasive ECV quantification. EMBs were stained with modified Trichrome ($n=25$). Additionally, immunohistochemical staining ($n=26$) with specific amyloid antibodies was performed. ECV in EMBs was quantified using TissueFAXS software in Trichrome stained (Histo-ECV) as well as in immunohistochemically stained samples (Immunohisto-ECV). ECV by CMR was quantified with T1 mapping using the Modified Look-Locker Inversion recovery (MOLLI) sequence (MOLLI-ECV). Spearman's correlation and Bland-Altman plots were used for correlation analysis and assessment of agreement.

Results: The study population consisted of 9 (34.6%) wild-type transthyretin and 17 (65.4%) light chain CA patients. Median Histo-ECV was 52.8% (IQR: 40.5–68.9), median Immunohisto-ECV was 32.8% (IQR: 23.6–52.5) and median MOLLI-ECV was of 48.3% (IQR: 41.7–59.2). MOLLI-ECV was strongly correlated with Histo-ECV (R = 0.764, $p<0.001$, Fig. 1|FP 1-4a) and Immunohisto-ECV (R = 0.526, $p=0.006$, Fig. 1|FP 1-4c). Additionally, MOLLI-ECV showed good agreement with Histo-ECV (Fig. 1|FP 1-4b) as well as Immunohisto-ECV (Fig. 1|FP 1-4d).

Conclusions: We could demonstrate that MOLLI-ECV accurately quantifies ECV and amyloid within the myocardium of CA patients. Thus, ECV by CMR has the potential of becoming a monitoring tool for new therapeutic agents in CA patients.

FP 1-5

Long-term survival in patients with different subtypes of amyloidosis at Medical University Innsbruck

F. Escher, C. Ensinger, M. M. Zaruba, J. Dörler, E. Stocker, G. Pölzl

Kardiologie, Medizinische Universität Innsbruck, Innsbruck, Austria

Background: Amyloidosis is a severe, systemic disease associated with poor prognosis. Prognosis depends primarily on amyloid subtype and cardiac involvement. Chemotherapy and immunomodulatory therapy are mandatory for the treatment of AL (light chain amyloidosis). It was the aim of our study to evaluate long-term prognosis of different amyloid subtypes (AL, ATTR – transthyretine related amyloidosis, AA – secondary amyloidosis), cardiac involvement and therapeutic management particularly in AL-amyloidosis managed at Medical University Innsbruck.

Methods: 72 patients with biopsy proven amyloidosis (AL: $n=53$, median age at diagnosis = 63.6 years; ATTR: $n=15$, median age at diagnosis = 74.3 years; AA: $n=4$, median age 45.2 years) diagnosed at Medical University Innsbruck between November 1997 and November 2016 were analysed. Data were obtained from electronic health records, phone calls (Table 1|FP 1-5) and public death registers. The endpoint was defined as death from any cause. Univariate cox regression analysis was used to compare survival between amyloid subtypes, patients with and without cardiac involvement, various

Table I. Patient characteristics (Overview)

Characteristic	AL (n=53)	ATTR (n=15)	AA (n=4)	p-value
Gender (male / female)	30 / 23 (56.6% / 43.4%)	14 / 1 (93.3% / 6.7%)	3 / 1 (75.0% / 25.0%)	
Age				p<.001
median	63.6	74.3	45.2	
range	36.5-80.0	68.9-83.7	40.9-67.5	
BMI				
median	23.4	25.2	23.8	p=.632
range	17.4-34.8	18.3-33.2	22.0-30.9	
NYHA Stadium				
mean	2.48	2.13	2.0	p=.217
I	9.1%	6.7%	0.0%	
II	38.6%	73.3%	100.0%	
III	47.7%	20.0%	0.0%	
IV	4.5%	0.0%	0.0%	
Mayo Score				
mean	2.67	2.60	2.25	
Low Risk Type I	4.4%	0.0%	0%	p=.346
Intermedium Risk Type II	24.4%	40.0%	75.0%	
High Risk Type III	71.1%	60.0%	25.0%	

Figure I. AL vs. ATTR /AA (Univariate Cox Regression Analysis)

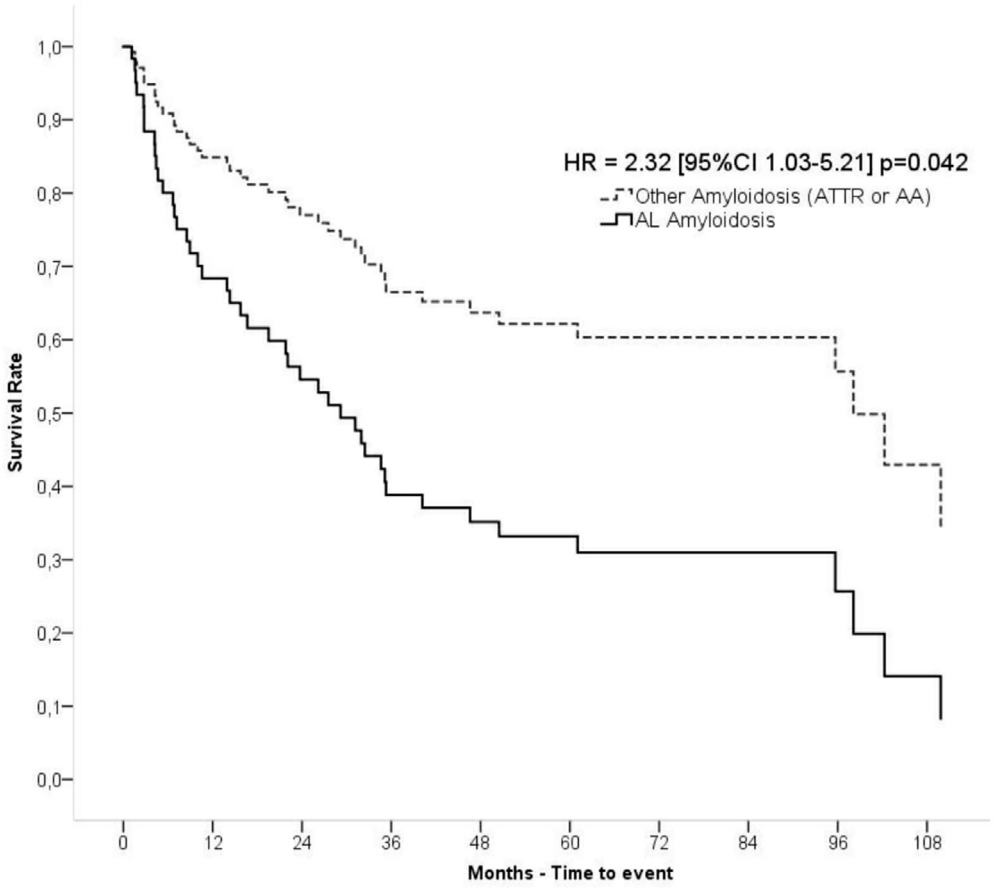


Fig. 1|FP 1-5

chemo- and/or immunomodulatory therapies, and autologous stem cell transplantation (ASCT).

Results: The endpoint was recorded in 44 patients (AL $n=37$, ATTR $n=5$, AA $n=2$). Survival of patients with AL-amyloidosis was significantly worse compared to patients with ATTR or AA- amyloidosis (HR = 2.32; [95%CI = 1.03–5.21]; $p=0.042$, 1-year survival rate 68% vs. 85%, median survival time 30 months vs. 102 months) (Fig. 1 | FP 1-5). No difference in survival was found between patients with ($n=56$) and without ($n=16$) cardiac involvement. Similar results were seen in the subgroup of patients with AL-amyloidosis. AL patients who underwent chemotherapy both with and without immunomodulatory therapy had a significant better survival than patients without oncological therapy (HR = 0.230; [95%CI = 0.086–0.617]; $p=0.004$, 1-year survival rate 69% vs. 20%, median survival time 32 months vs. 5 months). Patients with ASCT on top of chemotherapy and immunomodulatory therapy had a significantly better outcome than AL patients treated with chemo- and immunomodulatory therapy alone (HR = 0.249; [95%CI = 0.087–0.707]; $p=0.009$, 1-year survival rate 88% vs. 58%, median survival time 22 months vs. 110 months).

Conclusions: Prognosis was worse for AL amyloidosis in our cohort of patients. Interestingly, cardiac involvement had no impact on survival. In AL amyloidosis, chemotherapy and or immunomodulatory therapy as well as ASCT were associated with better long-term survival.

FP 1-6

Transcatheter aortic valve implantation without balloon valvuloplasty is not associated with transient left ventricular dysfunction

M. Mirna, B. Wernly, S. Eder, M. Lichtenauer, C. Jung, C. Reiter, A. Kypta, U. Hoppe, M. Hammerer

Christian Doppler Labor für Diagnose und Regeneration von Herz- und Thoraxerkrankungen, Universitätsklinik Jena, Jena, Germany
Universitätsklinik für Innere Medizin II, Kardiologie, Paracelsus Medizinische Universität Salzburg, Salzburg, Austria
Abteilung für Kardiologie, Pneumologie & Angiologie, Universitätsklinikum Düsseldorf, Dusseldorf, Germany
Klinik für Interne Medizin 1 – Schwerpunkt Kardiologie und internistische Intensivmedizin, Johannes Kepler Universität Linz, Linz, Austria

Background: Transcatheter aortic valve implantation (TAVI) is a therapeutic alternative to conventional heart surgery in patients with high-grade aortic valve stenosis. Balloon aortic valvuloplasty (BAV) under rapid ventricular pacing (RVP) has been a routine part of TAVI. However, it carries substantial risks and therefore an increasing number of interventionists have started to refrain from it. In our study, we investigated if TAVI without prior balloon valvuloplasty ("direct TAVI") was associated with a similar increase in cardiac biomarkers and decrease in ejection fraction as reported previously.

Methods: A total of 164 consecutive patients undergoing "direct-TAVI" were followed up for one year and were retrospectively analyzed regarding mortality, safety and efficacy endpoints as well as common laboratory and echocardiographic values.

Results: According to the VARC2 (Valve Academic Research Consortium) 89.1% of patients remained free of a combined safety endpoint and technical success rate was 96.3%. Mortality rates at 30 days and 1 year were 3.0% ($n=5$) and 10.4% ($n=17$), respectively.

TAVI without rapid ventricular pacing was highly effective in lowering aortic valve peak velocity from 4.36 ±0.63 m/s before to 1.7 ± 0.45 m/s post intervention, resulting in a significant decrease of mean aortic valve peak velocity ($p<0.01$). Left ventricular function remained unaltered (50.64 ±10% prior to TAVI and 50.86 ±8.99% post TAVI) after the intervention, whereas high sensitive troponin T, a well-established marker for myocardial injury, increased significantly from 26 ng/L (IQR = 18.00–44.00) to 119 ng/L (IQR = 73.25–166.00, $p<0.001$) during this time. Myocardial injury (>15 ULN) was associated with mortality at one month (10% vs 2%; $p=0.04$) and one year (8% vs 23%; HR 4.28; 95%CI 1.63–11.28; $p=0.003$).

Conclusions: "Direct TAVI" is feasible, safe and effective. Mortality and safety resulted in similar outcomes as the frequently used approach with rapid ventricular pacing and balloon valvuloplasty. In contrast to a cohort of patients who underwent TAVI with BAV and RVP previously published by another center, our cohort did not suffer from transient impairment of left ventricular function. Furthermore, hs-troponin showed a less pronounced increase than reported previously. We therefore conclude that "direct TAVI" is a less invasive option involving less myocardial stress and might therefore be better suited for the elderly and multimorbid.

FP 1-7

Incidence and predictors of automatic and manual triggered device alarms in patients with wearable cardioverter defibrillator (WCD) – results of the Astrian WCD Registry

V. Sachsenhauser, T. Odeneg, M. Manninger, C. Ebner, D. Mörtl, H. Keller, A. Dirninger, G. Stix, B. Föger, G. Grimm, M. Stühlinger, C. Steinwender, D. Scherr

Medizinische Universität Graz, Graz, Austria
Elisabethinen Linz, Linz, Austria
LKH St. Pölten, St. Pölten, Austria
Rudolfstiftung Wien, Vienna, Austria
LKH Hochsteiermark, Bruck an der Mur, Austria
AKH Wien, Vienna, Austria
LKH Bregenz, Bregenz, Austria
LKH Klagenfurt, Klagenfurt, Austria
LKH Innsbruck, Innsbruck, Austria
AKH Linz, Linz, Austria

Background: The wearable cardioverter defibrillator (WCD; LifeVest©) is a treatment option for patients at high risk for ventricular arrhythmia, either in whom this risk may be intermittently present or in whom an implantable cardioverter defibrillator (ICD) implantation is currently not possible. Besides its automated shock function in case of VT/VF, the WCD permits storage and telemetric transmission of all recorded ECGs, which can be manually or automatically triggered. Manual ECG recordings are triggered actively by the WCD patient or by bystanders by pressing the response buttons on the LifeVest in case of syncope, palpitations, diziness or other related symptoms. Automatic ECG recordings can be triggered by WCD in case of presumed ventricular arrhythmia. In all these cases the WCD transmits the ECG recording via telemetry and introduces a siren alarm. The aim of this study was to analyze all manually and automatically triggered ECGs.

Methods: Retrospective analysis of all automatically and manualyl recorded WCD ECGs of all 449 patients of the Austrian WCD Registry included 2010–2016. Main indications for the WCD were: Newly diagnosed severe cardiomyopathy (21%), recent myocardial infarction (20%), ischemic cardiomyopathy with recent PCI (14%), delayed ICD implantation (12%), acute myocarditis (10%), ICD-associated infection (10%).

Results: 10.201 automatically recorded ECGs in 300 patients and 2787 manual ECGs in 248 patients were analyzed.149 patients (33%) had no automated and 201 (45%) patients had no manual alarm during the WCD period.

Of all automatically recorded ECGs, 165 ECGs in 46 patients showed a ventricular arrhythmia, whereas 10.036 ECGs in 290 patients showed other arrhythmias or artifacts. 22 VT/VF events were recorded and triggered WCD shocks in 11 patients (2,4%). 19VT/VF events were successfully terminated with the first shock, one VT event was successfully terminated with the second shock, one VF event was terminated with the third shock and one VF event could not be terminated with WCD shocks. Mean heart rate of shocked VTs was 214+/–38/min. Reasons for non shocked adequate automatic ECGs were: sustained VTs suppressed by patient ($n=35$ in 16 patients, mean heart rate 187+/–33/min), non-sustained VF ($n=1$), bradycardia ($n=2$/2patients), asystole ($n=1$), non sustained VT ($n=107$ in 29 patients). Inadequate automatic alarms were triggered by: artefacts ($n=9716$ in 285 patients), pacemaker oversensing ($n=71$ in 1 patient), supraventricular tachykardia ($n=124$ in 19 patients), atrial fibrillation ($n=110$ in 11 patients) and others ($n=15$ in 3 patients) such as multiple ventricular exrtasystole.

Furthermore 2787 manual ECGs were recorded. These included 56 adequate alarms and 2731 inadequate alarms. Reasons for adequate alarms were atrial fibrillation ($n=23$/11 patients)), bradycardia ($n=3$/2 patients), non sustained VTs (27/7 patients)and slow sustained VT ($n=3$/2 patients). Reasons for inadequate alarms ($n=2734$) were ventricular extrasystole, sinus tachycardia and normal ECGs. In three patients atrial fibrillation was newly detected by WCD recordings

Conlusions: The WCD is an effective treatment option in patients at high risk for ventricular arrhythmia, but it also triggers a significant amount of alarms. Although many inadequate alarms occurred, adequate alarms led to arrhythmia detection such as in VT/VF events which were successfully terminated by the WCD in 2.4% of patients.

FP 1-8

Subcutaneous treprostinil for the treatment of non-operable chronic thromboembolic pulmonary hypertension: A randomized, controlled trial (CTREPH)

R. Sadushi-Kolici, P. Jansa, G. Kopec, A. Torbicki, I.-A. Campean, G. Höffken, N. Skoro-Sajer, I. Simkova, K. Karlocai, R. Steringer-Mascherbauer, W. Klepetko, J. Lindner, I. Lang

Innere Medizin II, Kardiologie, Medizinische Universität Wien
General University Hospital – 2nd Clinic of Int. Medicine for Cardiology and Angiology, Prag, Czech Republic
Cardiac and Vascular Diseases Jagiellonian University Medical College, Krakow, Poland
Instytut Gruzlicy i Chorob Pluc, Warszawa, Poland
Universitätsklinik Carl Gustav Carus Medizinische Fakultät der Technischen Universität Dresden, Germany
Slovak Medical University, Cardiology, Bratislava, Slovakia
Semmelweis University Heart Center, Cardiology, Budapest, Hungary
Elisabethinen University Teaching Hospital, Linz, Linz, Austria
2nd Surgical Department of Cardiovascular Surgery, First Faculty of Medicine, Charles University and General University Hospital, Prag, Czech Republic

Background: Treprostinil, a prostacyclin analogue, is effective for the treatment of pulmonary arterial hypertension (PAH), but little information exists on treprostinil treatment of non-operable chronic thromboembolic pulmonary hypertension (CTEPH).

Methods: In a phase III, double-blind, randomized, controlled, multicenter trial (ClinicalTrials.gov: NCT01416636) 105 patients (mean age 64 years, 46.7% females) with severe, non-operable CTEPH were randomly assigned to low-dose subcutaneous treprostinil (scTRE, target dose 3 ng/kg/min at week 12) or high-dose scTRE (target dose 30 ng/kg/min at week 12) in several European expert centers. Primary study endpoint was change from baseline in 6-minute walking distance (6MWD) at week 24. Secondary endpoints included clinical worsening and the change from baseline in hemodynamics, World Health Organization functional class (WHO FC), Borg dyspnea score, oxygen saturation, heart rate, NT-proBNP, quality of life and safety.

Results: Patients predominantly in WHO FC class III and IV with a mean baseline 6MWD of 304 ± 78 m, a mean pulmonary artery pressure (mPAP) of 49 ± 11 mmHg and a mean pulmonary vascular resistance (PVR) of 827 ± 343 dyn.s.cm^{-5} were randomized to low dose scTRE ($n=52$) or to high dose scTRE ($n=53$). Four patients (three in the low-dose and one in the high-dose group) stopped treatment prior to week 24 because of infusion site pain and 5 patients were withdrawn because of clinical worsening (three in the high-dose and two in the low-dose group). Three deaths occurred within the study period, two of which were in the high-dose group.

By 24 weeks 6MWD had increased by a mean of 45 m in the high-dose group and by a mean of 4 m in the low-dose group ($P=0.0003$). PVR decreased by a mean of 214 dyn.s.cm^{-5} in the high-dose group and increased by a mean of 73 dyn.s.cm^{-5} in the low-dose group ($P=0.00001$). Mean PAP decreased by a mean of 3.5 mmHg in the high-dose group and by 0.4 mmHg in the low-dose group ($P=0.029$). High-dose treprostinil was associated with a significant improvement of WHO FC ($P=0.003$).

Conclusions: Treatment with subcutaneous treprostinil was safe, and improved exercise capacity, hemodynamics, and WHO FC in patients with severe, non-operable CTEPH.

FP 1-9

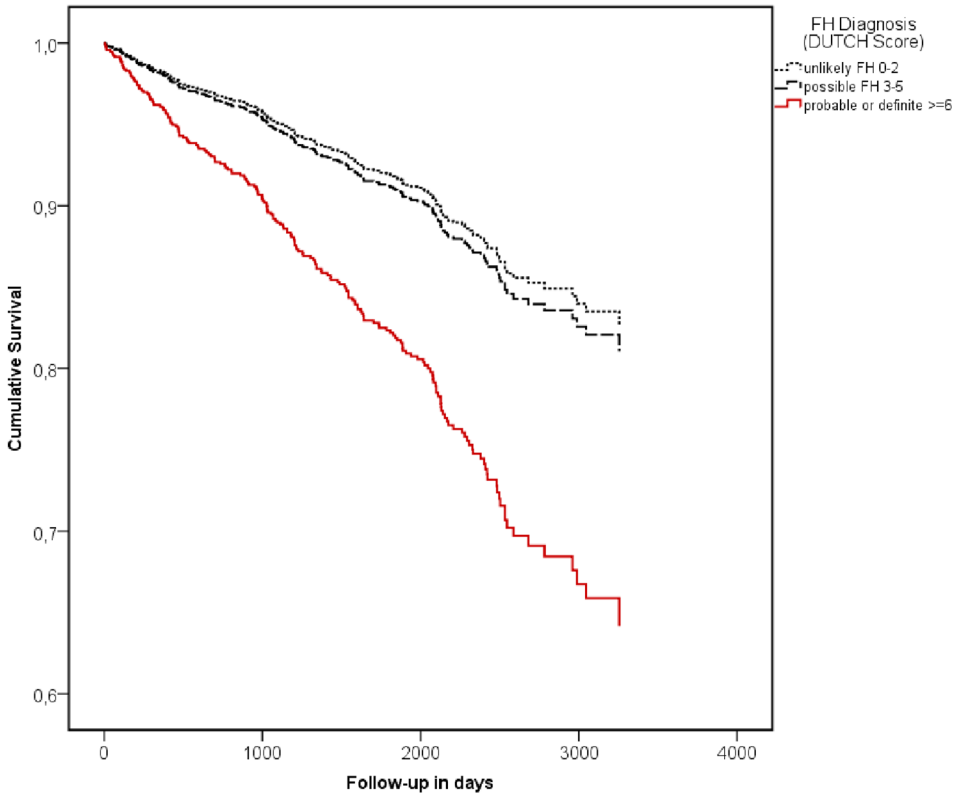
Prevalence, management and prognostic impact on long-term mortality of familial hypercholesterolemia in patients with acute or stable coronary artery disease

M. Tscharre, R. Herman, M. Rohla, S. Farhan, I. Tentzeris, M.K. Freynhofer, T.W. Weiss, K. Huber

3. Medizinische Abteilung mit Kardiologie und Intensivmedizin, Wilhelminenspital, Vienna, Austria
Sigmund Freud Universität, Medical School Wien, Vienna, Austria

Background: Patients suffering from familial hypercholesterolemia (FH) are at increased risk for premature and sub-

Fig. 1 | FP 1-9



sequent cardiovascular disease. However, data on long-term adverse outcome in patients with FH after coronary stenting is scarce. We aimed to assess the prevalence, the rate of optimal lipid-lowering therapy at discharge (by means of high-intensity statins) and long-term adverse outcome of clinical diagnosed FH among patients undergoing coronary stenting presenting with stable coronary artery disease (SCAD) or acute coronary syndromes (ACS).

Methods: We analysed 1582 patients of a single-centre registry undergoing coronary stenting between 2007 and 2012, of whom 746 patients had SCAD while 836 patients presented with ACS. Patients were stratified into "unlikely FH" (0–2 points), "possible FH" (3–5 points) and "probable or definite FH" (≥6 points) based to the Dutch Lipid Clinic Network criteria. As primary endpoint, we assessed the prevalence and management of FH in this cohort. As secondary endpoint, we compared long-term all-cause mortality between these groups in Cox proportional hazards analysis adjusting for ACS/SCAD, age, gender, body mass index, kidney function, admission with shock, atrial fibrillation, heart failure, hypertension, smoking status, diabetes mellitus, malignancy, femoral or radial access site, number of affected vessels, use of drug-eluting stents, and discharge with high-intensity statins.

Results: Among our cohort, 76 (4.8%) patients had probable or definite FH, 345 (21.8%) had possible FH and 1161 (73.4%) were unlikely to suffer from FH. Fifty-three (70.7%) patients with probable or definite FH, 251 (73.8%) patients with possible FH and 660 (58.8%) of the patients with unlikely FH were discharged with high-intensity statins.

After adjusting for multiple confounders, patients with probable or definite FH (HR 2.316 [95% CI 1.053–5.095], $p=0.037$), but not patients with possible FH (HR 1.097, $p=0.658$), had an approximately 2-fold increased relative risk of all-cause death after a mean follow-up of 7.9 years (Fig. 1 | FP 1-9).

Conclusions: Clinical diagnosis of FH is not uncommon in patients presenting with coronary artery disease. Patients with probable or possible FH face a >2-fold increased risk of long-term all-cause mortality compared to patients without FH despite the widespread use of high-intensity statins.

FP 1-10

Safety of epicardial ablation of ventricular tachycardia: A large single center experience

A. Weber, L. Bertagnolli, B. Dinov, P. Sommer, A. Bollmann, G. Hindricks, A. Arya

Rhythmologie, Herzzentrum Leipzig, Leipzig, Germany

Background: The presence of transmural or epicardial substrate in patients with ventricular tachycardia often requires epicardial access to achieve successful ablation. In previous studies a complication rate up to 20% is reported. In two large multicenter studies major complication rates of 4.1% and 5.0% have been reported.

Methods: 190 patients (109 male, mean age 54) receiving 216 epicardial VT-ablations between 2008 and 2015 were included in this investigation. The underlying structural heart diseases were ischemic cardiomyopathy ($n=29$), arrhythmogenic right ventricular cardiomyopathy ($n=17$), and non-ischemic cardiomyopathy ($n=144$).

Results: Epicardial access was obtained via subxyphoidal puncture in 208 procedures, five of them with double percutaneous epicardial access, and via surgical approach in 6 patients. Re-ablation was required in 28 (14.7%) patients. The epicardium could not be accessed in 2 procedures. Among 190 patients receiving epicardial ablation major complications were

seen in 2 patients with myocardial perforation requiring emergency cardiac surgery. No patient died due to procedure related complications.

Three patients had minor pericardial bleeding after procedure requiring draining with a pigtail catheter. One patient developed a femoral aneurysm and had to undergo vascular surgery. No coronary artery or phrenic nerve injury were observed.

Conclusions: Epicardial ablation in high volume center performed by experienced operators has a low complication (2.7%) and mortality (0.0%) rates.

Featured Poster Session 2

FP 2-1

Catestatin protects from myocardial ischemia/reperfusion injury in-vivo and promotes cardiac vascular cell function via bFGF-signaling

M. Theurl, C. Gutmann, D. Lener, A. Beer, R. Kirchmair

Universitätsklinik für Innere Medizin (Kardiologie, Angiologie, Nephrologie), Medizinische Universität Innsbruck, Innsbruck, Austria

Background: Myocardial infarction (MI) induces irreversible tissue damage, eventually leading to heart failure. Exogenous induction of angiogenesis is recognized to influence positively ventricular remodeling after a MI. The neuropeptide catestatin (CST) is a derivate of the prohormone chromogranin A (CgA) which is produced in many tissues, including in neuroendocrine cells and myocardial cells. Recently, we could show that CST restores reperfusion in the mouse hind limb ischemia model by the induction of angio-, arterio- and vasculogenesis. Moreover, it has been demonstrated that CST influences cardiac Ca2+-handling and that a low CgA to CST conversion is associated with a worse outcome after admission for heart failure. Thus, we assumed that myocardial overexpression of CST might improve experimental heart failure.

Methods and Results: To investigate the role of CST on cardiac angiogenesis experiments with human coronary artery endothelial cells (HCAEC) were performed. Incubation of HCAEC with CST significantly mediated chemotaxis and in-vitro angiogenesis in the matrigel assay. The observed effects were comparable to basic fibroblast growth factor (bFGF), which was used as positive control (rel. tube formation vs. ctr.: CST 1 nM 2.69 ± 0.3, $n=3$, $P<0.001$). Interestingly, blockade of bFGF either by a bFGF-antibody (Ab) or a specific receptor blocker (PD173074) resulted in abrogation of in-vitro angiogenesis suggesting a bFGF-depending mechanism. Moreover, CST induced proliferation of HCAEC and human coronary artery smooth muscle cells (HCASMC) as determined by BrdU-incorporation. Similar to the matrigel assay blockade of bFGF attenuated the effect (HCAEC: rel. proliferation vs. ctr.: CST 1 nM 1.5 ± 0.1, $P<0.001$; CST+bFGF-Ab 1.1 ± 0.1, $P<0.01$ vs. CST; CST+PD173074 0.7 ± 0.1, $P<0.001$ vs. CST; HCASMC: rel. proliferation vs. ctr.: CST 1 nM 1.8 ± 0.03, $P<0.01$; CST+bFGF-Ab 1.2 ± 0.1, $P<0.01$ vs. CST; CST+PD173074 0.9 ± 0.1, $P<0.001$ vs. CST; $n=3$). Consistent with these findings western blot assays revealed a bFGF-dependent phosphorylation of extracellular-signal regulated kinase-1/2 (ERK-1/2) by CST in these cell lines. In contrast, inhibition of VEGF-signaling had no effect on CST-induced ERK-1/2 phosphorylation. In addition, CST protected human cardiomyocytes (HCM) from apoptosis and activated the PI3-kinase/Akt signaling pathway in these cells.

To evaluate the effect of CST on cardiomyocyte apoptosis in-vivo the mouse myocardial ischemia/reperfusion model was performed. After reversible ligation of the left anterior descending artery an intra-myocardial injection of CST or saline 0.9% (control) was performed. In this animal model CST-treatment was associated with a significant reduction of cardiomyocyte apoptosis (apoptotic cardiomyocytes/HPF: CST 9.16 ± 0.95 vs. ctr. 19.36 ± 1.74, $n=8$/group, $P<0.01$).

Conclusions: Due to its favorable effects on cardiac vascular cells CST might qualifiy as a potential candidate for the treatment of ischemic heart failure. Future in-vivo experiments using our CST-expressing plasmid or a CST-expressing adeno-associated virus will be necessary to strengthen our data.

FP 2-2

The golden window of survival in cardiovascular surgery patients with extracorporeal membrane oxygenation support

K. Distelmaier, D. Wiedemann, C. Binder, T. Haberl, D. Zimpfer, G. Heinz, H. Koinig, A. Felli, B. Steinlechner, A. Niessner, G. Laufer, I. Lang, G. Goliasch

Innere Medizin 2, Kardiologie, Medizinische Universität Wien, Vienna, Austria
Universität Krems, Krems, Austria

Background: The overall therapeutic goal of veno-arterial extracorporeal membrane oxygenation (ECMO) in patients with post-cardiotomy shock is bridging to myocardial recovery. However, in patients with irreversible myocardial damage prolonged ECMO treatment would cause a delay or even withhold of further permanent potentially life-saving therapeutic options. We therefore assessed the prognostic impact of duration of ECMO support on survival in adult patients following cardiovascular surgery.

Methods and Results: We enrolled into our single-center registry a total of 354 patients undergoing veno-arterial ECMO support following cardiovascular surgery at a university-affiliated tertiary care center. Through a median follow-up period of 45 months (IQR 20- 81 months), 245 patients (69%) died. We identified a significant independent adverse association of ECMO duration on mortality with an adj. HR of 2.27 (95% CI 1.36–3.81; $p=0.002$) for 30-day mortality and an adj. HR of 2.08 (95% CI 1.41–3.08; $p<0.001$) for 2-year long-term mortality when comparing the third tertile (≥7 days of ECMO support) with the second tertile of ECMO duration (Fig. 1|FP 2-2).

Conclusions: Prolonged veno-arterial ECMO support is associated with poor outcome in adult patients following cardiovascular surgery. Our data suggest to reevaluate therapeutic strategies after seven days of ECMO support as mortality disproportionally increases afterwards.

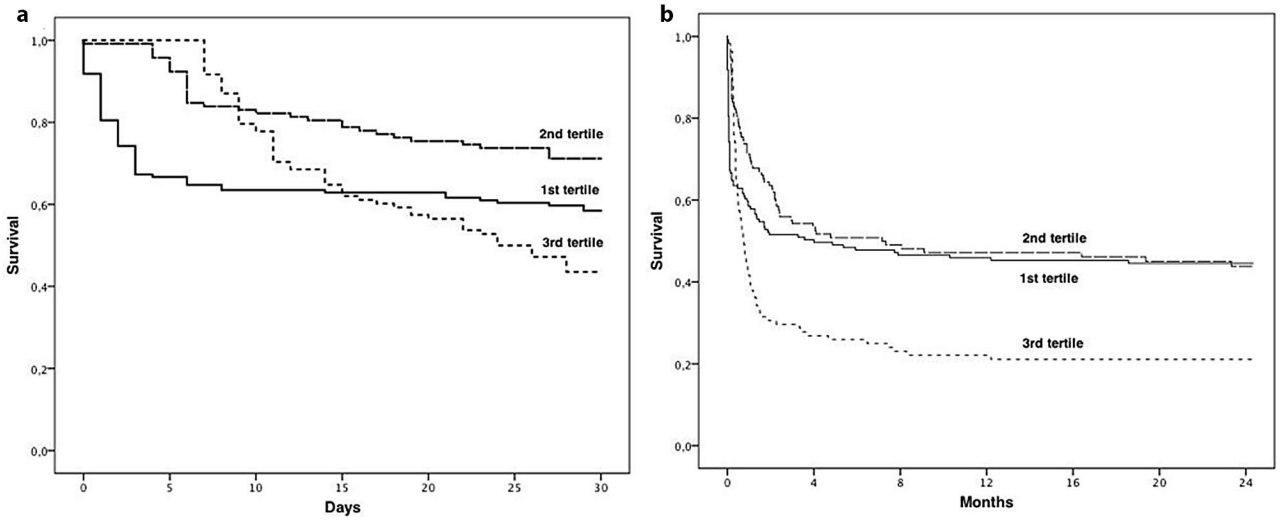


Fig. 1|FP 2-2

FP 2-3

Minicircle-HIF-1α transfected mesenchymal stem cell implantation enhance cardiac repair via releasing cardioprotective miRNA and pro-angiogenic secretome

E. Gara, SG Ong, J. Winkler, K. Zlabinger, D. Lukovic, M. Emmert, S. P. Hoerstrup, P. Wolint, A. Jakab, B. Merkely, J. C. Wu, M. Gyöngyösi, N. Pavo

Innere Medizin II, Medical University Vienna, Vienna, Austria
Stanford Cardiovascular Institute, Stanford, USA
Institute for Regenerative Medicine, Zürich, Switzerland
Heart and Vascular Centre, Budapest, Hungary

Background: Intracoronary and intramyocardial autologous or allogeneic mesenchymal stem cell (MSC) therapy for treatment of acute and chronic ischemic heart disease has shown promising results in preclinical and early clinical trials. Regenerative capacity of MSCs thought to be mainly via the rich paracrine production, however cell retention rate and paracrine effect on ischemic myocardium is insufficient. Hypoxia-inducible factor-1α (HIF1α) modulates angiogenesis and secretion of regenerative growth factors, thus acts as strong anti-ischemic factor.

Purpose: Porcine allogeneic MSCs were transfected with virus-free minicircle plasmid driving HIF1α transgene (MSC-MiCi-HIF1α), to enhance paracrine, anti-ischemic and anti-remodelling efficacy of cell therapy.

Methods: Domestic male pigs ($n=16$) underwent closed-chest reperfused acute myocardial infarction (MI) via balloon-occlusion of the mid-LAD for 90 minutes, followed by reperfusion. One month later (chronic ischemic left ventricular remodelling), the animals were randomized to receive either MSCs alone ($n=6$) or MSC-MiCi-HIF1α ($n=10$) (15 ± 3 x10^6 cells). Cells were injected into the border zone of infarction by using the 3D guided NOGA electro-anatomical mapping system (9 ± 1 locations). One animal at 3, 12, 24 hr and 1 week of the MSC-MiCi-HIF1α group was harvested to prove the HIF1α expression and early angiogenesis in the heart. Magnetic resonance imaging with late enhancement was performed in the surviving 6 animals of each group for assessment of left ventricular (LV) function. Angiogenesis proteome profiling were performed and RT-PCR quantified mRNA (Angiopoietin-2, VEGF-A, CD31) and miRNA (miR-1, miR-24, miR132) expressions. Immunohistology sections were stained with anti-caspase-3 antibody and apoptosis rate was quantified.

Results: Success of transfection procedure was confirmed by Western blots of the cell culture medium, showing HIF1α expression. Proteome profiling from short-term follow-up revealed upregulation of wide range of proteins, String analyses proved their angiogenic network (Fig. 1|FP 2-3 and Fig. 2|FP 2-3). Anti-hypertrophic miR-1, pro-angiogenic miR-132, and anti-fibrotic miR-24 levels were increased in response to MSC-MiCi-HIF1α treatment (fold-changes vs control: 7.51 ± 0.61 miR1, 23.01 ± 4.87 miR132 and 6.50 ± 2.95 miR24) between 12 and 24 hr post-transfected cell injections. MSC-MiCi-HIF1α delivery resulted in moderate improvement of LV ejection fraction, and reduced infarct size and LV end-diastolic volume (111 ± 17 vs 133 ± 16 mL, $p<0.05$) at 1 month post treatment. Apoptosis in infarct border zone also decreased after MSC-MiCi-HIF1α delivery (fold-change vs control: 0.75 ± 0.07).

Conclusions: In a pre-clinical translational model of chronic post-infarction heart failure, intramyocardial injection of MSCs transfected with virus-free minicircle-HIF1α plasmid significantly decreases infarct size and improves adverse remodelling via modulation of pro-angiogenic and antifibrotic process in the heart.

FP 2-4

Charakterisierung einer familiären dilatativen Kardiomyopathie mit neuer LMNA-Nonsense-Mutation und ausgeprägtem arrhythmogenem Phänotyp – Characterization of inherited cardiomyopathy with novel LMNA nonsense mutation and a pronounced arrhythmogenic pheno

C. Glöcklhofer, G. Franke, J. Steinfurt, P. Rainer, T. Glantschnig, S. Perez-Feliz, M. Brunner, C. Bode, K. E. Odening

Abteilung für Kardiologie und Angiologie I, Universitäts-Herzzentrum Freiburg, Freiburg, Deutschland
Klinische Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Österreich

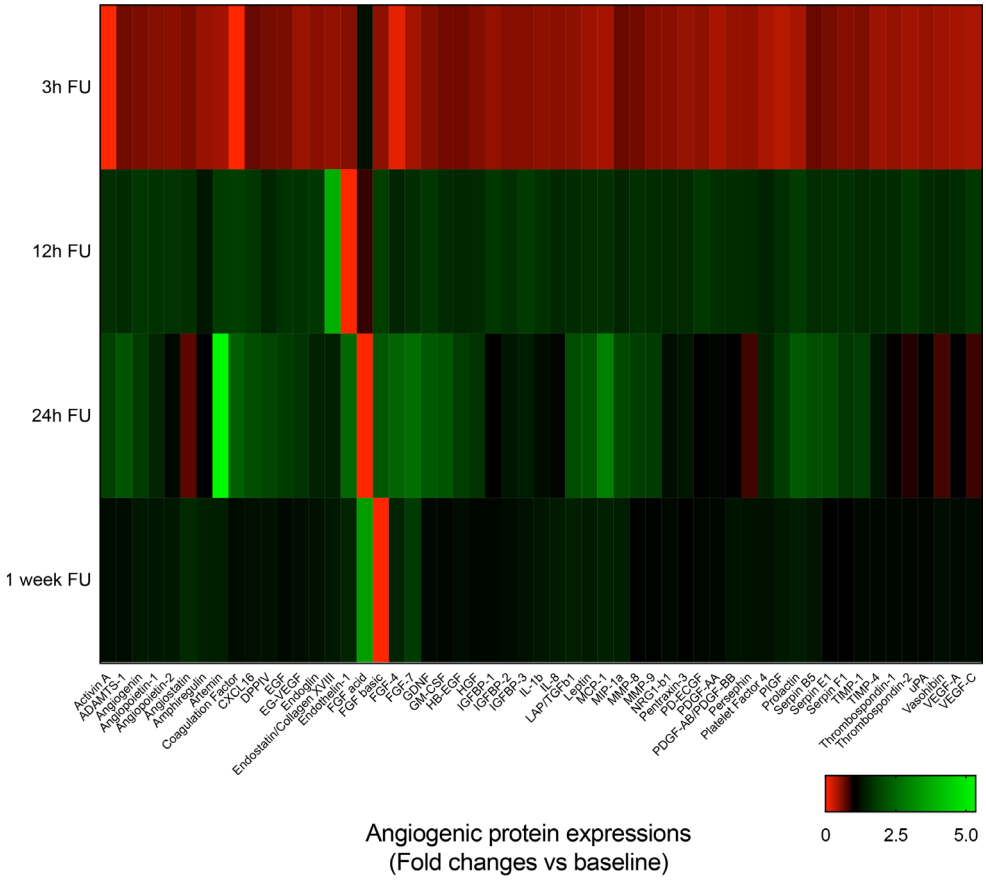
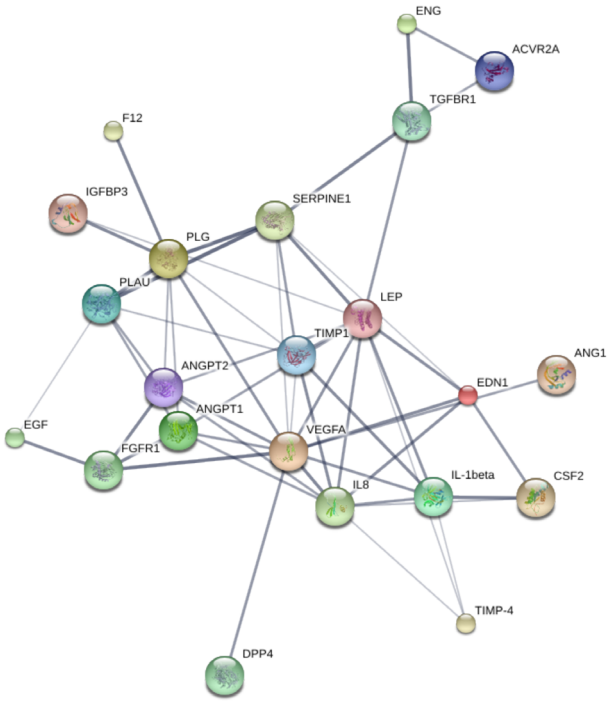

3h FU
12h FU
24h FU
1 week FU
Activin A
ADAMTS-1
Angiogenin
Angiopoietin-1
Angiopoietin-2
Angiostatin
Amphiregulin
Artemin
Coagulation Factor
CXCL16
DPPIV
EGF
EG-VEGF
Endoglin
Endostatin/Collagen XVIII
Endothelin-1
FGF acid
FGF basic
FGF-4
FGF-7
GDNF
GM-CSF
HB-EGF
HGF
IGFBP-1
IGFBP-2
IGFBP-3
IL-1b
IL-8
LAP/TGFB1
Leptin
MCP-1
MIP-1a
MMP-8
MMP-9
NRG1-b1
Pentraxin-3
PD-ECGF
PDGF-AA
PDGF-AB/PDGF-BB
Periostin
Platelet Factor 4
PlGF
Prolactin
Serpin B5
Serpin E1
Serpin F1
TIMP-1
TIMP-4
Thrombospondin-1
Thrombospondin-2
uPA
Vasohibin
VEGF-A
VEGF-C
0
2.5
5.0
Angiogenic protein expressions
(Fold changes vs baseline)

Fig. 1 | FP2-3


ENG
ACVR2A
TGFBR1
F12
IGFBP3
SERPINE1
PLG
PLAU
LEP
TIMP1
ANG1
ANGPT2
EDN1
ANGPT1
EGF
VEGFA
FGFR1
IL-1beta
CSF2
IL8
TIMP-4
DPP4

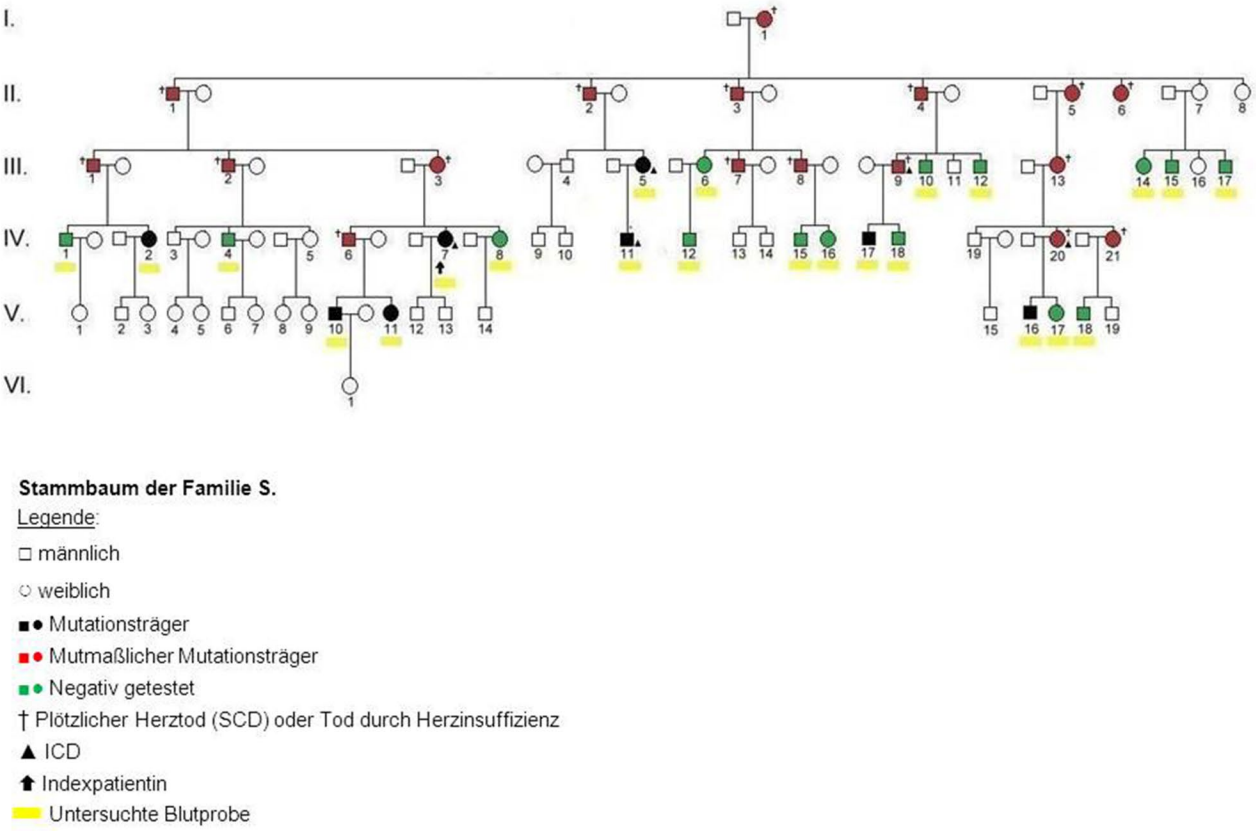


Abb. 1 | FP 2-4

Grundlagen: Bei 50 % der dilatativen Kardiomyopathien (DCM) liegt eine genetisch bedingte, familiäre Form vor. Mutationen im LMNA-Gen (Lamin A/C) bilden die zweithäufigste Ursache (6 %) der familiären DCM. Diese Laminopathien führen zu einer Vielfalt klinischer Symptome mit Herzinsuffizienz, Reizleitungsstörungen, Vorhofflimmern, ventrikulären Tachykardien, plötzlichem Herztod und (Skelett)Muskeldystrophie.

Wir haben bei einer Patientin eine neue Nonsense-Mutation c.544C>T im Exon 3 des LMNA-Gens identifiziert, die zu einem vorzeitigen Abbruch der Proteintranslation führt. Ziel dieser Studie ist es, diese bisher noch nicht beschriebene Mutation zu charakterisieren.

Methodik: Ein Stammbaum der Familie wurde erstellt (s. Abb.) und Blut von 19 Familienmitgliedern analysiert. Mittels Exon-umspannender PCR wurde die gDNA von LMNA Exon 3 amplifiziert und anschließend mit dem Restriktionsenzym MaeIII verdaut. Nach dem Verdau zeigte die Gelelektrophorese bei Negativ-Kontrollen eine Bande, bei Mutationsträgern drei Banden. Alle positiven Proben wurden sequenziert, um das Vorliegen der Mutation zu verifizieren. Von allen Familienmitgliedern wurden mittels standardisierter Fragebögen, klinischer Untersuchungsergebnisse und Arztbriefen klinische Daten gesammelt.

Ergebnisse: 8/23 untersuchte Familienmitglieder konnten als sichere sowie weitere 17 bereits Verstorbene als mutmaßliche Mutationsträger identifiziert werden. In 3 Generationen ereigneten sich 17 plötzliche Herztodesfälle; das mittlere Todesalter lag bei 49,3 ± 10,0 Jahren (30–63 J.). Von den lebenden Mutationsträgern sind 4/8 bisher asymptomatisch (37,5 ± 6,1 J.), 4/8 (49,5 ± 13,7 J.) zeigen Symptome.

Bei allen symptomatischen Patienten traten zunächst rhythmogene Symptome auf: Erste Symptome (Palpitationen bei supraventrikulärer und ventrikulärer Extrasystolie; Bradykardie mit AV-Block I°) begannen mit 35,5 ± 9,4 Jahren. Paroxysmales VHF lag mit 38 ± 8 Jahren, permanentes VHF mit 41,6 ± 7,6 Jahren vor. In der Folge nahm die AV-Leitungsstörung zu und es traten Schrittmacherabhängigkeit, nicht anhaltende Kammertachykardien (41,2 ± 7,5 J.) und Synkopen auf. Auch Muskeldystrophien in den Extremitäten, konnten bei zwei Patienten nachgewiesen werden. Ohne ICD führten im weiteren Verlauf maligne Rhythmusstörungen (Kammertachykardien und -flimmern) zum plötzlichen Herztod. Bei 5 Patienten, die mit einem ICD versorgt waren, entwickelte sich im Verlauf eine zunehmende DCM mit schwerer Herzinsuffizienz (45,2 ± 10,6 J.).

In einer Subfamilie wurde ein anderer, rasch progredienter, maligner Verlauf festgestellt. Zwei zur Herztransplantation (HTX) gelistete Patienten verstarben auf der Warteliste, während ein Patient im Alter von 32 Jahren eine High Urgency HTX erhielt. Bei einer Patientin trat als Sonderfall im Alter von 30 Jahren (nachdem zuvor nur ventrikuläre Extrasystolie und Sinusbradykardie dokumentiert waren) eine peripartum-assoziierte Aggravierung mit schwerer Herzinsuffizienz auf, die 3 Wochen nach der Sectio caesarea zum Tod führte.

Schlussfolgerungen: Die neue LMNA-Nonsense-Mutation c.544C>T (Q182X) führt zu einer familiären Kardiomyopathie mit ausgeprägtem primär arrhythmogenem Phänotyp und späterer DCM. Im Mittel rund 15 Jahre nach Symptombeginn sterben die Patienten am plötzlichen Herztod, wenn kein ICD implantiert wird. Bei Überleben maligner Rhythmusstörungen durch den ICD entwickelt sich eine rasch progrediente, schwere Herzinsuffizienz. Aus diesen Gründen ist eine frühe HTX erforderlich.

FP 2-5

Early detection of pump thrombosis in patients with left ventricular assist device

J. Grabska, T. Schlöglhofer, C. Gross, K. Dimitrov, D. Wiedemann, D. Zimpfer, H. Schima, F. Moscato

Zentrum für Medizinische Physik und Biomedizinische Technik, Medizinische Universität Wien, Vienna, Austria
Klinische Abteilung für Herzchirurgie, Medizinische Universität Wien, Vienna, Austria
Ludwig-Boltzmann-Cluster for Cardiovascular Research, Wien, Vienna, Austria

Background: Left ventricular assist device (LVAD) is increasingly seen as a therapeutic option for patients with advanced heart failure. Pump thrombosis (PT) is an uncommon but clinical significant adverse event, due to the increased morbidity and mortality associated with its development and treatment. This study aims to determine whether extensive analysis of pump parameters and clinical diagnostic data may enable prediction of PT.

Methods: This retrospective, single-center analysis included 115 patients who received an LVAD between January 2012 and May 2015. Patients were excluded if death occurred before discharge ($n=24$), when acetylsalicylic acid (ASA) antiplatelet monotherapy was not used ($n=2$) or because of missing data ($n=1$). In the remaining patients ($n=88$) those with intra-pump thrombosis were identified. A one-to-one propensity-score matched group was created using demographic, basic clinical and pre-operative risk factors. In this group time periods were matched with time preceding thrombosis. Anticoagulation therapy was assessed by the INR time in therapeutic range (TTR) based on the Rosendaal Method for 60 days preceding PT. Furthermore, pump data (power, estimated flow, speed) in HeartWare HVAD patients were analyzed 7 days prior to PT. A mixed-design analysis of variance (ANOVA) was carried out to investigate temporal changes in pump data.

Results: 15 patients (13 males, age 58 ± 10y, BMI 26.7 ± 5 kg/m^2, 7 HMII and 8 HVAD) had PT which was treated with thrombolytic therapy at median POD 343 (interquartile range 165–617). INR therapeutic range (2.0–3.0) and ASA daily doses (100–200 mg) were similar for both groups, however, patients with PT spent a lower proportion of time within therapeutic range (36% vs. 65%; $p=0.025$). A mixed-model ANOVA showed both significant main effect of time ($p=0.01$) and interaction between time and PT on LVAD power ($p=0.004$). There was no significant difference between groups at baseline ($p=0.31$) and power did not change in control group over time ($p>0.99$). In patients with PT power increased significantly from 4.4 ± 0.8 W at baseline to 4.9 ± 0.8 W ($p=0.007$) two days before readmission and to 6.5 ± 1.8 W ($p=0.015$) on readmission day. Pumps were operated at speed within the clinically recommended range.

Conclusions: PT is associated with a lower percentage of TTR prior to the event. A better monitoring of pump parameters would enable PT detection already two days in advance. Implementation of "smarter" alarms may allow timely diagnosis and better management of PT.

FP 2-6

Diastolic retrograde flow in the descending aorta by cardiovascular magnetic resonance imaging for the quantification of aortic regurgitation

A. Kammerlander, M, Wiesinger, F. Duca, S. Aschauer, C. Zotter-Tufaro, M. Schwaiger, R. Badr Eslam, B. Marzluf, P. Bartko, D. Bonderman, J. Mascherbauer

Universitätsklinik für Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Echocardiography is the standard method for quantification of aortic regurgitation (AR). However, accurate estimation of AR severity by echo may be challenging due to inherent limitations of applied methods. Cardiovascular magnetic resonance imaging (CMR) has recently been advertised as an accurate method for AR quantification, irrespective of acoustic windows.

The present prospective study sought to evaluate the usefulness of CMR for the quantification of AR.

Methods and Results: 228 consecutive patients (33% female, 57 ± 18 years) with varying degrees of AR by echocardiography (90 mild, 57 moderate, and 42 severe, 39 with inconclusive echocardiographic results – "moderate to severe" AR) were invited to undergo CMR within 4 weeks. CMR consisted of standard protocols including phase-contrast velocity-encoded imaging for regurgitant fraction (RegF) at the sinutubular junction and assessment of holodiastolic retrograde flow (HRF) in the descending aorta.

Severe AR was defined as the presence of HRF in the descending aorta by CMR.

Left ventricular (LV) end-diastolic volumes (EDV) by CMR significantly increased with increasing AR severity by echo (LVEDV: mild: 151 ± 60 ml, moderate: 184 ± 71 ml, "moderate to severe": 210 ± 93 ml, severe: 238 ± 68 ml; $p<0.001$), as did RegF

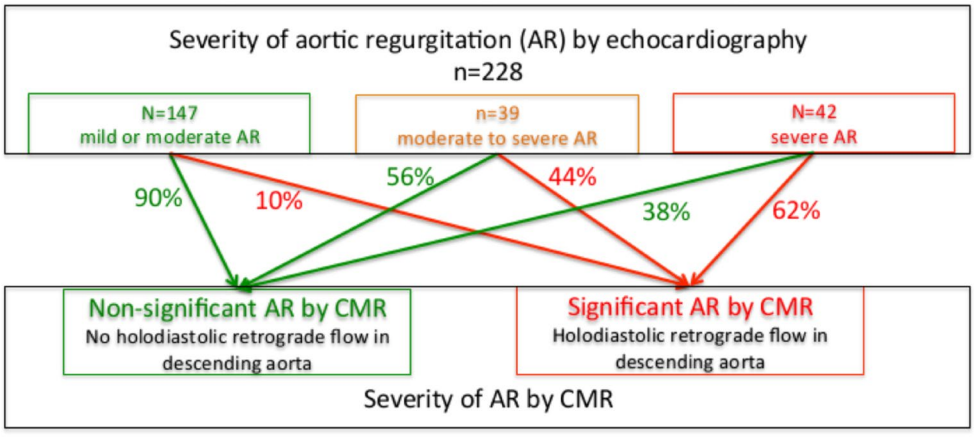


Fig. 1 | FP2-6

at the sinutubular junction (mild: 7 ± 14%, moderate: 13 ± 14%, "moderate to severe": 22 ± 17%, severe: 35 ± 15%; $p < 0.001$).

Among the 186 patients with non-severe AR by echo, 10% had HRF by CMR, indicating severe AR.

Among the 42 patients with severe AR by echo, 38% did not show HRF by CMR, suggesting overestimation of AR severity in these patients.

In patients with inconclusive echo results, 44% had HRF in the descending aorta, indicative for severe AR.

Presence of HRF by CMR was associated with significantly higher RegF at the sinutubular junction (9 ± 12% versus 38 ± 18%, $p < 0.001$) and more dilated LVs (165 ± 61 ml versus 250 ± 85 ml, $p < 0.001$).

Conclusions: Quantification of AR by CMR is feasible and highly reproducible. HRF in the descending aorta by CMR is an easily measurable marker that is very helpful for the distinction between severe and non-severe AR, especially when echocardiographic results are inconclusive.

FP 2-7

Extreme RAS regulation in HFrEF already on optimal treatment: the low and high renin phenotype heart failure

N. Pavo, G. Goliasch, J. Novak, R. Wurm, G. Strunk, M. Gyöngyösi, M. Poglitsch, M. Säemann, M. Hülsmann

Universitätsklinik für Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria
Complexity Research Austria, Vienna, Austria
Attoquant Diagnostics, Vienna, Austria
Wilhelminenspital, Vienna, Austria

Background: Blockade of the renin-angiotensin-system (RAS) is a cornerstone in the treatment of heart failure with

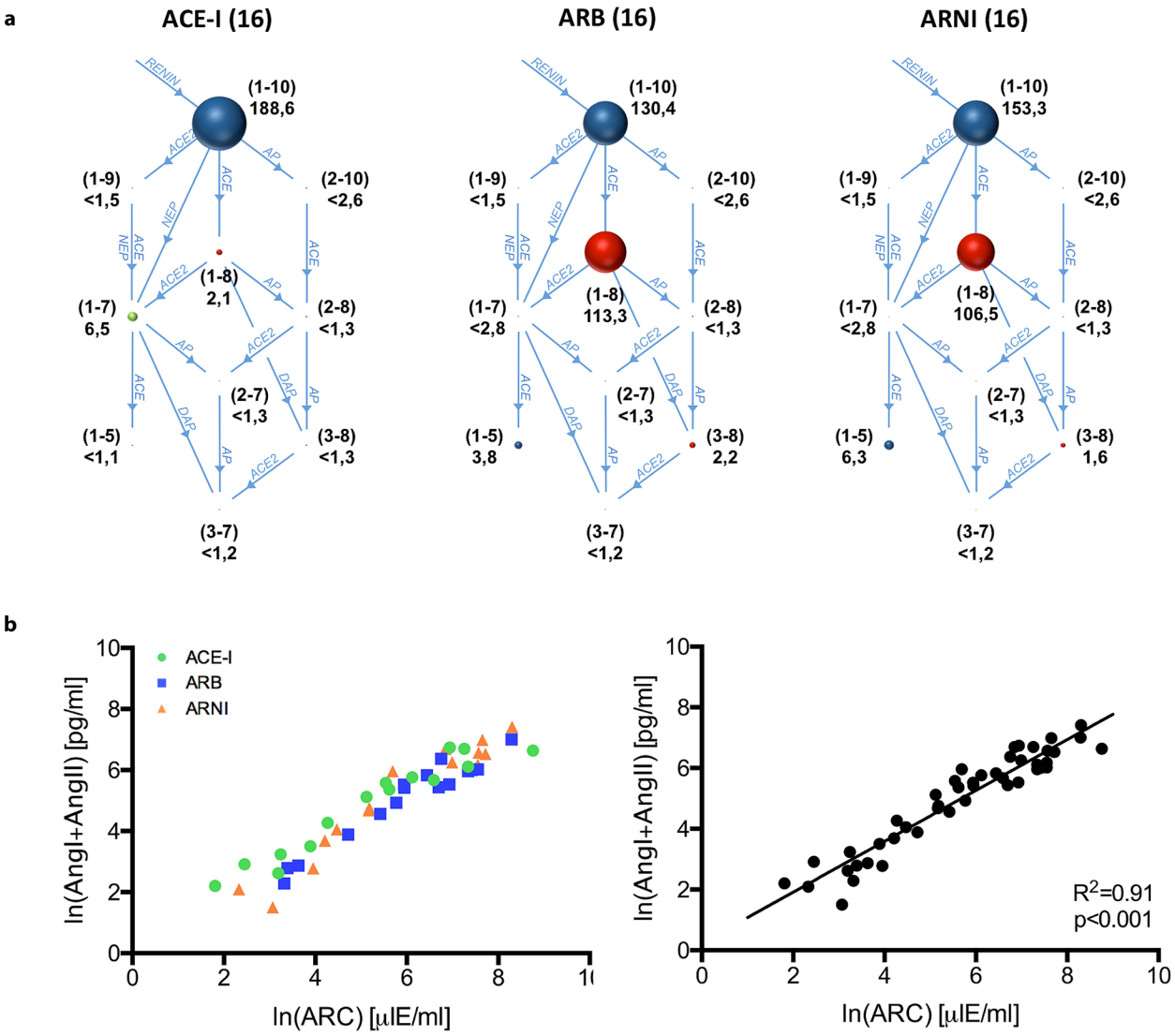


Fig. 1 | FP 2-7 **a**. Mass spectrometry based RAS patterns of HFrEF patients with ACE-I, ARB and ARNI. RAS is displayed as a pedigree. Each intersection represents a specific angiotensin peptide, involved enzymes are indicated at the connecting lines. Numbers in brackets indicate the amino-acid sequence of the angiotensins. Size of spheres and numbers beside represent absolute concentrations (pg/ml, median value). **b**. Correlation between ARC and (AngI+AngII). Therapy groups are indicated by different colors: blue for ACE-I, green for ARB and yellow for ARNI. Additionally a linear regression model was calculated

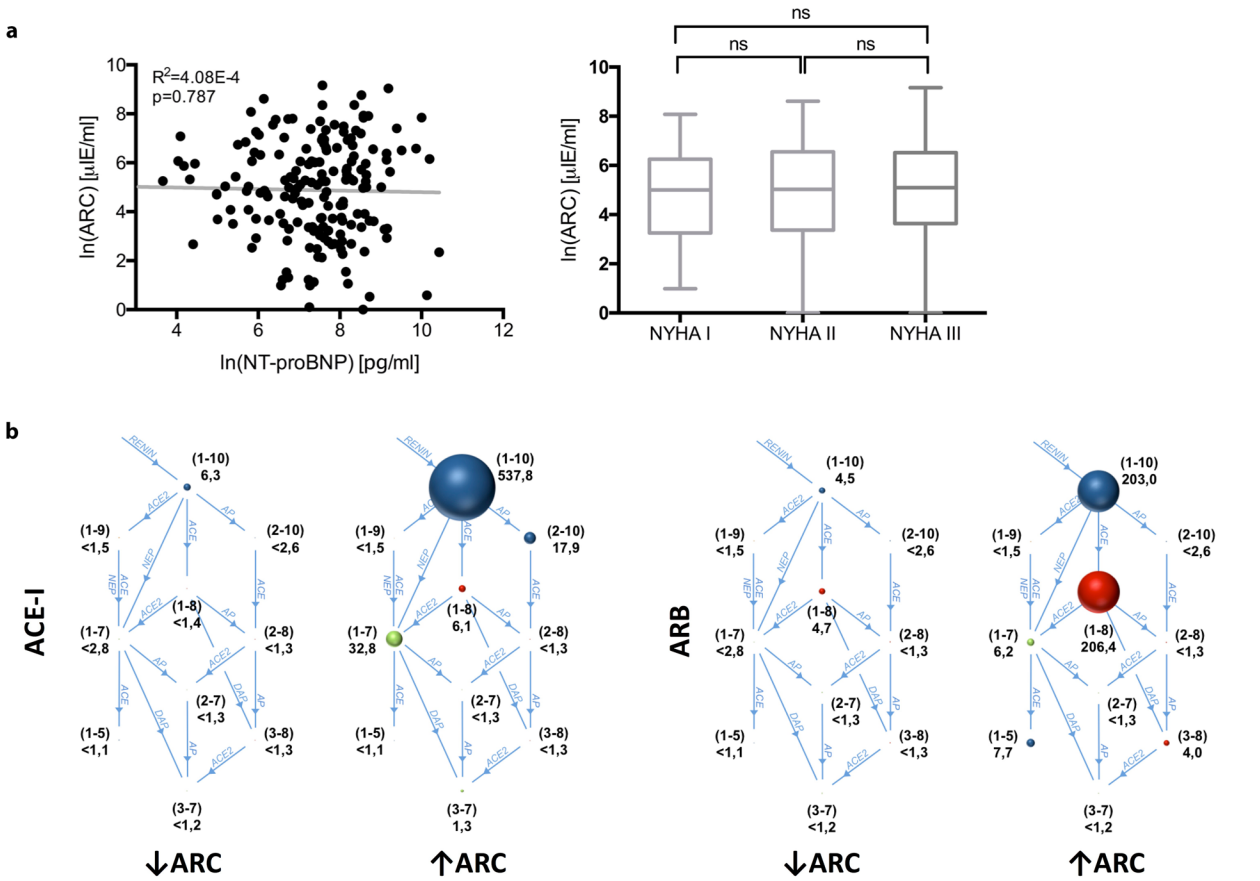


Fig. 2|FP 2-7 **a.** ARC shows a wide distribution without correlation with HFrEF disease severity reflected by NT-proBNP and NYHA stages. **b.** Mass spectrometry based RAS patterns of HFrEF patients with extreme RAS regulation identified by ARC screening. AngI – Ang1-10; AngII – Ang1-8

reduced ejection fraction (HFrEF). Although high renin HFrEF patients seem to benefit more from mono or even dual RAS-blockade, evidence for a renin-guided therapy is lacking, especially when using active renin concentration (ARC).

Methods: A first cohort HFrEF patients were enrolled with ACE-I ($n=16$), ARB ($n=16$) and ARNI ($n=16$) treatment. Circulating angiotensin metabolites were measured using a mass spectrometry based assay for the generation of RAS fingerprints. ARC levels were correlated to the sum of AngI and AngII concentrations. Then a second cohort with 200 consecutive HFrEF patients on optimal medical treatment (OMT) was enrolled and screened for ARC levels. Low ARC and high ARC patients with ACE-I and ARB monotherapy were invited for a second visit and RAS fingerprinting was performed ($n=33$ completed). Angiotensin levels were compared between groups.

Table 1|FP 2-7

	resuscitated (hypothermic) % Aggregation - median (IQR)	non- resuscitated % Aggregation - median (IQR)
Copidogrel	25 (15–45)	20 (13–33)
Prasugrel	26 (13,5–31)	17,5 (13,5–24)
Ticagrelor	24 (18,5–44,25)	16 (13–23)
Overall	23 (17–42)	17 (14–24) p = 0, 033
ASS/Collagen	11 (5–25)	16,5 (8–27) n.s.
Arachidonicacid	2 (1–3)	2 (1–3) n.s.

Results: ACE-I, ARB and ARNI therapy show distinct RAS patterns with respect to angiotensin ratios and share the dependance of (AngI+AngII) peptide concentrations on ARC [r = 0.95, $p<0.001$] irrespective of the RAS-blocker used.(Fig. 1|FP 2-7) ARC itself distributes widely across therapy modalities and disease states [r = 0.03, $p=0.682$ for the correlation with NT-proBNP and $p=0.790$ for the difference between NYHA stages], suggesting an independent regulation.(Fig. 2|FP 2-7a) ARC screening cut-offs were 10.0 µIE/ml and 1546.0 µIE/ml for ACE-I and 21.0 µIE/ml and 1893.0 µIE/ml for ARB, respectively. Low ARC patients had higher blood pressure and better cardiac function but were otherwise similar in baseline characteristics to the high ARC group particularly regarding medical treatment, NT-proBNP, sodium and aldosterone levels. While angiotensin levels were profoundly diminshed for the low ARC group, high ARC groups showed vast amounts of AngI [6.3 (IQR 2.1–12.5) pg/ml vs. 537.8 (423.1–728.4) pg/ml, $p<0.001$ for ACE-I and 4.5 (IQR 1.4–11.2) pg/ml vs. 203.0 (IQR 130.2–247.9) pg/ml, $p=0.003$ for ARB] and AngII [4.7 (IQR 1.3–12.3) pg/ml vs. 206.4 (IQR 142.2–234.4) pg/ml, $p<0.001$ for ARB]. (Fig. 2|FP 2-7b)

Conclusions: ARC is a reliable predictor for RAS activation reflected by (AngI+AngII) concentrations independendently from the mode of RAS-blockade. Despite OMT, ARC defines different HFrEF phenotypes characterized by low and high renin levels offering a rationale for adapted pharmacological interventions.

FP 2-8

Persistent T-wave inversion predicts myocardial damage after ST-elevation myocardial infarction

M. Reindl, S. Reinstadler, H.-J. Feistritzer, L. Niess, C. Koch, A. Mayr, G. Klug, B. Metzler

University Clinic of Internal Medicine III, Cardiology and Angiology, Medical University Innsbruck, Innsbruck, Austria
University Clinic of Radiology, Medical University Innsbruck, Innsbruck, Austria

Background: Persistent T-wave inversion (PTI) after ST-elevation myocardial infarction (STEMI) is associated with worse clinical outcome; however, the underlying mechanism between PTI and poor prognosis is incompletely understood. We sought to investigate the relationship between PTI and myocardial damage assessed by cardiac magnetic resonance (CMR) following STEMI.

Methods: In this prospective observational study, we included 142 consecutive revascularized STEMI patients. Electrocardiography to determine the presence and amplitude of PTI and pathological Q-waves was conducted 4 months after infarction. CMR was performed within 1 week after infarction and at 4 months follow-up to evaluate infarct characteristics and myocardial function.

Results: Patients with PTI ($n=103,73\%$) showed a significantly larger acute (21[11–29] vs. 6[1–13]%; $p<0.001$) and chronic infarct size (14[8–19] vs. 3[1–8]%; $p<0.001$) and more frequently microvascular obstruction (59 vs. 33%; $p=0.02$). The association between PTI and chronic infarct size remained significant (odds ratio: 9.02, 95%CI 3.49–23.35; $p<0.001$) after adjustment for pathological Q-wave and other infarct size estimators (high-sensitivity cardiac troponin T and C-reactive protein, N-terminal pro B-type natriuretic peptide, culprit vessel, pre-interventional TIMI flow). The value of PTI amplitude for the prediction of large chronic infarct size >11% (AUC:0.84, 95%CI 0.77–0.90) was significantly higher as compared to Q-wave amplitude (AUC:0.72, 95%CI 0.63–0.80; $p=0.009$), and the addition of PTI to pathological Q-wave led to an net reclassification improvement of 0.66 (95%CI 0.42–0.91; $p<0.001$) and to an integrated discrimination improvement of 0.22 (95%CI 0.15–0.28; $p<0.001$).

Conclusions: PTI following STEMI is independently associated with more extensive myocardial damage as visualized by CMR. Moreover, PTI provides incremental predictive validity above and beyond pathological Q-wave.

FP 2-9

Low income predicts cardiovascular event risk independently from the presence of type 2 diabetes and pre-existing coronary artery disease

C. H. Saely, A. Vonbank, C. Lins, D. Zanolin, A. Leiherer, A. Schuler, P. Schwerzler, A. Mader, A. Muendlein, H. Drexel

VIVIT-Institute, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
Private University of the Principality of Liechtenstein, Triesen, Liechtenstein

Background: A low socioeconomic status has been associated with an increased cardiovascular event risk. Whether low income predicts cardiovascular event risk independently from the presence of type 2 diabetes (T2 DM) and pre-existing coronary artery disease (CAD) is not known and is addressed in the present study.

Methods: We assessed the annual net income through a standardized questionnaire in a consecutive series of 389 patients referred to coronary angiography for the evaluation of established or suspected stable coronary artery disease (CAD). Prospectively, we recorded cardiovascular events over a mean follow-up period of 8.0 ± 3.7 years.

Results: Annual net income was <€ 20.000 in 58%, € 20.000–35.000 in 33.1% and >€ 35.000 in 8.9% of our patients. It was significantly lower in women (<€ 20.000 in 70.4%, € 20.000–35.000 in 25.6%, >€ 35.000 in 4.0%) than in men (<€ 20.000 in 53.0%, € 20.000–35.000 in 36.1%, >€ 35.000 in 10.9%; $p<0.001$) but did not differ significantly between patients with T2 DM ($n=116$) and nondiabetic subjects ($p=0.180$) nor between patients with CAD ($n=353$) and those who did not have CAD at angiography ($p=0.108$). During follow-up, the incidence of cardiovascular events significantly increased with decreasing income: it was 62.4%, 32.4%, and 5.3% in patients with net incomes of <€ 20.000, € 20.000–35.000 and >€ 35.000, respectively; $p=0.042$). Annual net income significantly predicted the incidence of cardiovascular events both univariately (HR 0.77 [0.60–0.98]; $p=0.037$) and after adjustment for age, gender, smoking, LDL cholesterol, HDL cholesterol, hypertension, BMI, waist circumference, T2 DM and angiographically determined baseline CAD (HR 0.68 [0.51–0,92]; $p=0.011$).

Conclusions: We conclude that a low net income predicts cardiovascular event risk independently from the presence of T2 DM and pre-existing coronary artery disease.

FP 2-10

Impact of long-term endurance training on serum sRAGE levels

M. Sponder, I.-A. Campean, M. Emich, M. Fritzer-Szekeres, B. Litschauer, S. Graf, D. Dalos, J. Strametz-Juranek

Cardiology, Medical University Vienna, Vienna, Austria
Federal Ministry of Defence and Sports, Vienna, Austria

Background: There is growing evidence that low levels of the circulating soluble receptor of advanced glycation end products (sRAGE) are a valuable predictor of cardiovascular disease (CVD). The aim of this prospective study was to investigate the influence of long-term physical activity on serum sRAGE levels.

Methods and Results: 98 participants completed the study. Participants were asked to perform exercise within the calculated training pulse for 8 months. The performance gain was measured/quantified by bicycle stress tests at the beginning and end of the observation period. sRAGE was measured at baseline and after 2/6/8 months by ELISA. At baseline, sRAGE levels correlated negatively with BMI and lipoprotein a. Compared to subjects with a performance gain ≤4.9% subjects with a gain >5% showed a significant increase in sRAGE levels up to 22% (Table 1|FP 2-10).

Conclusions: Significant predictors for baseline sRAGE levels were BMI and lipoprotein a. Long-term physical activity leads to a significant increase in sRAGE levels (9–22%) and the sRAGE-increase is most pronounced in subjects with initially low performance levels. The sports-mediated increase of sRAGE might be a sign of decreased AGE-mediated inflammation and highlight the protective effect of sports on CVD and other disease which are partly mediated by inflammation.

Tab. 1 | FP 2-10

Table	Initially non-sportive ($n=37$)			Initially sportive ($n=61$)	
	Group 1 ($n=14$)	Group 2 ($n=23$)		Group 3 ($n=27$)	Group 4 ($n=34$)
sRAGE1	339/258/380	330/280/367		346/275/480	366/288/481
sRAGE2	330/252/450	375/285/437		429/310/465	409/292/505
sRAGE3	366/246/437	392/321/488		424/316/543	401/296/519
sRAGE4	311/228/448	404/311/442		366/316/504	400/322/489
Change (%)	*–8,3*	*22,4*		*5,8*	*9,3*
p-value	*0,392*	*0,015*		*0,184*	*<0,001*
hsCRP1	0,09/0,05/0,22	0,14/0,08/0,31		0,11/0,05/0,23	0,09/0,06/0,12
hsCRP2	0,15/0,05/0,24	0,13/0,07/0,26		0,09/0,07/0,27	0,08/0,04/0,17
hsCRP3	0,07/0,05/0,21	0,15/0,06/0,26		0,14/0,05/0,36	0,09/0,05/0,17
hsCRP4	0,18/0,08/0,27	0,11/0,05/0,27		0,12/0,06/0,25	0,07/0,04/0,11
p-value	*0,532*	*0,076*		*0,567*	*0,113*
IL-6 1	3,2/1,9/3,6	2,6/1,8/3,2		1,9/1,5/3,0	2,1/1,5/2,9
IL-6 2	2,4/1,7/2,8	2,4/0,0/3,4		1,7/1,5/2,3	1,9/1,5/2,6
IL-6 3	2,1/1,5/2,9	2,3/1,6/3,0		2,4/0,8/3,3	1,8/1,5/2,8
IL-6 4	2,2/0,8/3,0	2,1/0,0/3,4		1,7/0,8/2,4	1,7/1,1/2,6
p-value	*0,169*	*0,138*		*0,197*	*0,397*

group 1: ≤99 % performance at baseline and performance gain ≤4,9 %;
group 2: ≤99 % performance at baseline and performance gain >5 %;
group 3: >100 % performance at baseline and performance gain ≤4,9 %;
group 4: >100 % performance at baseline and performance gain >5 %.

Postersitzung 1 – Basic Science 1

1-1

Associations between circulating microRNAs and coronary artery disease in patients with type 2 diabetes

A. Muendlein, K. Geiger, A. Leiherer, C. H. Saely, J. Ebner, E.-M. Brandtner, D. Zanolin, A. Vonbank, A. Schuler, P. Schwerzler, A. Mader, P. Fraunberger, H. Drexel

VIVIT-Institute, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
Medizinisches Zentrallabor Feldkirch, Feldkirch, Austria
Private University of the Principality of Liechtenstein, Triesen, Liechtenstein

Background: Type 2 diabetes (T2 DM) is a major risk factor for coronary artery disease (CAD) and is commonly accompanied by other CAD risk factors, such as hypertension, obesity, and dyslipidemia. Although critically important, these traditional risk factors do not fully explain cardiovascular risk in people with diabetes. Recently, circulating microRNAs (miRNAs) have been proposed as new attractive biomarkers in both morbidities, CAD and T2 DM. However, the influence of T2 DM on the association between miRNAs and CAD is unclear.

Methods: In the present study we therefore investigated the association between a panel of 40 candidate-miRNAs, previously linked with cardiovascular disease, and angiographically determined CAD (defined as the presence of stenoses with a lumen narrowing ≥50%) in 120 coronary patients with ($n=65$) and without ($n=55$) T2 DM, respectively.

Results: In the total patient cohort, plasma levels of 15 out of 40 investigated candidate-miRNAs were significantly linked with the presence of CAD at a nominal level of significance: One miRNA (miR-15a-5p) was significantly increased and 14 miRNAs (miR-423-3p, miR-24-3p, miR-221-3p, miR-23a-3p, miR-223-3p, miR-197-3p, miR-17-5p, miR-30b-5p, miR-27a-3p, miR-320b, miR-26a-5p, miR-98-5p, miR-20a-5p, and miR-99b-5p) were significantly decreased in patients with CAD. Association between miR-423-3p, miR-24-3p, miR-221-3p, miR-23a-3p, and miR-223-3p and CAD still remained significant after correction for multiple testing. In the subgroup of patients with T2 DM association between 10 miRNAs (miR-423-3p, miR-24-3p, miR-221-3p, miR-23a-3p, miR-223-3p, miR-197-3p, miR-17–5p, miR-30b-5p, miR-27a-3p, miR-15a-5p) and CAD was nominally significant. In patients without T2 DM none of said miRNAs correlated significantly with CAD.

Conclusions: We conclude that numerous circulating microRNAs are significantly associated with CAD, particularly in patients with T2 DM.

1-2

Characterization of miRNA expression in cardiac isograft vasculopathy using a heterotopic abdominal mouse heart transplantation model

A. Schaefer, A. Kiss, S. Skalicky, M. Hackl, B. K. Podesser

Ludwig Boltzmann Cluster for Cardiovascular Research, Center for Biomedical Research, Medical University of Vienna, Vienna, Austria
TAmiRNA GmbH, Vienna, Austria

Background: Cardiac allograft vasculopathy (CAV) is still limiting long term survival after cardiac transplantation. There is substantial evidence that endothelial injury and dysfunction resulting from organ preservation- as well as ischemia and reperfusion (IR) -injury play a pivotal role in the progression of CAV. Altered expression of endothelial transcription factor GATA-2 and its target endothelial enriched miR-126 or miR-92a are considered to be involved in vascular injury, however their role in CAV is unknown. Materials and Methods: Isogenic transplantations were performed in male C57BL/6 (8–9 weeks old) mice. Donor hearts were harvested and stored in HTK-N solution for 12 h. Hearts were heterotopically transplanted anastomosing the donor's ascending aorta to the abdominal aorta and donor's pulmonary artery to the recipient's inferior vena cava. Two months after transplantation, left ventricle myocardial tissue samples from native and transplanted hearts were harvested. The expression of GATA-2, miR-126 and miR-92a was evaluated by RT-qPCR.

Results: Six transplantations were conducted successfully and vital grafts were harvested 2 months after transplantation. Mir-92a was shown slightly upregulated in transplanted hearts in comparison to native hearts (−3.8 ± 0.2 vs. −4.1 ± 0.08; normalized expression to U6 snRNA). In contrast, the expression of miR-126 (0.4 ± 0.1 vs. 1.5 ± 0.08; normalized expression to U6 snRNA, $P < 0.01$) and GATA-2 was significantly decreased in transplanted hearts (−7.1 ± 0.2 vs. −5.1 ± 0.1; normalized expression to ACTB; $P < 0.01$). Left ventricle expression of mir-126 and GATA-2 positively correlated (r2 = 0.65, $P < 0.001$, slope 1.5 ± 0.2).

Conclusions: Our results demonstrate for the first time that organ preservation – as well as IR – injury markedly decrease the expression of endothelial transcription factor GATA-2 and its target miR-126 in heterotopically transplanted hearts. Thus, modulation of GATA-2 and miR-126 signalling might represent a disease mechanism and provide a therapeutic target in CAV.

1-3

Is cardioprotection through β-Blockers brought about by evoking a specific, hypoxia-resistant phenotype of myocardial metabolism?

R. Gasser, S. Pätzold, S. Gasser

Kardiologie, Universitätsklinik Innere Medizin, Medizinische Universität Graz, Graz, Austria

In heart, the fetal phenotype of metabolism predominantly uses glucose as a substrate, thus making the myocardium resistant to low oxygen levels of fetal circulation. In contrast, the adult individual mainly metabolises fatty acids and hence is kless resistant to hypoxia. During special conditions, like hypoxia and exercise, the adult phenotype of myocardial metabolism, however, has the ability to convert to the fetal one, again preferably using glucose as a substrate. It has been shown that a preferentially glucose oriented cardiac metabolism is beneficial in myocardial ischemia. Shifting myocardial metabolism to the fetal phenotype has become a new target for anti-anginal treatment in the aging heart. Either by augmentation of glucose metabolism or by inhibiting fatty acid metabolism. The latter has been successfully targeted by drugs like trimetazidine and ranolazine.

Our own microarray experiments confirm those data. Here we find that gene-expression of biological processes which are associated with glucose metabolism are up-regulated during hypoxia, whereas those associated with fatty acid and amino-acid metabolism are downregulated. Testing the effects of β-blockers (atenolol and nebivolol) we find a similar shift in well oxigenized preparations, suggesting that the cardiorotective action of β-blockers is brought about by a shift from adult to fetal phenotype of metabolism.

Myocardial ischemia thus increases glucose uptake through translocation of GLUT1 and GLUT4 from an intracellular compartment to the sarcolemma. This appears to be beneficial during ischemia and possibly recovery. Here, we find a significant difference between the expression of GLUT1 in well oxygenised preparations with (0.087 + 0.02) and without nebivolol (0.62 + 0.02; +SEM; $P < 0.05$). Similarly, atenolol led to an increase of GLUT1 – expression in well oxygenated preparations compared to controls: 1.18 + 0.08 and 0.62 + 0.02 respectively (+SEM; $P < 0.05$). Furthermore, there is a significant difference between the expression of GLUT4 in well oxygenised preparations with (0.52 + 0.01) and without nebivolol (0.29 + 0.02; +SEM; $P < 0.05$). Similarly, atenolol led to an increase of GLUT4-expression in well oxygenated preparations compared to controls: 0.92 + 0.10 and 0.29 + 0.02 respectively (+SEM; $P < 0.05$). These results mirror the increased utilisation of glucose as a substrate in the presence of β-blockers, thus exerting a durable cardioprotective effect throughout treatment.

In summary, here it has been shown for the first time that some of the anti-anginal effects of beta blockers may possibly be conveyed by their action on GLUT 1/4 expression in myocardial cells saw eel as by facilitating glucose metabolism and in turn causing a shift to the fetal phenotype of metabolism in the adult human heart.

1-4

MicroRNA-146a expression in infarcted myocardium is correlated to sustained LVEF and limitation of scar area after stem cell application in a pig AMI model

J. Winkler, D. Lukovic, K. Zlabinger, A. Gugerell, J. Dawkins, E. Marbán, H. J. Ankersmit, M. Gyöngyösi

Universitätsklinik für Innere Medizin II, Abteilung für Kardiologie, Medizinische Universität Wien, Vienna, Austria
Cedars-Sinai Heart Institute, Los Angeles, USA
Abteilung für Chirurgie, Medizinische Universität Wien, Vienna, Austria

Background: Cardiac regeneration after myocardial infarction (MI) through the application of stem cells has been investigated intensively during the last decades, with mixed success. Although basic and preclinical research has indicated beneficial effects of applying stem cells after myocardial injury, most clinical trials have indicated insufficient clinical benefit. Thus, improvement of stem cells themselves or the respective treatment modalities is a necessity. To identify potential biomarkers for treatment success, we investigated the tissue expression of selected markers in a large animal model after induction of myocardial infarction and application of either cardiosphere derived cells (CDCs), Aposec (the secretome of apoptotic peripheral blood mononuclear cells), CDCs that were preconditioned with Aposec (CDC-Apo), or a combination of Aposec and CDC-Apo.

Methods: Domestic pigs underwent AMI via percutaneous balloon occlusion of the mid-LAD for 90 min followed by balloon deflation. Fifteen min after reperfusion the pigs were randomized and received intracoronary infusion (3 ml/min, stop-flow technique) of either CDCs ($n = 6$), CDC-Apo ($n = 8$), Aposec

($n=5$), or CDC-Apo+Aposec ($n=5$) or placebo injection (AMI control, $n=4$). Cardiac 18F-FDG-PET-MRI with late enhancement was performed at 30-day follow-up to assess the infarcted area as well as left ventricular ejection fraction (LVEF). After completing the imaging, pigs were sacrificed and hearts were explanted for gene and miRNA expression analyses. Total RNA including small transcripts was isolated, reverse transcribed to cDNA, and expression levels of genes or miRNAs were quantified with qPCR.

Results: Pigs treated with CDCs (9.9±2.8%) or CDC-Apo (13.1±7.4%) had a lower infarcted area than the AMI control group (22.3±2.3%). The cardiac-specific miR-1 was found to have decreased expression in the infarct zone of the AMI control group compared to healthy myocardium, with a trend towards restoration of expression in treated animals. We investigated expression of miR-126 and miR-146a, both implicated in stem cell recruitment, proliferation, and tissue regeneration. Across all treatment groups, the expression of miR-146a in the infarct area correlated significantly with LVEF ($p=0.005$), and cardiac output ($p=0.031$), and inversely with the infarcted area ($p=0.037$), and LV end systolic volume ($p=0.028$). Expression of CXCL12 (SDF-1), which is both functioning upstream of miR-146a and is its target, was increased in infarcted myocardium, and even higher CXCL12 expression was detected in the CDC and Aposec (but not CDC-Apo) groups. CXCL12 expression in the infarct area was dependent on miR-146a expression, confirming the interaction of miR-146a and CXCL12. The expression of pro-angiogenic miR-126 in affected myocardium correlated inversely with the infarcted area ($p=0.022$) across all treatment groups.

Conclusions: Our data indicate that miR-146a plays a role in determining success of cardiac stem cell therapy, possibly by enhancing engraftment of exogenous or endogenous stem cells. The abundance of miR-146a in the infarcted myocardium may be a predictor for mitigation of ischemia after stem cell application and is worthwhile to be explored as a target for miRNA-based therapeutic approaches.

1-5

Remote ischemic conditioning improves post-ischemic cardiac function: the role of Neuregulin-1

O. Hamza, A. Kiss, P. Pilz, I. Fonseca Gonçalves, M. Inci, D. Santer, F. Nagel, B.K. Podesser

Ludwig Boltzmann Cluster for Cardiovascular Research, Center for Biomedical Research, Medical University of Vienna, Vienna, Austria

Background: There is substantial evidence that remote ischemic conditioning (RIC) induced by short repeated episodes of ischemia and reperfusion (IR) on the arm or himdlimb is a clinically applicable method to protect the myocardium against acute IR injury. Neuregulin-1 (NRG-1) is critical for cardiac development and repair, and recombinant forms are currently being assessed as potential novel therapeutics for systolic heart failure.

Aims: The present study was aimed to investigate the effect of RIC on post-ischemic cardiac function in association/correlation with the plasma levels of NRG-1.

Methods: Adult male anaesthetized OFA-1 rats were subjected to 30 min left coronary artery occlusion followed by 2–3 weeks reperfusion and allocated to (1) sham operated (SOP, without occlusion; $n=8$); (2) IR ($n=10$) and (3) IR+RIC (3 cycles of 5 minutes of hindlimb ischemia, 5 minutes of reperfusion, started at 5th min of index ischemia; $n=12$). In vivo cardiac function was evaluated by transthoracic echocardiography by calculating the ejection fraction (EF) and left ventricle end-systolic (ESD) as well as end-diastolic diameters (EDD). In addition, functional parameters of the heart such as cardiac output (CO) and external heart work (EHW) were evaluated on an isolated erythrocyte-perfused working heart model. Cardiac pump function was evaluated by rise afterload from 30 to 170 mm Hg in 10 mm Hg steps while CO was recorded. Plasma levels of NRG-1 were measured by ELISA.

Results: Myocardial IR resulted in significant increase of left ventricle/body weight ratio compared to SOP group ($P<0.05$). This was in line with the reduction in CO (29.6±1.6 ml/min/g heart vs. 43.7±1 ml/min/g heart, $P<0.01$), EHW (12.8±0.3 ml mm Hg/g heart vs. 21.1±0.7 ml mm Hg/g heart; $p<0.01$) and EF (65±2% vs 80±1; $p<0.01$). The concentration of NRG-1 was significantly dropped following IR (2.1±0.5 vs. 6.1±0.6 ng/µl in SOP, $P<0.05$) as well as NRG-1 and CO positively correlated (r2=0.51, $P<0.001$, slope 2.6±0.76). RIC markedly improved post-infarcted cardiac function compared to IR group (CO: 39.5±1.6 ml/min/g heart, EHW: 17.8±0.9 ml mm Hg/g heart and EF: 73±1% $P<0.05$, respectively) and enhanced NRG-1 levels (4.3±0.5 ng/µl). Cardiac pump function was significantly impaired following IR (80 mm Hg: 24.4±1.6 vs. 37.9±1.4 in SOP, $P<0.01$) and EDD (9.1±0.1 mm vs 8.6±0.1 mm in SOP; $P<0.05$) and ESD (6.2±0.2 mm vs 4.2±0.4 mm in SOP; $P<0.01$) were higher. The enlargement of EDD (8.9±0.1 mm) and ESD (5.4±0.1 mm; $P<0.05$) was reversed by RIC as well as cardiac pump function was preserved (cardiac output at 80 mm Hg: 32.4±2; $P<0.05$)

Conclusions: We demonstrated for the first time that the improvement of post-infarcted cardiac function initiated by RIC is associated and correlated with the plasma levels of NRG-1. This findings might represent a novel cardioprotective mechanism of RIC mediates via the upregulation of NRG-1.

1-6

The positive Inotropic effect of GLP 1 receptor activation is influenced by the presence of glucose

T. Krainer, E. Kolesnik, M. Wallner, N. Djalinac, C. Koyani, H. Mächler, P. Rainer, B. Pelzmann, D. von Lewinski

Division of Cardiology, Medical University Graz, Graz, Austria
Temple University School of Medicine, Cardiovascular Research Center, Philadelphia, USA
Institute of Biophysics, Medical University Graz, Graz, Austria
Division of Surgery, Medical University Graz, Graz, Austria

Background: Type-2 diabetes mellitus is a major cardiovascular risk factor damaging both big and small blood vessels and thereby leading to severe cardiovascular diseases such as myocardial infarction, ischemic heart failure, or stroke. Glucagon-like peptide 1 (GLP1) receptor agonists constitute a new therapeutic approach for the treatment of type-2 diabetes mellitus. The anti-diabetic effect is caused by a glucose dependent insulin secretion from pancreatic beta cells via the GLP1 receptor. This mechanism prevents potential harmful hypoglycemic conditions, a side effect of many anti-diabetic drugs. Additionally, GLP1 receptor activation increases intracellular calcium levels in a protein kinase A dependent manner causing a transient positive inotropic effect in atrial cardiomyocytes. Furthermore, the translocation of GLUT1 and Epac2 gets promoted. In light of previous studies that par-

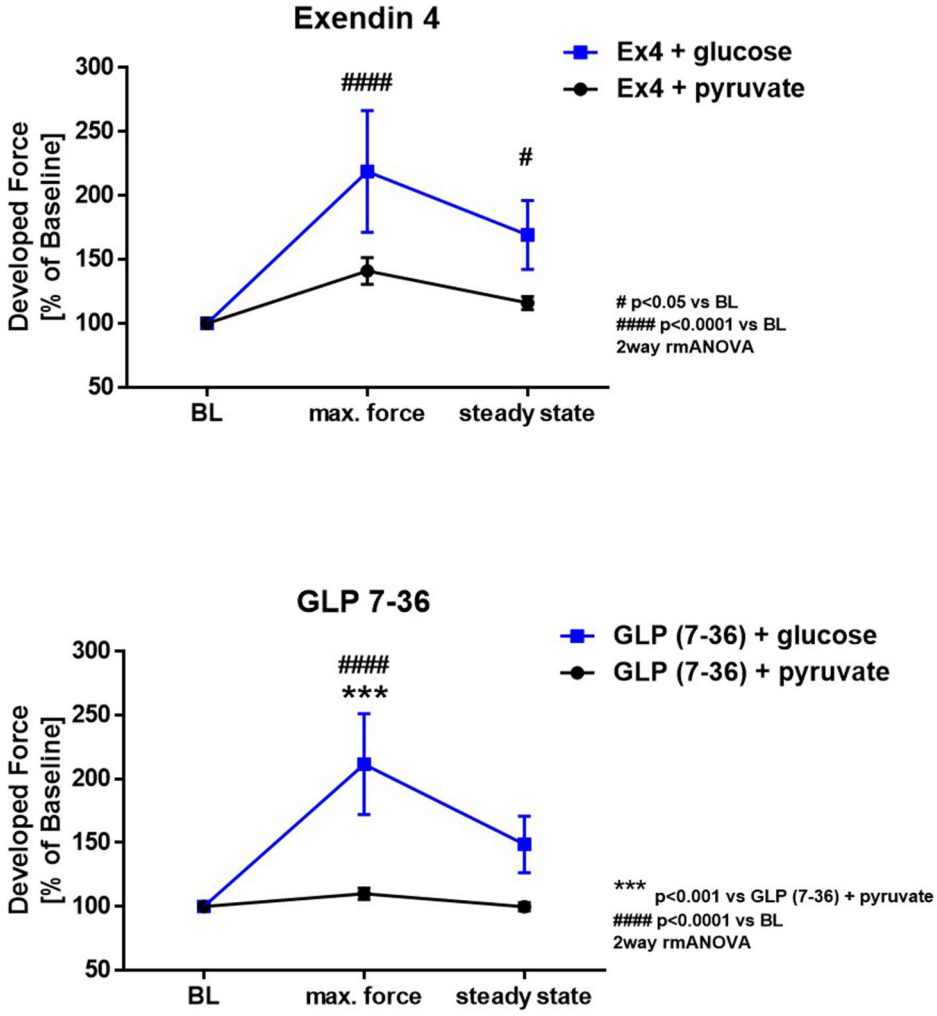


Fig. 1|P 1-6

tially elucidated the underlying mechanisms of the positive inotropic effect, we assessed the role of the energy substrate.

Methods: Muscle strips (trabeculae) were isolated from human right atrial appendages obtained from patients undergoing heart surgery ($n=20$), fixed on hooks, electrically stimulated (1 Hz) and treated with a single dose of exenatide (15 nM) and GLP 1 (7–36) amide (180 nM). Modified Tyrode's solution with a calcium concentration of 2.5 mM was used with either glucose or pyruvate serving as energy substrate. Developed force and diastolic tension were recorded and analyzed at the time point of maximal developed force and after reaching steady state conditions. Data are expressed as mean ± SEM. Differences between factors were tested by using 2way ANOVA for repeated measurements followed by Sidak's multiple comparison test.

Results: Administration of exenatide leads to a transient positive inotropic effect in the presence of pyruvate and glucose. This effect tends to be more evident in glucose-treated muscle strips at the time point of maximal developed force (218.9% ± 47.5% in glucose versus 141.2% ± 10.5% in pyruvate) and at steady state conditions after 20 minutes (169.2% ± 26.9% in glucose versus 116.1 ± 5.1% in pyruvate; $p=0.06$, Fig. 1a|P 1-6). A similar effect was observed after administration of GLP 1 (7–36) amide at the time point of maximal developed force (211.7% ± 39.5% in glucose versus 110.0% ± 4.4% in pyruvate) and at steady state conditions after 20 minutes (148.8% ± 22.1% in glucose versus 99.9% ± 3.3% in pyruvate; $p<0.05$, Fig. 1b|P 1-6).

Conclusions: The administration of GLP1 receptor agonists leads to a positive inotropic effect in the presence of glucose and pyruvate. Interestingly, this effect is more pronounced in glucose enriched Tyrode's solution, suggesting substrate dependent inotropic differences after GLP-1 receptor activation, which might be linked to previously reported translocation of GLUT1.

1-7

The impact of the temperature of cardioplegic solutions on microRNA profile in a pig model of cardiopulmonary bypass

A. Kiss, D. Santer, A. Kramer, K. Aumayr, H. Fallouh, S. Hallström, M. Hackl, S. Skalicky, D. J Chambers, B. K. Podesser

Ludwig Boltzmann Cluster for Cardiovascular Research at the Center for Biomedical Research, Medical University Vienna, Austria
Clinical Institute for Pathology, AKH Wien, Medical University Vienna, Austria

Cardiac Surgical Research, The Rayne Institute (King's College London), Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK
Institute of Physiological Chemistry, Center for Physiological Medicine, Medical University Graz, Austria
TAmiRNA GmbH, Vienna, Austria

Background: MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression through a process called RNA interference play role in the progression of cardiovascular disease and have potential biomarkers as well as therapeutic targets. Controversy results are exist regarding the optimal techniques for myocardial protection during heart surgery in terms of using warm versus cold cardioplegia. The present study was designed to investigate the impact of the temperature of blood cardioplegia on miRNAs profile in a pig model of cardiopulmonary bypass (CPB).

Methods: Adult pigs were anesthetized and monitored for baseline hemodynamic function. After sternotomy, CPB and aortic cross-clamping, hearts were arrested by antegrade administration of St. Thomas' blood cardioplegia (cold (4 °C, $n=6$) vs. warm (37 °C, $n=6$)) for 60 min of ischemia followed by 60 min of on-pump reperfusion. After weaning from CPB, hemodynamics were monitored for further 90 min of reperfusion. Left ventricle (LV) tissue sample were taken for the assessment of global microRNA expression profiling using next-generation sequencing technology. Additionally, the biochemical analysis of high-energy phosphate (HEP) was performed by using HPLC.

Results: The warm group showed improved systolic left ventricular pressure ($P<0.05$) and significantly reduced wedge pressure during reperfusion ($P<0.01$). CK-MB levels were significantly lower in the warm group ($P<0.01$). Overall 238 miRNAs were detected in all samples with a minimum read count of 1 Tags per million (TPM, expression level). Principal component analysis suggested that miRNAs expression in the LV samples was primarily influenced by the temperature of cardioplegic solution. Furthermore, microRNAs considered to relate to cardioprotection such as miR-144 (570±153 vs 310±213 TPM; $P<0.05$) and miR-451 (1395±493 vs 453±199 TPM; $P<0.05$) showed significantly higher expression in LV samples from hearts protected with warm cardioplegia.. In contrast, miR-146b expression was markedly increased in pigs protected with cold cardioplegia (63±15 vs 41±9 TPM; $P<0.05$) which considered to be involve the progression of ischmemia-reperfusion injury. Interestingly, microRNA cluster miR-199a-214 (targets myocardial PPAR-gamma and was increased due to cardiac impaired energy metabolism) enhanced in cold group.

Conclusions: Our results demonstrate for the first time the significant impact of temperature of cardioplegia on microRNA expression pattern in the myocardium following CPB. Superior cardioprotection, initiated by warm cardioplegic arrest, is associated with elevation of miR-144 and miR-451. These findings might represent a novel therapeutic approach to optimize cardioprotection during open heart surgery.

Postersitzung 2 – Akutes Koronarsyndrom 1

2-1

Adjunct remote ischemic conditioning for the reduction of infarct size in patients with ST-elevation myocardial infarction: a systematic review and meta-analysis

P. M. Haller, K. G. Vargas, M. C. Haller, A. Kiss, B. K. Podesser, J. Wojta, K. Huber

3. Med. Abteilung mit Kardiologie und internistischer Intensivmedizin, Chest Pain Unit, Wilhelminenspital Wien, Vienna, Austria
Institut für Klinische Biometrie, Medizinische Universität Wien, Vienna, Austria
Department für Biomedizinische Forschung, Medizinische Universität Wien, Vienna, Austria
Universitätsklinik für Innere Medizin II, Klinische Abteilung für Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Despite great efforts to reduce infarct size in STEMI patients, no technique or drug directly targeting ischemia/reperfusion injury has yet been established in clinical practice. Remote ischemic conditioning (RIC) has proven

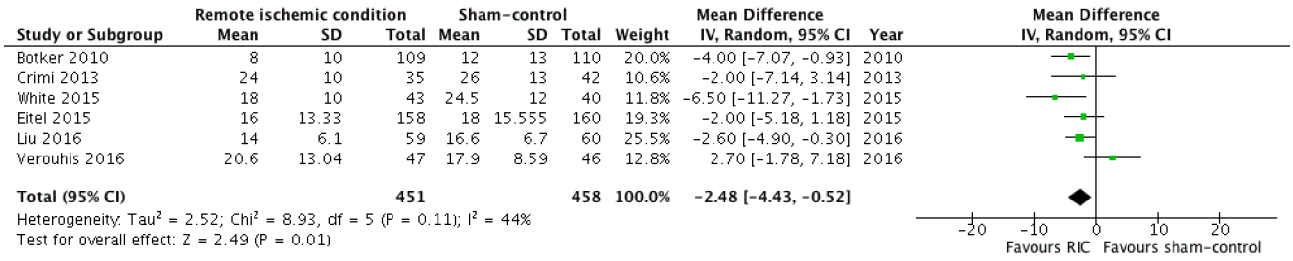


Fig. 1 | P 2-1

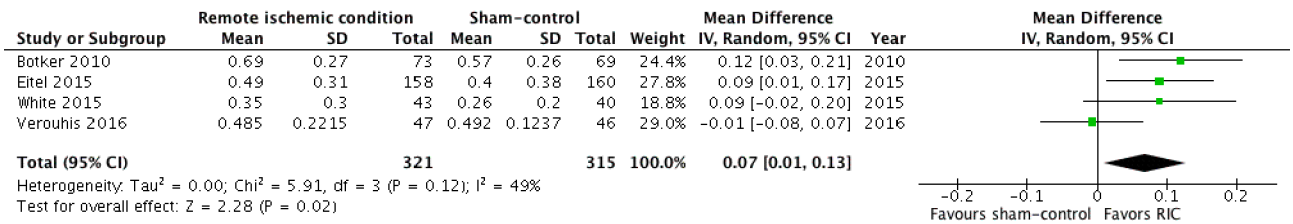


Fig. 2 | P 2-1

its feasibility in various animal models of ischemia/reperfusion injury. In contrast, clinical trials, mostly of small sample size, report partly inconsistent results. Little evidence is available on the overall effectiveness of RIC to reduce myocardial infarct size in STEMI patients.

Purpose: To perform a systematic review and meta-analysis of published randomized clinical trials and to determine the effect of RIC on infarct size.

Methods: We performed systematic searches in the main databases PubMed, EMBASE and Web of Science from inception until December 08th, 2016 for randomized controlled trials comparing an intervention group (any RIC protocol) with the standard-of-care/sham-control group. We included all studies reporting infarct size measurements by either imaging (cardiac MRI or SPECT) or cardiac biomarker release (CK-MB or troponin). All comparisons were made using random-effects models. Infarct size and myocardial salvage index were compared by mean difference and biomarker comparisons by standardized mean difference.

Results: The search yielded 355 citations, of which 9 studies, (1886 participants; RIC $n=940$ and control $n=946$) met the inclusion criteria. RIC significantly reduced infarct size as measured by imaging techniques compared to sham-controlled standard-of-care (mean difference in %: −2,48; 95%CI: −4,43 to −0,52; $P=0,01$, $n=909$, Fig. 1|2-1). Myocardial salvage index significantly increased with RIC (mean difference 0,07; 95%CI: 0,01 to 0,13; $P=0,02$, $n=636$). Consistently, RIC significantly reduced peak (mean std. difference −0,27; 95%CI: −0,47 to −0,07, $P=0,01$, $n=1249$, Fig. 2|2-1) and AUC values of biomarker release (mean std. difference −0,42; 95%CI: −0,69 to −0,15, $P=0,01$, $n=934$). While the risk of bias was generally low for random sequence generation, allocation concealment, blinding of outcome assessment, and attrition and detection bias, the risk was mostly uncertain on blinding of both the patient and the operator due to the nature of the intervention.

Conclusions: This meta-analysis shows that RIC significantly reduces infarct sizes as measured by imaging and biomarker modalities. Further studies are needed to investigate whether the benefits obtained by RIC translates into decreased morbidity and mortality among STEMI patients.

2-2

Analysis of novel cardiovascular biomarkers (ST-2, GDF-15, suPAR and FABP3) in patients with acute myocardial infarction

C. Schernthaner, P. Jirak, M. Lichtenauer, B. Wernly, V. Paar, R. Pistulli, I. Rohm, C. Jung, U. Hoppe, P.C. Schulze, D. Kretzschmar

Christian Doppler Labor für Diagnose und Regeneration von Herz- und Thoraxerkrankungen, Universitätsklinik Jena, Jena, Germany
Universitätsklinik für Innere Medizin II, Kardiologie, Paracelsus Medizinische Universität Salzburg, Salzburg, Vienna, Austria
Universitätsklinik für Innere Medizin I, Kardiologie, Jena, Jena, Germany
Abteilung für Kardiologie, Pneumologie & Angiologie, Universitätsklinikum Düsseldorf, Dusseldorf, Germany

Background: The incremental value of novel biomarkers for risk startification in acute myocardial infarction is elusive. Various Biomarkers representing different pathobiological pathways and their role in patients with acute myocardial infarction (AMI) were studied.

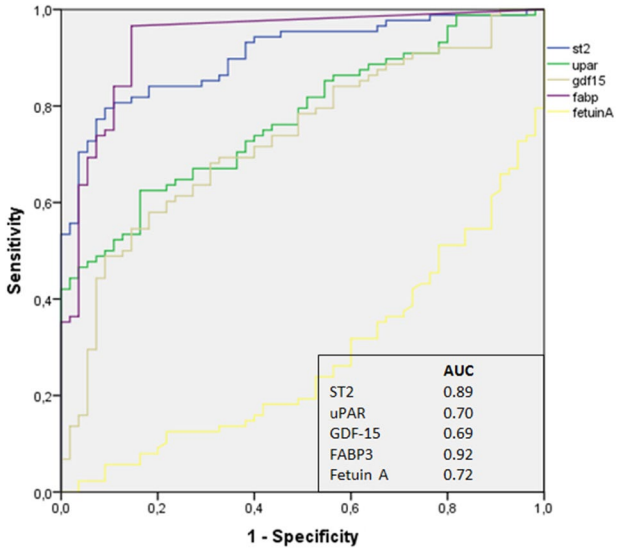


Fig. 1|P 2-2

Methods: We analyzed serum levels of suppression of tumorigenicity (ST-2), growth-differentiation factor-15 (GDF-15), soluble urokinase plasminogen activator receptor (suPAR) and heart-type fatty acid-binding protein (FABP3) and plasma fetuin-A in blood of patients with acute coronary syndrome with (STEMI, $n=61$) or without ST-segment elevation myocardial infarction (NSTEMI, $n=57$) compared to controls with excluded coronary artery disease ($n=76$). Furthermore, detailed correlation analysis with different biochemical and clinical parameters were performed.

Results: Compared with controls, in patients with STEMI and NSTEMI higher levels expressed as median of ST2 (STEMI: 13.210 pg/ml, NSTEMI 11.989 pg/ml vs control group 5248 pg/ml; $p<0.001$), GDF-15 (STEMI: 819 pg/ml, NSTEMI 678 pg/ml vs control group 549 pg/ml, $p<0.001$), suPAR (STEMI: 3461 pg/ml, NSTEMI 3467 pg/ml vs control group 2464 pg/ml; $p<0.001$), FABP3 (STEMI: 5.8 ng/ml, NSTEMI 5.4 ng/ml vs control group 0.0 ng/ml; $p<0.001$) and lower plasma fetuin-A levels (STEMI: 95 µg/ml, NSTEMI 54 µg/ml vs control group 116.6 µg/ml; $p<0.001$) were detected (Fig. 1|2-2). Correlation analysis found clinical and biochemical parameters such as ejection fraction, length of hospital stay, creatinine kinase, B-type natriuretic peptide and troponin I levels as well as inflammatory markers (CRP, white blood cells) to be signifcantly correlated with novel biomarkers.

Conclusions: Novel biomarkers reflecting different pathobiological pathways play a crucial role in the complex pathophysiology of patients suffering from AMI. The combination of traditional and novel biomarkers might further improve risk stratification of patients with AMI.

2-3

BMPRII signaling of fibrocytes is increased in STEMI and dyslipidemia and predicts poor systolic function at follow-up

T. Hofbauer, A. Mangold, T. Scherz, A. Panzenböck, M. Schneider, J. Müller, N. Staier, H. Heidari, I. M. Lang

Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Inflammation is a hallmark feature of ST-elevation myocardial infarction (STEMI). Fibrocytes, Collagen-I+CD34+CD45+ mesenchymal progenitor cells with both leukocyte and fibroblast properties, accumulate in cardiac tissue of a murine ischemia/reperfusion model and are decreased in patients with acute coronary syndrome. Physiological expression of bone morphogenic protein receptor II (BMPRII) is lost in advanced atherosclerotic plaques. Therefore, we studied the frequency and BMPRII expression of fibrocytes at the culprit lesion site (CLS).

Methods: Blood samples from the CLS and femoral site were drawn in the course of primary percutaneous coronary intervention (pPCI) from STEMI patients ($n=50$, male = 78%, mean age = 61 ± 13y). Another sample was acquired 72 h after pPCI ($n=21$). Fibrocytes were characterized using flow cytometry. Wall motion score index (WMSI) was assessed by transthoracic echocardiography 23 [IQR 17–28] months after STEMI ($n=19$).

Results: Fibrocytes were significantly increased two-fold at the CLS compared to femoral blood. No differences were found in BMPRII expression between CLS and femoral blood. However, in patients suffering from dyslipidemia, BMPRII on fibrocytes was increased both at the CLS and femoral site. 72 h after pPCI, BMPRII was significantly upregulated. After adjusting for cardiovascular risk factors, BMPRII expression on fibrocytes at baseline positively predicted WMSI at follow-up.

Conclusions: Fibrocytes contribute to adverse cardiac remodelling and poor functional outcome. Increased BMPRII expression could promote enhanced fibrocyte migration.

2-4

Der Stellenwert von Copeptin in der Diagnostik des akuten Myokardinfarktes

J. Pannold, R. Gasser, H. Mangge

Univ.-Klinik für Innere Medizin, Kardiologie, Medizinische Universität Graz, Graz, Österreich
Abteilung Labormedizin, Medizinische Universität Graz, Graz, Österreich

Ischämische Herzerkrankungen, zu denen auch der Myokardinfarkt gehört, stehen gemeinsam mit Tumorerkrankungen an vorderster Stelle aller Todesursachen. Neben dem EKG haben sich auch verschiedene labormedizinische Biomarker in der Akut-Diagnostik bewährt. Etabliert ist die Analyse der Troponine T und I, wo man jedoch aufgrund eines verspäteten Anstiegs auf weitere Verlaufsmessungen angewiesen ist, zu diesem Zeitpunkt ist allerdings bereits ein großer Teil des Myokards untergegangen. Aus der vorhandenen Literatur läßt sich die Arbeitshypothese ableiten, daß Copeptin als endogener Stressmarker eine schnellere Diagnosestellung bei unklaren Thoraxschmerzen ermöglichen könnte.

Um die Hypothese zu prüfen, wurden retrospektiv Daten von 197 Patientinnen und Patienten ausgewertet, die sich mit ACS-typischer Symptomatik in der EBA präsentierten. Benötigte Laborparameter waren die Troponinwerte zum Zeitpunkt der Aufnahme und Verlaufsmessungen nach einer und/oder drei Stunden. Des Weiteren wurde nachträglich aus eingefrorenen Restproben der Copeptinwert der initialen Blutabnahme ermittelt. Wir verglichen die Ergebnisse des verwendeten Troponin-Algorithmus mit den Copeptinwerten und es wurde untersucht, in wie weit der gemessene Copeptinwert die Aufnahmediagnose reflektiert.

In einem Zeitraum von sieben Monaten wurden retrospektiv 197 Fälle identifiziert.(Patienten bei denen TnT aufgrund von V. a. ACS bestimmt wurde. Bei diesen wurde aus der eingefrorenen Blutprobe der Copeptinwert bestimmt). Aus diesen Daten waren zwei Subgruppen ($n=53$ bzw. $n=40$) statistisch verwertbar. Daraus ließ sich für Copeptin eine Sensitivität von 75 % und eine Spezifität von 44,94 % im Bezug zur Aufnahmediagnose „NSTEMI“ errechnen. Die Verteilung von Copeptin war nicht signifikant ($p=0{,}158$) bezogen auf die Aufnahmediagnosen.

Unsere Daten zeigen, dass Copeptin als alleiniger Marker für den Nachweis eines NSTEMI nicht geeignet ist, jedoch könnte man mit einer Copeptinbestimmung bei Patientinnen und Patienten mit initial grenzwertig erhöhten Troponinwerten ohne weitere Verlaufsbestimmung einen schnelleren Infarktausschluss erzielen.

2-5

Outpatient cardiac rehabilitation in Austria – What does it change?

B. Reich, K. Mayr, H. Ocenasek, H, Harpf, A. Podolsky, A. Philippi, B. Eber, C. Pülacher, J. Sykora, G. Zenker, W. Ziegelmeyer, W. Benzer, J. Niebauer

Universitätsinstitut für präventive und rehabilitative Sportmedizin, Paracelsus Medizinische Universität, Salzburg, Salzburg, Austria
Cardiomed, Kardiologische Rehabilitation Linz, Linz, Austria
ZARG – Zentrum für ambulante Rehabilitation Graz, Graz, Austria
Klinisches Institut für Präventiv- und angewandte Sportmedizin, Universitätsklinikum Krems, Krems, Austria
REHA-SPORT-INSTITUT, Feldkirch, Austria
Cardio-Vital-WELS, Institut für Präventiv- und Rehabilitationsmedizin Wels, Wels, Austria
REHAMED – Krankenanstalt und Zentrum für ambulante kardiale und pulmonale Rehabilitation, Innsbruck, Austria
Ambulatorium für Herz-Kreislaufrehabilitation Klagenfurt – Privatklinik Maria Hilf, Klagenfurt, Austria
REHA BRUCK ambulante medizinische Rehabilitation der Stadtwerke Bruck an der Mur, Austria
Zentrum für ambulante kardiologische Rehabilitation, Steyr
Praxis für Innere Medizin und Kardiologie Sportmedizin und Prävention, Feldkirch, Austria

Background: Cardiac rehabilitation is a key component of the treatment of cardiac patients. Our Working Group on Out-Patient Cardiac Rehabilitation (AGAKAR) has previously published guidelines which were endorsed by the Austrian Society of Cardiology. It was the aim of this study to assess the short-term (phase II) and long-term (phase III) effects of these guidelines by use of a nationwide registry.

Methods: All AGAKAR accredited Austrian out-patient rehabilitation facilities entered data of all patients who completed phase II and/or III rehabilitation between 01.01.2008–31.12.2015 into a database.

Venous blood samples were analyzed at local laboratories for cholesterol (CHOL), high-density-lipoprotein (HDL), low-density-lipoprotein (LDL), triglycerides (TG) and glucose (Gluc). Maximal exercise performance was assessed on a bicycle ergometer using a ramp protocol, according to the current Austri-an guidelines.

Results: A total of 4771 patients were included into the study. Following outpatient cardiac rehabilitation phase II, CHOL was reduced by 8.8%, LDL by 14.6%, TG by 7.7% and Gluc by 4.0%, respectively; HDL increased by 1.1% and physical exercise capacity by 15., 8% (all $p<.001$).

The subgroup of patients who continued with phase III following phase II outpatient cardiac rehabilitation ($N=2403$) significantly improved their HDL by another 4.7 % and physical exercise capacity by 9.6 % (both $p<.001$) within 9 months, whereas all other parameters did not change.

Phase III patients ($N=2793$) after inpatient phase II, increased their HDL by 4.1 % ($p<.001$) and maximal physical capacity by 19.8 % ($p<.001$), LDL was reduced by 3.8 % ($p<.001$) but Tri increased by 7.2 % ($p<.001$).

Conclusions: Our data demonstrate beneficial short- and long-term effects of the Austrian model of outpatient cardiac rehabilitation and provide support for comprehensive long-term rehabilitation programs. It is hoped that these data will motivate colleagues to refer their patients also to outpatient cardiac rehabilitation facilities and that our results may stimulate insurance companies to grant further and comprehensive contracts to provide access for all suitable patients.

University Institute of Sports Medicine, Prevention and Rehabilitation,

2-6

Epinephrine-Induced Reverse Takotsubo Cardiomyopathy

E. Gruber, C. Eyth, R. Gasser

Kardiologie, Medizinische Universität Graz, Graz, Austria

Takotsubo cardiomyopathy, also known as stress cardiomyopathy, apical ballooning syndrome, broken heart syndrome, neurogenic myocardial stunning or ampulla cardiomyopathy, was first described by Satoh et al in 1990. Mimicking acute myocardial infarction in the absence of significant coronary artery stenosis, the wall motion abnormalities of the left ventricle are of transient nature, spreading beyond the region of a single coronary artery. 2 % to 3 % of all patients with acute coronary syndrome suffer from Takotsubo cardiomyopathy, of which approximately 78 % to 86 % are postmenopausal women with an average age of 60 to 75 years.

Here, we report the case of a 44-year-old female patient who was in inpatient care for violent back pain with suspected adjacent segment disease following lumbar spinal fusion L2/L3. and was diagnosed with a benign spinal tumor that was removed by surgery in combination with stabilization of the lumbar spine.

At first, local pain therapy with Xylanaest® (lidocaine) was undertaken. In the course of the infiltration therapy our patient developed an anaphylactic reaction with severe dyspnea, hypotension and tachycardia. She was successfully treated with intravenous fluid therapy, cortisone, antihistamines and epinephrine. Afterwards she was taken to the intensive care unit for observation. Two days later she complained about chest pain without concomitant dyspnea. Troponin T was elevated at 126 pg/mL, creatine kinase at 165 U/L, creatine kinase MB-fraction at 30 U/L and NT-proBNP at 3783 pg/mL on initial laboratory tests.

Furthermore a 12-lead electrocardiogram revealed T wave inversion in II, III, aVF and V2 to V6. After consulting the cardiologic emergency service she was initially treated with 500 mg acetylsalicylic acid, 60 mg prasugrel, 40 mg enoxaparin sodium and oxygen at intensive care unit. At 9:30 p.m. she was taken to cardiac catheter examination on suspected instable angina pectoris.

Cardiac catheterization revealed normal coronary arteries, but ventriculography showed akinesia of the basal segments of the left ventricle consistent with reverse Takotsubo cardiomyopathy presumably in consequence of epinephrine injection due to anaphylaxis. Susequently, echocardiography confirmed the diagnosis of reverse Takotsubo cardiomyopathy with an ejection fraction of 40%. A control echocardiography a month later revealed slight basal hypokinesia with an ejection fraction of 55% to 60%, and a control echocardiography 6 months later revealed complete normalization of myocardial contractility.

2-7

Therapeutic hypothermia impairs platelet-function in resuscitated patients after myocardial infarction

D. von Lewinski, O.L. Milke, L. Bis, J. Siller-Matula, F. Fruhwald, D. Scherr, S. Altmanninger-Sock, S. Pätzold, H. Sourij, F. Prüller

Kardiologie, Medizinische Universität Graz, Graz, Austria
Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Aim of the study was to quantify platelet function in resuscitated patients with dual anti-platelet therapy (DAPT) after myocardial infarction (MI) during and after treatment with therapeutic hypothermia. We hypothesized that hypothermia at 34–36 °C for 24 h in combination with gastroparesis and impaired hemodynamics results in reduced platelet inhibition. We further tested if there are differences between the clopidogrel treatment and the treatment with newer P2Y12 inhibitors (ticagrelor and prasugrel) in this setting.

Methods: This observational single-centre study was done in 25 resuscitated patients, while 77 hemodynamically stable non-resuscitated patients with MI served as controls. Platelet function was monitored daily for 5 days in the resuscitated patients, covering the cooling period, the rewarming phase and steady-state post rewarming. Platelet function was measured with optical aggregometry and after stimulation with either acetylic acid or ADP-antagonists. The protocol was approved by the Local Ethics Committee and registered at clinicaltrials gov with the ID NCT02914795.

Results: All P2Y12 inhibitors showed 25–30% higher platelet aggregation values in resuscitated patients in comparison with non-resuscitated patients during the first days. Differences between the three P2Y12 inhibitors could not be detected. In contrast, aspirin was of comparable effect between the two groups (Table) and the positive control using TRAP-6 (TRAP: thrombin receptor-activating peptide), too.

Conclusions: P2Y12-inhibitor mediated platelet function inhibition is impaired in resuscitated patients treated with target temperature management (TTM). This could be observed for all three oral inhibitors tested. Aspirin, however, administered intravenously was of comparable inhibitory effects in resuscitated and non-resuscitated patients. Therefore, resuscitation

with consecutive hypothermia and/or gastroparesis impairs the pharmacological effect of oral P2Y12 inhibitors. Intravenous P2Y12 inhibitors might be able to overcome this problem.

Postersitzung 3 – Diverses

3-1

Clinical relevance of *p*-wave variability in patients receiving transcatheter aortic valve implantation

F. Bechtoldt, D. Zweiker, D. Scherr, I. M. Keeling, M. Puchinger, O. E. Dapunt

Klinische Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Austria
Klinische Abteilung für Herzchirurgie, Medizinische Universität Graz, Graz, Austria
Forschungseinheit Med. Technik und Datenverarbeitung der Klinischen Abteilung für Chirurgie, Medizinische Universität Graz, Graz, Austria

Background: In recent years, several retrospective studies showed the significance of *P*-wave dispersion (Pd) as a predictor for the development of cardiovascular diseases, including stroke, cognitive dysfunction and atrial fibrillation (AF) in the healthy population and in patients with cardiovascular preconditions. A Pd >40 ms was found to correlate with the occurrence of AF in healthy patients, patients post coronary bypass surgery and in those suffering from arterial hypertension. Stroke, cognitive dysfunction, AF and diastolic cardiac dysfunction occur frequently in patients after transcatheter aortic valve implantation (TAVI). The results mentioned above could, therefore, suggest a similar significance of Pd in patients undergoing this procedure. The intention of this study was to evaluate this hypothesis and to investigate a potential correlation between Pd and 1-year mortality and hospitalization.

Methods: This retrospective study is based on a population of 398 patients treated with TAVI at the University hospital of Graz, Austria, between 2007 and 2014. Standard preoperative 12-lead ECGs could be collected from 251 out of these 398 patients and P-wave duration and Pd were calculated. These results were analyzed with SPSS® concerning the correlation between Pd and outcome parameters and occurrence of various cardiac arrhythmias. In addition, bivariate analysis of Pd with other parameters was performed. 40 ECG's were randomly picked for the investigation of the inter- and intraobserver error.

Results: The evaluation of all 251 ECGs showed a mean Pd of 40.12ms ± 10.83. Postinterventional cardiac arrhythmias were found in 90 patients: 14 patients developed new-onset AF, 8 patients showed a complete atrioventricular block (AVB III) and 68 patients had a left bundle branch block (LBBB). 35 patients died within one year. Furthermore, 79 patients were hospitalized repeatedly for various cardiac conditions. In our study, we were unable to detect a significant correlation between Pd and outcome parameters, such as 1-year-mortality and rehospitalization. Furthermore, we could not find a significant correlation between Pd cut-off of 40ms and occurrence of new-onset of various cardiac arrhythmias, namely AF, AVB III and LBBB.

Conclusions: Our study showed that the cut-off for Pd in patients after TAVI implantation might deviate from the cut-off for Pd reported in literature for healthy individuals. A subsequent study is needed to further evaluate the specific cut-off for this group of cardiac patients.

3-2

A single episode of blood glucose deviation is associated with adverse outcome in critically ill patients

B. Wernly, M. Lichtenauer, M. Franz, B. Kabisch, J. Muessig, M. Masyuk, U. Hoppe, M. Kelm, C. Jung

Christian Doppler Labor für Diagnose und Regeneration von Herz- und Thoraxerkrankungen, Universitätsklinik Jena, Jena, Germany
Clinic of Internal Medicine II, Department of Cardiology, Paracelsus Medical University Salzburg, Salzburg, Austria
University Hospital Jena, Friedrich Schiller University Jena, Jena, Germany
Division of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty, University Duesseldorf, Dusseldorf, Germany

Background: Hypo- and hyperglycemia are common in critically ill patients. Keeping blood glucose concentration below 180 mg/dL failed to improve and even worsened outcome in patients admitted to an intensive care unit (ICU). As both severe hyperglycemia (>200 mg/dl) and hypoglycemia (<40 mg/dL) are known to be associated with adverse outcome in critically ill patients, we investigated the incidence and associations of as little as a single episode of blood glucose deviation (concentration either below 40 mg/dL or above 200 mg/dL) after admission to an intensive care unit (ICU) stay with mortality.

Methods: We retrospectively investigated 4694 patients (64 ± 16 years; 33% female; 67% male; 12.2% patients suffering from type 2 diabetes (T2 DM)) who were admitted to a German ICU in a tertiary care hospital from 2006 to 2009. All available blood glucose measurements were analyzed ($n = 62659$). Admission diagnosis were e. g. sepsis ($n = 522$), acute myocardial infarction (AMI; $n = 1316$), pulmonary embolism ($n = 127$), acute heart failure ($n = 532$) and cardiopulmonary resuscitation (CPR; $n = 372$). Between May 2013 and November 2013 follow-up of patients was performed.

Results: Mean ICU stay was 71 hours. 1.1% patients had a hypoglycemic episode during ICU stay, and 29.6% of patients had a hyperglycemic episode. 30.3% suffered from either hypo- or hyperglycemia during the ICU stay, i. e., a glucose deviation. A single glucose deviation was associated with adverse outcome both in intra-ICU mortality, (20% vs 12%; HR 2.06; 95%CI 1.75–2.43; $p < 0.001$) and long term mortality (HR 1.72; 95%CI 1.54–1.93; $p < 0.001$). At admission, patients who suffered from glucose deviation during their ICU stay, were sicker as expressed by higher APACHE (21 ± 9 vs 25 ± 9; $p < 0.001$) and SAPS2 (41 ± 19 vs 48 ± 20; $p < 0.001$) scores, had higher lactate concentrations (3.8 ± 4.8 mmol/L vs 2.2 ± 2.7 mmol/L; $p < 0.001$) and were older (68 ± 13 vs 64 ± 16; $p < 0.001$). In patients suffering from type 2 diabetes, though more prone to suffer from a glucose deviation (50% vs 27%; $p < 0.001$), a glucose deviation was not associated with mortality, neither intra-ICU (15% vs 13%; $p = 0.43$) nor long-term (HR1.18; 95%CI 0.88–1.57; $p = 0.27$). In non-diabetic patients, a single glucose deviation during ICU stay remained associated with increased mortality even after correction for SAPS2 and age in a multivariate Cox regression analysis (HR 1.19; 95%CI 1.03–1.38; $p = 0.02$).

Conclusions: Critically ill patients suffering from just a single glucose deviation (i. e., blood glucose concentration either above 200 mg/dL or below 40 mg/dL) during their ICU stay, evidenced a significantly increased mortality rate (both intra-ICU and in the long-term). As these patients were clinically sicker,

glucose deviation might primarily be a surrogate parameter for severity of illness, but also represents an independent risk factor. On the other hand, in diabetic patients, although they were more prone to suffer from a glucose deviation, this condition was not associated with mortality. Close monitoring and, if necessary, even a continuous measurement of blood glucose concentration could help to optimize the outcome of critically ill patients.

3-3

Even mild anemia is associated with worsened outcome after cardiopulmonary resuscitation (CPR)

B. Wernly, M. Lichtenauer, M. Franz, B. Kabisch, J. Muessig, M. Masyuk, P. Jirak, U. Hoppe, M. Kelm, C. Jung

Christian Doppler Labor für Diagnose und Regeneration von Herz- und Thoraxerkrankungen, Universitätsklinik Jena, Jena, Germany
Clinic of Internal Medicine II, Department of Cardiology, Paracelsus Medical University Salzburg, Salzburg, Austria
Universitätsklinik für Innere Medizin I, Kardiologie, Jena, Jena, Germany
Division of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty, University Düsseldorf, Dusseldorf, Germany

Background: Mortality after cardiopulmonary resuscitation (CPR) remains high. Besides CPR quality minimized latency until chest compression remains of utmost importance. Early use of defibrillation constitutes another cornerstone for initial treatment. Additional parameters can be controlled by the treating physician: Anemia is known to be associated with adverse outcome after CPR. Still, a differential analysis is lacking. Therefore, we investigated the relation between hemoglobin concentration at admission and mortality after CPR.

Methods: 380 non-consecutive medical patients (186 male, 66 ± 1 years, APACHE2 Score 27 ± 1 pts, SAPS Score 55 ± 1 pts, heart rate 86 ± 1 bpm) who were admitted after CPR at a German intensive care unit (ICU) between 2004 and 2009 were retrospectively investigated. Minimum hemoglobin concentration on the day of admission was assessed for association with both long-term and intra-ICU mortality.

Results: Intra-ICU mortality was as high as 35%. A higher hemoglobin concentration was associated with better outcome in patients after CPR. Minimum hemoglobin concentration (per mmol/L) on the day of admission was associated with long-term mortality in a Cox regression analysis model (HR 0.75; 95%CI 0.65–0.87; $p < 0.001$). The Youden-Index was utilized to calculate an optimal cut-off which was found to be 6.8 mmol/L. Patients with hemoglobin concentrations below this cut-off were significantly sicker as expressed by higher APACHE2 (28 ± 1 vs 24 ± 1; $p = 0.003$) and SAPS2 scores (57 ± 2 vs 49 ± 2; $p = 0.01$) as well as higher lactate concentrations (3.0 ± 0.3 mmol/L vs 4.1 ± 0.3 mmol/L; $p = 0.002$). These patients had a worsened intra-ICU (19% vs 36%, HR 2.46 95%CI 1.33–4.54; $p = 0.002$) mortality rate. In the long-term, patients with a hemoglobin concentration below our cut-off of 6.8 mmol/L at admission day suffered from increased mortality (HR 2.11, 95%CI 1.37–3.23; $p = 0.001$). Interestingly, the amount of administered erythrocyte concentrates was not associated with adverse outcome (HR 0.99; 95%CI 0.94–1.04; $p = 0.57$).

Conclusions: In our cohort of patients treated at a medical ICU after CPR, even anemia was associated with adverse outcome in after CPR. Patients suffering from anemia were sicker, it therefore remains unclear whether thorough treatment of anemia might improve survival in this setting. For warranted future EC transfusion studies after CPR we report important values and calculated an optimal hemoglobin concentration cut-off, i. e. 6.8 mmol/L.

3-4

Produktfehler und korrektive Maßnahmen bei automatischen externen Defibrillatoren (AEDs) und deren Elektroden – Analyse der 2012–2016 vom BfArM veröffentlichten Kundeninformationen

R. Siekmeier

Bundesinstitut für Arzneimittel u Medizinprodukte, Bonn, Deutschland
Drug Regulatory Affairs, Pharmazie, Rheinische Friedrich-Wilhelms-Universität Bonn, Bonn, Deutschland

Grundlagen: Vermarktung und Marktüberwachung von Medizinprodukten und In-vitro Diagnostika werden in Europa durch europäische Direktiven (z. B. The European Directive 93/42/EEC, Directive 98/79/EC) geregelt. Bei Vorkommnissen und korrektiven Maßnahmen (Field Safety Corrective Action, FSCA) müssen die Hersteller diese den zuständigen nationalen Behörden (Competent Authority (CA); in Deutschland das Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) für die meisten Medizinprodukte und In-vitro Diagnostika (IVD) bzw. das Paul Ehrlich-Institut (PEI) für ausgewählte IVD; in AU: BASG) melden und die Kunden über Kundeninformationen (Field safety notice, FSN) informieren, die auch den Behörden zur Verfügung gestellt werden. Ziel der Studie war die Untersuchung von FSN bei FSCA zu automatischen externen Defibrillatoren (AEDs) und deren Elektroden, die von Anfang 2012 bis Ende 2016 auf der Homepage des BfArM veröffentlicht wurden, in Hinblick auf vorliegende Produktprobleme und damit einhergehende Risiken sowie Art der FSCA.

Methodik: Für die in die Studie eingeschlossenen Produkte erfolgte eine Analyse der vom BfArM Anfang 2012 bis Ende 2016 auf der Homepage (http://www.bfarm.de/DE/Medizinprodukte/riskinfo/kundeninfo/functions/kundeninfo-node.html) veröffentlichten FSCA und FSN.

Ergebnisse: Im Untersuchungszeitraum fanden sich 68 FSCA zu den in die Studie eingeschlossenen Produkten, von denen 48 die Defibrillatoren, 17 die zugehörigen Elektroden (einschl. 1 Folgemeldung) und 3 Defibrillatoren und Elektroden betrafen. Typische Risiken waren Geräteversagen (z. B. Geräteausfall und -abschaltung, vorzeitige Batterieentleerung, fehlerhafte Schockabgabe) mit dadurch möglicher Patientenschädigung und Kontaktstörungen/Kurzschlüsse bei Elektroden mit potentieller Anwender- oder Patientenschädigung. Nur in wenigen Fällen wurde das Vorliegen einer Patientenschädigung angegeben. Bei Defibrillatoren fanden sich in 46 FSN Hinweise zum Produktfehler, meist Softwarefehler (25) und Komponentenfehler (16, z. B. Platinenfehler, Displayfehler, Akkufehler), während bei Elektrodenmeldungen nur in 8 FSN Angaben zur Fehlerursache vorlagen (meist Produktionsfehler, 5) und die kombinierten Meldungen alle Fehler durch Verschleiß beschrieben. Häufigste korrektive Maßnahmen waren bei Defibrillatoren Kundeninformationen mit teils umfangreichen Handlungsanweisungen, Software-Upgrade (24) und Hardware-Upgrade (14, z. B. Austausch von Platinen, Display oder Akku), während bei Elektroden die Produktrückholung/-vernichtung weit im Vordergrund stand (15).

Schlussfolgerungen: FSCA zu AEDs und deren Elektroden stellen aufgrund ihres Gefährdungspotentials bei Vorliegen von Produktmängeln eine wichtige Produktgruppe dar. Nur in wenigen FSN fanden sich Angaben über bis zum Zeitpunkt der Veröffentlichung vorliegende Personenschäden. Bedingt durch die höhere Komplexität der Fehlerbilder und der von Anwendern zu treffenden Maßnahmen waren FSN zu Geräten ausführlicher als solche zu Elektroden. Zugrundeliegende Fehler und durchzuführende Maßnahmen unterschieden sich in beiden Produktgruppen – bei Geräten überwogen Softwarefehler, die oft zu umfänglichen Handlungsanweisungen für Anwender und Software-Upgrades führten, während sich bei Elektroden oft Produktionsfehler fanden und das Produkt verworfen wurde. Aufgrund der Bedeutung der FSN zur Verminderung vom Produkt ausgehender Risiken im Falle einer FSCA sollten Form und Inhalt der FSN jedoch weiter verbessert werden.

3-5

Analysis of the novel cardiac biomarkers sST2, Galectin-3, GDF-15 and Fetuin-A in patients with peripheral artery disease

P. Jirak, M. Lichtenauer, B. Wernly, V. Paar, R. Pistulli, I. Rohm, M. Mirna, C. Prodinger, C. Jung, Uta Hoppe, P.C. Schulze, D. Kretzschmar

Christian Doppler Labor für Diagnose und Regeneration von Herz- und Thoraxerkrankungen, Universitätsklinik Jena, Jena, Germany
Universitätsklinik für Innere Medizin II, Kardiologie, Paracelsus Medizinische Universität Salzburg, Salzburg, Austria
Universitätsklinik für Innere Medizin I, Kardiologie, Friedrich Schiller Universität Jena, Jena, Germany
Abteilung für Dermatologie, Paracelsus Medizinische Universität Salzburg, Salzburg, Austria
Universitätsklinikum Düsseldorf, Abteilung für Kardiologie, Pneumologie & Angiologie, Dusseldorf, Germany

Background: Peripheral artery disease (PAD) is a common form of manifestation of atherosclerosis, mainly triggered by classical cardiovascular risk factors and inflammatory processes. Affecting over 10% of people over 50 years of age, PAD has an considerable impact on morbidity, hospitalisation rates and health-care costs. Biomarkers have been introduced in many cardiovascular diesease entities over the last years. However, an analysis on the correlation of biomarker levels and PAD is still lacking, giving rise to further investigations.

Purpose: Aim of this study was to investigate the role of four novel cardiac biomarkers, namely sST2, Galectin-3, GDF-15 and Fetuin-A in patients suffering from PAD.

Methods: A total of 106 patients were enrolled in this current study, 51 that were diagnosed with PAD and 55 with excluded coronary and peripheral artery disease as controls. During outpatient visits, plasma samples of all patients were obtained and analyzed for sST2 (hemodynamics and inflammation), Galectin-3 (fibrosis and remodeling), GDF-15 (remodeling and inflammation), uPAR (inflammation), and Fetuin-A (vascular calcification) by use of ELISA after informed consent. Additionally, Rutherford stages and CRP levels as surrogate for inflammatory processes were analyzed and correlated with biomarker levels.

Results: Compared with controls, patients with PAD showed significantly higher levels of sST2 (5248 vs. 7503 pg/ml, $p<0.0001$), uPAR (2267 vs. 2414 pg/ml, $p=0.0207$), Galectin-3 (2795 vs. 4494 pg/ml, $p<0.0001$) and GDF-15 (549 vs. 767 pg/ml, $p<0.0001$, Fig. 1|3-5). Fetuin-A showed lower levels in patients with PAD (117 vs. 100 ng/ml, $p=0.119$) in trend. A positive correlation with Rutherford Stages was found for sST2 ($r=0.36$, $p<0.0001$), Galectin-3 ($r=0.27$, $p=0.019$) and GDF-15 ($r=0.34$, $p<0.0001$). In contrast, Fetuin-A showed no correlation with Rutherford stages ($r=0.12$, $p=0.26$). CRP levels correlated with sST2 ($p=0.02$) and GDF-15 ($p=0.009$), while Galectin-3 ($p=0.135$) and Fetuin-A ($p=0.20$) were not associated with elevated CRP levels.

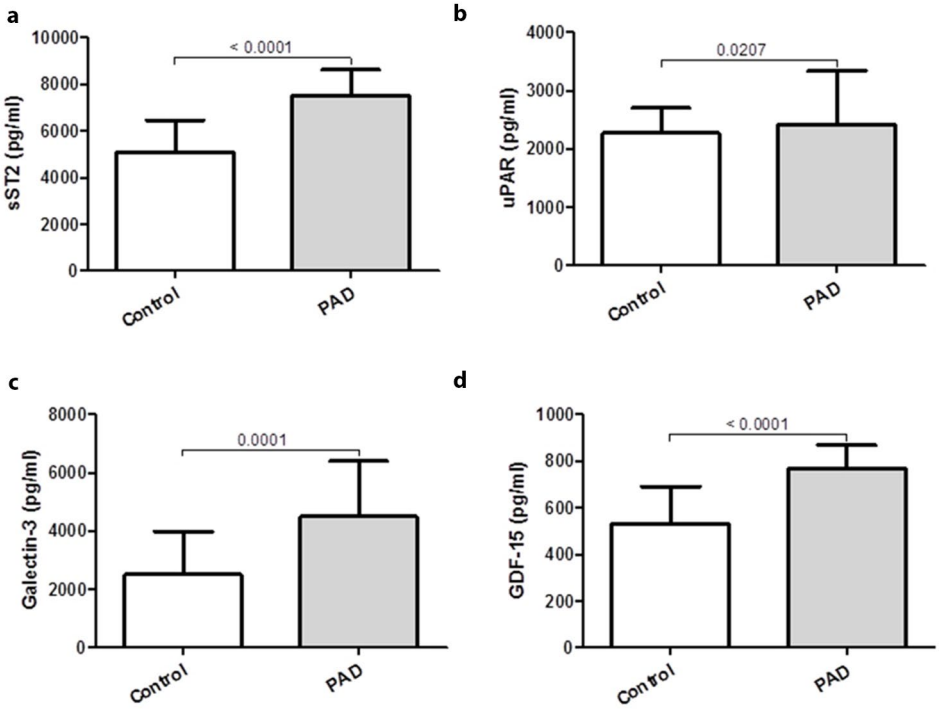


Fig. 1|P 3-5

Conclusions: Circulating levels of sST2, uPAR, Galectin-3 and GDF-15 were significantly elevated in PAD patients and correlated with Rutherford stages. In contrast, Fetuin-A levels showed a decrease in PAD patients indicating increased vascular calcification. Thus, by incorporating different pathophysiological processes present in PAD, tested novel biomarkers facilitate a more precise diagnosis as well as a more accurate evaluation of disease severity and progression.

3-6

Interessenkonflikte von Autoren der 2016 publizierten Leitlinien der Europäischen Gesellschaft für Kardiologie (ESC)

C. Stöllberger, B. Schneider

2. Medizinische Abteilung, Krankenanstalt Rudolfstiftung, Wien, Österreich
Sana Klinik, Lübeck, Deutschland

Grundlagen: Interessenkonflikte (IK) werden definiert als Situationen, die ein Risiko dafür schaffen, dass professionelles Urteilsvermögen oder Handeln, welches sich auf ein primäres Interesse bezieht, durch ein sekundäres Interesse unangemessen beeinflusst wird. Ein IK tritt auf, wenn materielle oder soziale Vorteile in einer Spannung zu primären medizinisch-ethischen Zielen stehen. Auch Autoren der Leitlinien werden verpflichtet, ihre IKs anzugeben. Das Institute of Medicine (IOM) in Washington hat 2011 Standards für den Umgang mit IKs bei der Erstellung von Leitlinien herausgegeben: Das IOM empfiehlt, dass nur eine Minderheit der Mitglieder der Leitlinien–Ersteller IKs haben sollen und der Vorsitzende keinen IK. Leitlinien-Ersteller sollen nur bei solchen Themen stimmberechtigt sein, bei denen sie keinen IK haben.

Ziel unserer Analyse war es, die 2016 publizierten Leitlinien der ESC zu Herzinsuffizienz und Vorhofflimmern im Hinblick auf IKs der Autoren zu untersuchen und mit früheren Jahren zu vergleichen.

Methodik: Die IK-Erklärungen der Autoren der 2016 erschienenen und der korrespondierenden früheren Leitlinien wurden auf der Homepage der ESC gesucht und ausgewertet.

Ergebnisse: IK-Erklärungen der Vorhofflimmer- und Herzinsuffizienz-Leitlinien 2016 wurden auf der ESC Homepage gefunden. Die IK-Erklärungen früherer Leitlinien wurden von der ESC nicht zur Verfügung gestellt, lagen aber in ausgedruckter Form für die Vorhofflimmern-Leitlinien 2010 vor.

Von den 17 Autoren der Vorhofflimmer-Leitlinien 2016 hatten nur 2 (12 %) keinen IK. Der Vorsitzende der Leitlinien Task force hatte die zweitmeisten IKs ($n=30$). Die Anzahl der IKs lag im Mittel bei 12,1 ± 10,2 (range 1–32), davon hatten 14/17 Autoren (82 %) persönliche Zahlungen und 10/17 Autoren (59 %) ein Research funding für die Abteilung erhalten. Gegenüber den Vorhofflimmer-Leitlinien aus dem Jahr 2010 haben sowohl der Anteil von Autoren mit IKs (von 68 % auf 88 %) als auch die Anzahl der IKs pro Autor (von 8,7 ± 10,2 auf 12,1 ± 10,2) zugenommen, außerdem hat sich der Anteil von Autoren mit Erhalt persönlicher Zahlungen (von 60 % auf 82 %) und die Anzahl von IKs infolge persönlicher Zahlungen (von 5,9 ± 7,3 auf 7,7 ± 7,4 pro Autor) erhöht.

Von den 21 Autoren der Herzinsuffizienz-Leitlinien 2016 hatten nur 2 (10 %) keinen IK. Im Mittel gaben die Autoren 13,2 ± 9,9 (range 1–35) IKs an. Am häufigsten (von 17 der 21 Autoren, 81 %) wurden persönlich erhaltene Zahlungen angegeben, 12 der 21 Autoren (57 %) hatten ein Research funding für die Abteilung erhalten. Der Vorsitzende der Leitlinien Task force hatte die zweitmeisten IKs ($n=33$) und sein Stellvertreter die viertmeisten IKs ($n=21$). Unter den 87 Reviewern der Leitlinien waren nur 18 (21 %) ohne IK.

Schlussfolgerungen: Den IKs und einem verantwortlichen Umgang mit ihnen sollte mehr Aufmerksamkeit geschenkt werden. Da es ein großes Interesse an Leitlinien gibt, denen wir vertrauen können, sollte die ESC bei der Erstellung von Leitlinien den Empfehlungen des IOM folgen.

3-7

Is Austria ready for implementation of Core Curricula for Nurses and allied professionals?

L. Hinterbuchner

Cardiology Medizin 2, PMU Salzburg, Salzburg, Austria

Background: The role and competency requirements of specialty cardiac nurses and allied professionals (NAPs) have both changed. In the treatment of patients with severe cardiac conditions the contribution of NAPs as part of a multidisciplinary team is vital. This reinforces the need for well-educated professionals. The NAPs from various communities of the ESC have worked hard to develop curriculum to meet these needs. We would like to encourage you to consider how these can be used as a framework for national courses and training of new personnel.

Methods: All curricula were developed from a panel of experts from various health professions working in that specialty field, representing different levels of expertise from a multidisciplinary team. The diverse levels of education and rules and regulations for NAPs according to country specific professional policy were taken into consideration.

Results: In the last 3 years 3 Core curriculums for Nurses and Allied Professional (NAP) have been developed and published. The reason for the development of these curricula is to provide a standardized educational structure for cardiovascular NAP wanting to specialize. Using general guidelines for standardization of academic and clinical criteria for specialist training in Cardiology for NAPs will standardize the specialties with in Europe. Due to the complexity and diverse educational standards for NAP this is quite a challenge. To ensure essential content is covered during education and a basic level of quality is established in the cardiovascular specialty areas for NAPS throughout Europe, these curriculums should be implemented.

Conclusions: There will be difficulties in implementing due to legislation, regulation and differences in scope of practice with in Europe. Standardization of the competencies required to work in the highly specialized areas of cardiology will contribute to the ESC mission to reduce the burden of cardiovascular disease in Europe. We would encourage the local cardiovascular NAP specialist managers to consider using the learning objectives and competencies to demonstrate an expertise in their specialty area of practice. Using Matrixes to document training of specialty knowledge and skills can also be used for proof in quality or eventual certification of personnel.

3-8

Effizienz der Rehabilitation nach operativen Eingriffen an der thorakalen Aorta

S. Niederreiter

Medizinische Universität Innsbruck, Innsbruck, Österreich

Jolliffe et al [1] wiesen nach, dass spezielle Trainingsprogramme die Gesamtmortalitätsrate von Patienten/Innen mit koronarer Herzerkrankung senken. Derzeit gibt es noch wenige Studienanalysen von Rehabilitationsprogrammen mit Patienten/Innen nach einem operativen Eingriff an der thorakalen Aorta.

Die retrospektive Auswertung erfolgte anhand von 122 Arztbriefen im Zeitraum von Juli 2011 bis Oktober 2016, welche vom Rehazentrum Münster zur Verfügung gestellt wurden. Des Weiteren wurden bei 107 Patienten/Innen eine ausführliche Stufenanalyse bei Aufnahme und Entlassung durchgeführt. Als primäre Zielgrößen wurden die maximale Wattleistung bei Aufnahme- und Entlassungsergometrie bestimmt.

Die mediane Wattleistung bei Aufnahme betrug 115 Watt [26–264], bei Entlassung 140 Watt [30–347]. Eine postoperative Pneumonie stand im Zusammenhang mit einer niedrigeren Leistungsdifferenz ($p=0{,}048$; 12,5 Watt [(−23)–41]; 21 Watt [(−20)–83]) und einer längeren Gesamtbeatmungsdauer. ($p=0{,}024$; 70,5 Stunden (8–682); 15 Stunden (0–549))

Die Stufenanalyse bei Entlassung zeigte ein medianes Metabolisches Äquivalent (MET) von 6,95 bei Stufe 10. ($n=70$; [3,8–10,7]) 46 Patienten/Innen erreichten Stufe 12 bei Entlassung mit einer medianen MET Leistung von 7,9 (4,3–12,6). (Vergleich Aufnahme: 7,7 (4,3–12,9; $n=24$)

Männer wiesen bei Aufnahme eine mediane EuroQuol Punktezahl von 60 (20–80) auf, während Frauen im Median 50 (20–90) Punkte erreichten. ($p=0{,}054$). Bei Entlassung zeigten beide Geschlechter eine mediane Bewertung mit 80 Punkten. [♂ (50–100); ♀ (45–100); $p=0{,}330$]

Patienten/Innen mit einer Transitorische Ischämische Attacke als postoperativer Komplikation bewerteten zu Aufnahmezeitpunkt den EuroQuol Fragebogen niedriger als die Vergleichsgruppe. [$p=0{,}024$; wenn ja 45 (40–50); wenn nein 60 (20–90)] Trotzdem konnte eine Verbesserung der Lebensqualität während der Rehabilitation erreicht werden. [TIA Patienten/Innen mediane Verbesserung von 17,5 (10–39) Punkten; nicht TIA Patienten/Innen eine Verbesserung um 20 [(−5) – 80]; ($p=0{,}992$)]

Zusammenfassend lässt sich sagen, dass Patienten/Innen nach einem Eingriff an der thorakalen Aorta in einem Rehabilitationsprogramm gefördert werden sollen, da es zu einer erwartenden Leistungsverbesserung kommt. Zusätzlich kommt es zu einem Anstieg der Lebensqualität. Männer und Frauen können wieder eine moderate körperliche Anstrengung nach einer herzchirurgischen Operation aufnehmen, wodurch dem Patienten/der Patientin die Bewältigung des Alltags erleichtert wird. Auch Personen, die im Verlauf eine postoperative Komplikationen aufweisen, profitieren von einer gezielten Rehabilitation.

Literatur

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3-9

Die P-Wellenvariabilität (PWV) nach TAVI und sutureless Aortenklappen-Implantation

I. Hable, F. Bechtoldt, I. M. Keeling, D. Zweiker, D. Scherr, M. Puchinger, O. E. Dapunt

Klinische Abteilung für Herzchirurgie, Medizinische Universität Graz, Graz, Österreich

Tab. 1 | P 3-9 Herzrhythmus bei PatientInnen vor bzw. nach TAVI-Implantation ($n=149$)

	Anzahl Vor-HR	Anzahl Nach-HR
Sinusrhythmus	118	106
Vorhofflimmern	20	27
Herzschrittmacherrhythmus	5	11
Kammereigenrhythmus	6	5

Tab. 2 Ergebnis der prä- und postoperativen EKG-Auswertung ($n=149$)

	Vor-HF (ms)	Vor-PWV (ms)	Nach-HF (ms)	Nach-PWV (ms)
Mittelwert	72,73	64,36*	74,40	67,97*
Median	69,0	60	72	60
Standardabweichung	14,93	23,50	15,36	21,34

*$p<0.083$

Klinische Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Österreich
Forschungseinheit Med. Technik und Datenverarbeitung der Klinischen Abteilung für Chirurgie, Medizinische Universität Graz, Graz, Österreich

Grundlagen: In den letzten Jahren wurde ein neuer EKG-Marker, die P-Wellen Variabilität (PWV), bei gesunden und kranken PatientInnenkollektiven hinsichtlich ihres Auftretens untersucht. PatientInnen nach TAVI-Implantation wurden noch nicht bezüglich der PWV untersucht. Da eine verlängerte PWV mit Vorhofflimmern assoziiert ist, könnte durch die Erhebung ein Erkenntnisgewinn für diese PatientInnen erzielt werden.

Methodik: Bei 203 PatientInnen (82 Männer (40.4 %), 121 Frauen (59,6 %), Durchschnittsalter: 78 ± 7 Jahre) wurde im Zeitraum vom März 2015 bis August 2016 70 minimal-invasive und 133 transkutane Aortenklappenimplantationen durchgeführt. Von 203 PatientInnen mit archivierten EKGs konnte bei 149 PatientInnen vollständige Datensätze ausgewertet werden. Folgende Parameter wurden untersucht: Patientenalter bei Operation, Operationsweg, Herzklappentyp, sowie prä- und postoperativer Herzrhythmus (HR), Herzfrequenz (HF) und P-Wellen-Variabilität (PWV).

Ergebnisse: Unsere PatientInnen zeigten nach ihrer TAVI-Implantation sowohl in den präoperativen als auch den postoperativen EKGs großteils eine Überschreitung des Cut-Offs von 40ms in der PWV. Bei der EKG-Auswertung konnte bei 1 PatientInnen postoperativ ein PWV unter diesem Cut-Off festgestellt werden. Bei 11 Patienten trat Vorhofflimmern postoperativ neu auf (Tab. 1). Die präoperative PWV dieser PatientInnen war verlängert. Die PWV war postoperativ tendentiell höher als präoperativ (Tab. 2, $p<0.083$).

Schlussfolgerungen: Die von uns prä- und postoperativ festgestellte, über dem Cut-Off von 40ms bei gesunden Probanden liegende, PWV bei PatientInnen mit TAVI-Operation könnte in einer Folge-Studie anhand von einheitlich geschriebenen EKGs überprüft werden. Besonderes Augenmerk sollte auf Komorbiditäten bzw. Gesundheitsstatus, u. a. Body-Mass-Index, gelegt werden, welche die PWV ebenfalls verändern können. Ob ein möglicher Einbezug der PWV-Auswertung in die Beurteilung von PatientInnen mit Vorhofflimmern nach interventioneller bzw. minimal invasiver chirurgischen Behandlung einer Aortenklappenstenose von Vorteil wäre, bleibt derzeit fraglich.

Erstellt im Rahmen eines FFG-Praktikums 2016 an der Klinischen Abt. für Herzchirurgie, Medizinische Universität Graz.

Postersitzung 4 – Interventionelle Kardiologie 1

4-1

A prospective natural history study of coronary atherosclerosis using fractional flow reserve

G. Toth-Gayor, E. Barbato, N. Johnson, N. Pijls, W. Fearon, P. Tonino, Z. Piroth, P. Jüni, B. De Bruyne

Abteilung für Kardiologie, Medizinische Universität Graz
OLV Aalst, Aalst, Belgium
University of Texas, Houston, USA
Catharina Hospital, Eindhoven, Belgium
Stanford University, Stanford, USA
National Institute of Cardiology, Budapest, Hungary
University of Toronto, Canada

Background: In patients with coronary artery disease, clinical outcome depends on the extent of reversible myocardial ischemia. Whether the outcome also depends on the severity of the stenosis as determined by fractional flow reserve (FFR) remains unknown.

Objectives: This study sought to investigate the relationship between FFR values and vessel-related clinical outcome.

Methods: We prospectively studied major adverse cardiovascular events (MACE) at 2 years in 607 patients in whom all stenoses were assessed by FFR and who were treated with medical therapy alone. The relationship between FFR and 2-year MACE was assessed as a continuous function. Logistic and Cox proportional hazards regression models were used to calculate the average decrease in the risk of MACE per 0.05-U increase in FFR.

Results: MACE occurred in 272 (26.5%) of 1,029 lesions. Target lesions with diameter stenosis ≥70% were more often present in the MACE group ($p<0.01$). Median FFR was significantly lower in the MACE group versus the non-MACE group (0.68 [interquartile range: 0.54 to 0.77] vs. 0.80 [interquartile range: 0.70 to 0.88]; $p<0.01$). The cumulative incidence of MACE significantly increased (Fig. 1 | P 4-1) with increasing FFR quartiles. An average decrease in MACE per 0.05-unit increase in FFR was statistically significant even after adjustment for all clinical and angiographic features (odds ratio: 0.81; 95% confidence interval: 0.76 to 0.86]). The strongest increase in MACE occurred for FFR values between 0.80 and 0.60. In multivariable Cox regression analysis, FFR was significantly associated with MACE up to 2 years (hazard ratio: 0.87; 95% confidence interval: 0.83 to 0.91]).

Conclusions: In patients with stable coronary disease, stenosis severity as assessed by FFR is a major and independent predictor of lesion-related outcome.

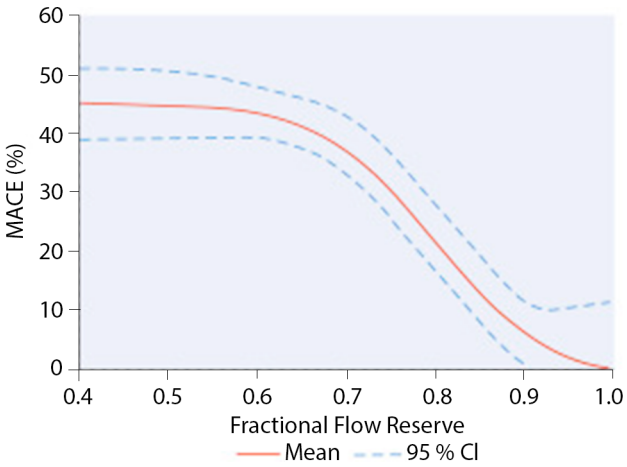


Fig. 1 | P 4-1

4-2

Cost analysis of transcatheter valve replacement over the learning curve

G. Toth-Gayor, O. Bodea, E. Barbato, A. Schmidt, F. Casselman, I. Degrieck, B. De Bruyne

Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Austria
Grand Hôpital de Charleroi, Charleroi, Belgium
OLV Aalst, Aalst, Belgium

Background: Reimbursement of TAVI procedures shows marked variation between different countries and so costs often remain the major burden for its further penetration. The aim of our study was to evaluate the overall cost of the TAVI program over the learning curve and to compare it with the cost of surgical aortic valve replacement (SAVR) in a similar group.

Methods: We enrolled the first 100 patients (pts), who underwent TAVI procedure with balloon expandable device in a low-volume centre. Costs were recorded prospectively based on official financial reports, categorized as (I) cost of the device and (II) additional costs. Latter included all periprocedural medical and non-medical interventions. Results were compared with the group of 100 oldest patients, undergoing SAVR during the same period.

Results: Procedures were performed in a five years period (2007–2012) with early increase in the yearly volume (9 vs 11 vs 17 vs 21 vs 20 vs 22 pts over the six calendar years). Median age of pts was 83 years (80; 86), EuroScore was 15 (7; 25). Median overall cost was 28.436 € (27.108; 32.677), which was dominated by the cost of the device (72% [63; 76]) over additional costs. Over the 5 years of learning curve there was no trend of any change in the perioperative costs ($F=0.065$, $p=0.799$; Fig. 1 | 4-2).

When comparing to the surgical group we found that SAVR pts were significantly younger (81 years [79; 84]; $p<0.001$) with lower EuroScore (8 [7; 9]; $p=0.008$), justifying the proper practice of the centre. Considering the additional costs alone TAVI was found to be more economic as compared to SAVR-group

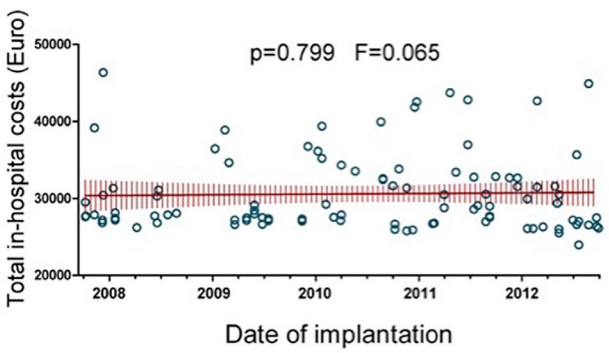


Fig. 1 | P 4-2

(7890 € [6 562; 12.130] vs 11.270 € [9 952; 15.010], respectively; $p < 0.001$).

Conclusions: In elderly patients undergoing TAVI the perioperative costs are dominated by the valve, while additional expenses are markedly below the same of surgical procedures. Costs of a TAVI procedure are independent from the phase of the learning curve.

4-3

Der EuroSCORE als Prädiktor für das Langzeit Outcome nach interventioneller ungeschützter Hauptstammintervention – ein retrospektives Langzeit Follow-up

H. Blessberger, P. Sihorsch, D. Hrncic, S. Schwarz, J. A. Starnawski, A. Kypta, T. Lambert, A. Nahler, J. Kellermair, D. Kiblböck, M. Grund, C. Steinwender, J. Kammler

I. Medizinische Abteilung mit Kardiologie, Kepler Universitätsklinikum Linz, Linz, Österreich

Grundlagen: Der EuroSCORE (European System for Cardiac Operative Risk Evaluation) ist ein Set von 18 ausgewählten klinischen und eingriffsspezifischen Risikofaktoren, das zur Abschätzung der 30-Tages Mortalität nach herzchirurgischen Eingriffen entwickelt und validiert wurde. Obwohl der EuroSCORE primär nur die peri- und postoperative Mortalität einschätzt, besteht die Hypothese, dass eine gute Kurzzeitprognose – repräsentiert durch einen niedrigen EuroSCORE – auch mit einer geringeren Inzidenz an MACCE (major adverse cardiac and cerebrovacular events) und Todesfällen in weiterer Folge verbunden sei. Wir evaluierten in unserer Kohorte an Patienten nach ungeschützter Hauptstammintervention, ob die Höhe des EuroSCOREs zum Zeitpunkt des Eingriffes mit der Inzidenz an MACCE und dem Überleben im weiteren Verlauf assoziiert war.

Methodik: Es wurden Patienten aus dem UNPROLEMA (UNPROtected LEft MAin disease) Register für ungeschützte Hauptstamminterventionen des Kepler Universitätsklinikums Linz analysiert, die zwischen 11/2002 und 12/2013 eine ungeschützte Hauptstammintervention erhalten hatten. Die Nachverfolgung wurde mittels strukturierter Telefon-Interviews und Meldeamtsanfragen sowie Durchsicht der jeweiligen Krankengeschichten durchgeführt. Der logistische EuroSCORE II wurde mit einem online Rechner ermittelt. Die Patienten wurden nach EuroSCORE Terzilen in 3 Gruppen unterteilt. Die Gesamtmortalität und das Auftreten von MACCE (definiert als STEMI, NSTEMI, Zielgefäßrevaskularisation [interventionell oder mittels aortokoronarem Bypass], Insult/TIA oder Tod jedweder Genese) wurden mittels Kaplan-Meier Kurven analysiert. Ein Logrank Test wurde zur Prüfung der statistischen Signifikanz durchgeführt. Schließlich wurden Cox Proportional Hazards (CPH) Modelle berechnet, in denen für potentielle Confounder wie u. a. Revaskularisationstechnik, Ausmaß der KHK und Stenosegrad adjustiert wurde.

Ergebnisse: Im genannten Zeitraum erhielten 253 Pat. eine ungeschützte Hauptstammintervention (Alter 71,0 ± 10,4 Jahre, 78 [30,8 %] weiblich, 58 [22,9 %] Diabetiker). Der EuroSCORE betrug im Mittel 3,3 ± 4,0 (Spannweite: 0,5–35,5). Die Patienten teilten sich auf die Terzile wie folgt auf: 1. Terzile (EuroSCORE 0 bis kleiner 1,23) = 84 Pat., 2. Terzile (EuroSCORE 1,23 bis kleiner 2,86) = 84 Pat., 3. Terzile (EuroSCORE größer 2,86) = 85 Pat. Während einer medianen Follow-up Zeit von 4,2 Jahren (IQR: 2,0–7,0) unterschieden sich die Kaplan-Meier Kurven für Tod jedweder Genese signifikant (Logrank $p < 0{,}00001$, HR 2.24 [95 % CI: 1,67–2,98] pro Anstieg um eine Terzile). In einem CPH Modell mit Adjustierung für potentielle Confounder blieb diese Assoziation praktisch unverändert (HR 2,29, 95 %CI: 1,68–3,12, $p < 0{,}0001$). Von der Analyse der MACCE mussten 13 Pat. (5,1 %) ausgeschlossen werden, die am Leben waren, für die aber keine Follow-up Daten erhebbar waren. Auch die Wahrscheinlichkeit für das Auftreten von MACCE unterschied sich signifikant zwischen den Gruppen (Logrank $p = 0{,}002$, HR 1,50 [95 % CI: 1,19–1,89] pro Anstieg um eine Terzile). In einem CPH Modell verblieb auch nach Adjustierung für potentielle Confounder ein statistisch signifikanter Zusammenhang bestehen (HR 1.35, 95 %CI: 1,05–1,75, $p = 0{,}019$).

Schlussfolgerungen: Obwohl für diese Indikation noch nicht validiert, erwies sich der logistische EuroSCORE II in unserem Patientenkollektiv nach ungeschützter interventioneller Hauptstamm-revaskularisation als robuster Prädiktor für Mortalität und MACCE im Langzeit Follow-up.

4-4

Einfluss der glomerulären Filtrationsrate auf das Langzeit Outcome nach interventioneller ungeschützter Hauptstammintervention – ein retrospektives Langzeit Follow-up

J. A. Starnawski, H. Blessberger, J. Kammler, D. Hrncic, S. Schwarz, A. Kypta, T. Lambert, A. Nahler, C. Reiter, J. Kellermair, D. Kiblböck, M. Grund, C. Steinwender

Klinik für Kardiologie und internistische Intensivmedizin, Kepler Universitätsklinikum, Linz, Österreich

Grundlagen: In Österreich leiden 5 % der Bevölkerung an chronischer Niereninsuffizienz Grad 3 oder höher (glomeruläre Filtrationsrate GRF <60 ml/min/1,73 m^2). In diesem Patientenkollektiv sind kardiovaskuläre Erkrankungen die Haupttodesursache. Dabei werden unterschiedliche Gründe für die Assoziation von kardiovaskulären Erkrankungen und chronischer Niereninsuffizienz diskutiert: Einerseits ist sie häufig mit anderen Risikofaktoren wie Diabetes oder arterieller Hypertonie vergesellschaftet, andererseits wirkt sich diese auch auf den Lipidmetabolismus, oxidativen Stress sowie das Gerinnungssystem aus. Wir evaluierten das Langzeit Outcome bei Patienten nach ungeschützter Hauptstammrevaskularisation unter Berücksichtigung der GFR.

Methodik: Es wurden Patienten aus dem UNPROLEMA (UNPROtected LEft MAin disease) Register für ungeschützte Hauptstamminterventionen an unserem Institut analysiert, bei denen zwischen 11/2002 und 12/2013 eine ungeschützte Hauptstammintervention durchgeführt wurde. Dabei wurden im Rahmen des Registers die Patientendaten durch Informationen aus Krankengeschichten sowie aus strukturierten Telefon-Interviews und Meldeamtsanfragen bzgl. Follow-up komplettiert. Die Patienten wurden gemäß ihrer GFR in 2 Gruppen unterteilt: 1 = GFR>60 ml/min/1,73 m^2, 2 = GFR<60 ml/min/1,73 m^2. Dabei erfolgte die Bestimmung der GFR nach der MDRD-Formel. Die Gesamtmortalität und das Auftreten von major adverse cardiac and cerebrovascular events (MACCE: definiert als STEMI, NSTEMI, Zielgefäßrevaskularisation [interventionell oder mittels aortokoronarem Bypass], Insult/TIA oder Tod jedweder Genese) wurden mittels Kaplan-Meier Kurven analysiert. Ein Log-rank Test wurde zur Prüfung der statistischen Signifikanz ermittelt. Schließlich wurde ein Cox Proporti-

onal Hazards (CPH) Model, in dem für potentielle Confounder wie Alter, Geschlecht, Diabetes, linksventrikuläre Auswurffraktion und weitere kardiale Risikofaktoren adjustiert wurde.

Ergebnisse: Im genannten Zeitraum erhielten 214 Pat. eine ungeschützte Hauptstammintervention, bei denen auch eine GFR-Messung vor dem Eingriff durchgeführt wurde (Alter 71,1 ± 10,7 Jahre, 66 [30,8 %] weiblich, 38 [17,8 %] nicht insulinpflichtige, 7 [3,3 %] insulinpflichtige Diabetiker),

Es wurden zwei Gruppen wie folgt aufgeteilt: 1 = 151 Pat., 2 = 63 Pat.. Während einer medianen Follow-up Zeit von 3,6 Jahren (IQR: 1,9–5,9) unterschieden sich die Kaplan-Meier Kurven für Tod jedweder Genese signifikant ($p < 0{,}00001$), wobei Patienten der Gruppe 2 ein 3,7-fach erhöhtes Risiko aufwiesen. Auch nach Adjustierung für potenzielle Confounder blieb diese Signifikanz erhalten. Von der Analyse der MACCE mussten 10 Pat. (4,6 %) ausgeschlossen werden, welche nicht verstorben waren, jedoch keine Follow-up-Daten erhoben werden konnten. Auch die Wahrscheinlichkeit für das Auftreten von MACCE unterschied sich signifikant zwischen den Gruppen ($p = 0{,}022$) mit höherer Inzidenz in Gruppe 2. In einem CPH Model mit Adjustierung für potenzielle Confounder verlor jedoch die Assoziation der MACCE Inzidenz mit der GFR-Gruppe ihre Signifikanz (HR 1.37, 95 % CI: 0,84–2,24, $p = 0{,}211$).

Schlussfolgerungen: Eine eingeschränkte Nierenfunktion mit einer GFR unter 60 ml/min/1,73 m² war in unserer Kohorte von Patienten mit ungeschützter Hauptstammrevaskularisation robust mit einer erhöhten Mortalität assoziiert. Bezüglich der MACCE Inzidenz während des Follow-up-Zeitraumes bestätigte sich der Einfluss der Komorbiditäten bei chronischer Niereninsuffizienz als relevanter Faktor.

4-5

Impact of right ventricular performance in patients undergoing extracorporeal membrane oxygenation following cardiac surgery

P. Bartko, D. Wiedemann, L. Schrutka, C. Binder, A. Zuckermann, H. Koinig, G. Heinz, A. Niessner, D. Zimpfer, G. Laufer, I. Lang, K. Distelmaier, G. Goliasch

Innere Medizin 2/Kardiologie, Medizinische Universität Wien, Vienna, Austria
Herzchirurgie, Medizinische Universität Wien, Vienna, Austria

Background: Extracorporeal membrane oxygenation (ECMO) following cardiac surgery safeguards end-organ oxygenation in critically ill patients, but unfavorably alters cardiac hemodynamics. Along with the detrimental effects of cardiac surgery to the right heart, this might impact outcome – particularly in patients with preexisting right ventricular dysfunction. We set out to determine the prognostic impact of right ventricular (RV) function and to improve established risk prediction models in patients undergoing ECMO after cardiovascular surgery.

Methods and Results: 240 patients underwent ECMO support following cardiac surgery of which 111 had a comprehensive echocardiographic exam at our institution prior to ECMO implantation and were thus included in this analysis. During a median follow-up of 27 months (IQR 16- 63 months), 75 patients (68%) died. Metrics of RV function were the strongest predictors of outcome (Fig. 1|4-5a and Fig. 1|4-5a), even stronger than measures of left ventricular function. Specifically, RV free-wall strain was the most powerful predictor: HR of 0.44 (95%CI 0.30–0.66; $P < 0.001$) for 30-day mortality with an AUC of 0.76 and a HR of 0.50 (95%CI 0.36–0.69; $P < 0.001$) for long-term mortality with an AUC of 0.74. The effect was even stronger after adjustment for clinical variables, SAPS-3 score, tricuspid regurgitation, type of surgery, and procedure duration with adj. HRs of 0.41 (95% CI 0.24–0.68; $P = 0.001$) for 30-day mortality, and 0.48 (95% CI 0.33–0.71; $P < 0.001$) for long-term mortality (Fig. 2|4-5a). Combined assessment of the additive EuroSCORE and RV free-wall strain improved risk classification by a net reclas-

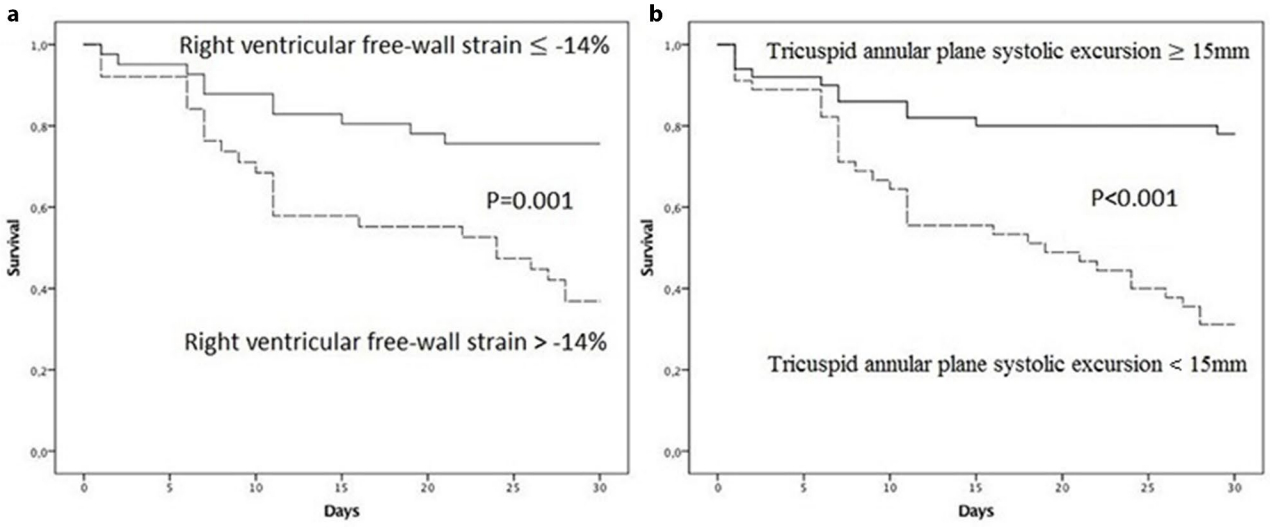


Fig. 1|4-5

		30-day mortality		Long-term mortality	
	SD	Adj. HR (95% CI)	P-value	Adj. HR (95% CI)	P-value
LVEDV, ml	57	1.09 (0.68- 1.74)	0.74	0.72 (0.63- 1.372)	0.93
EF, %	13	1.58 (0.98- 2.55)	0.06	1.35 (0.92- 1.98)	0.13
LV global longitudinal strain, %	-5	1.44 (0.87- 2.39)	0.16	1.24 (0.82- 1.87)	0.31
RVEDA, cm^2	9	0.93 (0.79- 0.93)	0.79	0.84 (0.57- 1.25)	0.82
FAC, %	10	0.85 (0.55- 1.31)	0.46	0.56 (0.62- 1.30)	0.56
RV function	--	1.51 (1.21- 2.03)	0.007	1.64 (1.26- 2.13)	<0.001
TAPSE, mm	5	1.56 (0.36- 0.86)	0.008	0.51 (0.34- 0.75)	0.001
RV free-wall long. strain, %	-6	0.41 (0.24- 0.68)	0.001	0.48 (0.33- 0.71)	<0.001
sPAP, mmHg	19	1.25 (0.86- 1.81)	0.25	1.20 (0.89- 1.68)	0.29

Fig. 2| 4-5

sification index of 57% for 30-day mortality ($P=0.01$) and 56% for long-term mortality ($P=0.02$) compared with the additive EuroSCORE alone.

Conclusions: Right ventricular function is strongly linked to mortality, even after adjustment for baseline variables, clinical risk scores, and careful consideration of confounders. Surrogates of RV performance improve established risk prediction models for both: short-, and long-term mortality.

4-6

Instent-Restenosen nach Carotis Stent Implantation – Langzeit Follow-up einer Single-Center Kohorte

J. Kammler, H. Blessberger, T. Lambert, J. Kellermair, M. Grund, A. Nahler, M. Lichtenauer, S. Schwarz, C. Reiter, A. Fellner, D. Hrncic, C. Steinwender, A. Kypta

Klinik für Kardiologie und internistische Intensivmedizin; Kepler Universitätsklinikum Linz, Linz, Österreich
Klinik für Innere Medizin II; Paracelsus Medizinische Privatuniversität Salzburg, Salzburg, Österreich

Grundlagen: Die Stentrevaskularisation signifikanter Arteria carotis interna (ACI) Stenosen ist ein etabliertes Verfahren, bei dem die Entwicklung von Instent-Restenosen (ISR) im Langzeitverlauf ein ernst zu nehmendes Problem darstellen kann. Wir wollen über die Rate an ISR in unserem Patientenkollektiv berichten.

Methodik: Zwischen Dezember 1997 und Jänner 2016 wurden an unserer Abteilung 1165 signifikante ACI Stenosen einer Stentrevaskularisation unterzogen. Postinterventionell wurden unsere Patienten (P) mittels Ultraschall nach 1, 6 sowie 12 Monaten und dann jährlich nachkontrolliert. Eine ISR >70 % wurde als Strömungsgeschwindigkeit von >300 cm/s im Stent definiert.

Ergebnisse: Insgesamt wurden 1165 signifikante (asymptomatisch ≥80 %, symptomatisch ≥70 %) ACI-Stenosen mittels Stent revaskularisiert. Die peri-interventionelle neurologische Komplikationsrate (minor oder major stroke) betrug 2.5 %. Dem Lauf der technischen Entwicklung folgend, wurden nach anfänglicher Verwendung Ballon-expandierbarer Stents (die ersten 453 Prozeduren) im weiteren Verlauf durchwegs selbst-expandierbare Stents (712 Prozeduren) verwendet. Letztere unterteilen sich wieder in solche mit „getapertem" sowie in „nicht getapertem" Design.

Bei 39 P (3,4 %) kam es zu einer signifikanten ISR (>70 %) im Follow-up (median 19,6 Monate; IQR 5,1–49,6 Monate; range: 0,0–170 Monate), wobei eine logistische Regressionanalyse keinen Zusammenhang zwischen Follow-up-Zeit und Entwicklung einer ISR zeigte ($p=0{,}243$). Alle P, die eine ISR entwickelten waren klinisch asymptomatisch.

Bei 13 P zeigte sich als Ursache der Restenose ein Stent-Crush, ein Phänomen welches ausschließlich bei Verwendung Ballon-expandierbarer Stents auftrat. Bei 31 P mit ISR erfolgte eine Re-Intervention im Sinne einer Stent-in-Stent Implantation.

Es zeigte sich in unserem Kollektiv, dass die Verwendung kürzerer Stents ($p<0{,}00001$), die Verwendung Stents mit geringeren Diametern ($p<0{,}00001$) sowie der Stent-Typ (Verwendung selbstexpandierbarer Stents; log-rank Test $p=0{,}003$) und die Durchführung einer Nachdilatation bei Verwendung Ballon-expandierbarer Stents ($p=0{,}027$) bei der Index-Prozedur das Auftreten von ISR signifikant beeinflussen.

Schlussfolgerungen: Signifikante ISR >70 % nach interventioneller Sanierung signifikanter ACI-Stenosen sind selten (3,4 % in unserer Kohorte von 1165 Prozeduren). Dies gilt vor allem für die Verwendung selbstexpandierbarer Stents (1 %). Bei der Verwendung Ballon-expandierbarer Stents kann eine Nachdilatation die Rate an ISR verringern. Die niedrige peri-interventionelle Insultrate, die niedrige Inzidenz von ISR und das Faktum, dass alle unsere Patienten mit ISR klinisch asymptomatisch waren lassen darauf schließen, dass die interventionelle Sanierung von ACI Stenosen insgesamt, aber vor allem in Hinblick auf den Langzeitverlauf eine gute therapeutische Option darstellt.

4-7

Intracardiac versus transesophageal echocardiography for left atrial appendage occlusion with Watchman

A. Frangieh, J. Alibegovic, S. Obeid, R. Manka, T. F. Lüscher, R. Binder

Klinik für Kardiologie, Universität Zürich, Zurich, Switzerland

Background: Left atrial appendage occlusion (LAAO) is mostly performed by transesophageal echocardiography (TEE) guidance. Intracardiac echocardiography (ICE) may be an alternative imaging modality for LAAO that precludes the need for general anesthesia or sedation.

Methods and Results: All consecutive single center, single operator LAAO candidates were analyzed. Baseline clinical and procedural characteristics and in-hospital outcomes were compared between patients in whom a Watchman was implanted with ICE versus TEE guidance.

In 76 consecutive patients the Watchman device was deployed under ICE in 32 patients (42%) and under TEE guidance in 44 patients (58%). Baseline characteristics were comparable between groups, except that patients in the TEE group were older (81 [75–85] years vs. 75 [68–80] years, $p=0.007$). Total injected contrast media as well as fluoroscopy time were comparable between groups (90 ml [54–140] vs. 85 ml [80–110], $p=0.86$ and 7.9 min [6.4–15.5] vs. 9.8 min [7.0–13.2], $p=0.51$, for TEE vs. ICE, respectively). However, time from femoral venous puncture to transseptal puncture and to closure was longer in the ICE group (14 min [7.3–20] vs. 6 min [3.3–11], $p=0.007$ and 48 min [40–60] vs. 34.5 min [27–44], $p=0.003$, respectively).

In the TEE group one patient suffered esophageal erosion with bleeding, which was managed conservatively and one non-LAAO related in-hospital mortality occurred in an 88-year-old patient. Device implantation success rate was 100% in both groups. No device embolization, no significant peri-device leak, no tamponade, no stroke and no access site bleeding occurred in any patient. Total hospital stay for stand-alone LAAO was comparable between groups (2 days [2–2] vs. 2 days [2–3.3], $p=0.17$, in ICE vs. TEE, respectively).

Conclusions: ICE guidance for LAAO with the Watchman device is feasible and comparable to TEE, and may become the preferred imaging modality for LAAO.

4-8

Prolongation of HV-interval during TAVI procedures as possible indicator for permanent pacemaker requirement – early data analysis

C. Reiter, T. Lambert, M. Grund, A. Nahler, J. Kellermair, S. Schwarz, D. Hrncic, M. Patrasso, C. Steinwender

Klinik für Kardiologie und Internistische Intensivmedizin, Kepler Universitätsklinikum Linz, Linz, Austria

Background: Transcatheter aortic valve implantation (TAVI) has rapidly become a treatment option for selected patients with severe aortic valve stenosis. However, despite improvements of TAVI devices, the need for permanent pacemaker implantation after TAVI shows a wide variation due to conduction disturbances caused by the valve prothesis. We prospectively assessed HV-interval prolongations during TAVI procedures and the need for permanent pacemaker implantation rate in a consecutive series of patients.

Methods: In our ongoing clinical trial, we systematically investigate intra-procedural real-time HV-intervals by the use of a portable EP system (EPS), which is located in the cath lab during the TAVI procedures. Via an additional venous puncture in the left groin, a HIS catheter is positioned in each patient and a real-time HV-interval is monitored during the TAVI procedure. In addition, surface ECG recordings are obtained at baseline, immediately after TAVI as well as 24 h, 48 h and 72 h after TAVI, respectively, and the rate of pacemaker implantations is documented.

Results: Early statistical analysis of the recorded data by means of the Wilcoxon-test after recruitment of 8 patients undergoing TAVI in the setting of our ongoing clinical trial revealed a significant intra-procedural increase of the mean HV-interval (Δ 22.4 ± 14.8 ms; $p=0.027$) and the QRS-complex duration (Δ 37.3 ± 19.4 ms; $p=0.017$). Furthermore, comparison of surface ECG recordings revealed significant increases of the PQ-interval immediately after TAVI (Δ 27.7 ± 9.4 ms; $p=0.018$) and 72 h later (Δ 42.3 ± 22.3 ms; $p=0.027$) as well as QRS-complex duration immediately after TAVI (Δ 36.6 ± 24.8 ms; $p=0.017$) and 72 h later (Δ 26.5 ± 29.1 ms; $p=0.025$).

Three patients had to undergo permanent pacemaker implantation: In the first patient, third-degree AV-block was diagnosed immediately after deposition of the valve prosthesis in the landing zone. The second patient suffered from third-degree AV-block on the first postprocedural day after intraprocedural measurements had revealed an increase of the HV-interval of 23 ms and an increase of QRS-complex duration of 35 ms with intraprocedural new-onset left bundle branch block. The third patient was developed third-degree AV-block on the third postprocedural day with a documented intraprocedural increase of the HV-interval of 40 ms and an increase of QRS-complex duration of 38 ms.

Conclusions: In this early analysis of our ongoing clinical trial, significant increases of intraprocedural HV-interval and QRS-complex duration, as well as significant increases of periprocedural PQ-interval and QRS-complex duration in the recorded ECGs were observed. Final analysis after inclusion of approximately 100 patients undergoing TAVI might give insight in a possible correlation of these findings with the onset of conduction disturbances necessitating permanent pacemaker implantation.

4-9

Ungeschützte Hauptstammintervention im Rahmen eines akuten Koronarsyndroms – ein retrospektives Langzeit-Follow-up

D. Hrncic, H. Blessberger, J. Kammler, S. Schwarz, J. Starnawski, A. Kypta, T. Lambert, A. Nahler, C. Reiter, J. Kellermair, M. Grund, D. Kiblböck, C. Steinwender

Klinik für Kardiologie und Internistische Intensivmedizin, Kepler Universitätsklinikum Linz, Linz, Österreich

Grundlagen: Eine Hauptstammstenose ist noch immer ein Krankheitsbild, das den behandelnden Arzt vor große Herausforderungen stellt und seit Jahrzehnten eine Domäne der Herzchirurgie ist. Mittlerweile, jedoch haben mehrere Studien gezeigt, dass eine interventionelle Sanierung von Hauptstammstenosen für ausgewählte Patienten sicher durchgeführt

werden kann. Nichtsdestotrotz existieren für Hauptstammstenosen im Rahmen eines akuten Koronarsyndroms (ACS), welches per se eine Hochrisiko-Erkrankung repräsentiert, deutlich weniger Daten.

Methodik: Es wurden Patienten aus dem UNPROLEMA (UNPROtected LEft Main revascularization) Register für ungeschützte Hauptstamminterventionen des Kepler Universitätsklinikums analysiert, die sich zwischen 11/2002 und 12/2013 einer ungeschützten Hauptstammintervention unterzogen hatten. Im Rahmen des Registers wurde ein Follow-up der Patienten mittels Informationen aus Krankengeschichten sowie mit strukturierten Telefoninterviews und Meldeamtsanfragen durchgeführt. Die Patienten unterteilten wir in zwei Gruppen, eine ACS-Gruppe und eine Nicht-ACS-Gruppe. Die ACS-Gruppe bestand aus Patienten bei denen die Hauptstammintervention im Rahmen eines akuten Koronarsyndroms durchgeführt wurde und subsummierte die Untergruppen NSTEMI, STEMI und STEMI mit Schock. Die Nicht-ACS-Vergleichsgruppe bildeten Patienten mit stabiler koronarer Herzkrankheit. Die Gesamtsterblichkeit und das Auftreten von Major Adverse Cardiac and Cerebrovascular Events (MACCE) wurden mittels Kaplan-Meier Analysen evaluiert. Als MACCE wurden folgende Ereignisse klassifiziert: Myokardinfarkt, aortokoronare Bypassoperation, Re-Intervention im Zielgefäß, TIA/Insult und Tod jedweder Ursache.

Ergebnisse: Von den 262 untersuchten Patienten waren 219 in der Nicht-ACS-Gruppe (83,6 %) und 43 in der ACS-Gruppe (16,4 %), davon 19 NSTEMI, 18 STEMI, 6 STEMI mit kardiogenem Schock.

In einer medianen Follow-up Zeit von 4.1 Jahren (Interquartilenbreite: 2,0–7,0, Spannweite: 0–12) konnte in der Kaplan-Meier-Analyse für Tod jedweder Genese kein Unterschied festgestellt werden. ($p = 0{,}523$)

Von der Analyse der MACCE mussten 13 Patienten (5,0 %) ausgeschlossen werden, die am Leben waren, für die aber keine Follow-up Daten erhebbar waren. Von den verbliebenen 249 Patienten betrug die mediane Follow-Up-Dauer 2,8 Jahre (IQR 1,1–5,5 Jahre). In der Kaplan-Meier-Analyse ($p = 0{,}908$) und im Cox proportional hazards Modell konnte, nach Adjustierung für potentielle Confounder wie das Ausmaß der koronaren Herzkrankheit, Ein/Zwei-Stent-Strategie, Geschlecht, Kreatinin, Alter, Hypercholesterinämie, AHT, pAVK, Diabetes, EF, kein signifikanter Unterschied festgestellt werden. (HR 1,24, 95 % CI: 0.72–2.12, $p = 0{,}434$)

Schlussfolgerungen: Ein ACS zum Zeitpunkt der Hauptstammintervention war in unserer Kohorte nicht mit einem statistisch signifikant schlechteren Langzeit-Outcome assoziiert. Ursache dafür könnte die ältere Patientenpopulation sein, die aufgrund der Multimorbidität mit einer hohen Hintergrundmortalität und -morbidität assoziiert ist. Ebenso ist die Fallzahl limitiert. Andererseits zeigte sich in dieser retrospektiven Analyse, dass auch bei akutem Setting, wo möglicherweise die Zeit für eine chirurgische Revaskularisation zu lange ist und das perioperative Risiko deutlich höher ist, eine ungeschützte Hauptstammintervention eine mögliche Therapieoption darstellt.

Postersitzung 5 – Rhythmologie 1

5-1

Gender differences in the perception of atrial fibrillation in patients presenting for pulmonary vein isolation

M.-S. Huber, R. Schönbauer, L. Fiedler, M. Pfeffer, F. X. Roithinger

4. Medizinische Abteilung mit Kardiologie, Krankenhaus Hietzing, Wien, Vienna, Austria
2. Interne Abteilung, Landesklinikum Wiener Neustadt, Vienna, Austria

Background: Women suffering from atrial fibrillation (AF) are frequently thought to have lower quality of life (QoL) than men, although this issue has not been well addressed in clinical studies.

Introduction: The aim of this prospective study is to compare different QoL issues in men und women with symptomatic AF presenting for pulmonary vein isolation (PVI). To achieve this goal, 7 validated questionnaires, including disease-specific and generic QoL questionnaires, were used.

Methods: From 2015 to 2016, 120 consecutive patients with symptomatic AF (33% female) presenting for catheterinterventional PVI were included in our prospective registry.

All study participants completed seven QoL questionnaires (AF severity score (AFSS), AF symptom checklist (AFSC), Illnes intrusiveness (Ii), Major Depression Inventory (MDI), WHO-5-Well-Being-Index (WHO), Sleep and Vegetative disorder (SV), Vital Exhaustion (VE)) before ablation procedure.

Results: Women presenting for AF ablation were older ($p = 0.012$), less often on Dabigatran ($p = 0.006$), but more frequently on ACE-inhibitors ($p = 0.032$). They had higher levels of N-terminal pro-brain natriuretic peptide ($p = 0.041$) and lower glomerular filtration rate ($p = <0.001$). AF subtype, echocardiographic and PVI procedure parameters did not differ significantly with respect to gender.

Women had lower QoL as described by AFSS ($p = 0.017$), MDI ($p = 0.003$), SV ($p = 0.048$), VE ($p = 0.009$) and Ii ($p = <0.001$). There was a trend toward a lower QoL in women in the WHO-questionnaire ($p = 0.100$) but no gender difference in AF symptoms as described by AFSC ($p = 0.393$).

Conclusions: There is no significant gender related difference in AF symptoms (Fig. 1|5-1). However, women have a

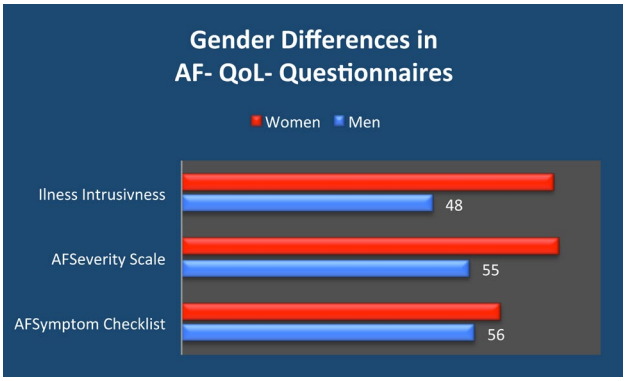


Fig. 1 | 5-1

more severe perception of the disease. Nevertheless, they are presenting later for AF ablation.

5-2

Impact of non-VKA oral anticoagulants on AF ablation outcome

D. Zweiker, M. Manninger, J. Ebner, R. Sieghartsleitner, B. Ohnewein, E. Bisping, P. Lercher, G. Prenner, R. Riedlbauer, H. Brussee, D. Scherr

Klinische Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Austria

Background: Non vitamin K antagonist (VKA) oral anticoagulants (NOACs) have been introduced as antithrombotic treatment of atrial fibrillation. NOACs have been proposed to have antiarrhythmic properties besides their anticoagulatory effects. Currently, there is limited data on the impact of NOAC therapy on the outcome of atrial fibrillation (AF) ablation therapy.

Purpose: To investigate the outcome of AF ablation therapy in patients receiving NOAC compared with standard treatment (VKA group).

Methods: We analysed the AF recurrence rate in NOAC vs. VKA patients 90–365 days after AF ablation. We excluded patients that were not followed up for over 90 days or received either therapy during 1-year follow up (i. e., NOAC and VKA). 220 ablations from 195 patients (24.1% female) were included in this analysis. NOACs were used in 128 cases (58.1%) after the ablation procedure (rivaroxaban, 60.9%; dabigatran, 21.1%; apixaban, 18.0%). Prevalence of persistent AF was similar in both patient groups (NOAC group, 21.2%; VKA group, 23.1%, $p=0.74$). NOAC patients were younger (median [interquartile range] 55 [48–63] vs. 60 [48–68] years, $p=0.02$), and had lower stroke and bleeding risk (CHA2DS2-VASc score 1 [0–2] vs. 2 [1–3]; $p<0.01$; HAS-BLED score 1 [0–2] vs. 2 [2–3]; $p<0.01$) due to lower prevalence of arterial hypertension (48.4% vs. 73.9%; $p<0.01$), coronary artery disease (7.0% vs. 17.4%, $p=0.03$), and vascular disease (23.4% vs. 44.6%, $p<0.01$) compared with VKA patients. Pre-existing antiarrhythmic drug (AAD) use was less prevalent in NOAC group (35.9% vs. 55.4%; $p<0.01$).

Results: Median follow up time was 326 (120–464) days in NOAC group and 360 (208–478) days in VKA group ($p=0.07$). Continuous AAD use during follow up was less prevalent in NOAC group (28.1% vs. 53.3%; $p<0.01$). We observed no significant difference in cumulative recurrence-free 1-year survival (NOAC group, 75.2%; VKA group, 61.8%; Log Rank $p=0.14$).

Conclusions: This analysis shows that NOAC treatment after AF ablation therapy was not associated with lower AF recurrence rate.

5-3

Indications for and outcome in patients with the wearable cardioverter defibrillator (WCD) – results of the Austrian WCD registry

T. Odeneg, M. Manninger-Wünscher, C. Ebner, D. Mörtl, H. Keller, A. Dirninger, G. Stix, B. Föger, G. Grimm, M. Stühlinger, C. Steinwender, C. Haider, D. Scherr

Abteilung für Innere Medizin, Kardiologie, Medizinische Universität Graz, Graz, Austria
Krankenhaus Elisabethinen, Linz, Austria
Landeskrankenhaus St. Pölten, Austria
Krankenanstalt Rudolfstiftung, Vienna
Landeskrankenhaus Hochsteiermark, Bruck an der Mur, Austria
AKH Wien, Vienna, Austria
Landeskrankenhaus Bregenz, Bregenz, Austria
Landeskrankenhaus Klagenfurt, Klagenfurt, Austria
Medizinische Universität Innsbruck, Innsbruck, Austria
AKH Linz, Linz, Austria

Background: The wearable cardioverter defibrillator (WCD; LifeVest©) is a treatment option for patients at high risk for ventricular tachycardia (VT) or ventricular fibrillation (VF), either in whom this risk may be present temporarily or in whom an implantable cardioverter defibrillator (ICD) implantation is currently not possible.

Methods: Retrospective registry of all patients in Austria who received a WCD 2009–2017.

Results: 588 Austrian patients in 48 centers (62 ± 14 years; 26% female) received a WCD. Main indications were: Newly diagnosed severe non-ischemic cardiomyopathy (20%), recent myocardial infarction with severely depressed left ventricular ejection fraction (19%), delayed ICD implantation (16%), ischemic cardiomyopathy with recent PCI (11%), acute myocarditis (11%), ICD-associated infection (10%) or other (13%). Left ventricular ejection fraction (LVEF) was 32 ± 15%, median CHA2DS2-VASc-Score 3 (2–5). 48% of all patients had VT/VF before the WCD period. The median WCD duration was 56 (1–436) days. There was no difference in WCD compliance between patients wearing the WCD <60 days vs. >60 days (23 (3–24) h/day vs. 22 (1–24) h/day; n. s.). 21 patients (3.6%) received 36 adequate WCD shocks, which appropriately terminated 16 VT events and 20 VF events with the 1st shock ($n=33$), the 2nd shock ($n=1$), the 3rd shock ($n=1$), or did not terminate the arrhythmia ($n=1$). 15 of these patients received an ICD, one patient received a CABG, one refused ICD Implantation, two patients died subsequently due to cardiogenic shock and two patients are still wearing the WCD. Four patients (0.7%) received five inadequate shocks due to artefacts ($n=2$), asystole ($n=1$) or VT events which terminated immediately before shock delivery ($n=2$). Reasons for termination of the WCD period were: ICD Implantation (56%), restitution of left ventricular function with no further need for an ICD (26%), patient desire (4%), ablation (2%) or PCI/CABG (2%), or other (10%). 92 (16%) patients are still wearing the WCD. Four patients (0.7%) died during WCD period due to asystole ($n=1$) or did not wear the WCD at time point of death ($n=3$).

Of the 63 patients with myocarditis, only nine patients (19%) required an ICD versus 60% of all other WCD patients ($p<0.001$).

Conclusions: The WCD is an effective treatment option in patients at high risk for VT/VF and/or mandated waiting period for ICD implantation. Only 56% of patients require an ICD after the WCD period.

5-4

Is there a difference in outcome in patients undergoing first vs. second line ablation of atrial fibrillation?

J. Ebner, M. Manninger, R. Sieghartsleitner, D. Zweiker, B. Mastnak, E. Bisping, P. Lercher, R. Riedlbauer, B. Rotmann, H. Brussee, D. Scherr

Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Austria

Background: Catheter ablation of atrial fibrillation (AF) is an established second line therapy (after failed antiarrhythmic drug [AAD] treatment) for patients with symptomatic paroxysmal AF (PAF). According to the recent ESC guidelines, AF ablation may be considered as a first line therapy in selected low-risk patients who are highly symptomatic.

Our study investigated whether a first line ablation approach may result in improved sinus rhythm maintenance after ablation.

Methods: A total of 153 patients undergoing pulmonary vein isolation for PAF were included in the study (age 55 ± 12 years, 29% female). Seventy nine patients underwent first line AF ablation and 74 patients underwent second line AF ablation after a failed AAD therapy (57% class I AAD, 51% class III AAD, 1% class IV AAD). There was no significant difference in baseline characteristics such as age (median [range]: 56 [25,78] vs. 57 [25,75] years in first vs. second line patients), gender (30 vs. 27% female), CHADS2 score (1 [0.3] vs. 1 [0.4]), CHA2DS2-VASc-Score (2 [0.4] vs. 2 [0.4]), history of AF (36 [1.315] vs. 36 [2.294] months), left atrial size (longitudinal axis [mean±SD] 51 ± 5 vs. 52 ± 7 mm), or left ventricular ejection fraction (65 [41,76] vs. 65 [32,80] %) between groups. Success was defined as AF and atrial tachycardia free survival during follow up by means of serial ECG Holter monitoring during 12 months of follow-up.

Results: The median follow up time was 352 (7,365) days in first line patients vs. 356 (6.365) days in second line patients (n. s.). There was no significant difference in cumulative arrhythmia-free survival between those patients who received AF ablation as a first or second line therapy (single procedure success 79% in the first line group vs. 77% in the second line group; Log rank test $p = 0.82$; multiple procedure success 87 vs. 91%, Logrank test $p = 0.35$).

Conclusions: Success of AF ablation did not differ between patients who received AF ablation as first line therapy and those who received AF ablation as a second line therapy. Based on these data, a trial of AAD therapy before AF ablation may be justified in most patients with symptomatic paroxysmal AF eligible for rhythm control.

5-5

Long-term clinical outcome in patients with early repolarization pattern and the diagnosis of idiopathic ventricular fibrillation

D. Dalos, M. Sponder, L. Fiedler, C. Schukro

Universitätsklinik für Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria
Landesklinikum Thermenregion Mödling, Mödling, Austria

Background: Idiopathic ventricular fibrillation (iVF) is diagnosed in up to 14% of sudden cardiac death survivors. Early repolarization syndrome (ERS) in patients with ventricular tachyarrhythmia is characterized by specific ECG patterns with an elevated J-point in the inferior and/or antero-lateral leads. However, data regarding the prevalence of ERS in patients with iVF are scarce.

Purpose: The objectives of this study were to determine the occurrence of ERS in patients with the diagnosis of iVF, and to evaluate potential differences in outcome between ERS and iVF without early repolarization pattern (ERP).

Methods: Out of 2398 implantable cardioverter defibrillator (ICD) carriers, 510 sudden cardiac death survivors were retrospectively identified from the database of the Division of Cardiology of the Medical University of Vienna within the last three decades. ERP was classified either as “notching” or “slurring” of the J-point elevation in inferior and/or antero-lateral leads. Clinical endpoints were defined as appropriate ICD therapy, either anti-tachycardia pacing or shock, and all-cause mortality.

Results: After exclusion of recognized reasons for sudden cardiac death, 40 patients were assigned to the diagnosis of iVF (7.8%). An ERP was identified in 8 patients (1.6%), most of them with notching ($n = 6$). After a mean follow-up of 10.8 ± 6.9 years, appropriate ICD therapy for ventricular tachyarrhythmia was found in 3 patients with ERS and in 11 iVF patients without ERP (37.5% vs. 34.4%, $p = 0.868$). In ERS patients, all ICD therapies were related to the notching pattern. Similarly, no significant difference was found in inappropriate ICD therapies, concerning one ERS patient and 5 iVF patients (12.5% vs. 15.6%, $p = 0.825$). Finally, there was no difference in all-cause mortality between ERS and iVF (0% vs. 6.2%, $p = 0.468$).

Conclusions: In our cohort of 510 sudden cardiac death survivors, we found a low prevalence of both, iVF and ERS. Between these groups, no significant difference could be shown regarding all-cause mortality and appropriate ICD therapy for ventricular tachyarrhythmia.

5-6

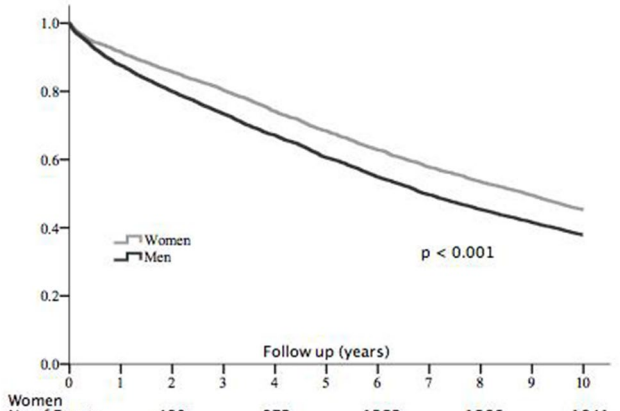
Morbidity and mortality in patients with pacemaker; a large-scale cohort study

M. Riesenhuber, J. Bergler-Klein, G. Maurer, F. Rauscha, H. Schmidinger, M. Andreas, M. Gyöngyösi

Abteilung für Kardiologie, Medizinische Universität Wien, Vienna, Austria

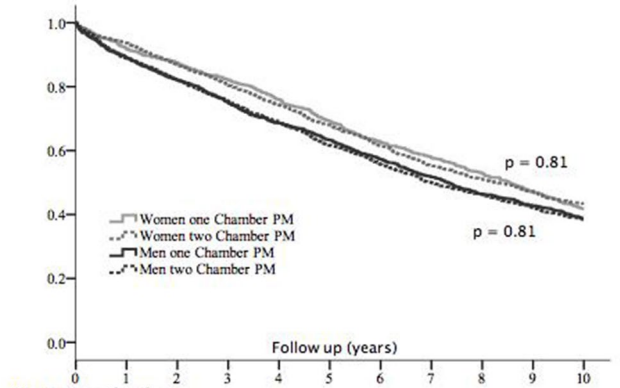
Background: According to previous analysis gender differences in mortality in patients with pacemaker might exist. The aim of our analysis was to evaluate the influence of gender, type of pacemaker and atherosclerotic comorbidities on the mortality of the patients with pacemaker (PM).

Methods: The pacemaker database (PMDB) of the Medical University of Vienna, Department of Cardiology, has been retrospectively analyzed. The database contained 11.449 patients visited the outpatients ward from Mai 2000 to April 2015 including the following parameters: sex, date of birth, first implantation date, type of implanted device. 90.4% of patients in PMDB could be matched with validated data from hospital’s information system to provide high quality survival data. Survival data were obtained from Statistik Austria including date and cause of death (ICD-code). The general clinic-wide patient database has been scanned for following comorbidities: diabetes, coronary



Women					
No of Events	480	872	1252	1566	1841
No of Cases	2884	2492	2112	1798	1523
Men					
No of Events	1003	1640	2251	2727	3101
No of Cases	3985	3348	2737	2261	1887

Fig. 1|P 5-6 Kaplan-Meier Plot of survival comparing all men ($n=4988$) and women ($n=3364$) with available mortality data in a 10 years follow up. Number of events and number of cases at 2, 4, 6, 8 and 10 years



Women one Chamber					
No of Events	89	170	264	333	411
No of Cases	617	536	442	373	295
Women two Chambers					
No of Events	133	256	384	486	561
No of Cases	859	736	608	506	431
Men one Chamber					
No of Events	194	340	461	579	661
No of Cases	884	738	617	499	417
Men two Chambers					
No of Events	283	487	697	845	967
No of Cases	1288	1084	874	726	604

Fig. 2|P 5-6 Kaplan-Meier Plot of survival comparing men ($n=2649$) with one/two chamber peacemakers and women ($n=1698$) with one/two chamber peacemakers in a 10 years follow up. Number of events and number of cases at 2, 4, 6, 8 and 10 years

artery disease (CAD), heart failure (HF). To provide high quality data only patients with at least one documented ICD-code in the clinic-wide patient information system were included (46.1% of men and 42.2% of women). Kaplan-Meier method for survival analysis and chi-square test for cause of death and comorbidities has been used.

Results: Ten years after pacemaker implantation 37.8% of men and 45.3% of women were alive ($p<0.001$) as shown in Fig. 1|5-6. Surprisingly, survival rates of patients with one or two chamber pacemakers did not show differences after 10 years follow up (Fig. 2|5-6). Analyzing cause of death showed significant higher rates of cardiovascular deaths for women compared with men (men 63.1%, women 65.7%, $p=0.03$). Men had significant higher rates of malign deaths (men 14.8%, women 10.8%, $p<0.001$). 854 men (27.3% of men) and 479 women (24.3% of women) had diabetes ($p=0.019$). 1609 men (51.4%) and 770 women (39.1%) had CAD ($p<0.001$). 1478 men (47.2%) and 671 women (34.1%) had HF ($p<0.001$). Diabetic patients with PM had lower survival rates compared with non-diabetic patients (diabetes 44.1%, no diabetes 51.3%, $p<0.001$). Male patients didn't show differences in mortality (men with diabetes 44.2%, men without diabetes 48.4%, $p=0.07$), whereas survival rates of female patients with diabetes decreases to levels of male patients with diabetes (women with diabetes 44.0%, women without diabetes 55.1%, $p<0.001$). CAD was associated with lower survival rates (CAD 43.9%, no CAD 53.8%, $p<0.001$). Gender subanalysis showed similar results (men with CAD 42.7%, men without CAD 52.2%, $p<0.001$; women with CAD 46.5%, women without CAD 55.9%, $p<0.001$). HF was related to decrease of survival rates (HF 41.4%, no HF 55.5%, $p<0.001$). Gender subanalysis showed similar results (men with HF 39.9%, men without HF 54.9%, $p<0.001$; women with HF 44.9%, women without HF 56.3%, $p<0.001$).

Conclusions: Male patients with pacemaker have lower survival rate as compared with women. Interestingly, we found no differences in survival rates comparing one and two chamber devices. Diabetes, CAD and HF influences survival of PM patients significantly.

5-7

The prognostic potential of natriuretic peptides on the development of post-operative atrial fibrillation after elective cardiac surgery

P. Sulzgruber, M. Steininger, A. Pilz, A. Goldschmied, N. Kazem, R. Marculescu, T. Fleck, B. Steinlechner, L. Koller, G. Goliasch, J. Wojta, A. Niessner

Universitätsklinik für Innere Medizin II, Medizinische Universität Wien, Vienna, Austria

Background: Post-Operative Atrial Fibrillation (POAF) represents a common complication after cardiac valve and/or coronary artery bypass graft surgery associated with major cardiac adverse events and poor patient-outcome. Despite its frequent incidence in clinical practice, data on its pathophysiological etiology remain inconclusive, but seem of utmost importance for risk prediction and secondary prevention. While the natriuretic peptides BNP (brain-natriuretic peptide) and ANP (atrial-natriuretic peptide) represent valid marker mirroring cardiac function and strain, its prognostic potential on the development of POAF has not been investigated so far. Therefore, we aimed to determine the association of the natriuretic peptides ANP and BNP on the development of POAF.

Methods: We prospectively enrolled 270 patients undergoing elective cardiac valve and/or coronary artery bypass surgery. Patients had to be free of any type of atrial fibrillation at the time of study-enrolment. Preoperative blood samples were assessed to elucidate MR-proANP values via an automated immunofluorescent assay. NT-proBNP was routinely measured at the time of hospital admission and assessed via the patients' digital medical records. Patients were followed prospectively via continuous electrocardiogram leads for 9 days after the surgical intervention and screened for the development of POAF. Binary regression analysis were performed to investigate the association of natriuretic peptides on the development of POAF.

Results: We found that a total of 116 individuals (43.4%) developed POAF within our observation period. Median concentration of MR-proANP was 123.6 pmol/l (IQR: 78.5–211.9) and for NT-proBNP 481.50 pg/ml (IQR: 184.8–1631.0) respectively. MR-proANP was significantly associated with the development of POAF with a crude odds ratio (OR) per one standard deviation (1-SD) of 1.81 (95%CI 1.32–2.47; $p<0.001$). Even after adjustment for potential confounders MR-proANP remained a strong and independent predictor for the development of POAF with an adjusted OR per 1-SD of 1.58 (95%CI 1.05–2.39; $p=0.03$), while the predictive potential of NT-proBNP was lost with an adj. OR per 1-SD of 1.21 (95%CI 0.96–1.52; $p=0.097$).

Conclusions: We found that MR-proANP proved to be a strong and independent predictor for the development of POAF even showing superiority to NT-proBNP as a well-established marker. The benefit of a standardized preoperative evaluation of MR-proANP values that might help to identify patients at risk for POAF, needs to be elucidated in further studies.

Postersitzung 6 – Basic Science 2

6-1

Aneurysms of the ascending aorta are associated with Telomere shortening

A. Panzenböck, J. Hüblauer, P. Werner, A. Kocher, C. Mannhalter, S. Shabanian, M. Ehrlich, M. Andreas, I. Lang

Department of Cardiology, Department of Surgery, Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Vienna, Vienna, Austria

Background: Patients with aneurysms of the ascending aorta are at risk for severe adverse events including aortic rupture. Mechanisms for disease progression are still unknown in the majority of patients, but genetic disorders are likely involved.

Methods: 271 patients with aneurysms of the ascending aorta were compared to healthy controls ($n=31$). Other forms of aneurysms or known gene defects (e. g. Marfan syndrome) were excluded. DNA was isolated from ascending aorta aneurysms and healthy aortic walls and telomere length was determined by real-time PCR. Statistical analyses were carried out in SPSS 21.0.

Results: Aneurysm patients were younger (53 ± 21 vs. 60 ± 14 years years; $p=0.031$), and more likely female (35% vs. 16%; $p=0.059$). Patients with aortic aneurysms of any kind hat significantly shorter telomeres than healthy controls (-0.88 ± 1.72 vs. 0.00 ± 1.11; $p=0.006$). In a logistic regression analysis including telomere length and age, telomere length was found as a significant predictor of ascending aorta aneurysm. No difference in telomere length were observed in ascending aortic aneurysm associated with tricuspid ($n=40$) or bicuspid aortic valve stenoses ($n=49$; $p=0.637$).

Conclusions: We report an age independent shortening of telomeres in patients with aneurysms of the ascending aorta. This might be due to increased cellular turnover in the aortic wall of patients developing aneurysms. Further trials are required to study the underlying pathologic mechanisms related to this observation.

6-2

Angiotensin-II boosts neutrophil extracellular trap formation in an AT1R and NADPH oxidase-dependent manner

T. Hofbauer, A. Mangold, T. Scherz, N. Staier, J. Müller, H. Heidari, I. M. Lang

Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Arterial hypertension is a major risk factor for coronary artery disease (CAD). By formation of neutrophil extracellular traps (NETs), neutrophils release their nuclear content into the extracellular space, in order to combat pathogens. We recently observed a positive correlation between blood pressure and NETosis ex vivo in CAD patients, implicating that blood pressure modulates NETosis. Angiotensin-II (Ang-II) is an important mediator of arterial hypertension via its potent vasoconstrictive properties, but also exerts pro-inflammatory functions via the angiotensin type 1 receptor (AT1R). AT1R is expressed on neutrophils. We thus hypothesized that Ang-II might influence NETosis.

Methods: We measured ex vivo NETosis of isolated neutrophils upon stimulation with ionomycin using Sytox® Green Nucleic Acid Stain, a dye exclusively staining extracellular DNA released from cells with disrupted membranes, which is a hallmark feature of NETosis. Extent of NETosis was computed as percentage of positive Triton control.

Results: In line with previous literature, ionomycin induced NETosis in a dose-dependent manner. After pre-treatment with Ang-II, NETosis was significantly enhanced to 80–90% of positive control, irrespective of ionomycin concentration. The AT1R antagonist losartan abolished the effect of Ang-II on NETosis, suggesting an AT1R-dependent pathway. Since Ang-II induces intracellular ROS formation in neutrophils via activation of NADPH oxidase, we pre-treated neutrophils with the NADPH oxidase inhibitor diphenyleneiodonium (DPI). DPI antagonized the effect of Ang-II on NETosis.

Conclusions: Our results implicate that via Ang-II, arterial hypertension increases the propensity of neutrophils to undergo NETosis by increasing intracellular ROS production, which in turn makes neutrophils more susceptible to a second hit. This provides new insight in how effective blood pressure lowering might lead to more favorable outcome in CAD.

6-3

B cells in thrombus resolution and chronic thromboembolic pulmonary hypertension

J. Altmann, A. Alimohammadi, S. Sharma, V. Seidl, T. Saito, M. Rabinovitch, I. Lang

Innere Medizin II/Kardiologie, Medizinische Universität Wien Stanford University, Stanford, USA

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare consequence of venous thromboembolism. Mechanisms underlying thrombus persistence are unclear. Since splenectomy is a risk factor for CTEPH and the spleen is important for B cell maturation, we investigated the role of B cells in venous thrombus resolution and in CTEPH.

Methods: We studied thrombus resolution in a mouse model of venous thrombosis. We splenectomized female Balb/c

mice and after 4 weeks subjected them to partial ligation of the inferior vena cava to induce the formation of a thrombus. After the surgery, we injected isolated splenic B cells intraperitoneally, a control group received PBS. We monitored thrombus resolution over a period of 28 days using the Vevo 2100 high-frequency ultrasound system.

In addition, we analyzed peripheral B cells of 9 CTEPH patients by mass cytometry and compared them with cells from 9 idiopathic pulmonary arterial hypertension (IPAH) patients and 11 healthy control subjects. We stained peripheral blood mononuclear cells (PBMCs) with a panel of metal-conjugated antibodies recognizing 21 surface antigens to define different B cell subsets. These extracellular markers were combined with two different sets of antibodies detecting intracellular targets, analyzing phosphosignaling as well as cytokine production both at baseline and after cell stimulation. Data was collected on a CyTOF2 mass cytometer.

Results: In our mouse model, treating splenectomized mice with a single injection of purified splenic B cells after IVC ligation resulted in significantly reduced thrombus size at day 1 and day 3 after thrombus induction, while we observed no effect in the later course of thrombus resolution.

Mass cytometry of CTEPH, IPAH and control PBMCs revealed a decrease in total B cell numbers in CTEPH compared to IPAH and controls. Importantly, this decrease did not affect the subpopulation of B1 cells, resulting in an increase of B1 cell frequency relative to total B cells in CTEPH. Interestingly, CTEPH B cells shared functional characteristics with IPAH B cells, with increased production of inflammatory cytokines (IL-6, TNF) and increased phosphorylation of Stat1 at baseline.

Conclusions: Our data suggest an important role for B lymphocytes in venous thrombus resolution. Injection of B cells promoted resolution in a mouse model of venous thrombosis, and individuals with CTEPH, a model disease for thrombus non-resolution, were characterized by decreased number of circulating B cells. Interestingly, B cells of CTEPH patients, despite being reduced in number, had an activated phenotype similar to IPAH B cells, which may reflect spontaneous germinal center formation and increased (auto-) antibody production. Further studies will be necessary to better describe the role of B cells in CTEPH and to discern changes in B cell function related to thrombus persistence from those related to pulmonary hypertension.

6-4

Development of a fast and easy assay to determine DNase activity in plasma samples

A. Ondracek, T. Hofbauer, A. Mangold, I. M. Lang

Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Activated neutrophils are able to release their chromatin contents from the nucleus into extracellular space forming net-like structures. Although neutrophil extracellular trap (NET) formation is effectively counterbalanced by the endonuclease deoxyribonuclease I (DNase) under steady state conditions, their pro-inflammatory, cytotoxic, and pro-thrombotic effects represent important risk factors for acute coronary syndrome (ACS). Previous results of our group exhibited a correlation between increased DNase activity and increased ST segment resolution as well as smaller infarct size.

Due to the fact that commercially available products have been removed from the market and several published methods proved to be irreproducible, we aimed to establish a cost-efficient assay to accurately quantify DNase in coronary and periphery blood samples of ACS patients.

Methods: We explored several approaches to indirectly determine DNase activity by providing a DNA substrate that is degraded relative to DNase content of the added sample. Digestion was carried out in different buffers or when DNA was coated to a solid phase at 37 °C. Remaining DNA was inversely proportional to DNase activity and measured using methyl-green or fluorescent dyes after different time intervals. DNase concentration could be calculated by including a standard curve in each setup.

Results: Although standards exhibited concentration dependent degradation of DNA substrate independent of the approach, kinetic measurements revealed that high plasma concentrations did not only interfere with binding of dyes but degrading behavior was not comparable to standards. To reduce plasma derived contaminants, samples were serially diluted and added to DNA captured to wells instead of aiming for degradation in solution.

The final assay protocol allows quantification of DNase within range of 0.3125 to 10 ng/ml in 5 mM $MgCl^2$. DNA is coated overnight to 96 well immunoplates at 4 °C. Plates are washed before incubation of standards and plasma samples (1:10 in 5 mM $MgCl^2$) at 37 °C. Wells are emptied and washed before staining residual DNA with SYBR Green, and measured at an excitation and emission wavelength of 490 and 520 nm.

Conclusions: We have established a reliable and cost-efficient assay for quantification of DNase in plasma samples which allows to further study the role of DNase in cardiovascular disease.

6-5

Gene expression profiling of trigger induced early cardiac remodeling

N. Djalinac, J. Katzbeck, M. Calineata, E, Kolesnik, H. Mächler, D. von Lewinski, E. Bisping

Medical University of Graz, Graz, Austria

Background: Early cardiac remodeling triggers – tachycardia (TC) and stretch (ST) both induce hypertrophy in neonatal rat ventricular cardiomyocytes (NRVCM) on the cellular level while ST stimulation leads to upregulation of mRNA levels of pro-hypertrophic genes, as we showed previously. With a new gene expression dataset for TC we aimed to investigate the similarities and differences between the triggers in NRVCM as well as to translate these findings into specimens deriving from human patients.

Methods: Primary NRVCM were isolated from 2–3 day old Wistar rats and stretched for 24 hours by a Flexcell culture tension system versus control or stimulated to tachycardia for 24 hours by an EP cell stimulator versus control. Human atrial trabeculae (HA) were isolated from right atrial appendages obtained from patients undergoing cardiac surgery, mounted on hooks, and kept in an oxygenated organ bath setup for 6 hours under trigger specific conditions: HA stretched to maximal physiological length (Lmax) in comparison to non-stretched HA (slack length) or 2.5 Hz stimulation rate (tachycardia) in comparison to 1 Hz stimulation rate (physiological rate). Gene expression was performed by real-time PCR using SYBR green. In addition RNA microarray hybridizations are currently in progress.

Results: Time dependent gene expression profiling of NRVCM previously done for stretch stimulation revealed a 24

hour gene expression peak which was compared to the 24 hour gene expression time point during tachycardia stimulation for the selected pro-hypertrophic marker gene candidates. Both TC and ST show significant upregulation for the natriuretic peptides NppA (2.06-fold ± 0.25, $P=0.0017$, $n=4$ in TC and 1.78-fold ± 0.17, $P<0.001$, $n=21$ in ST) and NppB (5.22-fold ± 0.22, $P<0.001$, $n=4$ in TC and 1.66-fold ± 0.21, $p=0.005$, $n=26$ in ST) while no upregulation is seen in case of RCAN1. ACTA1 shows moderate upregulation in TC (1.28-fold ± 0.10, $n=13$) while it is significantly upregulated in ST (2.47-fold ± 0.18, $P<0.001$, $n=21$). FHL1 shows no trend towards upregulation in case of TC but is significantly upregulated in ST (1.76-fold ± 0.09, $P<0.001$, $n=26$). The selected marker gene candidates were further evaluated in HA with a gene expression peak seen at a 6 hour time point. NppA and NppB show no obvious trend towards upregulation neither for TC nor for ST while ACTA1 is significantly upregulated for both TC: ACTA1 (2.12-fold ± 0.43, $P=0.04$, $n=19$) and ST: ACTA1 (2.82-fold ± 0.56, $P<0.001$, $n=12$). In addition FHL1 and RCAN1 show a strong trend towards upregulation in TC: FHL1 (1.59-fold ± 0.53, $P=0.40$, $n=11$), RCAN1 (1.99-fold ± 0.60, $P=0.17$, $n=11$) as well as in ST: FHL (2.02-fold ± 0.38, $P=0.14$, $n=11$), RCAN1 (1.61-fold ± 0.35, $P=0.18$, $n=11$).

Conclusions: Current results indicate upregulation of natriuretic peptides as common between tachycardia and stretch but not consistent in human myocardium. However, ACTA1 is clearly identified as a marker gene for the common trunk of the remodelling process induced by both triggers and in both: Animal cells and human myocardium. The currently generated microarray dataset will be presented in detail and will more clearly elucidate the similarities and differences between tachycardia and stretch and encourage further molecular signalling pathway characterisation.

6-6

Interactions of polysialic acid and heparane sulfate with histones modulate degradation of neutrophil extracellular traps

N. Staier, T. Hofbauer, T. Scherz, H. Heidari, J. Müller, A. Mangold, I. Lang

Cardiology, Medical University of Vienna, Vienna, Austria

Background: Formation of neutrophil extracellular traps (NETs), an effector mechanism of polymorphonuclear cells (PMNs), promotes thrombosis. Degradation of NETs is predominantly mediated by DNase 1. Impaired NET degradation is related to cardiovascular events and increased myocardial infarct size. Mechanisms influencing NET degradation are poorly understood. Efficient DNA cleavage by DNase is dependent on accessibility of the DNA strands, which is limited by the histone-DNA conjunction. Polysialic acid (PSA) reduces NET-mediated cytotoxicity via interaction with linker histone H1. Heparane sulfate binds histone H2 through ionic interactions. We assessed the effect of PSA and heparane sulfate on NET degradation by DNase 1 utilizing our in-house built NET degradation assay.

Methods: PMNs were stimulated with PMA to generate NETs in 48-well culture plates. DNase 1 and respective reagents were added. After degradation of NETs and release of double-stranded DNA (dsDNA) fragments, supernatants were transferred to a 96-well plate and measured utilizing PicoGreen, a fluorescent nucleic acid stain. Lambda DNA served as a positive control and dsDNA levels were measured on a luminescence reader.

Results: PSA decreased NET degradation in a dose-dependent manner (Fig. 2|6-6). In the presence of heparane sulfate, NET degradation by DNase 1 was significantly enhanced.

Conclusion: DNase capacity to degrade NETs is highly dependent und inhibitory and promoting co-factors (Fig. 1|6-6). Identification of such factors will be useful to evaluate DNase as a potential therapeutic in diseases related to NETs.

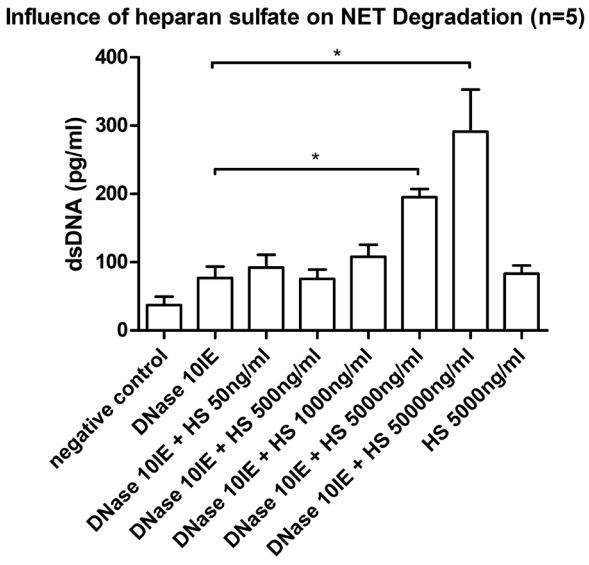


Fig. 1 | 6-6

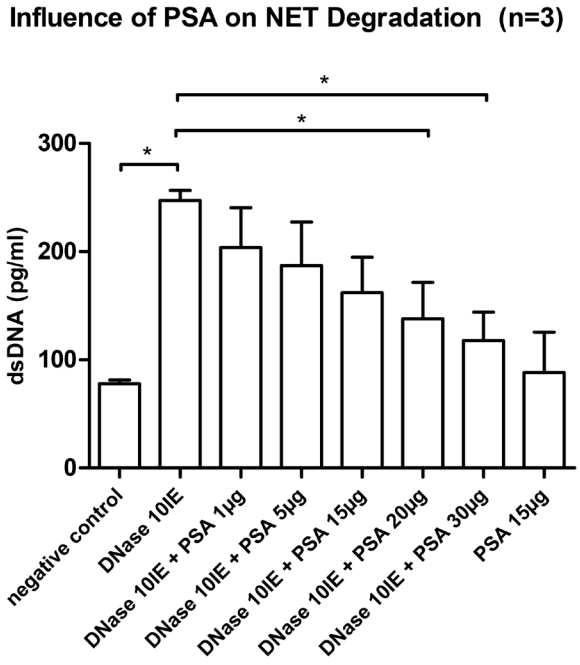


Fig. 2 | 6-6

6-7

Natural autophagy-inducer spermidine protects against cardiac aging

M. Abdellatif, T. Eisenberg, A. Schmidt, J. Schipke, T. Pendl, C. Magnes, W. Linke, J. Sadoshima, C. Muehlfeld, S. Kiechl, G. Kroemer, F. Madeo, S. Sedej

Department of Cardiology, Medical University Graz, Graz, Austria
Institute of Molecular Biosciences, NAWI Graz, University Graz, Graz, Austria
Institute of Functional and Applied Anatomy, Hannover Medical School, Hannover, Germany
Joanneum Research Forschungsgesellschaft m. b. H., HEALTH, Institute for Biomedicine and Health Sciences, Graz, Graz, Austria
Department of Cardiovascular Physiology, Ruhr University Bochum, Bochum, Germany
Department of Cell Biology and Molecular Medicine, Rutgers-New Jersey Medical School, Newark, USA
Department of Neurology, Medical University Innsbruck, Innsbruck, Austria

Background: Aging is associated with increased risk of cardiovascular disease and death. Autophagy is a major cellular repair process that promotes structural and functional homeostasis, and declines with age. Here, we tested if dietary supplementation of the natural autophagy-inducer spermidine protects against cardiac aging.

Methods: Polyamine spermidine (3 mmol/L) was supplemented in the drinking water of pre-aged (18 months) C57BL/6 wild-type male mice for 5 months. A comprehensive in vivo and in vitro cardiac characterization was performed using echocardiography, invasive hemodynamics, confocal and electron microscopy, immunoblotting, high-resolution respirometry, and ultrastructural analysis of cardiomyocytes by design-based stereology. Another subset of C57BL/6 mice was followed up for lifespan estimation and survival analysis. Cardiomyocyte-specific autophagy-deficient male mice (Atg5 fl/fl/MLC2aCre+, 4-month-old) that were fed spermidine for 3 months were employed to test whether the effects of spermidine are autophagy-dependent. To evaluate the clinical applicability and translational potential of the animal data, we carried out a study, in which dietary spermidine intake (based on food questionnaires) was correlated to cardiovascular disease incidence in humans (Bruneck Study).

Results: Dietary spermidine supplementation extended median lifespan (~10%) and exerted cardioprotective effects through reduction of cardiac hypertrophy and preservation of diastolic function in old mice. Spermidine-fed mice showed enhanced cardiac autophagy, mitophagy, mitochondrial respiration and mechano-elastical properties of cardiomyocytes in vivo, coinciding with increased titin phosphorylation and suppressed subclinical inflammation. Age-related effects on subcellular cardiomyocyte composition were reversed by spermidine, as reflected by increased relative mitochondrial and myofibrillar volumes and a reduced (organelle-free) sarcoplasmic volume. Spermidine failed to promote cardioprotection in mice with autophagy-deficient cardiomyocytes. In humans, higher spermidine intake was correlated with lower blood pressure and reduced risk of heart failure and cardiovascular disease in general (a composite of acute coronary artery disease, stroke and vascular death).

Conclusions: Our results suggest high dietary intake of spermidine as a novel and feasible strategy against aging-associated cardiovascular disease.

Postersitzung 7 – Bildgebung 1

7-1

Acute myocarditis is accompanied by a reversible impaired coronary flow reserve

J. Kellermair, D. Kiblböck, C. Reiter, T. Lambert, J. Kammler, C. Steinwender

Interne II, Klinikum Wels, Wels, Austria
Kepler Universitätsklinikum, Linz, Austria

Background: In the present study we aimed to evaluate echocardiographical coronary flow reserve (CFR) in patients with acute myocarditis which has not been described in literature before. CFR is a non-invasive technique to evaluate the functionality of cardiac microvasculature and is defined as the ratio between coronary blood flow corresponding to flow autoregulation plateau at rest and after maximal vasodilatation with adenosine. We assumed that CFR is reduced in the setting of acute myocarditis due to an inflammation-induced endothelial dysfunction and will return to normal values after complete myocardial recovery.

Methods: Patients with confirmed diagnosis of acute myocarditis by cardiac magnetic resonance imaging (CMR) were enrolled after exclusion of significant coronary artery disease via invasive coronary angiography or computed tomography coronary angiography. CFR was echocardiographically assessed by color-doppler guided PW doppler of the mid to distal segment of the left anterior descending artery. Peak diastolic flow velocity at rest (PDV1) and after 90 seconds of adenosine infusion (140 µg/kg/min; PDV2) was measured. After 3 months CFR (defined as PDV2/PDV1) was re-evaluated.

Results: Patients ($n=7$) with acute myocarditis had a mean age of 31 ± 18 years and presented with elevated baseline levels of troponin T (TnT) levels of 0.42 ± 0.3 ng/mL (normal: <0.014 ng/mL), creatine-kinase (CK) of 254 ± 112 U/L (normal: <190 U/L), proBNP levels of 620 ± 469 pg/mL (normal: <70 pg/mL) and c-reactive protein (CRP) levels of 5.4 ± 3.4 mg/dL (normal: <0.5 mg/dL). All patients showed typical T2-weighted oedema and late enhancement on CMR with a systolic ejection fraction ranging from 44% to 65%. Echocardiographical baseline PDV1 at rest showed a mean velocity of 54 ± 12 cm/s and a mean baseline PDV2 of 75 ± 28 cm/sec after adenosine infusion.

At follow up after 3 months, all patients showed normal levels of TnT, CK, proBNP and CRP indicating complete disease recovery. Follow-up PDV1 at rest showed a mean velocity of 53 ± 8 cm/s while follow-up PDV2 showed markedly higher mean velocities of 107 ± 21 cm/s. CFR (PDV2/PDV1; normal: ≥2.0) revealed a decreased mean ratio at baseline (1.3 ± 0.5) and a normal mean ratio at follow up (2.1 ± 0.1) [$p=0.0013$].

Conclusions: Patients with acute myocarditis showed a reversible CFR impairment suggesting reversible dysfunction of the cardiac microvasculature.

7-2

Biventricular thrombus formation in ischemic cardiomyopathy and non-compact left ventricular myocardium

C. Reiter, D. Kiblböck, C. Sautner, P. Schmit, T. Lukas, C. Steinwender

Klinik für Interne 1 – Kardiologie und internistische Intensivmedizin, Kepler Universitätsklinikum Linz, Linz, Austria
Zentrales Radiologieinstitut, Kepler Universitätsklinikum Linz, Linz, Austria

A 49-year-old male patient was referred to our department for further cardiac evaluation due to a newly diagnosed cardiomyopathy as well as two suspected intraventricular cardiac masses.

The patient was primarily admitted to the neurologic department of a cooperating hospital, because of recently developed persisting motoric aphasia. Furthermore the patient had experienced a transitory ischemic attack with left sided hemiparesis and hypaesthesia three days before admission. In addition, he complained about exertional dyspnea. Prior to this, the adipose patient didn't take any medication although his medical history included a metabolic syndrome with arterial hypertension, hypercholesterinemia and hepatic steatosis as well as chronic nicotine abuse.

Cerebral CT and MRI scans revealed subacute stroke of the anterior cerebral artery as well as several old lacunar defects in the left suprainsular, the right frontal and right parietal region. Carotid duplex sonography showed bilateral plaques without any hemodynamically significant stenoses. Heart rhythm monitoring at the stroke unit revealed several episodes of non-sustained ventricular tachycardia, but no atrial fibrillation.

For further cardiac evaluation, transthoracic and transesophageal echocardiography were performed, which displayed cardiomyopathy with dilatation as well as severe reduction of contractility of both ventricles. Furthermore, two cardiac masses were suspected to be present, one in the left ventricular apex and one in the subvalvular region of the right ventricle.

After referral to our cardiologic department, a cardiac MRI scan was performed (Fig. 1|7-2), which confirmed dilatation of both ventricles with a left ventricular ejection fraction of 20% as well as a right ventricular ejection fraction of 18%. Late gadolinium enhancement revealed ischemic cardiomyopathy in the presence of a transmural inferior myocardial infarction with a scar reaching from the basal to distal posterolateral to inferoseptal region of the left ventricle as well as the inferior region of the right ventricle.

Remarkably, a spherical non-enhancing formation with a diameter of two centimeters was present adjacent to the scar in the right ventricle, as well as another similar formation with a diameter of just a few millimeters in the apex of the left ventricle – both morphologically consistent with thrombus formation. In the area of the left ventricular apical thrombus, non-compact myocardium reaching from the apex to the lateral wall could also be depicted.

Correlating to these findings, coronary angiography showed a chronic occlusion of the right coronary artery. Due to the transmural extent of the scar, as seen in the cardiac MRI scan, we refrained from revascularization. Medical heart failure therapy with an ACE-inhibitor as well as a beta blocker was prescribed in addition to a statin and oral anticoagulation. The indication for ICD-implantation will be reevaluated after three months of optimal medical therapy.

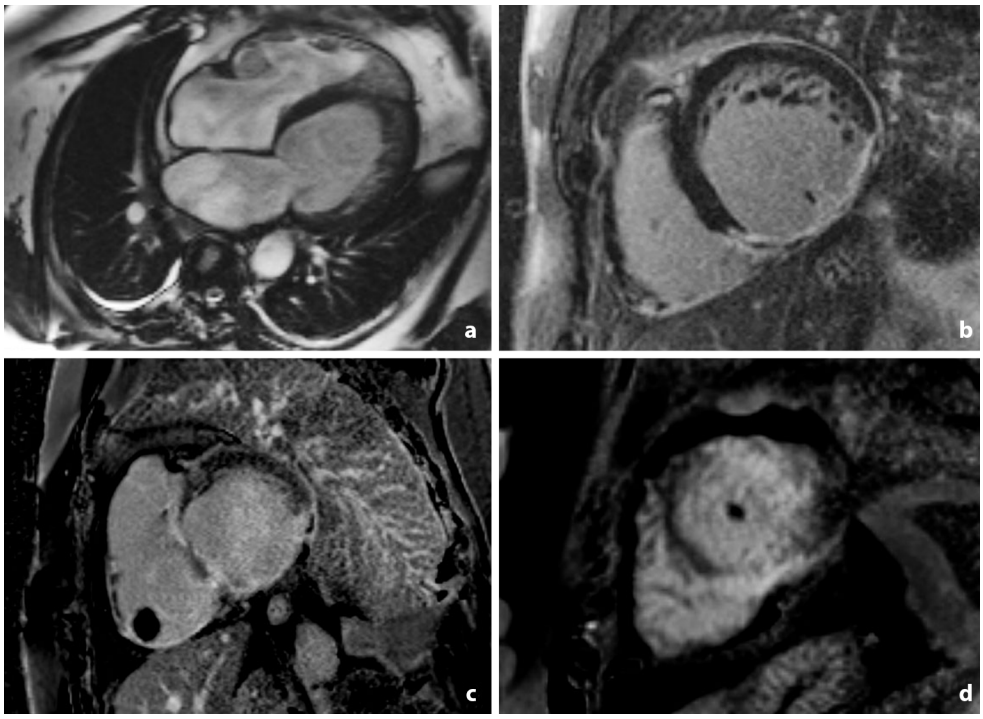


Fig. 1|P 7-2

7-3

Dabigatran added to dual antiplatelet therapy to treat a left ventricular thrombus in a patient with high bleeding risk

M. Noflatscher, N. Moes, E.-M. Gassner, P. Marschang

Innere Medizin III (Kardiologie/Angiologie), Medizinische Universität Innsbruck, Innsbruck, Austria
Radiologie), Medizinische Universität Innsbruck, Innsbruck, Austria

Background: A left ventricular (LV) thrombus is detected in approximately 5–10% of patients after myocardial infarction (MI). When untreated, these LV thrombi carry a significant risk of complications including embolic stroke. According to current guidelines, anticoagulation with vitamin K antagonists is indicated to treat a LV thrombus.

Case report: An 87 year old patient was referred to our department with non-ST-elevation MI. Five months before, he had been diagnosed with a subacute ST elevation MI, which had been treated conservatively. Recently, a rectal neoplasia had been diagnosed, but not operated yet. The patient underwent coronary angiography with implantation of two drug eluting stents (Cre8) requiring dual antiplatelet therapy. During ventriculography, apical and septal akinesia with an apical LV thrombus of 16 mm diameter was detected. Due to the high bleeding risk in this patient, vitamin K antagonist therapy with potentially fluctuating INR values was considered unsuitable. Therefore, dabigatran at a dose of 110 mg bid was chosen as anticoagulation therapy. After 4 weeks, cardiac computed tomography was performed, which failed to detect a LV thrombus. Notably, triple therapy with dabigatran, clopidogrel and aspirin was well tolerated without evidence for overt bleeding. The surgical resection of the rectal neoplasm was performed 2 months later without bleeding complications.

Conclusions: Anticoagulation is effective in patients with MI and a LV thrombus in reducing the risk of embolization and in dissolving the thrombus. Our case is complex due to the required triple therapy, old age and significant bleeding risk because of the rectal neoplasia of our patient. Although only few reports are available for the use of non-vitamin K antagonist oral anticoagulants (NOAC) in this indication, we chose dabigatran at a dose of 110 mg bid added to dual antiplatelet therapy for our patient. Besides the advantage of a predictable pharmacokinetic profile of NOAC in contrast to vitamin K antagonists, the effect of dabigatran can rapidly be reversed by idaruzicumab in the case of severe bleeding. Physicians should carefully weigh the risk of thromboembolic events versus the risk of bleeding when combining antiplatelet with anticoagulation therapy.

7-4

Left ventricular myocardial strain in assessing myocardial viability: comparison between two and three dimensional speckle tracking echocardiography

Hong Ran, Ping-Yang Zhang, You-Xiang Zhang, Jian-Xin Zhang, Wen-Fang Wu, Jing Dong, Xiao-Wu Ma

Department of Echocardiography, Nanjing First Hospital Affiliated to Nanjing Medical University, Nanjing, China

Background: To investigate whether three dimensional speckle tracking (3D-STE) imaging could provide a feasible way to assess myocardial viability in patients who got myocardial infarction (MI) which is better than two dimensional speckle tracking (2D-STE) imaging.

Methods: All of the MI patients underwent routine echocardiography, 2D-STE and 3D-STE examinations, and then were given radionuclide myocardial perfusion/metabolic imaging that was served as the "gold standard" to define the viable and nonviable myocardium.

Results: The 3D-STE and 2D-STE indexes of Rs, Ls and Cs did not correlate well (r: 0.67, 0.51 and 0.22), indicating that these 2 techniques were not interchangeable. Additionally, the strain data were highly reproducible based on the intra-observer and inter-observer variabilities. There were no significant differences in radial peak-systolic strain (Rs), longitudinal peak-systolic strain (Ls) and circumferential peak-systolic strain (Cs) by 2D-STE between viable versus nonviable groups. Meanwhile, there was no significant difference in Cs between two groups with 3D-STE. Rs and Ls in the nonviable from 3D-STE were much lower than those in the viable. Moreover, 3D strain and area strain decreased significantly in the nonviable segments than viable ones.

Conclusions: 3D-STE might serve as a marker of residual myocardial viability in MI patients, which is more feasibly than 2D-STE for detecting viable myocardium.

7-5

Morphologic analysis of artifacts of leadless pacemaker systems in cardiac magnetic resonance imaging (MRI)

C. Edlinger, M. Granitz, V. Paar, C. Jung, A. Pfeil, S. Eder, B. Wernly, J. Kammler, K. Hergan, U. Hoppe, C. Steinwender, M. Lichtenauer, A. Kypta

Christian Doppler Labor für Diagnose und Regeneration von Herz- und Thoraxerkrankungen, Jena, Germany
Universitätsklinik für Innere Medizin II, Kardiologie, Paracelsus Medizinische Universität Salzburg, Salzburg, Austria
Universitätsklink für Radiologie, Paracelsus Medizinische Universität Salzburg, Salzburg, Austria
Abteilung für Kardiologie, Pneumologie & Angiologie, Universitätsklinikum Düsseldorf, Dusseldorf, Germany
Klinik für Innere Medizin III, Friedrich Schiller Universität Jena, Jena, Germany
Klinik für Interne Medizin 1 – Schwerpunkt Kardiologie und internistische Intensivmedizin, Johannes Kepler Universität Linz, Linz, Austria

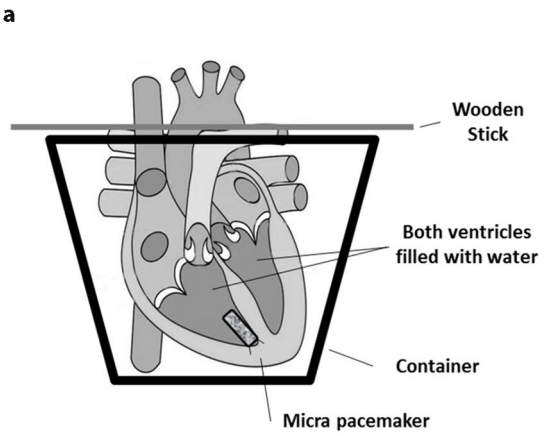


Fig. 1|P 7-5

Background: Leadless pacemaker systems are an important upcoming device in clinical rhythmology. Currently two different products are available with the Micra system being the most used in the clinical setting to this date. The possibility to perform magnetic resonance imaging (MRI) is an important feature of modern pacemaker devices.

Purpose: Even though the Micra system is suitable for MRI, little is yet know on its impact on artefacts within the images. The aim of our ex vivo study was to perform cardiac MRI to quantify the appearing artefacts in size and to evaluate if artefacts limit/prohibit the assessment of the surrounding myocardium.

Methods: Being the most common model of the human heart, pig hearts were chosen as a model for our study. Fifteen pig hearts were purchased from a local slaughterhouse and delivered to our laboratory within two hours after slaughter. Functional, previously implanted, devices were kindly provided by the University Hospital of Linz, all of them were primarily in clinical use and explanted after non-pacemaker associated death of the patients. After a brief visual check on obvious signs of myocardial injuries, ex vivo implantation of the leadless pacemaker was performed by the use of the original implantation tool. In a second step, hearts were filled with saline to simulate intracardiac fluid and fixed to wooden sticks upon a plastic container by using the big vessels (as shown in Fig. 1|7-5a). Lung parenchyma was simulated by ambient air. Three separate sessions were held to examine the model at 1.5 and further more at 3 Tesla. In addition, conventional X-rays and a CT scans were performed.

Results: Correct implantation of the device could be performed in all hearts. Orthotopic placement in the apico-septal region of the right ventricle could be documented in a conventional x-ray. A characteristic shamrock shaped artifact was generated (see Fig. 1|7-5b).

The occurring artifact was larger at 3 Tesla (17.1% in long axis and 25.2% in short axis, expressed as % of total myocardial area) than compared to images obtained at 1.5 Tesla (14.8% in long axis and 17.8% in short axis).

A similar result was found for the scar-sequence. The late enhancement (scar-) sequences were only slightly more prone to artifacts at 3.0 Tesla, leaving the right ventricle and the septum affected by a bright, hyperintense perifocal rim (12.4% and 12.1% at 1.5 Tesla vs. 11.9% and 14.9% at 3.0 Tesla). However, a large proportion of the left ventricular myocardium still remained accessible for image analysis. In almost all MRI-sequences, assessment of the right ventricle and the septal region surrounding the pacemaker device was limited by artefacts, while the rest of the myocardium remained evaluable for common radiologic diagnostics.

Conclusions: The use of the Micra system in cardiac MRI appeared to be feasible. We observed that performing the most common sequences in Micra patients is possible, even though the right ventricle and the surrounding septal region might be overshadowed by occurring artifacts. In our opinion, the most important clinical MRI evaluations (the detection of major ischemic areas or inflammatory processes) will still be possible in Micra patients. We suggest the use of 1.5 Tesla MRI will be the preferred method in clinical practice.

7-6

Reliability of echocardiographic speckle-tracking derived bi-atrial strain assessment under different hemodynamic conditions

M. Sareban, T. Perz, F. Macholz, B. Reich, P. Schmidt, S. Fried, H. Mairbäurl, M. Berger, J. Niebauer

Institut für Sportmedizin, Paracelsus Medizinische Privatuniversität Salzburg, Salzburg, Austria
Universitätsklinik Heidelberg, Heidelberg, Germany

Background: Atrial strain obtained by two-dimensional (2D) speckle-tracking echocardiography (STE) is a promising tool for the assessment of atrial function. Of concern, however, is the lack of robust data on intra- and inter-observer variability. Therefore, we set out to evaluate the reliability of left (LA) and right atrial (RA) strain indices in a healthy group of individuals at low altitude and after rapid ascent to high altitude in order to provoke increased systemic and pulmonary artery pressure seen in various cardiac diseases in which atrial function assessment plays an important role.

Methods: Twenty healthy subjects of a high altitude study were randomly assigned to 2D echocardiography with optimized image adjustment of both atria. Data were acquired during a baseline examination at low altitude (424 m) as well as 7, 20 and 44 h after arrival at high altitude (4559 m). Atrial strain indices (i. e. reservoir, conduit and contractile strain) were determined off-line by two independent observers using commercial software (Philips QLAB). Intra- and inter-observer reproducibility of variables was assessed by intra-class correlation coefficients (ICCs), coefficients of variation (CVs), coefficients of repeatibilty (CRs) and Bland Altman plots.

Results: Heart rate, systemic blood pressure and pulmonary artery pressure increased significantly from low-altitude to the first examination at high-altitude but did not change thereafter. RA maximal volume increased significantly from low-

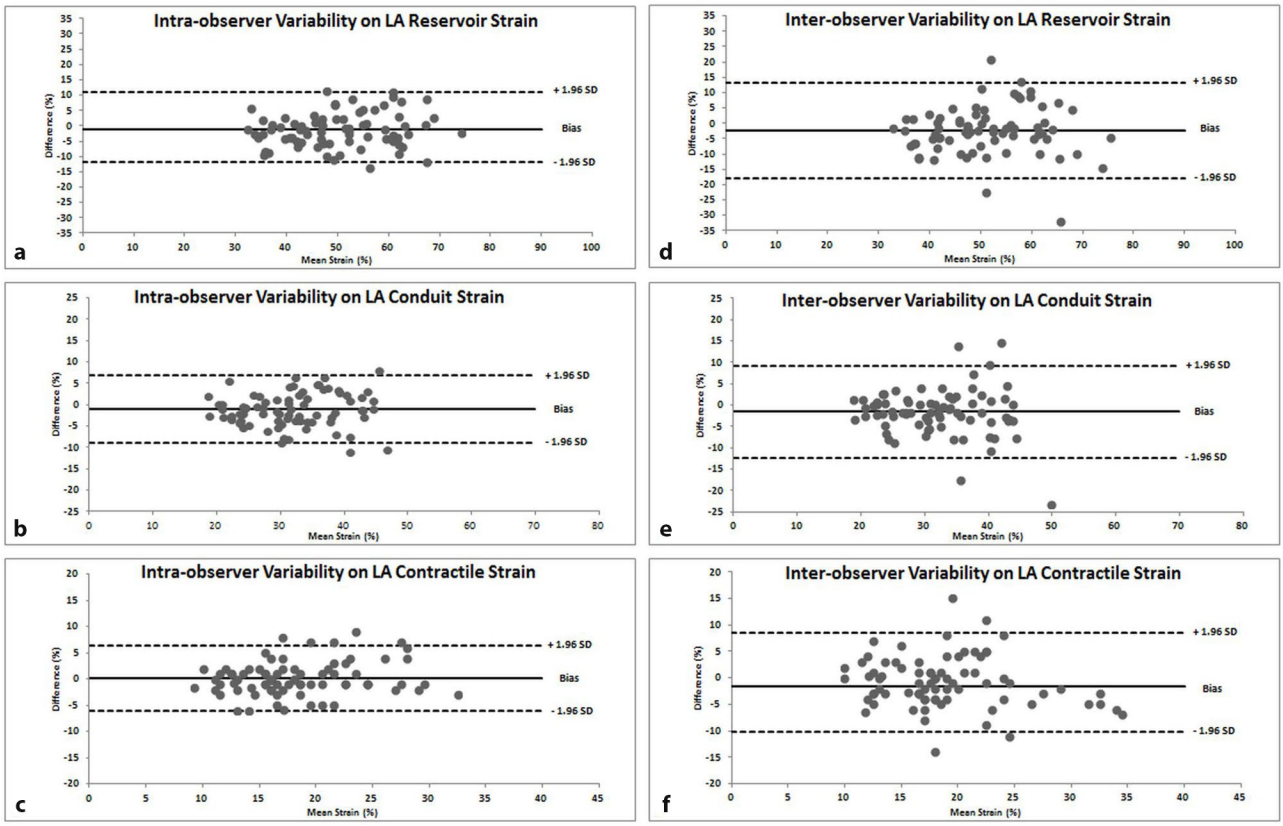


Fig. 1|P 7-6

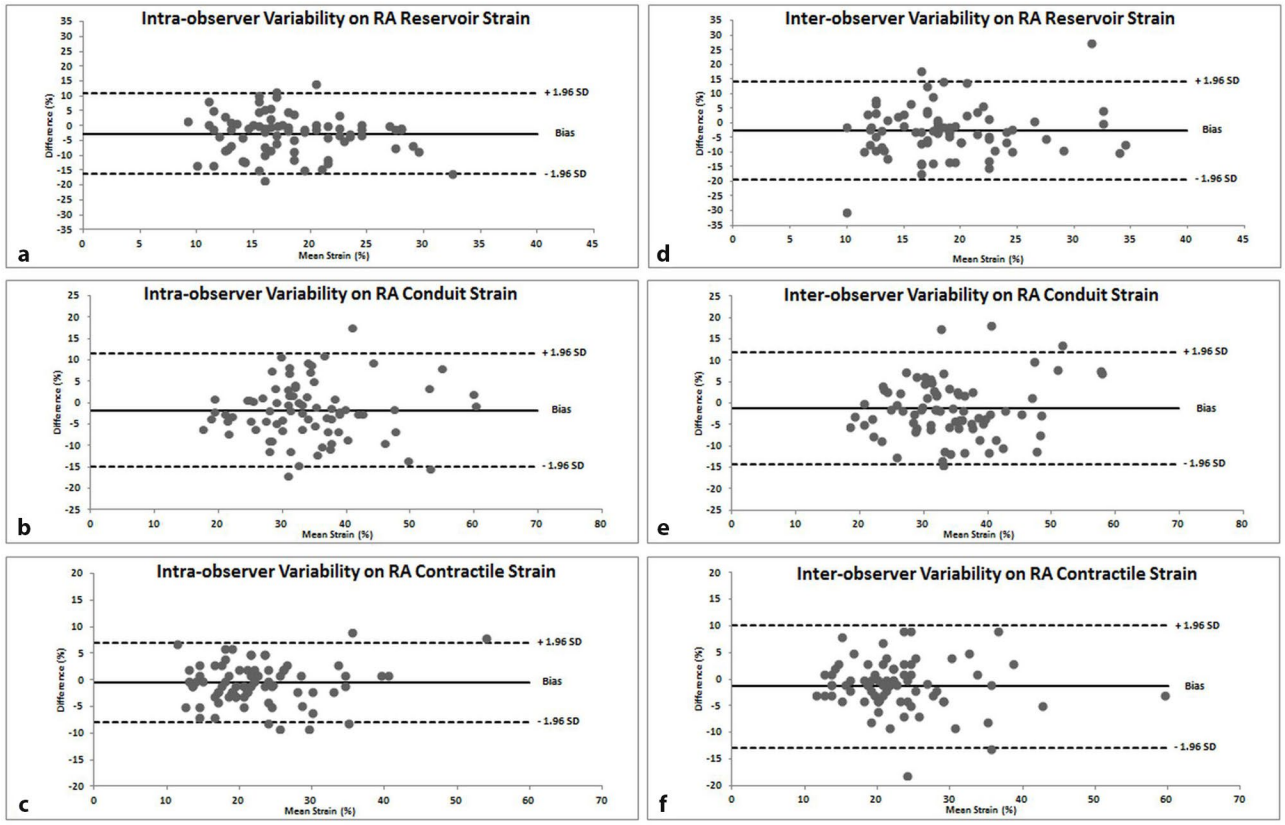


Fig. 2|P 7-6

altitude to the first examination at high-altitude and decreased during the following examinations whereas LA maximal volume did not change (Fig. 1|P 7-6). Intra-observer ICCs were ≥0.90 and CVs <10% for all analyzed parameters except for RA conduit strain with an ICC of 0.86 and a CV of 11.6%, respectively (Fig. 2|P 7-6). Intra-observer CRs were <10% for all analyzed parameters except for RA reservoir strain which was 10.83%. The mean intra-observer differences were small and limits of agreement of relative differences were narrow for all atrial strain parameters (<3% and <16%, respectively). Inter-observer ICCs (0.80–0.90), CVs (<15%), CRs (<15%), mean biases and limits of agreement (<4% and <20%, respectively) were greater than intra-observer results for all analyzed parameters. Intra- and inter-obserer ICCs for all atrial strain variables did not differ between low and high altitude.

Conclusions: 2D STE-derived bi-atrial strain function indices were found to have excellent intra- and moderate inter-observer reproducibility. High altitude-induced changes in systemic and pumonary hemodynamic conditions did neither compromise intra- nor inter-observer reproducibility. These results encourage a wider use of 2D STE atrial strain assessment which may further enhance our understanding of atrial mechanics and possibly improve clinical care.

7-7

Right coronary artery motion analysis: A novel method to measure right ventricular systolic function by selective coronary angiography

F. Baumann, S. Obeid, T. Gilhofer, R. Manka, P. Siegrist, J. Alibegovic, F. Tanner, T.F. Lüscher, R. Binder

Klinik für Kardiologie, Universität Zürich, Zurich, Switzerland

Background: During cardiac catheterization left ventricular systolic function is routinely measured by left ventricular angiography. However, right ventricular systolic function is not commonly assessed in the catheterization laboratory. Therefore, we developed a method to assess right ventricular systolic function during selective coronary angiography by analyzing the systolic translational motion of the right coronary artery thereby reproducing the tricuspid annular plane systolic excursion as measured by echocardiography.

Methods: In consecutive patients who underwent transthoracic echocardiography and selective coronary angiography, the angiographic motion of the right coronary artery (RCA) in a thirty degree right anterior oblique view was analyzed by two independent operators on two occasions. The motion distance and maximum speed of the mid-portion of the RCA (mid-point between the RCA ostium and the crux cordis) during systole towards the apex was compared to the tricuspid annular plane systolic excursion by echocardiography as gold standard.

Results: In 97 patients the mid-portion of the RCA moved 25.9 +/– 9.9 millimeter with a maximum speed of 11.3 +/– 4.9 centimeter per second during systole towards the apex. During independent repeat measurements the reliability of operator A was 94.7% (95% CI 92.1–96.5, $p<0.001$) and 95.6% (95% CI 93.5–97.1, $p<0.001$) and of operator B 98.1% (95% CI 97.2–98.7, $p<0.001$) and 95.6% (95% CI 93.5–97.1, $p<0.001$) for the RCA motion distance and RCA speed, respectively. Inter-observer variability was excellent for both measurements (Cronbachs's alpha for distance 0.976, 95% CI 0.964–0.984, $p<0.001$; for speed 0.967, 95% CI 0.951–0.978, $p<0.001$). There was a significant correlation of the RCA motion distance and RCA maximum speed with the tricuspid annular plane systolic excursion measured by echocardiography (RCA distance: r=0.57, $p<0.001$; RCA speed: r=0.35, $p<0.001$). In patients with a normal right ventricular systolic function measured by echocardiography the RCA motion distance was 27.8 +/– 9.2 millimeter and the RCA maximum speed was 12.0 +/– 4.6 centimeter per second. The area under the receiver operating curve for the RCA motion distance was 0.88 (95% CI 0.80–0.94) for discrimination of normal and abnormal right ventricular systolic function. The odds ratio for identifying a normal right ventricular systolic function increased 23 percent per point for the RCA motion distance (OR 1.23, 95% CI 1.11–1.37, $p<0.001$). A cut-off value of less than 22.2 millimeter systolic RCA motion had a specificity of 93.3% and a sensitivity of 75.6% for identifying an abnormal right ventricular systolic function.

Conclusions: Analysis of the RCA motion is a novel reproducible and reliable method to indirectly measure right ventricular systolic function during selective coronary angiography. It is a simple and useful tool to asses right ventricular function in the catheterization laboratory and may serve for risk assessment of right ventricular failure.

7-8

Value of sizing the anatomic aortic valve orifice area by computed tomography in low-flow low-gradient aortic stenosis: comparison with TTE, TEE and invasive catheterization

F. Barbieri, A. Adukauskaite, S. Dobner, F. Plank, S. Müller, J. Holfeld, N. Bonaros, G. Friedrich, W. Dichtl, G. Feuchtner

Abteilung für Innere Medizin III, Medizinische Universität Innsbruck, Innsbruck, Austria
Universitätsspital Bern, Bern, Switzerland

Background: Low-flow low-gradient aortic stenosis (LFLGAS) is a subform of severe aortic stenosis with low flow (stroke volume index ≤35 ml/m²), low gradient (<40 mmHg) and either preserved (≥50%, paradoxical form) or reduced ejection fraction (<50%, classic form). Precise measurement of the anatomic aortic valve orifice area (AVA) is crucial in LFLGAS for accurately

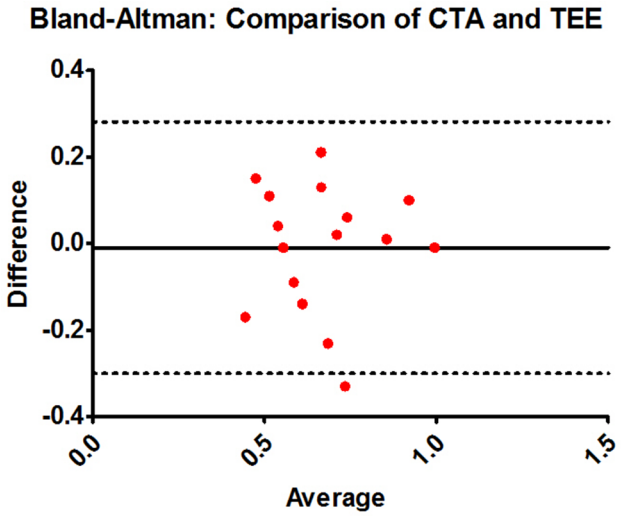


Fig. 1|P 7-8

estimating the severity of the aortic stenosis (≤ 1 cm^2; ≤ 0.6 cm^2/m^2) and to avoid underestimation.

Purpose: First time validation of the measurement of the anatomic AVA by computed tomography angiography (CTA) in patients with LFLGAS in comparison with transthoracic echocardiography (TTE; VTI-continuity equation), transoesophageal echocardiography (TEE; planimetry) and invasive catheterization (IC; gorlin formula).

Methods: Retrospective ECG-gated 128-slice dual-source computed tomography angiography (CTA) (Siemens Definition Flash) was performed in patients with LFLGAS for clinical indications (e. g. surgery planning). The smallest anatomic AVA was identified on multiphase image datasets (1 mm/0.7) and reconstructed at 5% increments during systolic phase, and measured using Multiplanar Reformations (MPR) on a dedicated 3-D post-processing software (SyngoVIA, Siemens). CTA was compared with TTE, TEE and IC, all performed as part of standard preoperative diagnostics. Intermodality correlations were calculated using bivariate spearman correlation and for analysis of differences, Bland-Altman method was performed. For exclusion of proportionality bias one sample t-tests and linear regression were performed.

Results: 17 patients (paradoxical LFLGAS $n=6$; classic LFLGAS $n=11$) from our database were included. For analysis 15% ($n=1$; 5.9%), 25% ($n=11$; 64.7%) and 30% ($n=5$; 29.4%) increments were used. The AVA by CTA was highly correlated ($n=16$; r = 0.595; $p=0.015$) with TEE with only small divergences (mean difference (MD) −0.009; standard deviation (SD) +/−0.148; 95% confidence interval (CI) −0.299–0.281, Fig. 1 | P 7-8). There were weaker, non-significant, correlation between the anatomic AVA by CTA and the effective flow-derived AVA by TTE ($n=15$; r = 0.362; $p=0.184$) and IC ($n=12$; r = 0.360; $p=0.250$). There was also a higher degree of the AVA overestimation by CTA compared to both flow-dependent techniques, TTE (MD −0.025; SD +/−0.170; 95% CI −0.357–0.308) and IC (-0.038; +/−0.192; 95% CI −0.413–0.338). No proportionality bias was found (CTA vs. TEE: $p=0.952$; CT vs. TTE: $p=0.429$; CT vs. IC: $p=0.668$). Correlations using the mean of 5 cranial to caudal 1 mm stack AVA measurements showed a high degree of overestimation compared to TEE.

Conclusions: The anatomic AVA measured by CTA is a valuable new parameter for assessing the degree of severity of stenosis in LFLGAS thus adds novel information in the decision making process during clinical management (e. g. conventional vs. aortic valve replacement) in these patients.

Postersitzung 8 – Herzinsuffizienz 1

8-1

Comparison of office heart rate and mean 24-hours ambulatory heart rate in chronic heart failure patients

V. Habenicht, E. Kolesnik, J. Schmid, K. Brandner, A. Tomaschitz, S. Pilz, F. Fruhwald, D. von Lewinski, K. Ablasser, N. Verheyen

Kardiologie, Medizinische Universität Graz, Graz, Austria

Background: Heart rate (HR) control in heart failure patients is commonly based on single office measurements at rest. However, 24-hours ambulatory heart rate measurement may yield a more accurate surrogate parameter of individual HR than single measurements. In a pilot study, we investigated the association between measures of office HR and mean 24-hours ambulatory heart rate in chronic patients with heart failure.

Methods: Patients with stable chronic heart-failure and a left ventricular ejection fraction (EF) < 50% were prospectively enrolled in the outpatient clinic of a tertiary care hospital. Office HR was measured after 5 minutes rest both in the sitting and in supine position, mean ambulatory HR was determined using a certified ambulatory blood pressure monitoring device (Mobil-O-Graph, I. E. M. GmbH, Stolberg, Germany) and was calculated as the mean of all successful HR measurements during 24 hours. HR > = 70 beats per minute (bpm) was considered elevated.

Results: We enrolled 28 subjects with mean age of 62.6 +/− 10.3 years (35% females) and mean EF of 34 +/− 9%. Mean sitting HR was 69.5 +/−15.6 bpm and mean supine HR was 71.5 +/− 15.3 bpm, mean 24-hours ambulatory HR was 67.6 +/− 10.6 bpm. Ambulatory HR was correlated with sitting HR (Pearson's r = 0.620, $P=0.001$) and supine HR (r = 0.398, $P=0.044$) HR was elevated in 9 subjects (33.3%) in sitting position, in 13 subjects (46.4%) in supine position, and in 13 subjects (48.1%) in ambulatory read-outs.

Among those with a normal supine HR ($n=14$), 3 (21.4%) had an elevated ambulatory HR. Vice versa, 3 individuals (23.1%) of those with elevated supine HR revealed a normal ambulatory HR.

Comparing sitting HR with ambulatory HR, 5 (29.4%) had an elevated ambulatory HR, although presenting with a normal sitting HR, while 2 (22.2%) of those with elevated sitting HR had a normal amulatory HR.

Conclusions: Office HR measurements and ambulatory HR show only moderate correlation in subjects with chronic heart failure. Office HR measurements tend to be higher than ambulatory measurements. Approximately one in five patients with normal office HR has elevated ambulatory HR, while a similar proportion of subjects with elevated office HR have normal ambulatory HR. After confirmation in larger cohorts, the clinical relevance of this divergence and the usefulness of 24-hours ambulatory HR beyond office HR as target parameter in heart failure treatment should be investigated in future studies.

8-2

Cardiac remote organ response in multiple myeloma

A. Cho, N. Pavo, R. Wurm, G. Strunk, M. Krauth, H. Agis, M. Hülsmann

Department of Internal Medicine II, Division of Cardiology, Medical University Vienna, Vienna, Austria
Department of Internal Medicine I, Division of Hematooncology, Medical University Vienna, Vienna, Austria

Background: Elevated levels of cardiovascular markers including N-terminal B-type natriuretic peptide (NT-proBNP) have been shown to be elevated and associated with mortality in cancer patients free from cardiac disease. The aim of this study was to investigate whether NT-proBNP levels are associated with disease severity in multiple myeloma (MM) specifically and how NT-proBNP levels evolve during the course of the disease.

Methods: We retrospectively analyzed data of a total of 118 patients with multiple myeloma, which were clinically followed-up (FUP) at the oncologic department. NT-proBNP, beta-2-microglobulin (B2M) and plasma levels of light chains were

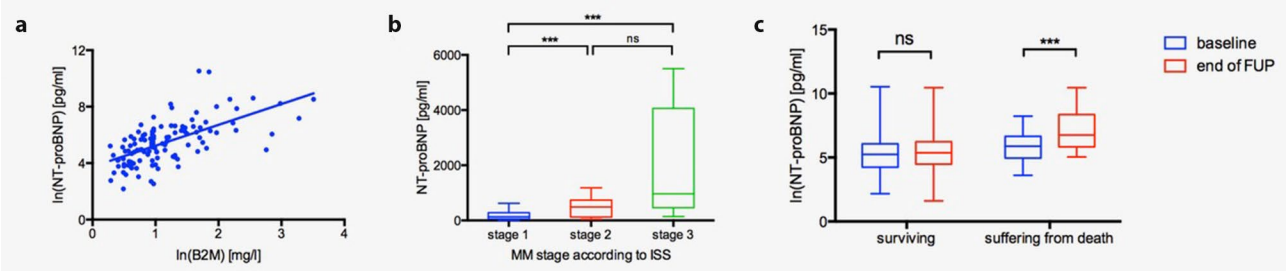


Fig. 1|P 8-2

measured at baseline and FUP visits. The primary study endpoint was defined as a positive correlation between NT-proBNP and disease severity reflected by B2M, MM stage according to the International Scoring System (ISS) and paraprotein levels. Secondary endpoints were the difference in NT-proBNP for survivors and patients sufferng from death between baseline and last contact.

Results: Baseline NT-proBNP showed a highly significant positive correlation with beta-2-microglobulin (B2M) in the total cohort ($r = 0.65$, $p < 0.001$) and likewise in patients with normal or not normal cardiac status ($r = 0.60$, $p < 0.001$ and $r = 0.54$, $p < 0.001$) (Fig. 1|8-2a). Moreover NT-proBNP correlated positively with levels of IgG in patients with an IgG kappa or IgG lambda gammopathy ($r = 0.32$, $p = 0.038$), the most common gammopathies. NT-proBNP values for different disease stages of MM were 133.3 (IQR 51.5–282.0) pg/ml for stage 1, 487.4 (IQR 123.8–738.3) pg/ml for stage 2 and 969.1 (IQR 472.8–3748.0) pg/ml for stage 3 ($p < 0.001$ for the comparison between all groups) (Fig. 1|8-2b). During a median follow-up (FUP) of 845 (IQR 683–978) days 31 (26%) patients died. NT-proBNP increased significantly between the two timepoints [356.6 (IQR 142.9–782.3) pg/ml vs. 862.9 (IQR 338.8–4215.0) pg/ml, $p < 0.001$] (Fig. 1|8-2c) alongside significant changes in parameters associated with MM severity as B2M [3.34 (IQR 2.40–5.52) mg/l vs. 4.95 (IQR 3.20–10.71) mg/l, $p = 0.014$], albumin [40.2 (IQR 38.1–43.0) g/l vs. 35.6 (IQR 26.1–39.9) g/l, $p < 0.001$], hemoglobin [11.1 (IQR 10.4–12.3) g/dl vs. 10.0 (IQR 8.7–11.1) g/dl, $p < 0.001$] and C-reactive protein [0.46 (IQR 0.23–1.69) mg/dl vs. 2.38 (IQR 0.95–8.73) mg/dl, $p = 0.004$] for patients with 534 (315–659) and 43 (22–105) days at baseline and last contact before the adverse outcome, whereas no significant changes were observed for surviving patients during a relatively longer FUP.

Conclusions: Levels of the cardiovascular marker NT-proBNP are associated with disease severity in patients with MM independently from a present cardiac comorbidity suggesting remote organ response of the heart to malignant disease.

8-3

Depressive disorders and peculiarities of cardiohemodynamics in patients with chronic heart failure and comorbidity

G. Tytova, O. Liepieieva, N. Ryndina

Kharkiv National Medical University, Kharkiv, Ukraine

Anemia and kidney dysfunction are considered to be predictors of unfavorable course of chronic heart failure. Numerous studies proved that depressive disorders are a risk factor for re-hospitalization and death in patients with CHF.

Purose: Study of morpho-functional myocardial changes and estimation of depressive disorders in anemic patients with chronic heart failure and chronic kidney disease.

Methods: 145 patients (age 71.42 ± 8.66 y.) with CHF II- IVFC as a result of IHD. Main group consisted of 87 patients with anemia and CKD II-III st. on a background of CHF. The comparison group consisted of 58 pts with CHF without anemia and CKD. FC of CHF was estimated by NYHA classification. CKD was defined by USA NKF classification K/DOQ. Anemia – by ICST, 1989 classification. Thus mild anemia was found in 50 pts (Igr), moderate – in 25 pts (II gr) and severe in 12 pts (III gr) of the main group. In order to study the structural and functional myocardium echocardiography was used. Beck depression inventory was used to study depressive disorders.

Results: There was no significant difference in LVESD and LVEDD in mild anemic patients with CHF and CKD. Patients of II gr had tendency for increasing LVESD and LVEDD, pts of III gr had significally increased ($p \leq 0.05$) comparing to group of pts without anemia and CKD. Patients of the I gr. had significally decreased LVPWd, IVS, EF and increased sizes of RA and RV comparing to group of comparison. Comparing these parameters in pts of I and II groups with comparison group there were no significant differences ($p \geq 0.05$). There was significant increasing of LVESD, LVEDD, LVESV, LVEDV, sizes of LA and RV, and decreasing of LVPWd, EF in pts of III gr comparing to pts of I and II gr. Due to Beck scale symptoms of depression grew in proportion to severity of anemia with maximum in pts of the III gr. Patients of the Igr mostly had cognitive-affective disorders. Patients of II and III gr, mostly had cognitive-affective disorders as well as somatic manifestation of depression.

Conclusions: Negative influence of anemic syndrome on myocardium was seen in formation of anemic cardiomyopathy with dilation of heart chambers and decreased EF and also in emotional sphere as development of depressive disorders, which worsen not just a course of CHF but also decrease life quality ruining social and family functioning and behavior in general, aimed at overcoming the disease.

8-4

Ivabradine in patients with chronic cor pulmonale and right heart failure

G. Tytova, Ol. Liepieieva

Kharkiv National Medical University, Kharkiv, Ukraine

Cor pulmonale-reason of the RHFand tachycardia.Heart rate more than 70 bpm increases myocardial oxygen demand and leads to myocardial ischemia.Prescribtion of beta-blockers for decreasement of HR is limited due to their influence on hyperresponsivness of airways.

Table 1 | P 8-4

	1 group		2 group	
	Before	After	Before	After
PV Base diameter RVD1, cm	3.31 ± 0.28	3.23 ± 0.23	3.36 ± 0.19	3.18 ± 0.34*
PV Mid diameter, RVD2, cm	3.82 ± 0.12	3.71 ± 0.17*	3.73 ± 0.20	3.52 ± 0.18*
PV Longitudal diameter, RVD3, cm	8.48 ± 0.21	8.18 ± 0.25*	8.51 ± 0.17	8.15 ± 0.08*
PA diameter, cm	2.37 ± 0.18	2.23 ± 0.10*	2.40 ±0.17	2.17 ± 0.09*
EF % (M mode)	43.2 ± 5.1	50.1 ± 3.2*	44.3 ± 6.2	53.4 ± 2.8*
PpA, mmHg	30.2 ± 2.1	27.4 ± 1.5*	31.3 ± 2.2	26.1 ± 1.3*
RVWT, cm	0.69 ±0.14	0.64 ± 0.18	0.68 ± 0.13	0.63 ± 0.15
Myocardial performance index (Index Tei)	0.41 ± 0.15	0.32 ± 0.17*	0.42 ± 0.17	0.30 ± 0.19*
Heart rate	108 ± 8	94 ± 6*	110 ± 6	86 ± 5*

* – $P < 0.05$ comparing 1st and 2nd groups before and after treatment.

Purpose: To investigate the influence of ivabradine on structure-functional peculiarities of the right ventricle, HR and life quality in pts with chronic cor pulmonale (CCP).

Methods: 72 pts (38 men, 34 women, 41.3 ± 3.8 yrs) with CCP on a background of COPD and bronchial asthma (non severe) without IHD were examined. Pts were divided into 2 groups due to prescribtion of ivabradine in addition to basic treatment. The 1st gr-36 pts with Ca ch blockers (diltiazem), ACEi, low doses of loop diuretics; 2nd gr-36 pts with ivabradine 7.5 mg BD. All pts underwent a transthoracic echocardiography in A4C in dynamics within 12 weeks. Life quality was estimated on the basis of SF-36. Patients' functional status and therapy efficacy were estimated by 6MWT.

Results: Results are shown in the Table 1. It was found that pts of the 2nd gr had more significant tendency to normalization of structure-functional data of the right heart chambers due to significant decreasing of the HR. 6MWT showed that pts of the 2nd gr were able to walk 121.3 ± 17.6 meters more than pts of the 1st gr. Estimating results of SF-36 it was found that pts of 2nd group had significant improvement at such scales as RPF, GH, Vitality, RE and MH comparing to pts of the 1st gr.

Conclusions: 6 MWT confirmed efficacy of ivabradin in pts with CCP and RHF. Early prescription of ivabradine in this cohort of pts prevents worsening of RHFimproving the structure-functional data of the right heart chambers, which has a positive influence on life quality of these pts.

8-5

Growth Differentiation Factor (GDF)-15 is associated with mortality in patients with severe acute heart failure or cardiogenic shock

M. Lenz, K.A. Krychtiuk, S. Kastl, J. Wojta, G. Heinz, W.S. Speidl

Universitätsklinik für Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria
Ludwig Boltzmann Cluster for Cardiovascular Research/Core Facilities, Medizinische Universität Wien, Vienna, Austria

Background: Growth differentiation factor (GDF)-15 levels are associated with all-cause mortality in patients with acute coronary syndromes, however data in patients with acute heart failure are conflicting. The aim of this study was to investigate the predictive value of GDF-15 in patients with severe acute heart failure (AHF) or cardiogenic shock requiring admission to an intensive care unit.

Methods: We included 90 consecutive patients with AHF or cardiogenic shock admitted to a cardiac ICU. GDF-15 was measured at admission utilising ELISA and patients were followed for 30 days.

Results: Mean age of the patients was 62.1 ± 16.0 with a male to female ratio of 76.7% to 23.3%. Median NT-proBNP levels were markedly increased (4986, IQR 1525–23.842 pg/mL). 30-day mortality was 35.6%. ICU-non-survivors displayed increased GDF-15 levels (median = 7119.5, IQR 3816.2–10.168.2 ng/mL) as compared to survivors (median = 2719.7, IQR 1472.9–7099.9 ng/mL) with a p-value of < 0.001. Patients within the third tertile of GDF-15 had a 5.1-fold increased risk of death ($p < 0.005$) independently of demographics, NT-proBNP and vasopressor usage. Interestingly, GDF-15 and NT-proBNP showed additive prognostic value. When patients were stratified according to the median of NT-proBNP and GDF-15, those with both GDF-15 and NT-proBNP levels above the median had the highest risk of dying (HR 5.8, $p < 0.005$).

Conclusions: GDF-15 is a strong predictor of mortality in patients with severe acute heart failure or cardiogenic shock requiring admission to a cardiac ICU. Furthermore, it adds additional prognostic value to NT-proBNP levels.

8-6

Mitochondrial DNA Predicts Mortality in Acute but not in Chronic Heart Failure

K.A. Krychtiuk, R. Wurm, S. Ruhittel, M. Lenz, K. Huber, J. Wojta, G. Heinz, M. Hülsmann, W.S. Speidl

Universitätsklinik für Innere Medizin II, Abteilung Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Severe acute heart failure (AHF) is associated with a poor short-term outcome, while patients with chronic heart failure (CHF) exhibit a poor long-term prognosis. Tissue hypoxia may lead to cellular damage and the release of intracellular mitochondrial DNA (mtDNA), which may activate the immune system due to its resemblance to bacterial DNA. The aim of this study was to analyze circulating levels of mtDNA as a possible predictor of outcome in patients with AHF and CHF.

Methods and Results: Plasma levels of circulating mtDNA were measured in 90 consecutive patients with AHF admitted

to our ICU and in 109 consecutive patients with CHF at our HF outpatient department. Patients in the ICU group were 64.7 (49.4–74.3) years old and median NT-proBNP levels were 4986 (1525–23.842) pg/mL. 30-day survival was 64.4%. In the CHF group, median age was 63 (IQR 52–72) years. 49.5% of patients had ischemic and 50.5% had a non-ischemic etiology of CHF. 38.5% were in NYHA class III/IV, and patients had a median NT-proBNP level of 1025 (IQR 450–3480) pg/mL.

Patients with AHF showed significantly higher circulating levels of mtDNA as compared to patients with CHF (27.0 IQR 8.2–52.2 ng/mL vs. 14.5 IQR 8.5–25.4 ng/mL, $p<0.005$). In CHF patients, mtDNA levels were associated with NYHA functional class but did not differ according to HF etiology and outcome. On the contrary, in patients with severe AHF, mtDNA levels were significantly higher in patients that died within 30 days after ICU admission (30.6 IQR 13.0–90.1 ng/mL vs. 22.8 IQR 6.4–41.6 ng/mL, $p<0.05$). Patients with plasma levels of mtDNA in the highest quartile (mtDNA>50.9 ng/mL) had a 3.1-fold risk ($p=0.002$) of dying.

Conclusions: Circulating levels of mtDNA predict mortality in patients with severe AHF but are not associated with outcome in patients with CHF. Reduced tissue perfusion with release of mtDNA may play a role within the pathophysiology of AHF and severe CHF.

8-7

Predictors of positive response to immunosuppressive therapy in virus negative lymphocytic inflammatory cardiomyopathy

P. Hörmann, C. Mussner Seeber, J. Dörler, E. Stocker, S. Gstrein, C. Ensinger, M. M. Zaruba, M. Frick, G. Pölzl

Innere Medizin I, LKH Feldkirch, Feldkirch, Austria
Universitätsklinik für Innere Medizin III, Medizinische Universität Innsbruck, Innsbruck, Austria
Universitätsklinik für Pathologie, Medizinische Universität Innsbruck, Innsbruck, Austria

Background: Immunosuppressive therapy appears to be beneficial in patients with virus-negative lymphocytic inflammatory cardiomyopathy. It was the aim of this single-center study to identify potential baseline characteristics that may predict positive response to therapy.

Methods: Virus-negative inflammatory cardiomyopathy was diagnosed in endomyocardial biopsies of 127 patients. After exclusion of contraindications cortisone and azathioprin for six months in addition to standard heart failure therapy was started. Endomyocardial biopsy and hemodynamic evaluation was repeated at six-months follow-up. Patients were classified as responders if NYHA class improved by at least one class or remained stable in class I and serum NT-proBNP dropped by = 30%.

Results: At this stage complete 6-months follow-up is available in 84 patients (age: 46 ± 11.3, female: 36%, median disease duration: 3 months [0.25–42]). Compared to baseline we observed a significant improvement in NYHA class (I/II 61%, III/IV 39% before vs I/II 98%, III/IV 2% after therapy, $p<0.001$) and NTproBNP (958 ng/l [49–27.054] vs 234 ng/l [45–8099], $p<0.001$) in the entire cohort. Also left ventricular ejection fraction (LV-EF) (30 ± 11% vs 44 ± 12%, $p<0.001$) and left ventricular enddiastolic volume index (LVEDVI) (120 ± 38 ml/m^2 vs 100 ± 36 ml/m^2, $p<0.001$) improved, as did cardiac index (1.9 ± 0.5 l/min/m^2 vs 2.2 ± 0.5 l/min/m^2, $p<0.001$) and pulmonary capillary wedge pressure (15 mmHg [4–42] vs 11 mmHg [6–26], $p<0.001$). Responders ($n=44$, 52%) were characterized by higher NYHA class (III/IV 57% vs 20%, $p=0.01$), higher NTproBNP levels (1448 ng/l [81–27.054] vs 426 ng/l [49–5329], $p=0.001$), lower LV-EF (27 ± 10% vs 33 ± 11%, $p=0.005$) and higher leucocytes (8.3 ± 2.5 G/l vs 7.1 ± 2 G/l, $p=0.02$) at baseline. Interestingly, no significant differences were found between groups with regard to hemodynamics, LVEDVI and the extent of myocardial inflammation/fibrosis. Standard heart failure therapy was comparable between groups at baseline and 6-months follow-up. Multivariate logistic regression analyses including disease duration, LV-EF, LVEDVI, CI, leucocytes, CD14 positive lymphocytes/mm2 revealed high leucocytes and low LV-EF at baseline as independent predictors of positive response to therapy.

Conclusions: From our data it appears that a positive response to immunosuppressive therapy in virus- negative lymphocytic inflammatory cardiomyopathy is more likely in patients with higher serum leucocytes and low LV-EF at baseline.

8-8

RAS fingerprints during therapy conversion from ACE-I/ARB to ARNI

J. Novak, N. Pavo, G. Goliasch, R. Wurm, G. Strunk, M. Gyöngyösi, M. Poglitsch, M. Saemann, M. Hülsmann

Departments of Cardiology and Nephrology, Medical University Vienna, Vienna, Austria
Complexity Research, Vienna, Austria

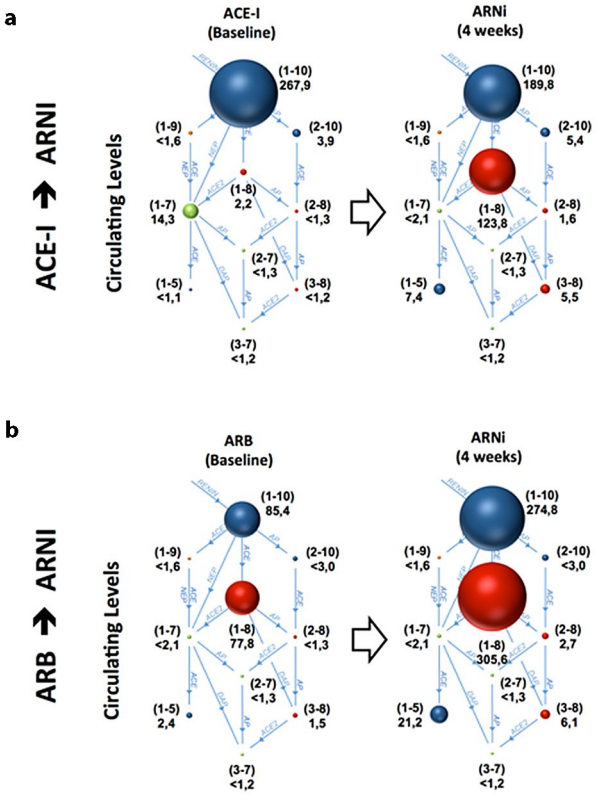


Fig. 1 | P 8-8

Attoquant, Vienna, Austria

Background: The combined inhibition of the angiotensin-receptor and neprilysin (ARNI) has been proven beneficial in HFrEF and was consequently embedded in the treatment guidelines alongside ACE-I and ARB therapy. While neprilysin (NEP) has pleiotropic effects on numerous vasoactive peptides, it is also an enzyme of RAS. The exact mechanisms of NEP inhibition (NEPi) attributing to the clear clinical benefit of ARNI remain unclear.

Methods: Blood samples of stable chronic HFrEF patients were collected four hours after the ingestion of morning medication including the RAS-blocker at baseline (ACE-I: $n=6$ and ARB: $n=6$) and six weeks after therapy conversion to ARNI. Blood samples were immediately stabilized for the determination of circulating angiotensin levels by mass-spectrometry. Moreover, plasmatic NEP activity was measured directly by a kinetic assay using Ang1-10 as the natural substrate of NEP and measuring the formation of its product Ang1-7 by mass spectrometry.

Results: NEP activity was significantly reduced after therapy conversion to ARNI [68.7 ng(Ang1-7)/ml/h (IQR45.9–169.6) vs. 35.9 (IQR17.1–48.2); $p=0.004$] confirming an efficient uptake of the drug. Likewise NT-proBNP levels decreased significantly [1933 pg/ml (IQR862-3134) vs. 1309 pg/ml (IQR469-2184), $p=0.041$] as observed in the clinical study. Interestingly there was a trend for higher renin levels after induction of ARNI [425 µIE/ml (IQR33-944) vs. 1016 µIE/ml (IQR132-2016), $p=0.071$]. RAS fingerprints are displayed in Fig. 1|8-8. For the converted ACE-I group a significant increase in Ang1-8, Ang1-5 and Ang3-8 was apparent. When converting from ARB to ARNI (introduction of NEPi), the proportions of angiotensins remained similar. However, patients displayed higher concentrations of all systemic angiotensins with significantly higher levels of the downstream metabolites Ang1-5 and Ang3-8.

Conclusions: The profound clinical benefits of NEPi may lie in its net effects on the interplay of vasoactive peptides, yet it seems that NEPi also triggers RAS activation. Resulting elevated angiotensin metabolite concentrations could exert beneficial RAS effects alongside an efficient AT1R-blockade.

Postersitzung 9 – KHK

9-1

Evaluation of long term graft patency in patients undergoing multiple arterial revascularization

E. Ruttmann, M. Dietl, J. Kilo, M. Grimm, H. Ulmer, G. Feuchtner, N. Bonaros, B. Metzler

Department of Cardiac Surgery, Medical University Innsbruck, Innsbruck, Austria
Department of Medical Statistic, Informatics, and Health Economy, Innsbruck, Austria
Department of Radiology, Medical University Innsbruck, Innsbruck, Austria
Department of Cardiology, Medical University Innsbruck, Innsbruck, Austria

Background: Multiple arterial revascularization (MAR) using right internal thoracic arteries (RITA) and radial arteries (RA) in addition to a left internal thoracic artery (LITA) has become a mainstay for surgical revascularization in patients with longer life expectancy.

Methods: This prospective longitudinal follow up study was implemented in order to investigate the long term performance of MAR. The Institutional Review Board permitted the conduction of this study and patients were followed up in 4 to 5 year intervals after CABG procedure. All MACCE events and coronary diagnostic procedures, either by coronary angiography (CA) or coronary computed tomography (CTA) were evaluated and independent predictors for graft patency were calculated by Kaplan-Meier survival analysis and multivariable COX proportional hazards model. Graft stenosis of more than 70%, string phenomenon and graft occlusion were defined as non-functioning grafts.

Results: The study population consisted of a total of 1652 consecutive patients receiving first, non-emergent MAR with a mean follow up of 7.4±4.0 years (11.914 patient years). BITA grafting was performed among 907 patients (54.9%), 745 patients (45.1%) received LITA together with at least one RA. Among BITA patients, 187 patients received a RA as a third arterial conduit (187 patients, 20.6%).

Among 455 patients (27.5%), coronary diagnostic procedures based on 373 CA and 82 CTA investigations were performed. Graft analysis included 475 LITA (33.8%), 146 RITA (10.4%),

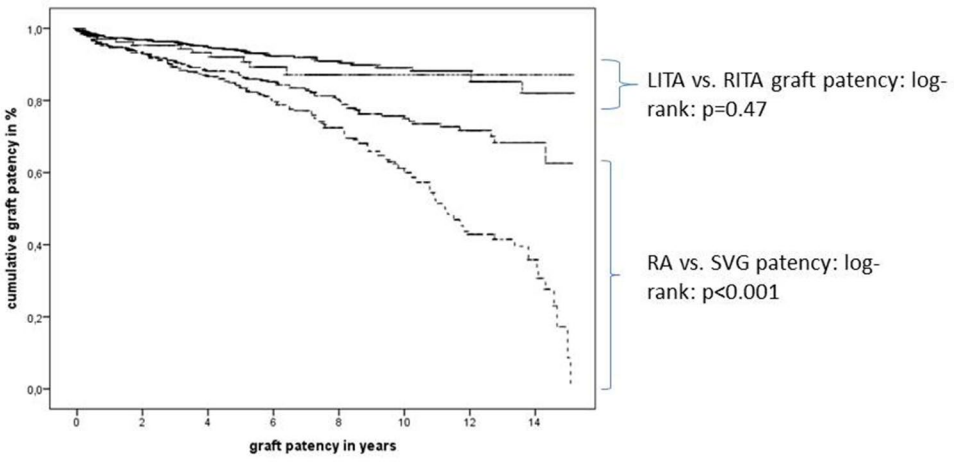
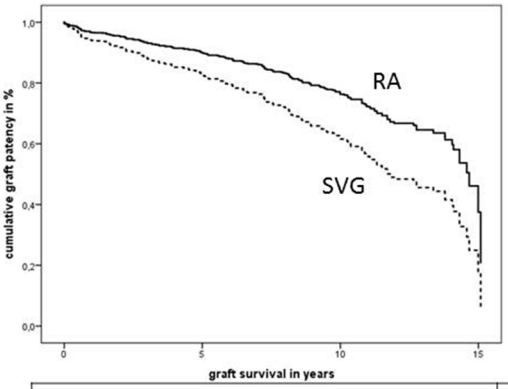


Fig. 1|P 9-1 Kaplan-Meier curves of cumulativepatency rates according to type of bypass graft. Right internal thoracic artery grafts showed similar patency rates compared to left internal thoracic arterv grafts (log-rank: $p=0.47$). Radial artery bypass grafts showed significantly higher graft patenca up to 15 years compared to saphenous vein grafts (log-rank: $p=0.001$)



	Wald	HR (95% CI)	p-value
Male gender	**7.27**	**1.83 (1.18 – 2.85)**	**0.007**
Age (per year)	0.078	1.04 (0.97 – 1.018)	0.78
Radial artery	**14.7**	**1.89 (1.37 – 2.60)**	**<0.001**
Graft territory right coronary artery	0.82	0.83 (0.55 – 1.25)	0.37
Target vessel stenosis >80%	3.0	0.71 (0.49 – 1.04)	0.082
Diabetes	0.001	0.99 (0.73 – 1.36)	0.98
Non smoking	**6.4**	**1.49 (1.09 – 2.02)**	**0.009**
Peripheral vascular disease	0.65	1.16 (0.81 – 1.67)	0.65

Fig. 2|P 9-1 Cumulative graft patency of RA (solid line) and SVG (dashed line) resulting from COX proportional hazards analysis adjusted for age, gender, current smoking, perphral arterial disease, graft territory (either circumflex or right coronary artery), diabetes and target vessel stenosis (80 % or more). RA grafting resulted in a 1.89 fold adjusted higher probability for graft patency oder 15 years (HR: 1.89; 95 %, CI: 1.32–2.45; $p<0.001$)

372 RA (26.5 %) and 411 SVG (29.3 %) at risk. Cumulative graft patency was highest among LITA and RITA grafts (LITA vs. RITA: log-rank $p=0.47$, Fig. 1|P 9-1), and RA grafts were superior regarding graft patency compared to SVG (RA vs. SVG: log-rank $p<0.001$, Fig. 2|P 9-1). Moreover in situ RITA grafting was associated with significantly higher patency rate compared to RITA free grafts (94.7 % vs. 83.9 %, $p=0.039$). Multivariable graft patency analysis of non ITA grafts revealed RA grafting (HR: 1.89; 95 % CI 1.37–2.60; $p<0.001$), male gender (HR: 1.83; 95 % CI 1.18–2.85; $p=0.007$) and non-smoking (HR: 1.49; 95 % CI 1.09–2.02; $p=0.009$) to be independent predictors of long term graft patency.

Conclusions: In MAR, the use of in situ RITA grafting shows similar long term patency compared to LITA grafts (Table 1|P 9-1). The use of RA shows superior patency rates compared to SVG with cumulative patency rates diverging beyond 5 years after CABG.

9-2

Possible role for microRNAs to identify patients at risk for an exercise-induced cardiac event

B. Mayr, E. E. Müller, C. Schäfer, S. Droese, H. Breitenbach-Koller, M. Schönfelder, J. Niebauer

University Institute of Sports Medicine, Prevention and Rehabilitation, Paracelsus Medical University, Salzburg, Salzburg, Austria
Research Institute of Molecular Sports Medicine and Rehabilitation, Paracelsus Medical University, Salzburg, Austria
Department of Cell Biology, University Salzburg, Salzburg, Austria
Faculty of Sport and Health Sciences, Exercise Biology, Technical University Munich, Munich, Germany

Background: Acute exercise is a trigger of cardiac events even in patients with unknown or stable cardiac disease and there's a paucity of biomarkers that could possibly identify patients at risk. Several micro ribonucleic acids (miRNAs), which are small non-coding RNA molecules that control gene expression by translational inhibition, however, have been associated with atherogenesis and coronary artery disease (CAD). We set out to assess in a great number of atherogenic miRNAs whether their responsiveness to an acute bout of exercise differed between healthy subjects and patients with CAD.

Methods: In this study, 40 participants (10 healthy males and 10 healthy females; 10 male and 10 female patients with CAD) performed an all-out cycle ergometry. All plasma samples were extracted for total RNA before and after exercise. Each sample was analyzed via quantitative reverse transcription polymerase chain reaction (qRT-PCR) for a set of 187 potential target miRNAs, initially validated by a screening array and by literature. In this analysis we focused on miRNAs known to be associated with atherogenesis.

Results: 77 miRNAs were responsive to a single all-out exercise in one or both groups (all $p<0.05$). Focusing on atherogenic miRNAs, five were significantly modulated in both groups. The antiatherogenic miR-143–3p; miR-145–5p and miR-23b-3p showed stronger up-regulation and the proatherogenic miR-17–5p and miR-92a-3p a weaker down regulation in healthy subjects compared to CAD patients. Additional five miRNAs were significantly modulated only in the CAD patients and two miRNA only in the healthy participants. Using a multi variance analysis, significant differences between groups could be confirmed for the anti-atherogenic miR-101–3p, which showed a significant down regulation in the CAD patients, but a slightly up regulation in the healthy participants.

Conclusions: This study shows that miRNAs respond differently to an acute bout of exercise in healthy subjects as compared to CAD patients. By further characterizing a panel of responsive and atherogenic miRNAs it may eventually be possible to evaluate the atheroprotective state of CAD patients and to identify patients at risk for an exercise-induced cardiac event.

9-3

Use of beta-blocker and mortality in patients with coronary artery disease with or without COPD: a retrospective data analysis

S. Sheikh Rezaei, C. Rinner, P. Ratajczak, W. Grossmann, W. Gall, M. Wolzt

Universitätsklinik für Klinische Pharmakologie, Medizinische Universität Wien, Vienna, Austria

Background: Beta-blockers are indicated for secondary prevention of coronary artery disease (CAD). However, in patients with co-morbidity of chronic obstructive pulmonary disease (COPD) an under-use of beta-blocker has been reported. It is unclear if this group of patients has a higher mortality if not as stringently treated.

Methods: Prescription and demographic data and information on hospital discharge diagnoses from 13 Austrian health insurance funds for the years 2006 to 2007 were analysed. The primary end point was the number of deaths in patients with CAD with or without COPD and its association with use of beta-blockers.

Results: In 2006 and 2007, 65.717 patients (37% female, 63% male) were discharged with a diagnosis of CAD and had a mean number of 24 hospitalization days. Among these patients, 30.117 had a co-diagnosis of COPD (45.8%), 16.033 had diabetes (24.4%), and 49.469 received beta-blockers (75.3%). Diabetes was found more frequently in patients with CAD and COPD with 48% compared to patients without COPD with 4.4%. 36% of patients with co-diagnosis diabetes were beta-blocker users, and 23% were non-users. Beta-blockers were comparably used in CAD patients with COPD and without COPD with 77.6% and 74.2%, respectively. During an observation period of 12 months the mortality in CAD patients was 22%. In comparison, the mortality of patients with co-diagnosis of CAD and COPD was 27%, and 29% in patients with CAD and diabetes. When grouped by use of beta-blockers, the mortality of users was 18% and lower than that of non-users with 32%.

Conclusions: Use of beta-blockers was similar in patients with or without COPD. Patients with diabetes had more often beta-blockers. However, mortality of users of beta-blocker was markedly lower than that of non-users.

9-4

Neutrophil to lymphocyte ratio is associated with the severity of coronary heart disease

M. Pfeffer, L. Fiedler, R. Schönbauer, F. Egger, T. Culinovic, A. Haiden, M. Haumer, F.X. Roithinger

Innere Medizin, Landesklinikum Mödling, Landesklinikum Wiener Neustadt, Vienna, Austria
Wilhelminenspital, Vienna, Austria
FH Wiener Neustadt, Vienna, Austria

Background: Atherosclerosis and coronary heart disease (CHD) have a complex pathophysiology and it is known that an inflammatory process plays an important role. It is also known that elevated rates of inflammatory markers like neutrophil to lymphocyte ratio (NLR) are associated with CHD. Goal of this study was to evaluate the association between NLR and the severity of CHD using the Gensini score.

Methods: All patients who underwent coronary angiography in LK Mödling between May and November 2012 were recruited in this study retrospectively. Coronary angiography was performed by experienced cardiologists and laboratory parameters were accessed in all patients before angiography, including inflammatory parameter as well as lipids and coronary enzymes.

To define the severity of CHD the Gensini score was used. A narrowing of the lumen of coronary arteries is calculated as 1 for 1% to 25% stenosis, 2 for 26% to 50%, 4 for 51% to 75%, 8 for 76% to 90%, 16 for 91% to 99% and 32 for total occlusion. High Gensini scores were defined as rates over 20.

Statistical analysis was performed with SPSS version 23. Independent sample t-test or Mann-Whitney U-test was used to compare parametric continuous variables and the Pearson or Spearman test for correlating NLR with the Gensini score.

Results: 437 patients were recruited in this study (63.2% male and 36.8% female). 27.7% of the patients underwent coronary angiography because of acute coronary syndrome (ACS) and 72.3% because of objective ischemic signs. In 35% of the patients with ACS ST-segment elevation myocardial infarction (STEMI) was present and in 64.5% a non-ST-segment elevation myocardial infarction (NSTEMI). An amount of 5% of all patients already had a coronary artery bypass graft (CABG) operation and 18.5% a percutaneous transluminal coronary angioplasty (PTCA).

NLR was significantly higher in patients with ACS ($n=437$, $p<0.001$) but did not differ in patients with STEMI and NSTEMI ($n=121$, $p=0.112$). High rates of Gensini score were found in 66.1% in patients with ACS and in 39.7% in patients without ACS. Patients with high and low Gensini score did not differ in terms of comorbidities and risk factors like hypertonia, hyperlipidemia, obesity, diabetes, smoking and cardiac family history. In all patients, with and without ACS, NLR significantly correlated with the amount of Gensini score ($n=436$, $p<0.001$) and thus with severity of CHD. In this population NLR was significantly higher in patients with high Gensini score ($p<0.001$). In patients without ACS, NLR also correlated with the amount of Gensini score ($n=315$, $p=0.001$). In this population NLR was significantly higher in patients with high Gensini Score ($p=0.035$) as well.

Conclusions: NLR is significantly higher in patients with ACS, STEMI as well as in NSTEMI, than in patients without ACS. In the future, it may be useful for earlier identification of an NSTEMI. Furthermore, the severity of CHD measured by the Gensini score is significantly correlating with elevated NLR rates and may also be a useful laboratory parameter in identifying the severity of CHD. Of course, this is a retrospective study and to support this hypothesis more prospective studies are needed.

9-5

Pro-B-type natriuretic peptide strongly predicts cardiovascular mortality in coronary artery disease patients with type 2 diabetes

D. Zanolin, P. Rein, C.H. Saely, A. Vonbank, C. Lins, A. Leiherer, A. Schuler, P. Schwerzler, A. Mader, A. Muendlein, H. Drexel

VIVIT-Institute, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
Private University of the Principality of Liechtenstein, Triesen, Liechtenstein

Background: Elevated pro-B-type natriuretic peptide (proBNP) is associated with an increased risk of cardiovascular events in various populations including patients with type 2 diabetes (T2 DM) and patients with coronary artery disease (CAD). The power of this biomarker to predict cardiovascular mortality in patients with the combination of T2 DM and CAD is unclear and is addressed in the present study.

Methods: We prospectively investigated a consecutive series of 591 patients with angiographically proven CAD over a mean follow-up period of 5.9 ± 1.1 years.

Results: At baseline, proBNP was significantly higher in patients with T2 DM ($n = 163$; 27.6% of the study population) than in nondiabetic subjects (793 ± 1249 vs. 685 ± 1401 pg/ml; $p = 0.020$). Prospectively, cardiovascular death occurred significantly more frequently in patients with T2 DM than in nondiabetic subjects (14.1 vs. 6.3%; $p = 0.002$) and cardiovascular death strongly increased over tertiles of proBNP in patients with T2 DM (4.3%, 21.7%, and 73.9%, respectively; $p = 0.019$) as well as in subjects without T2 DM (11.1%, 14.8%, and 74.1%, respectively; $p < 0.001$). Concordantly, serum proBNP significantly predicted cardiovascular mortality after adjustment for age, gender, smoking, LDL cholesterol, HDL cholesterol, hypertension, and eGFR both in patients with T2 DM (standardized adjusted HR 2.36 [1.48–3.77]; $p < 0.001$) and in those without T2 DM (HR 1.59 [1.19–2.11]; $p = 0.002$).

Conclusions: We conclude that serum proBNP strongly predicts cardiovascular mortality in CAD patients with T2 DM as well as in nondiabetic CAD patients.

9-6

Levels of platelet microRNA-223, microRNA-150 and microRNA-21 in patients with coronary artery disease during dual anti platelet therapy and after cessation of P2Y12-inhibitor therapy

B. Jäger, S. Stojkovic, P. M. Haller, E. Piackova, B. Kahl, T. Andric, J. Wojta, K. Huber

3. Med. Abteilung mit Kardiologie, Wilhelminenspital, Vienna, Austria
Universitätsklinik für Innere Medizin II, Medizinische Universität Wien, Vienna, Austria

Background: Platelet micro-RNA (miRNA) determination has been suggested for monitoring and guiding platelet reactivity in patients with coronary artery disease (CAD) on dual anti-platelet therapy (DAPT). Aim of this study was to investigate the course of miRNA-223, miRNA-150 and miRNA-21 levels in patients with stable CAD on DAPT (aspirin plus clopidogrel, or prasugrel or ticagrelor) following cessation of the respective P2Y12-inhibitor, and to compare micro-RNA levels in different P2Y12-inhibitors.

Methods: In total, 62 patients with stable CAD on DAPT with a planned and physician-driven cessation of P2Y12 inhibition (clopidogrel: $n = 19$, prasugrel: $n = 19$, ticagrelor: $n = 24$) were prospectively included. All patients were free from ischemic or bleeding events for at least 6 months. Expression levels of miRNA-223, miRNA-150 and miRNA-21 were assessed at 4 pre-specified time points: at baseline (BL, i. e. the last day of P2Y12-inhibitor intake before cessation), as well as on day 10, day 30 and day 180 following cessation of the P2Y12-inhibitor, respectively.

Result: We found no significant changes in platelet miRNA-223, miRNA-150 and miRNA-21 before and after cessation of the different P2Y12-inhibitors. However, in univariate analysis baseline miRNA-223 and miRNA-21 levels were significantly increased in patients taking ticagrelor as compared to prasugrel ($p < 0.05$). Expression levels of miRNA-223, miRNA-150 and miRNA-21 were also significantly increased on day 10 and day 30 following therapy with ticagrelor as compared to prasugrel ($p < 0.05$), but no difference was observed on day 180. No difference in miRNA levels was found between clopidogrel and prasugrel at any time during or after P2Y12-inhibitor intake.

After correction for confounders (by repeated measurement ANCOVA), choice of P2Y12-inhibitor, (but not time point) was the major predictor of miRNA-223, miRNA-150 and miRNA-21 levels in patients with planed cessation of DAPT with significant between-group difference for ticagrelor as compared to prasugrel and clopidogrel ($p < 0.01$).

Conclusions: No significant changes in platelet- miRNA-223, miRNA¬-150 and miRNA-21 levels were observed after cessation of the different P2Y12-inhibitors in stable patients following PCI. The significant difference in platelet microRNA expression levels (miRNA-223, miRNA-150 and miRNA-21) between ticagrelor and prasugrel or clopidogrel might indicate a more favorable action of ticagrelor as miRNA-223 has been shown to be protective for cardiovascular events.

9-7

Profile of ischemic heart disease in German immigrants and their descendants in a region of south of Brazil: A comparison of initial symptoms report between two generations

S. Zimmermann, A. Mansur, C. Vianna, M. Moretti, S. Starke, L. Cesar

Heart Institute (InCor), Sao Paulo University Medical School (FMUSP) – Sao Paulo, Sao Paulo, Brazil
Hospital Santa Catarina, Blumenau, Brazil

Background: We know nothing about ischaemic heart disease (IHD) in Germans arrived in Brazil in the beginning of last century, and their descendants. The aim is to compare them with their descendants of the first generation regarding clinical and age of presentation of the disease.

Methods: We performed analysis in all medical records of Germans and first generation descendants at hospitals and cardiology clinics in Blumenau, Brazil. We have evaluated risk factors (RF), how was the first presentation of IHD and coronary angiography data. A total of 177 from 299 records had information in who was possible to confirmed IHD. There were 68 patients born in Germany, Switzerland, Poland and Austria,

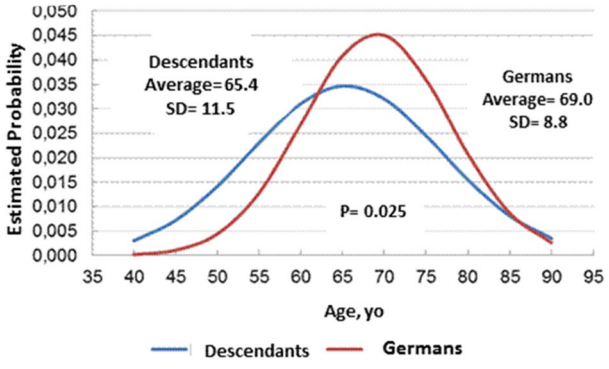


Fig. 1 | P 9-7

considered Germans (G) and 99 Descendants (D). In-group D, there were 29 with both parents been Germans and 70 with only one of the parents.

Results: The average age at diagnosis was 66.8 + 10.6 years and there were significant differences between the groups with group G (69.0 + 8.8 years) older than group D (65.4 + 11.5 years ($p = 0.025$), by 4 years at diagnose of IHD (Fig. 1 | P 9-7). There was a significant difference in relation to gender/age interaction when we looked at those men > 55 and women > 65 years old in the G group compared to those men < 55 and women < 65 years old ($p = 0.003$). We did observe no significant difference in relation to risk factors neither in coronary angiography aspects, but comparing lipid profiles we observed that groups were not significantly different for LDL-chol values ($p = 0.355$) but were for HDL-chol, with group G having higher values than group D, respectively 48.4 + 11.1 vs 43.3 + 11.2 ($p = 0.005$).

Conclusions: Inspite of the maintenance of their habits with a high fat diet, Germans had their first episode of IHD older than their descendants and new lifestyle in a new environmental may have a negative impact for risk factors.

Postersitzung 10 – Risikofaktoren Stoffwechsel Lipide 1

10-1

Single nucleotide polymorphisms at the HMGCR gene locus significantly predict total mortality in angiographied coronary patients with the metabolic syndrome

A. Leiherer, A. Muendlein, C. H. Saely, P. Rein, A. Vonbank, A. Schuler, P. Schwerzler, A. Mader, P. Fraunberger, H. Drexel

VIVIT-Institute, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
Private University of the Principality of Liechtenstein, Triesen, Liechtenstein
Medizinisches Zentrallabor, Feldkirch, Austria

Background: Hydroxy-methyl-glutaryl-CoA reductase (HMGCR) protein catalyzes the rate-limiting step in cholesterol synthesis and is the major target for cholesterol lowering drug therapy. Genetic variations at this locus have recently been linked with coronary heart disease. The association of HMGCR gene variants with mortality in patients with the metabolic syndrome (MetS) has not yet been evaluated and is addressed in the present study.

Methods: We assessed the HMGCR-genotype with respect to the tagging single nucleotide polymorphisms (SNPs) rs10515198, rs3846662, rs7717396, rs3846663, and rs4703670 as well as the previously investigated variants rs12654264 and rs12916 in a high-risk cohort of 299 MetS patients undergoing coronary angiography for the evaluation of established or suspected stable coronary artery disease. Prospectively, we recorded mortality over a follow-up of up to 8 years.

Results: As is shown in the table variants rs3846662, rs3846663, rs4703670, rs12654264 and rs12916 were significantly associated with mortality in our patients after multivariate adjustment including LDL cholesterol and statin therapy.

Conclusions: We conclude that common HMGCR variants are significantly linked with total mortality in angiographied coronary patients with the MetS.

SNP	HR [95%CI]	p-value
rs10515198	1.25 [0.67-2.33]	0.488
rs3846662,	1.57 [1.05-2.36]	0.030
rs7717396	1.44 [0.605-3.44]	0.409
rs3846663	1.81 [1.16-2.82]	0.009
rs4703670	1.71 [1.07-2.75]	0.026
rs12654264	1.82 [1.17-2.83]	0.008
rs12916	1.59 [1.05-2.42]	0.029

multivariate adjustment including LDL cholesterol and statin use

Fig. 1 | P 10-1 HGMCR SNPs as predictors of mortality in MetS patients

10-2

The creatinine to uromodulin ratio in serum predicts major cardiovascular events independently from the presence of type 2 diabetes

A. Leiherer, A. Muendlein, C. H. Saely, J. Ebner, E.-M. Brandtner, A. Schuler, P. Schwerzler, A. Mader, P. Fraunberger, H. Drexel

VIVIT-Institute, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
Private University of the Principality of Liechtenstein, Triesen, Liechtenstein
Medizinisches Zentrallabor Feldkirch, Feldkirch, Austria

Background: Low concentrations of the kidney protein uromodulin are associated with type 2 diabetes (T2 DM) and with chronic kidney disease (CKD). The serum creatinine to uromodulin ratio recently has attracted interest as a marker of CKD. Whether this ratio also is associated with the risk for major cardiovascular events is unknown and is addressed in the present study.

Methods: We measured uromodulin in 529 coronary patients and prospectively recorded major cardiovascular

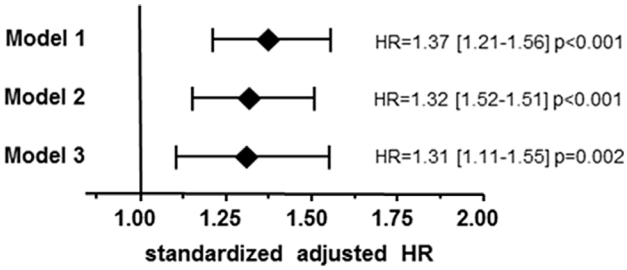


Fig. 1 | 10-2 The Forest plot represents the hazard ratios (HR) with 95% confidence interval (CI) for the association between the creatinine-uromodulin ratio and the risk for major cardiovascular events (B) in the study population. Model 1 represents univariate analyses. Model 2 includes the covariates age, gender, and body mass index (BMI). Model 3 includes the parameters included in Model 2 and in addition systolic blood pressure (SBP), diastolic blood pressure (DBP), high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, the type 2 diabetes (T2DM) status, the current smoking status, C-reactive protein (CRP), pro brain natriuretic protein (proBNP) and the baseline CAD status.

events (coronary death, fatal and non-fatal ischemic stroke, and non-fatal myocardial infarction) over up to 8 years.

Results: During follow-up, a total of 91 major cardiovascular events occurred. The incidence of major cardiovascular events was significantly higher in patients with T2 DM ($n=141$) than in those who did not have diabetes (25.4% vs. 14.6%; $p=0.004$). The creatinine to uromodulin ratio significantly predicted major cardiovascular events both univariately (HR 1.37 [95%CI 1.21–1.56], $p<0.001$) and after multivariate adjustment including the presence of T2 DM (HR 1.36 [CI 1.18–1.58], $p<0.001$, Fig. 1|10-2).

Conclusions: In conclusion, this study for the first time shows that the serum creatinine to uromodulin predicts major cardiovascular events independently from conventional risk factors including the presence of T2 DM. Given that the biological role of uromodulin is still elusive this result appears important and may stimulate future research on uromodulin.

10-3

Bariatric surgery alters the intrinsic coagulation cascade

B. Ebenbauer, P. Hohensinner, C. Kaun, M. Prager, J. Wojta, G. Rega-Kaun

Innere Medizin 2, Kardiologie, Medizinische Universität Wien
Krankenhaus Hietzing, Vienna, Austria
Wilhelminenspital, Vienna, Austria

Background: Obesity is associated with a prothrombotic milieu and increased risk for thrombotic events. Bariatric surgery is the most effective treatment for obesity resulting in dramatic weight loss and reduced inflammation and extrinsic coagulation pathway activation. The aim of our current study was to identify changes in the intrinsic coagulation pathway.

Methods: Blood samples were drawn from 76 patients undergoing Roux-en-Y gastric bypass surgery before and 1 year after. Activated partial thromboplastin time (APTT), total and active protein c (PC), soluble thrombomodulin (sThromb) and thrombin antithrombin complexes (TAT) were evaluated.

Results: APTT was increased one year after bariatric surgery from 28.9 ± 4.5 sec. to 31 ± 4.5 sec. ($p<0.001$). Changes in APTT were not due to increased levels of PC as total PC (187.5 ± 63% before surgery versus 121.7 ± 54.2% after bariatric surgery, $p<0.001$) and active PC (134 ± 58% before surgery versus 67.8 ± 63.9% after bariatric surgery, $p<0.001$) were similarly reduced one year after surgery. Concomitantly, sThromb was significantly reduced (5.8 ± 2.5 ng/ml before surgery versus 3.3 ± 1.6 ng/ml after surgery) indicating reduced activation of endothelial cells and less activation of PC. Surprisingly, TAT was significantly elevated one year after surgery (2.2 ± 5.7 ng/ml before surgery versus 4.6 ± 8.7 ng/ml after surgery, $p=0.01$) suggesting an increased thrombotic risk regardless of changes observed in APTT.

Conclusions: Bariatric surgery induced weight loss is associated with an amelioration of coagulation risk including a previously reported reduction in tissue factor and plasminogen activator inhibitor 1. However, bariatric surgery is also associated with deep vein thrombosis. Our current data partially support the notion of an amelioration of coagulation risk with increased APTT time independent of PC and reduced activation of thrombomodulin. However, we also find increased levels of TAT which could indicate a remaining dysfunctional coagulation system after bariatric surgery and support recent findings of increased risk of vein thrombosis.

10-4

Impact of past and current smoking on the risk of future cardiovascular events in angiographied coronary patients with type 2 diabetes

C. H. Saely, C. Lins, D. Zanolin, A. Leiherer, A. Vonbank, A. Schuler, P. Schwerzler, A. Mader, A. Muendlein, P. Rein, H. Drexel

VIVIT-Institute, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
Private University of the Principality of Liechtenstein, Triesen, Liechtenstein

Background: Smoking is a major risk factor for heart disease. When combined with other risk factors–such as unhealthy blood cholesterol levels, high blood pressure, and overweight or obesity–smoking further raises the risk of heart disease. The impact of smoking on cardiovascular event risk in angiographied coronary patients is unclear and is addressed in the present study.

Methods: We enrolled 1804 consecutive patients undergoing coronary angiography for the evaluation of established or suspected stable coronary disease (CAD). Patients who had smoked within 30 days prior to angiography were considered current smokers. Prospectively, cardiovascular events were recorded over a mean follow-up time of 6.3 ± 3.7 years.

Results: At baseline, both in patients with T2 DM ($n=522$; 28.9% of the study population) and in non-diabetic subjects the prevalence of a past (44.1 and 39.5%; $p=0.035$), and, albeit less so, of current smoking (18.0 and 17.7%; $p=0.247$) was high. Among patients with T2 DM the prevalence of significant CAD with lumen narrowing ≥50% was 61.0% in those who had never smoked vs. 70.9%, $p=0.032$ and 70.8%, $p=0.101$ and in past and current smokers, respectively. Among non-diabetic patients the corresponding prevalence rates of significant CAD were 45.9% vs. 63.8%, $p<0.001$ and 53.7%, $p=0.046$, respectively. Prospectively, current smoking independently predicted cardiovascular events after multivariate adjustment including baseline CAD in patients with diabetes (HR 1.93 [1.20–3.08]; $p=0.006$) as well as in non-diabetic patients (HR 1.50 [1.07–2.09]; $p=0.019$), whereas past smoking neither in patients with T2 DM nor in non-diabetic subjects was associated with cardiovascular events (HRs 1.07 [0.74–1.55]; $p=0.715$ and HR 1.11 [0.87–1.41]; $p=0.415$). An interaction term diabetes x current smoking was not significant ($p=0.350$), indicating that current smoking was equally predictive of cardiovascular events in patients with T2 DM and in nondiabetic subjects.

Conclusions: We conclude that current but not past smoking strongly increases cardiovascular event risk in patients with angiographied coronary patients with diabetes independently from the baseline CAD state.

10-5

Serum proBNP predicts a decline in kidney function independently of type 2 diabetes, the baseline kidney function and baseline coronary artery disease

C. H. Saely, C. Lins, D. Zanolin, A. Leiherer, A. Vonbank, A. Schuler, P. Schwerzler, A. Mader, A. Muendlein, P. Rein, H. Drexel

VIVIT-Institute, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
Private University of the Principality of Liechtenstein, Triesen, Liechtenstein

Background: Elevated pro-B-type natriuretic peptide (proBNP) is a marker of cardiovascular event risk in various patient populations including patients with type 2 diabetes (T2 DM) and patients with coronary artery disease (CAD). Whether proBNP also predicts a decline in kidney function is not known and is addressed in the present study.

Methods: Both at baseline and after 4 years of follow-up we assessed kidney function in 462 patients with angiographically proven coronary artery disease (CAD).

Results: At baseline, estimated glomerular filtration rate (eGFR) significantly decreased over tertiles of proBNP (82 ± 20, 80 ± 19, 74 ± 22 ml/min/1.73 m^2; $p = 0.003$). Further, serum proBNP significantly predicted a decline in eGFR from baseline to after 4 years after adjustment for age, gender, and baseline eGFR (F = 7.80; $p = 0.005$). The power of proBNP to predict a decline in kidney function was not attenuated after further adjustment for angiographically determined CAD (F = 7.90; $p = 0.005$) nor after additional adjustment for the presence of T2 DM (F = 7.57; $p = 0.006$).

Conclusions: We conclude that serum proBNP predicts a decline in kidney function independently from T2 DM, the baseline kidney function, and baseline CAD.

10-6

Type 2 diabetes, chronic kidney disease, and mortality in patients with established cardiovascular disease

C. H. Saely, A. Vonbank, C. Lins, D. Zanolin, A. Leiherer, A. Schuler, P. Schwerzler, A. Mader, P. Rein, A. Muendlein, H. Drexel

VIVIT-Institute, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
Private University of the Principality of Liechtenstein, Triesen, Liechtenstein

Background: Both type 2 diabetes (T2 DM) and chronic kidney disease (CKD) are associated with a high risk of cardiovascular disease (CVD) and premature death. We aimed at investigating the single and joint effects of T2 DM and of CKD on all-cause mortality in high-risk patients with established CVD.

Methods: We prospectively investigated 2108 patients with established CVD (1789 with angiographically proven coronary artery disease and 319 with sonographically proven peripheral artery disease) over 7.0 ± 2.7 years.

Results: Deaths occurred more frequently in T2 DM patients ($n = 652$) than in non-diabetic subjects (38.2% vs. 19.6%; $p < 0.001$) and in patients with CKD (estimated glomerular filtration rate eGFR <60 ml/min/1.73 m^2; $n = 357$) than in those with an eGFR ≥60 ml/min/1.73 m^2 (48.8% vs. 19.8%; $p < 0.001$). When both, T2 DM and CKD were considered, 1248 subjects had neither T2 DM nor CKD, 503 had T2 DM but not CKD, 208 did not have diabetes but had CKD, and 149 had both diabetes and CKD. When compared with mortality among patients with neither T2 DM nor CKD (16.1%), mortality was significantly higher in patients with T2 DM who did not have CKD (30.5%; $p < 0.001$) as well as in non-diabetic patients with CKD (40.1%; $p < 0.001$) and was highest in patients with both, T2 DM and CKD (62.4%; $p < 0.001$), in whom mortality was higher than in those with T2 DM but no CKD ($p < 0.001$) or those without T2 DM but with CKD ($p = 0.045$); mortality was higher in non-diabetic CKD patients than in in diabetic patients who did not have CKD ($p = 0.013$).

Conclusions: We conclude that CKD in patients with established CVD confers an even higher mortality risk than T2 DM. Mortality is extremely high in CVD patients with the combination of CKD and diabetes.

10-7

LDL cholesterol target achievement in coronary artery disease versus peripheral arterial disease patients with type 2 diabetes

A. Schuler, C. H. Saely, A. Vonbank, D. Zanolin, A. Leiherer, J. Ebner, A. Muendlein, P. Schwerzler, A. Mader, H. Drexel

VIVIT-Institute, Academic Teaching Hospital Feldkirch, Feldkrich, Austria
Private University of the Principality of Liechtenstein, Triesen, Liechtenstein

Background: Patients with the combination of type 2 diabetes (T2 DM) and coronary artery disease (CAD) or peripheral arterial disease (PAD) are at an extremely high cardiovascular risk and according to current guidelines should have LDL cholesterol values of at least <70 mg/dl.

Whether LDL cholesterol target achievement is better in CAD or in PAD patients with T2 DM is not known and is addressed in the present study.

Methods: We enrolled 582 Caucasian patients with T2 DM in a Central European tertiary care center, of whom 446 had angiographically proven CAD and 136 sonographically proven PAD.

Results: Achievement of the <70 mg/dl LDL cholesterol target was very low in CAD patients (6.5%) and higher but still low in those with PAD (21.3%). Statin use was lower in CAD than in PAD patients (54.0 vs. 70.6%; $p = 0.055$), but CAD remained significantly associated with poorer LDL cholesterol target achievement after adjustment for statin therapy, age and gender (OR 3.51 CI [1.99–6.18]; $p < 0.001$).

Conclusions: We conclude that the LDL cholesterol target of <70 mg/dl is met by a minority of T2 DM patients with CAD or PAD. Target achievement is even worse in CAD than in PAD patients with T2 DM.

10-8

Screening von Risikofaktoren als Sekundärprävention durch betriebliche Gesundheits-Checks

M. Luger, B. Ritmannsberger, E. Luger, L. Angelmaier, M. Schätzer, M. Lechleitner, A. Rieder, F. Hoppichler

Special Institute for Preventive Cardiology And Nutrition – SIPCAN, Salzburg, Österreich
Abteilung für Sozial- und Präventivmedizin, Zentrum für Public Health, Medizinische Universität Wien, Wien, Österreich
Abteilung für Innere Medizin, Landeskrankenhaus Hochzirl, Hochzirl, Österreich

Grundlagen: Herz-Kreislauf-Erkrankungen (KHK) haben eine hohe Mortalitätsrate in Österreich (43% aller Todesfälle, 2012). Folglich ist ein Risikoscreening als Sekundärprävention essentiell, um das Risiko für KHK einzuschätzen. Dazu gibt es eine Reihe von multivariaten Risikomodellen: Framingham Risk Score (2008), Prospective Cardiovascular Münster Study (PROCAM), Systematic Coronary Risk Evaluation (SCORE; 2003), ACC/AHA pooled cohort hard CVD risk calculator (1998/2013), QRISK CVD risk estimator (2007), Reynolds CVD risk score (2007/2008), ASCVD Risk Estimator (2013), Joint British Societies (JBS) risk score (2014), Multi-Ethnic Study of Atherosclerosis (MESA) risk score (2015), China-PAR (Predication for ASCVD Risk) risk predictor (2016). Ziel dieser Untersuchung war es, Risikofaktoren zu identifizieren und mittels des ASCVD Risikoschätzers das Risiko für KHK bei österreichischen ArbeitnehmernInnen im Rahmen eines betrieblichen Gesundheits-Checks zu erheben. Zudem wurde die Assoziation der nicht im ASCVD Risikoschätzer inkludierten Parameter analysiert.

Methodik: In der Region Salzburg wurden ArbeitnehmerInnen auf deren Gesundheitsstatus gescreent ($n=408$; 2016). Körpergewicht, -größe, Bauchumfang, Blutdruck, -parameter wurden gemessen, Anamnese, EKG, sowie das 10-Jahres-Risiko für atherosklerotische KHK (ASCVD; inkludierte Parameter: Geschlecht, Alter, Ethnie, Gesamtcholesterin, HDL, systolischer Blutdruck, Diabetes mellitus, Behandlung der Hypertonie, Raucherstatus) wurden durchgeführt. Mittels uni- und multivariater linearer Regressionen wurde die Assoziation der zusätzlich erhobenen Parameter (Familienanamnese KHK und Myokardinfarkt, glomeruläre Filtrationsrate GFR, lipidsenkende Behandlung, BMI, Bauchumfang und C-reaktives Protein), die nicht im ASCVD Risikoschätzer inkludiert sind, aber in anderen Modellen berücksichtigt werden, auf das 10-Jahres-KHK-Risiko analysiert.

Ergebnisse: 267 Männer und 141 Frauen hatten ein mittleres Alter von 45 (Standardabweichung: 10) Jahren, BMI von 25,2 (3,8) kg/m² und Bauchumfang von 92,0 (9,7) (♂) und 81,0 (10,5) cm (♀). Davon waren 21% in einer Führungsposition und 79% Angestellte. 19% der ProbandInnen waren RaucherInnen und 22% Ex-RaucherInnen. Bei 7% bestand bereits diagnostizierte Hypertonie, bei 7% Hyperlipidämie und bei 1% Diabetes mellitus Typ 2. 37% der ProbandInnen waren übergewichtig, 11% adipös und 40% abdominell adipös. 43% konnten als Prä- und 43% als HypertonikerInnen eingestuft werden. Bei 8% wurde ein abnormaler EKG-Befund abgeleitet. Das 10-Jahres-Risiko für atherosklerotische KHK lag zwischen 0% und 21%, im Durchschnitt bei 2,5 (3,3) %, wobei 4% ein erhöhtes (>10%) und 12% ein leicht erhöhtes Risiko (5–10%) aufwiesen. Das 10-Jahres-Risiko für atherosklerotische KHK ist mit folgenden Parametern assoziiert: Bauchumfang ($\beta=0{,}361$, $p<0{,}001$) und GFR ($\beta=-0{,}140$, $p<0{,}05$).

Schlussfolgerungen: Ein hoher Anteil dieser Population wurde als übergewichtig und als Prä- und Hypertoniker klassifiziert. Jede/r 6. ProbandIn zeigte ein (leicht) erhöhtes 10-Jahres-Risiko, durch Verwendung des ASCVD Risikoschätzers. Unter Miteinbeziehung von weiteren Risikofaktoren, zeigte sich, dass ein erhöhter Bauchumfang sowie eine erniedrigte GFR mit einem erhöhten Risiko assoziiert waren. Folglich ist es ratsam, dass im Rahmen eines Risikoscreening auch diese Parameter miteinbezogen werden.

10-9

The A-Body-Shape-Index and type 2 diabetes are mutually independent predictors of cardiovascular events risk in angiographied coronary patients

A. Vonbank, C. H. Saely, C. Lins, D. Zanolin, A. Leiherer, A. Schuler, P. Schwerzler, A. Mader, A. Muendlein, H. Drexel

VIVIT-Institute, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
Private University of the Principality of Liechtenstein, Triesen, Liechtenstein

Background: The A-Body-Shape-Index (ABSI) is calculated based on waist circumference, height and BMI and provides a measure of visceral adiposity. In the general population, this index has been associated with premature mortality. Its power to predict cardiovascular events in high-risk patients is not known and is addressed in the present study.

Methods: We prospectively investigated a large series of 1355 patients undergoing coronary angiography for the evaluation of established or suspected coronary artery disease over 5.0 ± 2.4 years.

Results: At baseline, ABSI scores were significantly higher in patients with T2 DM ($n=419$) than in non-diabetic subjects (14.4 ± 1.3 vs. 14.1 ± 1.2; $p<0.001$). During follow-up, a total of 421 cardiovascular events were recorded. Cardiovascular event risk was significantly higher in patients with T2 DM than in non-diabetic subjects (44.6% vs. 26.0%; $p<0.001$), and in univariate analysis the ABSI significantly predicted cardiovascular events (HR 1.14 [1.06–1.23]; $p<0.001$). In multivariate analyses, both T2 DM and ABSI proved independently predictive of cardiovascular events, with standardized adjusted HRs of 1.68 [1.37–2.06]; $p<0.001$ and 1.12 [1.02–1.24]; $p=0.016$, respectively.

Conclusions: We conclude that ABSI and T2 DM are mutually independent predictors of cardiovascular events in angiographied coronary patients.

Postersitzung 11 – Basic Science 3

11-1

Circulating miRNA as potential biomarkers related to 18-FDG PET-MRI perfusion- metabolism mismatch

J. Mester-Tonczar, J. Winkler, D. Lukovic, A. Gugerell, K. Zlabinger, M. Gyöngyösi

Department für Kardiologie, Allgemeines Krankenhaus der Stadt Wien, Vienna, Austria

Background: Positron emission tomography (PET) imaging with the radiotracer 18- fluoro-desoxy glucose (18-FDG) is used for detecting myocardial viability based on glucose uptake. In ischemic injured, but viable cardiomyocytes, glucose uptake increases because of a metabolism shift from fatty acid to anaerobic glycolysis. After reperfused acute myocardial infarction (AMI) in pigs, varying degrees of severity in ischemic heart failure and left ventricular remodelling were observed. The divergent intensity of the ischemic injury can be investigated by using combined PET-MRI, since the 18F-FDG- glucose PET shows the myocardial viability, while MRI presents the global and segmental wall motion abnormalities. In the present project selected biomarkers were investigated in porcine plasma samples and correlated to the imaging results.

Methods: Closed-chest reperfused myocardial infarction (MI) was induced in pigs by balloon occlusion of the left anterior descending coronary artery. 18-FDG-PET-MRI was performed 3 and 30 days after MI for assessing the area at risk, infarction, and left ventricular function. Four blood samples were drawn from the pigs (in chronological order): before myocardial infarction, directly after occlusion and one hour after reperfusion and at the one month follow up. Plasma was then separated from the blood and stored at –80°C. RNA isolation, followed by cDNA transcription, was performed. Expression levels of miR-21, miR-122, and miR-208 were determined using qPCR. The detected myocardial expression was normalized to a spike-in control (Ce-miR-39). Statistical significance was calculated using a two-tailed t-test.

Results: Combined 18F-FDG-PET-MRI showed that 7 animals presented a mismatch between the two imaging modalities (high cellular FD-glucose uptake in severely hypo-akinetic areas, a currently unexplored phenomenon) 3 days after reperfused AMI. Seven other pigs with "match" between PET and MRI (parallel reduction of myocardial viability and wall motion) served as AMI controls. MRI assessment at the 30 day follow-up showed severely reduced LV global ejection fraction in animals with a FDG-mismatch at 3 days, in contrast with the "match" imaging results of the AMI control pigs (LV EF 35 ± 6% vs 41 ± 6%, $p < 0.05$) (Fig. 1 | 11-1). Plasma concentration of miR-21, typically up- regulated after myocardial injury and in heart failure, increased one month after MI 1.8- fold in the mismatch AMI group and 6.7-fold in the AMI match group over baseline values (p 0.057 between groups). Levels of miR-122, a potential novel biomarker for MI, were upregulated in both groups one month after MI (2.3-fold in the mismatch group and 15.4-fold in the AMI control group). An increase in cardioprotective miR-208 concentration was detected in both groups 1 h after MI (16.5-fold in the mismatch group and 10.2-fold in the control group), with a reduction nearly back to baseline values one month after MI.

Conclusions: A mismatch between perfusion (MRI) and metabolism (18-FDG PET) 3days after reperfused MI predicted worse cardiac function in pigs, interestingly opposite with cardiac biomarker levels. Additional examination is indispensable to determine the importance of the specific miRNAs for being potential myocardial biomarkers.

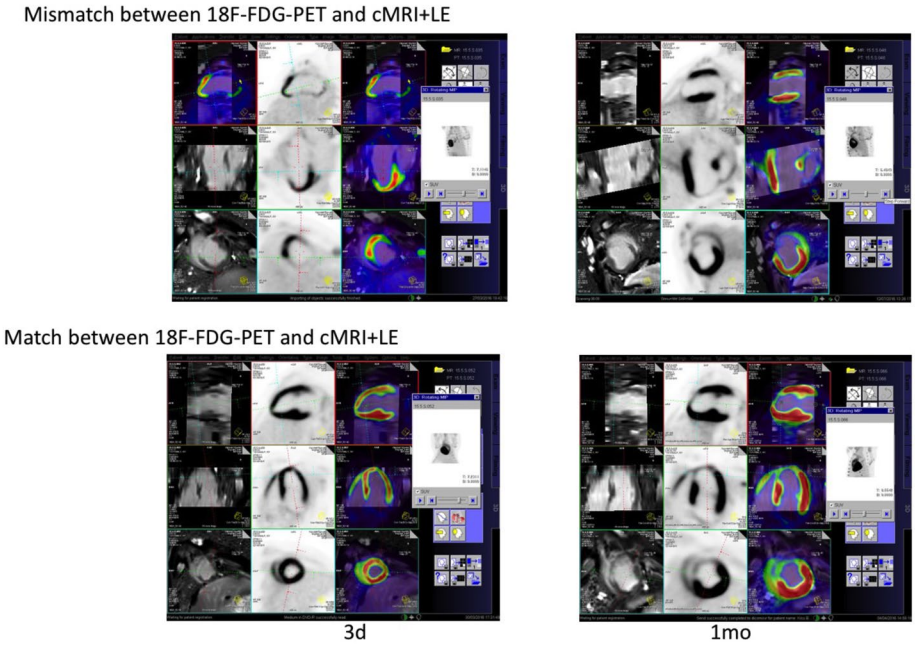


Fig. 1 | 11-1

11-2

Circulating NEP levels are not associated with acute ischemic myocardial injury

D. Traxler, M. Gyöngyösi, J. Winkler, K. Zlabinger, A. Gugerell, A. Spannbauer, D. Lukovic, N. Pavo

Klinische Abteilung für Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Finding a circulating biomarker that can be used for prognosis or monitoring in acute myocardial ischemic injury is a major objective in current cardiovascular research. Circulating Neprilysin (NEP), N-terminal B-type natriuretic peptide (NT-proBNP), neutrophil gelatinase-associated lipocalin (NGAL), endothelin-1 (ET1) and osteopontin are currently thoroughly investigated as cardiac biomarkers to characterize acute myocardial ischemic injury. The aim of our study was to evaluate suitability of these biomarkers in a porcine model of acute myocardial infarction (MI).

Methods: MI was induced in a total of 24 pigs by 90 minutes of percutaneous balloon occlusion of the mid left anterior descending coronary artery (LAD), followed by balloon deflation (reperfusion). Cardiac magnetic resonance imaging (cMRI) was performed at day 3 after MI to determine infarction size and left ventricular (LV) parameters (LV ejection fraction (LVEF), LV end-systolic and -diastolic volume). NEP concentrations alongside other cardiac biomarkers such as NT-proBNP, NGAL, ET1 and osteopontin were measured by ELISA. Expression of the cardiac associated miRs miRNA21 and miRNA29 were determined using rtPCR. The course of biomarkers and their correlations with cMRI parameters were investigated.

Results: cMRI showed an area at risk of 16.4% LV (IQR 14.3–18.9) at day 3 after acute MI accompanying a depressed LV function with 36.1% (IQR 32.5–42.9) of LVEF. NT-proBNP, NGAL as well as miRNA21 and miRNA29 were significantly elevated at 3 weeks compared to baseline levels. ET1 showed an inverse correlation with infarction size [r = –0.67, $p = 0.033$]. Baseline plasma NEP concentrations were 336.6 pg/ml (IQR 136.1–595.6), which is approximately half the level reported for samples from HFrEF patients. Changes in plasma NEP concentrations could not be revealed during the acute and subacute phase of MI [$p = 0.824$] and no correlations with infarction size and LVEF at day 3 [r = –0.10, $p = 0.664$, r = –0.11, $p = 0.604$] were found.

Conclusions: In contrast to a proposed impact of circulating NEP concentrations in chronic heart failure, plasma NEP levels were not associated with acute ischemic injury in a porcine model of reperfused myocardial infarction.

11-3

Development of plasma-exosome miR-1, miR-133 and miR-208 levels during acute myocardial infarction in a porcine model

A. Spannbauer, D. Traxler, D. Lukovic, J. Winkler, A. Borger, K. Zlabinger, A. Gugerell, M Gyöngyösi

Universitätsklinik für Innere Medizin II, Medizinische Universität Wien, Vienna, Austria

Background: Circulating exosomes are important carriers of stable microRNAs (miR) in plasma. The levels of several acute myocardial infarction (AMI) – related miRs have previously been shown to change several hours after AMI. We have investigated the change of exosomal levels of miR-1, miR-133 and miR-208 during the ischemic period of an AMI.

Methods: Under general anaesthesia, pigs underwent 90-min percutaneous occlusion of the mid LAD followed by reperfusion. EDTA blood samples were taken at baseline and at 10, 30, 60 and 90 minutes of occlusion. Plasma was prepared for exosome isolation by progressive centrifugation steps of 1200 × g for 10 minutes, 1800 × g for 10 minutes and 10.000 × g for 20 minutes. The resulting plasma was then filtered through 0.2 µm syringe filters. One mL of thusly prepared plasma was suspended in 9 mL of PBS and ultra-centrifugated at 100 000 × g for 120 minutes, followed by a washing step and another round of centrifugation at 100 000 × g for 120 minutes. miRs were isolated using QIAGEN miRNeasy Serum/Plasma kits, reverse transcribed using QIAGEN miScript RT kit and qPCR was performed using miScript SYBR® Green PCR Kit. Fold changes were normalized using ce-miR-39 Spike-in-Control of the QIAGEN Serum/Plasma kit. Relative fold changes of miR-1, miR-133 and miR-208 at baseline, 10, 30, 60 and 90 minutes after begin of occlusion were evaluated.

Results: Relative fold changes are shown in boxplots. All 3 miRNAs could be detected in the plasma exosomes. However, no significant changes of miR-1 (Fig. 1|11-3), miR-133 (Fig. 2|11-3) and miR-208 (Fig. 3|11-3) levels could be detected

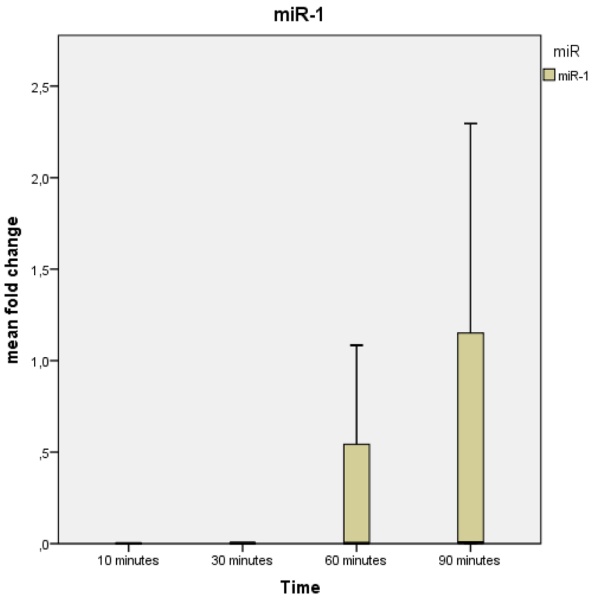


Fig. 1 | 11-3

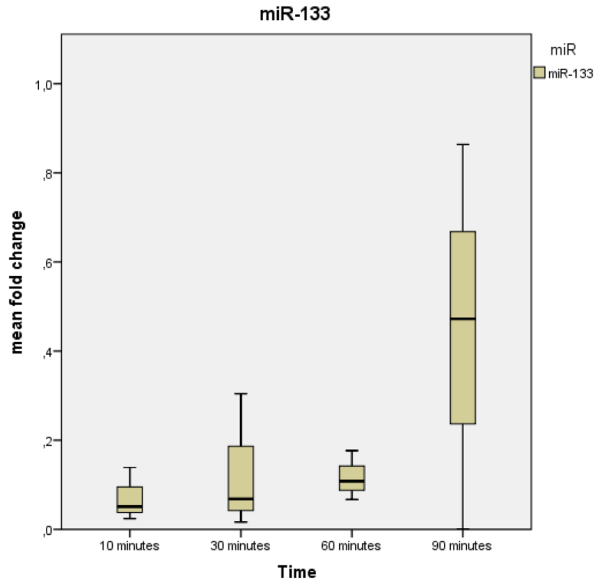


Fig. 2 | 11-3

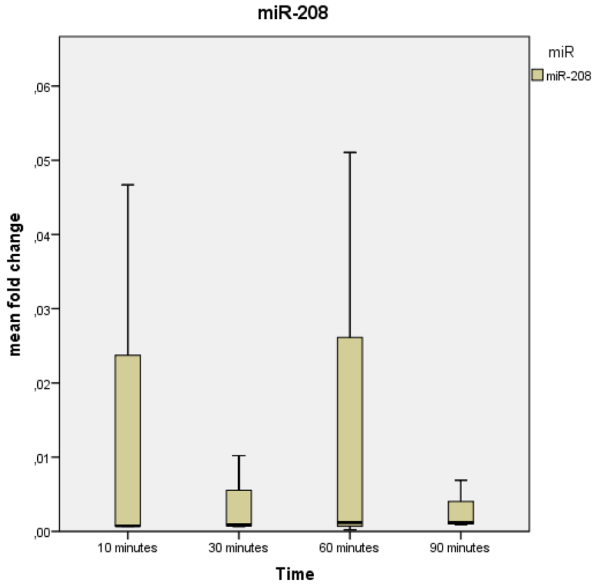


Fig. 3 | 11-3

at the different time points during the course of acute myocardial infarction in the present study.

Conclusions: While all investigated miRNAs could be detected in plasma exosomes, no significant relative changes in miR-1, miR-133 and miR-208 levels could be detected in the present study. It is likely that 90 minutes of ischemia are too short to appreciably change levels of miR expression and their levels in circulating plasma-exosomes.

11-4

Differences in protein expression levels in fibrous heart tissue after heart remodeling following myocardial infarction

A. Gugerell, D. Lukovic, K. Zlabinger, A. Spannbauer, D. Traxler, J. Mester-Tonczar, L. Mandic, C. Müller, J. Winkler, M. Gyöngyösi

Universitätsklinik für Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: To parallel assess the area of myocardial infarction and left ventricular (LV) function, combined imaging modality, 18-fluoro-deoxy-glucose-positron emission tomography with cardiac magnetic resonance imaging with late enhancement (18F-FDG-PET-MRI-LE) was used in an in vivo myocardial infarction model in pigs. 18F-FDG imaging tracer is known as a viability marker in the cardiology imaging. Interestingly, high FDG-uptake in the infarcted area 3 days after reperfused AMI was observed in some cases ("high FDG"). These findings did not match with the corresponding MRI data showing severe segmental hypo-akinesia in the ischemia-affected area. During the 1-month follow-up, these animals developed more severe tissue damage (like fibrosis) and deteriorated heart function with severe adverse remodeling, in contrast with the animals showing uptake-defect (decreased myocardial viability) in the disturbed segmental wall motion areas with less severe LV remodeling. In this experiment, we investigated the molecular basis of the two distinct LV remodeling (high or low 18F-FDG uptake in the infarcted area at 3 days). Therefore, we isolated proteins from the fibrous tissue in the remote zone of the affected hearts using laser capture microdissection.

Methods: Domestic pigs underwent closed chest re-perfused acute myocardial infarction (AMI) via percutaneous balloon occlusion of the mid-LAD for 90 min followed by balloon deflation. Infarct area was evaluated by 18F-FDG-PET-MRI-LE. Heart tissues were collected after 30 days and frozen in liquid nitrogen.

Serial cryo-sections were made from heart tissue of the remote (remodeled) zone. One section was stained with picro sirius red to determine fibrous tissue. From the associated proximate section, the fibrotic tissue area showing picrosirius staining was cut on a laser caption microdissection microscope and collected in lysis buffer. Proteins were isolated and tested for myocardial related as well as fibrosis related biomarkers. Pigs with normal glucose uptake served as AMI-control.

Results: Western blot analysis showed a significant higher level of caspase 3 (+24.4%) and cleaved caspase 3 (+69.4%) in "high FDG" animals. This is attended to a significant lower level of HIF1α (–50%) in this group. Moreover, also p38 MAPK expression is lowered (–24%).

Conclusions: We could show distinct protein expression of the remodeling process after myocardial infarction, depending from the lipid/glucose metabolism after myocardial infarction. The expression of proteins involved in apoptosis were higher in the high-FDG group with switching of the lipid metabolism to anaerob glucose metabolism, as compared to hearts with lack of glucose uptake in the ischemic area. Proteins responsible for cell protection, vascularization and repair mechanisms are upregulated in heart tissue with viability/metabolism match, in contrast with the hearts with viability/metabolism mismatch 3 days post-AMI.

11-5

In vitro effects of anti-anginal drugs on inflammation and coagulation in endothelial cells – a comparative study of nicorandil, trimetazidine and ranolazine

M. Lenz, Z. Krivaja, K.A. Krychtiuk, C. Kaun, S. Rauscher, S. Stojkovic, P.J. Hohensinner, G. Maurer, K. Huber, J. Wojta, W.S. Speidl

Department of Internal Medicine II, MUW Wien, Vienna, Austria
Skin and Endothelium Research Division, Department of Dermatology, MUW Wien, Vienna, Austria
3rd Medical Department, Wilhelminenhospital/Ludwig Boltzmann for Cardiovascular Research, Vienna, Austria
Ludwig Boltzmann Cluster for Cardiovascular Research/Core Facilities, MUW Wien, Vienna, Austria

Background: A substantial body of evidence suggests that atherosclerosis is a chronic inflammatory disease affecting the vessel wall. Increased expression of adhesion molecules and proinflammatory cytokines is associated with an elevated risk for acute cardiac events. Nicorandil, trimetazidine and ranolazine are approved for symptom relieve in patients with stable coronary artery disease. Considering the emphasized role of inflammation in atherogenesis and atherosclerosis, the aim of this study was to test whether these drugs have direct effects on inflammation, coagulation and fibrinolysis in vascular cells in vitro.

Methods: Human umbilical vein endothelial cells (HUVEC) were stimulated with interleukin-1β (IL-1β: 200U/ml) and treated with nicorandil, trimetazidine or ranolazine (500 µM respectively) for 2–24 hours. Expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin) and tissue factor (TF) was measured using flow cytometry as well as real time-PCR. Furthermore, interleukin 6 (IL-6), interleukin 8 (IL-8) and phospho-I-kappa-B-alpha were quantified by specific enzyme-linked immunosorbent assays.

Results: Treatment with ranolazine strongly attenuated IL-1β-induced expression of adhesion molecules, TF, IL-6 and IL-8. Further phospho-I-kappa-B-alpha was significantly reduced. Treatment with trimetazidine resulted in a decreased expression of VCAM-1 and IL-6 without effects on protein expression of ICAM-1, E-selectin and TF. Treatment with nicorandil had no significant effect on expression of adhesion molecules, TF and the cytokines IL-6 and IL-8.

Conclusions: Our findings indicate that ranolazine exhibits anti-inflammatory effects on endothelial cells in vitro by inhibition of NF-kappa-B. Whereas nicorandil as no effects on inflammatory and procoagulant proteins in vitro. The effects of trimetazidine need further studies in detail.

11-6

The impact of age on extracellular matrix protein expression in post-infarction remodeling of the murine heart

F. Nagel, D. Santer, S. Stojkovic, C. Kaun, M. Krssak, J. Wojta, K. Trescher, A. Kiss, B.K. Podesser

Department for Biomedical Research, Ludwig Boltzmann Cluster for Cardiovascular Research, Medical University Vienna, Vienna, Austria
Department of Internal Medicine II, Medical University Vienna, Vienna, Austria
Centre of Excellence High Field MR, Department of Radiology, Medical University Vienna, Vienna, Austria

Background: Aging is associated with higher incidence, mortality and complication rate of myocardial infarction (MI). The extracellular matrix (ECM) is one of the key players in post-infarction remodeling. The aim of this study was to describe potential associations in the expression of ECM proteins in post-infarction remodeling of the geriatric heart.

Methods: In male geriatric (age: 18 months) and young (age: 11 weeks) OF1 mice MI was induced by permanent left anterior descending artery (LAD) ligation. In SHAM groups the procedure was performed without LAD occlusion. 32 days after MI, cardiac MRI was used for hemodynamic evaluation. Plasma and tissue samples were collected 3, 7, and 32 days post-MI. TNC plasma and septum tissue concentrations were assessed by ELISA. Levels of active and total MMP-9 in plasma were measured by activity assay. The mRNA expression of MMP-2, TIMP-1, –2, –3, –4 and Col1 in remote left ventricular myocardium were evaluated by RT-qPCR.

Results: The factors age and MI were associated with impaired cardiac function and LV dilatation in MRI. TNC levels were decreased in geriatric mice after MI compared to the young control group in plasma (3 days: $p<0.001$, 7 days: $p<0.05$) and septum (7 days: $p<0.01$). Whereas no significant differences in total MMP-9 levels were found, active MMP-9 in plasma was increased in geriatric mice after MI (3 days: $p<0.01$). MMP-2 (7 days: $p<0.05$), TIMP-1 (7 days: $p<0.05$), TIMP-2 (7 days: $p<0.05$) and Col1 (3 days and 7 days: $p<0.05$) were significantly more expressed in young mice than in geriatric mice after MI. Young sham-operated mice showed increased expression of TIMP-4 compared to all geriatric sham operated groups and MI groups ($p<0.01$).

Conclusions: In this study geriatric mice after MI showed increased levels of active MMP-9 – a factor described as associated with adverse remodeling. In addition, geriatric mice showed lower levels of Tenascin-C compared to the young control group. However, previous studies demonstrated that elevated expression of TNC contributed to worse cardiac function in patients after MI. Further clinical studies in geriatric patients are needed for the validation of ECM proteins as markers for adverse post-MI remodeling.

11-7

The regulatory role of Tenascin C on matrix metalloproteases expression induced by hypoxia and reoxygenation in H9C2 cardiomyocytes cell line

I. Goncalves, L. Soto-Gonzalez, E. Verena Tretter, K.U. Klein, A. Kiss, B. Podesser

Ludwig Boltzmann Cluster for Cardiovascular Research at the Center for Biomedical Research, Medical University Vienna, Vienna, Austria
Department of General Anesthesiology and Intensive Care, Medical University Vienna, Vienna, Austria

Background: Upregulation of Tenascin C (TNC) plays a role in the progression of maladaptive left ventricle remodelling following myocardial infarction and hypertension, however the underlying mechanisms are not fully elicited.

Aim: This study aims to evaluate the effect of hypoxia on the expression of TNC, MMP2 and MMP9 as well as whether TNC regulates MMPs formation in cardiomyocytes.

Methods: H9C2 rat cardiomyocytes cell line were submitted to 6, 16 and 24 hours of hypoxia in a 95% N^2 and 5% CO^2 atmosphere, with and without 60 minutes of reoxygenation. Additionally, TNC was added to the same cell line under normoxic conditions in 1, 3 and 10 µg/mL, for 6 and 24 hours. The mRNA expression of TNC, MMP2 as well as MMP9 were determined by RT-qPCR and normalised to β-actin as housekeeping gene.

Results: Under normoxic conditions TNC expression was not detectable. In contrast, hypoxia significantly induced TNC expression in all time points ($P<0.05$, respectively). mRNA expression of MMP2 was obtained after 6 hours of hypoxia and 60 minutes reoxygenation (2.1 fold-change). The expression of MMP9 was increased following 24 hours hypoxia (15.8 fold-change). Interestingly, both MMP2 and MMP9 were markedly increased by the administration of human TNC following 24 hrs (1.5 and 2.8 fold change, respectively).

Conclusions: This study first time demonstrated that hypoxia and reoxygenation markedly increased the expression of TNC. Additionally, TNC has a significant effect on MMP2 and MMP9 regulation. These results might indicate the novel mechanism of MMPs regulation by TNC as well as represent a therapeutic target to reverse maladaptive left ventricle remodeling.

Postersitzung 12 – Bildgebung 2

12-1

Abschätzung transmitraler und pulmonalvenöser Blutflussprofile aus volumetrischen MRT Funktionsparametern des linken Ventrikels und linken Atriums

C. Reiter, G. Reiter, C. Kräuter, A. Greiser, M. Fuchsjäger, D. Scherr, U. Reiter, A. Schmidt

Universitätsklinik für Innere Medizin, Klinische Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Österreich
Siemens Healthcare Diagnostics GmbH, Graz, Österreich
Klinische Abteilung für allgemeine radiologische Diagnostik, Medizinische Universität Graz, Graz, Österreich
Siemens Healthcare GmbH, Erlagen, Deutschland

Grundlagen: Die Cine-Bildgebung der Herz-Magnetresonanztomographie (MRT) stellt die klinische Referenz-Standardmethode zur Bestimmung linksventrikulärer (LV) und linksatrialer (LA) Volumina dar. Aus der zeitlichen Ableitung der LV und LA Volumen-Zeit Kurven lassen sich darüber hinaus maximale Füll- und Auswurfraten dieser kardialen Kammern bestimmten, welche generisch als Flussgrößen (Volumsänderungen pro Zeit) interpretiert werden können. Ziel der Studie war es zu untersuchen, ob transmitrale und pulmonalvenöse Blutflussprofile aus volumetrischen maximalen Füll- und Auswurfraten des LV und LA abgeschätzt werden können.

Methodik: 42 PatientInnenen ohne höhergradige Klappenvitien (Alter 61 ± 8 Jahre; m/w = 21/21) wurden in die prospektive Studie eingeschlossen und mittels EKG-getriggerter 3T MRT Cine-Realtime- und 4D-Phasenkontrast-Bildgebung (4D-Flow) des linken Herzens untersucht. Zur Bestimmung der LV und LA Volumen-Zeit Kurven wurde das linke Herz mit einem Stapel von Cine-Realtime-Serien in 4-Kammerblick Orientierung ohne Abstand überdeckt (Schichtdicke, 7 mm; Schichtanzahl, typisch 15; Aufnahmezeit, 30 Herzschläge). LV und LA Volumen-Zeit Kurven wurden mittels semi-automatischer Segmentierung der Herzkammern in allen kardialen Phasen ermittelt. Die früh- und spätdiastolischen maximalen linksventrikulären Füllraten (LV-PFRE, LV-PFRA), die maximale linksatriale systolische Füllrate (LA-PFRS) sowie die maximale linksatriale frühdiastolische Auswurfrate (LA-PERD) wurden aus der zeitlichen Ableitung der Volumen-Zeit Kurven bestimmt. Transmitrale (E, A) und pulmonalvenöse (S, D) maximale Blutflüsse wurden aus 4D-Flow Datensätzen mittels multiplanarer Rekonstruktion der Messebenen ausgewertet, wobei S und D aus der Summe der Flüsse aller Pulmonalvenen berechnet wurde. Die Zusammenhänge zwischen fluss- und volumetrie-basierten Größen wurden mittels Korrelations-, Regressions- und Bland-Altman-Analyse untersucht.

Ergebnisse: Maximale Flüsse und volumetrische Füll- und Auswurfraten korrelierten signifikant (r = 0.85 für E und LV-PFR¬E, r = 0.59 für A und LV-PFRA, r = 0.56 für S und PFRS, r = -0.63 für D und LA-PERD; $p<0.0001$ in allen Fällen). Volumetrische Füllraten unterschätzten die maximalen Flüsse um 27–30 ml/s im Vergleich zu 4D Flussdaten. Sowohl E/A als auch S/D korrelierten stark mit den korrespondieren volumetrischen Verhältnissen der maximalen Füll- und Auswurfraten (r = 0.84 für E/A und LV-PFRE/LV-PFRA; r = 0.70 für S/D und dem Betrag von LA-PFRS/LA-PERD). Die Standardabweichungen für die Schätzung von flussbasierten aus volumetrischen Verhältnissen waren jeweils 0.24.

Schlussfolgerungen: Bei PatientInnen ohne höhergradige Klappenvitien erlaubt MRT Cine-Realtime Bildgebung die Abschätzung der transmitralen und pulmonalvenösen Blutflussprofile aus volumetrischen maximalen Füll- und Auswurfraten des LV und LA. Die Messung ist schnell und könnte fallweise die zeitintensive Planung und Messung von MRT-Phasenkontrastdaten ersparen.

12-2

Einfluss von inspiratorischem Atemanhalten auf linksventrikuläre und linksatriale volumetrische Herz-MRT Funktionsparameter

C. Reiter, G. Reiter, C. Kräuter, M. Fuchsjäger, A. Schmidt, D. Scherr, U. Reiter

Klinische Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Österreich

Siemens Healthcare Diagnostics GmbH, Graz, Österreich
Klinische Abteilung für allgemeine radiologische Diagnostik, Medizinische Universität Graz, Graz, Österreich

Grundlagen: Die Evaluierung linksventrikulärer (LV) und linksatrialer (LA) Volumina und Auswurffraktionen aus magnetresonanztomogaphischen (MRT) Cine-Serien und Simpson-Scheibchensummations-Methode zeichnet sich durch hohe Genauigkeit und Reproduzierbarkeit aus. Je nach Atemanhaltevermögen des Patienten werden die Daten unter Atemanhalten oder in freier Atmung akquiriert. Der Einfluss des Atemanhaltens auf resultierende LV und LA Volumina sowie die Vergleichbarkeit von LV und LA Funktionsparametern in unterschiedlichem Atemzustand wird kontrovers diskutiert. Ziel der Studie war es, LV und LA Volumina und volumetrische Funktionsparameter während inspiratorischem Atemanhalten und freier Atmung mit identer MR Cine-Bildgebungtechnik aufzunehmen und zu vergleichen.

Methodik: 35 kardiovaskulär asymptomatische Personen (w/m, 20/15; mittleres Alter, 61 ± 8 Jahre) wurden im Rahmen der prospektiven Studie mittels 3T MRT untersucht. Zur Evaluierung der LV und LA Funktion nach der Simpson-Scheibchensummations-Methode wurde das linke Herz mit einem Stapel von Cine-Realtime-Serien in 4-Kammerblick Orientierung ohne Abstand sowohl während inspiratorischem Atemanhalten als auch unter freier Atmung überdeckt (zeitliche Auflösung, 38 ms; Schichtdicke, 7 mm; Schichtanzahl, 15; Aufnahmezeit, 30 Herzschläge; Atemanhaltezeit, dreimal 10 Herzschläge). Maximale und minimale LV und LA Volumina wurden mittels manueller Segmentierung der endokardialen Konturen ausgewertet. Die LV Auswurffraktion (EF) und das LV Schlagvolumen (SV) wurden aus dem LV enddiastolischem (EDV) und endsystolischem (ESV) Volumen berechnet. Aus dem maximalen (LAVmax), minimalen (LAVmin) und LA Volumen vor Kontraktion (LAVbc) ergaben sich die Auswurffraktionen des LA gemäß LATEF = 100×(LAVmax-LAVmin)/LAVmax, LAPEF = 100×(LAVmax-LAVbc)/LAVmax und LACEF = 100×(LAVbc-LAVmin)/LAVbc. LV und LA Volumina, sowie die resultierenden volumetrischen Funktionsparameter unter inspiratorischem Atemanhalten und freier Atmung wurden mittels gepaartem t-Test und Korrelationssanalyse verglichen.

Ergebnisse: Das mittlere RR-Intervall zwischen inspiratorischem Atemanhalten (930 ± 120 ms) und freier Atmung (920 ± 116 ms) unterschied sich nicht ($p = 0.26$). Alle linksventrikulären sowie links atrialen Volumina verringerten sich während inspiratorischem Luftanhalten, EDV, ESV und LAVmax signifikant; EDV: 136 ± 28 ml vs. 130 ± 32 ml ($p = 0.03$), ESV: 64 ± 18 ml vs. 60 ± 17 ml ($p = 0.02$), SV: 71 ± 14 ml vs. 69 ± 17 ml ($p = 0.14$), LAVmax: 86 ± 19 ml vs. 79 ± 18 ml ($p < 0.01$), LAVmin: 47 ± 12 ml vs. 46 ± 13 ml ($p = 0.37$) und LAVbc: 63 ± 16 ml vs. 62 ± 16 ml ($p = 0.18$). LATEF (45 ± 10 % vs. 41 ± 11 %, $p < 0.01$) und LAPEF (27 ± 5 % vs. 22 ± 7 %, $p < 0.01$) verringerten sich während inspiratorischem Luftanhalten, während die linksventrikuläre EF (53 ± 6 % vs. 53 ± 5 %, $p = 0.41$) und LACEF (27 ± 6 % vs. 26 ± 7 %, $p = 0.51$) keine signifikanten Unterschiede zeigte. Die Korrelation der Parameter zwischen freier Atmung und Luftanhalten reichte von r = 0.69 für LACEF bis r = 0.88 für LAVmin.

Schlussfolgerungen: Inspiratorisches Luftanhalten verändert LV und LA Volumina und Funktionsparameter signifikant. Atemmanöver sollten vor allem bei klinischen Follow-Up und Therapie-Monitoring Untersuchungen sowie beim Vergleich von Echo und MRT Parametern berücksichtigt werden.

12-3

Cardiac Magnetic Resonance Imaging in Hemodialysis Patients: Associations with Volume Status

M. Antlanger, S. Aschauer, A. Kammerlander, F. Duca, M. Säemann, D. Bonderman, J. Mascherbauer

Klinik für Innere Medizin III, Abt. für Nephrologie und Dialyse, Medizinische Universität Wien, Vienna, Austria
Klinik für Innere Medizin II, Abteilung für Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Diffuse myocardial fibrosis is one of the key pathophysiologic features in heart failure and can be quantified by cardiac magnetic resonance (CMR) T1 mapping. However, increases in myocardial free water also prolong native T1 times and may impact on fibrosis quantification depending on patient volume status. So far, potential associations of native T1 time with fluid overload remain unknown.

Methods: As volume status is meticulously followed in patients on maintenance hemodialysis (HD), they constitute an ideal study population. In the present study, CMR data of 37 consecutive HD patients were compared with 35 healthy controls. In addition to clinical and echocardiographic data, volume status was quantified by bioimpedance spectroscopy and correlated with CMR T1 time.

Results: While no differences between HD patients and controls were present with regard to age ($p = 0.509$), height ($p = 0.623$), weight ($p = 0.557$) and left ventricular (LV) ejection fraction ($p = 0.273$), cardiac volume was significantly larger in the HD group (LV end-diastolic volume 164 ± 53 vs. 132 ± 26 ml, $p = 0.002$, right ventricular end-diastolic volume 160 ± 45 vs. 139 ± 27 ml, $p = 0.017$). Further, native T1 time was significantly longer in HD patients (1,022 ± 50 vs. 998 ± 47 ms, $p = 0.043$). When taking volume status into account, only fluid overloaded HD patients had longer mean T1 times (short axis: 1,042 ± 46 vs. 1,005 ± 49 ms, $p = 0.055$; 4-chamber: 1,056 ± 52 vs. 1006 ± 50 ms, $p = 0.019$). By simple regression analysis, a significant correlation between fluid status and T1 time was found (R = 0.409, $p = 0.031$).

Conclusions: Patients on HD have larger hearts than healthy controls, possibly due to adaption to shunt volume. Nevertheless, native T1 time was not prolonged among normovolemic HD patients compared to healthy controls. On the contrary, native T1 was significantly longer in fluid overloaded patients. These data indicate an important influence of volume status on native T1 time by CMR mapping, which should be considered also in patients who are not on maintenance HD.

12-4

Cardiovascular MR to guide transcatheter aortic valve replacement: A comparison with CT

A. Mayr, G. Klug, S. Reinstadler, H. J. Feistritzer, M. Reindl, S. Wöhrer, C. Kremser, C. Kranewitter, N. Bonaros, G. Friedrich, G. Feuchtner, B. Metzler

University Clinic of Radiology, Medical University Innsbruck, Innsbruck, Austria
University Clinic of Internal Medicine III, Cardiology and Angiology, Medical University Innsbruck, Innsbruck, Austria

University Clinic of Cardiac Surgery, Medical University Innsbruck, Innsbruck, Austria

Background: Up to 80% of patients undergoing transcatheter aortic valve replacement (TAVR) suffer from chronic renal insufficiency. Therefore, alternatives to reduce the need for iodinated contrast agents are desirable. This study sought to compare a comprehensive cardiovascular magnetic resonance (CMR) imaging protocol with contrast-enhanced computed tomography angiography (CTA) for guidance in TAVR evaluation.

Methods: Non-contrast three-dimensional (3D) "whole heart" CMR imaging for aortic annulus sizing and measurements of coronary ostia heights, contrast-enhanced CMR angiography (MRA) for evaluation of transfemoral routes as well as 128-slice high-pitch dual-source aortoiliofemoral CTA were performed in 16 patients referred for evaluation of TAVR.

Results: Aortic annulus measurements by non-contrast 3D "whole heart" CMR and CTA showed a very strong correlation ($r = 0.956$, $p < 0.0001$; effective annulus area for CMR 430 ± 74 vs. 428 ± 78 mm^2 for CTA, $p = 0.629$, Fig. 1 | 12-4). Regarding decision for valve size there was an excellent agreement between non-contrast 3D "whole heart" CMR and CTA. Moreover, vessel luminal diameters and angulations of aortoiliofemoral access as measured by MRA and CTA showed overall very strong correlations ($r = 0.819$ to 0.996, all $p < 0.001$), the agreement of minimal vessel diameter between the two modalities revealed a bias of 0.02 mm (upper and lower limit of agreement: 1.02 mm and −0.98 mm, Fig. 2 | 12-4).

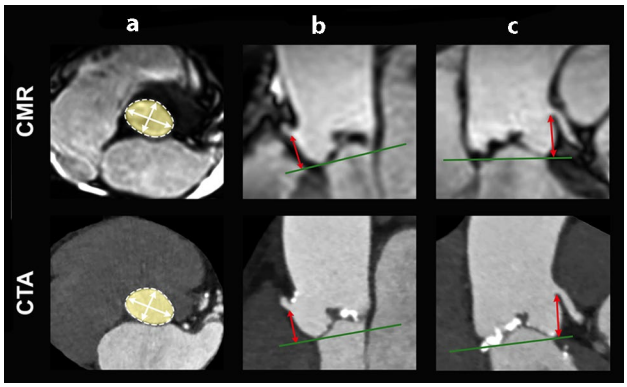


Fig. 1 | 12-4

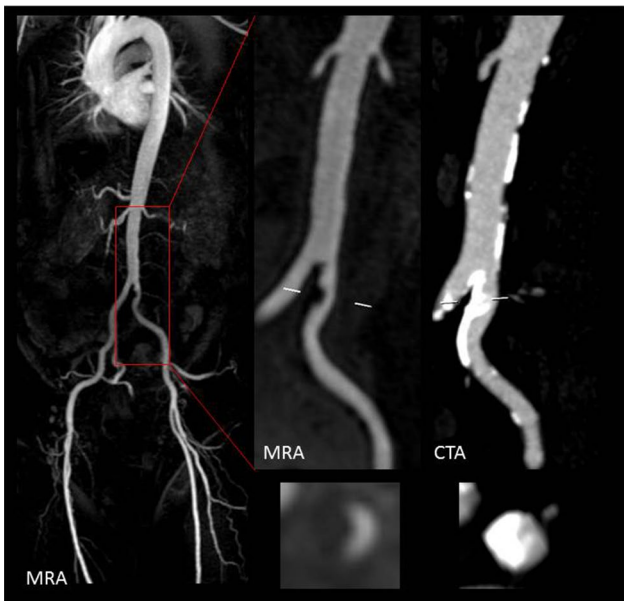


Fig. 2 | 12-4

Conclusions: In patients referred for TAVR, CMR measurements of aortic annulus, coronary ostia heights and minimal aortoiliofemoral luminal diameters showed good to excellent agreement. Decisions based on CMR measurements regrading prosthesis sizing and transfemoral access would not have modified TAVR strategy as compared to a CTA based choice.

12-5

Comparison of 201-Tl-persantin single photon emission computed tomography (SPECT) with contrast enhanced coronary computed tomography angiography in assessment of myocardial ischemia – a retrospective analysis

J. Astl, M. Gyöngyösi, N. Pavo, M. Gottsauner-Wolf, C. Loewe, S. Graf

Department of Cardiology, Medical University Vienna, Vienna, Austria

Background: Coronary artery disease (CAD) remains one of the most frequent causes of mortality in the world. Therefore, it is important to detect CAD and causal risk factors sufficiently early to ensure the best prevention. The role of non-invasive cardiac imaging for risk stratification in primary prevention has been considerably evolving in recent years. Nevertheless there is still room for improvement. A stepwise approach to diagnose CAD including medical history and coronary computed tomography angiography (CCTA) identifies patients with significant CAD but normal stress-test myocardial 201-Tl-Persantin single photon emission computed tomography (SPECT) who may benefit from invasive treatment. Therefore, it is important to evaluate both the predictive values of both examinations and influencing factors causing both false negative and false positive results. The aim of this monocenter retrospective study was to compare the diagnostic performance of both CCTA and SPECT with the results of invasive coronary angiography (ICA) in patients with suspected CAD and to analyse factors contributing to false positive and negative results, respectively.

Methods: Our study reviewed 159 patients between 2006 and 2015 with strong clinical suspicion of CAD and typical angina pectoris retrospectively who underwent both CCTA and SPECT within maximally 1 year for the evaluation of possible CAD. The mean time between both examinations was 23 ± 131 days. Both investigations were performed in a standard manner. The CCTA protocols included both calcium scan according to Agatston method and evaluation of stenosis in all main coronary arteries including the LAD/LM, RCA and RCX. The SPECT protocols included both evaluation of possible ischemia in the areas provided by the relative coronary artery and further myocardial vitality scoring (Summed Difference Score). Basic information was collected from the patients including age, gender, body mass index, risk factors, medical history and diverse laboratory parameters. In 41 patients, an additional diagnostic ICA was performed in a standard manner.

Results: Table 1 lists the clinical characteristics and results of both CCTA and SPECT. Totally, 36 patients (23%) showed reversible defect on SPECT, while 66 patients (42%) had pathological findings on CCTA (significant stenosis in at least one coronary artery). Only in the patient cohort that first underwent

CCTA and showed no significant stenosis at all ($n=36$) a positive correlation between the findings of CCTA and SPECT was found. Thereof, 94% ($n=34$) of these patients also showed no ischemia on SPECT, as shown in Fig. 1|12-5. In comparison with ICA, predictive values including sensitivity, specificity, positive predictive value and negative predictive value for CCTA were 70%, 57%, 76% and 50%, as well as for SPECT were 26%, 86%, 78% and 38%. Between the Agatston Score and the Summed Difference Score no correlation was found, at a p-value of 0,036.

Conclusions: SPECT and CCTA are valuable complimentary investigations for the more exact non-invasive diagnostic of CAD. Compared to other studies predictive values for both investigations were lower in our study. This may be due to the smaller amount of patients. Furthermore, this is a retrospective study and further prospective studies comparing both CCTA and SPECT with ICA are required. Further investigations including gold standard ICA are necessary to estimate the predictive values of the combined non-invasive tests.

12-6

Concordance of cardiac magnetic resonance with 2D-echocardiography for determination of left ventricular function and morphology

G. Klug, A. Kammerlander, S. J. Reinstadler, H.-J. Feistritzer, C. Diem, A. Mayr, S. Müller, J. Mascherbauer, B. Metzler

Innere Medizin III, Kardiologie, Medizinischen Universität Innsbruck, Innsbruck, Austria
Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Several studies have investigated the concordance of 2D-echocardiography with cardiac magnetic resonance imaging (CMR) for the determination of left ventricular function, volumes and mass. However these studies are mostly performed by imaging core labs and might overestimate the agreement of both methods in daily routine. Therefore, the aim of this study was to determine the agreement of CMR and echocardiography in a large cohort of consecutive patients.

Methods: Records of patients who underwent a CMR study at two tertiary care centers between 2013 and 2016 were screened retrospectively whether an echocardiography was performed within the same month. 483 patients were identified and included for further analysis (36% female; median age: 55, IQR: 43–68 years; median body surface area: 1.88, IQR: 1.64–2.05 m^2). Left ventricular ejection fraction (LVEF), enddiastolic (EDV) and endsystolic (ESV) volumes as well as left ventricular myocardial mass (LVMM) were obtained from written clinical reports.

Results: orrelation between methods was moderate for LVEF (r: 0.564, $p<0.001$), EDV (r: 0.714, $p<0.001$), ESV (r: 0.729, $p<0.001$) and LVMM (r: 0.426, $p<0.001$). Mean differences and 2SD between CMR and echocardiography were 2.3 ± 24.6%, −34.9 ± 88 ml, −23.6 ± 65 ml and 60.0 ± 200 gram for LVEF, EDV, ESV and LVMM respectively. All differences were statistically significant ($p<0.001$). Using established cut-offs for normal LVEF (CMR male >56%, female >58%, echo male >52%, female >54%) a reduced LVEF was detected in 293 patients (61%) by CMR and in 211 patients (47%) patients by echocardiography (chi-square: 84.7, $p<0.0001$). A severely reduced LVEF <35%, which is used as a common cut-off for therapeutic decisions, was found in 83 patients (17%) by CMR and 54 patients (11%) by echocardiography (chi-square: 176.6, $p<0.0001$).

Conclusions: Absolute biases between CMR and echocardiography are comparable to previous studies while variances are higher in real-life conditions than in core lab controlled studies. LVEF is higher and LV volumes are smaller when measured by echocardiography compared to CMR. Large differences have been observed for LVMM because of known limitations of 2D-echocardiography.

12-7

Bestimmung der Aortenklappenöffnungsfläche bei PatientInnen vor Transkatheter-Aortenklappenimplantation (TAVI): Ein Vergleich zwischen transthorakaler Echokardiographie, Linksherzkatheter und Magnetresonanztomographie

M. Alberer, U. Reiter, G. Reiter, A. Greiser, M. Fuchsjäger, A. Schmidt

Klinische Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Österreich
Siemens Healthcare Diagnostics GesmbH, Graz, Österreich
Siemens Healthcare, Erlangen, Deutschland

Grundlagen: Die Aortenklappenöffnungsfläche (AVA) ist ein zentraler, therapie-entscheidender Parameter in der Evaluierung von PatientInnen mit Aortenklappenstenosen, wobei die transthorakale Echokardiographie (TTE) die Referenz-Standard Methode zur Bestimmung darstellt. Ist die echokardiographische Beurteilung der AVA inkonklusiv, kann diese alternativ mittels Linksherzkatheter (LHC) ermittelt werden. Herz-Magnetresonanztomographie (CMR) erlaubt die Planimetrie von AVAs, allerdings ist die Auswertung hochgradiger Aortenklappenstenosen aus anatomischen Cine-Bildern bei 3T herausfordernd. Ziel der Studie war der Vergleich der AVAs aus CMR 4D-Flow Messungen, TTE und LHC von PatientInnen vor Transkatheter-Aortenklappenimplantation (TAVI).

Methodik: 16 symptomatische PatientInnen mit Aortenklappenstenose (w/m, 9/7; Alter, 79 ± 6 Jahre) wurden mit TTE, LHC und 3T CMR untersucht. Entsprechend dem klinischen Standardprotokoll wurden die AVAs mit TTE und LHC über die Kontinuitätsgleichung, beziehungsweise die Gorlinformel, bestimmt. Zur Evaluierung der AVA mit CMR wurde die Aortenklappe mittels einer EKG-getriggerten und Navigator-gegateten Work-In-Progress 4D-Flow Sequenz (12 Schichten, 3 mm Schichtdicke, 6–9 min Aufnahmezeit) unter freier Atmung dargestellt. Die AVA wurde in den zeitaufgelösten 3D-Blutflussgeschwindigkeits-Magnitudenbildern manuell planimetriert. Die aus TTE, LHC und CMR resultierenden AVAs wurden mittels gepaartem t-Test, Korrelations- und Bland-Altman-Analyse verglichen und in Hinblick auf die Schweregradbestimmung der Aortenklappenstenose bewertet.

Ergebnisse: Die Mittelwerte der AVAs für TTE (0.73 ± 0.25 cm^2), LHC (0.67 ± 0.21 cm^2) und CMR (0.70 ± 0.21 cm^2) unterschieden sich nicht signifikant. Korrelationen und die Standardabweichung der Fehler waren r = 0.56 und SDE = 0.22 für den Vergleich zwischen TTE und LHC, r = 0.92 und SDE = 0.10 für den Vergleich zwischen TTE und CMR, sowie r = 0.52 und SDE = 0.21 für den Vergleich zwischen LHC und CMR. TTE graduierte bei 14 PatientInnen die Aortenklappenstenose als hochgradig. Die Genauigkeit der Diagnose hochgradiger Aortenklappenstenosen mit LHC war 81 %, mit CMR 94 %.

Schlussfolgerungen: CMR 4D-Flow erlaubt die Bestimmung der AVA und die Graduierung des Schweregrads der Aor-

tenklappenstenose mit hoher Übereinstimmung zum TTE, besser als LHC. Damit präsentiert sich CMR 4D-Flow als attraktive, nicht-invasive Methode zur Bestimmung der AVA vor TAVI.

12-8

Extracellular volume by CMR T1-mapping – do we need the hematocrit?

A. Kammerlander, F. Duca, C. Binder, S. Aschauer, C. Zotter-Tufaro, B. Marzluf, D. Bonderman, J. Mascherbauer

Universitätsklinik für Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Cardiovascular magnetic resonance (CMR) is the gold standard for evaluation of right and left ventricular size and function. Unlike echocardiography, CMR furthermore allows characterization of extracellular matrix. With the recently described T1-mapping technique, it is possible to non-invasively estimate the extracellular volume (ECV) using T1-times before and after gadolinium application. However, this technique demands the hematocrit value, which limits its utility in routine application.

Recently, a strong correlation between native T1-times of the LV blood pool and the hematocrit was described.

Methods: 513 consecutive patients undergoing CMR including T1-mapping were analyzed for this study. Blood for hematocrit measurement was drawn when placing the i. v.-line for contrast agent application.

Data from the first 200 consecutive patients (derivation cohort) were used to establish a regression formula allowing "synthetic hematocrit" calculation, which was then validated in the following 313 patients (validation cohort). "Synthetic ECV" was calculated using synthetic hematocrit and was compared with conventional ECV results.

Results: Among the entire cohort of 513 patients (57.4 ± 17.5 years old, 49.1% female) conventionally measured hematocrit was 39.9 ± 4.7% and native T1-times of LV blood pool were 1570.6 ± 117.8 ms, and they showed a significant correlation (r = 0.533, $p < 0.001$). By linear regression analysis, the following formula was retrieved from the derivation cohort:

Synthetic hematocrit = T1 blood time x (−0.026) + 80.9

Synthetic and conventional hematocrit as well as ECV showed an excellent correlation in the validation (r = 0.533, $p < 0.001$ and r = 0.943, $p < 0.001$, respectively) as well as the overall cohort (r = 0.552, $p < 0.001$ and r = 0.957, $p < 0.001$, Fig. 1 | 12-8). By Bland Altman analysis, good agreement between conventional and synthetic ECV was found in the validation cohort (mean difference: 0.007 % [limits of agreement: ¬–4.32 and 4.33 %], Fig. 2 | 12-8).

Conclusions: Synthetic ECV using the hematocrit derived from LV blood pool T1 times shows excellent correlation and agreement with the conventional method. Future software programs may allow automatic ECV mapping without the need for entering hematocrit values.

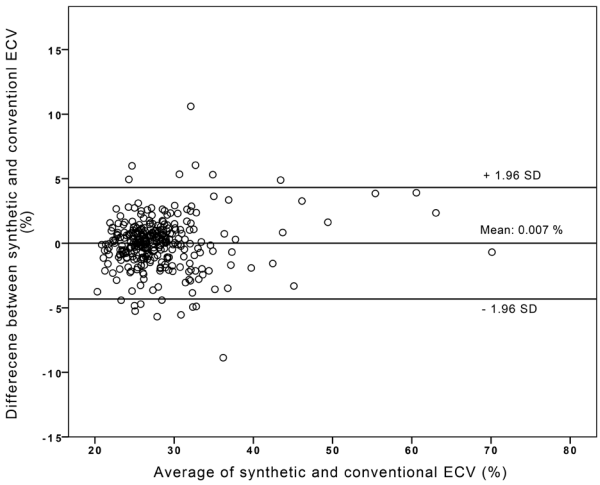


Fig. 1 | 12-8

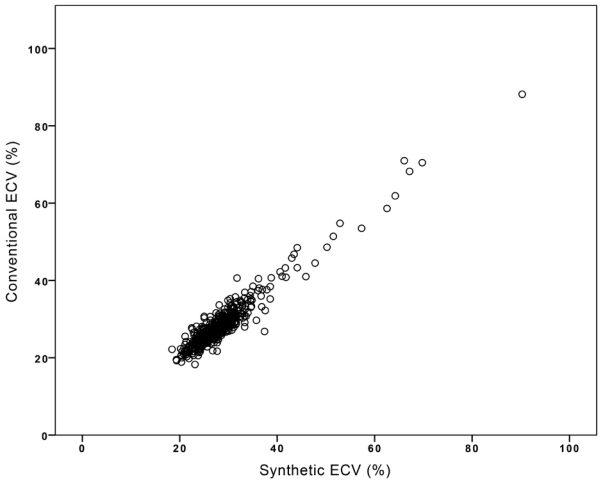


Fig. 2 | 12-8

12-9

Multi-view approach for the diagnosis of pulmonary hypertension using transthoracic echocardiography

M. Schneider, A. M. Pistritto, C. Gerges, M. Gerges, C. Binder, I. Lang, G. Maurer, T. Binder, G. Goliasch

Universitätsklinik für Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria
2. Emergency Department, Division of Cardiology, San Paolo Hospital, Sao Paolo, Brazil
Savona, Italy

Background: Pulmonary hypertension (PH) is a disease with severe morbidity and mortality. Echocardiography plays an essential role in the screening of PH. The quality of the acquired continuous wave Doppler signal is the major limitation of the method and can greatly affect the accuracy of estimated pulmonary pressures. The aim of this study was to evaluate the clinical need to image from multiple ultrasound windows in patients with suspected pulmonary hypertension.

Methods and Results: We prospectively evaluated 65 patients (43% male, mean age 67.2 years) with echocardiography and right heart catheterization (RHC). 17% had invasively normal pulmonary pressures, 83% had pulmonary hypertension. Peak tricuspid regurgitation (TR) velocity was imaged in five echocardiographic views. Sufficient Doppler signal was recorded in 94% of the patients. Correlation for overall peak TR velocity with invasively measured systolic pulmonary artery pressure was r = 0.83 ($p < 0.001$). Considering all five imaging windows resulted in a sensitivity of 87%, and a specificity of 91% for correct diagnosis of PH with an AUC of 0.89. Compared to sole imaging from the right ventricular modified apical 4-chamber view, additional imaging from atypical views changed the overall peak TR velocity in 32% of the patients. A multiple-view approach changed the echocardiographic diagnosis of PH in 11% of the patients as opposed to sole imaging from an apical 4-chamber view.

Conclusions: This study comprehensively assessed the impact on clinical decision making when evaluating patients with an echocardiographic multiplane approach for suspected PH. This approach substantially increased sensitivity without a decrease in specificity.

Postersitzung 13 – Herzinsuffizienz 2

13-1

A dilated cardiac phenotype and neuromuscular disorders predict mortality in left ventricular hypertrabeculation/noncompaction

C. Stöllberger, C. Wegner, J. Finsterer

2. Medizinische Abteilung, Krankenanstalt Rudolfstiftung, Wien, Vienna, Austria

Background: Aim of the study was to assess whether in patients with left ventricular hypertrabeculation/noncompaction (LVHT) the prognosis is dependent on the cardiac phenotype and on neuromuscular disorders (NMDs).

Methods: Included were LVHT-patients diagnosed between 1995–2016. The phenotype was assessed as "dilated" if the left ventricular enddiastolic diameter (LVEDD) was >57 mm and the left ventricular fractional shortening (FS) was <26%, as "hypertrophic" if the LVEDD was <58 mm, the FS >25% and left ventricular posterior wall (LVPWT) as well as interventricular septal thickness (IVST) both were >13 mm, as "intermediate" if LVEDD was >57 mm and FS >25% or if LVEDD was <58 mm und FS <26% and as "normal" if LVEDD was <58 mm, FS >25%, and IVST and LVPWT <14 mm. The therapy was carried out by the treating physicians.

Results: LVHT was diagnosed in 273 patients (80 females, 53 ± 16 years). One-hundred-ninety-six patients (72%) were investigated neurologically. A specific NMD was diagnosed in 16%, NMD of unknown etiology was diagnosed in 60%, and the neurological investigation was normal in 25%. The phenotype was assessed as dilated in 126 patients (46%), hypertrophic in 22(8%), intermediate in 45 (17%) and normal in 80 (29%).

During 7.4 (±5.7) years, 59 patients received electronic devices. Eighty-four patients died, 6 underwent cardiac transplantation. The rate of death and transplantation was highest in the dilated and lowest in the hypertrophic group. Among the dilated phenotype, mortality was higher in patients with than without NMDs.

Conclusions: LVHT-patients with the dilated phenotype have the worst prognosis. It has to be assessed if close follow-up and which therapy may improve the prognosis of these patients.

13-2

Analysis of the novel cardiac biomarkers ST2, GDF-15, suPAR, H-FABP and Fetuin A in patients with heart failure with reduced ejection fraction (HFrEF)

P. Jirak, M. Lichtenauer, B. Wernly, V. Paar, I. Rohm, C. Jung, A. Yilmaz, U. Hoppe, P. C. Schulze, D. Kretzschmar, R. Pistulli

Christian Doppler Labor für Diagnose und Regeneration von Herz- und Thoraxerkrankungen, Universitätsklinik Jena, Jena, Germany
Clinic of Internal Medicine II, Department of Cardiology, Paracelsus Medical University Salzburg, Salzburg, Austria
Universitätsklinikum Düsseldorf, Abteilung für Kardiologie, Pneumologie & Angiologie, Dusseldorf, Germany
Clinic of Internal Medicine II, Elisabeth Klinikum Schmalkalden, Schmalkalden, Germany
Department of Internal Medicine I, Division of Cardiology, Angiology, Pneumology and Intensive Medical Care, University Hospital Jena, Friedrich Schiller University Jena, Jena, Germany

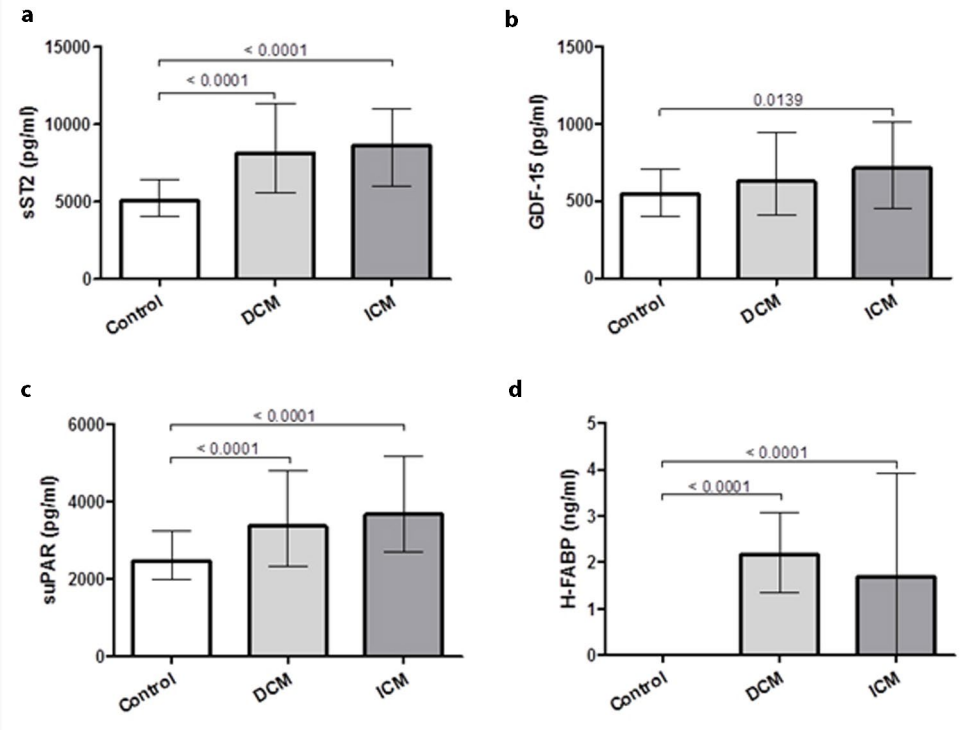
Background: Heart failure (HF) with reduced ejection fraction constitutes a major therapeutic challenge with a considerable impact on morbidity, hospitalisation rates and health-care costs worldwide. Biomarkers represent an indispensable tool in the clinical setting for diagnosis and monitoring of treatment in patients suffering from HF.

Purpose: Aim of this study was to investigate the role of four novel cardiovascular biomarkers, namely suppression of tumorigenicity (ST2), soluble urokinase plasminogen activator receptor (suPAR) and heart-type fatty acid binding protein (H-FABP) in patients suffering from ischaemic cardiomyopathy (ICM) or dilative cardiomyopathy (DCM). Further we sought to investigate the capability of Fetuin A as a discriminator between these two disease entities.

Methods: A total of 200 patients were enrolled in this current study, 65 that were diagnosed with DCM and 59 patients that suffered from ICM were included. 76 patients without coronary artery disease or signs of heart failure were included as controls. During outpatient visits, plasma samples of all patients were obtained and analyzed for ST2 (hemodynamics and inflammation), suPAR (inflammation) H-FABP (ischaemia) and Fetuin A (vascular calcification).

Results: Levels of ST2, suPAR and H-FABP were significantly higher in ICM and DCM patients compared to the control group ($p < 0.0001$). There were no significant differences between ICM and DCM in levels of ST2, suPAR and H-FABP (ST2 $p = 0.6725$, suPAR $p = 0.3521$, H-FABP $p = 0.1191$). Fetuin-A levels were significantly lower in ICM patients compared to DCM patients ($p < 0.0001$). ST2, suPAR and H-FABP correlated inversely with ejection fraction (ST2 $p < 0.0001$, suPAR $p = 0.0029$, H-FABP $p < 0.0001$). A positive correlation with biomarker levels was observed for BNP levels (ST2 $p < 0.0001$, suPAR $p < 0.0001$, H-FABP $p = 0.0004$) as well as CRP levels (ST2 $p = 0.0006$, suPAR $p < 0.0001$, H-FABP $p = 0.0002$), renal insufficiency (ST2 $p < 0.0001$, suPAR $p < 0.0001$, H-FABP $p < 0.0001$) and Diabetes (ST2 $p = 0.0021$, suPAR $p = 0.0339$, H-FABP $p = 0.0010$).

Fig. 1|13-2



Hypertension had no effect on biomarker levels (ST2 $p=0.4911$, suPAR $p=0.2410$, H-FABP $p=0.3141$, Fig. 1|13-2).

Conclusions: By integrating the information obtained by measuring levels of several important factors in HF, tested novel biomarkers represent a promising opportunity for a more precise diagnosis, incorporating different pathophysiological processes present in HF. However, while H-FABP, ST2 and suPAR, represent suitable markers for ICM and DCM, Fetuin A rather constitutes a discriminator and biomarker for the differential diagnosis between these two disease entities.

13-3

Effects of Ivabradine on levels of novel cardiac biomarkers ST2, GDF-15, uPAR and H-FABP in patients with chronic heart failure

D. Fejzic, P. Jirak, V. Paar, B. Wernly, R. Pistulli, I. Rohm, C. Jung, U. Hoppe, P.C. Schulze, M. Lichtenauer, D. Kretzschmar

Christian Doppler Labor für Diagnose und Regeneration von Herz- und Thoraxerkrankungen, Universitätsklinik Jena, Jena, Germany
Universitätsklinik für Innere Medizin II, Kardiologie, Paracelsus Medizinische Universität Salzburg, Salzburg, Austria
Universitätsklinik für Innere Medizin I, Kardiologie, Jena, Germany
Universitätsklinikum Düsseldorf, Abteilung für Kardiologie, Pneumologie & Angiologie, Dusseldorf, Germany

Background: Chronic heart failure (CHF) is associated with increased morbidity and mortality representing a leading cause of hospitalization in developed countries.

Purpose: The aim of this study was to investigate effects of Ivabradine on heart rate, symptoms of CHF and four novel cardiovascular biomarkers, namely suppression of tumorigenicity (ST2, indicating haemodynamic stress), growth-differentiation factor-15 (GDF-15, indicating redmodelling), urokinase plasminogen activator receptor (uPAR, indicating inflammation) and heart-type fatty acid binding protein 3 (H-FABP, indicating subclinical ischaemia) in patients suffering from ischaemic (ICM), dilative (DCM) and hypertensive cardiomyopathy (HCM).

Methods: The study enrolled a total of 64 patients at the University Hospital of Jena with CHF and a resting heart rate ≥ 69 b. p. m. Patients were divided into three groups, according to the etiology of CHF: Group 1 – patients with ischemic cardiomyopathy (ICM), Group 2 – patients with dilated cardiomyopathy and Group 3 – patients with hypertensive cardiomyopathy (HCM). Analysis of cardiovascular biomarkers and inflammatory parameters (ST-2, GDF-15, H-FABP, uPAR, hsCRP and IL-6) was performed at baseline and at 3- and 6-month follow-ups.

Results: Heart rate reduction was observed in all subgroups from 79.71 ± 1.07 b. p. m. to 58.21 ± 3.70 after 6 months, while the lowest heart rate was shown in patients with DCM (49.90 ± 7.69 b. p. m.) compared to ICM (62.20 ± 5.22 b. p. m.) and HCM (63.5 ± 2.89 b. p. m.).

Median concentration of GDF-15 in the overall cohort was significantly lower in all groups after a follow-up of 6 months (baseline, 768.5 µg/mL vs. 6 months, 567.5 µg/mL; $p=0.0215$) indicating a reduction in the progress of cardiac remodelling. H-FABP median concentration was significantly lower in DCM patients compared to ICM patients and HCM patients (1.89 µg/mL vs. 3.24 µg/mL vs. 3.80 µg/mL; $p<0.0151$) and also decreased in the total cohort over the 6-month follow-up ($p=0.0151$). Interestingly, uPAR median levels were still elevated implying major ongoing inflammatory processes. ST-2 median levels evidenced no significant differences (Fig. 1|13-3).

Conclusions: Ivabradine treatment led to a significant decrease in resting heart rate in all patients with CHF regardless of disease etiology. The analysis of novel cardiovascular biomarkers supported our hypothesis that Ivabradine could elicit beneficial effects in CHF patients. As shown by a significant decrease in GDF-15 and H-FABP levels a reduction in ventricular remodeling and sub-clinical ischaemia could be assumed.

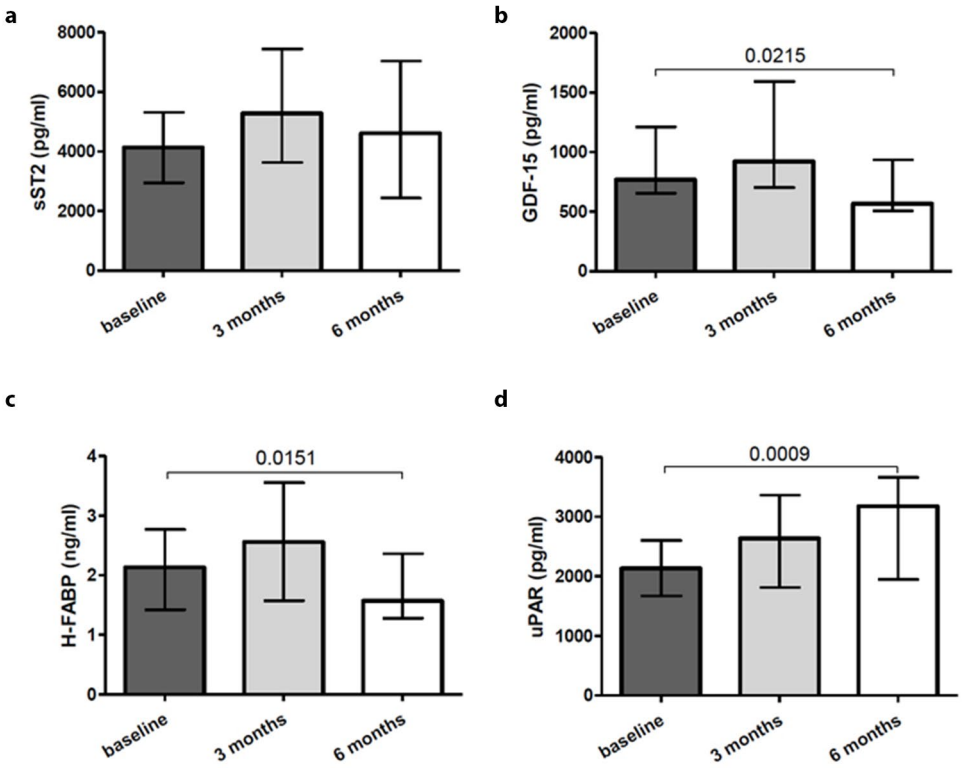


Fig. 1 | 13-3

However, markers of haemodynamic stress (ST2) and inflammation (uPAR) evidenced no change or showed even a progression after 6 months. Further studies are necessary to validate the clinical applicability of novel biomarkers. Though, they can represent an indispensable tool for the diagnosis and monitoring of CHF enabling a better understanding of the underlying pathophysiological conditions.

13-4

Functional, haemodynamic and prognostic impact of mitral regurgitation in patients with heart failure and preserved ejection fraction

S. Aschauer, C. Zotter-Tufaro, F. Duca, A. Kammerlander, C. Binder, J. Mascherbauer, D. Bonderman

Innere Medizin II, Abteilung für Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Secondary mitral regurgitation (MR) is a common finding in various heart failure entities. In patients with heart failure and reduced ejection fraction (HFrEF), the mitral clip procedure has emerged as therapeutic option and has been shown to improve functional status. By contrast, the role of secondary MR in heart failure and preserved ejection fraction (HFpEF) is fairly unknown. In the light of a dismal prognosis of HFpEF with only limited therapeutic options the aim of the present study was to determine the impact of MR on functional status, haemodynamics and prognosis in order to evaluate a possible rationale for MR interventions.

Methods and Results: Consecutive HFpEF patients were enrolled in this prospective, observational study. Confirmatory diagnostic tests including echocardiography and invasive hemodynamic assessments were performed. Of the 263 patients registered between December 2010 and January 2016, 21% ($n=55$) had significant (moderate or severe) MR. Patients were followed for a mean of 24 ± 17 months.

Patients with MR were significantly older ($P=0.025$), had higher NT-pro BNP serum levels ($P<0.001$) and more often had a history of atrial fibrillation ($P<0.001$). No between group differences were found with respect to functional class ($P=0.562$) or exercise capacity ($P=0.879$, Table 1 | 13-4).

Tab. 1 | 13-4 Baseline characteristics of HFpEF patients, stratified by mitral regurgitation severity

	Non-significant MR ($n=207$)	Significant MR ($n=55$)	p-value
Age, years	70.7 ± 8.8	73.6 ± 7.1	0.025
Female, [%]	69.1	67.9	0.868
History of atrial fibrillation, [%]	52.5	79.3	<0.001
NYHA			0.883
II, [%]	34.5	30.2	
III, [%]	57.5	62.3	
IV, [%]	7.5	7.6	0.880
6-min walk distance, meters	316.4 ± 120.9	319.4 ± 116.9	0.002
NT-pro BNP, pg/mL	1511.5 ± 1924.5	2734.6 ± 565.9	0.001
PAP systolic, mm Hg	55.9 ± 17.6	65.5 ± 20.8	0.038
PAWP, mm Hg	19.8 ± 5.2	21.9 ± 5.5	0.037
RV end-diastolic diameter, mm	35.5 ± 8.8	38.2 ± 8.3	0.016
RVSD, [%]	22.2	38.2	

MR indicates mitral regurgitation; *NYHA* New York Heart Association functional class; *PAP* pulmonary artery pressure; *PAWP* pulmonary artery wedge pressure; *RV* right ventricular; *RVSD* right ventricular systolic dysfunction

With respect to structural and haemodynamic parameters MR was associated with worse right ventricular function ($P=0.019$) and size ($P=0.037$) as well as higher right and left ventricular filling pressures ($P=0.038$, $P=0.045$, Table 1). While secondary MR was associated with the outcome by univariable analysis (logrank $P=0.022$) it failed to predict event- free survival in the multivariable model.

Conclusions: Although secondary MR in HFpEF was associated with higher left and right- sided filling pressures as well as worse right ventricular function, it was not independently associated with outcome. Whether secondary MR may be a meaningful therapeutic target in HFpEF patients needs to be elucidated in further studies.

13-5

Impact of HIV infection and antiretroviral treatment on NT-proBNP as surrogate of myocardial function

C. Binder, C. Schuster, R. Strassl, M. Aichelburg, E. Blackwell, N. Pavo, M. Ramharter, M. Hülsmann, K. Grabmeier-Pfistershammer, A. Rieger, G. Goliasch

Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: The impact of HIV infection on the neurohumoral pathways of the heart and its potential reversibility by antiretroviral therapy (ART) remains unclear.

Methods and Results: We assessed serum levels of NT-proBNP in 219 ART-naïve HIV infected patients at treatment initiation and follow-up. Prior to antiretroviral therapy, NT-proBNP as a surrogate of myocardial function displayed a significant correlation with absolute CD4 cell count ($r=-0.31$; $P<0.001$) as well as with HIV viral load ($r=0.26$; $P<0.001$). The median levels of NT-proBNP were 80 pg/ml (36–205) in patients with a CD4 count<200, and 42 pg/ml (20–80; $P<0.001$) with a CD4 count>500. After viremic control no statistical correlation was present.

Conclusions: Higher NT-proBNP levels were observed in treatment-naïve patients with low CD4 count and high HIV viral load indicating a subclinical impact of HIV infection on myocardial function. This association is reversible by the initiation of ART and subsequent viral suppression.

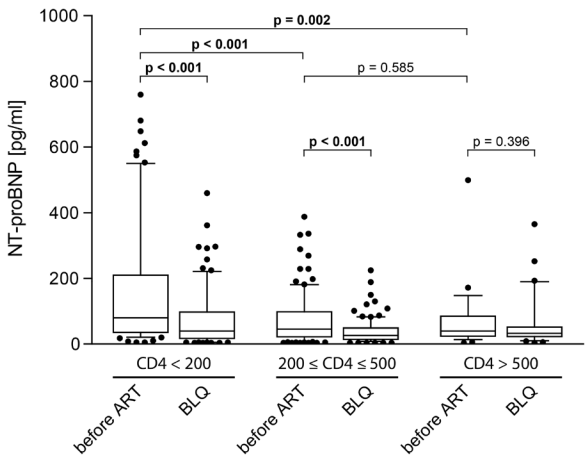


Fig. 1 | 13-5

13-6

Modes of Death in Cardiac Amyloidosis

C. Binder, S. Aschauer, F. Duca, P. Stelzer, H. Agis, R. Kain, A. Kammerlander, J. Mascherbauer, D. Bonderman

Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Cardiac Amyloidosis (CA) used to be seen as a very rare disease, however it may not be as uncommon as previously perceived. With the help of modern imaging techniques and a rising awareness for this disease, cases of amyloidosis with cardiac involvement are being recognized more frequently. However, little is known about the clinical course of the disease, especially in the end-stages of this condition. Our aim was to characterize patients with CA and achieve a better understanding of the modes of death in this highly malignant condition.

Methods: Between May 2008 and January 2017 we included patients with light-chain amyloidosis (AL) or transthyretin amyloidosis (TTR) into our prospective registry at the Vienna General Hospital, a university affiliated tertiary care center. The diagnosis of CA was made by myocardial biopsy in most cases, or by the diagnostic algorithm recently proposed by Gillmore et al. for patients with TTR-amyloidosis. Cases of death were evaluated thoroughly and reviewed by at least two specialized physicians. Patient records, imaging modalities including echocardiography and cardiac magnetic resonance imaging, as well as N-terminal pro brain natriuretic peptide levels were reviewed to understand the mode of death in each given patient.

Results: In total, 70 patients were enrolled in our registry. Thirty-seven patients (53%) were diagnosed with AL- amyloidosis and 33 (47%) with either wild-type or familial TTR-amyloidosis. During a mean follow-up time of 70 months 25 patients (36%) died, however four patients were lost to follow-up and therefore modes of death could not be determined. Even though follow-up could not be reviewed in these four patients, records indicate that three of these patients died. Of the patients who passed away, 22 (88%) had been diagnosed with AL-amyloidosis and 3 with TTR-amyloidosis (12%). Thirteen patients (62%) died from heart failure, of which the mode of death was right heart failure in 9 patients (69%) and left heart failure in 4 patients (31%). Other modes of death were myocardial infarction in 2 patients and failure of another involved organ in 2 further patients. The 4 remaining subjects died from infection or other causes primarily unrelated to amyloidosis (Fig. 1 | 13-6).

Conclusions: In our cohort, subjects with AL-amyloidosis had a worse prognosis than patients with TTR -amyloidosis. When cardiac involvement is present, more than half of patients die from heart failure, most commonly right heart failure.

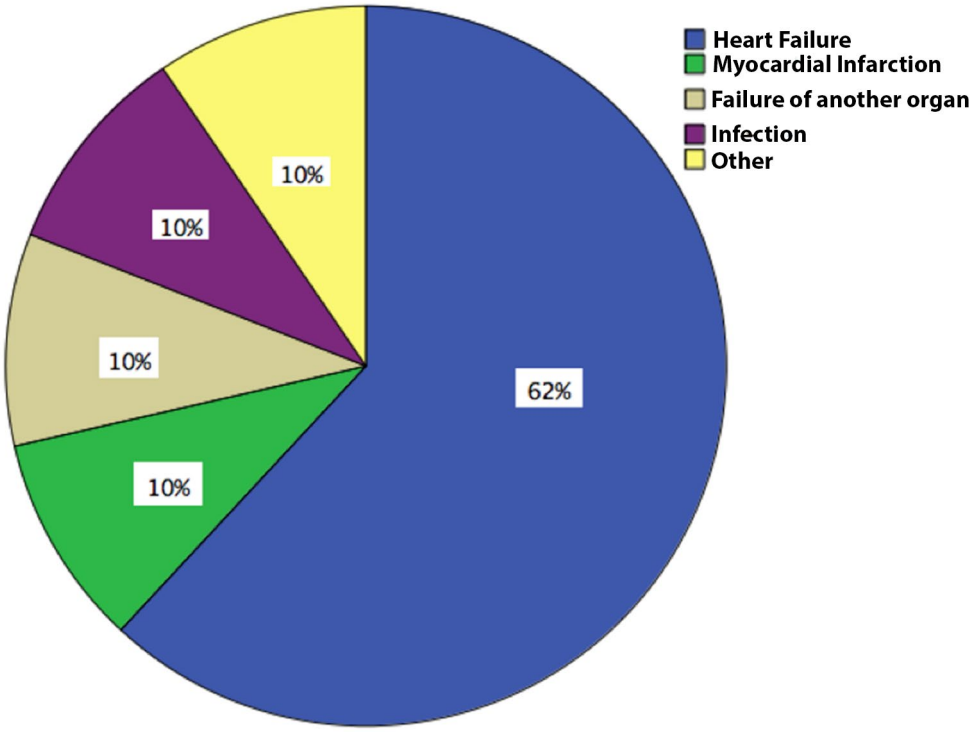


Fig. 1 | 13-6 Modes of death in patients with cardiac amyloidosis

13-7

Persistent atrial fibrillation in heart failure with preserved ejection fraction – association with extracellular volume accumulation, invasive hemodynamics, and outcome

R. Schönbauer, F. Duca, A. Kammerlander, S. Aschauer, C. Binder, C. Zotter-Tufaro, M. Koschutnik, L. Fiedler, F.X. Roithinger, D. Bonderman, J. Mascherbauer

Rhythmologie, Herzzentrum Leipzig, Leipzig, Germany
2. Interne Abteilung, Landesklinikum Wiener Neustadt Abteilung für Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) frequently occur together. However, data on AF subtype and its association with comorbidities, extracellular volume (ECV) by cardiac magnetic resonance imaging (CMR), hemodynamics, and relation to outcome in HFpEF are sparse.

Methods and Results: From 2011 to 2015 152 consecutive HFpEF patients were enrolled in our prospective observational registry. All patients underwent echocardiography, left and right heart catheterization (RHC), and CMR including T1 mapping with the modified Look-Locker inversion recovery (MOLLI) sequence. Patients with significant coronary artery disease were excluded.

105 patients (69 %) suffered from AF, 85 (56 %) had persistent and 20 (13 %) had paroxysmal AF.

Patients with persistent AF were in worse New York Heart Association functional class ($p=0.006$), and more often suffered from chronic obstructive pulmonary disease ($p=0.018$) than patients with paroxysmal AF or sinus rhythm. They had higher levels of N-terminal pro-brain natriuretic peptide (NTproBNP) ($p=<0.001$), and worse renal function ($p=0.041$). Invasive hemodynamics showed higher right atrial pressures ($p=0.014$) and pulmonary capillary wedge pressures ($p=0.050$). Echocardiography revealed more pronounced atrial dilatation ($p=<0.001$) as well as a more dilated right ventricle ($p=0.001$) and higher systolic pulmonary artery pressures ($p=0.037$). By CMR left and right atria as well as the right ventricle were more dilated ($p=0.001$, 0.002, and 0.001, respectively) and left and right ventricular ejection fractions were lower in patients with persistent AF ($p=0.002$ and <0.001 respectively). Furthermore, these patients had higher levels of ECV by T1 mapping ($p=0.018$).

After a median follow-up of 46 months (13–71) 63 patients (41 %) reached the combined endpoint defined as hospitalization for HF and/or cardiovascular death. By multivariate Cox regression analysis only persistent AF ($p=0.039$, HR 2.013, 95 %

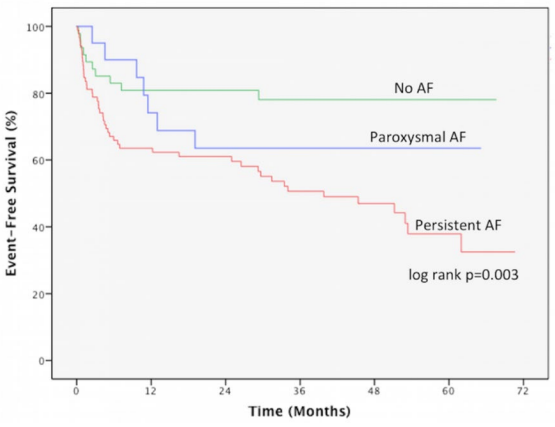


Fig. 1 | 13-7

CI 1.035–3.915) and six-minute walk distance ($p=0.013$, HR 0.997, 95 % CI 0.994–0.999) were independently associated with outcome (Fig. 1|13-7).

Conclusions: More than 50% of HFpEF patients suffer from persistent AF. Persistent but not paroxysmal AF is significantly related with markers of disease severity, extracellular volume accumulation, and worse cardiovascular outcome.

13-8

The natural course of heart failure with preserved ejection fraction (HFpEF) – insights from an exploratory echocardiographic registry

M. Koschutnik, C. Binder, C. Zotter-Tufaro, S. Aschauer, F. Duca, A. Kammerlander, M. Schwaiger, D. Bonderman, J. Mascherbauer

Klinische Abteilung für Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Despite recent efforts, a profound understanding of pathophysiological abnormalities and natural course of heart failure with preserved ejection fraction (HFpEF) is still lacking.

Objectives: Echocardiography is the method of choice for diagnostic evaluation as well as follow-up assessment of HFpEF patients. The purpose of this exploratory study is to investigate the natural course of HFpEF using echocardiographic and clinical parameters.

Methods: A total of 161 HFpEF patients (mean age 70.5 ± 8.2 years, 67.1% females) were consecutively enrolled: medical history, physical examination, New York Heart Association (NYHA) functional class, 6-minute walk distance and routine blood tests including serum NT-proBNP measurement were evaluated at baseline and follow-up visits. Furthermore, comprehensive transthoracic echocardiography (TTE) was performed at baseline and at 20.8 ± 14.0 months of follow-up.

Results: TTE revealed an increase of left atrial (LA) size over time (62.0 vs. 63.3 mm, $p=0.006$), while no significant changes of right atrial (RA) and ventricular size were observed (RA: mean 62.4 vs. 62.4 mm, $p=0.883$; left ventricle, LV: mean 44.0 vs. 44.2 mm, $p=0.6$; right ventricle, RV: 36.8 vs. 37.4 mm, $p=0.353$). LV systolic function by biplane Simpson's method indicated a significant decrease of LV ejection fraction at follow-up (mean 61.6 ± 7.5 vs. 56.8 ± 7.7%, $p=0.038$). E/E' ratio derived from Tissue Doppler measurement remained unchanged (mean 16.0 ± 7.5 vs. 15.8 ± 8.5, $p=0.858$). RV systolic function significantly deteriorated (moderately to severely abnormal: 15.5% vs. 24.2%, $p<0.001$) alongside with evidence of tricuspid regurgitation worsening (moderate to severe: 54.7% vs. 67.1%, $p<0.001$) compared to baseline examination. Serum NT-proBNP levels remained unchanged at follow-up (mean 1898.1 ± 3049.7 vs. 2105.8 ± 3785.2 pg/mL, $p=0.303$).

Conclusions: Our work demonstrates increasing LA size, deterioration of RV systolic function, and worsening of tricuspid regurgitation in HFpEF patients over time. Although HFpEF is generally regarded as a disease of the LV, recent investigations provide strong evidence of RV contribution to morbidity and mortality in these patients.

Postersitzung 14 – Pulmonale Hypertension

14-1

Experience with subcutaneous treprostinil therapy in PH patients not able to manage the pump

C. Huber, S. Schneiderbauer-Porod, E. Sigmund, M. Grünberger, J. Aichinger, R. Steringer-Mascherbauer

Kardiologie, Angiologie, Intensivmedizin, Krankenhaus Elisabethinen Linz, Linz, Austria

Background: Despite its unparalleled efficacy, the parenteral administration of prostanoids is a challenge for treating physicians but above all for patients. Training on infusion pump handling is time consuming and regularly provided refresher trainings are necessary during long-term therapy. However not all patients are physically or mentally able to manage pump handling themselves. Over the last decade we have acquired vast experience with caretaking tailored to the individual patient with subcutaneous treprostinil, the prostanoid of choice at our center.

Objectives: To evaluate the impact of tailored service concepts provided by specialized caretaking staff- specialised nurses for patients not able to handle the external infusion pump for parenteral prostanoid therapy.

Methods: At our center all data of patients with pulmonary hypertension are documented by means of the ELPHREG (ELisabethinen Pulmonary Hypertension REGistry) since 2011. In this analysis we included all patients who were initiated with subcutaneous treprostinil treatment over the last decade and were not able to reliably handle the infusion pump alone.

Results: We identified 45 patients – age from 36 to 87, for whom the pump handling was exclusively done by relatives. Main reasons for inability to handle the infusion pump were visual disorders, mechanical issues with pump handling due to eg Raynaud phenomenon but also mental impairment. At the beginning of therapy nearly for all patients relatives are trained as well. For these 45 patients relatives took care of the pumps during long-term therapy. In additional 4 patients also local caregivers were trained due to the wish of the relatives to assist patients with pump handling. Relatives and caretakers were retrained on a regular basis by specialised nurses, as we do this with all patients on subcutaneous treprostinil. In one patient all pump handling has been performed or supervised by specialist nurses over 4 years. 20 of these patients were transitioned to intravenous treprostinil with the implantable pump. None of the patients discontinued treprostinil therapy due to technical issues or site pain

Conclusions: Given continuous support provided by specialised nurses subcutaneous administration of treprostinil is feasible also in patients who are not able to handle the necessary medical device.

14-2

Tenascin-C deficiency in combination with chronic hypoxia leads to a Cpc-PH phenotype

M.-P. Winter, A. Panzenböck, V. Seidl, S. Sharma, J. Altmann, D. Santer, F. Nagel, B. Podesser, I. Lang

Innere Medizin II, Kardiologie, Medizinische Universität Wien, Abteilung für Biomedizinische Forschung, Medizinische Universität Wien, Vienna, Austria

Background: Heart failure associated hemodynamic alterations expose the lung vasculature to pressure induced challenges that trigger, if sustained pulmonary hypertension (PH). The developments of PH and right ventricular (RV) dysfunction are frequent and have important impact on disease progression. Despite recent advances in understanding the haemodynamic interrelations in combined post- and pre-capillary PH there is no adequate murine model resembling the disease. Tenascin-C (TnC) is an extracellular matrix protein that is not only critically involved in the pathogenesis of PH but also in cardiac remodeling after injury and inflammation. Aim of our study was to investigate if TnC inhibition by direct gene manipulation in combination with chronic hypoxic treatment might result in HF with associated pulmonary hypertension.

Methods: We utilized mice with a homozygous TnC knockout (TnC KO) and A/J wild types (WT). Both TnC KO and WT littermates were held in an environmental chamber with FiO2 of 10% or under normoxia for 4 weeks. We investigated the effect of TnC deletion and chronic normobaric hypoxia on parameters of pulmonary vascular resistance such as right ventricular systolic pressure (RSVP) and right ventricular hypertrophy (Fulton Index/right to left ventricular-ratio). To assess the degree of smooth muscle cell hyperplasia, alpha-smooth muscle actin antibody staining was performed. Furthermore we performed echocardiography to asses left ventricular function. RT-PCR and histologic examination of the ventricles were used to assess myocardial fibrosis.

Results: TnC KO mice showed significantly increased right ventricular pressures after 4 weeks under normoxic conditions, compared with wild type controls (15.2 vs. 21.95 mmHg, $p<0.001$). Under 4 weeks hypoxic breeding TnC KO mice revealed significantly higher right ventricular pressures (27.3 vs. 34.9 mmHg, $p<0.001$), and Fulton indices than controls (0.43 vs 0.50, $p<0.001$). Under both normoxic and hypoxic conditions TNC KO mice revealed significant increased media thickness. Echocardiography revealed a mild HF phenotype with significant decrease of LVEF after 4 weeks of hypoxic but not normoxic breeding ($p<0.001$). TnC KO mice showed a significant decrease in the myocardial TGF-beta pathway with subsequent decrease of myocardial connective tissue.

Conclusions: TnC knock-out leads to failure of tissue remodeling during chronic hypoxic breeding and results in a n Cpc-PH phenotype.

14-3

Immediate switch from subcutaneous to intravenous treprostinil administered with an implantable pump in pulmonary hypertension – single center experience

M. Grünberger, C. Huber, S. Schneiderbauer-Porod, E. Sigmund, J. Aichinger, R. Steringer-Mascherbauer

Kardiologie, Angiologie, Intensivmedizin, KH Elisabethinen Linz, Linz, Austria

Any events possibly related to over- or underdosing of treprostinil within 24 postoperative hours.

Conclusions: To the best of our knowledge this is the first report on a series of patients with the immediate switch from subcutaneous to intravenous treprostinil administration with a fully implantable gas driven pump. As intravenous treprostinil was administered by an infusion pump requiring surgery, all patients were closely monitored for at least 24 hours postoperatively. In this setting patients can safely be switched from subcutaneous to intravenous treprostinil in a 1:1 ratio.

14-4

Therapieversagen von Rivaroxaban bei einer adipösen Patientin

T. Schuh, C. Stöllberger

2. Medizinische Abteilung, Krankenanstalt Rudolfstiftung, Wien, Wien, Österreich

Grundlagen: Rivaroxaban, ein oraler Faktor Xa Inhibitor, ist zur Behandlung venöser Thromboembolien zugelassen. Es ist unklar, ob die Dosis von 20 mg/Tag auch bei Patienten mit einem body mass index (BMI) >40 kg/m^2 ausreichend ist.

Fallbericht: Eine Patientin mit einem BMI von 59,3 kg/m^2 erlitt unter 20 mg/Tag Rivaroxaban eine Rezidiv-Pulmonalembolie. Wegen einer Pulmonalembolie vor 30 Monaten und einer heterozygoten Faktor V Leiden-Mutation stand sie unter oraler Antikoagulation, zunächst mit Phenprocoumon, das wegen geringer Adhärenz vor 29 Monaten auf Rivaroxaban 20 mg/Tag umgestellt wurde. Seit mehr als 20 Jahren lag eine morbide Adipositas vor mit einem BMI zwischen 59–64 kg/m^2. Vor 6 Monaten hatte sie Rivaroxaban wegen eines zahnärztlichen Eingriffes pausiert, was zu einer Rezidiv-Pulmonalembolie führte. Die Antikoagulationstherapie mit Rivaroxaban wurde damals nicht verändert.

Sechzehn Stunden nach Symptomenbeginn, 22 Stunden nach der letzten Einnahme, betrug der Serum-Rivaroxaban-Spiegel 137 ng/ml und 55 Stunden nach Einnahme 30 ng/ml. Die Patientin erhielt Enoxaparin-Natrium in therapeutischer Dosis (100 mg sc. zweimal täglich), die Therapie mit Rivaroxaban wurde beendet und eine orale Antikoagulation mit Phenprocoumon, verbunden mit intensiver Aufklärung der Patientin und Rücksprache mit dem betreuenden Hausarzt, begonnen.

Diskussion: Laut den Herstellern beträgt der therapeutische Spiegel-Bereich von Rivaroxaban nach 2–4 Stunden 22–535 ng/ml, und nach 24 Stunden 6–239 ng/ml. Die Pulmonalembolie ist somit vermutlich zu einem Zeitpunkt aufgetreten, in dem der Rivaroxaban-Spiegel im therapeutischen Bereich lag. Es ist nicht bekannt, ob Patienten, die trotz Rivaroxaban eine Thromboembolie erlitten hatten, sich hinsichtlich des BMI oder Rivaroxaban-Spiegels von Patienten unterschieden haben, die

keine Thromboembolie erlitten haben. Subgruppenanalysen der EINSTEIN DVT und EINSTEIN-PE Studien haben keinen Unterschied in der Rezidiv-Thromboembolie-Rate zwischen Patienten, die <50 kg, 50–100 kg und >100 kg gewogen haben, gefunden. Allerdings wurden Patienten mit morbider Adipositas in diese Studien nicht eingeschlossen.

Schlussfolgerungen: Es ist unklar, ob die Dosis von Rivaroxaban erhöht werden sollte, wenn Patienten mit einem BMI >40 kg/m² behandelt werden. Die Empfehlungen der „International Society for Thrombosis and Haemostasis" sollten befolgt werden: Rivaroxaban soll nicht verwendet werden bei Patienten mit einem BMI >40 kg/m² oder einem Gewicht >120 kg, weil es nur wenige Daten über diese Patientengruppe gibt.

14-5

Effect of moderate altitude on biomarkers of cardiovascular inflammation and endothelial function and their differential modulation by dual endothelin receptor blockade

V. Paar, M. Lichtenauer, B. Goebel, B. Wernly, T. Gecks, I. Rohm, M. Förster, S. Betge, H.-R. Figulla, U. Hoppe, M. Kelm, M. Franz, C. Jung

Christian Doppler Labor für Diagnose und Regeneration von Herz- und Thoraxerkrankungen, Universitätsklinik Jena, Jena, Germany
Universitätsklinik für Innere Medizin II, Kardiologie, Paracelsus Mediznische Universität Salzburg, Salzburg, Austria
Universitätsklinik für Innere Medizin I, Kardiologie, Friedrich Schiller Universität, Jena, Germany
Abteilung für Kardiologie, Pneumologie & Angiologie, Universitätsklinikum Düsseldorf, Dusseldorf, Germany

Background: Endothelial dysfunction, e.g. in atherosclerosis, is accompanied by the release of microparticles (MP). In this study, we sought to investigate the effect of moderate hypoxia on circulatory levels of microparticles, biomarkers of cardiovascular function and inflammation and on echocardiographic parameters in healthy volunteers staying at an altitude of 2978 m.

Methods: Eighteen healthy volunteers were subjected to moderate hypoxia by staying at a mountain lodge in Diavolezza, Switzerland (2978 m above sea level). Blood samples were evaluated for MP using flow cytometry. ELISA analysis was performed for four novel cardiovascular biomarkers, namely suppression of tumorigenicity (ST2, indicating haemodynamic stress), growth-differentiation factor-15 (GDF-15, indicating remodeling), urokinase plasminogen activator receptor (uPAR, indicating inflammation) and heart-type fatty acid binding protein 3 (H-FABP, indicating sub-clinical ischaemia). Moreover, the effect of dual endothelin-receptor blockade (by macitentan) on MP, sST2, H-FABP, suPAR, GDF-15 and echocardiographic parameters was investigated at moderate altitude and during physical exercise.

Results: During the experiment, oxygen saturation decreased to 93%. A significant decrease of endothelial and platelet MP levels was found. For example, CD31+/CD42- MP concentration at baseline was 5.09% (±1.26% SEM) at the start of the experiment. After acclimatization at 2978 m above mean sea level, MP levels evidenced a significant decline to 1.19% (±0.14% SEM). After returning to 143 m a significant rise to 2.88% (±0.43% SEM) was recorded again. These results were corroborated by a similar response in sST2, H-FABP and suPAR plasma concentration (Fig. 1|14-5). Endothelin-receptor blockade by macitentan only had a marginal influence on EMP, sST2, H-FABP, suPAR and GDF-15 levels, though it led to a significant amelioration of echocardiographic parameters of right heart function.

Conclusions: These experimental results show that moderate hypoxia due to altitude exposition led to a reduction in

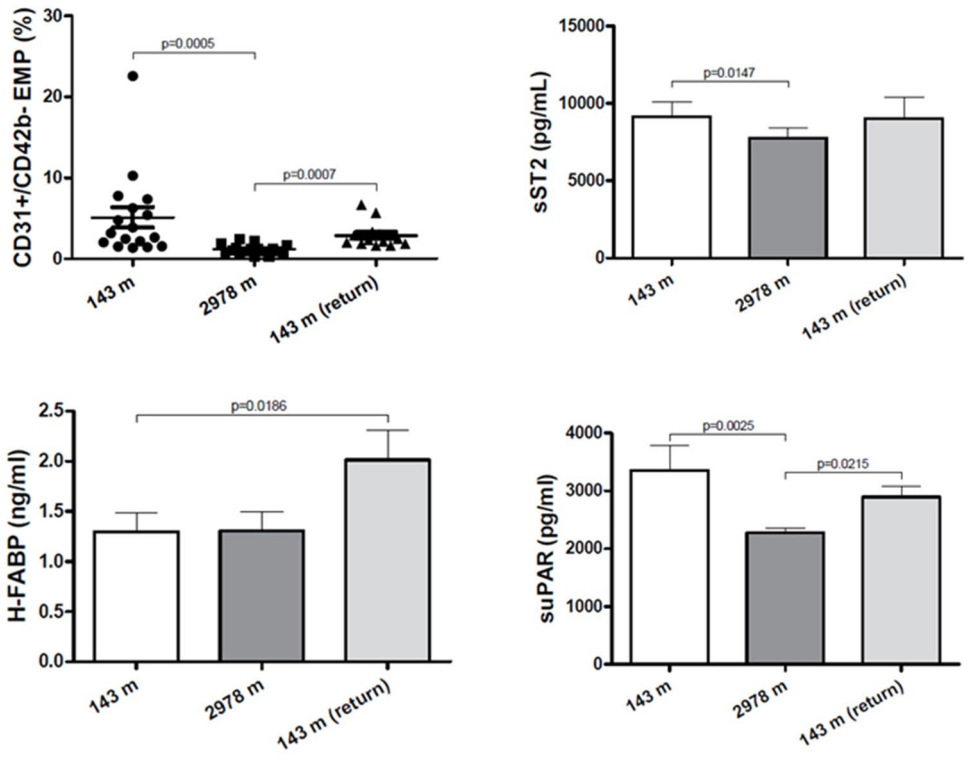


Fig. 1|14-5

parameters of endothelial dysfunction as shown by a decrease in endothelial and platelet MP, sST2 and suPAR levels. A slight increase in pulmonary pressure in moderate altitude was decreased by dual endothelin receptor blockade.

14-6

Plasma ADAMTS13 activity in chronic thromboembolic pulmonary hypertension

A. Panzenböck, R. Sadushi-Kolici, P. Turecek, I.-A. Campean, N. Skoro-Sajer, W. Klepetko, I. Lang

Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Deficiency of ADAMTS13 activity leads to von Willebrand factor giant multimers with high affinity for platelets and high thrombotic risk. Because elevated levels of vWF are associated with thrombosis, we tested the hypothesis that ADAMTS13 activity is involved in major vessel thrombosis of pulmonary hypertension. Therefore, we determined ADAMTS13 activity in non-thromboembolic pulmonary arterial hypertension (PAH), and in chronic thromboembolic pulmonary hypertension (CTEPH).

Methods: ADAMTS13 activity was measured in a kinetic assay using the fluorescence resonance energy transfer substrate VWF 73, and ADAMTS13 concentration was measured in an enzyme-linked immunosorbent assay. Plasma samples of 89 patients (mean age 55 ± 14 years) were obtained at time of diagnosis.

Results: Of 89 patients (female 63%), 45 patients (51%) were diagnosed with CTEPH, 36 patients (40%) with PAH {(18 patients with idiopathic PAH, hereditary PAH and PAH associated with drug/toxins, 10 patients with PAH associated with connective tissue disease (CTD), 4 patients with portopulmonary PAH, 4 patients with PAH associated with congenital heart disease (CHD)}, and 8 (9%) patients with pulmonary hypertension (PH) due to lung disease and/or hypoxia.

ADAMTS13 activity and concentration correlated significantly (rho = 0.78, $P < 0.001$). ADAMTS13 activity and concentration showed no significant difference between patients with CTEPH (0.97 ± 0.26 U/mL; 0.59 ± 0.17 µg/mL), PAH (0.98 ± 0.29 U/mL; 0.58 ± 0.21 µg/mL, P = ns) and patients with PH due to lung disease and/or hypoxia (0.80 ± 0.22U/mL; 0.54 ± 0.17 µg/mL, P = ns, all mean values). However, a significant reduction of ADAMTS13 activity and concentration was found in patients with PAH associated with CTD (0.77 ± 0.27 U/mL; 0.46 ± 0.22 µg/mL) compared to patients with idiopathic PAH, hereditary PAH and PAH associated drug/toxins (1.06 ± 0.27 U/mL, $P \leq 0.01$; 0.62 ± 0.19 µg/mL, $P \leq 0.05$), and also in patients with PH due to lung disease and/or hypoxia (0.80 ± 0.21 U/mL). Gel-based analysis of the size of multimers was in accordance with these findings.

Conclusions: No significant difference of ADAMTS13 activity and concentration was observed in plasma levels of patients with CTEPH compared to PAH or PH due to lung disease and/or hypoxia. However significantly reduced ADAMTS13 activity and concentration were found in patients with PAH associated with CTD, and PH due to lung disease and/or hypoxia.

Postersitzung 15 – Risikofaktoren Stoffwechsel Lipide 2

15-1

Prognostic impact of soluble P-selectin on long-term adverse cardiovascular outcome in patients with acute and stable coronary artery disease

M. Tscharre, S. Farhan, B. Vogel, I. Tentzeris, M. K. Freynhofer, M. Rohla, C. Ay, J. Wojta, T. W. Weiss, K. Huber

3. Medizinische Abteilung mit Kardiologie und Intensivmedizin, Wilhelminenspital, Vienna, Austria
Medizinische Universität Wien, Vienna, Austria

Background: Soluble P-selectin (sP-selectin), a biomarker of inflammatory related pathologies including cardiovascular diseases, also has pro-atherosclerotic effects including the ability to increase leukocyte recruitment and modulate thrombotic responses in vivo.

Purpose: We aimed to assess the prognostic impact of elevated levels of sP-Selectin on long-term cardiovascular outcome in patients after coronary stenting for stable coronary artery disease (SCAD) or acute coronary syndromes (ACS).

Methods: We analysed 747 patients of a prospective single-centre registry undergoing successful coronary stenting between 2003 and 2006. Blood samples were analysed for sP-Selectin antigen concentration by means of commercially available enzyme-linked immunoassays. As endpoint of interest, we assessed long-term major adverse cardiovascular events (MACE), a composite of all-cause death, myocardial infarction and stroke, for sP-Selectin as continuous and as dichotomized (median) variable with Cox proportional hazard analysis.

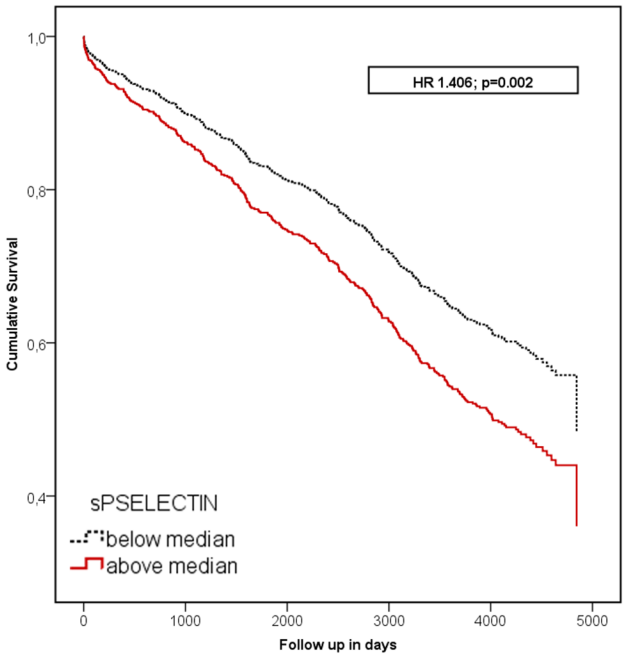


Fig. 1 | 15-1

Results: Out of 747 included patients, 48.5% had SCAD. Mean age was 64.2 ± 12.0 years and 525 (70.3%) were male. After a mean follow-up period of 9.6 years, 357 (47.8%) patients suffered from MACE. In multivariable Cox regression analysis adjusting for potential confounders, sP-Selectin was associated with long-term MACE both as continuous (HR per 1 ng/ml increase 1.009 [95% CI 1.002–1.017]; $p = 0.014$) and as dichotomized (HR 1.406 [95% CI 1.130–1.749]; $p = 0.002$) variable (Fig. 1 | 15-1).

Conclusions: Elevated levels of sP-Selectin have a significant prognostic impact on long-term MACE in patients with coronary artery disease after percutaneous intervention.

15-2

Lowering blood pressure in primary care in Vienna (LOW-BP-VIENNA) – preliminary data from a cluster randomised trial

M. Rohla jr., M. Tscharre, K. Huber, T. W. Weiss

3rd Medical Department, Cardiology and Intensive Care Medicine, Wilhelminenhospital, Vienna, Austria

Background: In Austria, only 41% of diagnosed, treated and predominantly adherent patients with hypertension (HTN) have their blood pressure (BP) controlled. We sought to investigate a strategy to improve BP control in primary care in a cluster-randomised fashion.

Methods: The preliminary analysis included 15 general practitioners who were randomised to either experimental care or of standard care for HTN. Practitioners randomised to experimental care up-titrated antihypertensive therapy with a fixed-dose combination drug (olmesartan, amlodipine and hydrochlorothiazde) in 4-week intervals. The primary efficacy endpoint was the proportion of patients achieving the target office BP of 140/90 mmHg at 6 months. The main secondary endpoint was the improvement in 24 h ambulatory BP (ABPM). The trial was registered with www.clinicaltrials.gov (NCT02377661).

Results: The preliminary analysis included 114 patients, of whom 50 were enrolled into the experimental group. Mean age was 59 years, 51% were women. Sociodemographic characteristics and cardiovascular risk factors were well balanced.

Baseline office BP was 164/94 mmHg in the experimental and 161/95 mmHg in the standard arm (p = NS between groups). Baseline 24 h-ABPM was 143/86 vs. 141/87 mmHg, respectively (p = NS between groups).

There was a tendency towards a greater mean office BP reduction in the experimental vs. the standard arm (−25/−10 mmHg vs. −20/−8 mmHg, p = NS between groups, $p < 0.01$ for baseline vs. 6 months for both groups).

Office BP was controlled in in 52 vs. 48% at 6 months ($p = 0.10$). Similar non-significant trends could be observed for 24 h-ABPM reductions (−12/−7 mmHg vs. −10/−7 mmHg, p = NS between groups, $p < 0.01$ for baseline vs. 6 months for both groups). Prior to trial enrolment, pre-treated patients received an average of 1.5 ± 0.8 vs. 1.7 ± 0.9 antihypertensive drugs ($p = 0.31$). At 6 months, the respective BP reductions were achieved with an average of 1.1 ± 0.5 drugs in experimental vs. 1.8 ± 0.9 in standard care ($p < 0.01$).

Serious adverse events were infrequent and occurred at a similar rate between groups.

Conclusions: The trial demonstrated statistically and clinically significant BP reductions in both groups after 6 months of follow-up. Experimental care was not superior to standard care, however, BP reductions were achieved with a significantly lower medication burden, which has been shown to enhance adherence.

15-3

New frailty assessment based on routine nurse anamnesis before discharge is a strong predictor of all-cause mortality in patients with myocardial infarction

P. M. Haller, S. Weis, B. Jäger, K. Huber

3. Med. Abteilung mit Kardiologie und internistischer Intensivmedizin, Wilhelminenspital Wien, Vienna, Austria

Background: Age and frailty are well-established risk factors in patients with acute myocardial infarction (AMI). Many frailty assessments are based on questionnaires and physical tests, which are not practical in daily clinical routine. At our department all patients are assessed daily by the nursing staff for their nursing demands, including activities of daily living (ADL; eat/drink, stool, mobility, hygiene) in 3 different grading (not, partly, fully self-sufficient).

Purpose: We hypothesised that theses data is enough to calculate a predictive frailty score.

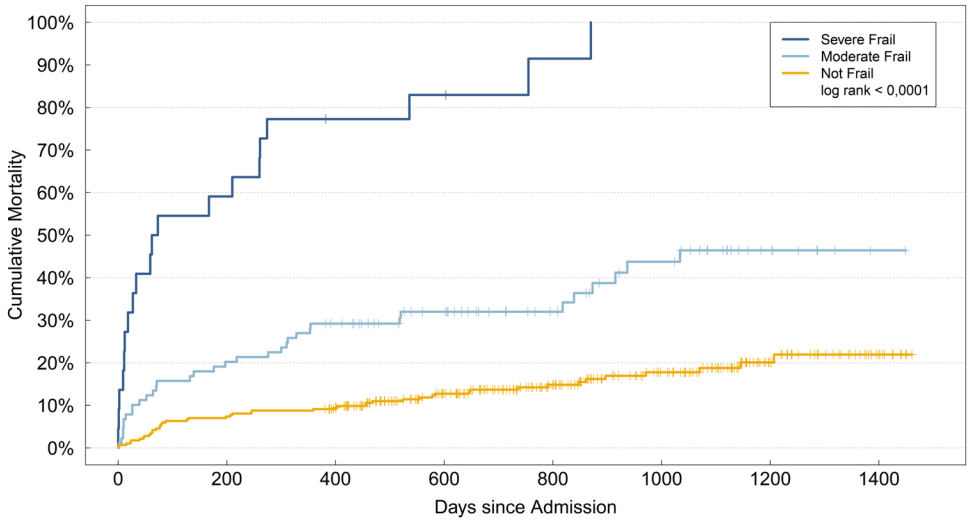


Fig. 1 | 15-3

Methods: We performed a retrospective analysis (inclusion of: Type-1 AMI, ≥65 years, years 2012–2014; exclusion: cardiogenic shock) and collected the patient's anamnesis and ADL assessments before discharge. Depending on the grading within each ADL category (0 points = not, 1 point = partly, 2 points = fully self-sufficient, respectively), patients were stratified into 3 different groups: severe (0–3 points), moderate (4–6 points) and not frail (7–8 points), respectively. Primary endpoint was all-cause mortality on 31st December 2015. We performed a descriptive analysis of data. Differences in mortality were assessed by log-rank test, independent predictors were investigated by linear and cox-regression models.

Results: We identified 396 patients (35.6% STEMI, 44.4% females, mean age 76.7 years). Of those, 5.6% were severe, 22.5% were moderate, and 72.0% were non-frail according to our score. Overall all-cause mortality was 25.3% (median follow-up 2.5 years). Frail patients were older ($p = 0.001$), had significantly more often STEMI at presentation ($p = 0.022$), increased conservative therapy ($p < 0.001$), known heart failure ($p = 0.025$), atrial fibrillation ($p < 0.001$), a history of stroke ($p = 0.043$) and were more likely to be female ($p = 0.012$). Independent predictors for frailty score at discharge (adjusted for baseline characteristics) were age (OR-0.38; −0.064–0.012; $p = 0.004$), reperfusion therapy (OR 0.989; 0.548–1.43; $p < 0.001$) and atrial fibrillation (OR-1.242; −1.769 to −0.716; $p < 0.001$).

Mortality rates for frailty cohorts are depicted in Fig. 1|15-3 (log-rank <0.0001 between groups). Independent predictors for long-term all-cause mortality were frailty score ($p < 0.0001$; HR 0.755; 0.687–0.830), age ($p = 0{,}001$; HR 1.05; 1.021–1.080), kidney function (MDRD) ($p = 0.002$; HR 0.986; 0.978–0.995), known heart failure ($p = 0.017$; HR1.911; 1.121–3.257) and reperfusion therapy ($p = 0.032$; HR 0.586; 0.36–0.955). There was no interaction between age and the frailty score ($p = 0.636$).

Conclusions: Our frailty score is very easy to assess and to calculate. After adjustment for prognostic baseline characteristics, our score serves as an independent predictor for long-term all-cause mortality in patients after AMI ≥65 years.

15-4

Omega-9 fatty acids and mortality – the ludwigshafen risk and cardiovascular health study

G. Delgado de Moissl, B. K. Krämer, S. Lorkowski, W. März, C. von Schacky, M. Kleber

Medizinische Klinik V, Medizinische Fakultät Mannheim, Universität Heidelberg, Mannheim, Germany
Institute of Nutrition, Friedrich Schiller University, Jena, Germany
Klinisches Institut für Medizinische und Chemische Labordiagnostik, Medizinische Universität Graz, Graz, Austria
Abteilung Präventive Kardiologie, Medizinische Klinik und Poliklinik I, Ludwig-Maximilians-Universität, München, Munich, Germany

Background: The association of polyunsaturated omega-3 and omega-6 fatty acids with mortality has been extensively studied. Far less is known about the association of omega-9 monounsaturated fatty acids (omega-9 MUFA) with mortality.

Objective: We aimed to study the association of individual omega-MUFA with all-cause and cardiovascular mortality.

Methods: Omega-9 MUFA proportions were measured in erythrocytes in 3259 patients participating in the Ludwigshafen Risk and Cardiovascular Health Study using the HS-Omega-3 Index method. Associations with mortality were analysed by Cox proportional hazards regression with adjustment for conventional risk factors.

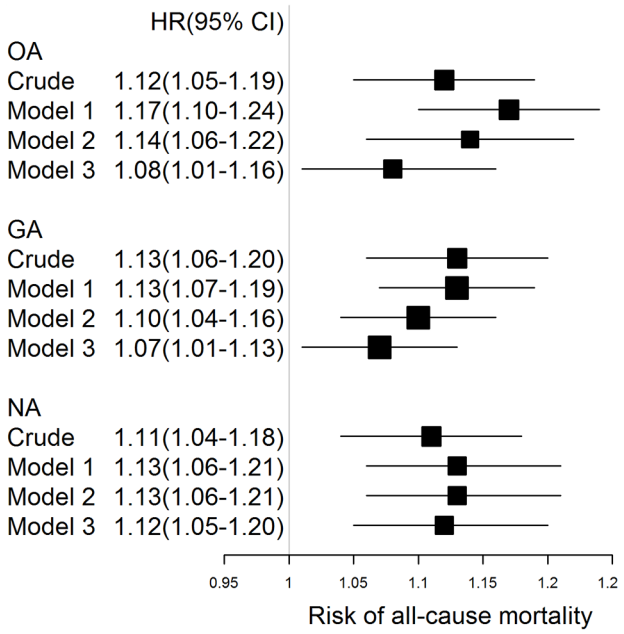


Fig. 1|15-4

Results: During a median follow-up of 10.0 years, 975 patients (29.9%) died. Partial correlation analysis adjusted for age and gender showed inverse correlations of oleic acid (OA), gondoic acid (GA) and nervonic acid (NA) with LDL-C, HDL-C and eGFR, but direct correlations with markers of inflammation and endothelial activation as well as heart failure. A 1-SD increase in OA, GA and NA was associated with increased risk of all-cause mortality with HRs (95%CI) of 1.08 (1.01–1.16), 1.07 (1.01–1.13) and 1.12 (1.05–1.20), respectively (Fig. 1|15-4). The association between OA and mortality seems to be U-shaped with a nadir at a concentration of approx. 14%.

Conclusions: All three omega-9 MUFA showed direct associations with mortality. Further studies are warranted to explore biologic and prognostic properties of omega-9 fatty acids, with a focus on nervonic acid.

15-5

Plasma renin levels in a young patient with chest pain and hypertensive crisis

S. Gasser, R. Gasser

Univ.-Klinik für Innere Medizin, Experimentelle Kardiologie, Medizinische Universität Graz, Graz, Austria

Background: The renin-angiotensin system plays a decisive role in the pathophysiology of hypertension. Renin release is regulated by a number of factors, including circulating angiotensin II (Ang II), the so-called short feedback loop. Both angiotensin-converting enzyme inhibitors and ATII receptor blockers show dose dependent effects on plasma renin activity. Renin-secreting tumors of both renal and non-renal origin have been known for a long time and cause a surgically curable form of hypertension. Hyperreninemia can derive from various sources and is thus involved in the pathophysiology of arterial hypertension. Hence, hyperreninemic hypertension in a patient cer-

tainly warrents special attention under the aspect of diagnosis and treatment.

Case report: A 28 year old man (75 kg/179 cm) presented with acute chest pain, dyspnoea and arterial hypertension of 240/120 at rest. He had arterial hypertension for 15 years and and a positive family history. At admission, he had already been under treatment with lercanidipin and candesartan.

Physical examination, chest x-ray, CT of head/brain, abdominal sonography, ocular fundus, EEG, CCDS of renal arteries, renal flow szintigraphy as well as renal MR angiography were normal. The initially very high BP was treated with intravenous urapidil and, after 10 days, the patient could leave hospital with a multidrug antihypertensive therapy (lercanidipine 10 mg bid, candesartan 8 mg bid, hydrochlorothiazide 12,5 mg once a day, urapidil 60 mg bid and rilmenidin 1 mg once a day. Routine laboratory: within the normal range. 24 h urine catecholamins were normal. Several months later, in order to exclude hyperaldosteronism, radio immune assay analysis of basal plama aldosteron had been performed. The latter was 5.0 ng/dl (normal: 3.0–15) and basal plasma renin (horizontal position of patient) was >500 µU/ml (normal: 2.4–29 horizontal position, 3.3–41.0 vertical position). CT of the abdomen and retroperitoneum provided no evidence for a tumor. Under the assumption that hyperreninemia could possibly not be the cause of hypertension in this case, but be the effect of treatment, candesartan was discontinued for 1 month and basal renin returned to 30.8 µU/ml, while basal aldosteron was down at 2.7 ng/dl. Then, candesartan was again administered at a dose of 8 mg bid and within 3 weeks basal plasma renin rose to 213,3 µU/ml.

Conclusions: Hyperreninemia can per se be the cause of hypertension and, especially in severe hypertension, one tends to a more complex investigation including measurement of basal plasma renin and aldosterone. We conclude that basal plasma renin activity and aldosterone should be measured in patients with severe hypertension, however, it is important to be viewed at in the context of ACE-inhibion or ATII receptor blockade.

15-6

Influence of long-term physical activity on serum PCSK9, HDL/LDL-cholesterol and lipoprotein a-levels

M. Sponder, I.-A. Campean, D. Dalos, M. Emich, M. Fritzer-Szekeres, B. Litschauer, J. Bergler-Klein, S. Graf, J. Strametz-Juranek

Cardiology, Medical University Vienna, Vienna, Austria
Federal Ministry of Defence and Sports, Vienna, Austria

Background: Since PCSK9 (proprotein convertase subtilisin/kexin type 9)-inhibitors were brought to market, the interest in PCSK9 metabolism has increased dramatically. The present study investigates prospectively the influence of long-term physical activity on PCSK9, high and low-density lipoprotein cholesterol (HDL-C/LDL-C) and lipoprotein a [Lp(a)].

Methods: 109 subjects were recruited and instructed to increase their sport pensum by 75 minutes/week of vigorous or 150 minutes/week of moderate intensity endurance training (or a mixture) within the calculated training pulse for 8 months. Bicycle stress tests were performed at the beginning and end of the study to prove/quantify the performance gain. PCSK9 was measured at baseline and after 2, 6 and 8 months. HDL-C, LDL-C and Lp(a) were measured at baseline and every 2 months.

Results: Analysis was done with 77 subjects (12 did not complete the study; 20 did not reach a performance gain) and showed a mean performance gain of 11.4%. PCSK9 and HDL-C-levels increased significantly from 224.7±66.8 to 243.4±84.0 ng/ml ($p=0.040$) and 58.3±18.4 to 61.1±18.5 mg/dl ($p=0.014$) resp. LDL-C-levels decreased significantly from 115.0±33.4 to 109.8±31.7 mg/dl ($p=0.040$) but there was no significant change in Lp(a)-levels (37.9±51.9 to 43.3±60.6 nmol/l; $p=0.218$, Fig. 1|15-6).

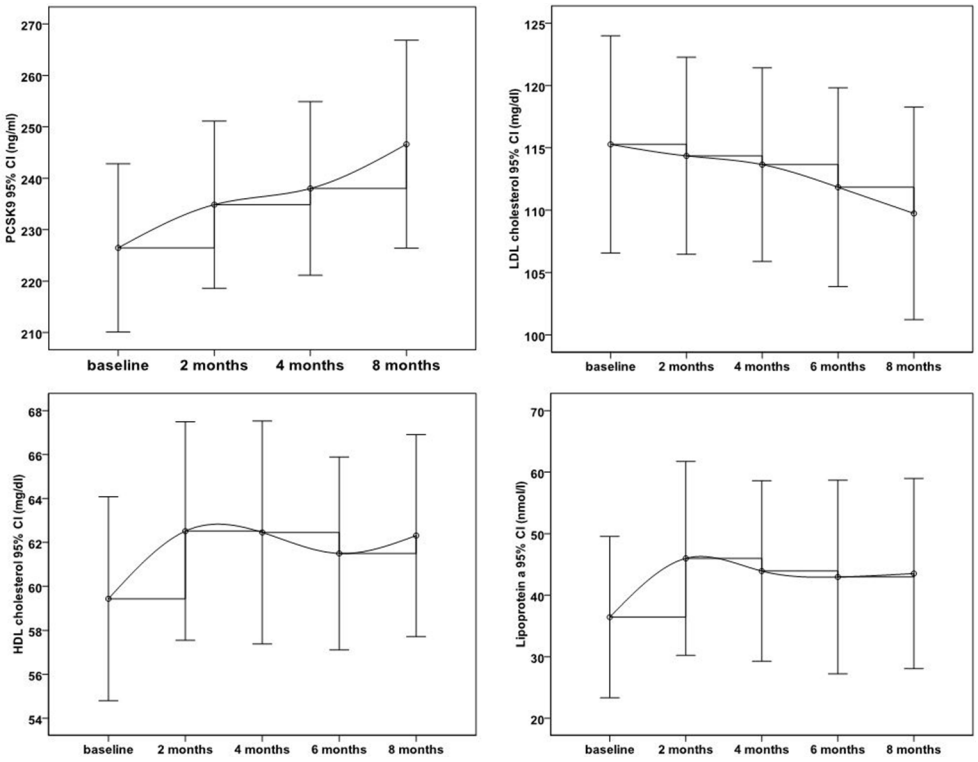


Fig. 1|15-6

Conclusions: We could show a sports-induced decrease of LDL-C with a simultaneous increase of PCSK9. Our data suggest that regular physical activity leads to decreasing levels of circulating LDL-C independently from (increasing) PCSK9-levels, probably because less PCSK9 is used up due to lower circulating LDL-C amounts.

15-7

Sports and HDL-quality reflected by serum amyloid A and surfactant protein B

M. Sponder, C. Kopecky, I.-A. Campean, M. Emich, M. Fritzer-Szekeres, B. Litschauer, S. Graf, M. Säemann, J. Strametz-Juranek

Cardiology, Medical University Vienna, Vienna, Austria
Federal Ministry of Defence and Sports, Vienna, Austria

Background: The aim of this prospective study was to investigate the influence of long-term physical activity on HDL quality, reflected by serum amyloid A (SAA) and surfactant protein B (SPB).

Methods and Results: 109 healthy subjects were recruited, 97 completed the study. Participants were asked to perform within the calculated training pulse for 8 months. The performance gain was measured/quantified by bicycle stress tests at the beginning and end of the observation period. SAA and SPB were measured at baseline, after 4/8 months by ELISA. In contrary to HDL-quantity, there was no sports-induced change in SAA or SPB observable. However, significant predictors for SPB-levels were smoking status (Fig. 1|15-7), BMI and weekly alcohol consumption and for SAA weekly alcohol consumption together with sex and hsCRP-levels.

Conclusions: Long-term physical activity increases HDL-quantity but has no impact on HDL-quality reflected by SAA and SPB. Smoking is associated with higher SPB-levels and the weekly alcohol intake is associated with both higher SAA and SPB-levels suggesting a damaging effect of smoking and drinking alcohol on the HDL-quality. We assume that HDL-quality is at least as important as HDL-quantity when investigating the role of HDL in (cardiovascular) disease and should be receive attention in further studies dealing with HDL.

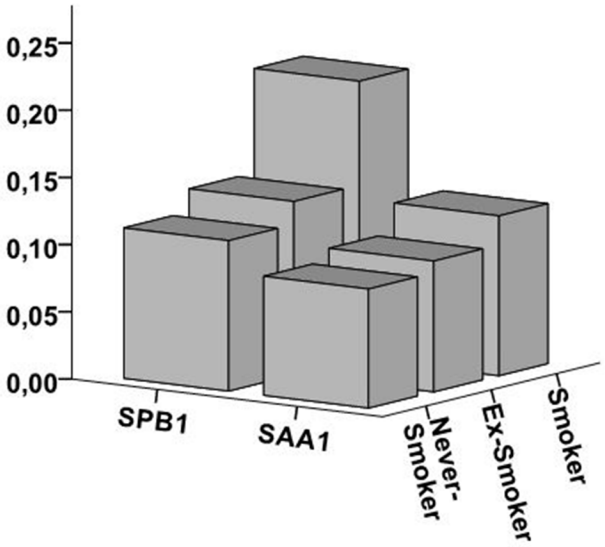
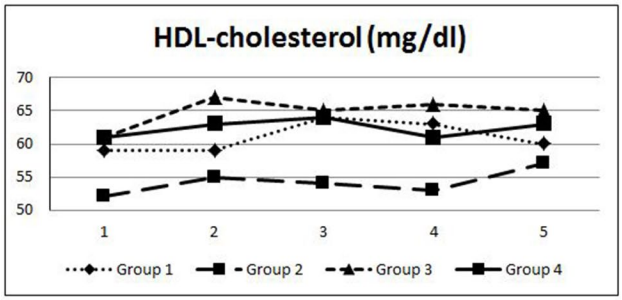
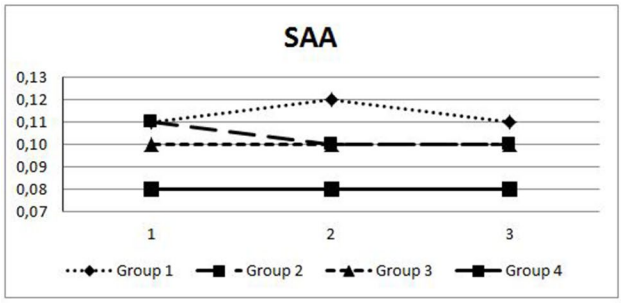


Fig. 1|15-7





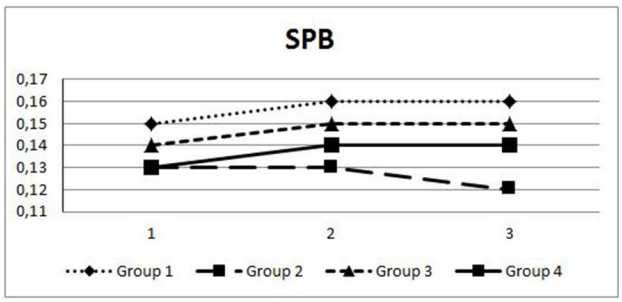


Fig. 2|15-7

15-8

Untersuchungen über den Einfluß von Meditation auf den Blutdruck bei arterieller Hypertonie

L. Veigl, R. Gasser

Kardiologie, Medizinische Universität Graz, Graz, Österreich

Seit 2013 wird in den Empfehlungen der American Heart Association transzendentale Meditation 2013 als alternative Methode zur Blutdrucksenkung in Betracht empfohlen. Zahlreiche Publikationen, in teilweise angesehenen Fachzeitschriften wurden dazu in den letzten 10 Jahren veröffentlicht. Zahlreiche Untersuchungen belegen den physiologischen Effekt von diversen Meditationsformen auf das sympathische Nervensystem, EEG, HRV, sowie auf Cortisol- und Aldosteronspiegel. Als Wirkweise der Meditation werden Stressreduktion und Sympaticuseinfluß postuliert.

Die vorliegende eigene Analyse von über hundert wissenschaftlichen Arbeiten zeigt bei genauerer Hinsicht jedoch ein heterogenes Bild und es bestehen nicht nur unterschiedliche Ergebnisse zwischen verschiedenen Meditationstechniken, sondern es gibt auch Arbeiten, welche eine gegenteilige Wirkung (Stimmungsschwankungen, Angst, Depression bzw. soziale Isolierung mit negativer Auswirkung auf den Blutdruck) feststellen konnten. Regelmäßige Meditation wirkt sich objektiv (gemessen über Stresshormonspiegel im Blut, Hautwiderstand, Herzfrequenzvariabilität) und subjektiv (geringeres Stressempfinden, besserer Umgang mit Stresssituationen) positiv auf

Stress aus. Da Stress als schon lange diskutierter Faktor bei der Entstehung der essentiellen Hypertonie eine Rolle zu spielen scheint, liefert vor allem diese stressreduzierende Wirkung der Meditation einen interessanten Therapieansatz.

Diese Arbeit weist auf die inhomogene Studienlage hin und nach Beurteilung der in den letzten Jahren veröffentlichten Studien kann zumindest die Transzendentale Meditation als „Class IIB, level of evidence: B" eingestuft werden und die Analyse der Daten wird präsentiert. Es wird dargelegt, ob sich aus der bisher vorhandenen Studienlage eine robuste Evidenz für die blutdrucksenkende Wirkung von Meditation ergibt und ob Mediation auch im deutschsprachigen Raum in die Empfehlungen zur Blutdrucktherapie aufgenommen werden sollte.

15-9

Amino acids kynurenine and quinolinic acid and target organ damage in hypertensive patients – novel insights from the Styrian hypertension study

N. Verheyen, M. Gaksch, A. Meinitzer, M. Grübler, C. Trummer, V. Schwetz, K. Ablasser, E. Kolesnik, D. von Lewinski, H. Brussee, W. März, A. Tomaschitz, S. Pilz

Klinische Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Austria
Inselspital Bern, Bern, Switzerland
Ruperto Carola University Heidelberg, Heidelberg, Germany

Background: Experimental studies indicated a contribution of the essential amino acids kynurenine and quinolinic acid to cardiovascular disease. We therefore investigated the associations between their serum concentrations and surrogates of hypertensive target organ damage in a cohort of hypertensive patients.

Methods: Cross-sectional data from 514 hypertensive participants of the Styrian Hypertension Study were analyzed who had been enrolled at a single tertiary care hospital. Serum concentrations of kynurenine and quinolinic acid were correlated with N-terminal pro-brain B-type natriuretic peptide (NT-proBNP) and 24-hours urinary protein-to-creatinine-ratio (PCR) in multivariate linear regression analyses.

Results: Mean age was 61.2 +/- 10.5 years (52.5% females) and mean 24-hours ambulatory blood pressure was 127.5/76.4 +/- 13.8/9.5 mmHg. Medians and interquartile ranges of NT-proBNP and PCR were 82 (42–152) pg/ml and 67.5 (52–93.4) mg/mmol creatinine, respectively. Both kynurenine and quinolinic acid were significanty related with NT-proBNP and PCR in univariate analyses. After adjustment for age, sex, systolic nighttime blood pressure, estimated glomerular filtration rate, body mass index, C-reactive protein, concomitant blood pressure and heart failure medication and other traditional cardiovascular risk factors, quinolinic acid was significantly related with NT-proBNP (adjusted beta-coefficient = 0.133, $P = 0.003$) and PCR (beta = 0.216, $P < 0.001$), while kynurenine was not. Restricting these analyses to patients with NT-proBNP > 125 pg/ml ($n = 171$), both amino acids were independently related with NT-proBNP (quinolinic acid: beta = 0.249, $P = 0.027$; kynurenine: beta = 0.207, $P = 0.027$).

Conclusions: Serum concentrations of quinolinic acid and, to a less extent, kynurenine determine hypertensive target organ damage independently of potentially confounding factors. These clinical data extend previous experimental studies indicating that quinolinic acid and kynurenine may mediate target organ damage in patients with arterial hypertension.

Postersitzung 16 – Basic Science 4

16-1

miR-19a-3p containing exosomes improve cardiac function in ischemic myocardium

L. Pölzl, M. Graber, J. Hirsch, M. Blumer, E. Kirchmair, R.Kirchmair, P. Paulus, M. Grimm, J. Holfeld, C. Tepeköylü

Universitätsklinik für Herzchirurgie, Medizinische Universität Innsbruck, Innsbruck, Austria
Department für klinisch-funktionelle Anatomie, Medizinische Universität Innsbruck, Innsbruck, Austria
Universitätsklinik für Innere Medizin III, Medizinische Universität Innsbruck Kepler Universitätsklinikum Linz, Klinik für Anästhesiologie und operative Intensivmedizin, Linz, Austria

Background: Regeneration of ischemic myocardium for patients with ischemic heart disease represents a major challenge in the field of cardiovascular research. Exosomes were shown to exert regenerative effects in ischemic myocardium. We could show recently that mechanical stimulation of ischemic tissue via shock waves causes exosome release. We hypothesized that released exosomes improve cardiac function in ischemic hearts.

Methods: Human umbilical vein endothelial cells (HUVECs) underwent mechanical stimulation via shock waves to induce exosome release. Exosomes were isolated subsequently from the supernatant and characterized by transmission electron microscopy and nanoparticle tracking analysis. Functional in vitro assays were performed to analyze the angiogenic potential of released exosomes. Exosome content was evaluated via a miRNA sequencing array. Exosomes and miRNA were injected intramyocardially in SCID mice after left anterior descending (LAD) ligation ($n = 10$). Heart function was analyzed via transthoracic echocardiography. qPCR for angiogenic genes and immunofluorescence staining for vessels was performed. Myocardial scar was quantified via Masson Trichrome staining.

Results: Exosomes exhibited strong angiogenic potential in vitro and resulted in AKT and ERK activation. miRNA assay showed high exosomal miR 19a-3p content. miR 19a-3p induced capillary tube formation and endothelial proliferation. Anitmir-19a-3p antagonized exosome effects. Injection of released exosomes in a murine model of LAD ligation resulted in improved left ventricular function (EF in %: 13,453.56 vs. 27,872.18, $p = 0.041$) and decreased fibrosis (%: 59,777.0 vs. 33,835.95, $p = 0.025$). Exosome treatment caused increased myocardial expression of VEGF and VEGFR2 resulting in increased numbers of capillaries and arterioles. Myocardial injection of miR 19a-3p in ischemic hearts lead to improvement of left ventricular function, induction of angiogenesis and decreased fibrosis.

Conclusions: Intramyocardial injection of SW exosomes in ischemic myocardium results in significantly improved cardiac function and myocardial regeneration. miR 19a-3p was identified as responsible exosomal cargo for the observed regenerative effects. 19a-3p containing exosomes could develop an innovative approach for the regeneration of ischemic myocardium.

16-2

Molecular mechanisms affecting cardiotoxicity

D. Lukovic, K. Zlabinger, N. Pavo, A. Spannbauer, D. Traxler, J. Winkler, A. Gugerell, L. Mandic, M. Gyöngyösi

Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria

Background: Anthracyclines, such as doxorubicin are effective standard cytotoxic medications to treat cancer. One of the major side effects of these drugs is the cardiotoxicity, leading to moderately or severely reduced cardiac function, which may lead to cardiac death, in spite of successful treatment of the malignant disease. In order to prevent cardiotoxicity, anticancer drugs may be encapsulated to liposomes, which may prevent the penetration of the drug into healthy tissues with normal capillaries. Previously we have reported that doxorubicin-citrate complex (Myocet® MYO) exhibited reduced cardiotoxicity proven by preserved left and right ventricular (LV, RV) function and decreased endomyocardial fibrosis as compared to Doxorubicin (DOX) treatment in clinically relevant porcine model. However, the molecular mechanisms of distinct cardiotoxic effect induced by DOX and MYO have not been fully explored.

Methods: Human doses of DOX ($n=6$), MYO ($n=9$) and physiologic saline (Control, $n=6$) were administrated intravenously in 3 cycles in domestic pig (38 ± 3 kg). Two weeks after the final dose, the animals were humanely euthanized and hearts were explanted. Transcriptomic profile of myocardial samples collected from LV and RV was assessed utilizing next generation sequencing approach. Gene ontology enrichment analysis was displayed using the String Database.

Results: Analysis of genes involved in DOX-induced cardiomyopathies, heart failure, and hypertension showed analogous transcriptional response between DOX and MYO group in both LV and RV. However, analysis of genes with opposite regulation in DOX and MYO group revealed 350 significantly expressed genes. Functional clustering of significantly deregulated transcripts showed prominent transcriptional changes in the LV. We observed downregulated expression of heat shock proteins (HSP) in MYO group following downregulation of cell cycle progression as compared to DOX. Upregulated Rho-GTP-ase pathway in MYO group affected upregulation of genes coding cytoskeleton. In addition, process of protein degradation and ubiquitination was significantly upregulated in DOX group as compared to MYO group.

Conclusions: Here, we demonstrate that molecular changes, such as HSP expression and Rho-GTP-ase pathway might mediate distinct cardiotoxic effect of DOX and MYO on LV and RV function. Better understanding of the mechanisms by which distinct therapies affect the heart tissue during the anticancer treatment plays pivotal role in drug design.

16-3

Monocyte activation via protease-activated receptor 1 (PAR1) leads to an upregulation of molecules involved in fibrinolysis

B. Thaler, P. Hohensinner, J. Baumgartner, C. Schörgenhofer, M. Fischer, B. Jilma, W. Speidl, J. Wojta

Universitätsklinik für Innere Medizin II, Medizinische Universität Wien, Vienna, Austria

Background: Thrombin, a serine protease, plays a crucial role in haemostasis and inflammation. Next to its ability to activate fibrinogen, it also functions as a signal molecule via the activation of protease-activated receptors PAR1,3 and 4 on a variety of cell types including monocytes. Monocytes can be divided into three subsets: classical monocytes (CM, CD14++, CD16-), intermediate monocytes (IM, CD14++, CD16+) and non-classical monocytes (NCM, CD14+, CD16+) and it could have been shown that those subsets have distinct functions. CMs are the typical phagocytic cells, whereas IMs are rather pro-inflammatory and NCMs display patrolling behaviour along the endothelium.

We hypothesized that due to the different functions of monocyte subsets, they might also differentially express PAR1,3 and 4 and exhibit differences in their responses toward PAR1 activation.

Methods: LPS treated and untreated whole blood samples were stained with antibodies against CD14, CD16 and PAR1, 3 and 4 and were analysed via flow cytometry. Moreover, whole blood samples were incubated with brefeldin A and were then stimulated with LPS for 4 h. Subsequently, samples were stained for flow cytometry. In addition, monocytes were stimulated in vitro with TRAP-6 or additionally pre-treated with LPS and RNA was isolated for qPCRs. Furthermore, monocytes were isolated from blood samples of volunteers who received a dose of vorapaxar prior to LPS infusion and RNA was isolated for qPCRs.

Results and Conclusions: CD16 positive monocytes, namely IMs and NCMs have significantly more PAR1 compared to CMs ($p=0.05$, $p=0.03$). IMs also express significantly more PAR3 and NCM more than CMs (IM vs CM $p=0.002$, IM vs NCM $p=0.05$). All three subsets show a similar expression pattern for PAR4. When monocytes are activated with LPS they respond with an upregulation of PARs on their surface in vitro and in vivo and experiments with brefeldin A showed that this might be because of an intracellular storage pool. When activated with LPS and stimulated with TRAP-6, monocytes react with an increased expression of PAI-1, uPA and TFPI ($p=0.02$, $p=0.05$, $p=0.025$). When PAR1 activation is blocked by vorapaxar in vivo, PAI-1 and TFPI are significantly down regulated ($p=0.02$, $p=0.04$).

In conclusion, based on our data, thrombin is not just involved in coagulation and inflammation but also activates genes of the proteolytic system in monocytes.

16-4

Myocardial transcriptome in clinically relevant porcine model of ischemic postconditioning

L. Mandic, D. Lukovic, D. Pils, N. Pavo, K. Zlabinger, A. Gugerell, J. Winkler, A. Spannbauer, D. Traxler-Weidenauer, M. Gyöngyösi, G. Koncsos, Z. Giricz, P. Ferdinandy

Department of Cardiology, Medical University of Vienna, Vienna, Austria
Semmelweis University, Budapest, Hungary

Background: Ischemic postconditioning (IPostC) present sublethal ischemia/reperfusion stimuli applied after prolonged ischemic insult aiming to render the myocardium more resistant against ischemia/reperfusion injury. Although the concept of IPostC showed a promising strategy to attenuate ischemic injury in pre-clinical animal models, translation to clinical scenarios has not met success. This study proposes a comprehensive analysis of transcriptional changes elicited by IPostC in the translational porcine model of reperfused MI.

Methods: Anaesthetized pigs were randomised to groups IPostC ($n=3$) and myocardial infarction (MI, $n=3$); sham-operated animals served as controls ($n=3$). MI was induced by 90 min percutaneous balloon occlusion of the left anterior descending artery following reperfusion (balloon deflation). IPostC was elicited by 6×30 sec cycles of ischemia/reperfusion after 90 min ischemia. Left ventricular (LV) function was assessed by cardiac MRI (three days follow-up) and transcriptome analysis was performed using next-generation sequencing of myocardial samples collected at three days follow-up from the infarcted and remote area in each experimental group.

Results: IPostC had no effect on LV function and infarct size; however, the myocardial oedema and microvascular obstruction were significantly attenuated as compared to the MI group. We detected relevant molecular changes in remote area of MI and IPostC groups at three days follow-up and identified genes with the opposite regulation in MI and IPostC groups. Genes with opposite regulation were organized into functional clusters associated with regulation of extracellular matrix and focal adhesion, coding of ribosomal subunits, vesicle transport, activation of blood cells and cardiac hypertrophy.

Conclusions: Our results indicate that the effect of IPostC is limited to confer benefits on coronary microvasculature. In addition, analysis of transcriptome indicates that substantial genomic response occurs in the remote area of the myocard and IPostC implicates increased regulation of extracellular matrix, inhibited translation and vesicular transport of the proteins, inactivation of blood cells, and downregulation of genes associated with hypertrophy after three days post infarction.

16-5

Overexpression of MicroRNA-34a disrupts postnatal cardiac development and regeneration

T. Schuetz, J. M. Penninger, B. J. Haubner

Department of Internal Medicine III (Cardiology), Medical University Innsbruck, Innsbruck, Austria
Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria

Background: Myocardial infarction (MI) represents a major health burden due to subsequent reduction of cardiac function leading to ischemic cardiomyopathy. In contrast to other adult tissues i. e. liver, myocardium cannot be sufficiently regenerated following hypoxic injury. Recently our group demonstrated efficient cardiac regeneration in a neonatal mouse MI model of left anterior descending artery (LAD) ligation. Of note, our group and others reported similar observations in newborn human babies suffering from neonatal MI.

The mechanisms of neonatal mammalian cardiac regeneration remain unclear. Here we show the crucial role of miR-34a, which was found in our time-course transcriptome analysis of neonatal mouse hearts

Methods: Adeno-associated viruses (AVV9) containing a GFP-mmu-mir-34a vector under the control of a chicken cardiac troponin T (cTNT) promoter were injected into the mediastinum of postnatal day 1 (P0.5) C57BL/6J mice at a dose of 5E13 viral genomes per kg bodyweight. On postnatal day two (P1.5) mice were randomized into either a LAD-ligation or SHAM-surgery group. One day post injury (1 dpi) heart function was assessed by echocardiography. M-Mode and B-Mode images were acquired. 5 days post virus injection the heart of one mouse was harvested to assess viral transduction efficiency, using immunohistochemistry (IHC) for GFP detection. 21 days post injury (21dpi) final echocardiography was performed, followed by harvesting of the hearts and subsequent histological processing and evaluation

Results: Viral infection of cardiomyocytes was highly efficient as confirmed by IHC.

Strikingly, 22 days post virus injection (21 days post surgery), out of originally 7 mice in the LAD group and 4 mice in the SHAM group, only 1 mouse of the SHAM group was alive. All others did not survive until three weeks post surgery. Echocardiographic imaging 21dpi of the sole surviving SHAM mouse revealed massive dilatation with markedly reduced left-ventricular ejection fraction (LVEF).

Conclusions: AAV9 mediated cardiomyocyte specific overexpression of miR-34a in neonatal murine hearts not only completely blocks cardiac regeneration but also severely impairs cardiac function. These data confirm our transcriptional analysis of regenerating neonatal mouse hearts and highlight the critical role of miR-34a in cardiac homeostasis.

16-6

Porcine cardiac progenitor cells as source for porcine in vitro cardiac models

K. Zlabinger, A. Gugerell, D. Lukovic, J. Winkler, D. Traxler-Weidenauer, A. Spannbauer, L. Mandic, M. Pavone-Gyöngyösi

Universitätsklinik für Innere Medizin II/Kardiologieforschung, Medizinische Universität Wien, Vienna, Austria

Background: Cell culture experiments represent a suitable alternative for large animal models in basic therapeutic research. In spite of growing evidence of necessity of porcine translational model, no commercial porcine cardiomyocytes are available, with consequent lack of porcine cardiomyocytes for in vitro experiments. The overall goal of this work was to establish a porcine cardiac progenitor (pCPC) cell culture serving as fundament for cardiac cell culture models. Differentiated into cardiomyocytes (CMC) they offer great opportunities to mimic cardiac issues in vitro, and can replace in vivo experiments. Furthermore therapeutic agents and capabilities can be defined by the use of such a model.

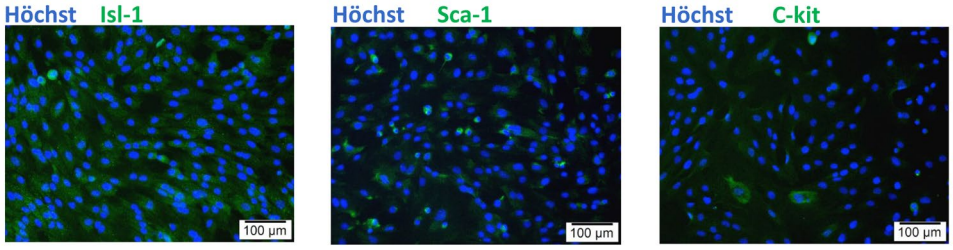
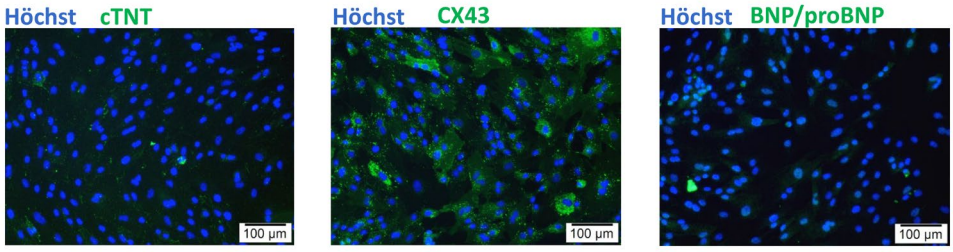


Fig. 1 | 16-6



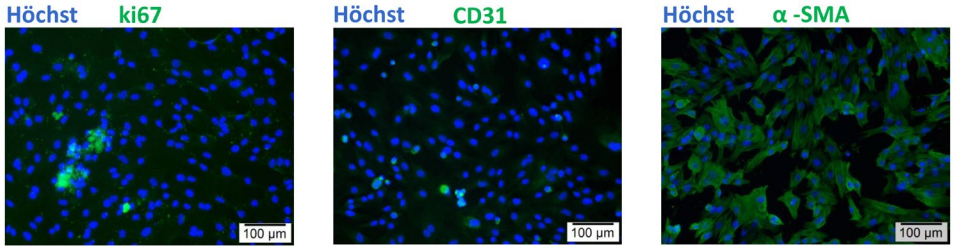
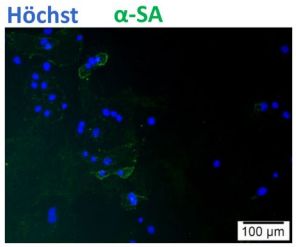


Fig. 2 | 16-6



Methods: For the isolation of cardiac progenitor cells, porcine heart muscle was minced into small pieces and added to MACS C-Tubes together with 5 ml 0.02% Collagenase II. Then heart pieces were dissociated on GentleMACS dissociator running the heart-program (for 2×30 sec). Afterwards the tubes were incubated for 10 minutes in a 37 °C water bath and 5 ml fresh full medium (DMEM, +10% FBS, +1% PenStrep) was added to the dissociated cell-collagenase mixture before filtration through 100 µm cell strainers into a new 50 ml tube. 30 ml EBSS was pipetted through the cell strainer to wash out residual cells before centrifugation for 5 minutes at 1500 rpm. The supernatant was discarded and the cell pellet was re-suspended in fresh medium and added to T25 flasks. Every 2–3 day media was changed, and cells were splitted in a 1:5 ratio at 80% confluency. Cardiac progenitor cell markers such as Isl-1, Sca-1 and c-kit were stained with immunofluorescence staining, as well as other cardiac specific markers like BNP/pro BNP, Cx43, cTNT and α-SA. Proliferation marker ki67, endothelial cell marker CD31 and α-SMA for smooth muscle cells were also stained.

Results: Porcine cardiac progenitor cells grow in colony-forming units and show spindle shaped morphology. Immunofluorescence staining revealed mixed cell populations expressing the three cardiac progenitor cell markers Isl-1, Sca-1 and c-Kit in different intensities. Isl-1 was expressed in almost all of the isolated cells, whereas Sca-1 was only expressed in some cells and c-kit in an even less number of cells (Fig. 1|16-6). Some cells were positive for ki67 (proliferation marker), CD31, BNP/proBNP or α-SA. CX43 and α-SMA were highly expressed and cTNT slightly expressed in most of the cells (Fig. 2|16-6).

Conclusions: Our findings prove the successful isolation of cardiac progenitor cells from porcine heart muscle. Currently, there are different types of cardiac progenitor cells known expressing Isl-1, Sca-1 or c-Kit, but also mixed expression of those markers was reported. The presence of differentiated cardiac cell specific markers (CD31 for endothelial cells; α-SA, BNP/proBNP, CX43 and cTNT for cardiomyocytes; α-SMA for cardiac smooth muscle cells) indicates a differentiation capability to all types of cells present in the heart. These porcine cardiac progenitor cells will be further used for the establishment of porcine cardiomyocyte cell culture models, mimicking pathologies like cardiac hypertrophy or they will be used for in vitro testing of drugs and regenerative therapies prior to in vivo experiments.

16-7

Potential new biomarkers in myocardial ischaemia

C. Steiner, K. Zlabinger, D. Lukovic, A. Gugerell, J. Winkler, M. Gyöngyösi

Universitätsklinik für Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: Cardiovascular diseases and their consequences are the most frequent causes of death in industrial nations. The establishment of rapid intervention possibilities led to an astonishing reduction of the mortality in acute myocardial infarction (AMI). Pre-infarction (warm-up) angina pectoris has been shown to reduce infarcted area due to release of cardioprotective substances prior to ischaemic attack. Ischemic preconditioning (IP) is one of the most powerful mechanism to reduce infarction area and corresponds to experimental IP. Maximal levels of cardiac ischemic biomarkers such as troponin T and creatine kinase are of prognostic values for clinical outcome. However, these biomarkers increase earliest at 2 h, therefore, more sensitive and earlier biomarkers are searched. Moreover, currently no biomarker of IP has been reported. Clusterin (CLU), a molecular chaperon, is detected in damaged cardiomyocytes in close relation to the membrane attack complex (MAC) of the complement system and appears to protect these cells from apoptosis. High-mobility-group-protein-1 (HMGB-1) is an early mediator of ischemia, reperfusion and inflammation. In our study we investigated the association of ischemia/reperfusion and IP of the myocardium with the plasma concentrations of HMGB-1 and CLU in a closed chest reperfused myocardial infarction in pigs with/without IP.

Methods: In anesthetized pigs, a percutaneous occlusion of the mid LAD was performed for 90 min, followed by reperfusion. The pigs were randomized to either group of IP-AMI ($n=11$) or AMI ($n=12$). IP was induced by three times occlusion/reperfusion of the LAD for 5 min of each period prior to the 90 min occlusion. Blood samples were collected at the beginning, after the IP, after the 90 min and 60 min post reperfusion. The concentrations of HMGB-1 and CLU were measured by means of the sandwich ELISA method. The evaluation was performed with analysis of variance with repeated measurements ($p<0.05$).

Results: The plasma concentrations of HMGB-1 increased immediately after IP with 165%, in contrast with the CLU, where IP did not influence the CLU level (Fig. 1|16-7, Fig. 2|16-7). During the 90min coronary occlusion, the levels of HMGB-1 remained unchanged in both IP-AMI and AMI groups, while IP led to decrease of CLU level, with slight increase in AMI group. Levels of HMGB-1 increased rapidly in both groups after induction of reperfusion constantly, while the level of CLU increased at the first 30min of reperfusion with decrease to normal level at the 60min reperfusion time in both groups (Fig. 1|16-7, Fig. 2|16-7).

Conclusions: HMGB-1 might be an early indicator of reperfusion after long-lasting ischemia, while CLU might be useful as an early indicator of myocardial ischemia. In contrast with the AMI group, IP led to temporary decrease of CLU level, indicating less ischemic stress of the cardiac tissue. Longer reperfusion time decreased the CLU level, suggesting benefit of the reperfusion therapy.

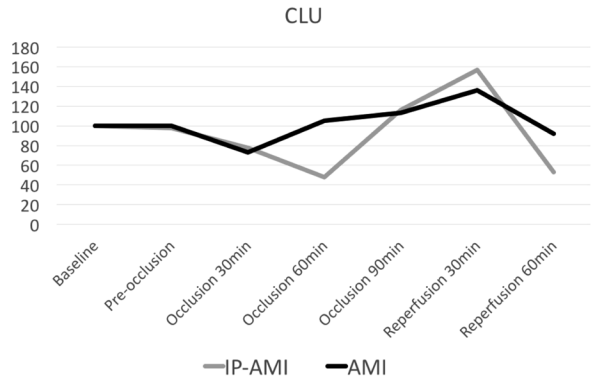


Fig. 1|16-7

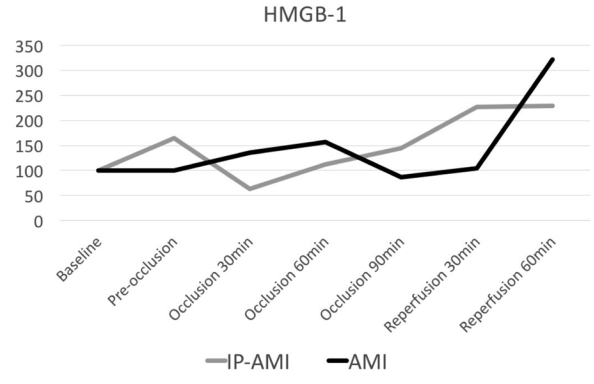


Fig. 2|16-7

Postersitzung 17 – Akutes Koronarsyndrom 2

17-1

Cardiac arrest as an age-dependent prognosticator for mortality in patients suffering acute coronary syndrome

P. Sulzgruber, S. Schnaubelt, L. Koller, G. Goliasch, J. Niederdöckl, A. Simon, F. El-Hamid, S. Forster, J. Wojta, A. Niessner

Universitätsklinik für Innere Medizin II, Kardiologie, Medizinische Universität Wien, Vienna, Austria

Background: The development of cardiac arrhythmias, such as ventricular fibrillation (VF), or pulseless ventricular tachycardia (VT) resulting in cardiac arrest, represents a severe complication in patients suffering acute coronary syndrome (ACS). While the worsening of prognosis in this vulnerable patient collective is well known, less attention has been paid to its age-specific relevance so far from a long-term perspective.

Methods: We enrolled 832 patients suffering ACS within the current analysis. Patients were randomized and stratified into equal groups ($n=208$/group) according to age "<45years", "45–64 years", "65–84 years" and ">85 years". Cox regression hazard analysis was used to assess the influence of cardiac arrest on long-term survival. The multivariate model was adjusted for potential confounders.

Results: The total umber of cardiac arrest significantly differ between age groups, demonstrating the highest incidence in the youngest collective with 18.8% ($n=39$; <45 years), and a significantly lower incidence by increasing age (9.6% ($n=20$) 45–64 years; 15.9% ($n=33$) 65–84 years; 7.2% ($n=15$) >85 years, $p=0.01$ for comparison of the youngest age group with all other patients). After a mean follow-up time of 5.0 years, a total of 185 patients (22.8%) died due to cardiovascular causes.

Within the total study collective cardiac arrest was a strong and independent predictor for mortality with an adjusted HR of 2.17 (95% CI 1.52–3.10, $p<0.001$). While there was no significant association with mortality within very young patients (<45 years; adj. HR of 1.32 (95% CI 0.42–4.11, $p=0.637$), there was an association with increasing age detectable in young patients (45–64 years; adj. HR of 3.82 (95% CI 1.04–13.98, $p=0.043$), elderly patients (65–84 years with an HR of 4.51 (95% CI 2.48–8.19, $p<0.001$) and very old patients (>85 years; adj. HR of 7.52 (95% CI 4.13–13.68, $p<0.001$). A significant interaction between cardiac arrest and age groups was found ($p=0.05$).

Conclusions: We were able to demonstrate that arrhythmias resulting in cardiac arrest are more common in very young ACS patients compared to their older counterparts. While cardiac arrest significantly worsens outcome in ACS patients >45 years, we did not find a significant impact on mortality within very young individuals.

17-2

Synergistic inhibition of both P2Y1 and P2Y12 adenosine diphosphate receptors as novel approach to rapidly attenuate platelet-mediated thrombosis

T. Gremmel, I. Yanachkov, G. Wright, A. Michelson, A. Frelinger, K. Przyklenk

Universitätsklinik für Innere Medizin II, Medizinische Universität Wien, Vienna, Austria
GLSynthesis Inc, Worcester, USA
Harvard Medical School, Boston, USA
Wayne State University School of Medicine, Detroit, USA

Background: Dual antiplatelet therapy with aspirin and an adenosine diphosphate (ADP) receptor inhibitor is a mainstay of pharmacological therapy in acute coronary syndromes (ACS). In aspirin-treated patients with non-ST-segment elevation ACS, the co-administration of the P2Y12 receptor antagonist clopidogrel reduced the composite of cardiovascular death, myocardial infarction and stroke by 20% compared to placebo. The newer ADP receptor inhibitors prasugrel and ticagrelor yielded an even greater reduction of ischemic outcomes in ACS patients than clopidogrel at the expense of a significantly increased bleeding risk. The latter is particularly problematic in patients who cannot be treated by percutaneous coronary intervention but must immediately undergo coronary artery bypass graft surgery. Despite these recent advances, ischemic events like acute stent thrombosis still impair the prognosis of many ACS patients.

Unlike currently approved ADP receptor antagonists, the new diadenosine tetraphosphate derivative GLS-409 targets not only P2Y12 but also the second human platelet ADP receptor P2Y1. Moreover, it is a rapidly acting and rapidly reversible

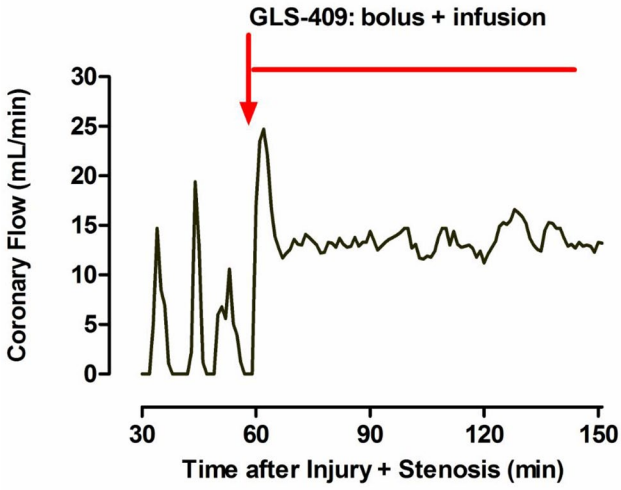


Fig. 1|17-2

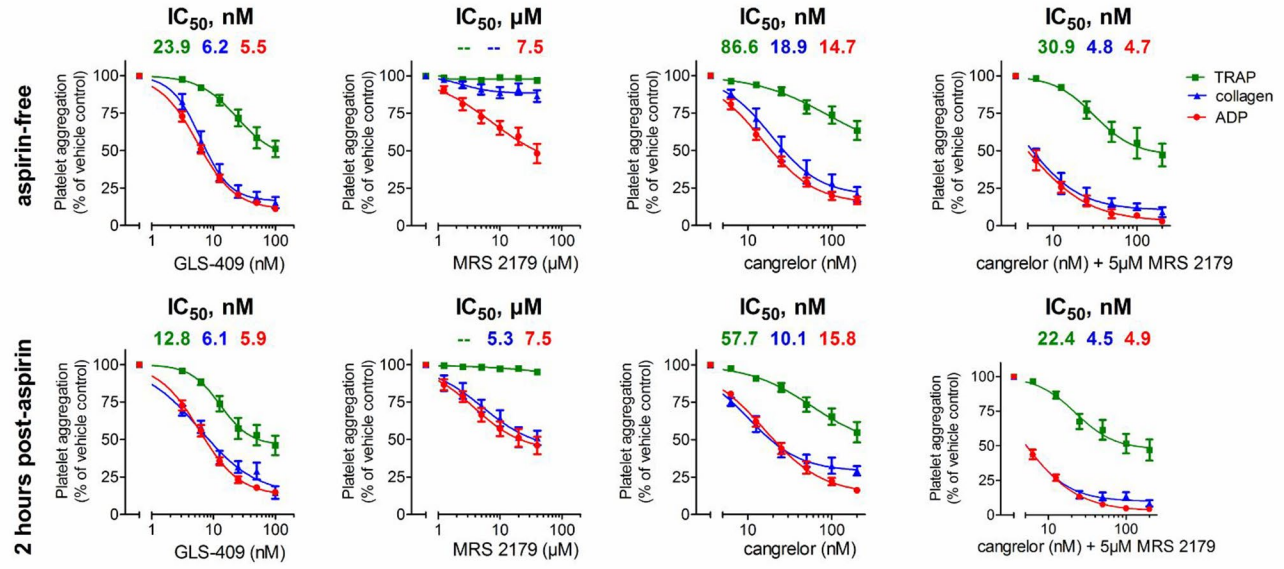


Fig. 2|17-2

antiplatelet agent and may therefore be a promising antiplatelet drug candidate. The current study is the first to investigate the in vivo antithrombotic effects of GLS-409.

Methods: We studied (1) the in vivo effects of GLS-409 on agonist-stimulated platelet aggregation in anesthetized rats by whole blood impedance aggregometry, (2) the antithrombotic activity of GLS-409 and the associated effect on the bleeding time in a canine model of platelet-mediated coronary artery thrombosis, and (3) the inhibition of agonist-stimulated platelet aggregation by GLS-409 versus selective P2Y1 and P2Y12 inhibition in vitro in samples from healthy human subjects before and 2 hours after aspirin intake.

Results: In vivo treatment with GLS-409 significantly inhibited ADP- and collagen-stimulated platelet aggregation in rats. Further, GLS-409 attenuated cyclic flow variation, i.e., platelet-mediated thrombosis, in vivo in our canine model of unstable angina (Fig. 1|17-2). The improvement in coronary patency was accompanied by a non-significant 30% increase in bleeding time. Of note, GLS-409 exerted its effects without affecting rat and canine hemodynamics. Finally, in vitro treatment with GLS-409 showed effects similar to that of cangrelor and the combination of cangrelor with the selective P2Y1 inhibitor MRS 2179 on agonist-stimulated platelet aggregation in human platelet-rich plasma and whole blood before and 2 hours after aspirin intake (Fig. 2|17-2).

Conclusions: Our data demonstrate the antithrombotic efficacy of GLS-409 in vivo, and show that it rapidly and potently inhibits agonist-stimulated human platelet aggregation in vitro with and without concomitant aspirin therapy. Moreover, GLS-409 did not affect hemodynamics in our rat and canine model, and was only associated with a moderate non-significant increase in median bleeding time in our canine model, while showing a fast plasma clearance. GLS-409 is therefore a promising antiplatelet drug candidate, in particular for the initial phase of ACS.

17-3

Impact of hyperuricemia on long-term adverse cardiovascular outcome in patients presenting with acute coronary syndrome undergoing coronary stenting

M. Tscharre, M. Rohla, C. Hauser, S. Farhan, M.K. Freynhofer, K. Huber, T.W. Weiss

3. Medizinische Abteilung mit Kardiologie und Intensivmedizin, Wilhelminenspital, Vienna, Austria

Background: A large body of evidence links uric acid with the promotion of atherosclerosis and vascular adverse events. However, data on long-term adverse outcome in patients with elevated levels of uric acid after coronary stenting is scarce.

Purpose: We aimed to assess the prognostic impact of hyperuricemia on long-term adverse cardiovascular outcome in patients after ACS.

Methods: We analysed 1240 patients of a prospective single centre registry presenting with ACS all undergoing successful coronary stenting from 2006–2012. Hyperuricemia was defined as uric acid plasma levels above 6.0 mg/dl in women, and above 7.0 mg/dl in men. As endpoint of interest, we assessed long-term major adverse cardiovascular events (MACE), a composite of all-cause death, myocardial infarction and stroke, between patients with and without hyperuricemia with Cox proportional hazard analysis (adjusting for age, gender, body-mass index, eGFR, atrial fibrillation, diabetes mellitus, hyperlipidaemia, arterial hypertension, familial coronary heart disease, smoking status, malignancy, shock at admission, fibrinolytic therapy, hyperglycaemia at admission, peak troponin, radial or femoral access site, and number of stenosed vessels).

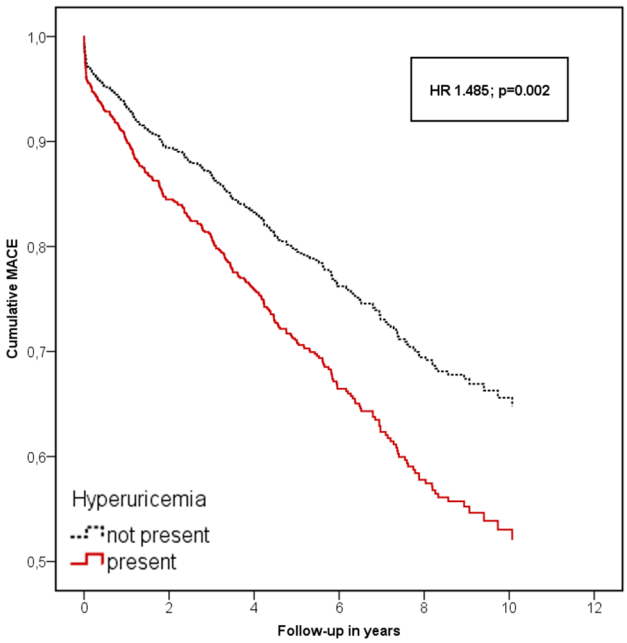


Fig. 1|17-3

Results: Mean age was 62.9±13.4 years and 825 (66.5%) were male. Hyperuricemia was present in 378 (30.5%) patients. After a mean follow-up time of 7.9±0.1 years, 441 (35.6%) patients suffered from MACE. In univariate Cox regression, hyperuricemia was significantly associated with long-term MACE (HR 2.370 [95% CI 1.963–2.861], $p<0.001$). After adjustment for confounders, hyperuricemia remained significantly associated with an approximate 1.5-fold relative risk increase for long-term MACE (HR 1.485 [95% CI 1.116–1.900]; $p=0.002$) (Fig. 1|17-3).

Conclusions: Hyperuricemia exhibits a significant prognostic value for long-term MACE in our cohort of ACS patients, even after adjustment for numerous confounders. If lowering uric acid in ischemic heart disease might be clinically beneficial remains to be elucidated by large prospective clinical trials.

17-4

Impact of timing of intraaortic balloon counterpulsation on mortality in cardiogenic shock – a subanalysis of the IABP-SHOCK II-trial

G. Fürnau, J. Ledwoch, I. Eitel, S. de Waha, S. Desch, K. Werdan, G. Schuler, U. Zeymer, H. Thiele

Department of Internal Medicine II, Cardiology/Angiology/Intensive Care Medicine, University Hospital Schleswig-Holstein, University Heart Center Lübeck, Lubeck, Germany
Heart Center, University Leipzig, Leipzig, Germany
Heart Center of Ludwigshafen, Heart Attack Research Center at the University Heidelberg, Ludwigshafen am Rhein, Germany

Background: Conflicting results exist whether initiation of intraaortic balloon pumping (IABP) before primary percutaneous coronary intervention (PPCI) in patients with acute myo-

cardial infarction (AMI) complicated by cardiogenic shock (CS) may have an impact on outcome.

Methods: The IABP-SHOCK II-trial randomized 600 patients with AMI and CS to IABP-support vs. control. We analyzed patients randomized to the intervention group regarding the timing of IABP implantation pre or post PPCI in a post-hoc analysis and its impact on outcome.

Results: In total 600 patients were included in the IABP-SHOCK II trial. Of these 301 were randomized to IABP-support. We analyzed the 275 (91%) patients of this group with PPCI as revascularization strategy and an implanted IABP surviving the initial procedure. The implantation was performed pre PPCI in 33 (12%) and post PCI in 242 (88%) patients. There were no differences in baseline serum lactate ($p=0.70$), Simplified Acute Physiology Score-II-score ($p=0.60$) and other important baseline characteristics such as age ($p=0.69$) and severity of coronary artery disease ($p=0.99$). No differences were observed for short- and long-term mortality (pre vs. post 30-day mortality: 36 vs. 36%, $p=0.99$; 1-year mortality: 52 vs. 48%, $p=0.73$). In multivariable Cox regression analysis adjusted for age, gender, need for invasive ventilation, prior stroke, peripheral artery disease, hypertension, diabetes, prior medication, kidney function, hemoglobin values, ECG findings, extent of coronary artery disease, serum lactate and TIMI-flow grades prior and post PPCI timing of IABP-implantation remained no significant predictor of long-term outcome (HR 1.24 [95%CI 0.74–2.10]; $p=0.41$).

Conclusions: Timing of IABP-implantation pre or post PPCI had no impact on outcome in patients with AMI complicated by CS.

17-5

Mild hypothermia in cardiogenic shock complicating myocardial infarction – the randomized SHOCK-COOL pilot trial

G. Fürnau, J. Beck, S. Desch, I. Eitel, C. Jung, S. Erbs, N. Mangner, K. Fengler, M. Sandri, G. Schuler, H. Thiele

University Heart Center Lübeck, Department of Internal Medicine II, Cardiology/Angiology/Intensive Care Medicine, University Hospital Schleswig-Holstein, Lubeck, Germany
Heart Center, Clinic for Internal Medicine/Cardiology, University Leipzig, Leipzig, Germany
Division of Cardiology, Pulmonology and Vascular Medicine, University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Dusseldorf, Germany

Background: In experimental animal studies and a small retrospective observational human study mild therapeutic hypothermia (MTH) has been found as possible beneficial treatment for cardiogenic shock (CS) following acute myocardial infarction (AMI). No randomized trial in CS patients addressed this question yet.

Methods: Intubated, mechanically ventilated Patients ($n=40$) with CS complicating AMI undergoing primary percutaneous intervention without classical indication for MTH underwent randomization in a 1:1 fashion to MTH for 24 h or to conventional therapy. The primary endpoint was cardiac power index (CPI) after 24 h, secondary endpoints included other hemodynamical parameters as well as serial measurements of serum lactate and sublingual microcirculation.

Results: Baseline characteristics were similar between the MTH ($n=20$) and control group ($n=20$). No differences were observed for the primary endpoint CPI measured by thermodilution (MTH vs. control: 0.30 [IQR 0.09–0.36] vs. 0.32 [IQR 0.16–0.52] W/m^2; $p=0.32$) or Fick's equation (MTH vs. control: 0.37 [IQR 0.23–0.51] vs. 0.34 [IQR 0.29–0.46] W/m^2; $p=0.78$). Similarly, all other hemodynamical measurements and also mixed venous oxygen saturation measurements were not statistically different ($p>0.05$ for all). Serum lactate levels after 6, 8 and 10 hours were significantly higher in patients in the MTH group (6 h: 3.3 [IQR 2.4–5.9] vs. 1.6 [IQR 1.1–2.6] mmol/L; $p=0.006$; 8 h: 3.7 [IQR 2.4–5.8] vs. 1.5 [IQR 1.3–2.9] mmol/L; $p=0.01$; 10 h: 2.7 [IQR 2.3–5.3] vs. 1.3 [IQR 1.0–3.8] mmol/L; $p=0.02$) reflecting a significant slower decline of lactate levels in the MTH group (p for interaction 0.03). No differences were observed in sublingual microcirculation measured by dark stream side field imaging ($p>0.05$ for all). Short-term and long-term mortality rates were similar between the groups (MTH vs. control: 30-day: 60% vs. 50%; $p=0.75$; 1-year: 65% vs. 65%; $p>0.99$).

Conclusions: In this randomized small pilot study MTH failed to show a beneficial effect in patients with CS after AMI on hemodynamic parameters, serum lactate and sublingual microcirculation.

17-6

Prognostic significance of remote myocardium alterations assessed by quantitative non-contrast T1 mapping in ST-elevation myocardial infarction

S. J. Reinstadler, T. Stiermaier, G. Fuernau, C. Eitel, S. de Waha, S. Desch, J. Poess, B. Metzler, H. Thiele, I. Eitel

Universitätsklinik für Innere Medizin III (Kardiologie), Medizinische Universität Innsbruck, Innsbruck, Austria
University Heart Center Lübeck, Lubeck, Germany

Background: The exact role and incremental prognostic relevance of remote myocardium native T1 mapping alterations assessed by cardiac magnetic resonance (CMR) after ST-elevation myocardial infarction (STEMI) remains unclear.

Objectives: To assess the prognostic significance of remote zone native T1 alterations for the prediction of clinical events in a STEMI population treated by primary percutaneous coronary intervention (PPCI) and to compare it with conventional markers of infarct severity.

Methods: We included 255 consecutive STEMI patients reperfused within 12 hours after symptom onset. CMR core laboratory analysis was performed to assess left ventricular (LV) function, standard infarct characteristics and native T1 values of the remote, non-infarcted myocardium. The primary endpoint was a composite of death, reinfarction and new congestive heart failure within 6 months (MACE).

Results: Patients with increased remote zone native T1 values (>1129 ms) had significantly larger infarcts ($p=0.012$), less myocardial salvage ($p=0.002$) and more pronounced LV dysfunction ($p=0.011$). In multivariable analysis, remote zone native T1 was independently associated with MACE after adjusting for clinical risk factors ($p=0.001$) or other CMR variables ($p=0.007$). In C-statistics, native T1 of remote myocardium provided incremental prognostic information above clinical risk factors, LV ejection fraction and other markers of infarct severity (all $p<0.05$). In line, the addition of remote zone native T1 to a model of prognostic CMR parameters (ejection fraction, infarct size and myocardial salvage index) led to net reclassification improvement of 0.82 (95%CI: 0.46–1.17, $p<0.001$) and

to an integrated discrimination improvement of 0.07 (95%CI: 0.02–0.13, $p=0.01$).

Conclusions: In STEMI patients treated by PPCI, evaluation of remote zone alterations by quantitative non-contrast T1 mapping provides independent and incremental prognostic information in addition to clinical risk factors and traditional CMR outcome markers. Remote zone alterations may thus represent a novel therapeutic target as well as a useful parameter for optimized risk-stratification.

17-7

Prognostic value of aortic stiffness in patients after ST-elevation myocardial infarction

H.-J. Feistritzer, G. Klug, S. J. Reinstadler, M. Reindl, L. Niess, T. Nalbach, C. Kremser, A. Mayr, B. Metzler

Univ.-Klinik für Innere Medizin III, Kardiologie und Angiologie, Medizinische Universität Innsbruck, Innsbruck, Austria
Univ.-Klinik für Radiologie, Medizinische Universität Innsbruck, Innsbruck, Austria

Background: High aortic stiffness has been shown to be a strong predictor of morbidity and mortality in the general population and several patient cohorts. However, in patients after ST-elevation myocardial infarction (STEMI) the prognostic value of high aortic stiffness is unknown so far.

Methods: This prospective, observational study included 160 consecutive patients with first acute STEMI. Aortic pulse wave velocity (PWV), a surrogate for aortic stiffness, was measured 2 (IQR 2–4 days) days after infarction using phase-contrast cardiac magnetic resonance imaging. The primary endpoint was defined as a composite endpoint of major adverse cardiac and cerebrovascular events (MACCE) comprising death, non-fatal myocardial re-infarction, new congestive heart failure and stroke.

Results: During a median follow-up of 1.2 years (IQR 1.0–3.1 years) 19 (12%) MACCE events occurred. Kaplan-Meier analysis showed a significant lower MACCE-free survival in patients with high PWV (PWV >7.3 m/s, log-rank $p=0.003$), high age (age >60 years, log-rank $p=0.005$), high N-terminal pro-B-type natriuretic peptides (NT-proBNP) concentrations (NT-proBNP >1736 ng/l, log-rank $p<0.001$) and multivessel disease (log-rank $p=0.020$) (Fig. 1 | 17-7). Multivariable Cox regression analysis revealed PWV >7.3 m/s as an independent predictor of MACCE, after adjusting for age, NT-proBNP levels and presence of multivessel disease (hazard ratios (HR) ≥4.1, 95% confidence interval (CI) 1.4–13.3; all $p\leq0.011$). In reclassification analysis, the addition of PWV to a risk model comprising age, NT-proBNP and mulitvessel disease led to a net reclassification improvement of 0.11 (95% CI 0.06–0.17, $p<0.001$).

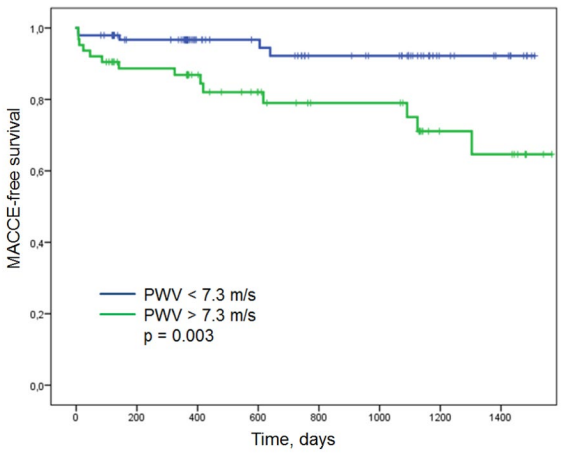


Fig. 1 | 17-7

Conclusions: Increased aortic stiffness is an independent predictor of MACCE after acute STEMI. Moreover, the assessment of aortic stiffness in addition to classical risk factors significantly improved early risk stratification.

Postersitzung 18 – Interventionelle Kardiologie 2

18-1

Simultaneous transcatheter aortic valve implantation and left atrial appendage occlusion versus both interventions as stand-alone procedures

T. Gilhofer, S. Obeid, T. F. Lüscher, R. Binder

Klinik für Kardiologie, Universität Zürich, Zurich, Switzerland

Background: Patients with atrial fibrillation undergoing transcatheter aortic valve implantation (TAVI) have a worse prognosis than patients in sinus rhythm. The bleeding risk associated with oral anticoagulation accounts for some of this difference. Left atrial appendage occlusion (LAAO) is a device-based intervention to omit the need for oral anticoagulation in patients with atrial fibrillation. We therefore investigated the feasibility of simultaneous TAVI and LAAO with Lotus and Watchman and compared the results to both interventions as stand-alone procedures.

Methods: Consecutive patients, who underwent either TAVI with Lotus, LAAO with Watchman or both procedures simultaneously were investigated. We compared the procedural characteristics, in-hospital- and 30-day-outcomes defined by VARC-2 criteria in these three groups.

Results: A total of 52 consecutive patients were included in the study. An isolated TAVI with Lotus was performed in 19 patients, an isolated LAAO with Watchman in 23 patients and a combined procedure in 10 patients. Patients in the isolated LAAO cohort were significantly younger (TAVI: 85.1 +/– 4.8 years; LAAO: 75.7 +/– 6.0 years; TAVI + LAAO: 84.2 +/– 5.7 years; $p<0.001$). There was no significant difference in the amount of contrast medium used between the three groups (TAVI: 89 +/– 29 ml; LAAO: 98 +/– 54 ml; TAVI + LAAO: 86 +/–29 ml; $p=0.923$). The total procedural time was significantly higher in the combined group than the isolated TAVI or LAAO group (TAVI: 57.1 +/– 18.0 minutes; LAAO: 42.7 +/– 16.0 minutes; TAVI + LAAO: 82.0 +/– 18.6 minutes; $p=0.001$). Procedural and device success was achieved in all patients. The length of hospital stay was significantly lower in the isolated LAAO group than the isolated TAVI or combined procedure group (TAVI: 9.7 +/– 4.3 days; LAAO: 2.0 +/– 2.1 days; TAVI + LAAO: 10 +/– 4 days; $p<0.001$). While there was no 30-day mortality in the isolated TAVI or isolated LAAO group, one sudden cardiac death occurred in the combined group at home on day 28. There was one cerebrovascular event in the isolated TAVI group but none in the LAAO or the combined group. Major bleeding occurred in one patient in the isolated TAVI group, but none in the isolated LAAO or the combined group.

Conclusions: Combining TAVI and LAAO with Lotus and Watchman is feasible and was comparable to both interventions as stand-alone procedures, although procedural time was higher when both interventions were performed simultaneously. Long-term follow-up will show, whether combining TAVI and LAAO improves prognosis in high-risk patients with atrial fibrillation and symptomatic severe aortic stenosis.

18-2

Has the presence of nonsignificant coronary artery stenosis vs. completely normal CAG an impact on outcome in patients with Tako-Tsubo syndrome?

E. Piackova, V. Weihs, A. Geppert, M. Nürnberg, E. Wessely, P. Smetana, T. Weiss, K. Huber

3. Medizinische Abteilung mit Kardiologie, Wilhelminenspital, Vienna, Austria

Background: With respect to the Mayo Clinic diagnostic criteria, Tako-Tsubo patients have coronary arteries either com-

Table 1 | 18-2 Baseline characteristics of 99 Tako-tsubo patients and groups based on the stenosis of coronary arteries. SD-Standard deviation, MI-myocardial infarction, PCI-percutaneous coronary intervention, CAD-coronary artery disease, COPD–chronic obstructive pulmonary disease, PAOD-peripheral arterial occlusive disease, EF-ejection fraction

Variables	Total (N=99)	Normal CAG (N=58)	Non-significant stenosis (N=41)	p-value
Age, yrs (mean +/- SD)	70,7 (±11,92)	70,2 (±13,22)	71,4 (±10,06)	0,607
Female (%)	81,8	46,5	35,4	0,444
Hypertension (%)	63,5	35,4	28,1	0,498
Hyperlipidemia (%)	32,0	19,6	12,4	0,730
Diabetes mellitus (%) on diet on oral antidiabetics on insulin	20,2 5,1 10,1 2,0	7,1 1,0 3,0 1,0	13,1 4,1 7,1 1,0	0,017 0,074 0,054 0,804
History of MI (%)	6,3	0	6,3	0,003
History of PCI (%)	5,2	0	5,2	0,007
Family history of CAD (%)	6,3	4,2	2,1	0,655
History of stroke (%)	7,3	5,2	2,1	0,468
COPD (%)	20,8	13,5	7,3	0,499
PAOD (%)	9,4	3,1	6,3	0,112
Atrial fibrillation (%)	12,5	8,3	4,2	0,533
Renal insufficiency (%)	12,5	5,2	7,3	0,213
Psychiatric disease (%)	10,5	8,4	2,1	0,137
Neurological disease (%)	10,4	3,1	7,3	0,067
Cancer (%)	6,1	2,0	4,1	0,197
Hospitalized for another reason (%)	26,6	13,8	12,8	0,443
Trigger (%) Emotional Physical Both	 5,1 36,4 3,0	 5,1 22,2 1,0	 0 14,2 2,0	 0,055 0,701 0,370
Smoking (%)	29,3	19,2	10,1	0,370
Alcohol addiction (%)	8,3	5,2	3,1	0,804
Complications (%) Cardiovascular Non-cardiovascular Both	13,1 10,1 6,0	6,1 6,1 2,0	7,0 4,0 4,0	0,711 0,924 0,197
Cardiac decompensation (%)	16,5	7,7	8,8	0,323
EF; % (mean, ±SD)	49,75 (±13,45)	49,9 (±13,22)	49,6 (±13,93)	0,929
Ventricle dysfunction (%) apical midventricular combined apical-midventricular basal	36,4 6,1 46,5 4,0	21,2 6,1 25,3 1,0	15,2 0 21,2 3,0	0,969 0,035 0,427 0,166

pletely normal or with non-significant luminal narrowing of less than 50% in all epicardial coronary arteries as confirmed by coronarography (CAG).

Aim: The aim of this study was to investigate potential differences in in-hospital and one-year mortality in Tako-Tsubo patients with completely normal coronary arteries and such with nonsignificant stenoses (luminal narrowing ≤ 50%) in CAG.

Methods: Data from 99 consecutive Tako-Tsubo patients who were admitted between 2006 and 2015 at the Wilhelminenhospital in Vienna were analyzed. Study population was divided into two groups of patients, either presenting with completely normal or with one or more coronary artery stenoses of ≤ 50%. Differences in variables such as patient's characteristics and levographic findings as well as in-hospital mortality and one-year mortality were investigated. Multivariate regression analysis was performed in order to correct for significant confounders seen in the univariate analysis.

Results: No differences in patient characteristics such as age, hypertension, hyperlipidemia, atrial fibrillation, psychiatric diseases, trigger of the Tako-Tsubo event, or ejection fraction were found (Table). Midventricular dysfunction measured by means of acute levography, although rare, was only present more often in Tako-Tsubo patients with normal CAG. Patients presenting with nonsignificant stenoses had more frequently diabetes mellitus, history of previous myocardial infarction, or percutaneous coronary intervention, respectively. Interestingly, in-hospital mortality (3.4% vs. 1.7%) and one-year mortality (8.4% vs. 4.2%) tended to be higher in the group with normal coronary arteries by unadjusted (in-hospital mortality: HR = 0.689; CI = 0.126–3.759, $p = 0.667$; one-year mortality: HR = 0.769; CI = 0.258–2.296, $p = 0.638$, respectively) or by multivariate analysis adjusted for confounders (in-hospital mortality: HR = 0.735; CI = 0.128–4.233, $p = 0.731$; one year mortality: HR = 0.883; CI = 0.288–2.710, $p = 0.828$, respectively).

Conclusions: CAG proven existence of visible wall irregularities vs. completely normal looking coronary arteries in patients presenting with Tako-Tsubo syndrome was associated with a higher cardiovascular risk profile, but had no impact on in-hospital or one-year mortality. Although it is hypothesized that Tako-Tsubo patients with normal looking coronary arteries in CAG have a better clinical outcome the results of this study contradict this statement. In case of Tako-Tsubo syndrome, the investigation of normal looking coronary arteries by imaging methods like OCT or IVUS might deliver further information about vessel pathologies.

18-3

Indications for and outcome with the left atrial appendage occluder – a single center experience

R. Sieghartsleitner, G. Toth-Gayor, D. Zweiker, M. Manninger-Wünscher, T. Odeneg, B. Mastnak, K. Ablasser, G. Stoschitzky, R. Maier, O. Luha, H. Brussee, D. Scherr

Division of Cardiology, Department of Medicine, Medical University Graz, Graz, Austria

Background: In patients with atrial fibrillation and an indication for oral anticoagulation, percutaneous left atrial appendage occlusion (LAAC) is, according to recent ESC guidelines, an established treatment option in case of severe bleeding, ischemic stroke despite anticoagulation, incompliance with anticoagulation, or in patients with increased bleeding risk. However, indications are heterogeneous, and there is limited evidence for post-procedural management and outcome in these patients. Furthermore, only a limited number of centers so far reported indications in and outcome with the LAAC.

Methods: Our aim was to investigate indications for and outcome in patients undergoing the LAAC procedure in a tertiary care center from 2012–2016.

Results: 33 patients (44% female) underwent 34 LAAC procedures. The mean age ± SD of the patients was 74 ± 7 years, mean CHA2DS2VASc was 4.7 ± 1.6 and the mean HAS-BLED score was 3.9 ± 1.1. As for the indication for the LAAC procedure, 24 (71%) had a severe bleeding, 1 (3%) had a thromboembolic stroke, and 9 (26%) had a contraindication for anticoagulation or another indication for the LAAC. In one patient, the procedure had to be aborted because the left atrial appendage was too small for the LAAC implantation. 25 Watchman devices (Boston Scientific) and 8 Amplatzer Devices St. Jude Medical/Abbott) were implanted. Procedural duration was 62 ± 21 minutes. Total fluoroscopy time was 19 ± 11 min. The procedure was performed under TEE guidance. No severe complications occurred. Total duration of hospitalisation was 4.4 days (range 2–19). The follow-up duration was 232 days (median 111, range 1–1435) and cumulative 20.1 patient-years. The procedure was successful in 97% of all cases. 36% had a minimal residual flow (<5 mm) into the left atrial appendage, and 0% had a significant residual flow ≥5 mm. During follow up, one patient experienced an embolic stroke, (event rate of 1 per 20.1 patient-years). There was no consistent scheme in anticoagulation after the procedure.

Conclusions: These data show that the LAAC is a safe and effective device for atrial fibrillation patients at high bleeding risk or with a history of stroke despite anticoagulation.

18-4

Long-term outcome after drug-eluting stent implantation in chronic total occlusions in comparison with bare metal stents

I. Tentzeris, T. Autrata, S. Farhan, A. Geppert, E. Wessely, M. Nürnberg, P. Smetana, T. Weiss, J. Wojta, K. Huber

3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminen Hospital, Vienna, Austria
Department of Cardiology, Medical University Vienna, Vienna, Austria

Background: Aim of our study was to evaluate the effect of drug-eluting stents (DES) in succefully reopened chronic total occlusions (CTO's) compared with bare metal stents (BMS) on all-cause mortality and target vessel revascularization (TVR) in a real world clinical setting.

Methods: Two hundred thirty-one consecutive patients, who underwent PCI and stent implantation for CTO, were included in a prospective registry from January 2003 until May 2016. Patients were subdivided retrospectively into three groups, those who received a new-generation DES (sirolimus-, everolimus-, zotarolimus- or biolimus-eluting), those who received an old-generation DES (sirolimus- or paclitaxel-eluting) and those who received a BMS on discretion of the interventionalist. The combined endpoint of all-cause long-term mortality or TVR during a mean follow-up period of 47.324.96 months was evaluated.

Results: Fifty patients (21.6%) received BMS, while 104 patients (45%) received new-generation DES and 77 (33.3%) received old-generation DES. In total 30 patients (13%) reached

the combined endpoint (all-cause death or TVR). 10 patients (20%) in the BMS group, 6 patients (7.8%) in the old-generation DES group and 14 patients (13.5%) in the new-generation DES group. Hazard ratio for new-generation DES versus old-generation DES 2.14; 95% CI 0.80 to 5.60; $p=0.11$. Hazard ratio for new-generation DES versus BMS 0.71; 95% CI 0.31 to 1.60; $p=0.41$. Hazard ratio for old-generation DES versus BMS 0.36; 95% CI 0.13 to 1.00; $p=0.05$. Hazard ratio for all DES versus BMS 0.56; 95% CI 0.26 to 1.21; $p=0.14$.

Conclusion: Our results obtained in a real world clinical setting showed in general a low long-term event rate after PCI and stent implantation for CTOs with a tendency of benefit for DES over BMS.

18-5

Multi-biomarker analysis in patients after TAVI

M. Mirna, B. Wernly, V. Paar, R. Pistulli, I. Rohm, C. Jung, H.-R. Figulla, A. Yilmaz, P.C. Schulze, U. Hoppe, D. Kretzschmar, M. Lichtenauer, A. Lauten

Christian Doppler Labor für Diagnose und Regeneration von Herz- und Thoraxerkrankungen, Universitätsklinik Jena, Jena, Germany
Clinic of Internal Medicine II, Department of Cardiology, Paracelsus Medical University Salzburg, Salzburg, Austria
Department of Internal Medicine I, Division of Cardiology, Angiology, Pneumology and Intensive Medical Care, University Hospital Jena, Friedrich Schiller University Jena, Jena, Germany
Abteilung für Kardiologie, Pneumologie & Angiologie, Universitätsklinikum Düsseldorf, Dusseldorf, Germany
Clinic of Internal Medicine II, Elisabeth Klinikum Schmalkalden, Schmalkalden, Germany

Background: Novel biomarkers have recently been investigated for their use in the risk stratification of patients with heart failure and acute coronary syndrome and they show promising results in predicting patient outcome. Since transcatheter aortic valve implantation (TAVI) is associated with myocardial injury, we sought to examine wether the procedure is followed by an increase in the plasma levels of GDF-15, H-FABP, Fetuin-A, Galectin-3 and suPAR. We believe that these biomarkers might help to improve periprocedural risk stratification of patients undergoing TAVI in the future.

Methods: We collected blood samples of 79 patients with high-grade aortic valve stenosis undergoing transcatheter aortic valve implantation (TAVI) before and after the intervention (at 7 days, 1 month, 3 months and 6 months post TAVI) and analyzed the plasma concentrations of GDF-15, H-FABP, Fetuin-A, Galectin-3 and suPAR.

Results: Compared to the baseline plasma levels, there was a statistically significant increase in the median concentrations of Fetuin-A (median 53.19, IQR 37,38–77.11 to median 113.2, IQR 85.39–142.6 post TAVI, $p<0.001$) and sUPAR (median 2758, IQR 2121–3665 to median 3291, IQR 2373–4177 post TAVI, $p<0.001$). H-FABP showed a statistically significant decrease after TAVI (median 4.903, IQR 2.419–6.618 to median 2.210, IQR 0.763–3.828 post TAVI, $p<0.001$). Galectin-3 and GDF-15 evidenced no significant change in serum concentration after TAVI.

Conclusions: Transcatheter aortic valve implantation was associated with a significant increase in the plasma levels of Fetuin-A and suPAR and a significant decrease in the concentration of H-FABP. In fact, it has recently been shown that the plasma levels of H-FABP and suPAR are elevated in conditions with ongoing myocardial damage and that they are associated with an increased risk for adverse events in patients with various cardiac diseases. Plasma levels of Fetuin-A have been found to be inversely associated with adverse events in coronary artery disease. The significant decrease in the concentration of H-FABP and the significant increase in the serum concentration of Fetuin-A in our cohort could be associated with a hemodynamic improvement after valve replacement. We therefore hypothesize that these novel biomarkers could add prognostic information for the individual patient and serve to improve periprocedural risk stratification of patients undergoing TAVI in the future.

18-6

Subendocardial viability index is associated with the severity of aortic stenosis – Pulse wave analysis in the setting of TAVR

C. Müller, S. Schachinger, St. Kastl, I. Lang, J. Kastner, T. Neunteufl, G. Delle-Karth, M. Gyöngyösi, M. Gottsauner-Wolf, N. Pavo

Department of Internal Medicine II, Medical University Vienna, Vienna, Austria
Department of Internal Medicine, Division of Cardiology, Krankenhaus Hietzing, Vienna, Austria

Background: Pulse wave analysis (PWA) is a well established tool for non-invasive assessment of hemodynamic changes. The diagnostic information measured by PWA in the setting of transfemoral transcatheter aortic valve replacement (TF-TAVR) has not been investigated yet.

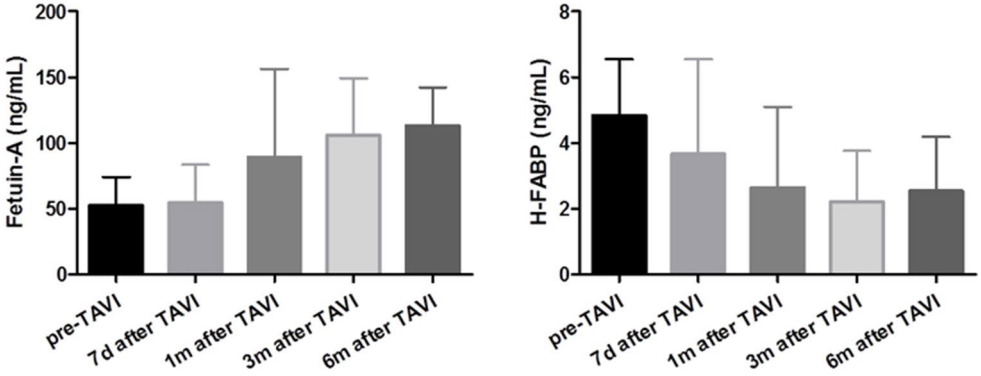


Fig. 1 | 18-5

Methods: We prospectively enrolled 40 consecutive patients presenting with severe aortic stenosis and receiving TF-TAVR. Peripheral radial and carotid pressure curves were measured using the SphygmoCor® CvMS system (Atcor Medicals, Australia) directly before TAVR and after a mean follow-up time of 5 days. Parameters of the calculated aortic pressure curves were compared between measurement sites and pre and post TAVR as well as correlated with echocardiographic and laboratory parameters. The subendocardial viability index (SVI), an indicator of subendocardial ischemia, as well as the augmentation index (AI), augmentation pressure/pulse height (AGPH) and max. dP/dt were defined as primary endpoint. Additionally, the association of these variables with outcome was assessed during a 12-month clinical follow up.

Results: All parameters of the calculated central aortic pressure curves yielded comparable results regardless of measurement site. SVI, but not AI, AGPH or max dP/dt correlated significantly with maximum velocity and mean pressure gradient over the aortic valve (AVmax and Pmean) and thereby with disease severity [SVI: r = –0.372, $p = 0.029$ for AVmax and r = –0.371, $p = 0.021$ for Pmean]. AVmax was reduced by TAVR procedure from 4.5 m/s (IQR 4.1–5.0) to 2.2 m/s (IQR 1.9–2.7) ($p < 0.001$) as expected. This resulted in a significant increase in SVI [135.30% (IQR 115.50–150.83) pre-TAVR vs. 140.30% (IQR 123–172.50) post-TAVR, $p = 0.039$] and max dP/dt [665.83 mmHg (IQR 489.17–891.17) pre-TAVR vs. 927 mmHg (IQR 693.33–1092.00) post-TAVR, $p < 0.001$], and concomitant reduction in AI [101.08% (IQR 92.65–108.96) pre-TAVR vs. 92% (IQR 78–106) post-TAVR; $p < 0.001$] and AGPH [34.08% (IQR 26.80–39.00) pre-TAVR vs. 25% (IQR 21.83–33.67) post-TAVR; $p = 0.002$] (Fig. 1 | 18-6; calculated from the radial site), confirming the beneficial hemodynamic effects of replacing the stenotic valve. However, no association with outcome could be revealed for neither pre nor post values of SVI, AI, AGPH and max dP/dt (Table 1 1 | 18-6).

Conclusions: PWA is a well established, non-invasive tool to assess hemodynamic changes in the setting of TAVR, irrespective of measurement site. TAVR results in a significant improvement of markers of subendocardial perfusion and left ventricular contractility. Common PWA parameters used in the characterization of vascular stiffness may be overestimated in the setting of aortic stenosis.

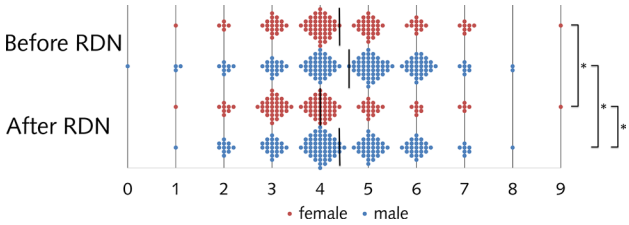


Fig. 1 | 18-7

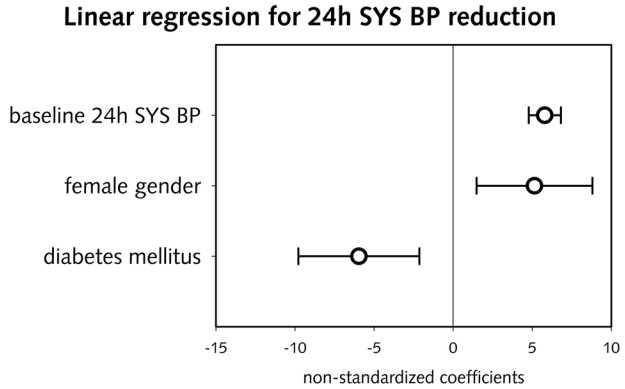


Fig. 2 | 18-7

18-7

The antihypertensive effect of renal denervation is stronger in female than in male patients

D. Zweiker, T. Lambert, T. Weber, E. Niederl, C. Koppelstätter, B. Watschinger, R. Reindl-Schwaighofer, T. Sturmberger, C. Kindslehner, P. Gruener, P. Maister, C. Dechant, R. Zweiker

Division of Cardiology, Department of Internal Medicine, Medical University Graz, Graz, Austria
Department of Cardiology, Kepler University Hospital, Linz, Austria

Table 1 | 18-6 Unadjusted and adjusted effects of central pulse wave analysis (PWA) parameters from radialis measurements on all-cause mortality in patients undergoing TAVR ($n = 40$). Cox proportional hazard models for all PWA parameters are shown. Hazard ratios (HR) refer to an increase of one IQR in continuous variables. Fonts in bold indicate statistical significance ($p < 0.05$).

Variables	IQR	Crude HR (95%CI)	Pvalue	Adj. HR1 (95%CI)	P-value
pre-SVI, %	35.33	1.80 (0.75–4.31)	0.187	1.04 (0.64–1.70)	0.862
post-SVI, %	49.50	1.47 (0.70–3.09)	0.309	1.51 (0.73–3.16)	0.269
Δ SVI, %	33.83	1.03 (0.63–1.69)	0.900	1.04 (0.64–1.70)	0.862
pre-AI, %	32.67	1.23 (0.72–2.09)	0.453	1.13 (0.70–1.92)	0.640
post-AI, %	23.50	0.52 (0.23–1.18)	0.115	0.54 (0.23–1.26)	0.152
Δ AI, %	29.57	0.71 (0.48–1.05)	0.082	0.76 (0.50–1.16)	0.202
pre-AGPH75, %	10.38	1.37 (0.56–3.36)	0.492	1.32 (0.53–3.29)	0.552
post-AGPH75, %	13.37	0.56 (0.27–1.17)	0.122	0.561 (0.26–1.19)	0.133
Δ AGPH75, %	15.67	0.38 (0.14–1.03)	0.058	0.39 (0.14–1.07)	0.067
pre-max dP/dt, mmHg	402.00	0.80 (0.31–2.11)	0.654	0.74 (0.27–2.03)	0.560
post-max dP/dt, mmHg	398.67	0.74 (0.34–1.61)	0.441	0.71 (0.32–1.58)	0.397
Δ max dP/dt, mmHg	407.00	0.74 (0.28–1.98)	0.553	0.75 (0.27–2.06)	0.571

SVI subendocardial viability index, *AI* augmentation index, *AGPH75* augementation pressure/pulse height at heart rate 75

Department of Internal Medicine II, Klinikum Wels-Grieskirchen, Wels, Austria
Department of Internal Medicine III, Medical University Innsbruck, Innsbruck, Austria
Division of Nephrology, Department of Internal Medicine III, Medical University Vienna, Vienna, Austria
Department of Internal Medicine II, Krankenhaus der Elisabethinen Linz, Linz, Austria
Department of Internal Medicine; Landeskrankenhaus Waidhofen an der Ybbs, Waidhofen an der Ybbs, Austria
Department of Internal Medicine II, Paracelsus Medical University Salzburg, Salzburg, Austria
Fifth Medical Department, Kaiser-Franz-Josef-Spital, Vienna, Austria

Background: Due to the lower prevalence of hypertension in women, there is only limited data of effects of renal sympathetic denervation (RDN) in female patients. Prevalence of female patients in RDN studies was as low as approximately one third. The purpose of this study was to determine gender differences in response to renal denervation.

Methods: We performed univariate and bivariate analysis of all patients with available follow up dataset (either 1, 3, 6 or 12 months after procedure) from the Austrian Transcatheter Renal Denervation Registry. In case of multiple available follow up data, we used the earliest dataset available. Additionally, we performed multiple linear regression analysis for 24-h systolic BP reduction.

Results: 293 patients (43% female) were included in this analysis. Median baseline ambulatory BP (systolic/diastolic) was 146 (IQR 134–160)/85 (75–93) mmHg vs. 149 (137–164)/90 (81–101) mmHg in female vs. male patients ($p=0.146/p<0.001$). We observed the following significant differences in baseline characteristics: lower diastolic ambulatory BP, lower height, lower weight, more prevalent use of alpha-blockers (61 vs. 44%, $p=0.008$) and less prevalent coronary artery disease (27 vs. 42%, $p=0.013$) in female patients. There was no difference in the number of antihypertensive medications per patient (female patients 4.4 ± 1.3; male patients 4.6 ± 1.4; $p=0.064$; Fig. 1|18-7).

After RDN, median ambulatory BP reduction was 12 (0–21)/4.5 (0–11) mmHg in women and 5 (−6–19)/2 (−4–11) mmHg in men ($p=0.038/p=0.124$). Office BP reduction was also more pronounced in female patients (11 [−1–24]/4 [−1–11] mmHg vs. 6 [−6–19]/2.5 [−5–12] mmHg, $p=0.047/p=0.031$, $n=261$). After RDN, antihypertensive medications were significantly lower in female vs. male patients (4.0 ± 1.3 vs. 4.4 ± 1.3; $p=0.003$) Linear regression revealed high baseline 24-h systolic BP, female gender and absence of diabetes mellitus to be associated with more pronounced reduction of 24-h systolic BP ($p<0.01$ for all; Fig. 2|18-7).

Conclusions: Ambulatory BP reductions after RDN were substantially more pronounced in female patients despite lower baseline BP. This analysis concludes that female patients may be more prone to react to renal denervation.

18-8

The value of on-site cardiac surgery for patients undergoing transfemoral transcatheter aortic valve implantation

F. Egger, D. Zweiker, A. Geppert, M. Rohla, O. Luha, G. Lamm, M. Hammerer, E. Maurer, M. Grund, T. Sturmberger, E. Zeindlhofer, K. Huber

3. Medizinische Abteilung mit Kardiologie, Wilhelminenspital, Wien, Vienna, Austria
Klinische Abteilung für Kardiologie, Medizinische Universität Graz, Graz, Austria
Klinische Abteilung für Innere Medizin 3, Universitätsklinikum St. Pölten, St. Pölten, Austria
Universitätsklinikum für Innere Medizin II, Kardiologie und internistische Intensivmedizin, Salzburg, Austria
Abteilung für Innere Medizin II – Kardiologie, Intensivmedizin, Wels/Grießkirchen, Austria
Klinik für Interne I – Kardiologie und internistische Intensivmedizin, Kepler Universitätsklinikum, Linz, Austria
Interne II – Kardiologie, Angiologie und Interne Intensivmedizin, Elisabethinen Linz, Linz, Austria
Interne II – Kardiologie, Barmherzige Schwestern Linz, Linz, Austria

Background: To investigate the influence of on-site cardiac surgery departments (OSCS) on the outcome of patients undergoing transfemoral transcatheter aortic valve implantation (TAVI).

Methods and Results: In this retrospective analysis of the prospective multicentre Austrian TAVI registry, 1235 consecutive patients with high-grade aortic stenosis undergoing transfemoral (TF) TAVI between January 2011 and November 2015 were analysed. One hundred ninety-six of them (15.9%) underwent TAVI at medical centres without OSCS but a visiting cardiac surgical team. Peri- and postprocedural outcomes were compared in an unadjusted as well as propensity score matched fashion for 196 patients.

Patients treated in hospitals without OSCS (no-OSCS group) were older (median 82 vs. 84 years; $p=0.004$), had a higher prevalence of coronary artery disease (61.2 vs 49.4%; $p=0.002$) and previous percutaneous coronary intervention (49.0 vs. 30.5%; $p=0.001$) and had a higher perioperative risk defined by the logistic EuroSCORE (15.5 vs. 21.6%; $p=0.001$) compared to OSCS patients. Unmatched analysis revealed similar procedural (98.0 vs. 98.7%; $p=0.46$) and 30-day survival (93.9 vs. 95.5%; $p=0.33$), but incidences of any in-hospital complication (54.6 vs. 26.8%, $p<0.001$*), major bleeding (9.2 vs. 3.6%, $p=0.002$), pneumonia (4.6 vs. 1.0%, $p=0.001$) and pacemaker implantation (43.9 vs. 17.5%, $p<0.001$) were significantly higher in no-OSCS group compared to patients treated in institutions providing OSCS. With respect to long-term survival, there was a tendency towards reduced survival rates in no-OSCS patients (1-year survival 80.3 vs. 85.4%; $p=0.059$; 2-year survival 74.0 vs. 76.9%; $p=0.214$; 3-year survival 59.8 vs. 68.1%; $p=0.071$). After matching, the procedural (98.0 vs. 98.5%; $p=0.70$), 30-day (93.9 vs. 93.9%; $p=0.99$) and long-term survival rates (1-year survival 80.3 vs. 83.9%; $p=0.37$; 2-year survival 74.0% vs. 73.7%; $p=0.870$; 3-year survival rate 59.8% vs. 62.4%; $p=0.709$) were almost identical. Except for pacemaker implantation (no OSCS 43.9 vs. matched OSCS 21.9%, $p<0.001$), there were no significant differences in in-hospital complications.

18-9

Vascular access complications after transfemoral TAVI – surgical cut-down versus percutaneous access. Data from the extended VIenna CardioThOracic Aortic Valve RegistrY (VICTORY)

M. Mach, M. Wilbring, E. Charitos, M. Silaschi, E. Polat, D. Santer, S. Franz, K. Alexiou, U. Kappert, G. Delle Karth, H. Treede, K. Matschke, M. Grabenwöger

I. Chirurgie, Abteilung für Herz- und Gefäßchirurgie, Krankenhaus Hietzing, Vienna, Austria
Uniklinik Halle, Halle, Germany
Herzzentrum Dresden, Dresden, Germany

Background: The ideal approach for transfemoral TAVI is still widely debated. Objective of the present study was to compare VARC-2 access and bleeding complications of a complete percutaneous versus a surgical cut-down approach for transfemoral TAVI "in a real world – all comers" setting.

Methods: The study included 610 consecutive patients, including 232 patients in the percutaneous and 378 patients in the cut-down group. Mean patient's age was 79.6 ± 9.5 years vs. 81.9 ± 6.0 years ($p = 0.11$). Calculated logistic EuroSCORE correlated an intermediate to high surgical risk (28.5 ± 25.4 vs. 17.4 ± 11.9%, $p < 0.01$). Primary study endpoints were vascular access site as well as bleeding complications according the VARC-2 criteria.

Results: Mean procedure time was significantly shorter in the cut-down group (89.5 ± 61.7 min [percutaneous] vs. 63 ± 32 min [cut-down]; $p < 0.01$). Overall rate of VARC-2 access complications were as frequently reported in both groups (12.9% [30/232] vs. 8.2% [31/378]; $p = 0.21$); the incidence of major vascular complications did also not differ significantly (2.5% [6/232], percutaneous] vs. 4.6% [18/378, cut-down]; $p = 0.11$). VARC-2 bleeding complications were more frequent in the percutaneous group (20.7% [48/232] vs. 4.2% [16/378]; $p < 0.01$). Major- or life-threatening bleeding was similar in both groups (3.4% [8/232; percutaneous] vs. 2.1% [8/378; cut-down]; $p = 0.37$). Hospital mortality was 3.9% [9/232] in the percutaneous group and 1.6% [6/378] in the cut-down group ($p = 0.30$).

Conclusions: Surgical cut-down provides a safe, fast and notably controlled access, thus resulting in less bleeding complications. Nonetheless, major bleeding complications and overall access complications were not significantly different. Therefore both approaches must be seen as complementary techniques and taken into consideration for optimal clinical benefit. A portfolio containing both techniques is the exclusive way to provide a tailor-made and patient-orientated approach.

Postersitzung 19 – Vitien

19-1

Fallbericht – Hochgradige Mitralstenose nach transfemoralem Aortenklappenersatz

D. Hrncic, H. Blessberger, M. Grund, C. Steinwender, T. Lambert

Klinik für Kardiologie und Internistische Intensivmedizin, Kepler Universitätsklinikum Linz, Linz, Austria

Eine 86-jährige Patientin wird aufgrund einer hochgradigen Aortenklappenstenose, mit zunehmender belastungsabhängiger Dyspnoe und Schwindelsymptomatik, von einem auswärtigen Krankenhaus zur weiteren Abklärung an unsere Abteilung transferiert. Echokardiographisch zeigte sich eine hämodynamisch wirksame Aortenklappenstenose mit einem Stenosegradienten von 88/53 mmHg, einer Maximalgeschwindigkeit von 4,7 m/s und einer Klappenöffnungsfläche von 0,7 cm^2. Koronarangiographisch konnte eine relevante koronare Herzerkrankung ausgeschlossen werden.

Bei geeigneter peripherer Gefäßsituation wurde die Patientin einem Transkatheter-Aortenklappenersatz über einen transfemoralen Zugang zugeführt.

Nach vorangegangener Valvuloplastie der hochgradig verkalkten Aortenklappe erfolgte die Implantation einer 25 mm Portico, St. Jude Medical – Aortenklappe. Unglücklicherweise verhakte sich beim Freilassen der Klappe der Verankerungsmechanismus, sodass der Entladevorgang gestört wurde und die Klappe etwas zu tief positioniert wurde. Es konnte zwar kein relevanter Gradient über der Aortenklappe mehr nachgewiesen werden, jedoch zeigte sich eine nicht unbeträchtliche Aortenklappeninsuffizienz. Daraufhin wurde versucht, mit einem Snare die Klappe höher zu ziehen und mit einem Ballon nachzudilatieren. Durch diese Manöver gelang es, die Insuffizienz angiographisch auf I°-II° zu reduzieren. Die Patientin wurde postinterventionell bei kardiorespiratorischer Stabilität auf die Intensivstation verlegt.

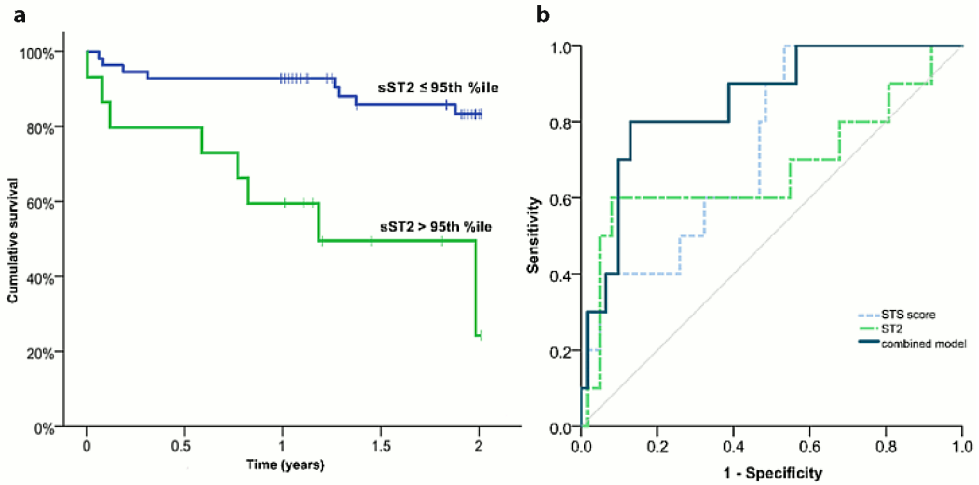


Fig. 1 | 19-2

Echokardiographisch zeigte sich der Aortenklappenersatz in den linken Ventrikel reichend mit einer Bedrängung des anterioren Mitralklappensegels und daraus resultierender höhergradiger Mitralstenose (mittlerer Gradient 10 mmHg). In der Verlaufsechokardiographie nahmen der Stenosegradient (mittlerer Gradient 15 mmHg) und der Druck im kleinen Kreislauf (90 mmHg) weiter zu.

Aufgrund anhaltender Dyspnoesymptomatik und einer kardialen Dekompensation wurde schließlich die Indikation zur operativen Revision gestellt. Die Klappenprothese konnte entfernt und eine biologische Aortenklappenprothese implantiert werden. Postoperativ erholte sich die Patientin rasch und konnte am 15. postoperativen Tag nach Hause entlassen werden. Ein Anschlussheilverfahren wurde vereinbart.

Diskussion: In diesem Fall wurde der Entladungsvorgang der Klappe, durch ein Verhaken des Verankerungsmechanismus, so gestört, dass die Klappe letztlich durch einen Korrekturversuch zu tief implantiert wurde. In weiterer Folge dürfte es zu einer weiteren Migrationsbewegung der Klappe Richtung Ventrikel gekommen sein. Die initial zu tiefe Implantation ist ein offensichtlicher Risikofaktor für weitere Migration der Klappe in Richtung linksventrikulärem Ausflusstrakt. Begünstigt wird dies durch die große retrograde Krafteinwirkung auf die implantierte Klappe während der Diastole, die zehn Mal höher ist als die antegrade in der Systole.

Zusammenfassend ist festzuhalten, dass bessere Entladungsmechanismen für transfemorale Aortenklappenprothesen notwendig sind, um die prozedurale Sicherheit weiter zu verbessern und möglicherweise eine Indikationserweiterung des Transkatheter-Aortenklappenersatzes auf Niedrig-Risiko-Patienten zu erreichen.

19-2

ST2 predicts survival in patients undergoing transcatheter aortic valve implantation

J. Schmid, D. Zweiker, T. Stojakovic, H. Scharnagl, R. Maderthaner, D. Scherr, R. Maier, A. Schmidt, W. März, J. Binder, P. Rainer

Cardiology, Medical University Graz, Graz, Austria
Radiology, Medical University Graz, Graz, Austria

Background: Suppression of tumorigenicity 2 (ST2) is the receptor of the IL-1 family alarmin IL-33 and involved in cardiac stress signaling. ST2 is elevated and prognostic in acute coronary syndromes and heart failure. We sought to assess ST2 levels and predict one-year mortality in patients undergoing transcatheter aortic valve implantation (TAVI).

Methods: 74 patients with severe aortic stenosis (AS) scheduled for TAVI were age- and sex matched to controls and underwent comprehensive imaging and laboratory examinations. Soluble ST2 (sST2) levels were determined by enzyme-linked immunosorbent assay (ELISA), their association with post procedural mortality was investigated using regression analyses, and the prognostic performance compared to established risk scores.

Results: AS patients had substantially higher sST2 levels than controls (39.5 vs. 17.8 ng/mL, $p<0.001$). sST2 significantly correlated with left and right atrial sizes ($r=0.25$, $p=0.033$ and $r=0.38$, $p=0.001$). At one year, 10 patients had died (14%). sST2 significantly predicted survival in multivariate Cox regression analysis in our cohort ($p=0.025$), while NT-proBNP was no significant predictor. AS patients above an sST2 cut-off at the 95th percentile of the control cohort (49 ng/mL) (15/72) were significantly more likely to die during follow up than patients below this threshold (one-year mortality 40% vs. 7%; $p<0.001$ by log-rank test; Fig. 1|19-2a). Adding sST2 to the established STS score significantly improved risk prediction (continuous NRI = 0.877 (95% CI: 0.243–1.512), ΔAUC = 0.119; Fig. 1|19-2b), and a model containing both sST2 and the STS score had a negative predictive value of 96% regarding one-year mortality.

Conclusions: sST2 is elevated in AS patients and a prognostic marker of survival after TAVI. Implementation of this marker in routine pre-TAVI workup may improve risk prediction and patient selection.

19-3

Late aortic aneurysm and stent fracture secondary to severe arterial hypertension in corrected coarctation and chronic renal failure

S. Gasser, R. Maier, M. Köstenberger, E. Sorantin, P. Oberwalder, I. Knez, A. Gamillscheg, B. Nagel

Univ.-Klinik für Innere Medizin, Experimentelle Kardiologie, Medizinische Universität Graz, Graz, Austria
Kinderklinik, Medizinische Universität Graz, Graz, Austria
Univ.-Klinik für Radiologie, Medizinische Universität Graz, Graz, Austria
Herzchirurgie, Medizinische Universität Graz, Graz, Austria

Aortic stent rupture with concomitant aortic aneurism resulting from arterial hypertension has not been described as yet. A patient, now aged 24 years, with coarctation has been operated at the age of three weeks with an end to end anastomosis of the aorta. Besause of a residual stenosis the toddler has been re-operated a day later. The procedure has been further complicated by renal failure with subsequent temporary hemodyalisis.

During the following years, arterial blood pressure has remained within the normal range, showing a gradient of 10 mmHg. From 2006 onwards, the patient has developed arterial hypertension, which has been difficult to cope with despite multiple antihypertensive medication. During this time, renal function has been constantly reduced with creatinine around 2.1 mg/dl and a reduced glomerular filtration rate. In 2006, MR-Angiography of the aortic arch showed a hypoplastic segment of several centimeters. This observation led to an implantation of a CP-stent in order provide more stability to the hypoplastic aortic segment. Six months later, MR-angiography and chest x-ray revealed a correctly positioned, intact stent.

Until 2012 MR-angiographies have been avoided because of the progressive renal dysfunction, which culminated in evaluation for renal transplantation (creatinine 6.2 mg/dl). Native MR-angiography revealed an aortic aneurysm within the stented segment and chest x-ray showed in the same region several stent fractures. Subsequently, the aortic segment with the stent has been surgically removed and replaced by a prothetic inter-ponate. Postoperatively, the patient had been subjected to hemodialysis for a week and renal transplantation has been postponed.

In summary, it is likely that the development of both renal failure and the aortic aneurysm has been enhanced and aggravated by the severe, drug restistant hypertension. It remains to discussion whether or not stent fracture has been also been facilitated by severe hypertension.

19-4

Prevalence of aquired von Willebrand Syndrome type II in low-flow, low gradient aortic stenosis

J. Kellermair, H. Ott, J. Tomasits, H. Blessberger, M. Derndorfer, M. Suppan, S. Schwarz, J. Kammler, C. Steinwender

Interne II, Klinikum Wels, Wels, Austria
Laboratorium Schottdorf, Augsburg, Germany
Institut für Labordiagnostik, Kepler Universitätsklinikum Linz, Linz, Austria
1. Medizinische Abteilung mit Kardiologie, Kepler Universitätsklinikum Linz, Linz, Austria

Background: Aquired von Willebrand Syndrome (AvWS) type II has been associated with classic severe aortic stenosis (AS) with a prevalence up to 80%. In these patients the loss of von Willebrand Factor (vWF) high molecular weight (HMW) multimers results from high sheer forces at the site of the stenosed aortic valve. However, there is a lack of data concerning the prevalence of AvWS type II in patients with low-flow, low-gradient (LF/LG) AS, an entity that comprises both a reduced systolic ejection fraction and a stenosed aortic valve. In patients the LF/LG AS the perivalvular sheer forces are significantly reduced compared to classic severe AS, thus, we expected a lower prevalence.

Methods: Consecutive patients with classic severe AS (defined as a peak aortic jet velocity ≥4 m/s, a mean transvalvular pressure gradient ≥40 mmHg and an AVA <1 cm^2) and with LF/LG AS (defined as a peak aortic jet velocity <4 m/s, a mean transvalvular pressure gradient <40 mmHg, an AVA <1 cm^2 and a stroke volume index (SVi) of <35 ml/m^2 in the presence of LVEF <50%) were prospectively recruited and blood was drawn for vWF multimer analysis which included a Western Blot and a densitometrical band pattern analysis.

Results: Patients with classic severe AS ($n=31$) had an abnormal vWF multimer band pattern in 20 out of 31 cases (64.5%) while patients with LF/LG AS ($n=30$) showed a vWF HMW multimer deficiency in 8 out of 30 cases (26.6%) [$p=0.046$]. The mean stenosis-induced sheer stress was calculated 107.4 ± 12.0 dyn/cm^2 for classic severe AS and 65.8 ± 17.0 dyn/cm^2 for LF/LG AS ($p<0.001$).

Conclusions: AvWS type II is significantly more common in classic severe AS compared to LF/LG AS which supports the mechanistic concept of sheer-stress-induced vWF HMW multimer degradation.

19-5

Von Willebrand Factor high molecular weight multimer deficiency for the discrimination between truly severe and pseudosevere low-flow, low-gradient aortic stenosis

J. Kellermair, H. Ott, J. Tomasits, M. Derndorfer, M. Suppan, Florian Obendorf, J. Kammler, C. Reiter, S. Schwarz, C. Steinwender

Interne II, Klinikum Wels, Wels, Austria
Laboratorium Schottdorf, Augsburg, Germany
Institut für Labordiagnostik, Kepler Universitätsklinikum Linz, Linz, Austria
Ordensklinikum Linz, Linz, Austria
1. Medizinische Abteilung mit Kardiologie, Kepler Universitätsklinikum Linz, Linz, Austria
Krankenhaus der Barmherzigen Brüder, Linz, Austria

Background: Low flow, low gradient (LF/LG) aortic stenosis (AS) – an entity that comprises AS and poor left ventricular ejection fraction (LVEF) – is subcategorized into truly severe LF/LG AS and pseudosevere LF/LG AS (where the reduced flow does not entirely open restricted leaflets). Dobutamine stress echocardiography (DSE) and computed tomography based quantification of valve calcification provide helpful information for differentiation. A biomarker-based distinction between truly severe LF/LG AS and pseudosevere LF/LG AS could simplify diagnostic work-up and avoid unnecessary or even harmful further imaging. However, valueable biomarkers have not been identified yet. The aim of the present study was to evaluate the diagnostic value of von Willebrand Factor (vWF) high molecular weight (HMW) multimer deficiency for the differentiation between truly severe and pseudosevere LF/LG AS.

Methods: Consecutive patients with LF/LG AS were prospectively enrolled and blood sampling for vWF multimer analysis was performed. All patients with LF/LG AS* underwent either low-dose DSE or (if contraindicated) computed-tomography-based aortic valve calcification scoring to differentiate truly severe from pseudosevere LF/LG AS. vWF multimer analysis included a Western Blot and a densitometrical band pattern quantification. vWF HMW multimer deficiency was defined as an absence of bands >13 on a high resolution agarose gel.

Results: Patients with diagnosis of LF/LG AS ($n=30$) were subclassified into truly severe LF/LG AS ($n=17$; 56.7%) and into pseudosevere LF/LG AS ($n=13$; 43.3%). vWF HMW multimer deficiency was detectable in 8 out of 17 (47.0%) patients diagnosed with truly severe LF/LG AS, while patients with pseu-

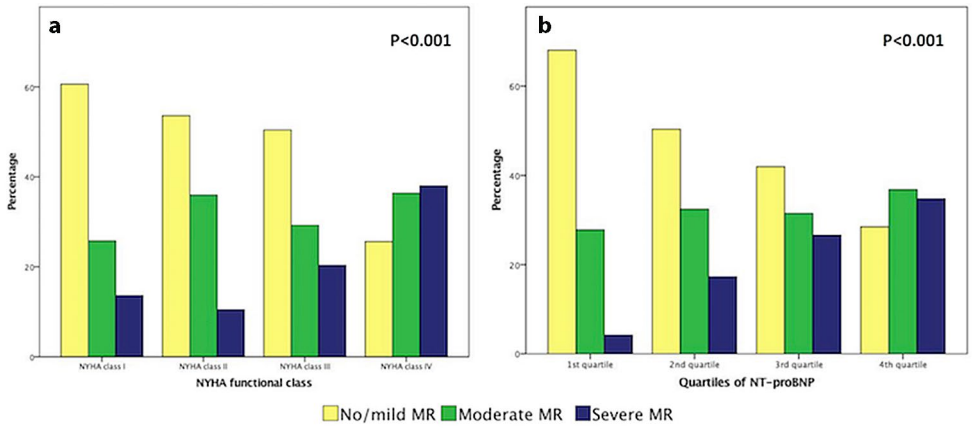


Fig. 1 | 19-6

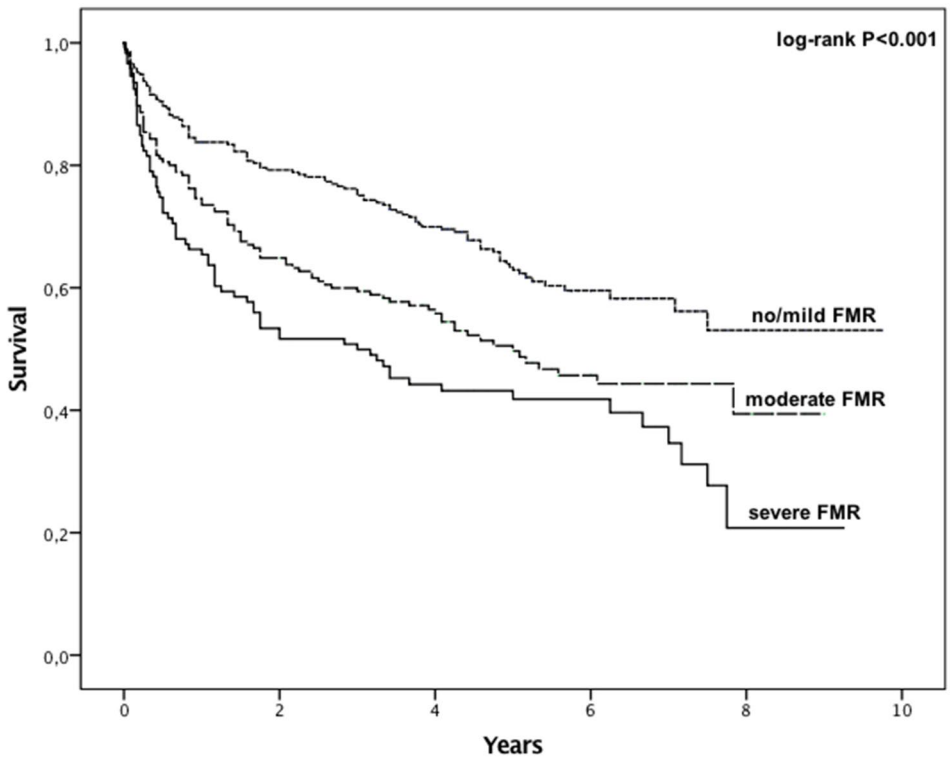


Fig. 2|19-6

dosevere LF/LG AS showed an abnormal vWF multimer band pattern in 0 out of 13 (0.0%) [$p=0.004$]. Taken together, the presence of vWF HMW multimer deficiency had a sensitivity of 47.0% and a specificity of 100% for the diagnosis of truly severe LF/LG AS in our patients.

Conclusions: The present study introduces a novel, promising laboratory test for the subclassification of LF/LG AS displaying a high specificity for the truly severe subform.

*defined as an echocardiographical peak aortic jet velocity <4 m/s, a mean transvalvular pressure gradient <40 mmHg, an AVA <1 cm^2 and a stroke volume index (SVi) of <35 ml/m^2 in the presence of LVEF <50%

19-6

Refining the prognostic impact of functional mitral regurgitation in chronic heart failure

G. Goliasch, P. Bartko, N. Pavo, S. Neuhold, R. Wurm, J. Mascherbauer, I. Lang, G. Strunk, M. Hülsmann

Universitätsklinik für Innere Medizin II, Medizinische Universität Wien, Vienna, Austria
Kaiser Franz Joseph Spital Wien, Vienna, Austria
FH Campus Vienna and Complexity Research, Vienna, Austria

Background: Significant efforts are currently undertaken to reduce functional mitral regurgitation (FMR) in patients with chronic heart failure in the hope to improve prognosis. We aimed to assess the prognostic impact of FMR in heart failure with reduced ejection fraction (HFrEF) under optimal medical therapy (OMT) and various conditions of HFrEF. We further intended to identify a heart failure phenotype, where FMR is most likely a driving force and not a mere bystander of the disease.

Methods and Results: We prospectively included 576 consecutive HFrEF patients into our long-term observational study. Functional (i. e. NYHA class), echocardiographic, invasive hemodynamic and biochemical (i. e. NT-proBNP, MR-proANP, MR-proADM, CT-proET-1, copeptin) measurements were performed at baseline. Severity of FMR increased with rising NYHA class ($P<0.001$, Fig. 1|19-6a) and NT-proBNP levels ($P<0.001$, Fig. 1|19-6b). During a median follow-up of 62 months (IQR 52–76), 47% of patients died. FMR severity was a significant predictor of mortality (HR 1.47; 95%CI 1.26–1.70; $P<0.001$, Fig. 2|19-6) for an increase of MR severity by one category, independent of clinical (HR 1.41; 95%CI 1.21–1.63; $P<0.001$) and echocardiographic (HR 1.20; 95%CI 1.01–1.43; $P=0.04$) confounders, OMT (HR 1.42; 95%CI 1.12–1.80 $P=0.004$) and neurohumoral activation (HR 1.31; 95%CI 1.13–1.53; $P=0.001$). Subanalysis revealed that severe FMR was associated with poor outcome only in an intermediate-failure phenotype of HFrEF i. e. patients with NYHA class II ($P=0.03$) and III ($P=0.008$), moderately reduced LV function ($P=0.002$) and within the second quartile (871–2360 pg/ml) of NT-proBNP ($P=0.009$). Furthermore, severe FMR was associated with impaired survival in patients with increased mean pulmonary artery pressure (mPAP ≥ 42 mmHg [3rd tertile]: adj. HR 3.10, 95%CI 1.29–7.43; $P=0.011$) and increased pulmonary artery wedge pressure (PAWP ≥ 26 mmHg [3rd tertile]: adj. HR 3.60, 95%CI 1.42–9.15; $P=0.007$).

Conclusions: This long-term observational study demonstrates the impact of FMR in patients with guideline adherent treatment and fully disclosed medical HF management including percentage of up-titration to recommended dosage regimens. The presented results confirm the rising prevalence of FMR with increasing HF severity and foster the notion that the adverse prognostic impact of FMR is given predominantly in a sub-cohort of a specific intermediate-failure phenotype – well defined functionally, hemodynamically, biochemically, and morphologically. Once the transition to a severe-failure phenotype has been completed, FMR is no longer of prognostic significance.

19-7

Preoperative high sensitivity troponin T plasma levels in patients with severe aortic stenosis: a gender specific analysis

F. Barbieri, A. Adukauskaite, S. Dobner, J. Holfeld, G. Feuchtner, W. Dichtl

Abteilung für Innere Medizin III, Medizinische Universität Innsbruck, Innsbruck, Austria
Universitätsspital Bern, Bern, Switzerland

Background: Optimal timing of aortic valve implantation in patients with severe aortic stenosis (AS) is under debate.1 Preprocedural biomarkers as high sensitivity troponin T (hsTnT) and N-terminal pro brain natriuretic peptide (NT-proBNP) may predict postoperative survival, and therefore may be helpful in selecting high-risk but still asymptomatic patients for earlier valve implantation.2 It is also necessary to determine if the predictive value of these biomarkers applies gender-neutrally.

Methods and Results: The Tyrolean Aortic Stenosis Study II included consecutive patients ($n=666$; ♀=287 (43.1%), ♂=379 (56.9%)) with severe AS undergoing valve implantation. During a mean follow up of 2.1±1.4 years, 86 patients (12.9%; ♀=28 (9.8%), ♂=58 (15.3%)) died, among them 54 (8.1%; ♀=20 (7.0%), ♂=34 (9.0%)) due to cardiovascular causes. Predefined groups (undetectable hsTnT (<5 ng/L), non pathological hsTnT (5–13.99 ng/L), mildly elevated hsTnT (14–50 ng/L) and severely elevated hsTnT (>50 ng/L)) were used to determine the predictive value in Kaplan-Meier curves. Further a cox regression model was conducted for multivariate analysis.

Postoperative all-cause, but not cardiovascular mortality, was statistically significant lower in female than in male patients ($p=0.021$; $p=0.263$). HsTnT showed gender-neutrally statistical significance predicting both, cardiovascular ($p<0.001$; ♀=0.012, ♂=0.005) and all-cause mortality ($p<0.001$; ♀=0.004, ♂=0.002). In patients with undetectable hsTnT plasma levels no cardiovascular death occured during the follow-up period. Cardiovascular and all-cause mortality gradually increased with hsTnT elevation independently of gender, reaching 22.5% (♀=26.7%, ♂=20.6%) and 32.7% (♀=33.3%, ♂=32.4%) in patients with hsTnT plasma levels above 50 ng/L, respectively. HsTnT also proved itself as the strongest independent risk factor for postoperative survival in Cox regression analysis including gender as potential mediator next to the well-known confounding factors age, renal function and concomitant significant coronary artery disease (hsTnT: hazard ratio [HR] per log unit 2.8, 95% confidence interval [CI] 1.6 to 4.7, $p<0.001$; gender: HR 2.2, 95% CI 1.4 to 3.7, $p=0.002$, respectively).

Conclusions: Postoperative survival in patients with severe AS undergoing valve implantation can be predicted by hsTnT irrespective of the gender.

References

1. Taniguchi T et al. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. J Am Coll Cardiol 2015;66:2827–38.
2. Everett BM et al. Troponin and cardiac events in stable ischemic heart disease and diabetes. N Engl J Med 2015;373:610–20.

Fig. 1|19-8

Anthropomorhic data		Male (n=263)	Female (n=79)	p-value
Age		74.47±9.58	76.01±11.06	0.233
Height		171.94±7.32	158.46±6.74	**<0.001**
Weight		80.33±16.29	67.86±15.96	**<0.001**
BSA		1.94±0.25	1.72±0.22	**<0.001**
Functional status and QOL				
NYHA Class		2.62±0.76	2.75±0.75	0.515
	Class I	18(5.5)	3(0.9)	
	Class II	83(25.4)	24(7.3)	
	Class III	125(38.2)	39(11.9)	
	Class IV	24(7.3)	11(3.4)	
Six Minutes Walk Test		291.73±126.18	199.49±119.97	**0.002**
DASI		22.85±14.53	16.53±9.82	**0.001**
Cardiac morphology and function at rest				
LVEDD		59.49±8.41	55.11±7.38	**<0.001**
LVEDD index		30.96±4.75	32.59±5.49	**0.028**
LVEF (Simpson)		29.65±8.62	30.51±8.95	0.532
EOA		0.86±0.21	0.74±0.23	**<0.001**
EOA index		0.55±0.14	0.55±0.16	0.995
AV peak gradient		40.81±13.58	41.24±13.31	0.821
AV mean gradient		24.29±8.24	23.71±8.09	0.608
Peak Stress				
SV (Doppler)		74.34±21.00	63.93±20.56	**0.009**
SV index		38.01±10.14	37.45±10.71	0.776
LVEF		35.56±9.53	38.65±10.40	0.242
EOA		1.07±0.26	0.935±0.25	**0.005**
EOA index		0.52±0.12	0.58±0.16	**0.047**

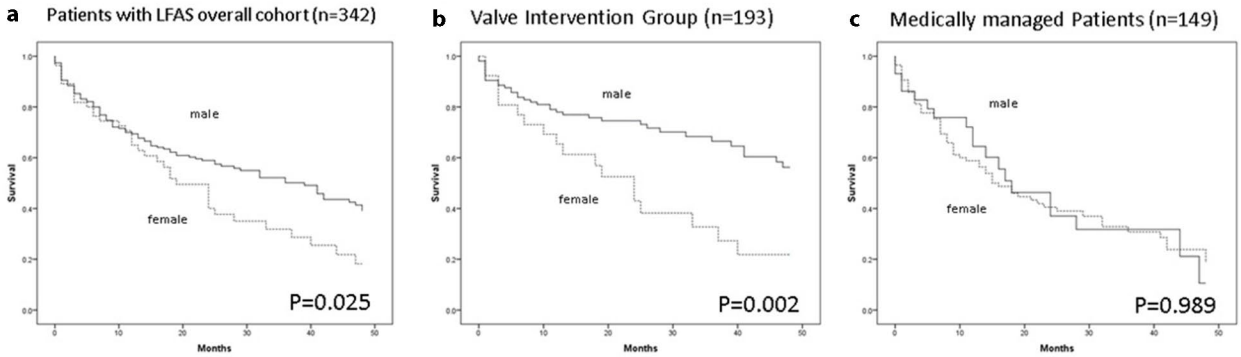


Fig. 2|19-8

19-8

Gender differences in low-flow, low-gradient aortic stenosis

P. Bartko, M.-A. Clavel, A. Dahou, R. Capoulade, H. Baumgartner, I. Lang, G. Mundigler, J. Bergler-Klein, J. Rodes-Cabau, P. Pibarot, J. Mascherbauer

Innere Medizin 2/Kardiologie, Medizinische Universität Wien
Quebec Heart Institute, Quebec, Canada
EMAH-Zentrum, Universitätsklinikum Münster, Muenster, Germany

Background: Prior research is limited with regards to sex related differences in patients with Low-Flow, Low-Gradient Aortic Stenosis (LFAS). The present TOPAS sub-study sought to investigate gender related effects on anthropomorphic data, clinical presentation and outcome in patients with LFAS.

Methods: 342 Patients (263 male and 79 female) with LFAS (valve area ≤ 1.2 cm^2, left ventricular (LV) ejection fraction (EF) ≤ 40%, mean gradient ≤ 40 mmHg) were prospectively enrolled. Anthropomorphic data, clinical history and symptomatic status were assessed. Dobutamine stress echocardiography was used to assess contractile reserve and stenosis severity.

Results: Size, weight and body surface area (BSA) were smaller in women than men ($p<0.001$, Table 1). Although women reported similar symptomatic status at study entry ($p=0.515$, Table 1) females had significantly worse 6-minute walk test (6MWT) performance and a lower duke activity status index (DASI) score (both $p<0.01$). Echocardiography at rest revealed larger LV end-diastolic (EDD) index at rest ($p=0.028$) despite similar effective orifice area (EOA) index ($p=0.995$) and mean gradients (MG) ($p=0.608$). At peak stress women had similar stroke volume index and ejection fraction ($p=0.776$ and $p=0.242$) but a larger EOA index compared to men (0.047) (Table 1).

During 4 year follow up 132 Patients died. 193 (56%; 152 male and 41 female) patients underwent valve intervention and 149 (44%; 111 male, 38 female) patients were managed medically. Kaplan-Meier and Univariate Cox regression analysis revealed a higher overall mortality in women compared to men (HR1.533, 95%CI 1.047–2.244, $p=0.028$), Fig. 1|19-8a. Sub-analysis according to treatment groups revealed that this was solely due to a higher mortality of women in the valve intervention group (HR 2.378, 95%CI 1.347–4.198, $p=0.003$, Fig. 1|19-8b) while no difference in overall survival was found between men and women in medically treated patients (HR 1.004 95% CI 0.598–1.685, $p=0.989$, Fig. 1|19-8c). In the intervention group, female gender remained independently associated with outcome even after correcting for age, BSA, stenosis severity and ejection fraction at peak stress (HR 2.672, 95%CI 1.069–6.680, $p=0.036$).

Conclusions: In patients with LFAS women report similar symptoms but are at an advanced stage of the disease as assessed by more objective tests like the 6MWT and DASI. Similar stenosis severity at rest and even larger EOA at peak stress but larger LV dimensions and worse exercise capacity indicate a more pronounced impact of the valvular lesion on female hearts and a more advanced disease stage that might not be reversible and result in worse outcome after valve intervention.

19-9

Invasive validation of a novel approach to determine aortic valve area with phase-contrast cardiac magnetic resonance

G. Klug, H.-J. Feistritzer, S. J. Reinstadler, S. Wöhrer, M. Reindl, L. Niess, A. Mayr, B. Metzler

Innere Medizin III, Kardiologie, Medizinischen Universität Innsbruck, Innsbruck, Austria

Background: Echocardiography is considered the standard for the screening and diagnosis of aortic stenosis. However, difficulties in the determination of stroke-volumes by the continuity equation might hamper the evaluation of patients with low-flow states. Phase contrast cardiac magnetic resonance (PC-CMR) might overcome these limitations by the simultaneous determination of flow volumes and velocities across the stenotic valve.

Purpose: Therefore the aim of this study was to validate a novel approach based on PC-CMR against the invasive determination of the aortic valve area (AVA).

Methods: We performed PC-CMR in 32 patients (11 women, 34%, mean age: 69 ± 11 years), which were referred for invasive evaluation of aortic stenosis (mean AVA: 0.64 cm^2, 8 (25%) with low-flow states). All patients underwent right- and left heart catheterization. Stroke volumes were determined invasively by the Fick-principle and AVA was calculated according to the Gorlin-formular. Determination of AVA by PC-CMR was performed by plotting flow across the valve versus flow velocities. According to (1) AVA = SV/Velocity

AVA can be calculated continuously over the whole cardiac cycle. We compared AVA at different time-points in the cardiac cycle to the invasively determined AVA.

Results: Stroke volumes determined PC-CMR (73 ± 32 ml) showed a good agreement with the Fick-method with only a small bias (r: 0.662, $p<0.001$, bias: 14 ml, $p<0.006$). AVA determined by PC-CMR during the phase from the beginning of the

valve opening to the maximal opening area showed a good correlation with invasive AVA (r: 0.635, $p<0.001$) without a significant bias (AVACMR: 0.7 cm^2 IQR: [0.4–0.96] versus AVAINVASIVE: 0.63 cm^2 IQR: [0.4–0.96], bias: 0.12 cm^2, $p=0.199$). Mean AVA during the whole systolic phase showed a slightly lower correlation (r: 0.511, $p=0.004$) with invasive AVA, but also a lower bias (AVACMR: 0.68 cm^2 IQR: [0.5–0.98], bias: 0.09 cm^2, $p=0.191$).

Conclusions: PC-CMR with continuous determination of flow volumes and flow velocities is able to determine AVA with good correlation and no bias to invasively determined AVA.

Postersitzung 20 – Rhythmologie 2

20-1

12-Monats-Ergebnisse nach Implantation eines sondenlosen Einkammer-Schrittmachersystems (Micra®)

H. Blessberger, A. Kypta, J. Kammler, D. Hrncic, S. Schwarz, K. Saleh, S. Hönig, T. Lambert, A. Nahler, J. A. Starnawski, J. Kellermair, D. Kiblböck, C. Steinwender

I. Medizinische Abteilung mit Kardiologie, Kepler Uniklinikum Linz, Linz, Österreich

Grundlagen: Patienten mit der Indikation zur Einkammer-Schrittmacherversorgung stehen neuerdings auch sondenlose Schrittmachersysteme zur Verfügung. Sie können über einen transfemoralen Zugang direkt in den rechten Ventrikel implantiert werden. Gegenüber den „konventionellen" Systemen besteht der potenzielle Vorteil einer geringeren Inzidenz an Sondenkomplikationen bzw. Taschen- und Sondeninfektionen. Wir evaluierten die 1-Jahresergebnisse nach sondenloser Systemimplantation.

Methodik: Es wurden alle Patienten erfasst (Gruppe 1, $n=90$), die an unserem Zentrum einen sondenlosen Schrittmacher (Micra®, Medtronic, Minneapolis, USA) zwischen 12/2013 und 04/2016 erhielten. Das Kontrollkollektiv (Gruppe 2, $n=90$) bildete eine gleiche Anzahl an Patienten, die an unserer Abteilung mit einem konventionellen Einkammer-System (stets mit Schraubelektrode) zwischen 12/2009 und 07/2015 versorgt wurde. Prozedurale und Geräteparameter sowie Komplikationen wurden bei der Implantation sowie im Verlauf des ersten Jahres danach erhoben und mit den Daten des Kontrollkollektivs verglichen. Die Unterschiede zwischen den Gruppen wurden mittels t-Test und Chi-Quadrat-Test analysiert.

Ergebnisse: 66 (73 %) Pat. der Gruppe 1 und 79 (88 %) der Gruppe 2 erhielten das System aufgrund eines permanenten Vorhofflimmerns mit symptomatischer Bradykardie oder höhergradigem AV-Block, während bei den übrigen Pat. die Indikation aufgrund eines Sick Sinus Syndroms oder eines neu aufgetretenen Linksschenkelblocks mit AV-Block Grad I nach TAVI gestellt wurde. Die OP-Zeit war zwischen beiden Gruppen nicht signifikant unterschiedlich (Gruppe 1: 35,6 ± 17,0 min., Gruppe 2: 39,0 ± 17,2 min., $p=0,193$). Die Durchleuchtungsdauer war jedoch bei Implantation eines sondenlosen Systems in etwa doppelt so hoch wie bei einem konventionellen System (Gruppe1: 7,2 ± 6,1 min., Gruppe 2: 3,1 ± 6,1 min., $p<0,00001$). Die Reizschwelle bei Implantation betrug in der Gruppe1 0,52 ± 0,28V und in der Gruppe 2 0,77 ± 0,53V. Im Verlauf blieben diese Werte im Wesentlichen unverändert ohne einen statistisch signifikanten Unterschied zwischen den beiden Gruppen. Die Impedanz nahm in beiden Gruppen während der Nachsorge ab, ohne dass ein signifikanter Unterschied in diesem Trend zwischen beiden Gruppen gezeigt werden konnte (Gruppe1: 689 ± 181 Ω auf 589 ± 98 Ω nach 12 Monaten, Gruppe 2: 687 ± 257 Ω auf 551 ± 106 Ω, $p=0,968$). Das Sensing zeigte jedoch in beiden Gruppen ein unterschiedliches Verhalten: Während es sich in Gruppe 1 verbesserte (10,6 ± 4,6mV auf 15,8 ± 4,5 mV nach 12 Monaten), verschlechterte es sich in Gruppe 2 leicht (12,9 ± 16,4 mV auf 11,2 ± 4,9 mV nach 12 Monaten, p-Wert für unterschiedliche Entwicklung zwischen den Gruppen nach 12 Monaten = 0,019). Während des Beobachtungszeitraumes traten in Gruppe1 zwei (Hämatom, Perikarderguss), und in Gruppe 2 vier Komplikationen auf (Sondenbruch, Hämatom, 2 Sondenrevisionen, $p=0,310$).

Schlussfolgerungen: Im Vergleich zu einem konventionellen System erwies sich der sondenlose Schrittmacher als effektiv und sicher. Bei der Implantation zeigte sich in unserer Analyse eine längere Durchleuchtungsdauer, wobei allerdings der Abstand des Implanteurs zu der Strahlenquelle wesentlich größer ist als bei dem konventionellen Eingriff. Der größere Abstand zwischen Elektrodenspitze und Fixationsmechanismus beim sondenlosen Schrittmacher mit konsekutiv vitalerem Myokard am primären Stimulationsort könnte mit dafür verantwortlich sein, dass sich das Sensing im Gegensatz zu einem konventionellen System im Verlauf verbesserte.

20-2

Alternative Positionierung eines sondenlosen Schrittmachers im rechtsventrikulären Septum – Ergebnisse mit dem Micra™ Transcatheter Pacing System

S. Schwarz, A. Kypta, K. Saleh, T. Lambert, J. Kammler, H. Blessberger, D. Kiblboeck, J. Kellermair, A. Nahler, C. Reiter, D. Hrncic, S. Hönig, C. Steinwender

Interne 1 – Kardiologie und Internistische Intensivmedizin, Kepler Universitätsklinikum Linz, Linz, Österreich

Grundlagen: Die Implantation sondenloser Schrittmacher stellt ein technisch neuartiges Konzept in der Schrittmachertherapie dar. In der ersten Phase der Implantation des Micra™ Transcatheter Pacing Systems (TPS) war die apikale Positionierung durch ein Studienprotokoll vorgegeben. Das Device ist jedoch auch für alternative Implantationsorte wie das rechtsventrikuläre Septum geeignet und zugelassen. Im weiteren Verlauf und in Analogie zur Implantation konventioneller Ventrikelschraubsonden wurde vermehrt eine septale Positionierung angestrebt, insbesondere, um das potentielle Perforationsrisiko bei apikaler Positionierung auszuschalten.

Methodik: Zwischen Dezember 2013 und Februar 2017 erhielten 124 Patienten an unserer Abteilung ein Micra™ TPS (Medtronic Inc., Minneapolis, MN, USA). Bei den ersten 50 Patienten erfolgte innerhalb der CE-Zulassungsstudie eine apikale Positionierung. Bei den folgenden 74 Patienten wurde das Device in 34 Fällen im rechtsventrikulären Septum implantiert. Die Freisetzung erfolgte obligat Kontrastmittel-unterstützt zur Kontrolle von Kontakt und Lage des Delivery-Systems am Septum und zusätzlich zu einer RAO-Projektion auch in einer LAO-35–40°-Projektion.

Ergebnisse: Von den 34 Patienten waren 9 weiblich und das Durchschnittsalter betrug 80,6 ± 11,1 Jahre. Die durchschnittliche Implantationszeit lag bei 33,1 ± 10,6 Minuten mit einer mittleren Durchleuchtungsdauer von 5,5 ± 4,2 Minuten. Bei einer durchschnittlichen Deployment-Rate von 1,9 ± 1,8 Ver-

suchen lag die maximale Anzahl an Deployment-Versuchen im Rahmen ein und derselben Prozedur bei 8. Das mittlere R-Wellen-Sensing betrug 11,3 ± 5,5 mV, die mittlere Reizschwelle 0,8 ± 1,4 V und die mittlere Impedanz 673,8 ± 151 Ω. Es traten keine peri- oder postprozeduralen Komplikationen auf.

Schlussfolgerungen: Die alternative Positionierung eines sondenlosen Schrittmachers im rechtsventrikulären Septum ist sicher und gewährleistet bei adäquaten elektrischen Messwerten eine effektive Stimulation. Das mögliche Risiko einer Ventrikelperforation wie bei apikaler Implantationstechnik kann hierdurch zur Gänze ausgeschaltet werden.

20-3

Apikale und septale Implantation eines sondenlosen Schrittmachers im Vergleich – Ergebnisse mit dem Micra™ Transcatheter Pacing System

S. Schwarz, C. Steinwender, K. Saleh, J. Kammler, H. Blessberger, T. Lambert, D. Kiblboeck, J. Kellermair, A. Nahler, D. Hrncic, C. Reiter, S. Hönig, A. Kypta

Interne 1 – Kardiologie und Internistische Intensivmedizin, Kepler Universitätsklinikum Linz, Linz, Österreich

Grundlagen: Das Micra™ Transcatheter Pacing System (TPS) ist nicht nur für die Implantation im rechtsventrikulären Apex, sondern auch für alternative rechtsventrikuläre Implantationsorte wie das Septum geeignet und zugelassen. Wenngleich im Rahmen der CE-Zulassungsstudie zunächst die apikale Implantation vorgegeben war, wurde im weiteren Verlauf und in Analogie zur Implantation konventioneller Ventrikelschraubsonden vermehrt eine septale Implantation angestrebt.

Methodik: Zwischen Dezember 2013 und Februar 2017 erhielten 124 Patienten an unserer Abteilung ein Micra™ TPS (Medtronic Inc., Minneapolis, MN, USA). Bei 90 Patienten wurde das Device im rechtsventrikulären Apex und bei 34 Patienten im rechtsventrikulären Septum implantiert. Voraussetzung für eine Wahl alternativer Implantationsorte ist die steuerbare Spitze des Delivery Systems, das die entsprechende Flexibilität gewährleistet. Während die apikale Implantationstechnik zu Beginn ohne Kontrastmittel durchgeführt wurde, erfolgte die Freisetzung im Septum obligat Kontrastmittel-unterstützt zur Kontrolle von Kontakt und Lage des Delivery-Systems am Septum.

Ergebnisse: Bei den 90 Patienten (42 weiblich) mit apikaler Implantation und einem durchschnittlichen Alter von 79,7 ± 6,8 Jahren wurden folgende Parameter erhoben: R-Wellen-Sensing 10,3 ± 4,3 mV, Reizschwelle 0,5 ± 0,3 V, Impedanz 692 ± 187 Ω, Dauer der Prozedur 39,4 ± 17,1 Minuten, Durchleuchtungszeit 7,2 ± 5,3 Minuten, postinterventioneller Aufenthalt 2,5 ± 2,0 Tage, eine nicht-tödliche Ventrikelperforation. In der Gruppe der 34 Patienten (9 weiblich) mit septaler Implantation und einem durchschnittlichen Alter von 80,6 ± 11,1 Jahren waren die Ergebnisse wie folgt: R-Wellen-Sensing 11,3 ± 5,5 mV, Reizschwelle 0,8 ± 1,4 V, Impedanz 673,8 ± 151 Ω, Dauer der Prozedur 33,1 ± 10,6 Minuten, Durchleuchtungszeit 5,5 ± 4,2 Minuten, postinterventioneller Aufenthalt 1,4 ± 1,3 Tage, keine Perforation.

Schlussfolgerungen: Bei vergleichbaren elektrischen Messwerten waren die durchschnittliche Dauer der Prozedur und die Durchleuchtungszeit in der Gruppe mit apikaler Implantation ebenso länger wie der durchschnittliche postinterventionelle Aufenthalt. In dieser Gruppe kam es auch zu einer Perforation mit nicht-tödlichem Ausgang, wogegen diese Komplikation in der Gruppe mit septaler Implantation erwartungsgemäß nicht auftrat. Aufgrund der vorliegenden Ergebnisse sollte bevorzugt die septale Implantationstechnik zur Anwendung kommen, insbesondere im Sinne der Patientensicherheit, da durch diese Technik das mögliche Perforationsrisiko des oft dünnwandigen rechtsventrikulären Apex umgangen werden kann.

20-4

Feasibility of HV-interval measurements with a mobile EP Lab during TAVI procedures in the Cath lab

A. Nahler, T. Lambert, C. Reiter, J. Kellermair, M. Grund, H. Blessberger, J. Kammler, D. Hrncic, M. Patrasso, C. Steinwender

Klinik für Interne 1 – Schwerpunkt Kardiologie und Intensivmedizin, Kepler Universitätsklinikum Linz, Linz, Austria

Background: Transcatheter aortic valve implantation (TAVI) has rapidly become a promising treatment option for selected patients with severe aortic valve stenosis. However, despite improvements in valve-design, the rate of permanent pacemaker implantation after TAVI is high due to conduction disturbances caused by the prosthetic valve. It was the target of this study to establish and assess the feasibility of intra-procedural real-time HV-interval monitoring during TAVI procedures.

Methods: We systematically investigated the feasibility of intra-procedural real-time HV-intervals measurements by the use of a customized mobile EP system (St.Jude Medical, WorkMate Claris 56 channel system w/EP-4 Stimulator) during TAVI procedures. Therefore, the EPS was positioned in the Cath lab during TAVI procedures. Via an additional venous puncture, a non-steerable HIS catheter (St. Jude Medical) was positioned in typical position and a real-time HV-interval was monitored during the entire TAVI procedure. Procedure time, quality of HIS- and V-potentials and complications were recorded in each patient.

Results: From January 1st, 2017 until March 1st, 2017 we performed HV-interval-measurements during 11 TAVI procedures (7 women, 4 men) with a mean age of 81.4 ± 5.0 years. A usable HIS-signal could be obtained in all patients with the need for 1.4 ± 0.8 repositionings of the HIS catheter. No HIS catheter-related complications occurred.

Mean procedure time (balloon insertion – vascular closure) was 24.7 ± 3.8 min with the mean HV-interval significantly increasing from 52.6 ± 8.7 ms before to 79.4 ± 18.7 ms after TAVI, respectively ($p < 0.05$).

Conclusions: Real-time HV-interval measurements during TAVI procedures with a portable EP Lab are feasible and safe. The acquired data can help to elucidate the pattern of HV-prolongations leading to pacemaker-implantations after TAVI.

20-5

Follow-up nach Radiofrequenzablation einer AV Knoten Reentry Tachykardie: Ergebnisse einer Pilotstudie

C. Siess, E. Gatterer, H. Keller, C. Stöllberger

2. Medizinische Abteilung, Krankenanstalt Rudolfstiftung, Wien, Österreich

Grundlagen: Die AV-Knoten Reentry Tachykardie (AVNRT) ist die häufigste supraventrikuläre Tachykardie. Die Prognose von PatientInnen mit AVNRT ist in der Regel nicht beeinträchtigt, allerdings können Angst und Leidensdruck erheblich sein. Den Goldstandard in der Therapie stellt, mit einer hohen Erfolgs- und niedrigen Komplikationsrate, die Radiofrequenz-Ablation (RFA) dar. Über den Langzeitverlauf von Patienten nach RFA einer AVNRT gibt es nur wenige Daten. Ziel der Pilot-Studie war es, die Langzeit-Auswirkungen der RF-Ablation auf das Reizleitungssystem des Herzens zu erfassen und Risikofaktoren für EKG Veränderungen zu identifizieren.

Methodik: Die Daten von allen PatientInnen, die sich zwischen 2007–2014 in einer Abteilung einer RFA einer AVNRT unterzogen haben, wurden retrospektiv ausgewertet. Eingeschlossen in die Pilotstudie wurden alle Patienten, von denen EKGs sowohl vor der RFA als auch mehr als ein Jahr nach der Krankenhausentlassung zur Verfügung gestanden sind.

Ergebnisse: Fünfzig Patienten (58 % weiblich, mittleres Alter 56 ± 17 Jahre) erfüllten die Einschlusskriterien. Eine Hypertonie-Anamnese hatten 48 %, Diabetes mellitus 12 % und eine koronare Herzkrankheit 10 %. Die Follow-up-Dauer betrug 2.6 ± 2,1 Jahre. Sechzehn Prozent der Patienten entwickelten im Follow-up, bei vorher normalem, einen pathologischen EKG-Befund (Vorhofflimmern $n = 4$, AV Block II $n = 2$, linker vorderer Hemiblock $n = 1$, QT-Verlängerung $n = 1$). Hohes Lebensalter und das männliche Geschlecht wurden als Faktoren identifiziert, die Entwicklung von EKG-Veränderungen begünstigen. Komorbiditäten zeigten keinen Einfluss. Drei PatientInnen entwickelten im Follow-up einen höhergraden AV-Block, zwei davon mit der Notwendigkeit einer Schrittmacherimplantation.

Schlussfolgerungen: PatientInnen mit AVNRT entwickeln häufiger EKG-Pathologien als aus epidemiologischen Daten der Normalbevölkerung bekannt ist. Hohes Lebensalter und das männliche Geschlecht scheinen Risikofaktoren für die Entwicklung von EKG-Veränderungen bei Patienten nach RFA einer AVNRT zu sein.

20-6

Koinzidenz von Brugada-Syndrom und Sick-Sinus-Syndrom mit signifikanten Pausen bei Patientin mit cerebralem Insult durch rechtsseitigen Carotisverschluss

C. Neuhold, H. Keller, F. Weidinger, E. Gatterer

II. Medizinische Abteilung, Krankenanstalt Rudolfstiftung, Wien, Österreich

Grundlagen: Das Spektrum der Phänotypen, die mit SCN5A Mutationen vergesellschaftet sind, beinhaltet Brugada-Syndrom (BS), Long-QT-Syndrom, progressive cardiac conduction disease und das Sick-Sinus-Syndrom (SSS). Die Koinzidenz von BS und SSS wird in der Literatur mit 9–17 % angegeben (1,2).

Fallbericht: Eine 64-jährige Patientin wurde an unserer neurologischen Abteilung mit einem Insult durch Verschluss der A. carotis interna rechts mit Vertigo, Herdblick und Facialisparese links aufgenommen. Die Patientin erhielt eine systemische rtPA-Lyse und wurde an der Stroke Unit kontinuierlich überwacht. Im Zuge des Monitorings zeigte sich, dass die Pati-

Abb. 1 | 20-6

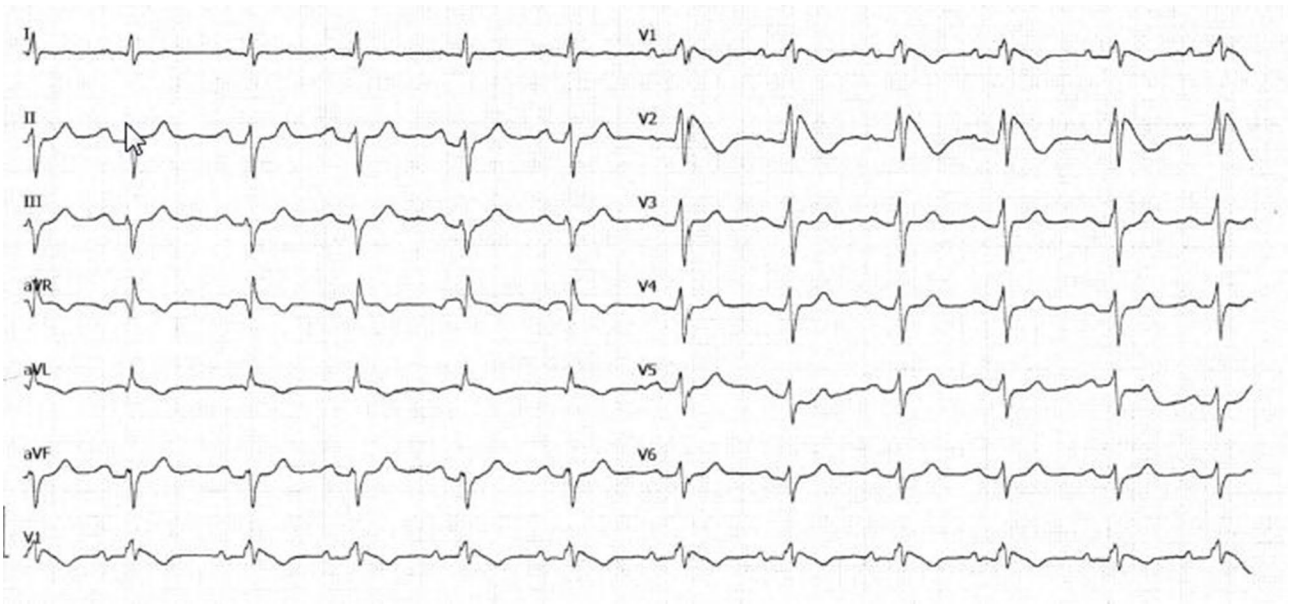


Abb. 2 | 20-6

entin Pausen mit bis zu 7,5 sec aufwies, die durch Sinusarrest bedingt waren. Das 12-Ableitungs-EKG war auffällig und zeigte ein Brugada-Typ I-EKG (Abb. 2). Anamnestisch war zu erheben, dass bei der Patientin bereits 2009 ein Brugada-Typ II-EKG diagnostiziert worden war, einer weiteren Abklärung hatte die Pat. damals jedoch nicht zugestimmt. Die Patientin hatte bisher keine Synkopen erlitten oder Arrhythmien verspürt, auch die Familienanamnese ist kardial unauffällig. Die aufgezeichneten Pausen hatte die Patientin im Rahmen des Aufenthaltes erstmalig als thorakales Druckgefühl wahrgenommen.

Ergebnisse: Die Patientin wurde an unserer Abteilung übernommen und telemetrisch überwacht. Auch nach über einer Woche nach dem Insult wurden neuerlich auch tagsüber symptomatische Pausen bis 5 sec (Abb. 1) und bradykarde Phasen dokumentiert, die Patientin erhielt deshalb eine temporäre Schrittmachersonde. Als nächste Massnahme wurde eine elektrophysiogische Untersuchung mit Ventrikelstimulation im rechtsventrikulären Apex und Ausflusstrakt mit maximal drei Extrastimuli bei den Basiszykluslängen 600, 500, 430 ms bis zu einer Vorzeitgkeit von minimal 200 ms durchgeführt. Es konnte lediglich eine einzige ventrikuläre Extrasystole induziert werden. Die Patientin wurde daher mit einem Zweikammerschrittmacher versorgt. Eine genetische Untersuchung wurde veranlasst.

Schlussfolgerungen: Da die Ventrikelstimulation beim BS einen hohen negativen prädiktiven Wert hat, und es in der Literatur Daten dafür gibt (1), dass Brugada-Patienten mit SSS, die ausschließlich mit einem Schrittmachersystem versorgt wurden, eine gute Prognose haben (kein Patient erlitt ventrikuläre Arrhythmien), haben wir bei unserer Patientin auf eine ICD-Implantation verzichtet.

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20-7

Titin Gen Mutation als Diagnose bei primären Verdacht einer Takotsubo Kardiomyopathie

H. Keller, C. Neuhold, F. Weidinger, E. Gatterer

2. Mededizinische Abteilung, Krankenanstalt Rudolfstiftung, Wien, Österreich

Grundlagen: Stopgain Mutationen im Titin Gen (tTTN) sind bei ca. 25 % der Patienten mit dilatativer Kardiomyopathie (DCMP) nachweisbar. TTN enkodiert das Sarkomer-Protein Titin, das größte Protein im menschlichen Körper (33.000 Aminosäuren); es ist für den Sarkomeraufbau und die aktive Kontraktilität maßgeblich verantwortlich. Mutationen im TTN sind häufig (1:100), im Tierversuch konnte gezeigt werden, dass durch erhöhten Energieaufwand Gendefekte kompensiert werden können; bei zusätzlichem Stress kann aber eine akute Herzinsuffizienz auftreten

Methodik: Bei einer 60-jährigen Patientin war 2011 nach psychischer Belastung verbunden mit linksthorakalem Druckgefühl echokardiografisch eine Hypokinesie des gesamten Septums mit mittelgradig reduzierte Linksventrikelfunktion (LVEF) diagnostiziert worden, die Koronarangiographie war bland, es wurde die Diagnose Takotsubo Kardiomyopathie (TTC) gestellt. Die LVEF erholte sich nicht vollständig (48 % im kardialen MRT mit diskreter Hypokinesie circumferentiell im mittleren und apikalen Drittel des LV), in der Ergometrie reduzierte Leistungsfähigkeit (LF 79 %); 2013 erstmalig dokumentiertes, spontan terminierendes tachykardes Vorhofflimmern (pro BNP 866 pg/ml), Nachweis isolierter VES. Nach Beginn mit einer neurohumoralen Therapie Besserung der LF (100 %) ohne Auftreten von VES, Verbesserung der LVEF auf 59 %, Rückgang des pro BNP (152 pg/ml). 2015 wieder Verschlechterung der LVEF auf 48 %, neuerlicher Therapieversuch mit BB, der nur in geringer Dosis toleriert wird. Weitere Abnahme der LVEF auf 40 % bis 5/2016 und Größenzunahme des linken Ventrikels (EDD 68 mm), korrelierend dazu Anstieg des pro BNP (1058 pg/ml) trotz stabilen Sinusrhythmus sowie klinisch imponierender rascher Ermüdung besonders nach psychischer Belastung.

Nach einer Pneumonie 12/2016 kardiale Dekompensation mit hochgradig red. LVEF von 18 %, angiographisch waren die Koronarien wieder bland. Versuch einer Sacubitril/Valsartantherapie, die Pat. wurde mit einer „lifeVest“ entlassen. Schon am nächsten Tag erlitt sie daheim einen Schock; unter stationären Bedingungen folgten in derselben Nacht drei weitere Episoden von Kammerflimmern, die adäquat durch die „lifeVest“ terminiert wurden. Es wurde der Entschluss zur ICD-Implantation gefasst, eine genetische Untersuchung veranlasst und die Vorstellung an der HTX-Ambulanz vereinbart.

Ergebnisse: Bei der genetischen Untersuchung wurden Exons von 40 Genen, die mit DCMP assoziiert sind, untersucht. Neben bekannten Polymorphismen wurde dabei eine bisher nicht beschriebene heterozygote Stopgain Mutation im TTN Gen (Cardiomyopathy, dilated, 1G, wahrscheinlich mit autosomal dominantem Erbgang) gefunden (TTN:NM_001256850:exon9:c.G1489T:p.E497X).

Schlussfolgerungen: Verschiedene Mutationen am TTN können dazu führen, dass 50 % der Titin Proteine des Herzens nicht mehr vollständig produziert werden. Welche Auslöser bei Menschen mit dieser Mutation schließlich krankheitsauslösend sind, ist noch nicht bekannt. Möglicherweise sind es Umwelteinflüsse, zusätzliche genetische Faktoren oder akute Erkrankungen.

Dieser Fall eröffnet die Diskussion, ob nicht Patienten mit der Diagnose einer TTC auch genetisch untersucht werden sollten, da bei Vorliegen einer Titin Genmutation ein erhöhtes Risiko bis hin zum plötzlichen Herztod besteht. Prospektive genetische Studien könnten die Häufigkeit dieser Mutation bei Patienten mit TTC im Vergleich zu einem gesunden Kollektiv untersuchen.

Chirurgie

C-1

Acute type a aortic dissection: Incidence of cystic medial necrosis (CMN) and surgical outcome in 157 patients

S. Pernerstorfer, M. Kitzwögerer, C. Holzinger, P. Bergmann

Klinisches Institut für Pathologie, Universitätsklinikum St. Pölten, St. Pölten, Austria
Klinische Abteilung für Herzchirurgie, Universitätsklinikum St. Pölten, St. Pölten, Austria

Background: Cystic medial necrosis (CMN) is one of the major histopathological changes of the thoracic aorta that has been seen in dissections. The aim of our study was 1.) To evaluate the incidence of CMN and other histopathological changes in patients operated on for acute type A aortic dissection and 2.) To correlate these histopathological findings with the surgical outcome of these patients.

Method: Histologic analysis and pathology reports were evaluated in 157 patients who underwent surgery for acute Type A aortic dissection between January 2006 and December 2015. Thirty – day mortality of pts with histological evidence of cystic medial necrosis (Group I) was compared to pts with atherosclerotic changes of the aortic wall (Group II), to pts with signs of atherosclerosis + cystic media necrosis (Group III), to pts without signs of inflammation or degeneration (Group IV) and to pts with heterogeneous, widely spread histopathological findings (Group V).

Results: Eighty – five pts (54.1%) were diagnosed as having CMN, Group II showed 26 pts with atherosclerotic changes (16.6%), Group III 13 pts with combined histopathological findings (8.3%) Group IV 17 pts (10.8%) and Group V 16 pts (10.2%). Thirty – day mortality was 14.1% in the CMN Group I and 5.9% in Group IV. Highest mortality was seen in pts with atherosclerotic changes of the aortic wall (34.6%).

Conclusions: In more than half of all our pts operated on for acute Type A aortic dissection, CMN was found in the histological samples (Group I and Group III). Postoperative outcome of these pts is inferior to those without any histopathological findings in their dissected aorta. However, until now there is no serious way to predict CMN preoperatively. Future studies, concerning early CMN detection, could crucially influence the decision of surgical point of intervention.

C-2

Hemodynamic and clinical outcome of surgical aortic valve replacement for aortic stenosis in small aortic roots

D. Santer, G. Weiss. S. Oliva, L. Niederbichler, Z. Arnold, H. Pisarik, M. Mach, F. Nagel, S. Folkmann, M. Harrer, M. Grabenwöger, R. Moidl

Heart Team Vienna
Karl Landsteiner Gesellschaft for Cardiosurgical Research, c/o Department of Cardiovascular Surgery, Hospital Hietzing, Vienna, Austria
Department of Cardiovascular Surgery, Hospital Hietzing, Vienna, Austria
LBC f. kardiovaskuläre Forschung, Bes. Einrichtung für biomedizinische Forschung, Vienna, Austria

Background: The aim of the present study was to analyze hemodynamic and clinical outcome of surgical aortic valve replacement (AVR) of various 19 and 21 mm size stented aortic valve prosthesis.

Methods: We report a series of 572 consecutive patients with small aortic roots (mean age 75±9 years, logistic predicted mortality LPM=10.8+/–9.3%; 1.3–78.5) undergoing AVR for aortic stenosis from 2005 to 2012. Patients received different types of porcine and bovine tissue valves. Size 19 mm and 21 mm valve prostheses were used in 171 (30%) and 401 (70%) respectively. Implanted prostheses included Medtronic Mosaic (M, $n=47$ (8%)), St. Jude Epic (E, $n=42$ (7%)), Sorin Mitroflow (MF, 149 (26%)), Carpentier-Edwards Magna Ease (ME, $n=119$ (21%)), Carpentier-Ewards Perimount Magna (PM, $n=98$ (17%)), St. Jude Trifecta (TF, $n=90$ (16%)) and Carpentier-Edwards Perimount (P, $n=27$ (5%)) valve. Concomitant procedures such as coronary artery bypass grafting (CABG) or other valve procedures were done in 47.2% of all patients. Moderate patient prosthesis mismatch (PPM) was calculated and defined as mismatch with EOAI ≤ 0.85 cm²/m², severe mismatch with EOAI ≤ 0.65 cm²/m².

Results: Moderate and severe PPM were observed in 39% and in 15% of all patients, respectively (M: 55 vs. 43%, E: 74 vs. 0%, MF: 49 vs. 44%, ME: 16 vs. 0%, M: 41 vs. 0%, TF 21 vs. 0%, P: 41 vs. 0%). Porcine valves (M and E) revealed a significantly higher incidence of PPM than bovine valves (48 vs. 87%, $p<0.001$). In the bovine group severe mismatch was observed significantly more frequently in patients with the MF-prosthesis (44%) than in any other bovine valve. ($p<0.001$) Five year follow-up data was available in 340 (51.2%) patients. Overall five-year survival was 31.5%. Of note, during follow-up mortality was significantly elevated in the porcine group vs. the bovine group (46 vs. 21%; $p<0.001$). In the prostheses sub-analysis five year mortality was significantly higher with the MF (50%) prosthesis than in any other bovine tissue valve ($p<0.05$). There were no significant differences in survival rates between 19 mm and 21 mm valves after 5-years of observation.

Conclusions: The Carpentier-Edwards as well as the St. Jude Medical Trifecta valves showed the lowest incidence of PPM. While 30 days mortality was still comparable in all valve types, 5 year mortality was significantly reduced in bovine valves when compared to porcine valves.

C-3

How atrioventricular regurgitation affects the outcome and survival of your TAVI patient Data from the VIenna CardioThOracic Aortic Valve RegistrY (VICTORY)

M. Mach, E. Polat, M. Koschutnik, D. Santer, H. Pisarik, G. Weiss, M. Harrer, S. Folkmann, A. Strouhal, C. Adlbrecht, F. Veit, G. Delle Karth, M. Grabenwöger

I. Chirurgie, Abteilung für Herz- und Gefäßchirurgie, Krankenhaus Hietzing, Vienna, Austria

Background: Currently there is limited data on the change of AV-Regurgitation after TAVI, thus the aim of this study was to investigate its importance as a risk factor for adverse clinical outcomes and mortality in patients selected for either transapical (TA) or transfemoral (TF) TAVI.

Methods: TR and MR changes were assessed in 279 patients before and after TAVI (disacharge and annually therafter) by comparing TEE and assessed by visual inspection and color-flow Doppler. The patients qualified as TA-TAVI candidates as they had severe symptomatic aortic stenosis and were at high or prohibitive surgical risk and prohibitive iliac access vessels.

Results: After the procedure, the number of patients suffering from MR was significantly reduced in both cohorts TF: 90.4% to 62.6% ($p<0.001$) TA: 87.6% to 53.4% ($p<0.001$). 48.2% with mod./severe MR had improved in the TF-cohort vs. 67.3% in the TA-cohort ($p=0.032$).

Even though TR improvement after TAVI was insignificant, patients with mod./severe TR tended to show more improvement when treated transapically (TA 26.4 % to 17.6 %, $p=0.056$ vs. TF 26.8 % to 18.9 %, $p=0.568$).

No significant differences were shown between groups concerning the post-procedural complications defined according the VARC-2 criteria and the 30-day mortality but longterm survival was significantly reduced in patients without improvement of concomitant TR (log rank $p=0.021$) and MR (log rank $p=0.033$). Patients with residual isolated mod/severe TR are associated with increased 1 year mortality (unadjusted HR; 2.80; 95 % CI; 0.91–4.46;) opposed to those with mod/severe TR and MR (undadjusted HR; 1.08; 95 %CI; 1.20–2.46).

Conclusions: Long term follow up showed a significant survival benefit in those patients with reduced TR and MR after TAVI. Therefore, concomitant MR and TR need to be obsereved closely after TAVI and treated accordingly if no improvement is seen during follow-up for optimal clinical benefit. These findings have to be confirmed in a larger multi-center study.

C-4

Langzeitergebnisse bei Aortenklappenstenose-Patienten folgend der Entscheidungsfindung des Universitären Heart-Teams Graz

O. Kraft, B. Zirngast, A. Vötsch, L. Holztrattner, A. Schmidt, O. Luha, W. Marte, A. Yates. M. Anelli Monti, O. Dapunt, H. Mächler

Universitäres Herzzentrum, Medizinische Universität Graz, Graz, Österreich

Grundlagen: 267 konsekutive Patienten (w: 162) wurden von Dezember 2010 bis Dezember 2012 dem universitären interdisziplinären Heart-Team Graz vorgestellt. Dessen Beschluss folgend wurden 66 Patienten mit AKE/AKE + CABG/andere OP), 141 mit TAVI, 60 konservativ/PCI ($n=46$) und 14 mittels Valvuloplastie versorgt. Die Datenauswertung erfolgte aus dem Steiermark-weiten Krankenhaus¬informations-System. Das Datum des letzten Patienten-Kontakts mit einer KAGES-Einrichtung wurde als Bestätigung des Überlebens gewählt, bestand länger als 1 a kein Eintrag, wurde telefonisch das Überleben ermittelt.

Ergebnisse: Als mittlere Beobachtungszeiträume fanden sich bei einem 98 FU% bei AKE/AKE-CABG: 40.5 Mo, bei TA-TAVI: 45,5 Mo, bei TAo-TAVI: 28,5 Mo, bei TF-TAVI: 28,5 Mo, konservativ/PCI/Valvuloplastie: 20,5 Mo. Bei AKE/AKE-CABG (79 (52–89) a) kam es in 1.3 % nie zu Re-Operationen aufgrund von Blutungen, bei TAVI (79 (68–87) a) fanden sich Zugangsblutungen in 4,5 % (Aneurysma spurium 8,9 %). Der ES II/logES war bei AKE 5,2/9,7, bei TAVI 5,5/9,5, bei konservativ/PCI/Valvuloplastie 7/13,2. Bei TF-TAVI war die Infektionsrate mit 2,7 % am geringsten. Die postoperative Delir-Rate lag am höchsten bei AKE (9,4 %), es kam in 3,1 % zu Insulten vs. 2,7 % bei TAVI. Die Rate an postoperativer Niereninsuffizienz war am höchsten in der TA-Gruppe (7,1 %) vs. 3,6 % bei TAVI. Die 30 d-/1 a- sowie Gesamtmortalität war in der AKE-Gruppe 3,1 %, 6,3 % und 12,5 %, bei TA-TAVI 0 %, 7,1 % und 7,1 %, bei TAo-TAVI 6,7 %, 20 % und 33,3 %, bei TF-TAVI 5,4 %, 12,5 % und 25,9 %, bei Valvuloplastie 57,1 %, in der konservativ/PCI-Gruppe 41,3 %. Der ES II/logES war in der operativen Gruppe 5.2 %/9.8 % und bei TAVI 5,5 %/10,4 %, bei konservativ/PCI/Valvuloplastie 7 % und 13,2 %.

Schlussfolgerungen: Die Bedeutung der interdisziplinären Entscheidungsfindung betreffend dem individuellen Patientenoutcome ist essentiell. Aufgrund des potentiell höheren Anteils an gebrechlichen Patienten in der TF-TAVI-Gruppe scheint dort das Überleben geringer zu sein. Limitierend ist der nicht evaluierte Anteil an post¬interventionellen pflegebedürftigen Patienten.

C-5

Less invasive LVAD implantation via bilateral thoracotomy is safe and reduces intraoperative blood product use: a propensity score analysis

J. Riebandt, P. Angleitner, D. Wiedemann, T. Schlöglhofer, K. Dimitrov, G. Laufer, D. Zimpfer

Herzchirurgie, Medizinische Universität Wien, Vienna, Austria

Background: Despite an increasing popularity and multiple postulated benefits, less invasive (LIS) left ventricular assist device (LVAD) implantation has not been compared to the standard sternotomy approach in a systematic fashion. We report the outcomes of a propensity score analysis designed to test the safety and efficacy of sternotomy sparing LVAD implantation compared to the standard sternotomy approach.

Methods: From September 2010 to August 2016, 162 consecutive patients underwent Heartware HVAD or St. Jude Heartmate III LVAD implantation with a standard sternotomy or LIS approach. To minimize confounding factors, outcomes were analyzed using proportional hazard Cox regression, with risk adjustment based on a LIS approach propensity score model computed from demographics, risk factors and operative covariates. A total of 75 patients were matched (HVAD 83% ($n=62$); LIS approach 43% ($n=32$); mean age 60 ± 12 yrs; 89% ($n=67$) male; 48% ($n=36$) ICMP; 37% ($n=28$) INTERMACS level I, 13% ($n=10$) INTERMACS level II, 23% ($n=17$) INTERMACS level III).

Results: Patient groups were comparable with regard to preoperative patient characteristics. Sternotomy sparing LVAD implantation was successful in all patients with no intraoperative conversions. 30-day and in-hospital mortality were 9% ($n=4$) and 16% ($n=7$) in the sternotomy group vs. 6% ($n=2$) and 12% ($n=4$) in the less invasive group ($p=0.63$ and 0.647, respectively) despite 37% Intermacs Level I patients. We observed a reduced need for intraoperative thrombocytes administration in the LIS group (median 0 (range 0–4)) as compared to the sternotomy group (median of 1 (range 0–3), ($p=0.025$)). Outcomes were comparable with regard to other intra- and postoperative variables as well as thromboembolic and bleeding complications.

Conclusions: Less invasive LVAD implantation is a feasible, safe and reduces intraoperative blood product use.

C-6

Low-dose intravenous thrombolytic therapy for pump thrombus formation in patients with HeartWare left ventricular assist device

K. Dimitrov, J. Riebandt, D. Wiedemann, P. Angleitner, R. Moayedifar, T. Schlöglhofer, P. Simon, C. Gross, M. Maw, G. Necid, H. Schima, G. Laufer, D. Zimpfer

Klinische Abteilung für Herzchirurgie, Medizinische Universität Wien, Vienna, Austria
Zentrum für medizinische Physik und biomedizinische Technik, Medizinische Universität Wien, Vienna, Austria

Background: Pump thrombus formation is a frequent challenge after left ventricular assist device (LVAD) implantation. Treatment options include thrombolytic therapy, augmentation of anticoagulation or antiplatelet therapy, pump exchange or urgent heart transplantation. We reviewed our institutional experience using recombinant tissue plasminogen activator (Alteplase) for thrombolytic therapy in patients with HeartWare LVAD pump thrombus formation.

Materials and Methods: Medical records of all patients that received HeartWare HVAD left ventricular assist device system (LVAS) were retrospectively analysed to identify those who received intravenous thrombolysis for pump thrombus formation. Patient characteristics and outcomes as well as dose of thrombolysis were collected. Thrombolytic therapy was our first line therapy for pump thrombus formation during the study period.

Results: From December 2006 to February 2017 44 incidences of pump thrombus formation were observed in 26 HeartWare HVAD® patients (mean age at implant 53.6 ± 12.4 (27–78) yrs., 88.5 male %). Median dose per thrombolytic cycle was 20 (20–20) mg Alteplase and median number of thrombolytic cycles per thrombus event was 2 (1–2). Thrombolytic therapy was successful in 77.3% of incidences, however more than one cycle of thrombolytic therapy was necessary in 50.0%. After failed lyses, 2.3% ($n=1$) underwent pump exchange and 6.8% ($n=3$) urgent heart transplantation. A fatal complication related to thrombolytic therapy was observed in 6.8% ($n=3$) cases. Fatal complications were, myocardial infarction with ventricular fibrillation (4.6%, $n=2$) and mesenteric embolism (2.3%, $n=1$). Non-fatal complications were observed in 40.9% and included surgical (2.3%) and non-surgical bleeding (34.1%).

Conclusions: Thrombolytic therapy using low-dose intravenous thrombolytic cycles is an effective treatment for pump thrombus formation in the HeartWare LVAS. Non-fatal complications are frequent but fatal complications are uncommon. Outcomes regarding safety concerns shall be evaluated in a greater patient population.

C-7

Midterm-results of valve sparing aortic root repair using a standardized step by step approach: a single center experience

C. Dinges, J. Steindl, M. Kirnbauer, A. Daburger, R. Seitelberger

Universitätsklinik für Herzchirurgie, Paracelsus Medizinische Privatuniversität, Salzburg, Austria
Universitätsklinik für Anästhesiologie, perioperative Medizin und allgemeine Intensivmedizin, Paracelsus Medizinische Privatuniversität, Salzburg, Austria
Universitätsklinik für Innere Medizin II, Paracelsus Medizinische Privatuniversität, Salzburg, Austria

Background: Valve sparing aortic root repair is the gold standard in young patients undergoing surgery for aortic valve insufficiency (AI) with/without aortic root dilatation. A modified remodeling procedure (CAVIAAR) was developed by Lansac et al. to address the reason for long-term failure of both remodeling and reimplantation technique. In 2012 our center started an aortic valve repair program based on the CAVIAAR technique.

Methods: From September 2012 to March 2017, forty-two patients underwent CAVIAAR procedure at our institution. Underlying pathology included aortic root aneurysm ($n=24$), acute aortic dissection ($n=7$) and isolated aortic valve insufficiency ($n=11$). Valve repair was done using the Schäfers-technique, including determination of the effective height. If indicated, root reconstruction and implantation of an extraaortic subannular ring were performed. Valve cuspidity included trisucpid ($n=23$), bicuspid ($n=15$) and unicuspid ($n=4$) valves. In some cases aortic arch replacement ($n=14$), mitral valve repair ($n=2$), CABG ($n=4$) and ASD-closure ($n=1$) were done as concomitant procedures.

Results: There was no perioperative death. Successful valve repair was obtained in 39 patients (92.8%). In three cases conversion to aortic valve replacement was done. In one patient mitral valve anuloplasty had to be performed due to mitral insufficiency after aortic valve repair. There was one major intraoperative complication resulting in myocardial infarction. Subsequently the patient died three months later from complication of further surgical treatment, leading to an overall late mortality of 2.3%. Median time on extracorporal circulation and median aortic crossclamp time was 228 (± 65) minutes and 157 (± 40) minutes respectively.

One patient developed severe aortic insufficiency on postoperative day 8, due to suture dehiscense and was successfully reoperated with no need of valve replacment. There was no case of perioperative pacemaker implantation.

Cumulative follow up was 708 months (1 to 48 months). Thirty-six of thirty-nine patients showed AI ≤ grade I (92.3 %). One patient developed AI grade II-III after 12 months and was subsequently reoperated for aortic valve replacement. In another case AI grade II was diagnosed at hospital discharge but there was no need for surgical revision.

Conclusions: The CAVIAAR technique leads to promising early and midterm postoperative results. Due to its standardized step by step approach for aortic valve repair, it offers a reproducible surgical outcome and is suitable for any kind of aortic valve cuspidity. However, long term results need to be gained for further evaluation of this technique.

C-8

Off-pump transapical mitral valve repair: First clinical experience with the NeoChord DS 1000 device

M. Harrer, A. Strouhal, G. Delle-Karth, M. Grabenwöger, R. Moidl

I. Chirurgie, Krankenhaus Hietzing, Vienna, Austria

Background: The standard technique for the treatment of severe mitral incompetence (MI) due to mitral leaflet prolapse is surgical repair with the use and potential side effects of the heart-lung machine (HLM). Older patients with comorbidities often were refused from surgery and have limited long-term survival. With the new NeoChord device, mitral valve prolapse repair through trans-apical approach is feasible without the need of HLM.

Method: We report our first experience in three patients (mean age 87 years) who underwent implantation of expanded neo-chordae (polytetrafluoroethylene ePTFE) with the NeoChord DS 1000 device. The left ventricular apex is accessed via standard triple purse string ventriculotomy through a left "TAVI" mini-thoracotomy. The device is inserted towards the mitral valve into the left atrium. Intra-cardiac orientation is achieved with both 2D and 3D echocardiographic guidance. With expandable jaws, the prolapse is captured and its effectiveness confirmed by observing the four fiber optic monitor lights changing from red (blood) to white (leaflet). Now the leaflet is penetrated with a needle with subsequent retrieval of the NeoChord ePTFE suture. After implantation of the necessary number of sutures, final assessment of the operative results is achieved using echocardiography. Now the properly tensioned NeoChords are secured to the LV apex with pledgets and knots.

Results: With the use of 3–4 ePTFE sutures per patient, we reduced MI severe to trivial in two patients intraoperatively. One patient with anterior prolapse was discharged with MI II but in significantly better conditions. One 89 year old lady with several events of right heart failure preoperatively (syst. PAP 87 mmHg) died 3 weeks after the procedure because of pneumonia.

Conclusions: NeoChord implantation without HLM via trans-apical approach is feasible and leads to significant reduction of MI in patients with mitral valve prolapse. Long term follow-up results has to be published. However, the first successful human applications have stable MI up to 3 years (Leipzig, Padua). Right heart failure is a challenging issue in the postoperative care.

C-9

Surgical AVR or TAVI in high-risk patients with impaired left ventricular ejection fraction

M.-E. Stelzmüller, B. Mora, G. Laufer, W. Wisser

Abteilung für Herzchirurgie, Medizinische Universität Wien, Vienna, Austria
Abteilung für Herz-Thorax Anästhesie und Intensivmedizin, Medizinische Universität Wien, Vienna, Austria

Background: Transcatheter aortic valve implantation (TAVI) is an established treatment for surgical inoperable and high risk patients. Criteria for TAVI are age >75 years and log Euroscore >20 or STS Score >10%. It still remains point of discussion which patient population clearly benefits from TAVI in terms of quality of life improvement and absence of multi morbidity, but not without only an extending of a non self-determined life.

This study compares surgical (SAVR) and TAVI patients presenting equal risk profile.

Method: Between March 2009 and February 2016 95 concomitant patients with reduced left ventricular ejection fraction (LVEF) <50%, age >75 years and log EuroScore >20% underwent either surgical aortic valve replacement (SAVR, $n=53$) or transapical TAVI ($n=42$). The mean age was 82 ± 4 years and 84 ± 4 years ($p=0.103$), mean log EuroScore was $32\%\pm16$ and $43\%\pm17$ ($p=0.223$) in the SAVR and TAVI group, respectively. The risk profile (PAVK, COPD, CAVK, etc.) was comparable in both groups.

Results: The 30 day mortality was 11% ($n=6$) and 9.8% ($n=4$) ($p=0.66$), postoperative pacemaker implantation rate 9.4% ($n=5$) and 4.7% ($n=2$) ($p=0.46$) in the SAVR and TAVI group, respectively. One patient in the TAVI group had a stroke. Two patients in the SVAR group presented bleeding and consecutive surgical revision was required. One patient of the SVAR group developed a mobile sternum.

Survival after 6 months was 81.1% and 73.8%, after 2 years 67.2% and 55.3% and after 5 years 53.8% and 20.8% ($p=0.018$) in the SAVR and TAVI group, respectively.

Aortic stenosis and concomitant moderate to severe mitral valve insufficiency and/or tricuspid valve insufficiency are limiting factors for midterm survival.

Conclusions: Decision making in high-risk patients with aortic valve stenosis and reduced left ventricular ejection fraction remains challenging, because life limiting comorbidity or frailty are not addressed by the common used risk scores. We found no differences in the early outcome, however in the midterm SVAR presented a significant higher survival rate.

C-10

Ten – Year Experience with 100 frozen elephant trunc procedures using the jotec evita open hybrid graft

Z. Arnold, D. Santer, H. Pisarik, M. Gorlitzer, M, Mach, M. Grabenwöger, G.I Weiss

LBC f. kardiovaskuläre Forschung, Bes. Einrichtung für biomedizinische Forschung, Vienna, Austria
Karl Landsteiner Gesellschaft for Cardiosurgical Research, c/o Department of Cardiovascular Surgery, Hospital Hietzing, Vienna, Austria
Department of Cardiovascular Surgery, Hospital Hietzing, Vienna, Austria

Background: The aim of the present study was to evaluate clinical outcome and need for re-intervention after frozen elephant trunc (FET) repair in aortic aneurysms (AA) and aortic dissections (AD).

Methods: Between August 2005 and February 2017 a total of 100 patients underwent a FET procedure for following indications: Type A AD (acute $n=29$, chronic $n=9$), Type B AD (acute $n=4$, chronic $n=9$) and AA (acute $n=4$, chronic $n=45$). Mean age was 60 ± 14 years, 57% were male gender. In all patients a Jotec Evita Open hybrid graft (Hechingen, Germany) was used.

Results: In-hospital mortality was 8%. Significant endoleak formation requiring endovascular re-intervention was observed in 11 patients (14%) (Type Ia $n=1$, Type Ib $n=8$, Type II $n=2$). Three patients underwent secondary planned thoracic endovascular aortic repair (TEVAR) due to an aneurysm, which

could not be completly excluded by the primary FET procedure. Eleven patients underwent a secondary conventional thoraco-abdominal (TAAA) repair after the primary FET procedure. Stroke and spinal cord injury occured in 5 and 2 patients, respectively. During a mean follow up period of 4639 months, three patients (3%) died of aortic related reasons (one aortic rupture, one aorto-bronchial fistule and one aortic-oesophageal fistule). Twelve patients (12%) died of non-aortic related reasons during the follow-up period. Permanent neurologic deficits occurred in 6 patients. The 1 year, 3 year and 5 year mortality was 7% (7/97), 18% (12/66) and 33% (16/49) respectively. The calculated median survival time is 131 (80–182) months, the mean survival time 102 (CI 6–90) months.

Conclusions: Our results confirm the feasibility of a simultaneous treatment of the ascending aorta, the aortic arch and the descending aorta by the FET technique to reduce the necessity for additional operations on the descending aorta and to improve long-term survival. However, if an additional intervention is required, the stent graft of the hybrid prosthesis offers an optimal landing zone for a secondary endovascular or even for conventional TAAA repair.

C-11

The new St Thomas' Hospital polarised vs. hyperkalaemic St. Thomas' cardioplegia: improved myocardial protection in pigs using cold blood cardioplegia

D. Santer, A. Kramer, A. Kiss, K. Aumayr, S. Hallström, F. Nagel, H. Fallouh, M. Hackl, S. Skalicky, D.J. Chambers, B.K. Podesser

LBC f. kardiovaskuläre Forschung, Bes. Einrichtung für biomedizinische Forschung, Vienna, Austria
Heart Team Vienna, Karl Landsteiner Gesellschaft for Cardiosurgical Research, c/o Department of Cardiovascular Surgery, Hospital Hietzing, Vienna, Austria
Department for Biomedical Research, Vienna, Austria
Clinical Institute for Pathology, Medical University Vienna, Vienna, Austria
Institute of Physiological Chemistry, Center for Physiological Medicine, Medical University Graz, Graz, Austria
Cardiac Surgical Research, The Rayne Institute (King's College London), St Thomas' Hospital, London, UK
TamiRNA, Vienna, Austria
Department of Cardiac Surgery, Landesklinikum St. Pölten, St. Pölten, Austria

Background: Increasingly, patients undergoing cardiac surgery are elderly and sicker, therefore, novel and more effective cardioprotective regimes are warranted. Maintaining cardiac arrest at a membrane potential closer to the resting potential (with 'polarising' cardioplegia) improved cardioprotection compared to the conventional high potassium based 'depolarising' cardioplegia in small animal (rodent) in crystalloid preparation. This study, in a large animal (pig) model of cardiopulmonary bypass (CPB), compared the cardioprotective efficacy of the new blood-based St Thomas' Hospital Polarising cardioplegia (STH-Pol): esmolol, adenosine, magnesium) to conventional (depolarising hyperkalaemic) blood-based St Thomas' Hospital cardioplegia (STH2).

Methods: Pigs (STH-Pol: 52 ± 4 kg vs. STH2: 62 ± 4 kg; NS) were aneasthetised and monitored for baseline hemodynamic function. After sternotomy, CPB and aortic cross-clamping, hearts were arrested via antegrade cold (4 °C) STH-Pol ($n=7$) vs STH2 ($n=6$) cardioplegia for 60 min of ischemia followed by 60 min of on-pump reperfusion. After weaning from CPB, hearts were monitored for 90 min reperfusion off-pump before sacrificed; tissue samples were taken to determine high-energy phosphates levels.

Results: STH-Pol hearts showed improved systolic arterial pressure (113 ± 12 vs 68 ± 15 mmHg; $p<0.05$), left ventricular systolic pressure (96 ± 5 vs 73 ± 5 mmHg; $p<0.01$) and stroke work (18 ± 2 vs 8 ± 3 ml/mmHg; $p<0.05$) in comparison to STH2 hearts. Coronary creatine kinase (CK-MB) release (334 ± 36 vs 467 ± 37 U/L; $p<0.05$) as well as wedge pressure (10 ± 1 vs 15 ± 1 mmHg; $p<0.05$) were lower in STH-Pol hearts during reperfusion. High-energy phosphate levels were comparable in both groups.

Conclusions: Polarised cardiac arrest improves systolic cardiac functional recovery and reduces ischemic damage in a model of CPB in pig hearts. These favourable results indicate possible clinical relevance for this novel blood based polarised cardioplegia.

C-12

Toll-Like receptor 3 mediates radiation induced calcific aortic valve disease

M. Graber, L. Pölzl, D. Lobenwein, V. Sladky, J. Hirsch, E. Kirchmair, E. Demetz, A. Wegmayr, D. Lener, A. Villunger, M. Grimm, J. Holfeld, C. Tepeköylü

Universitätsklinik für Herzchirurgie, Medizinische Universität Innsbruck, Innsbruck, Austria
Universitätsklinik für Radioonkologie, Medizinische Universität Innsbruck, Innsbruck, Austria

Background: Thoracic radiation for the treatment of thoracic malignancies is associated with the development of calcific aortic valve disease (CAVD) including all its comorbidities. It remains unknown how radiation leads to calcification of the aortic valve. Toll-like receptor 3 (TLR3) is part of the innate immune system, which is involved in the recognition of nucleic acids. It has been shown recently that TLR3 activation by released RNA is responsible for radiation-induced gastrointestinal syndrome. We hypothesized that TLR3 activation after radiation mediates the onset of CAVD.

Methods: Valvular interstitial cells (VICs) were isolated from aortic valves of healthy donors undergoing heart transplantation and treated with radiation therapy (10Gy). Expression levels of TLR3, inflammatory cytokines and osteoblastic markers were compared with cells treated either with TLR3 agonist poly (I:C) or a TLR3/dsRNA complex inhibitor. Osteoblastic activity was assessed via alkaline phosphatase assay and Alizarin Red staining. Cell cycle analysis via flow cytometry was performed after radiation. Aortic valve morphology and function of aged wild-type (WT) and TLR3-/- mice were analyzed via transthoracic echocardiography, microCT and histological evaluation after radiation (15Gy).

Results: Radiation of VICs resulted in significantly increased gene expression of TLR3, TNF-a, IL-6, IFN-y, IL-10, Runx2 and BMP2 and significantly enhanced osteoblastic activity of treated cells. TLR3 inhibition resulted in prevention of osteoblastic activity in radiated VICs. Aortic valves of radiated mice showed increased expression of TLR3 and osteoblastic markers. However, there was no osteoblastic activity after radiation in TLR3-/-. WT mice showed first signs of CAVD in transthoracic

echocardiographies and morphologic analysis. However, these changes were missing in TLR3-/- mice.

Conclusions: Radiation leads to activation of TLR3 with concomitant initiation of calcification. Inhibition of TLR3 prevents from calcific activity after radiation. TLR3-/- mice show no signs of CAVD after radiation. We show major involvement of TLR3 in the pathogenesis of CAVD after radiation. TLR3 could therefore become an effective therapeutic target for the prevention of CAVD after radiation.

C-13

Vergleich des 30-Tage-Outcomes basierend auf EuroScore-Evaluierung bei Aortenklappenstenose-Patienten der Entscheidungsfindung des Universitären Heart-Teams Graz folgend

L. Holztrattner, B. Zirngast, A. Vötsch, O. Kraft, W. Marte, A. Schmidt, O. Luha, P. Oberwalder, I. Knez, O. Dapunt, H. Mächler

Universitäres Herzzentrum, Medizinische Universität Graz, Graz, Österreich

Grundlagen: 619 konsekutive, potentielle TAVI-Patienten (w: 346, mittleres Alter 80 (52–96) a) mit symptomatischer Aortenklappenstenose wurden von kardiologischen Abteilungen zwischen 2011 und 2014 dem universitären interdisziplinären Heart-Team Graz vorgestellt. Retrospektiv wurden Kollektive A (niederes Risiko, ES II <4), B (intermediäres Risiko, ES II 4–8) und C (hohes Risiko, ES >8) betreffend des 30-d-Outcomes verglichen.

Ergebnisse: In der TAVI- vs. AKE-Gruppe fanden sich bei 100 % FU im Kollektiv A 188 Patienten (mittleres Alter 88 (55–93) a, w 52 %) vs. 87 Patienten (mittleres Alter 77 (60–87) a, w 52 %), im Kollektiv B 106 Patienten (mittleres Alter 82 (59–94) a, w 66 %) vs. 37 Patienten (mittleres Alter 78 (57–93) a, w 68 %), im Kollektiv C 61 Patienten (mittleres Alter 82 (69–93) a, w 59 %) vs. 19 Patienten (mittleres Alter 80 (73–88) a, w 84 %). TF-TAVIs überwogen in jedem Kollektiv mit respektive 74 %, 81 % und 87 % gegen 76 Patienten in der TA- und TAo-TAVI-Gruppe. Die 30-d-Mortalität lag bei TAVI im Kollektiv A bei 5,3 % mit einem mittleren ES von 2,6 % (logES 4,9 %) vs. 4,7 % mit mittleren ES 5,5 % (logES 10,5 %) im Kollektiv B vs. 8,2 % mit mittleren ES II 12,6 % (logES 23,8 %) im Kollektiv C. In der AKE-Gruppe respektive bei (A) 3,5 % mit einem mittleren ES 2,3 % (log ES 4,4 %) vs. (B) 5,4 % mit mittleren ES 5,5 % (log ES 10,4 %) vs. (C) 5,3 % mit mittleren ES 11 % (log ES 20,7 %). Die Insult-Rate lag in der TAVI-Gruppe bei 9 von 355 Patienten, in der AKE-Gruppe bei 2 von 143 Patienten. Einer PPM-Implantation bedurften (A) 16,5 %, (B) 5 %, (C) 19,7 % in der TAVI-Gruppe vs. respektive (A) 3,5 %, (B) 10,8 %, (C) 10,5 % in der AKE-Gruppe. Einen substitutionsbedürftigen Hb-Abfall erlitten mehr Patienten (8,2 %) in der TAVI-Gruppe mit ES >8 %. TAVI plus PCI wurde in (A) 13,3 %, (B) 17,9 %, (C) 27,9 % durchgeführt, Simultan-CABG in der AKE-Kohorte in (A) 23 %, (B) 54 % und (C) 58 % der Fälle.

Schlussfolgerungen: Die 30-d-Mortalitäten waren in den TAVI-Kollektiven A mit niedrigem und B mit intermediärem Risiko vergleichbar, in der Kohorte C mit hohem ES >8 verdoppelt. In der AKE-Gruppe waren die Mortalitäten in den jeweiligen Kohorten mit 3,5 vs. 5,4 vs. 5,3 % vergleichbar. Als limitierend ist die geringe Anzahl der AKE-Patienten mit dem hohen ES (n=19) und die fehlende Evaluation von prä- und postinterventioneller/-operativer Frailty, welche in der TAVI-Gruppe höher war, zu werten.

C-14

Video case presentation: Complex biatrial reconstruction after extensive tumor resection

C. Dinges, J. Steindl, R. Seitelberger

Universitätsklinik für Herzchirurgie, Paracelsus Medizinische Privatuniversität, Salzburg, Austria

Background: We present the case of a 79-year-old male patient who was admitted to hospital due to sudden severe weakness while swimming. Echocardiography revealed a 10×6×5 cm solid mass, mainly situated in the right atrium with ingrowth into the left atrium and uncertain involvement of the valvular apparatus. Subsequent CT scan showed spreading of the tumor into the inferior vena cava. Due to these findings and the presence of severe symptoms, indication for surgical tumor resection was made.

Methods: Median sternotomy was chosen as surgical approach. There was no sign of intrapericardial tumor growth. In regard of infestation of the inferior vena cava, venous cannulation for extracorporal circulation was done via femoral vein and superior vena cava. The aorta was used for arterial cannulation. Beating-heart-atriotomy was conducted for exploration of the right atrial cavity. Since the intraatrial septum was massively affected by tumor ingrowth, aorta was clamped and cardioplegia was administered in order to start tumor resection. Substantial parts of both, the right and the left atrium as well as the complete intraatrial septum were removed. There was no sign of valvular involvement. Subsequently, reconstruction of the septum and the resected atrial areas was successfully performed using bovine pericardium.

Results: The tumor could be resected in whole. There was no need for valve replacement. Due to postoperative sinusarrest, pacemaker implantation was performed. Since large areas of both atria were replaced by non-contractile bovine pericardium, oral anticoagulation was begun postoperatively. Echocardiography showed good ventricular function and no valvular insufficiency.

After an uneventful postoperative course the patient was transferred from the intensive care unit to our ward on postoperative day 5 and discharged from hospital on postoperative day 12 in good general condition. Histologic examination of the tumor revealed diagnosis of a hemangioma. No further medical therapy was needed.

Conclusions: Biatrial reconstruction using bovine pericardium provided an excellent outcome after extensive tumor resection.