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Characteristic distinction of energy-dependent hemodynamics in physiological and pathological left ventricular hypertrophy is related to different myocardial expression of mithocondrial regulators

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Topic(s):
Sports cardiology

Citation:
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Background and purpose: Left ventricular (LV) hypertrophy is a physiological (athlete's heart) or pathological response of LV myocardium to increased cardiac load. To date, a direct comparison of functional consequences of PhyH and PaH and possible underpinning mechanisms is missing. We aimed at comparing hemodynamic alterations in well established rat models of physiological (PhyH) and pathological hypertrophy (PaH) by using LV pressure-volume analysis and investigating underlying molecular mechanisms (oxidative stress, inflammatory markers, mitochondrial regulators).

Methods: PhyH and PaH were induced in rats by swim training and by abdominal aortic banding, respectively. Morphology of the heart was investigated by echocardiography. Detailed characterization of cardiac function was completed by LV pressure-volume analysis. In addition histological and molecular biological (gene expression analysis) measurements were performed. All data were normalized to the corresponding

control group.

Results: Echocardiography revealed myocardial hypertrophy of similar degree in both models (LV mass index: +21.7±2.1% PhyH vs. +27.3±3.3% PaH, n.s.), which was confirmed by post-mortem heart weight data. In aortic-banded rats we detected subendocardial fibrosis. Reactivation of fetal gene program could be observed only in PaH model. PhyH was associated with increased stroke volume, whereas unaltered stroke volume were detected in PaH along with markedly elevated end-systolic pressure values. Sensitive indices of LV contractility were increased in both models, in parallel with the degree of hypertrophy. Active relaxation was ameliorated in athlete's heart, while it showed marked impairment in PaH (time constant of LV pressure decay (τ): -7.7±2.6% PhyH vs. +37.0±11.1% PaH, $p<0.01$). Mechanical efficiency and ventriculo-arterial coupling were improved in PhyH, whereas remained unchanged in PaH (mechanical efficiency: +20.8±4.7% PhyH vs. +4.7±4.9% PaH, $p<0.05$). Myocardial gene expression of regulators related to mitochondrial biogenesis showed marked differences between PaH and PhyH (peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α): +19.1±10.3% PhyH vs. -37.8±7.2% PaH, $p<0.01$; nuclear respiratory factor 1 (NRF1): -4.5±2.8% PhyH vs. -27.4±7.6% PaH, $p<0.05$). Alterations in myocardial expression of oxidative stress and inflammatory markers did not differ between the two models.

Conclusions: We provided the first comparative hemodynamic characterization of PhyH and compensated PaH in relevant rodent models. Increased LV contractility could be observed in both types of LV hypertrophy, characteristic distinction was detected in energy-dependent diastolic function (active relaxation) and mechanoenergetics (mechanical efficiency), which might be explained by differences in expression of key regulators related to mitochondrial biogenesis.

Complex assessment of vulnerability markers associated with neoatherosclerotic plaques in patients with in-stent restenosis using cardiac CT, OCT and VH-IVUS

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Topic(s):
Multimodality / hybrid imaging, other imaging

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Introduction: In-stent restenosis (ISR) is traditionally associated with neointimal hyperplasia. However, the term of "neoatherosclerosis" has been recently introduced to characterize the development of new atheromatous process within the implanted stent. The extent in which this neoatherosclerosis is an unstable condition is not known in present, therefore in this study we aimed to assess the correlations between Cardiac Computed Tomographic Angiography (CCTA) markers associated with unstable plaques, such as a very low CT density of the restenotic tissue, and Optical Coherence Tomography (OCT) or Intravascular ultrasound (IVUS) markers of vulnerability in patients with ISR.

Material and methods: We included 28 patients with 36 coronary bare metal stents, having at least one symptomatic ISR as defined by >50% stenosis inside the implanted stent identified by both CCTA and coronary angiography, 6 months to 1 year after stent implantation. In total, 30 ISR lesions were screened and analyzed, including qualitative and quantitative analysis of the restenotic tissue by CCTA, OCT and virtual histology IVUS (VH-IVUS). Patients were divided in: group 1 - 21 cases in whom CCTA qualitative analysis identified the presence of dark spots representing areas with very low plaque density inside the restenotic tissue, and group 2 - 9 cases without dark spots inside the restenotic tissue.

Results: OCT analysis identified a significantly lower thickness of the fibrous cap in gr. 1 (35.5 μm vs 94.5 μm, $p<0.0001$). By OCT, restenotic tissue presented a heterogenous aspect in 80,95% of cases in gr.1 vs 22.22% of cases in gr.2, ($p=0.004$), an irregular shape in 76.19% vs 33.33% of cases ($p=0.04$), and a multilayered appearance in 85.71 vs 44.44% ($p=0.03$) of patients. The presence of microvessels was recorded in 80.95% vs 22.22%, $p=0.004$. Rupture of the neointima was significantly associated with a lower density plaque (76.19% in gr 1 vs 11,11% in gr 2, p=001). VH-IVUS plaque quantification identified a significantly larger necrotic core in patients with low density neoatheroma (44.5% vs 21.2%, $p<0.0001$). Multivariate analysis identified the presence of a low density plaque by CCTA (OR 3.2) and a>40% necrotic core (OR=2.4) as the most powerful predictors for plaque rupture.

Conclusions: An area with very low CT density within the restenotic tissue, visualized as a dark spot, is associated with a significantly lower thickness of the fibrous cap and with a higher risk for plaque rupture, thus representing a new potential marker for noninvasive assessment of plaque vulnerability in patients with ISR.

Intelligent cardiac CT registry: the feasibility of a structured reporting and automated registry generation in the daily routine

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Topic(s):
Big data analysis in cardiology, registries and databases

Citation:
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Background: Routine cardiac CT reporting and research data collection require detailed data acquisition and robust data management.

Purpose: We sought to test the feasibility of automated registry generation regarding patients' history, indications, image acquisition parameters and clinical findings in a cardiac CT program of a single center.

Methods: The intelligent cardiac CT registry (iCCTR) is a database generated by an in-house developed structured reporting tool that automatically stores all relevant data points, such as anamnestic data, indications, premedication, CT acquisition parameters, segment based coronary evaluation and clinical recommendation. In addition, the platform automatically calculates the pretest probability of obstructive coronary artery disease (CAD) using the Diamond-Forrester criterion and generates clinical report.

Results: In total 2866 consecutive patients (age 59.5±11.9 years, 41.3% females) were included in the iCCTR between August 2014 and September 2015. All examinations were performed with a 256-slice multi-detector row CT scanner. Suspected CAD was the main indication (60.1%) followed by left atrial angiography (20.3%). Based on the automated pretest probability estimation in patients with suspected CAD 3.4% had high, 90.0% had intermediate, 5.9% had low and 1.7% had very low probability of obstructive CAD. Average effective radiation dose of the cardiac CT was 4.0±1.4 mSv. For premedication 68.3% of the patients received metoprolol, 4.1% ivabradin and 98.5% nitroglycerin. Invasive coronary angiography was recommended in 14.3% and secondary prevention (statin and/or aspirin therapy) in 47% of the cases.

Conclusions: The majority of the patients had an intermediate pretest probability of obstructive CAD and the main indication for cardiac CT was to rule out severe coronary artery stenosis. Invasive coronary angiography was avoidable in the majority of patients. Structured cardiac CT reporting and automated registry generation is feasible using a dedicated software tool in the daily routine and it provides valuable data for quality assurance and scientific research.

Learning curve of the transradial approach of percutaneous carotid intervention

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Topic(s):
Carotid disease

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Purpose: Recently transradial (TR) approach became a safe and effective alternative of percutaneous carotid intervention. We report the learning curve over 6 years in two high-volume interventional centers during the transition from transfemoral (TF) to transradial approach.

Patients and methods: Between 2010 and 2015, 1773 patients underwent carotid intervention in our centers. Clinical characteristics, radiation doses, volume of contrast material, screening and procedure times of consecutive patients were recorded prospectively in a register and restrospectively analysed.

Results: Transradial approach was applied in 494 patients, mean age was 68±8 years, 67% of them was male. The ratio of TR has grown from 3 to 7, 25, 43, 48 and 60% of the carotid interventions, during the years respectively. While the duration of the procedure (26, 30, 25, 25, 22.5, 25 min), the fluoroscopy time (11, 11, 10, 8, 8, 9 min), and the applied contrast material (128, 142, 95, 69, 90, 75 ml) has significantly decreased in the first 4 years, then an elevation is observed, as more complicated cases were enrolled. Significant improvement was observed after the first 50 cases, in each parameter. Conversion to TF was needed in 7.5% and did not change significantly. No difference was observed in the incidence of minor or major vascular events and hospitalization days, over the years.

Conclusion: An initial learning curve was observed in the intervention parameters of transradial carotid stenting. The transition from TF to TR approach is achievable in 50 cases in experienced centers.

Electrical reverse remodeling following pressure unloading in a rat model of left ventricular hypertrophy

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Topic(s):
Ion channels and electrophysiology

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Introduction: Left ventricular hypertrophy (LVH) is the pathological response reaction of the heart to sustained pressure overload (hypertension, aortic stenosis) and it represents a major risk factor for the manifestation of malignant ventricular tachyarrhythmias and sudden cardiac death. On the other hand, pressure unloading often leads to myocardial reverse remodeling (reduction of increased left ventricular mass, attenuated myocardial fibrosis) which was previously reported to decrease LVH associated proarrhythmic vulnerability as well. However, the responsible mechanisms for the recovery of the adverse electrophysiological changes in LVH during reverse remodeling are still poorly explored.

Purpose: Therefore, we aimed at providing an electrocardiographic characterization of a rat model of LVH undergoing pressure unloading and in parallel indentify the underlying cellular and functional alterations.

Methods: Pressure overload was induced in rats by abdominal aortic banding for 6 or 12 weeks (AB 12th week), while sham operated animals served as controls. Pressure unloading was evoked by removing the aortic constriction after the 6th experimental week (debanded 12th week) to investigate the consequences of reverse remodeling. Serial echocardiography and electrocardiography were performed in order to investigate the development and the regression of LVH. Protein expression levels were detected by western blot technique. Myocardial fibrosis was assessed by Picrosirius red staining.

Results: Pressure unloading resulted in significant reduction of the prolonged QT interval (corrected QT interval: 69.9±2.0 vs. 91.5±1.6ms

debanded 12th week vs. AB 12th week, p<0.05), in correlation with the regression of LVH (left ventricular mass: 1.64±0.10 vs. 2.48±0.14mg debanded 12th week vs. AB 12th week, p<0.05), and in association with restored Kv4.3 and SERCA2 expression. Furthermore, pressure unloading prevented the functional decompensation of LVH (ejection fraction: 64±1 vs. 45±4% debanded 12th week vs. AB 12th week, p<0.05) and simultaneously preserved adequate atrioventricular conduction (PQ interval: 48.1±1.4 vs. 54.0±2.5ms debanded 12th week vs. AB 12th week, p<0.05). Finally, pressure unloading effectively preceded the broadening of the QRS complex (QRS complex: 22.2±0.6 vs. 26.0±0.9ms debanded 12th week vs. AB 12th week, p<0.05) in parallel with attenuated interstitial collagen accumulation (Picrosirius score: 1.163±0.08 vs. 1.60±0.12 debanded 12th week vs. AB 12th week, p<0.05).

Conclusion: Regression of LVH with restored expression of Kv4.3 and SERCA2, maintained cardiac function and decreased myocardial fibrosis contribute to pressure unloading induced electrical reverse remodeling.

Characteristic changes of systolic and diastolic function in rat models of type 1 versus type 2 diabetes mellitus assessed by speckle-tracking echocardiography

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Topic(s):
Echo-ventricular function and myocardial diseases

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Left ventricular (LV) dysfunction is a frequent consequence of diabetes mellitus (DM) even in the absence of coronary artery disease. Comparison of animal models of type 1 and type 2 DM may contribute to a deeper pathophysiologic understanding of diabetic cardiomyopathy. Gold standard LV pressure-volume (PV) analysis provides a detailed hemodynamic characterization, however, the non-invasive speckle-tracking

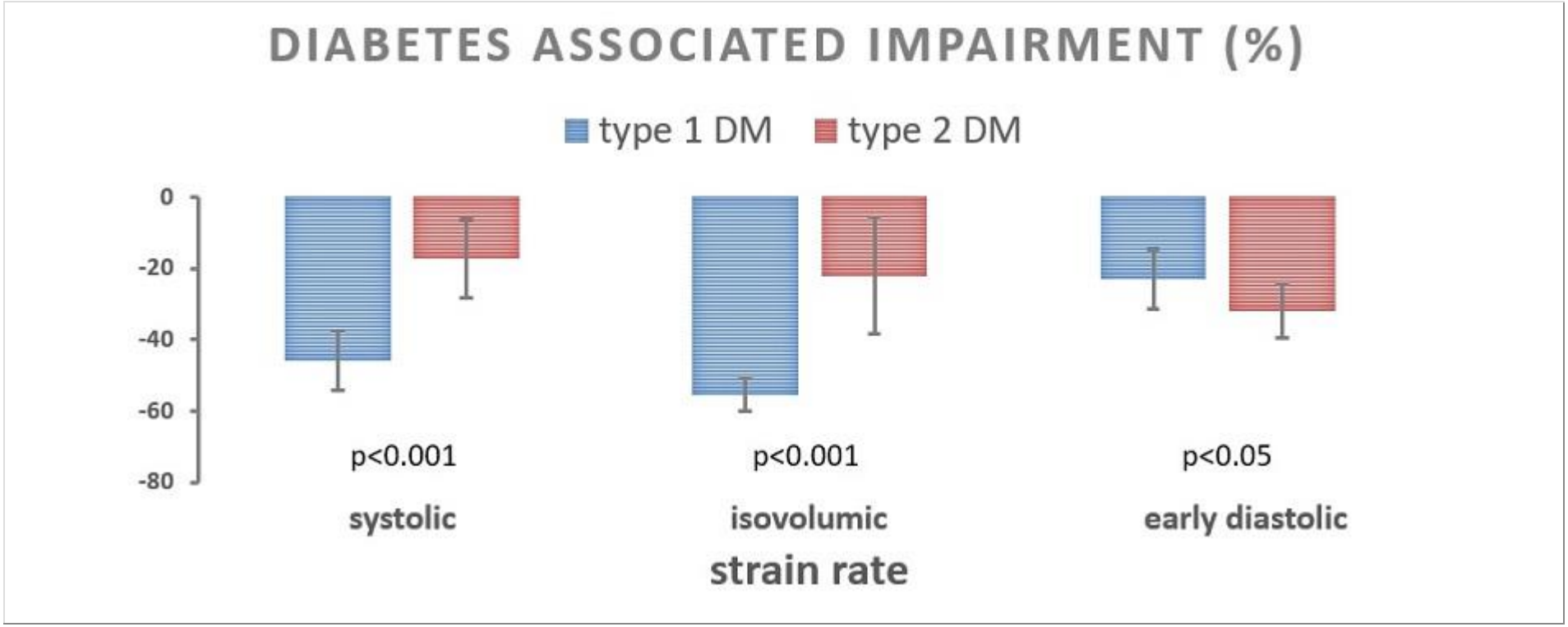
echocardiography (STE) may be a powerful method to assess the deterioration of systolic and diastolic function.

Therefore, we aimed to comparatively investigate diabetic cardiomyopathy by PV analysis and STE in rat models of type 1 and type 2 DM.

Rat models of type 1 (8 weeks after DM induction in Sprague-Dawley rats by streptozotocin, n=8) and type 2 DM (inbred Zucker Diabetic Fatty rats at the age of 32 weeks, n=7) and corresponding control animals (n=5 and n=8, respectively) were compared. Echocardiography was performed using a 13MHz linear transducer to obtain LV short-axis recordings for STE analysis (EchoPAC). Beyond global circumferential strain (GCS), peak strain rate values in systole (SrS), isovolumic relaxation (SrIVR) and early diastole (SrE) were measured. LV PV analysis was performed to calculate load-independent contractility indices (i.e. preload-recruitable stroke work [PRSW]), time constant of LV pressure decay (tau), and diastolic stiffness parameters (i.e. slope of end-diastolic PV relationship [EDPVR]).

In type 1 DM, contractility and active relaxation were deteriorated to a greater extent compared to type 2 (relative impairment type 1 vs. type 2 DM; PRSW 46±13 vs. 21±14%; tau: 64±20 vs. 10±7%, both $p<0.01$). In contrast, diastolic stiffness impaired more significantly in type 2 DM (EDPVR: 22±11 vs. 46±17%, $p<0.01$). Correspondingly, STE described more severe systolic dysfunction in type 1 (type 1 DM vs. control; GCS: -13.1±1.8 vs. -16.9±1.3%, SrS: -2.48±0.37 vs. -4.58±0.18 1/s, both $p<0.01$) compared to type 2 DM (type 2 DM vs. control; GCS: -14.2±1.8 vs. -16.0±2.1%, NS; SrS: -2.68±0.35 vs. -3.23±0.57 1/s, $p<0.05$; relative impairment type 1 vs. type 2 DM, SrS: 46±8 vs. 17±11%, $p<0.001$). Among diastolic STE parameters, SrIVR was more decreased in type 1 (relative impairment type 1 vs. type 2 DM; 55±5 vs. 22±16%), however, SrE referring to diastolic stiffness was more reduced in the type 2 DM model (23±8 vs. 32±7%, both $p<0.05$). In type 1 DM rats, SrS correlated robustly with PRSW ($r=-0.924$, $p<0.001$), SrIVR with tau ($r=-0.729$, $p<0.05$), while in type 2 DM rats SrE was closely related to EDPVR ($r=-0.722$, $p<0.01$).

Diabetic cardiomyopathy is characterized by overt systolic dysfunction and impaired active relaxation in type 1 DM, while increased diastolic stiffness is the leading abnormality in type 2 DM. STE corresponds to PV analysis by unveiling key differences between LV dysfunction caused by type 1 and type 2 DM.



Shift in relative contribution of longitudinal and radial motion to global right ventricular function in heart transplant patients

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Topic(s):

Medical aspects of transplantation

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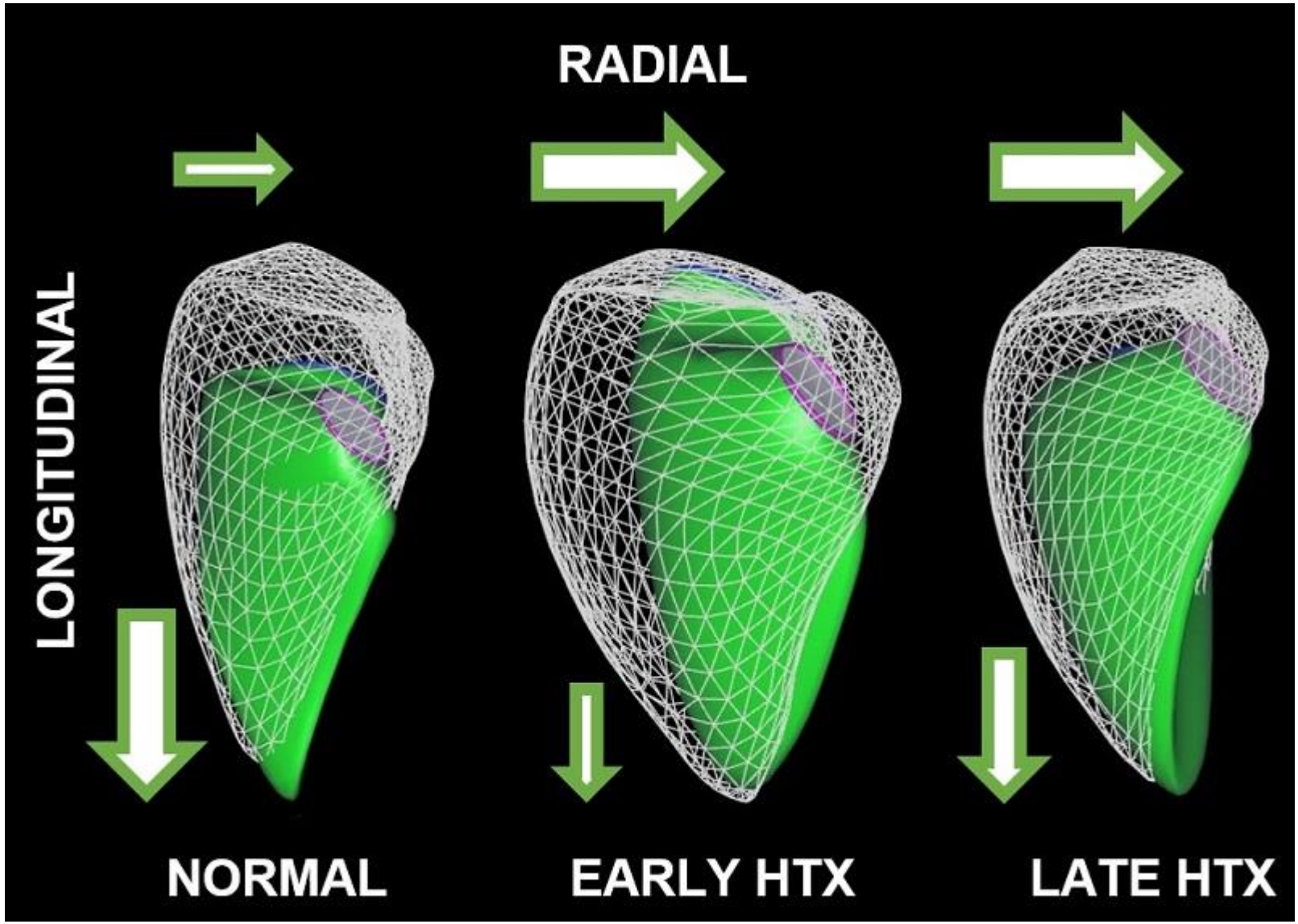
Longitudinal shortening is considered to be the most important motion determining right ventricular (RV) function. However, the radial direction ("bellows" effect) can gain particular importance in certain conditions.

Our aim was to quantify the longitudinal and the radial components of RV performance using three-dimensional (3D) echocardiography in patients after heart transplantation (HTX) and assess their relative contribution to RV function in time.

Fifty-one ambulatory HTX patients (median of 226 days after HTX) and 35 age- and gender matched healthy volunteers were enrolled. Fifteen HTX patients also completed one-year follow up. Beyond conventional echocardiographic protocol, full volume datasets were acquired using multi-beat reconstruction from 4 or 6 cardiac cycles. Using dedicated software for RV 3D and speckle-tracking analysis (4D RV-Function 2), 3D beutel model was created and exported volume-by-volume throughout the cardiac cycle. Beside end-diastolic volume (EDV) and total ejection fraction (TEF), we quantified longitudinal (LEF) and radial ejection fraction (REF) by decomposing the motion of each vertex of the reconstructed 3D beutel model along three orthogonal axes and omitting the other two directions.

EDV was higher, TEF was mildly decreased in HTX patients compared to controls (HTX vs. control; EDV: 96±27 vs. 80±26mL, TEF: 47±7 vs. 51±4%, both $p<0.01$). In normal subjects, TEF was mainly determined by longitudinal motion (LEF $\beta=0.64$, REF $\beta=0.54$, $R^2=0.52$, $p<0.001$), however, in HTX patients the radial motion became far dominant (LEF $\beta=0.49$, REF $\beta=0.84$, $R^2=0.87$, $p<0.001$). After one-year follow up, EDV and TEF did not change significantly (EDV: 96±27 to 101±21mL, TEF: 47±7 to 52±9%, both NS). Notably, longitudinal function improved in time (LEF: 12±4 to 15±5%, TAPSE: 14±3 to 17±3mm, free wall longitudinal strain: -19±6 to -26±5%, all $p<0.05$). Nevertheless, radial function remained dominant (LEF $\beta=0.48$, REF $\beta=0.66$, $R^2=0.65$, $p<0.001$). TAPSE and free wall longitudinal strain correlated with the time elapsed after HTX ($r=0.57$ and $r=-0.48$, respectively, both $p<0.001$).

Our software allows to quantify longitudinal and radial motion of the RV separately using 3D analysis. Current results confirm the empirical phenomenon on the superiority of radial motion in determining RV function in HTX patients. In time, longitudinal function may recover, however, radial motion remains dominant.


RADIAL
LONGITUDINAL
NORMAL
EARLY HTX
LATE HTX

Relative contribution to RV function

Significance of change in heart rate recovery from test to test

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Topic(s):
Exercise testing and training

Citation:
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Background: Heart rate recovery (HRRec) is a powerful predictor of mortality in many cardiovascular (CV) diseases. If so a change in HRRec should signal a change in mortality risk.

Purpose: We analyzed a large cohort of patients who underwent 2 stress tests to determine the significance of a test-to-test change in HRRec.

Methods: Non-imaging exercise tests performed on patients from Minnesota ages 30–89 years from 1994 through 2010 were reviewed. Patients with 2 tests performed a minimum of 6 months apart were included. Patients were assigned to 4 groups according to their HRRec change: NN = HRRec normal (<13 bpm) both tests; NA = normal becomes abnormal; AN = abnormal becomes normal; and AA = abnormal both tests. Mortality was determined from Minnesota and National Death Indices. Mortality risk according to HRRec change was assessed using Cox regression with adjustment for age, sex, presence of CV disease, hypertension, diabetes, current smoking, and use of a HR-lowering drug.

Results: A total of 6,512 qualifying patients (76% men) were included in the analysis. Mean age was 53±13 years. CV disease was established in 2540 patients (39%), hypertension in 1757 (27%), diabetes in 475 (7.3%), current smoking in 523 (8.6%), and use of HR-lowering drug in 2120 (33%). HRRec overall was similar between the first and second tests (17±9 vs 17±10) performed an average of 4.0±3.2 years apart. Number of patients by HRRec change was 3797 for NN (58%), 756 for NA (12%), 775 for AN (12%), and 1184 for AA (18%). There were 913 deaths (14%) over a mean follow-up of 10.2±4.7 years after the second test. Using NN with 232 deaths (6.1%) during follow-up as the referent, the age-

sex-risk factor-adjust hazard ratio [95% confidence interval] for total mortality was 2.01 [1.62–2.49] for NA, 1.50 [1.18–1.90] for AN, and 2.83 [2.38–3.36] for AA.

Conclusions: HRRec change on consecutive exercise tests has a significant independent impact on all-cause mortality. The best outcomes were seen in patients with NN HRRec. Compared to patients with AA HRRec, improved HRRec (AN) patients showed reduced risk. Similarly, worsening HRRec (NA) patients had increased risk versus NN HRRec patients.

Unfavourable outcome after the upgrade of an implantable cardioverter defibrillator to cardiac resynchronization therapy

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Topic(s):
Heart failure, other

Citation:
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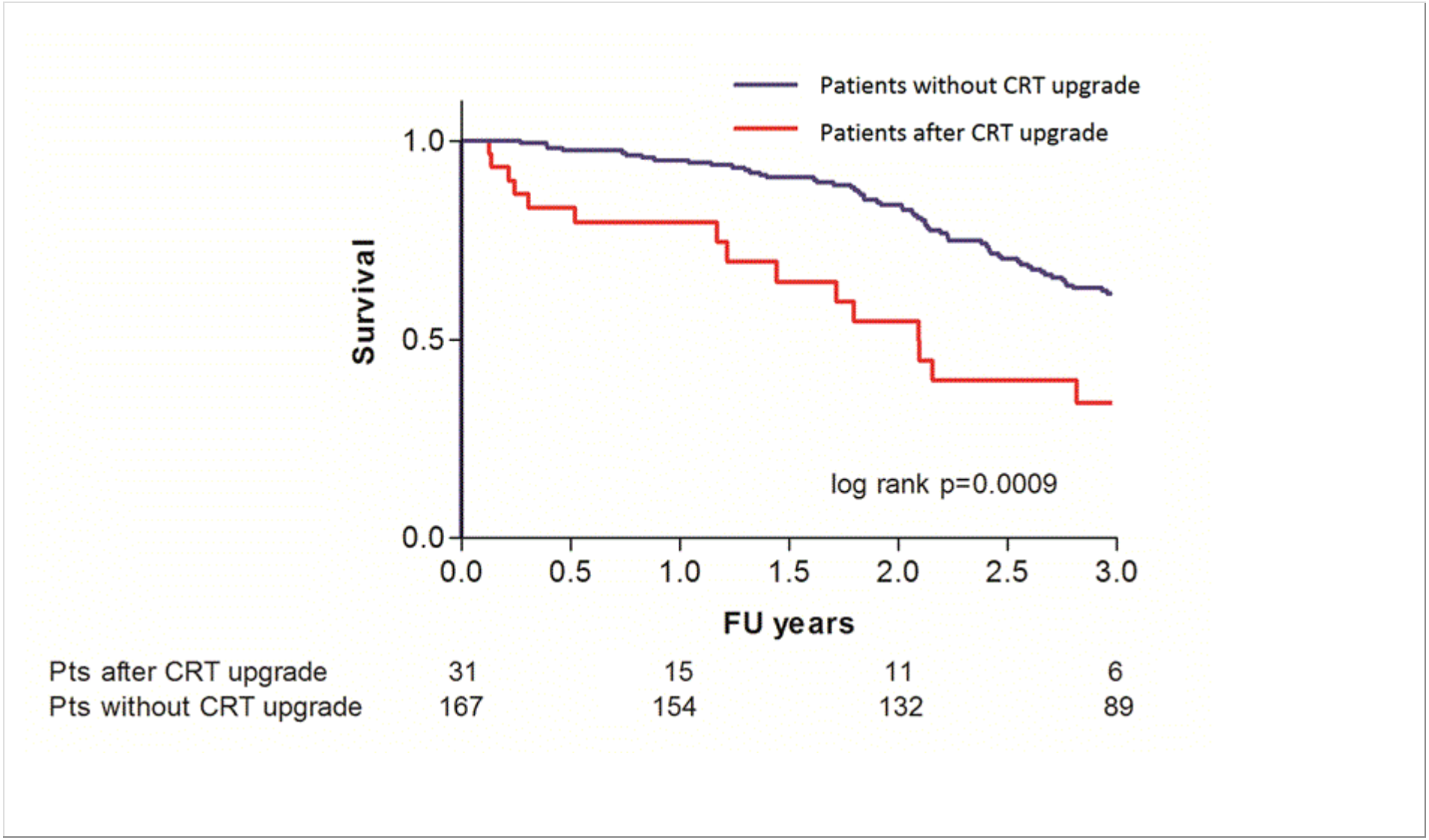
Background: Cardiac resynchronization therapy (CRT) improves survival in selected patients with heart failure (HF). As the potential survival benefit of CRT performed as an upgrade from a previously implanted cardioverter defibrillator (ICD) has not been explored, we evaluated total mortality after CRT upgrade in this context.

Methods and results: A total of 31 patients (27 male, mean age:63.7±9.6years) with structural heart disease underwent CRT device implantation as an upgrade of a previously implanted single or dual chamber ICD between 2004 and 2015 at our Institute. The indication for ICD implantation was prophylactic based on the MADIT II or SCD-HeFT criteria (in 13 patients) or secondary prevention after a sustained ventricular arrhythmia (in 18 patients). Mean left ventricular ejection fraction (LVEF) was 29.9±7.8% and mean NYHA status was 2.4±0.8 at the time of ICD implantation. No indication for CRT was present in any of these patients at the time of ICD implantation. CRT upgrade was performed after a mean follow-up of 3.9±2.9 years based on the following indications: widening of the QRS complex (from 108±20 to 158±24msec.) in 24, decreasing LVEF (from 41.5±2.1 to 26.5±2.1%) in the presence of LBBB in 2, and an increase in the need for right ventricular stimulation (burden >40%) in 5 patients. A significant reduction in the QRS width after CRT upgrade (from 160.3±26 to 130.3±23msec., $p<0.001$), an

improvement in NYHA class (from 3.1±0.8 to 2.5±1.0, p=0.16) and an increase in the mean LVEF (from 27.6 to 33.3%, p=0.049) was observed including 4 patients (13%) who demonstrated an increase in LVEF above 10% at the 1-year follow-up. 17/31 patients (55%) died during a mean follow-up of 19.0±16.6 months after CRT upgrade. No statistically significant prognostic factor of survival was found among the patients' baseline data by using the Cox proportional hazard model. Mortality rate in the control group (44/167; 26.4%) was significantly lower (log rank p=0.0009) during a similar follow-up period (Figure).

Conclusion: Despite a marked reduction in QRS width and a modest improvement in LV EF, mortality remains high after CRT upgrade in this patient cohort. This would argue for an earlier administration of alternative treatment modalities (assist device, heart transplantation) in HF patients who demonstrate QRS widening, a significant decrease in the LV EF or a need for ventricular stimulation.


Patients without CRT upgrade
Patients after CRT upgrade
Survival
1.0
0.5
0.0
log rank p=0.0009
0.0
0.5
1.0
1.5
2.0
2.5
3.0
FU years
Pts after CRT upgrade 31 15 11 6
Pts without CRT upgrade 167 154 132 89

Persistence of fixed and free combination of perindopril and amlodipine in hypertension

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Topic(s):
Treatment of hypertension

Citation:
European Heart Journal (2016) 37 (Abstract Supplement), 213

Introduction: Patient adherence is very important factor in the management of chronic disorders such hypertension. In hypertension cardiovascular risk reduction can be reached only by prolonged and effective pharmacotherapy.

Purpose: Our aim was to evaluate the persistence on one year treatment of free and fixed dose combination of perindopril and amlodipine in hypertension.

Methods: Information from the National Health Insurance of Hungary prescriptions database on pharmacy claims between October 1, 2012 and September 30, 2013 was analyzed. We identified patients who filled prescriptions for free and fixed dose combinations (FDC) of perindopril and amlodipine, prescribed for the first time for the therapeutic indication of hypertension. Patients have not received antihypertensive therapy with similar active substances during the one year preceding the study. To model the persistence, the apparatus of survival analysis was used, where "survival" was the time to abandon the medication. As it was available to month precision, discrete time survival analysis was applied: a generalized linear model was estimated with complementary log-log link function with the kind of drug being the only explanatory variable.

Results: 107,120 patients met the inclusion citeria. Combination antihypertensive therapy with perindopril and amlodipine was started with a free or a fixed combination of these agents in 19,365 and 87,755 patients, respectively. One year persistence rate in patients taking perindopril and amlodipine as a free combination was 27%, whereas it was 40% in those on the FDC. Analyzing persistence on treatment with these combinations showed that the actual rate of discontinuation was approx. twice higher during treatment with the free, compared with the use of the FDC (HR=1.94, 95% CI: [1.91–1.98], p<0.001).

Conclusions: In our study we demonstrated the clear benefit of initiating antihypertensive therapy with the FDC of perindopril and amlodipine

over starting treatment with the free combination.

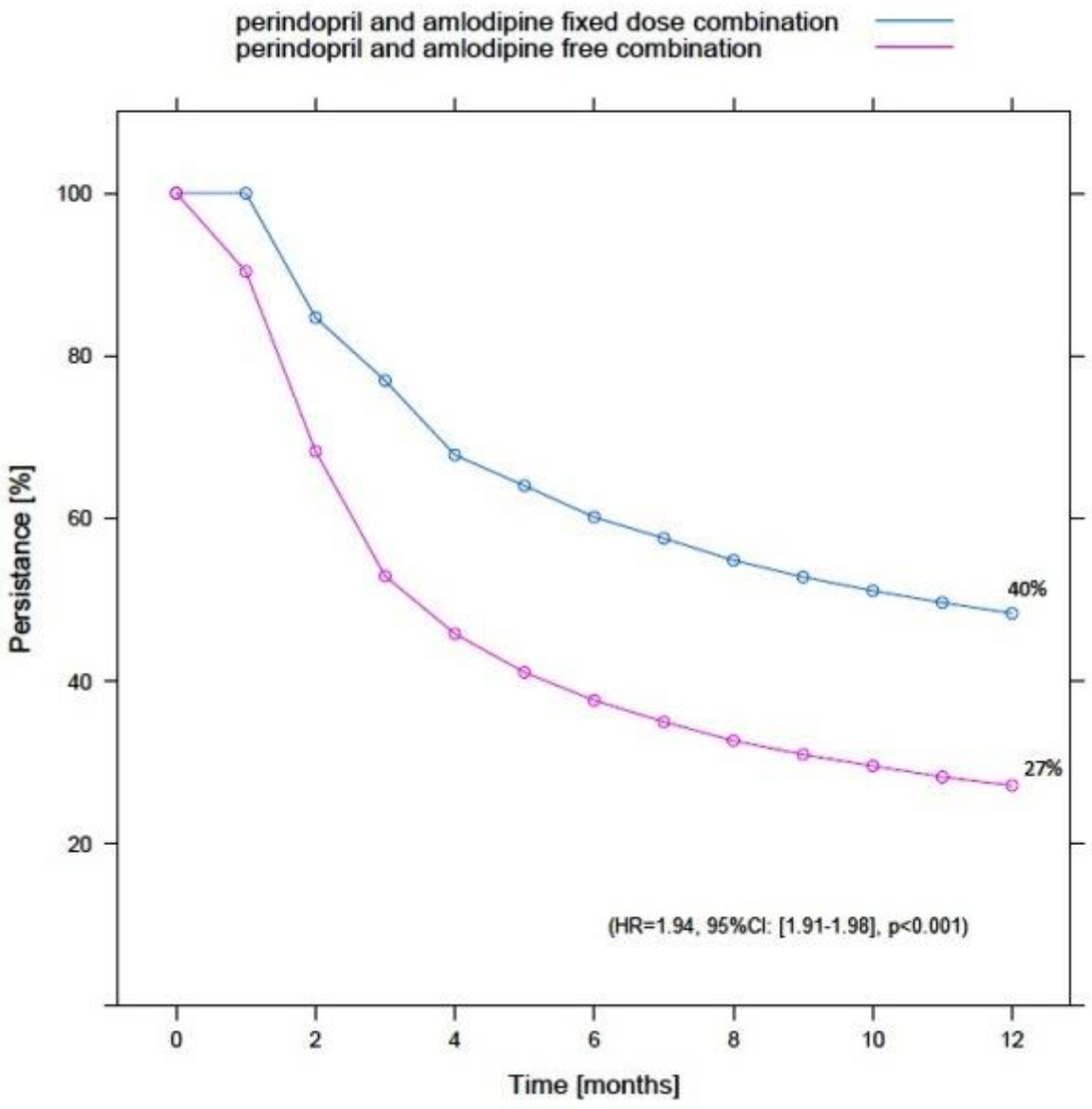
perindopril and amlodipine fixed dose combination
perindopril and amlodipine free combination
Persistance [%]
100
80
60
40
20
0
2
4
6
8
10
12
Time [months]
40%
27%
(HR=1.94, 95%CI: [1.91-1.98], p<0.001)

Figure 1

Changes of oral anticoagulation in elective cardioversion - results from a European cardioversion registry

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Topic(s):
Electrocardiography / cardioversion / defibrillation

Citation:
European Heart Journal (2016) 37 (Abstract Supplement), 236

Introduction: In patients with atrial fibrillation (AF) pharmacological or electrical cardioversion may be performed to restore sinus rhythm. The procedure is associated with an increased risk of thromboembolic events, which can be significantly reduced by adequate anticoagulation (AC).

Aim: Our aim was to create a partly prospective, partly retrospective cardioversion registry, particularly focusing on AC strategies in different European countries, and on emerging choice of AC over time.

Methods: From September 2014 to October 2015 the cardioversions due to AF performed in six European city hospitals in five European countries (Budapest – Hungary (two sites), Bari and Pisa – Italy, Amiens – France, Madrid – Spain, Kaunas – Lithuania) were recorded in the registry.

Results: A total of 1101 patients (retrospective/prospective: 679/422, male/female: 742/359, mean age: 67.3 years ± 11.2) were registered. Most

of the cardioversions were electrical (97%). Oral anticoagulants were administered in 87% of the patient, the usage of novel oral anticoagulants (NOACs) vs K-vitamin antagonists (VKA) was 31.5% vs 68.5%. 77% of the patients were given oral anticoagulants more than 3 weeks before the procedure, and 86% more than 4 weeks after the procedure. When using VKA, INR at cardioversion was above 2.0 in 76% of the cases. A decline in VKA usage ($p=0.033$) in elective cardioversion over approximately one year was observed (Fig. 1a). During the observation period an increase in apixaban ($p<0.001$), a slight increase in rivaroxaban ($p=0.028$) and no changes in dabigatran ($p=0.34$) usage for elective cardioversion was noticed (Fig. 1b). There were differences in use of AC between the countries: Spain used most VKA (89%), while France used least VKA (39%, $p<0.001$).

Conclusions: According to current AF guidelines NOACs are adequate alternatives to VKA for thrombembolic prevention in AF patients undergoing elective cardioversion. Our results show a significant decrease in VKA usage over time, while NOAC usage displays a gradual increase.

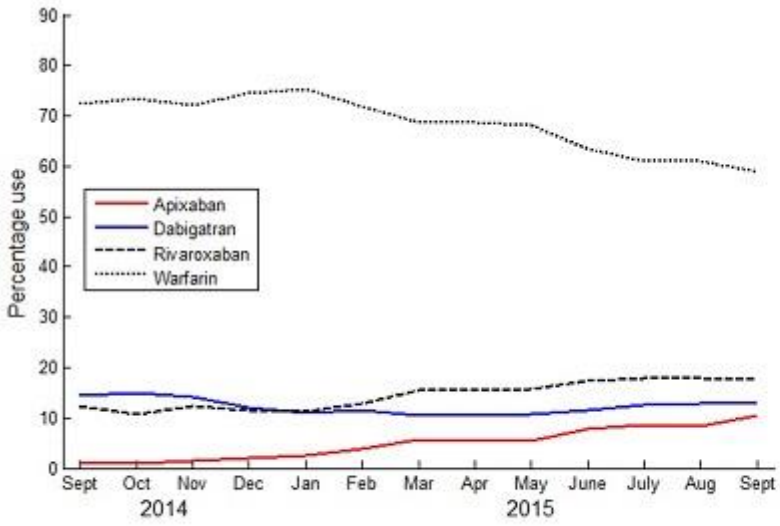

Fig. 1a

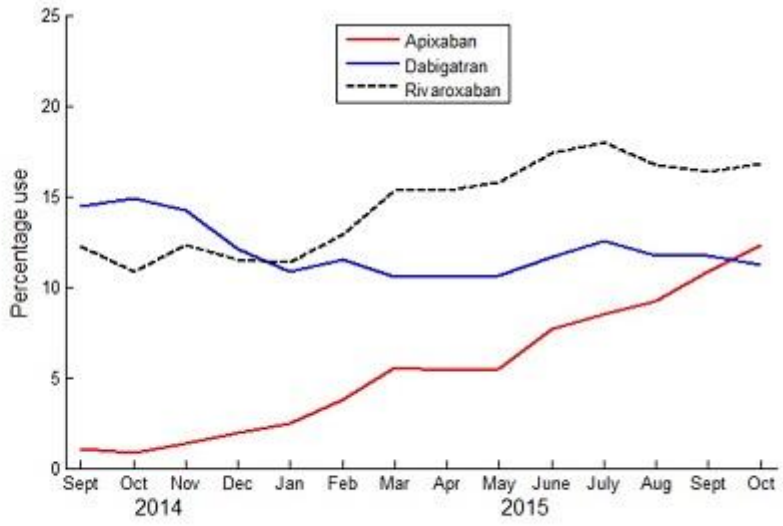

Fig. 1b

Determinants of the right atrial mechanics in systemic sclerosis

Authors:
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Topic(s):
Echo / Doppler, other

Citation:
European Heart Journal (2016) 37 (Abstract Supplement), 258

Cardiac involvement in systemic sclerosis has been recognized as a common and adverse finding associated with poor prognosis. Speckle-tracking-derived strain is a well-known diagnostic tool to detect early changes in right ventricular function in systemic sclerosis patients, but no data are available about the utility of this new technique in the estimation of right atrial function. The aim of our study was to investigate the determinants of the right atrial mechanics in systemic sclerosis by using two dimensional (2D) speckle tracking technique.

Patients and methods: 70 systemic sclerosis patients (age: 57±12 years, 64 female, 32 limited cutaneous form) were investigated. Patients with pulmonary arterial hypertension, atrial fibrillation or significant left sided valvular disease were excluded. As parameters of the right ventricular systolic function, tricuspid annular plane systolic excursion (TAPSE) and right ventricular fractional area change (RVFAC) were measured. Right atrial area as well as basal, mid-cavity, and longitudinal dimensions of the right ventricle were measured in apical four chamber view. Maximal and minimal diameters of the inferior vena cava were measured in subxyphoid view, and collapsibility index was calculated. In addition to the spectral Doppler parameters of the tricuspid inflow (E, A), systolic (s), early (e') and late (a') diastolic myocardial longitudinal velocities were measured on the lateral tricuspid annulus. E/A and E/e' ratios were calculated. Right ventricular systolic pressure was estimated as a sum of the pressure difference across the tricuspid valve calculated using the modified Bernoulli equation and an estimate of mean right atrial pressure based on diameter and collapsibility index of the inferior vena cava. Right atrial reservoir, conduit and contractile strain were measured with 2D speckle tracking technique. Right atrial stiffness was calculated as ratio of E/e' to right atrial reservoir strain.

Results: Right atrial stiffness showed significant positive correlation with calculated right ventricular pressure (r=0.284; p=0.043) and E/e' (r=0.778; p=0.000) values, while significant negative correlation with tricuspid e' (r=-0.595; p=0.000), tricuspid a' (r=-0.275; p=0.021), tricuspid S (r=-0.436; p=0.000), and TAPSE (r= -0.504; p=0.000) (Figure 1.). No correlations were found between atrial strain results and parameters of the right ventricular systolic or diastolic function.

Conclusion: Our results suggest that speckle-tracking-derived right atrial stiffness is a robust parameter of the right atrial function, which shows strong correlation with the deterioration of the right ventricular systolic and diastolic function in systemic sclerosis.

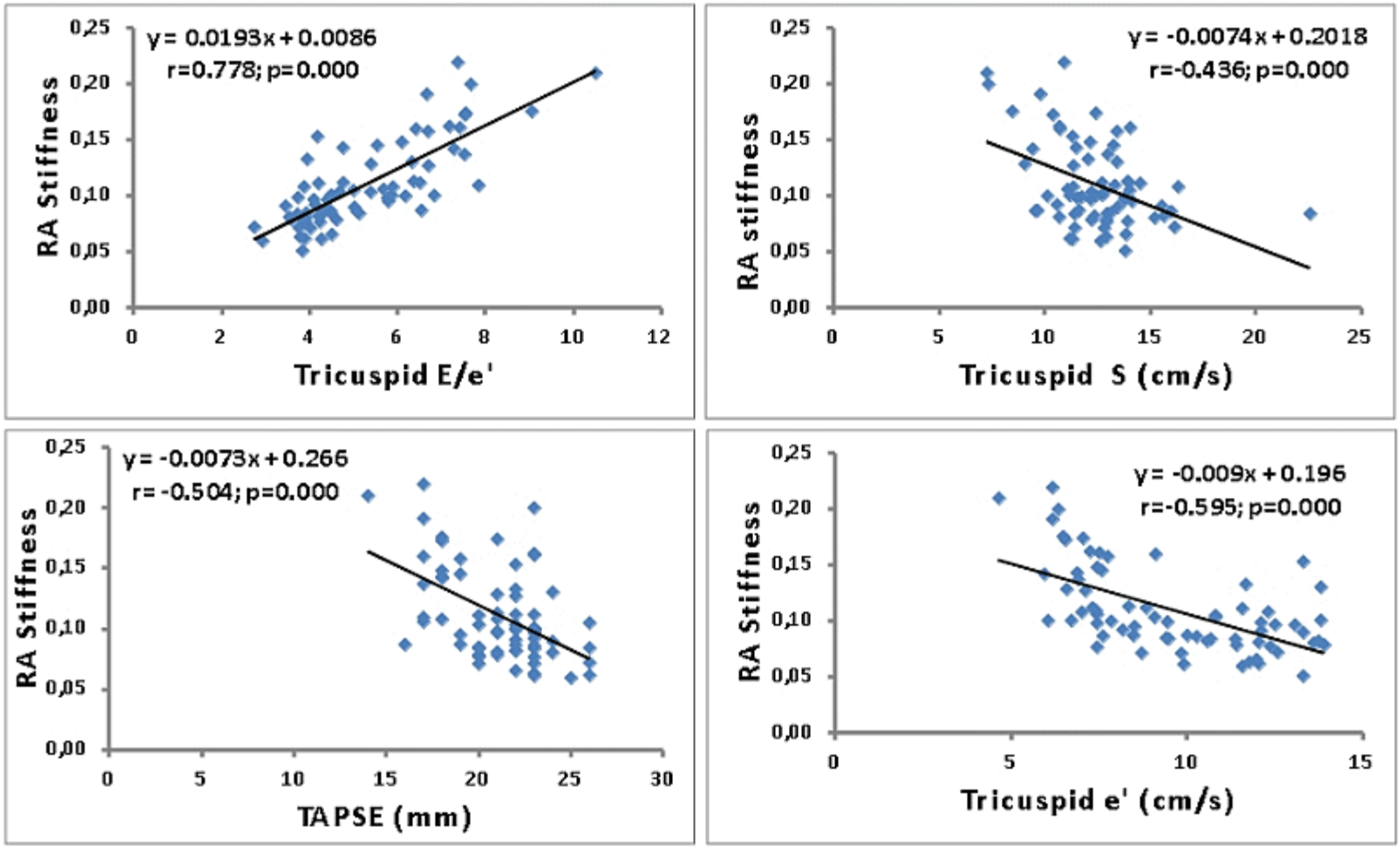

Figure 1.

Left ventricular diastolic function is a determinant of the left atrial mechanics in systemic sclerosis

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Topic(s):
Echo / Doppler, other

Citation:
European Heart Journal (2016) 37 (Abstract Supplement), 261

Left ventricular diastolic dysfunction is common in systemic sclerosis and is associated with poor prognosis. The correlation between left ventricular diastolic function and left atrial size has been already proved. Less is known about the relationship between left ventricular diastolic function and left atrial mechanics. Speckle-tracking-derived strain is a well-known tool to assess left atrial function. The aim of our study was to investigate the correlation between left ventricular diastolic function and left atrial mechanics in systemic sclerosis patients by using 2D speckle tracking technique.

Patients and methods: 72 systemic sclerosis patients (age: 57±11 years, 66 female, 33 limited cutaneous form) were investigated. Patients with pulmonary arterial hypertension, atrial fibrillation or significant left sided valvular disease were excluded. Maximal left atrial volume was measured with 2D Simpson's method. In addition to the spectral Doppler parameters of the mitral inflow (E, A), systolic (S), early- (e') and late- (a') diastolic myocardial longitudinal velocities were measured on the lateral and septal mitral annulus. Lateral and septal myocardial velocities were averaged. E/A and E/e' ratios were calculated. LV diastolic function was classified according to the recent guideline (I: normal, II: impaired relaxation, III: pseudonormal). LA reservoir (εR), conduit (εCD) and contractile (εCT) strain were measured with 2D speckle tracking technique. Differences between groups were tested for significance using ANOVA. Post hoc tests were performed by LSD method.

Results: Left atrial εR and εCD showed significant correlation with average mitral e' (εR: r=0.552, p=0.000; εCD: r=0.707, p=0.000), average

mitral E/e' (εR: r=−0.376, p=0.001; εCD: r=−0.374, p=0.001) and maximal left atrial volume (εR: r=−0.461, p=0.000; εCD: r=−0.438, p=0.000). εCT showed significant correlation with maximal left atrial volume (r=−0.248; p=0.036) and average mitral a' (r=0.512; p=0.000). εR (I: 45.5±8.6%, II: 40.8±7.2%, III: 35.8±6.8%; ANOVA p=0.001) and εCD (I: 27.7±5.5%, II: 20.5±5.2%, III: 18.9±6.3%, p=0.000) showed significant deterioration with the worsening of the diastolic dysfunction. The highest εCT values were measured in patients with impaired left ventricular relaxation (I: 17.7±4.6%, II: 20.2±3.9%, III: 16.9±2.9%, p=0.011) (Figure 1).

Conclusion: Left atrial εR and εCD show strong correlation with the deterioration of the left ventricular diastolic function in systemic sclerosis. The high value of εCT in the early stage of the diastolic dysfunction may be the sign of the compensatory behavior of the left atrium.

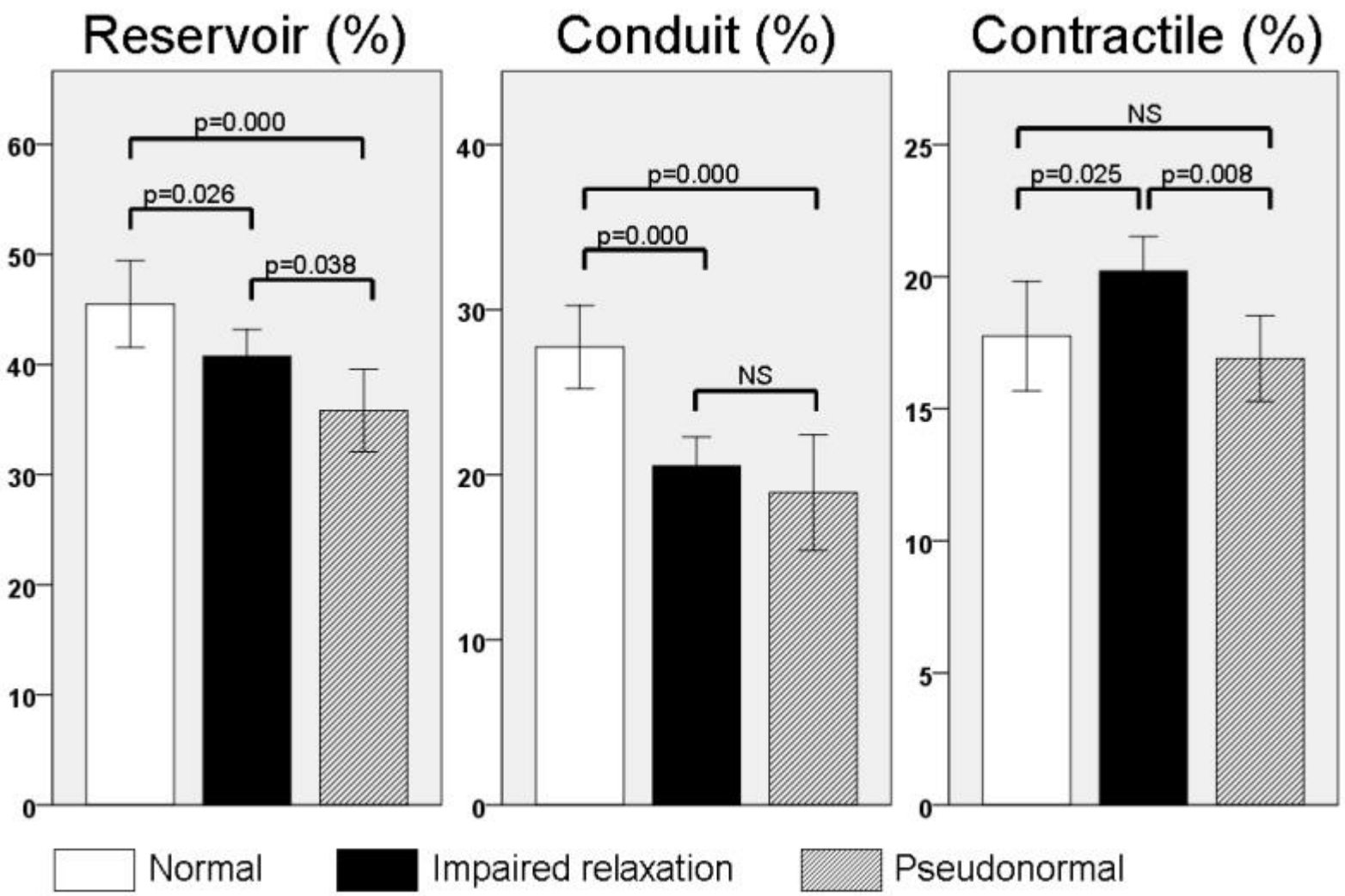
Reservoir (%)
Conduit (%)
Contractile (%)
p=0.000
p=0.026
p=0.038
p=0.000
p=0.000
NS
NS
p=0.025
p=0.008
60
50
40
30
20
10
0
40
30
20
10
0
25
20
15
10
5
0
Normal
Impaired relaxation
Pseudonormal

Figure 1

Inheritance of left ventricular structure and function implies no genetic predisposition to hypertensive heart disease in Caucasian twins

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Topic(s):
Morphology, pathology and genetics

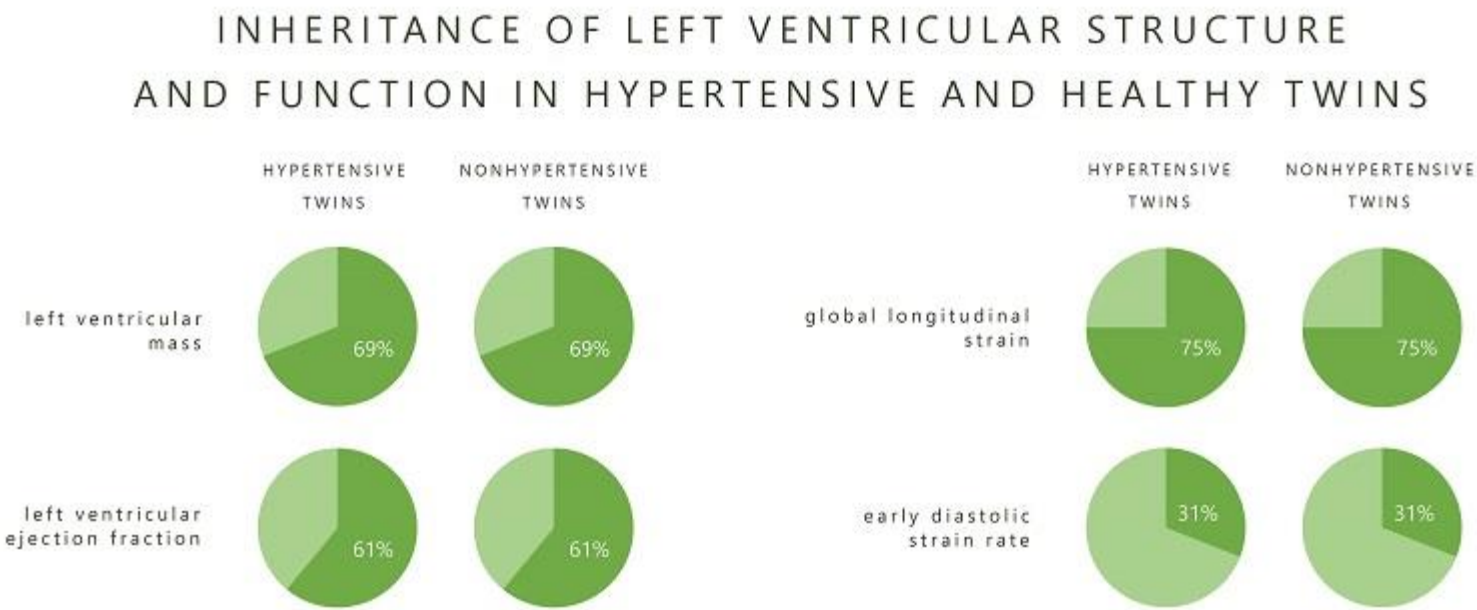
Citation:
European Heart Journal (2016) 37 (Abstract Supplement), 370

Arterial hypertension affects cardiac structure and function leading to hypertensive heart disease (HHD), which is the most common cardiac abnormality. Despite diagnostic and prognostic value of left ventricular (LV) structural and functional parameters, data on relative contribution of genetic and environmental factors are still controversial. The aim of our study was to assess the heritability of LV morphology and function, and to estimate the genetic susceptibility to HHD.

We recruited 92 Caucasian twin pairs (54 monozygotic and 38 same-sex dizygotic twin pairs, mean age 56±9 years) including 74 hypertensive siblings. Patients with obstructive coronary artery disease, any cardiomyopathy or severe valvular disease were excluded. Beyond standard echocardiographic protocol, advanced measures of LV function were performed including global longitudinal strain (GLS).

After adjusting for age, sex and hypertension, the univariate additive genetic (A), dominance genetic (D) and unique (E) environmental effects model showed 67–72% additive genetic component in the variance of LV morphological parameters, 0–46% for LV diastolic functional parameters. Systolic function showed high heritability (A: 61% for ejection fraction), with dominant genetic effect on GLS (D: 75%). Heterogeneity models revealed that there is no difference between hypertensive and non-hypertensive patients regarding heritability estimates.

LV morphology and systolic function are highly heritable. GLS shows even higher heritability suggesting dominant effects, which might be due to its inherent superior accuracy of measurement, as compared to conventional parameters. There is no difference in the heritability estimates of LV morphological and functional parameters in hypertensive and non-hypertensive twins, which suggests no genetic predisposition to HHD in this population.



The cytoprotective effect of biglycan core protein involves TLR4 signaling in primary cardiomyocytes

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On behalf: Metabolic Diseases and Cell Signaling Group (Medics)

Topic(s):

Ischaemia, experimental studies

Citation:
European Heart Journal (2016) 37 (Abstract Supplement), 378

Native biglycan consisting of a core protein and two glycosaminoglycan (GAG) chains has been shown to protect cardiomyocytes against simulated ischemia/reperfusion injury (SI/R) however, the mechanism of action is not clearly understood. In this study, we investigated which structural component of biglycan (core protein or GAG chains) is responsible for its cytoprotective effect and further explored molecular mechanisms responsible for this protection.

Primary neonatal cardiomyocytes isolated from Wistar rats were treated with glycanated biglycan, recombinant human biglycan core protein (rhBGNc), and the GAG components dermatan sulfate and chondroitin sulfate, and were subjected to SI/R followed by viability measurement. Glycanated biglycan and rhBGNc reduced dose-dependently SI/R-induced cell death, however, the GAG chains did not show protection. We have also demonstrated that pharmacological blockade of Toll-like receptor 4 (TLR4) signaling or its downstream mediators (IRAK1/4, JNK and p38 MAP kinases) abolished the cytoprotective effect of rhBGNc against SI/R injury. Pretreatment of cardiomyocytes with rhBGNc increased Akt phosphorylation and NO production without having a significant effect on phosphorylation of ERK1/2, STAT3, and production of superoxide. Blockade of NO synthesis abolished the cytoprotective effect of rhBGNc.

We conclude that the core protein of biglycan is able to protect cardiomyocytes from SI/R injury via TLR4-dependent signal mechanisms involving activation of JNK and p38 MAP kinases and increased NO production.

Platelet function guided antiplatelet therapy after coronary intervention for myocardial infarction, a propensity score matched analysis from the Hungarian national registry of myocardial infarction

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Topic(s):
Platelets and antiplatelets therapy

Citation:
European Heart Journal (2016) 37 (Abstract Supplement), 382

Funding Acknowledgements:
University of Pécs, Hungary (KA-2015-17)

Background: High platelet reactivity (HPR) is an acknowledged risk factor among patients with myocardial infarction (MI). However, due to the futility of multiple prior studies platelet function testing (PFT)-based treatment modification is not recommended. In Hungary, prasugrel is only reimbursed in patients with HPR, and therefore, the Multiplate whole-blood impedance aggregometer is widely used to guide P2Y12-inhibitor selection.

Methods: In the setting of a nation-wide MI registry, we collected clinical characteristics and platelet function data from centers of invasive cardiology. Follow-up data of patients treated with coronary intervention between March 1, 2013, and March 1, 2014 were analyzed. The risk of all-cause mortality at 1 year between patients receiving PFT-guided and non-guided antiplatelet therapies were compared using propensity score matching. HPR were uniformly defined as an ADP test value greater than 46 U.

Results: A total of 5583 patients with MI were registered. After exclusion of cases with contraindication to prasugrel, PS matching resulted in a sample of 2104 patients with adjusted characteristics. Patients with HPR received primarily prasugrel (76%) while 12% were treated with high and 12% with normal dose of clopidogrel. In the non-guided group, patients were treated predominantly with clopidogrel.

According to the adjusted analysis, 1-year mortality rates were lower for the PFT-guided than for the non-guided group. (Hazard ratio (HR) 0.574 [0.431–0.765]). In the guided group, patients with HPR switched to prasugrel had significantly improved survival when compared to those who received clopidogrel despite HPR (HR: 3.00 [95% CI 1.089–8.287], $p<0.05$.

Conclusion: In patients undergoing angioplasty for acute myocardial infarction, PFT-guided treatment is associated with lower 1-year mortality

rates than unguided therapy, in patients predominantly treated with clopidogrel.

Triple or dual antithrombotic management of patients with atrial fibrillation and coronary artery disease? An observational study from Italy, Lithuania and Hungary

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Topic(s):
Platelets and antiplatelets therapy

Citation:
European Heart Journal (2016) 37 (Abstract Supplement), 385

Background: Almost one third of patients with atrial fibrillation (AF) have concomitant coronary artery disease (CAD) with the need of stent implantation (SI). The optimal anticoagulation (AC) and antiplatelet (AP) management for this patient population is under debate and current guidelines are based on limited evidence. This study investigates AC and AP therapies in AF patients with SI in three countries and the relation to thromboembolic (TE) and bleeding complications.

Methods and results: 715 AF patients with SI either for acute coronary syndrome or stable CAD from 5 European centers were included (mean age: 74 (9); male: 64%, elective PCI: 44%, DES:27%). Based on the CHA2DS2-Vasc score 96.3% of patients had an indication for long term AC in addition to AP therapy. However, only 67% of these received triple antithrombotic therapy (TAT). There was no significant difference in the baseline clinical parameters between patients on TAT and those without TAT including age, gender, CHA2DS2-Vasc and HAS-BLED scores. However, patients with paroxysmal AF were less likely to receive TAT than persistent or permanent patients (47%, 68% and 84%, respectively, $p<0.0001$). There were 32 (3.2%) bleeding complications and 34 (4.7%) TE complications in the whole study population during a mean follow-up of 12.1 (9.6) months. No significant difference was detected in bleeding or TE events (5% vs 3.7%, $p=0.4$ and 4.6% vs 4.9%, $p=0.3$ respectively) between patients with and without TAT. Higher all cause mortality rate was observed in patients who did not receive TAT

after the SI (9.8% vs 4.1%, p<0.0001).

Conclusions: The choice of anti-platelet, anticoagulant strategy was not determined by CHA2DS2-Vasc or HAS-BLED scores. More than one third of patients did not receive TAT despite guideline indications, and in these patients significantly higher mortality was observed.

Galectin-3 is an independent predictor of survival in systemic sclerosis

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Topic(s):
Prognosis

Citation:
European Heart Journal (2016) 37 (Abstract Supplement), 443

Galectin-3 is a beta-galactoside-binding member of the lectin family. In previous studies, it has been shown to be an independent marker for outcome in heart failure and appeared to be particularly useful in heart failure with preserved left ventricular ejection fraction. High serum levels of galectin-3 have been described in a number of other conditions such as COPD, pneumonia, sepsis and kidney disease. In systemic sclerosis (SSc) galectin-3 may be related to organ sclerosis and aberrant activation of angiogenesis. The aim of our study was to determine the associations between galectin-3 levels and patient characteristics, as well as to investigate the long term prognostic value of galectin-3 in a large cohort of SSc patients.

Patients and methods: 152 SSc patients (55±11 years, 138 female) were included in the study. Blood samples and baseline clinical data were collected between 1st January 2005 and 31st December 2008. Primary outcome was all-cause mortality. Cardiovascular mortality was also investigated.

Results: After adjustments for age, gender and BSA, galectin-3 levels showed positive correlation with the grade of left ventricular diastolic function (r=0.193; p=0.026) and with the laboratory parameters of inflammation such as erythrocyte sedimentation rate (r=0.172; p=0.036) and

CRP (r=0.200; p=0.015). Negative correlation was found between galectin-3 and diffusing capacity for carbon monoxide (r=-0.228; p=0.006). During the follow-up time of 7.2±2.3 years, 35 SSc patients (23%) died, 16 of them suffered cardiovascular death. In Cox multivariate regression analysis galectin-3 was independent predictor of the all-cause mortality (HR: 2.780; p=0.007) and cardiovascular mortality (HR: 3.346; p=0.031) even after the inclusion of age, gender, BSA and NTproBNP levels. Using ROC analysis, galectin-3>10.25 ng/ml and NT-proBNP>140.1 pg/ml were the best predictors of the all-cause mortality. When evaluated by comparing groups above and below the cut-off value for each biomarker, NTproBNP and galectin-3 were discordant for 58 subjects (38.2%), divided approximately equally between high galectin-3/low NTproBNP (n=27) and low galectin-3/high NTproBNP (n=31). Compared with the reference group of low galectin-3/low NTproBNP, high galectin-3/low NT-proBNP (HR: 4.884, p=0.024) and low galectin-3/high NT-proBNP (HR: 4.196, p=0.026) groups had similarly higher mortality rate while the highest mortality was observed in the high galectin-3/high NT-proBNP group (HR: 12.180, p<0.0001) (Figure 1).

Conclusion: Our results suggest that galectin-3 is an independent predictor of all-cause and cardiovascular mortality in SSc. Added to NT-proBNP, galectin-3 provided complementary prognostic information, mainly by reflecting mortality risk associated to organ sclerosis and inflammation. Validation studies are required to establish whether galectin-3 may be considered as a useful and simple biomarker for selecting patients with high mortality risk in SSc.

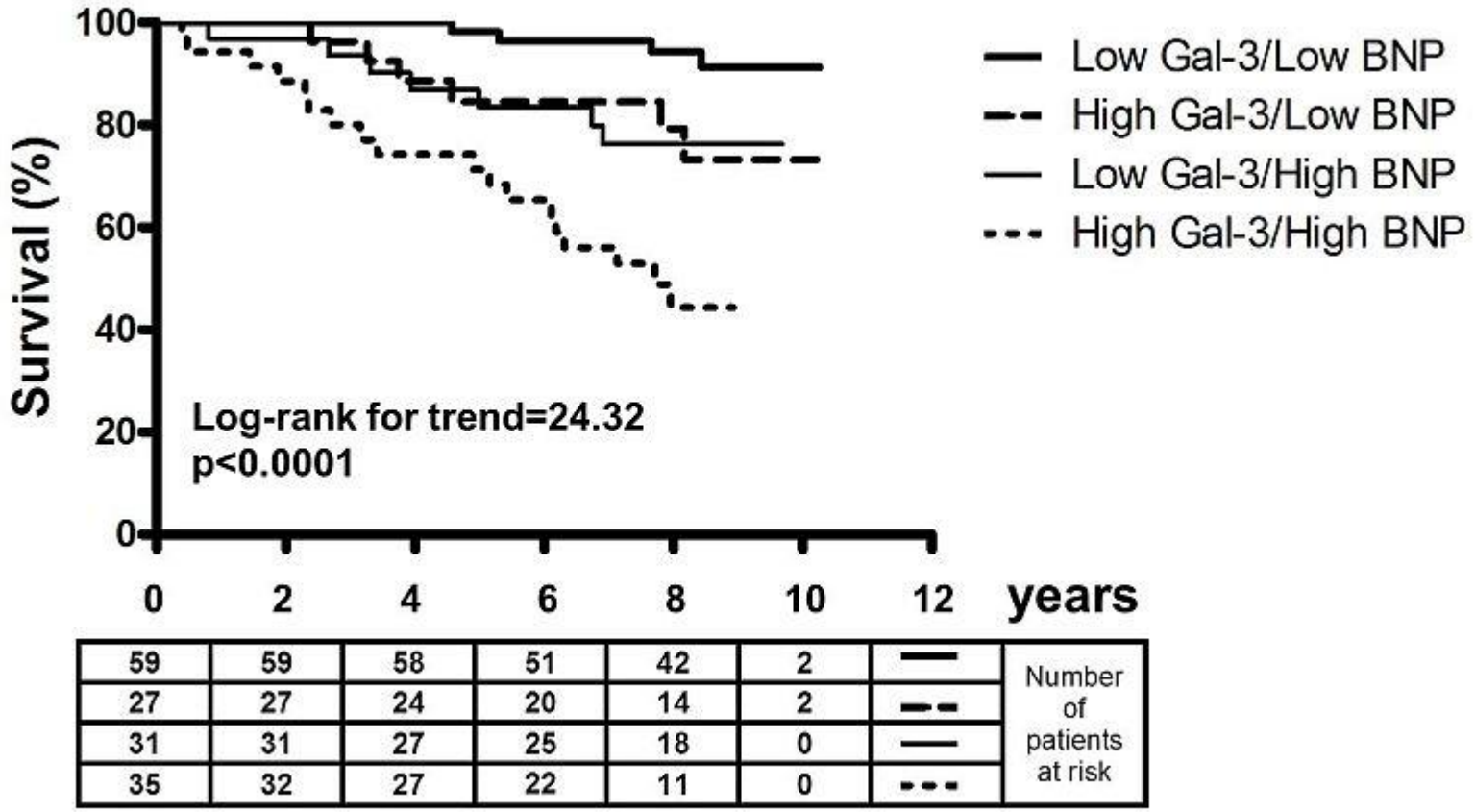
Survival (%)
100
80
60
40
20
0
Log-rank for trend=24.32
p<0.0001
0
2
4
6
8
10
12
years
Low Gal-3/Low BNP
High Gal-3/Low BNP
Low Gal-3/High BNP
High Gal-3/High BNP
59 59 58 51 42 2
27 27 24 20 14 2
31 31 27 25 18 0
35 32 27 22 11 0
Number of patients at risk

Figure 1

Effects of upgrade versus de-novo cardiac resynchronization therapy on clinical response and long-term survival: Results form a large multicenter study

Authors:
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Topic(s):
Resynchronisation therapy

Citation:
European Heart Journal (2016) 37 (Abstract Supplement), 444

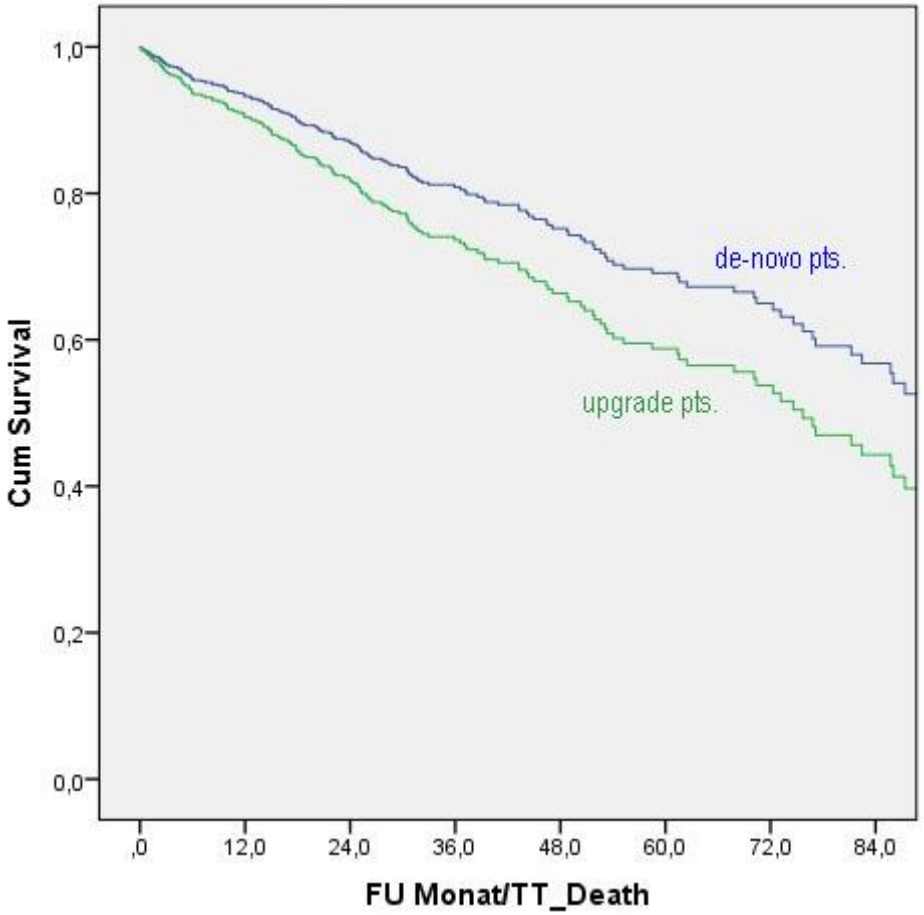
Introduction: Beneficial impact of cardiac resynchronization therapy (CRT) exerts beneficial effects on morbidity and mortality in selected patients. The number of upgrade procedures from single- or dual-chamber devices to CRT is increasing. However, there are only sparse data regarding the outcomes of patients (pts) undergoing upgrade procedures compared to de-novo CRT implantations.

Purpose: To evaluate clinical response and long-term survival in pts receiving de-novo vs. upgrade CRT defibrillator (CRT-D) therapy.

Methods: Prospectively collected outcome data were compared in pts undergoing de novo or upgrade CRT-D implantation at 3 implant centers in Germany and Hungary. Clinical response was assessed at 6 months and defined as improvement by at least 1 NYHA functional class.

Results: CRT implantation was performed in 554 consecutive pts of whom 377 underwent a de-novo and 177 an upgrade procedure. Pts in the upgrade group were more often implanted for secondary prevention, suffered more often from chronic kidney disease, diabetes, dyslipidemia, and had more often a non-LBBB wide QRS complex, lower eGFR and lower LVEF. Pts after upgrade procedures experienced a lower response rate compared to the de-novo group (67.9% vs. 56.7%, p=0.012). Further predictors for non-response were renal failure (p=0.032), diabetes (p=0.009), COPD (p=0.048), and high baseline NYHA class (p=0.024). During a follow-up period of 29.8±27.7 months, survival was significantly worse after upgrade procedures compared to the de-novo CRT-D implantations (HR 1.61, 95% CI 1.19–2.20, p=0.002) even after adjustment for possible confounders (adjusted HR 1.58, 95% CI 1.13–2.21, p=0.008, see Figure).

Conclusion: Both clinical response and long-term outcome were less favorable in pts undergoing upgrade CRT-D implantation compared to de-novo implantation, even after careful adjustment for possible confounders.



Survival after CRT-D implantation

Ratio of TEE usage in the era of NOACS: TALENT multicenter European Registry

Authors:
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On behalf: TALENT Cardioversion Registry Group

Topic(s):
Atrial fibrillation (AF)

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Introduction: Anticoagulant (AC) treatment timing for elective cardioversion (CV) is recommended by the guidelines. Transesophageal echocardiography (TEE) is not an obligatory measure before CV if the patient is pretreated by AC for at least 3 weeks before CV, though there are some centers which perform the TEE in the AC-pretreated cases also. In 5–15 of patients with AF, TEE before planned cardioversion revealed an LA or LAA thrombus. If there is longer than 48 hrs of Afib without any AC treatment it is reasonable to perform TEE to avoid thrombembolism according to the guidelines. TEE guidance is an alternative to 3 weeks of anticoagulation before cardioversion

Aim of our registry was to set up a cardioversion prospective+retrospective registry, particularly focusing on AC and TEE strategies in the participating European countries.

Methods: Patient records were collected between Sept 2014 to Oct 2015 in 7 European hospitals (Hungary and Italy 2 sites each, France, Spain and Lithuania). All the data of patients were collected consecutively who undewent CVs due to AF. Since it was unclear in the participating centers what is the ratio of TEE usage in AC-pretreated patients awaiting for CV, even whether NOAC treatment has any influence on the usage of TEE, our registry has recorded the duration of OAC usage before and after CV, which has been measured on a five category scale before CV (0, <3 weeks, ≥3 weeks, overlap with heparin, same day only).

Results: A total of 1101 patients (retrospective/prospective: 679/422, mean age: 67.3 years ± 11.2) were registered. 97% of the cardioversions

were electrical ones. TEE-guided CV was performed in 584 cases, vs nonTEE guided in 517 cases. The TEE-guided group was treated by apixaban in 3.5%, by dabigatran and rivaroxanban in 11% each, and by VKA in 75% of the cases (p<0.001). Ratio of OAC usage before cardioversion more than 3 weeks was found to be significant concerning of pretreatment in each AC groups in comparison to the other time-plans: apixaban 91%, dabigatran and rivaroxaban 81% each, warfarin in 79% of the cases (p=0.008). Over time non-TEE usage has increased in the apixaban (p<0.001) and rivaroxaban treated groups (p=0.015), but no change was observed in the dabigatran group, and decrease of VKA usage was found in the non-TEE group (p0.033).

Conclusion: In conclusion, TEE usage is not obligatory in routine elective cardioversion. Our results show that the usage of NOACs decrease the high number of TEEs performed though it is not recommended to be used routinely.

Combined use of transgenic LQT2, LQT5 and LQT2-5 rabbit models with decreased repolarization reserve as novel tool for pro-arrhythmia research

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Topic(s):
Ion channels and electrophysiology

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Background: Reliable prediction of in vivo pro-arrhythmic effects associated with ion channel-blocking properties of novel drugs remains elusive. Thus, there is an unmet need for new animal models with better predictive value.

Purpose: For this aim, different transgenic LQTS rabbit models with impaired repolarization reserve were generated (LQT2, HERG-G628S, loss of IKr; LQT5, KCNE1-G52R, decreased IKs; double-transgenic LQT2–5, loss of IKr/decreased IKs).

Methods: In vivo telemetric ECG (QTc, QTi (QT observed/QT expected)) and ex vivo monophasic action potential measurements in Langendorff-perfused hearts (action potential duration (APD75), triangulation (APD90-APD30), and spatial dispersion of repolarization (APDmax-APDmin)) were performed to assess the effects of several K^+ channel blockers on cardiac repolarization in wild type (WT), transgenic LQT2, LQT5, and LQT2–5 rabbits.

Results: At baseline, QTc (ms) was similar in LQT5 (135.3±5) as in WT (137.2±6) but was significantly prolonged in LQT2 and LQT2–5 rabbit models (162.9±11 and 167.9±15; $p<0.05$ vs. WT). Slight IKr-blockade by low dose dofetilide (0.02mg/kg, im) prolonged QT in vivo only in LQT5 (QTi (%), 104.5±3.5, $p<0.05$ vs. baseline) but not in WT, nor in LQT2 and LQT2–5 rabbits that lack IKr. IK1-blocker BaCl2 (0.3mg/kg, im) prolonged QT in all groups (QTi (%), WT 105.7±3.3, LQT5 104.9±4.1, LQT2 110.8±4.8, LQT2–5 104.9±2.6; $p<0.05$ vs. baseline). Ex vivo, IKr-blocker dofetilide (1nM) prolonged APD75 in all groups (changes (ms), WT +8.5±2.7, LQT5 +6.0±2.7, LQT2–5 +12.4±3.2; all $p<0.05$ vs. baseline) - except for LQT2 lacking IKr. APD75 prolongation induced by IKs-blocker HMR-1556 (100nM) was more pronounced in LQT2–5 as in WT or LQT5 (changes (ms), LQT2–5 +9.8±5.3 vs. WT +6.0±2.3 or LQT5 +5.5±2.8). IK1-blocker BaCl2 (10μM) or combined IK1/IKs-blockade by BaCl2+HMR prolonged APD75 significantly more in LQT2 and LQT2–5 than in WT (changes (ms), BaCl2: LQT2 +30.0±5, LQT2–5 +27.2±4 vs. WT +17.7±7; BaCl2+HMR: LQT2 +39.6±10, LQT2–5 +31.0±8 vs. WT +18.6±3; all $p<0.05$). Importantly, triangulation of APD was also more pronounced upon IK1-blockade or combined IK1/IKs-blockade in LQT2 and LQT2–5 than in WT (BaCl2: LQT2 +24.5±7, LQT2–5 +24.2±8 vs. WT +13.9±6; BaCl2+HMR: LQT2 +34.6±10, LQT2–5 +28.0±5 vs. WT +16.7±3; all $p<0.05$). Spatial dispersion of repolarization was increased significantly by BaCl2+HMR only in LQT2 (change +7.4±4.4 ms; $p<0.05$ vs. baseline) but in none of the other genotypes.

Conclusion: LQT2 and LQT2–5 rabbit models with pronounced reduction of repolarization reserve are very sensitive to K^+ channel blockers demonstrating not only QT prolongation but also increased APD triangulation and dispersion. The combined use of different transgenic LQTS rabbit models with different extents in reduction of repolarization reserve may provide further insights into pro-arrhythmic mechanisms of K^+ channel blocking drugs.

FOXO1A modifies arterial and venous endothelial development from human pluripotent stem cells; they establish 3D vascular structures in vitro and quantifiable vascular networks in vivo

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Topic(s):
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Background and purpose: Endothelial derivatives of human pluripotent stem cells may offer regenerative treatments in ischemic cardiovascular diseases. We aimed to investigate the regulatory role of PI3K/FOXO1A signalling pathway on arterial and venous identity of endothelial subpopulations as well as the fate of generated cells in 3D cultures in vitro and via transplantation into small animals in vivo.

Methods and results: Human embryonic stem cells (hESC) were differentiated via either embryoid body (EB) or monolayer method under normoxic and hypoxic conditions. CD31-positive endothelial cells (EC) were sorted by FACS and compared with human induced pluripotent stem cell-derived endothelial cells (hiPSC-EC). Both hESC-EC and hiPSC-EC showed mature endothelial phenotype in vitro, including cobblestone pattern, ac-LDL uptake and tube formation. Proteome profiling revealed high abundance of angiogenesis-related proteins both in cell lysates and supernatant. Expressions of arterial (EphrinB2, Notch1–2) and venous (EphB4) endothelial markers were increased during differentiation, suggesting the presence of mixed endothelial population in culture. Transfection of hESC-EC/hiPSC-EC with plasmids encoding FOXO1A-eGFP or pmaxGFP was carried out by electroporation. Human ESC-EC and hiPSC-EC with high FOXO1A showed downregulated expressions of universal (CD31, angiopoietin-2 and ve-cadherin) as well as arterial and venous markers. Indeed, arterial index (EphrinB2/EphB4 mRNA ratio) decreased in response to FOXO1A overexpression (hESC-EC 8.16±3.22 vs. 2.24±0.49, $p<0.01$; hiPSC-EC 6.46±2.75 vs. 1.67±0.72, $p<0.05$; n=3 biological replicates). This suggests a key role of PI3K/FOXO1A signalling pathway in the modulation of arterial and venous phenotype. For engineering 3D vascular constructs decellularised human aortic slices (300μm) were repopulated with hESC-EC and hiPSC-EC in small bioreactor systems. Cells remained viable on engineered matrices. Imaging with Calcein AM live staining and 3DHistech

analysis proved recellularisation with CD31-positive, viable endothelial cells. Human ESC-EC and hiPSC-EC were transplanted subcutaneously into athymic nude rats in Matrigel containing endothelial growth factors. 3DHistech analyses of transplantation sites proved development of capillary networks from CD31 positive human EC. Network area and number of CD31 positive cells in hESC-EC and hiPSC-EC structures were comparable with those in HUVEC control endothelial cells.

Conclusions: We found that PI3K/FOXO1A pathway has strong effects on arterial and venous endothelial identity. Human ESC-EC and hiPSC-EC remained viable on 3D vascular matrices and they formed capillary networks via transplantation in vivo. Human ESC-EC and hiPSC-EC behave comparable with mature control endothelial cells in vitro and in vivo. In-depth analyses of phenotype and functional characteristics of hESC-EC and hiPSC-EC may enhance their therapeutic application for vascular tissue engineering.

Coronary CT angiography detects twice as much atherosclerotic burden compared to invasive angiography

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Topic(s):
X-ray Computed Tomography (CT)

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Purpose: Despite widespread use of Coronary CT Angiography (CCTA) and Invasive Coronary Angiography (ICA) for coronary plaque burden

assessment, few studies have compared coronary CCTA and ICA regarding semi-quantitative plaque burden measurements.

Methods: We enrolled 71 consecutive patients (mean age 60.8±11.7 years, 36.6% women), who underwent 256-slice CCTA and conventional ICA. A total of 1016 coronary segments were imaged by both modalities. The images were analyzed according the modified 18-segment AHA classification. We excluded 16 segments treated with coronary stents. We calculated the segment stenosis score (SSS), which describes the amount and severity of the stenosis (0-normal, 1-minimal, 2-mild 3-moderate 4-severe 5-occluded). The presence of plaques was described by the segment involvement score (SIS) (0-intact, 1-plaque). The SSS index (SSSi)=SSS/all assessed segments and SIS index (SISi)=SIS/all assessed segments were also calculated. The CCTA and ICA scores were compared with Wilcoxon rank sum test.

Results: CT detected coronary artery plaques in 48.7% of all assessed segments (487/1000), whereas ICA showed coronary plaques in 23.5% (235/1000) of 1000 segments ($p<0.001$). CCTA detected atherosclerotic plaques in 34.8% (266/765) of coronary segments where the ICA was negative. We found significant differences between the two methods for segment involvement and luminal stenosis, CCTA versus ICA; SISi: 0.49±0.22 vs. 0.24±0.14 ($p<0.001$); SSSi: 1.17±0.64 vs. 0.67±0.50 ($p<0.001$).

Conclusion: CCTA detected approximately twice as many coronary segments with atherosclerotic plaques than ICA. Using CCTA for atherosclerotic plaque burden assessment may allow for better risk stratification and treatment of patients with coronary atherosclerosis.

Invasive management of iatrogenic pulmonary vein stenosis is effective in patients after atrial fibrillation ablation

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Topic(s):
Non coronary cardiac interventions

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Atrial fibrillation (AF) ablation has become the standard treatment of paroxysmal AF. Pulmonary vein (PV) stenosis (PVS) is a rare complication

of the procedure, which can be treated with percutaneous angioplasty (PTA) and stent implantation. Safety and efficacy of PV PTA and/or stenting was investigated in the present study.

The presence of significant PVS was verified with CT angiography in symptomatic patients with effort dyspnoe, frequent coughing. In all PVS patients PV PTA was performed. After transseptal puncture selective PV angiography, pressure measurements and then balloon dilatation and/or stent implantation was performed.

Results: Out of 3875 AF ablations since 2005 altogether 12 patients were symptomatic (0.31%). Balloon angioplasty alone as first procedure was performed in 10 out of the 25 stenotized veins, in 5 patient drug eluting balloon was used, two veins were stented with BMS afterward. Furthermore, in 11 veins BMS stents Biotronik Astron 10x40x135 and in 3 patients self expanding DES stents Cook Medical Zilver 8x40x135 mm were used (4 veins). Total PV occlusion was found in 3 cases, which could also be successfully treated with PTA. In one patient rupture of the PV was noticed after the balloon dilatation of the PV, surgical patch plasty of the PV was needed. During PTA of a totally occluded PV distal rupture occured after balloon dilatation causing massive haemoptoe, but it could be effectively treated with balloon reinflation. Restenosis could be observed after the first intervention in 4 patients, all of them were treated with reintervention, 3 out of 4 required a third intervention. 7 veins were affected, in 4 pts balloon dilatation, in 2 pts DES implantation and in 1 case BMS implantation was performed. After re-intervention no significant restenosis could be observed. All patients became asymptomatic, and all of them were put on combined antithrombotic and anticoagulant therapy for one month, after it only clopidogrel and warfarin therapy was continued for one year, when clopidogrel was stopped, and warfarin only was continued.

Conclusion: PV PTA seems to be a feasible method in the treatment of iatrogenic PVS, however the risk of specific complications remained notable. In the presence of verified PVS self expanding DES implantation seems to be the most effective method of treatment, however multicenter studies would be prefereable for the better therapy selection.

Haemostasis changes during percutaneous transcatheter isolation of the pulmonary veins in patients with atrial fibrillation

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Topic(s):
Catheter ablation

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Introduction: Silent or manifest cerebral thromboembolisation is a potential complication of left atrial (LA) ablation for atrial fibrillation (AF). The influence of different ablation techniques on different haemostasis parameters has not been explored.

Purpose: We evaluated haemostasis and endothelium activation parameters in the left atrium (LA) before and after pulmonary vein isolation (PVI) with cryoballoon (CB) or phased radiofrequency (RF) ablations.

Methods: 35 (CB: 17, RF: 18) consecutive patients undergoing PVI were enrolled. Any anticoagulant and platelet inhibitor was discontinued before the ablation. All patients underwent transesophageal echocardiography immediately before the ablation.

Blood samples were taken from the LA before and after ablation to measure haemostasis markers including FXIII activity, fibrin monomer, plasminogen activator inhibitor-1 (PAI-1) activity, plasminogen activity, D-dimer, plasmin-antiplasmin (PAP)-complex and endothelium activation marker soluble E-selectin.

Iv heparin was administered after taking the first sample from LA to reach a target ACT≥300 sec during the whole LA access time.

Results: Changes in hemostasis parameters were compatible with coagulation and fibrinolysis activation after the ablation with both techniques. This was indicated by a significant decrease in FXIII activity (%) (CB: from 128.27±32,25 to 119,83±26,42; p=0,04; RF: from 122,52±27,22 to 118,09±23,29; p=0,04), in the serum level of fibrin monomer (mg/L) (CB: from 68,82±40,80 to 31,86±29,54; p=0,0006; RF: from 99,4±41,65 to 33,04±14,66; p<0,0001), in PAI-1 activity (%) (CB: from 4,31±1,21 to 3,84±0,68; p=0,03; RF: from 4,75±1,23 to 3,87±0,82; p=0,002) and in plasminogen activity (%) (CB: from 117,54±18,23 to 104,92±16,35; p<0,0001; RF: from 107,53±13,87 to 97,7±11,76; p=0,0002).

Further, an increase was demonstrated in D-dimer (mgFEU/L) levels (CB: from 0,60±0,42 to 1,12±0,59; p<0,0001; RF: from 0,63±0,40 to 1,46±0,89 p=0,004) as well as in PAP-complex (ng/mL) levels (CB: from 273,12±115,96 to 356,58±142,88; p=0,04; RF: from 275,50±123,50 to

414,69±166,97; p=0,01).

E-selectin (ng/mL), the marker of endothelium activation increased only with phased RF ablation (from 28,60±11,19 to 32,89±11,54; p=0,023).

Conclusions: Our results indicate that while both PVI techniques activate the coagulation cascade, significant endothelium activation occurs only after RF ablation.

Alcohol consumption and presence of coronary artery disease

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Topic(s):
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Aims: Several observational studies suggested that light alcohol consumption decreases cardiovascular risk. However, the data regarding regular alcohol consumption and its association with coronary artery disease (CAD) still remain controversial.

Objectives: The aim of this prospective clinical study was to investigate the association between alcohol-consumption and the presence of CAD as detected by coronary computed tomography angiography (CTA).

Methods and materials: Consecutive patients who were referred for coronary CTA due to suspected CAD were enrolled in our study. We excluded patients under the age of 18 years and patients with history of stroke, acute myocardial infarction or coronary revascularization. The weekly alcohol consumption was registered using a questionnaire. Alcohol units were calculated as follows: 1 unit equals 2 dl beer or 1 dl wine or 4 cl spirit. Based on the presence or absence of any plaque on coronary CTA we classified the patients into CAD and no CAD groups.

Results: In total, 1925 patients were enrolled (mean age 57.3±16.1 years, females 43.1%). 61.3% participants had hypertension (HT), 13.7% had diabetes mellitus (DM), 40.7% had dyslipidemia (DLP) and 40.1% of the patients were current smokers. Atherosclerotic plaque was present in at least one coronary segment in 74.3% of the patients. Alcohol consumption was reported by 37.3% of the patients with a median of 6.7 (IQR: 3.3;10.8, range: 0.2–66.7) units weekly. Using univariate analysis to compare CAD positive patients and CAD negative patients we found significant difference regarding cardiovascular risk factors ($p<0.001$) but no difference in alcohol consumption ($p=0.35$). After adjusting for age, gender, HT, DM, DLP and smoking with logistic regression we found no association between alcohol consumption and the presence of CAD (OR:1.00; CI:0.98–1.02; $p=0.76$). We performed a secondary analysis to assess the relationship between alcohol consumption and CAD among no drinkers and light drinkers (maximum 14 units per week; 82.7% of alcohol drinkers) and found no association (OR: 1.02; CI:0.98–1.06; $p=0.33$). Furthermore, we have analyzed the effect of different alcohol types (wine, beer, spirit) on the presence of CAD, but no relationship was found between any of the alcohol types and CAD (all $p>0.05$).

Conclusion: Our study suggests that the amount of weekly alcohol consumption does not show association with the presence of CAD. We could not detect any association between alcohol consumption and CAD among light drinkers either. In addition, we did not find any association between the different alcohol types and the presence of coronary atherosclerosis.

Systemic ventricular-arterial coupling and interventricular interaction in isolated post-capillary and combined pre- and post-capillary pulmonary hypertension in severe mitral stenosis

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Topic(s):
Pulmonary circulation, imaging, other

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Background: Patients with secondary pulmonary hypertension (PH) can be further classified based on the degree of increase in pulmonary

arterial mean pressure relative to pulmonary artery occlusion pressure. In isolated post-capillary PH (Ipc-PH) elevated left atrial pressure (LAP) is passively transmitted to the pulmonary venous system, whereas in combined pre- and post-capillary PH (Cpc-PH) additional reactive changes of the pulmonary vasculature lead to further increase of the pulmonary vascular resistance. A detectable secondary disruption of the LV performance has been related to increased mortality in this latter cohort.

Purpose: Despite the prognostic relevance of distinguishing Ipc-PH from Cpc-PH, the haemodynamic profiles of these distinct PH cohorts have not been described. Using rheumatic mitral stenosis (MS) as a model we aimed to investigate the differential alterations in inter-ventricular interaction and ventriculo-arterial coupling in these two distinct forms of PH.

Methods: Invasive haemodynamic and echocardiographic data of 94 patients with PH secondary to MS, before and immediately after percutaneous valvulotomy, along with echocardiograms of 40 age-matched healthy controls were analyzed.

Results: At baseline, Cpc-PH patients displayed greater elevation in right ventricular (RV) pressures and more pronounced RV dysfunction compared to the Ipc-PH group. Interestingly, PH patients demonstrated increased left ventricular (LV) and arterial elastance along with ventriculo-arterial (VA) uncoupling, and these derangements were more evident in the Cpc-PH group. PH patients also displayed abnormal LV deformation, the degree of which was determined by the RV haemodynamic load in the septal region, however, was independent of RV pressure or function and associated with systemic afterload in case of the lateral free wall.

Conclusions: Detailed hemodynamic and echocardiographic profiles distinguishing Ipc-PH from Cpc-PH are presented. Our results provide novel insight into the pathophysiology of altered LV and RV mechanics in PH suggesting that additionally to a direct interaction between the two ventricles, an abnormal VA coupling contributes to the altered LV mechanics that has been associated with adverse prognosis in Cpc-PH.

Prognostic value of novel heart failure biomarkers in patients undergoing cardiac resynchronization therapy

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Topic(s):
Resynchronisation therapy

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Purpose: Cardiac resynchronization therapy (CRT) improves clinical outcomes in chronic heart failure (HF) patients with ventricular dyssynchrony, although some patients do not respond despite correct CRT indications. In this study we investigated a set of novel heart failure biomarkers associated with various pathophysiological pathways of heart failure. The purpose was to assess the ability to predict clinical outcomes after CRT.

Methods: We enrolled 136 HF patients undergoing CRT implantation to our prospective single-center observational study. We measured the plasma levels of pentraxin-3, fractalkine, hepatocyte growth factor, CA-125, TNF-α, MMP-9, and vitamin D before and six months after CRT with commercially available assays. Five year all-cause mortality was the primary endpoint of the study, six month reverse remodelling defined as at least 15% decrease in end systolic volume was considered as secondary end-point.

Results: During five years of follow-up 58 patients (43%) deceased, 66 were considered as non-responder. From baseline clinical variables age, NT-proBNP levels and NYHA class III-IV were predictive of reverse remodelling. Five years all-cause mortality was associated with beta blocker therapy, left brundle branch block and increasing NT-proBNP levels. After adjusting to all significant baseline parameters HGF was the only independent predictor of lack of reverse remodelling (OR: 1.83, CI for OR: 1.10–3.04, p=0.01) and 5-year mortality (HR: 1.35, CI for HR: 1.11–1.64, p=0.003). The reclassification analyses revealed that HGF reached a reclassification improvement of 39% [NRI= 0.39 (0.07–0-71), p=0.01] in reverse remodeling and 69% [NRI= 0.69 (0.39–0.99), p<0.0001] in 5-year mortality prediction. Moreover, discrimination development was 3% [IDI= 0.03 (0.00–0.06), p=0.02] in reverse remodelling and 6% [IDI=0.06 (0.02–0.11) in 5-year mortality prediction.

Conclusion: Of all studied novel biomarkers HGF, the pleiotropic cardioprotective growth factor was the only independent predictor of clinical outcomes in patients undergoing CRT, reclassification analyses showed that it may be useful in refining patient selection.

The predictive role of mitral regurgitation in ischemic heart failure patients undergoing cardiac resynchronization therapy

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Resynchronisation therapy

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Purpose: Cardiac resynchronization therapy (CRT) reduces mortality and morbidity in selected heart failure patients, although the predictors of non-response are not fully recognized. Ischemic cardiomyopathy is associated with reduced clinical response to CRT, moreover coronary artery disease (CAD) patient with significant mitral regurgitation (MR) have higher mortality risk regardless the presence of HF. The purpose of our study was to assess the impact of significant MR on clinical outcomes in ischemic and non-ischemic HF patients undergoing CRT.

Methods: We enrolled 117 consecutive patients undergoing CRT, the follow-up period lasted for 5 years. The primary end-point was 5-year all-cause mortality, 2-year HF hospitalization was considered as secondary end-point. Echocardiographic measurements were taken off-line, MR were quantified using the PISA method, according to recent EACVI guidelines.

Results: The mean age of patients were 70.2±10.3 years, 78% were male, 55% suffered from HF of ischemic origin. Baseline anthropometrics, severity of HF and comorbidities did not differ among patients with ischemic and (I) non-ischemic (N-I) HF. We observed significant MR in half of the patients (I:52% vs N-I:50%, p=0,088). During follow-up 42 patients (36%) reached the primary end-point, neither ischemic aetiology (p=0,816) nor the severity of baseline MR (p=0,28) predicated 5-year mortality. Analysing ischemic patients separately, baseline MR was not associated with mortality (p=0,244). This trend was observed regarding HF hospitalization as well, baseline MR (p=0,244) and ischemic aetiology (p=0,14) showed no significant correlation with hospitalization. MR decreased in both groups (I:-16±22 vs N-I:-7±15; p=0.067), although the decrease was higher in ischemic patients. Persisting significant MR predicted increased risk of both mortality (p=0,067) and HF

hospitalization (p=0,016), the aetiology of HF did not alter this association.

Conclusion: Baseline MR was not associated with clinical outcomes after CRT, both in ischemic and non-ischemic patients. On the other hand persisting significant MR predicted increased risk of mortality and morbidity regardless of HF aetiology.

Physiologic and prognostic implications of the negative diastolic pulmonary pressure gradient in patients with left heart disease

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Topic(s):
Chronic pulmonary hypertension

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Background: The diastolic pressure gradient (DPG) has been introduced as a reliable metric for defining combined pre-capillary pulmonary hypertension (Cpc-PH) in left heart disease (LHD). The hemodynamic advantage of DPG against the traditionally used trans pulmonary gradient and pulmonary vascular resistance was initially supported by the superiority of DPG as a prognostic marker. However, more recent studies have challenged the prognostic power of the DPG, evoking a need for a better understanding of the optimal use and limitations of this measure. In particular, the clinical relevance of negative DPG (DPGNEG) measurements remains to be clarified.
Objectives: We hypothesized that large V-waves in the pulmonary artery wedge (PAWP) curve that cause an asymmetric pressure transmission, conceivably influencing the DPG calculation are responsible for the frequently occurring phenomenon of DPGNEG values. This prospective study was undertaken in order to clarify the physiological meaning of DPGNEG measurements and to investigate their prognostic implication.
Methods: Right heart catheterization and echocardiography was performed in 316 patients with left heart disease (LHD) due to primary myocardial dysfunction or valvular disease (rheumatic mitral stenosis - MS). Simultaneous PAWP and direct left atrial pressure (LAP) measurements were performed in 51 patients.

Results: 256 patients had PH-LHD (MS 37%) of whom 48% had DPGNEG. The V-wave was inversely associated with DPG (r= -0.45, p<0.001) in patients with low pulmonary vascular resistance (PVR<3 WU), but not in those with elevated PVR (p>0.05). Patients with large V-wave had lower DPG as compared to those without augmented V-wave (p<0.001) despite similar PVR (p>0.05). Simultaneous PAWP and direct LAP measurement yielded similar DPGNEG incidence. Positive but normal DPG (0–6 mmHg) was associated with worse 2-year prognosis for death and heart transplantation compared to DPGNEG (adjusted hazard ratio: 2.97; p<0.05).
Conclusion: Our results advocate against the current notion of DPGNEG constituting a measurement bias. Instead, we propose that DPGNEG can be partly ascribed to large V-waves and carries a better prognosis as compared to DPG within the normal positive range.

Prognostic value of obstructive coronary artery disease on CTA in diabetic patients: a meta-analysis

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Topic(s):
CAD and comorbidities

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Background: There is still equipoise concerning the risk of significant stenosis by coronary computed tomography angiography (CTA) in diabetic patients.

Purpose: We performed a meta-analysis to assess the prognostic value of obstructive coronary artery disease (CAD) on CTA in diabetic

patients.

Methods: The meta-analysis was performed in in accordance with the MOOSE guidelines. PubMed and Embase were searched up to November 2015. Study subjects characteristics and outcomes were collected by one physician and checked by a second. Study quality was ascertained in consensus using the quality in prognosis studies (QUIPS) tool. We calculated the prevalence of obstructive CAD on CTA in diabetic patients, as well as annualized event rates, and assessed adjusted hazard ratios (HR). HR for obstructive CAD on CTA were pooled using generic inverse random model.

Results: Five studies were eligible for inclusion into this meta-analysis, with 5,070 participants, (weighted age 61, 55% male) with a follow-up period ranging from 20 to 66 months. The prevalence of obstructive CAD was 36.9%. Annualized event rate was 11.2% for obstructive CAD. Obstructive CAD was associated with an increased adjusted HR of 4.7 (95% CI 2.0–10.7).

Conclusions: Obstructive CAD on CTA is associated with increased event rates and significant higher HR in diabetic patients.

Integrated score of ST segment resolution following primary PCI - a new predictor of 1 year mortality in STEMI

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Topic(s):
Risk scores

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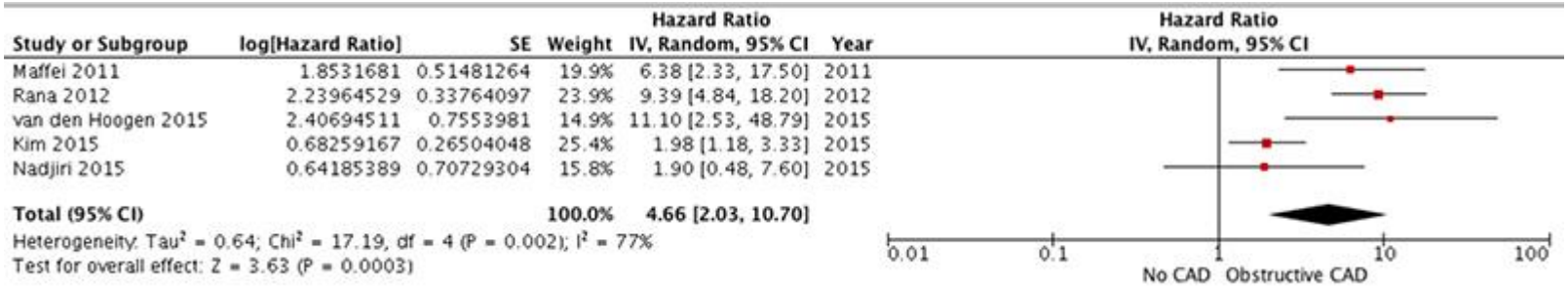
Introduction: ST-segment resolution reflects myocardial reperfusion in patients undergoing primary percutaneous coronary intervention (pPCI) for acute ST-segment elevation myocardial infarction (STEMI). However, this resolution is usually estimated using a qualitative analysis of the ECG tracings in one or two leads. Little is known on the correlation between the ST segment resolution after primary percutaneous coronary intervention (PCI), calculated as a global ECG score, and the future cardiovascular risk. This study aimed to assess the correlation between ST-segment resolution, calculated as an integrated score including all the ECG derivations where any elevation was present, and one-year mortality or MACE rates in patients undergoing primary PCI.

Material and methods: 580 consecutive patients with STEMI undergoing primary PCI were included in the study. Calculation of the ECG integrated score was based on summing all the ST segment elevations, from all the leads where any elevation was present. Calculation was performed immediately after admission and was repeated at 1 hour after the primary PCI. Patients were divided in two groups: gr 1 - 477 patients (82.2%) with>50% ST segment resolution and gr. 2 - 103 patients (17.7%) with <50% ST-segment resolution.

Results: Total amplitude of the ST-segment elevation at baseline did not present any significant difference between the groups (ST score 7.4 mm in gr. 1 vs 7.6 mm in gr. 2, p=0.002). However, lack of >50% ST segment resolution in the integrated score was associated with higher rates of death (15.5% vs 4.8%, p=0.0002), reinfarction (19.2% vs 4.4% p<0.0001) and revascularization (21.15% vs 5.8%, p<0.0001) at 1 year. Multivariate logistic regression analysis demonstrated that lack of regression of the ST segment score resolution independently predicted the occurrence of a MACE event in one year (OR 3.43, p=0.002).

Conclusions: Global regression of ST segment elevation on the surface ECG was associated with significantly lower death and MACE rates in STEMI patients undergoing primary PCI. The lack of regression of the integrated score of ST-segment elevation has been proved to be directly correlated with the risk of future cardiac events in these patients, this regression representing a new tool for risk stratification in STEMI patients.



Forest plot of Hazard ratio

Pharmacological preconditioning with gemfibrozil preserves cardiac function after heart transplantation

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Topic(s):
Ischaemia and protection

Citation:
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Background: The incidence of terminal heart failure is continuously growing, thereby increasing the clinical importance of its definitive treatment, heart transplantation. Pharmacological activation of soluble guanylate cyclase (sGC), thus increasing cGMP-signalling has been reported to have cardioprotective effects, however, potent sGC activator compounds are still under development thus they are not available for the clinical setting. Gemfibrozil, a widely used lipid-lowering fibrate has recently been shown to exert sGC activating properties in vitro. The aim

of the present study was to investigate whether pharmacological preconditioning of donor hearts with gemfibrozil could protect against ischemia/reperfusion injury and preserve myocardial function in a heterotopic rat heart transplantation model.

Methods: Donor Lewis rats received p.o. gemfibrozil (150mg/kg BW) or vehicle for 2 days. The hearts were explanted, stored for 1h in cold preservation solution, and heterotopically transplanted. 1h after starting reperfusion, left ventricular (LV) pressure-volume relations and coronary blood flow were assessed to evaluate early post-transplant graft function. Additional histological and molecular biological measurements were performed.

Results: After 1h reperfusion, LV contractility (LV systolic pressure: 178±10 vs. 87±7 mmHg, $p<0.001$; dP/dtmax: 4595±472 vs. 2348±306 mmHg, $p<0.001$ at 180µl LV volume, active relaxation (dP/dtmin: −2473±216 vs. −1273±138 mmHg, $p<0.001$ at 180 µl LV volume) and coronary blood flow (2,7±0,2 vs. 2,1±0,2 ml/min/g, $p=0.02$) were significantly improved in the gemfibrozil pretreated hearts when compared to controls.

Conclusion: Pharmacological preconditioning with gemfibrozil reduces reperfusion injury and preserves graft function after heart transplantation, which could be the consequence of enhanced myocardial cGMP-signalling. Gemfibrozil might represent a useful tool for cardioprotection in the clinical setting of heart transplantation surgery in the future.