

Basic Science – Vascular Diseases: Biomarkers

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Development of reactive pulmonary hypertension induced by left heart failure can be predicted by the assessment of the level of new biomarkers - results on experimental rat model

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Introduction: The most common cause of pulmonary hypertension (PH) in patients is due to left heart failure (HF). Diagnosis of early stages of HF or PH have not been clearly obvious, recently. Elevated filling pressures in the heart and pulmonary vascular remodelling is associated with expression changes of the various plasma levels of biomarkers.

Purpose: To assess the plasma levels of HF biomarkers on a new rodent model of HF induced by the left ventricle pressure-overload which leads to the development of reactive PH consist of pulmonary vascular remodelling.

Methods: The left heart failure was induced by pressure overload in adult male Wistar rats by inserting a polyethylene tubing into aorta through the right carotid artery. Three weeks later experimental animals were studied (the group E, n=6) and compared to the controls (n=6). Serial venous blood samples were taken from both experimental groups to determine levels of biomarkers involved in pathophysiology cardiac and vascular remodelling: Troponin I, N-proBNP, Copeptin, Apelin, Endostatin, Asymmetric dimethylarginine (ADMA), Growth/differentiation factor 15 (GDF-15), Ceruloplasmin and Cystatin-C. The biomarker levels were assessed by ELISA method.

Results: The left ventricle end-diastolic pressure was elevated in the group E (1.34 ± 0.07 mmHg vs. 0.41 ± 0.13 mmHg in the controls; $p < 0.0001$). Mean pulmonary arterial blood pressure measured by catheterization was increased 22.9 ± 0.7 mmHg compared to the controls 16.9 ± 1.0 mmHg; $p < 0.05$. Weight of the right ventricle relative to body weight was $5.5 \pm 0.3 \cdot 10^{-4}$ compared to the controls $4.6 \pm 0.2 \cdot 10^{-4}$; $p < 0.05$. In lung histology, 74% of small pulmonary vessels had muscularized media (24% in controls; $p < 0.01$).

Elevated blood plasma levels of biomarkers in the group E compared to the controls were found in: NT-proBNP (671.8 ± 61.2 pg.mL⁻¹ vs. 450.3 ± 47.5 pg.mL⁻¹; $p < 0.05$; respectively) and Copeptin (251.9 ± 41 pg.mL⁻¹ vs. 141.3 ± 10.1 pg.mL⁻¹; $p < 0.05$; respectively). Significantly decreased blood plasma levels of biomarkers in the group E compared to the controls were found in the values of Apelin (4.0 ± 0.09 ng.mL⁻¹ vs. 4.3 ± 0.05 ng.mL⁻¹; $p < 0.05$; respectively) and ADMA (12.1 ± 0.5 mg.mL⁻¹ vs. 15.3 ± 0.8 mg.mL⁻¹; $p < 0.05$; respectively). We found no significant changes in the blood plasma levels compared to the controls in the values of TnI, GDF-15, Endostatin, Cystatin-C and Ceruloplasmin.

Conclusion: We develop a brand new rodent model of PH accompanied with pulmonary vascular remodelling induced by left HF. Presented experimental model was associated with increased concentration of biomarker of cardiac remodelling: NT-proBNP and Copeptin and with decreased level of biomarkers that have protective effect against vascular remodelling: Apelin and ADMA.

Atherosclerosis, Cerebrovascular Diseases, Aneurysm, Restenosis

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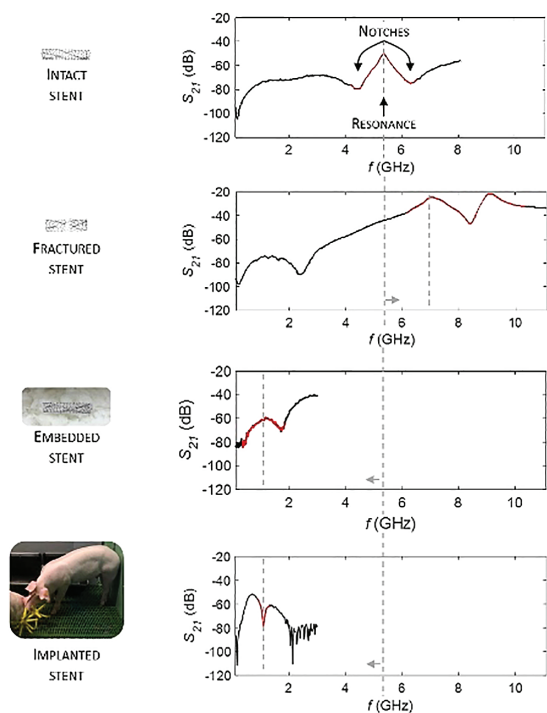
Microwave spectrometry for coronary stent monitoring

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Background: Coronary artery disease (CAD) is the leading cause of death worldwide, and percutaneous coronary intervention with stenting the most widely performed procedure to treat CAD. However, current stent monitoring techniques are invasive and/or ionizing. Microwave spectrometry (MWS) may provide a non-invasive, non-ionizing and cost-effective alternative capable of detecting stent-related pathologies before they cause fatal heart failure.



MWS response to monitor stent status

Purpose: To develop a new MWS-based technology to monitor coronary stents in an in vivo swine model.

Methodology: First, using a new MWS device, an in vitro experiment was carried out to demonstrate: (1) the ability of detecting the presence of a stent and (2) stent fractures (SF). To that end, an intact stent was distanced 3, 7, 11 and 15 mm from a MWS near-field probe in open-air conditions. Afterwards, three identical stents were piecemeal cut to emulate type I, II and III SF at different fractions of the stent's length (l): 1/5, 1/3 or 1/2. Additionally, the stent was measured in a phantom substance, to simulate in vivo conditions: it was distanced from 0 to 40 mm in steps of 5 mm. Likewise, a pair of MWS far-field antennas measured the stent at 10, 20, 30 and 40 mm.

Resynchronization Therapy

P569

Myocardial dyssynchrony and a different response to cardiac resynchronization therapy in patients with chronic heart failure and atrial fibrillation

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Background: The search for ideal responders to cardiac resynchronization therapy (CRT) remains relevant and is widely discussed nowadays.

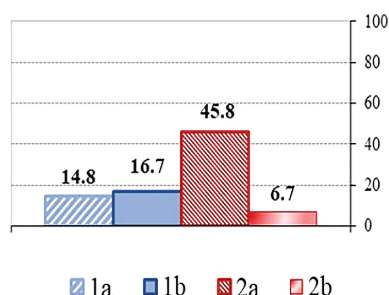
Purpose: To assess the echocardiographic response to CRT depending on the myocardial dyssynchrony in patients with chronic heart failure (CHF) and permanent atrial fibrillation (AF).

Methods: The study included 101 patients with CHF NYHA II – III, left ventricular ejection fraction <35% and QRS≥130 ms. All patients underwent CRT. Then atrioventricular node ablation was performed to 83 patients, but 18 patients refused it. The criterion for the effectiveness of CRT was a decrease in the end-systolic volume ≥15%. The survey was conducted initially, after 3 and 12 months from the date of inclusion in the study. According to the results of the prospective observation groups of patients with CHF and AF were formed in dependence on the duration and sustainability of the response to CRT: 1a – early response (3 month) and preservation of effect by 12 months, 1b – 'elusive' early effect, 2a – delayed response (12 month), 2b – non-responders.

Results: The study revealed the correlation between the increase in the presystolic delay on the aortic valve and the delayed response to CRT that was confirmed by the results of the frequency analysis of this interventricular delay. In groups 1a, 1b and 2b the frequency of cases of presystolic delay on the aortic valve varied from 67% to 73%, but in group 2a it was 100%. We obtained similar results analyzing dispersion of intraventricular contraction. In group 2a a variance of intraventricular contraction of more than 100 ms was found in 90.5% of patients (no more than 70.0% of patients in the remaining groups).

Responders and non-responders significantly differed in the incidence of moderately extended and wide QRS. Picture 1 demonstrates the incidence of QRS wide (>150 ms) in patients with a different response to CRT. The results indicated the dependence of the positive effect of CRT on the width of the QRS complex.

Conclusions: The early sustained response to CRT was more commonly detected in NYHA II patients. There were more non-responders among those with NYHA III. Patients with an early and sustained response to CRT were characterized by higher median values of the 6-minute walk test. Diabetes mellitus was more often detected in individuals with the 'escape' of the early positive effect. A smaller proportion of atrioventricular node ablation was found in the subgroup with an elusive effect, which allows us to conclude that ablation of the AV compound increases the effectiveness of CRT in individuals with AF.



QRS wide incidence and CRT response

Ventricular Assist Devices

P571

Effect of levosimendan infusion prior to left ventricular assist device implantation

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Introduction: Data on the safety and efficacy of preoperative levosimendan infusion in patients undergoing left ventricular assist device (LVAD) implantation is scarce.

Purpose: To investigate the clinical utility of preoperative levosimendan administration in patients prior to LVAD implantation. Our hypothesis was that preoperative

levosimendan will be associated with improved post-operative outcomes due to extended cardiovascular therapeutic effects from its long-acting active metabolites.

Methods: A retrospective analysis of all consecutive patients who received continuous-flow LVADs (HeartMate 2, 3, and HVAD) between August 2012 and May 2018 in a single tertiary center. INTERMACS profile 1 patients were excluded. Patients who received preoperative levosimendan were compared to patients who did not receive levosimendan preoperatively.

Results: The study cohort consisted of 62 patients (40 [65%] in the levosimendan group and 22 [35%] in the no-levosimendan group) with a median follow-up of 21 months.

Preoperative laboratory parameters were similar in both groups except for lower median albumin levels among patients in the levosimendan group (3.7 g/dL vs. 4 g/dL; $P=0.024$). Preoperative echocardiographic parameters, including left ventricular ejection fraction, the presence of enlarged right ventricle (RV), moderate to severe reduction in RV function and above moderate tricuspid regurgitation were similar between the levosimendan and no-levosimendan groups (median of 15% vs. 17.5%; 18% vs. 7%; 52.5% vs. 40.9%; and 10% vs. 13.6%, respectively; $p>0.1$ for all). Preoperative cardiac output, mean pulmonary artery and right atrium pressures and pulmonary vascular resistance were also similar between the groups (median of 2.93 L/min vs. 3.19 L/min; 41.5 mmHg vs. 33 mmHg; 10 mmHg vs. 8 mmHg; and 3.17 wood units vs. 4.02 wood units, respectively; $p>0.1$ for all). Preoperative median pre-capillary wedge pressure was higher in the levosimendan group (28 mmHg vs. 23.5 mmHg; $P=0.047$).

No patient in either group required right ventricular assist device support. There was no difference in post-operative inotropes and ventilation support time between the levosimendan and no-levosimendan groups (median of 51 hours vs. 72 hours; $P=0.41$ and 24 hours vs. 27 hours; $P=0.19$, respectively). Length of hospitalization, both total and in the intensive care unit was similar (median of 13 days vs. 16 days; $P=0.34$ and 3 days vs. 4 days; $P=0.44$, respectively).

Post-operative laboratory and echocardiographic parameters did not differ between the groups. The in-hospital complication rate including bleeding, surgical re-exploration and cardiac arrhythmias was also similar.

There was no significant difference in the in-hospital and long term mortality throughout the follow-up period between the groups (2.5% vs. 4.5%; $P>0.99$ and 10% vs. 27.3% respectively; $P=0.64$).

Conclusion: Levosimendan infusion prior to LVAD implantation was not associated with improved post-operative outcomes.

Chronic Heart Failure: Rehabilitation

P572

Characteristics of good response to aerobic exercise training in decompensated heart failure patients

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Introduction: Exercise training is an excellent tool to promote functional capacity in chronic heart failure (HF) patients. Although its benefits in this population, it needs to be demonstrated in decompensated HF patients. A way to optimize an intervention is to evaluate who are the good responders and understand the causes of no response. Knowing the factors of good response is also important to emphasize the feasibility of an intervention and to deliver it to the ones who get the most benefit of it.

Purpose: To identify the characteristics that lead a patient to have a better response to an aerobic exercise training program for decompensated HF inpatients – ERIC-HF (early rehabilitation in cardiology – heart failure)

Methods: 50 patients who performed ERIC-HF program during the phase of stabilization were evaluated in terms of their sociodemographic, functional and physiological characteristics and performance during the program. The main variable used to understand the performance of the patients was the variation of the distance walked in the 6-minute walking test (6MWT), performed as soon as the patient were able to do it (6MWTinitial) and at discharge (6MWTdischarge). A multiple linear regression was made in order to determine which variables are related to a better variation on the 6MWT, namely: age, LCADL and Barthel index (BI) scores at admission and discharge, number of days of hospitalization, number of cardiovascular risk factors, NYHA class, etiology of HF and ventricular function. Durbin-Watson test was used to analyze the existence of independence of residual random variables. It was assumed a significance level at $p<0.05$.

Results: Patient's average age was 71 (± 11) years old, 34 are male, 80% are in NYHA class III and 73% have severe left ventricular depression. Patients present a median of 76 points in BI at admission (minimum of 45 and maximum of 97) and a median of 32 at LCADL (minimum of 24 and maximum of 45 points). The mean distance walked in the 6MWTinitial performed by the patients was 199.9 (± 115.9) meters and 287.6 (± 128.9) meters at 6MWTdischarge, representing a 87.7 (± 170.6) meters variation.

According to the linear regression, an equation was obtained: Difference of the 6MWT = $454.694 - 1 \cdot 6MWT_{initial} + 2.981 \cdot Barthel_{initial} - 5.554 \cdot age$. This equation explains 65% of the variation of the model in this sample of patients. Using this variables it's possible to know how much distance a patient can walk, and understand if he is going to have a good performance in the program.

Conclusions: Patients with the worst results in the initial 6MWT, higher initial Barthel and younger ages, will get the most gains in terms of difference walked between the initial and final 6MWT and have the most benefit from the intervention program.

Chronic Heart Failure: Multidisciplinary Interventions

P574

The impact of percutaneous mitral valve repair with mitralclip in cardiopulmonary performance

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Aim: The aim of this study was to evaluate changes in New York Heart Association (NYHA) functional class, cardiopulmonary exercise test (CPET) variables, 6-min walk test (6MWT) in patients (pts) submitted to percutaneous mitral valve repair with MitraClip (MC).

Methods: Prospective analysis of 46 pts with moderate to severe mitral regurgitation - MR - (grades III-IV) submitted to MC between 2013 and 2019 in our institution. The Wilcoxon sign test was used to assess the procedure's effect on NYHA Class, CPET and 6MWT, by comparing several variables at baseline and at 1 year postprocedure follow-up. P-values < 0.05 were considered significant.

Results: 46pts, 61% male, with a mean age of 65 ± 14 years (Y) and mean follow-up time of 17 ± 14 months, of which 58.7% presented with grade IV MR (mean regurgitant volume - 49.6 ± 21 ml; mean EROA - 35.1 ± 13 mm²) and 75% with functional MR. Mean LVEF of $36\% \pm 11.8$, with 55% presenting a LVEF < 35%. Mean Euroscore II of 6.0 ± 7 . 27.5% had already undergone a previous cardiac surgery, in most cases CABG (63.6%). 34.8% had already suffered an acute coronary syndrome and 63% had atrial fibrillation. Mean pre-procedural peak oxygen uptake (pVO₂) of 14.3 mL/kg/min and mean distance in the 6 minute walk test (6MWT) of 322 ± 96 m. Device implantation was successful in 45 pts with a device success rate of 87% (successful implantation and reduction in MR to grade 2 or less), with 54% of pts presenting mild MR before discharge. There were immediate complications related to the procedure in 17.5% of pts, with 4pts experiencing tendinous cord rupture and 2pts leaflet tear. There were no cases of pericardial tamponade or embolic complications. Follow-up mortality of 34.8% (16pts), with 9 deaths in the first-year post-procedure, 1 pt referred to cardiac surgery due leaflet tear and 1pt to heart transplantation. Successful MC was associated with an improvement in pVO₂ (14.3 vs 18.6 mL/kg/min, $p=0.043$), 6MWT distance (322.2 m vs 373.2 m, $p=0.001$) at 1 year follow-up, irrespective of MR aetiology and left ventricular systolic function. It also led to an improvement in NYHA class both at 6 months (mean NYHA class: 2.9 vs 2.1 , $p=0.009$) and 1 year post-procedure (mean NYHA class: 2.9 vs 2.0 , $p=0.001$). However, these improvements weren't verified at the 1 and 6 months follow-up. MC wasn't associated with a reduction of neither the natriuretic peptide value (854.6 vs 450.1 pg/ml, $p=0.241$) nor the VE/VCO₂ slope value (36.2 vs 34.1 , $p=0.144$) at 1 year follow-up.

Conclusion: Percutaneous mitral valve repair with MitraClip was associated with an enhancement in cardiopulmonary performance and reduction in the symptomatic burden after the first year post-procedure.

Variable	Before MitraClip Implantation	1 year after MitraClip Implantation	p value
Peak Oxygen Uptake (mL/kg/min)	14.3	18.6	0.043
6-min walk test Distance (m)	322.2	373.2	0.001
NYHA Class	2.9	2.0	0.001

Chronic Heart Failure: Pharmacotherapy

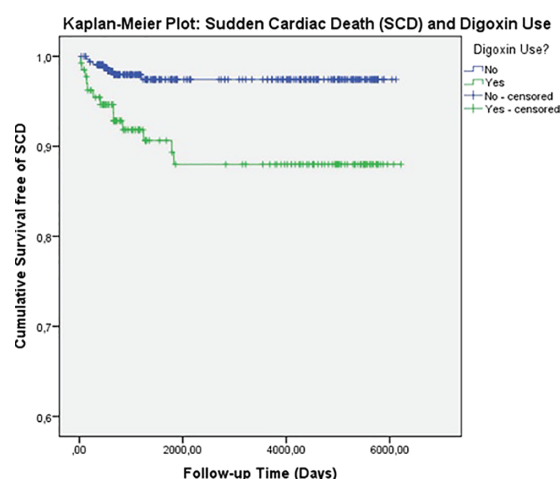
P575

Prognostic impact of digoxin use in a heart failure population

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Aim: Digoxin (D) may be considered in patients (pts) in sinus rhythm with symptomatic HFrEF to reduce the risk of hospitalization and in pts with HFrEF and atrial fibrillation (AF) for rate control. There are some controversies regarding its safety in this population, with some studies suggesting a higher risk of events, while others showed no deleterious effect on mortality.

Methods: Prospective evaluation of adult pts with HFrEF submitted to CPET in a tertiary centre. Pts were followed up for at least 1 year for the primary endpoints of cardiac death, urgent heart transplantation/ventricular assist device implantation in the first year of follow-up (MH1) and sudden cardiac death (SCD). Univariate followed by Cox multivariate regression analysis were performed to evaluate the impact of D use in the study's endpoints. Survival analysis was performed using Kaplan-Meier plots.



Results: CPET was performed in 487 HFrEF pts, with a mean age of 56.3 ± 12.5 years, of which 79.1% were male, 46.3% of ischemic aetiology (IA), with a mean LVEF of $30.4 \pm 7.6\%$, a mean heart failure survival score (HFss) of 8.6 ± 1.1 . At baseline, 134 (29.3%) pts were receiving D. These pts presented lower LVEF (26.7% vs 30.9% , $p<0.001$), HFss (8.3 vs 8.7 , $p<0.001$) and sodium values (137.0 vs 138.3 , $p<0.001$), a lower prevalence of coronary artery disease (38.8% vs 49.2% , $p=0.042$), but a higher prevalence of AF (38.8% vs 19.8% , $p<0.001$). There was no difference regarding patient's age, prevalence of chronic kidney disease (CKD), peak oxygen uptake (pVO₂) or VE/VCO₂ slope values. Baseline D use was independently associated with an increased risk of SCD in our population (HR: 3.45; 95%CI 1.28-9.27, 0.014), as well as in pts of IA (HR: 4.45, 95%CI 1.25-15.83, $p=0.014$) and with CKD (HR: 15.57, 95%CI 1.97-123.02, $p=0.009$). There was no association with SCD in pts of non-ischemic aetiology, preserved renal function and AF. Pts taking D presented a significantly higher incidence of SCD (log rank $p<0.001$). D use was not independently associated with MH1 in the general population ($p=0.122$ in multivariate analysis), but it was in pts of IA (HR: 4.94, 95%CI 1.32-18.39, $p=0.017$).

Conclusion: In our HF population, D use was an independent predictor of SCD, particularly in pts with coronary artery disease and CKD.

Resynchronization Therapy

P576

Prognostic value of submaximal cpet variables in heart failure patients with biventricular pacing

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Aims: The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation (HT) states that the peak volume of oxygen consumption