

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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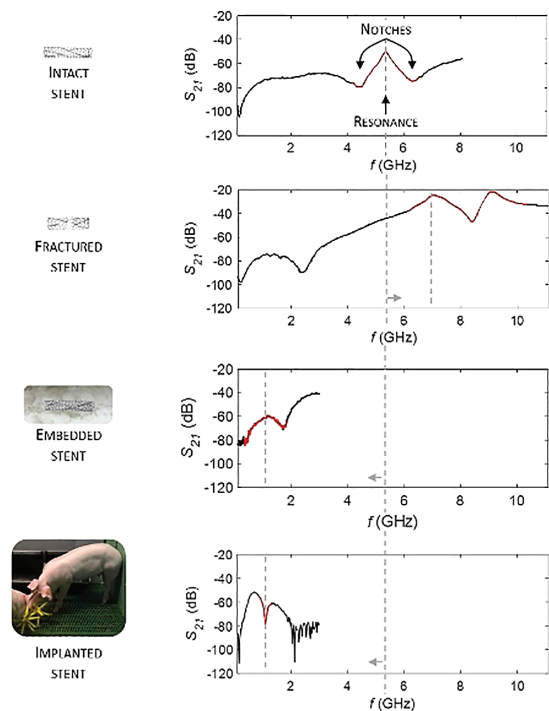
Microwave spectrometry for coronary stent monitoring

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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.

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Background: Heart failure (HF) contemporary management has significantly improved over the past two decades leading to better survival. How application of the contemporary HF management guidelines affects the risk of death estimated by available web-based risk scores is not elucidated.

Objective: To assess changes in mortality risk prediction after a 12-month management period in a multidisciplinary HF Clinic.

Methods: Out of 1.689 consecutive patients with HF admitted at our ambulatory HF Clinic from May 2006 to November 2018, those who completed one year follow-up were considered for the study. Patients without NTproBNP measurement or with more than 3 missing variables for risk estimation were excluded. Three contemporary web-based HF risk scores were evaluated: MAGGIC-HF, Seattle HF Model (SHFM) and the Barcelona Bio-HF Calculator containing NTproBNP (BCN Bio-HF). Risk of all-cause death at one year and at 3 years were calculated at baseline and re-evaluated after 12-month management in a multidisciplinary HF Clinic. Wilcoxon paired data test was used to compare changes in mortality risk estimation over time and test equality of matched pairs for comparing estimated change among tools. 442 patients used to derive the Barcelona Bio-HF Calculator were excluded for discrimination purposes.

Results: 1.157 patients were included (age 65.7 ± 12.7 years, 70.4% men). A significant reduction in mortality risk estimation was observed with the three HF risk scores evaluated at 12-months (Table). The BCN Bio-HF model showed significantly different changes in risk estimation, fact that indeed was partnered with numerically better discrimination. AUC at 1 and 3 years, respectively, were: BCN Bio-HF (0.773 and 0.775), MAGGIC HF (0.686 and 0.748) and SHFM (0.773 and 0.739).

Conclusions: The three web-based risk scores evaluated showed a significant reduction in mortality risk estimation after 12 month management in a multidisciplinary HF Clinic. The BCN Bio-HF score showed higher reduction in estimated risk, together with better discrimination, likely because it incorporates contemporary treatment and use of biomarkers.

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Effect of pulmonary rehabilitation on exercise tolerance and functional class in patients with heart failure and chronic obstructive pulmonary disease

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Background: Pulmonary rehabilitation (PR) is a complete intervention based on an evaluation of the patient and followed by adapted therapies for education, behavior change, and pulmonary physiotherapy to optimize the patient's condition and to improve: physical capacity, quality of life, dyspnea and fatigue, characteristic symptoms in Heart Failure (HF), and Chronic Obstructive Pulmonary Disease (COPD). However, there is evidence of the low exercise tolerance, and worse functional class affect their muscle functionality and prognosis. Therefore, PR has beneficial effects on these aspects. Despite this, no studies are demonstrating the benefit in patients with concomitant HF and COPD.

Groups differences			
	Before PR	After PR	p
Exercise tolerance (m)	349± 87.50	413.71±85.28	0.039
NYHAIII/IV	6 (42.86)	2 (14.29)	0.008
	7 (50.00)	9 (64.29)	
	1 (7.14)	3 (21.43)	
Handgrip strength (kg)	28.03± 7.19	29.22± 6.88	0.213
Phase angle	5.59± 0.66	5.63± 0.65	0.625

PR: Pulmonary Rehabilitation

Objective: To evaluate the effect of PR on exercise tolerance and functional class in patients with HF and COPD concomitant.

Materials and Methods: In a pilot clinical trial patients older than 40 years with a confirmed diagnosis of HF and COPD concomitant were included. Patients with cancer and exacerbations less than 3 months were excluded. They got into a pulmonary rehabilitation program 3 times a week for 3 months. Exercise tolerance was evaluated by the 6-minute walk test. A paired t-student and Wilcoxon was performed.

Results: Fourteen subjects were included, age was 67.86 ± 9.34 years, 86.7% were men, 40% had obesity, 33.3% diabetes, 20% OSAS, and 60% hypertension. After the intervention, exercise tolerance increases 64.72 ± 105.29 meters, $p = 0.038$. Besides, improved the functional class ($p = 0.004$). The rest of the variables, there was no significant difference.

Conclusions: The PR improves clinical status in patients with both pathologies. However, studies involving these types of patients are not carried out. Therefore a program PR in patients with concomitant HF and COPD improves tolerance to the exercise of quality of life and probably the prognosis.

Chronic Heart Failure: Rehabilitation

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ERIC-HF program (early rehabilitation in cardiology - heart failure) - pilot study

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Introduction: Decompensated Heart Failure (HF) patients are often characterized by functional dyspnea, fatigue, edema, functional dependence and impairment of performance in activities of daily living.

Aerobic exercise training (AET) is a well establish cardiac rehabilitation intervention which improves symptoms, promotes the functional capacity and even increase exercise tolerance. Although the benefits, exercise is not yet validated for inpatients during the phase of stabilization.

Purpose: To evaluate the feasibility and safety of an AET program for patients admitted due to decompensated HF: ERIC-HF (Early Rehabilitation in Cardiology - Heart Failure) program

Methods: Pilot randomized controlled single-blind trial Patients are randomized in training group (TG) or control group (CG). Data include cardiovascular history, HF history and two functional tools: London Chest of Daily Living Activities (LCADL) and Barthel Index (BI). TG patients performed the ERIC-HF program twice a day for 5 days per week. ERIC-HF program is a supervised AET program, with increasing levels of intensity, divided into 5 stages (respiratory training, cycleergometer training, gait training and climbing stairs, for progressive duration periods). Vital signs were evaluated before and immediately after the exercise, as well as the Borg Modified Perceived Exertion. CG patients performed physical activity in accordance with the guidelines available for inpatients, always supervised too. A six-minute walking test

Changes in 1- and 3-year mortality risk

	1-y risk at baseline	1-y risk at 12 m	Median relative risk reduction	p-value	3-y risk at baseline	3-y risk at 12 m	Median relative risk reduction	p-value
MAGGIC-HF	12.2 (7.7-19.1)	10.2 (6.3-16.0)	16.4%	<0.001	29.2 (19.1-42.7)	24.7 (16.0-36.9)	15.4%	<0.001
SHFM	4.33 (2.9-6.9)	3.60 (2.4-5.7)	16.3%	<0.001	12.4 (8.3-19.4)	10.4 (7.07-16.1)	16.1%	<0.001
BCN Bio-HF	11.9 (5.5-25.6)	7.8 (3.3-17.3)	34.5%	<0.001	38.5 (19.7-68.0)	26.9 (12.3-51.8)	30.1%	<0.001

*Median (IQR) values. #Wilcoxon paired data test.

(6MWT) was performed as soon as patients are able to do it. At discharge, all patients perform another 6MWT, as so as evaluation of LCADL and BI.

Results: 114 patients were randomized (64 in TG and 50 in CG) with an average of age of 72 (± 9) years old, 70 are male, 82% are in NYHA class III. At admission, both groups have the same level of functional dependence according to LCADL (31 vs 32) and Barthel (73 vs 73) scores. TG patients performed 932 sessions of exercise, with an average of 17 sessions each, for 15 (± 9) days of hospitalization. There is a difference of 83 meters between the two 6MWT performed by TG patients, which demonstrates clinical significance. At discharge, TG patients presented lower LCADL score (12 vs 16, $p=0.006$), higher BI (98 vs 92, $p=0.038$) score and a 64 meters difference on the 6MWT ($p=0.0032$) which represents a better functional capacity. There were absence of adverse events like falls, precordial pain, malignant arrhythmias and worsening of clinical state

Conclusions: ERIC-HF program demonstrated, in this sample of patients, to be safe and to promote functional capacity. We can also infer that probably AET is safe and viable, for this kind of patients, related to the absence of adverse events. No other study of our knowledge has demonstrated this findings.

Heart Transplantation

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Efficacy and safety of prothrombin complex concentrate use to reverse oral anticoagulation in patients undergoing heart transplantation

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Background: Performing heart transplantation (HT) in patients receiving oral anticoagulation (OAC) implies a bleeding risk, as normalizing the International Normalized Ratio (INR) with vitamin K takes up to 24 hours. Our aim was to study the efficacy and safety of Prothrombin Complex Concentrate (PCC) for reversing the INR prior to HT.

Methods: Retrospective study of patients undergoing elective HT from 2009 to March 2017 in two institutions. We designed a protocol for patients on OAC based on switching to Acenocoumarol when listed for HT and the administration of vitamin K and PCC at a dose of 25 UI/kg prior to intervention. Among patients with and without OAC we compared the use of blood products, major bleeding, thrombotic events and survival.

Results: 140 patients were included in the study (median age 60.5 years, 24.3% females). 74 patients received OAC and had a median INR of 2.44 on admission to hospital. After applying the PCC protocol, median INR in this group was 1.43. Results are summarized on table 1. Major bleeding was found in 41.9% of the OAC group and 42.4 % in the no OAC group ($p=0.949$). Patients listed for HT on OAC underwent re-sternotomy more frequently than non-OAC patients (13.5% vs 1.5%, $p=0.008$). Survival to discharge was similar in the two groups (91.9% in the OAC group vs 87.9% in the non-OAC group, $p=0.429$). Requirements for fresh frozen plasma were higher among the OAC patients ($p < 0.001$). One patient in each group had a ischemic stroke, with no other thrombotic complications.

Conclusion: The use of PCC to reverse OAC in patients undergoing HT is effective and safe.

Table 1

	No OAC (66)	OAC (74)	p value
Major bleeding (n%)*	28 (42.4)* 1	31 (41.9)*	0.949*
Re-intervention*	(1.5)* 27	10 (13.5)*	0.008*
Transfusion \geq 4PRC* NE	(40.9)* 34	30 (40.5)*	0.965*
> 0.1 μ g/Kg/min	(51.5)	42 (56.8)	0.740
Primary graft failure n(%)	11 (16.7)	13 (17.6)	0.987
CVVHD n(%)	16 (24.2)	13 (17.6)	0.331
Days in ICU	6 (4-11.5)	6 (4-11)	0.629
In-hospital mortality n(%)	8 (12.1)	6 (8.1)	0.429
PRC 72 hours after HT	4 (2-6)	4 (2-6.5)	0.891
Platelets 72 hours after HT	2 (0-2)	1 (0-3)	0.961
FFP 72 hours after HT	1 (0-1)	2 (1-4.5)	<0.001

Outcomes in patients treated and not treated with OAC and requirements of blood products. Quantitative variables are represented by median and interquartile range. CVVHD: Continuous venovenous hemodialysis. FFP: Fresh frozen plasma. ICU: Intensive care unit. NE: Norepinephrine. OAC: Oral anticoagulants. OR: Operation room. PPRC: Packed red cells.

Chronic Heart Failure: Multidisciplinary Interventions

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Echocardiographic evaluation of patients with diastolic dysfunction of the left ventricle treated with external counterpulsation

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Background: The influence of the external counterpulsation (ECP, EECp) on patients with diastolic dysfunction of the left ventricle (LV) is unclear. We aim to determine whether external counterpulsation therapy improves echocardiographic parameters in these patients.

Methods: We studied 57 patients with stable coronary artery disease undergoing one course of external counterpulsation therapy. The average age of the patients was 63.07 ± 7.44 years (there were 43 (75.4%) male and 14 (24.6%) women). All patients divided into two groups: patients with diastolic dysfunction of the left ventricle (E/e' ratio > 14 , total 15 patients, main group) and control group ($E/e' \leq 14$, total 42 patients). The mean age of the patients included in the main and control groups was 64.20 ± 5.93 and 62.67 ± 7.93 years ($p=0.36$). All patients treated with one course of ECP (EECP) treatment (33.26 ± 3.60 and 32.85 ± 4.56 sessions, $p=0.38$). Results from echocardiographic examinations after the treatment in these groups were compared. Echocardiographic assessment included evaluation of the chamber size, chamber volume, ejection fraction of the left ventricle (LV) by 2D and Doppler measurements.

Results: Echocardiographic parameters for main and control groups before treatment: the diastolic diameter of the LV (cm): 5.65 ± 0.97 and 5.20 ± 0.62 ($p=0.0913$); the end-diastolic volume of the LV (ml): 93.53 ± 28.38 and 75.45 ± 25.13 ($p=0.0163$); LV stroke volume (ml): 48.57 ± 11.47 and 43.02 ± 10.64 ($p=0.1471$); LV ejection fraction (%): 52.83 ± 10.12 and 59.11 ± 9.53 ($p=0.0340$); the volume of the left atrium (ml): 73.25 ± 22.79 and 57.86 ± 20.60 ($p=0.0229$); tissue Doppler velocity of the mitral annulus (e' , cm/s): 5.89 ± 1.18 and 7.43 ± 1.50 ($p=0.0006$); E/e' ratio: 18.85 ± 3.40 and 9.69 ± 1.95 ($p<0.0001$). Echocardiographic parameters for the main and control groups after treatment: the diastolic diameter of the LV (cm): 5.53 ± 0.85 and 5.15 ± 0.57 ($p=0.1879$); the end diastolic volume of the LV (ml): 92.91 ± 31.29 and 75.15 ± 22.78 ($p=0.0536$); LV stroke volume (ml): 50.77 ± 11.49 and 47.01 ± 11.24 ($p=0.2612$); LV ejection fraction (%): 56.81 ± 10.50 and 64.06 ± 7.67 ($p=0.0088$); the volume of the left atrium (ml): 60.84 ± 16.20 and 55.77 ± 17.53 ($p=0.2388$); tissue Doppler velocity of the mitral annulus (e' , cm/s): 6.15 ± 1.11 and 7.73 ± 1.90 ($p=0.0037$); E/e' ratio: 15.97 ± 5.39 and 10.08 ± 2.81 ($p<0.0001$). Statistically significant changes between two groups noted for the left atrium volume: decrease in 12.41 ± 16.33 ml and 2.09 ± 13.72 ml ($p=0.0124$) in both groups, and for E/e' ratio: decrease in -2.87 ± 3.94 in the main group and increase in 0.39 ± 2.12 in the control group ($p=0.0003$).

Conclusion: ECP treatment was associated with a decrease in the left atrium volume and E/e' ratio in patients with diastolic dysfunction of the left ventricle.