

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

M Milan Chovanec¹; F Malek²; Z Jiraskova-Zakostelska³; J Durisova⁴; B Kaftanova⁴; T Andreasova²; J Herget⁴; ¹Charles University of Prague and Na Homolce Hospital, Prague, Czechia; ²Na Homolce Hospital, Cardiology department, Prague, Czechia; ³Academy of Sciences of the Czech Republic, Laboratory of Cellular and Molecular Immunology, Institute of Microbiology, Prague, Czechia; ⁴Charles University Prague, 2nd Faculty of Medicine, Department of Physiology, Prague, Czechia;

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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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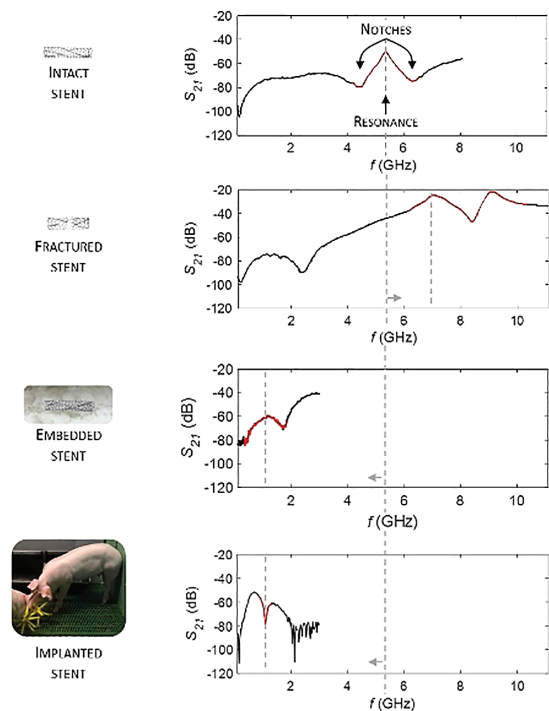
Microwave spectrometry for coronary stent monitoring

S Susana Amorós García De Valdecasas¹; GGL Gonzalez-Lopez¹; IJC Jimenez²; LLJ Jofre¹; ABG Bayes-Genis³; JT Tejada²; JOC O'callaghan Castella¹; ORL Rodriguez-Leor⁴; CGM Galvez-Montón³; ¹Polytechnic University of Catalonia,

Barcelona, Spain; ²University of Barcelona, Grup de Magnetisme, Departament de Física de la Matèria Condensada, Barcelona, Spain; ³Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, ICREC Research Program, Barcelona, Spain; ⁴Germans Trias i Pujol University Hospital, Servei de Cardiologia, Barcelona, Spain;

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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.

rate (74 ± 10 vs 65 ± 8 bpm $p < 0.001$) and mean systolic blood pressure (127 ± 20 vs 120 ± 19 mmHg $p = 0.04$) was observed.

13 patients (30%) did not achieved maximum target dose. The main cause was bradycardia, defined as heart rate < 55 bpm ($n = 7$; 16%). During the titration period no severe adverse effects, emergency visits or hospitalizations were observed.

In a univariate analysis, age, LVEF, NT-proBNP and systolic blood pressure were not significantly associated with achieving maximum target dose (all $p > 0.05$). However, a higher heart rate before starting titration (76 ± 10 vs 68 ± 9 bpm $p = 0.02$) was significantly associated with achieving maximum target dose.

Conclusions:

In our study beta-blockers dose titration by trained heart failure nurses was safe and effective. Most patients achieved maximum target dose, mainly those with a higher heart rate at baseline. Our results support the crucial role of trained heart failure nurses in improving management and outcomes in HFrEF patients.

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How much exercise heart failure inpatients can perform?

BM Bruno Miguel Delgado¹; I Lopes¹; B Gomes²; C Almeida³; A Novo⁴; ¹Hospital Center of Porto, Porto, Portugal; ²University of Porto, Porto, Portugal; ³Hospital Center of Setubal, Cardiology, Setubal, Portugal; ⁴Escola Superior de Saude do IPB, Bragança, Portugal;

Introduction: Decompensated Heart Failure (HF) patients have a significant functional dependence, impairment of performance in activities of daily living and low exercise tolerance. Exercise is a well establish cardiac rehabilitation intervention which leads to improvement of symptoms. The amount of Exercise is directly related to its benefits.

Purpose: To evaluate the volume of exercise that HF patients perform during the hospitalization

Methods: 64 patients performed an aerobic exercise training (AET) program (ERIC-HF: Early rehabilitation in cardiology – heart failure) with 5 sequential stages: respiratory training, cyclo ergometer for 5 to 10 min, walking training for 5 to 10 min and then for 10 to 15 min and walking training for 10 to 15 min followed by 5 min climbing stairs. The patient progresses on the program according to his synthons. The volume of exercise is registered in number of turns on the cyclo ergometer, meters walked, number of steps and total time of exercise. Subjective perception of exertion using Borg scale, and vital signs are evaluated in every training session (twice a day for 5 days a week). At discharge patients perform a 6 minute walking test (6MWT)

Results: Patients performed 932 sessions of AET with an average of 17 sessions each, for $15 (\pm 9)$ days of hospitalization. Patients performed progressive periods of exercise, for more time and with lower levels of perceived exertion, presenting an average value of $6 (\pm 3)$ in the admission and $2 (\pm 2)$ at the discharge. 34 patients reached the final stage of the program (climbing stairs) with an average of 91 steps in 5 minutes, not continuously. The patients who performed a bigger volume of Exercise walked more distance in the 6MWT: $291 (\pm 64)$ meters compared with patients who didn't performed stairs: $239 (\pm 27)$.

Conclusions: AET can be well tolerated by patients admitted due to decompensated HF and patients who are capable to perform a bigger volume of exercise can improve much more their functional capacity showed by the 6MWT results.

Volume of exercise		Average values
Cycloergometer	N° of turns	239 (± 123)
	N° of sessions	123
Walking training	Meters	425 (± 190)
	N° of sessions	560
Stairs	N° of steps	108 (± 62)
	N° of sessions	35
Time of exercise		12 minutes

Cardiovascular Drug Therapy

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Enhancement of the serum chloride concentration by administration of sodium-glucose cotransporter-2 inhibitor and its mechanisms and clinical significance in type 2 diabetic patients: a pilot study

H Hajime Kataoka¹; ¹Nishida Hospital, Oita, Japan;

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Background: Chloride is a key electrolyte that regulates the body fluid distribution. Accordingly, manipulating chloride kinetics by selecting a suitable diuretic could be an attractive strategy for correcting body fluid dysregulation.

Purpose: This study examined the effects and contributing factors of a sodium-glucose cotransporter-2 inhibitor (SGLT2i) on the serum chloride concentration in type 2 diabetic (T2DM) patients without heart failure.

Methods: Detailed analysis was performed on the data of six T2DM patients free from heart failure status treated with the SGLT2i empagliflozin (10 mg once daily). Physical examination, peripheral venous blood tests (hematologic, diabetic/metabolic, venous blood gas, and neurohormonal tests), and spot urinary test (electrolytes) were performed before and 1 month after treatment.

Results: Empagliflozin treatment for 1 month decreased body weight (-3.3 ± 2.2 kg), systolic blood pressure (-11 ± 6 mmHg), and HbA1c ($-0.9 \pm 0.5\%$; $p < 0.01$ for each). Mild increases in the hemoglobin ($+0.23 \pm 0.44$ g/dL) and hematocrit ($+0.8 \pm 1.2\%$) values were detected (5/6, 83%), but the serum creatinine concentration remained unchanged. The serum chloride concentration increased from 104 ± 2.23 to 106 ± 2.07 mEq/L ($p < 0.006$), but the sodium and potassium concentrations did not change. The spot urinary sodium concentration decreased from 159 ± 43 to 98 ± 35 mEq/L ($p < 0.02$) and the spot urinary chloride tended to decrease from 162 ± 59 to 104 ± 36 mEq/L, $p < 0.08$). Both renin and aldosterone tended to be activated (5/6, 83%). The strong organic acid metabolite concentrations of serum acetoacetate (from 42 ± 25 to 100 ± 45 μ mol/L, $p < 0.02$) and total ketone bodies (from 112 ± 64 to 300 ± 177 μ mol/L, $p < 0.04$) increased, but the actual HCO₃⁻ concentration decreased (from 27 ± 2.5 to 24 ± 1.6 mEq/L, $p < 0.008$).

Conclusions: The present study demonstrated that SGLT2i enhances the serum chloride concentration in T2DM patients and suggests that the effect is mediated by the possible following mechanisms: 1) enhanced reabsorption of urinary chloride by aldosterone activation due to blood pressure lowering and blood vessel contraction effects, 2) reciprocal increase in the serum chloride concentration by reducing the serum HCO₃⁻ concentration via a buffering effect of strong organic acid metabolites, and 3) reduced NaHCO₃ reabsorption and concurrently enhanced chloride reabsorption in the urinary tubules by inhibiting Na⁺-H⁺ exchanger 3 in the renal proximal tubules. Thus, the diuretic SGLT2i induces excessive extravascular fluid to drain into the vascular space by the enhanced vascular "tonicity" caused by the elevated serum chloride concentration.

Angiotensin-Renin-Bradykinine System

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Angiotensin-(1-7) and apelin levels depending on 12-month treatment with angiotensin receptor blocker or angiotensin-converting enzyme inhibitor in patients with hypertension and type 2 diabetes

K Yushko¹; S Koval¹; I Snihurska¹; T Starchenko¹; ¹L.T.Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine, Department of Arterial Hypertension and Prevention of Its Complications, Kharkiv, Ukraine;

Introduction: The renin-angiotensin system (RAS) plays the crucial role in the development of hypertension. The angiotensin-(1-7) is the metabolic product of angiotensin II. The apelin is one of the mediators of cardiovascular control. Both peptides are antagonists to the RAS effects and the important protective cardiovascular factors.

Purpose: The aim of the study was to evaluate the effect of combined treatment with angiotensin II receptor blocker (ARB) olmesartan or angiotensin-converting enzyme inhibitor (ACEi) ramipril on the blood levels of angiotensin-(1-7) and apelin in patients with hypertension and type 2 diabetes (T2D).

Methods: The study involved 76 patients with hypertension grades 2-3 and T2D (37 men and 39 women) aged 43 to 70. The patients were randomized into two groups: group O - patients treated with ARB olmesartan (20-40 mg/day) and calcium channel blocker lercanidipine (10-20 mg/day) ($n = 38$) and group R - patients who received ACEi ramipril (5-10 mg/day) with lercanidipine (10-20 mg/day) ($n = 38$). All patients treated with lipid-lowering therapy (atorvastatin 20-40 mg/day) and antidiabetic therapy (metformin 1000-2000 mg/day) additionally. The angiotensin-(1-7) and apelin levels in the blood were determined by ELISA at baseline and after 12 months of therapy.

Results: Both groups did not differ significantly by angiotensin-(1-7) and apelin levels at baseline. After 12 months from the start of the treatment in both groups there was powerful antihypertensive effect, which was not different depending on the combination of antihypertensive treatment. Targeted blood pressure levels were reached in 84.2% of patients ($n = 32$) treated with olmesartan and in 81.6% of patients ($n = 31$) treated with ramipril ($p > 0.05$ - intergroup). In the end of the treatment the levels of angiotensin-(1-7) were differed significantly only in patients of group O - there was increasing in its concentration by 20.3% (from $108.39 (92.32; 121.17)$ ng/l to $130.43 (124.42; 138.37)$ ng/l, $p < 0.01$). In group R the levels of angiotensin-(1-7) were $112.09 (104.3; 115.33)$ ng/l, which was not significantly different from the basal levels ($p > 0.05$). There was a significant increase in the levels of apelin in both groups after 12-month therapy, which did not reach the values of the control group. Among patients in group O at the end of the treatment, apelin levels were