

rats, hyperglycemia and hyper-insulinemia occurred. The coronary reactivity was maintained at the same level as in their lean littermates. Finally, in streptozotocin-injected rats, the high glycaemia and low insulinemia were associated with a large decrease in the function of coronary endothelial and smooth muscle cells. We conclude that the function of coronary vessels progressively decreases with the development of hyperglycemia and hypo-insulinemia. This shift leads to disequilibrium between energy production and utilization which induces ischemia and development of diabetic cardiomyopathy.

Abstract n° P-11-04

Comparative investigation of left ventricular function by pressure-volume analysis in rat models of physiological and pathological left ventricular hypertrophy

Attila OLÁH, Balázs Tamás Németh, Csaba Mátyás, Árpád Lux, Mihály Ruppert, Dalma Kellermayer, Lilla Szabó, Marianna Török, Anna Meltzer, Béla Merkely, Tamás Radovits

Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Background: Left ventricular (LV) hypertrophy is a physiological (PhyH) or pathological (PaH) response of LV myocardium to increased cardiac load and is associated with characteristic molecular changes. To date, a direct comparison of functional consequences of PhyH and PaH is missing. We aimed at investigating and comparing in vivo hemodynamic alterations in rat models of PhyH and PaH by using LV pressure-volume (P-V) analysis.

Methods and results: PhyH and PaH were induced in rats by swim training (athlete's heart) and by suprarenal abdominal aortic banding (AB), respectively. Morphology of the heart was investigated by echocardiography. Characterization of cardiac function was completed by LV P-V analysis. In addition histological and molecular biological measurements were performed. All data were normalized to the corresponding control group. Myocardial hypertrophy was observed in both models by echocardiography and post mortem heart weight data. In AB we detected subendocardial fibrosis. Reactivation of the fetal gene program could be observed only in the PaH model. PhyH was associated with increased stroke volume (SV) and ejection fraction (EF). In contrast, markedly higher LV end-systolic pressure and unaltered SV and EF were detected in PaH, indicating its compensated nature. Active relaxation was ameliorated in athlete's heart, while it showed a marked impairment in AB (Tau: $-7.7 \pm 2.6\%$ PhyH vs. $+42.1 \pm 11.1\%$ PaH, $p < 0.01$). Load-independent indices of LV contractility were increased in both models, in parallel with the degree of hypertrophy. Stroke work increased in both models, whereas mechanical efficiency of LV was improved only in PhyH ($+20.8 \pm 4.7\%$ FH vs. $+4.7 \pm 4.9\%$ PaH, $p < 0.05$).

Conclusion: In this project we provided the first comparative hemodynamic characterization of PhyH and PaH in relevant rodent models. Increased contractility could be observed in both LV hypertrophy, characteristic differences were detected in diastolic function and mechanoenergetics.

Abstract n° P-11-05

Transgenic rat model overexpressing human β_3 -adrenoceptor in endothelium: a new model for heart failure with preserved ejection fraction

Valentine PRAT¹, Marine FERRON¹, David ROUL¹, Nicolas PIRIOU², Damien GUIJARRO², Virginie AILLERIE¹, Angélique ERRAUD¹, Amandine GRABHERR¹, Benjamin LAUZIER¹, Bertrand ROZEC³, Chantal GAUTHIER¹

¹L'Institut du thorax-INSERM UMR 1087-CNRS UMR 6291, Nantes, France

²Department of Cardiology of Nantes-Laennec Hospital, France

³Department of anaesthesiology and intensive care unit of Nantes-Laennec Hospital, France

Background: Heart failure (HF) with preserved ejection fraction (pEF) is a growing health burden affecting the elderly. Patients present impaired cardiac relaxation and filling with various comorbidities (hypertension, diabetes, or renal failure). Due to the lack of patient biopsies and accurate animal models, its physiopathology is not completely understood and no specific treatment is available. In this context, our team developed a rat model of HFpEF.

Material and Methods: Our model is a transgenic rat (Tg β_3) overexpressing in endothelium human β_3 -adrenoceptor gene upon ICAM2 promoter. Cardiac function of 15, 30 and 45 weeks-old male and female, ovariectomized or not, was investigated by echography. Arterial and left ventricular pressure as well as histology of pulmonary and renal vasculature were analyzed at 45 weeks.

Results: At 45 weeks of age, Tg β_3 male rats, but not females, presented an increase in left ventricle end diastolic pressure (LVEDP; WT: 5.6 ± 1.2 mmHg; Tg β_3 : 11.7 ± 1.1 mmHg; $p < 0.01$) characteristic of an increase in LV stiffness, without any arterial hypertension nor tachycardia. Cardiac echography showed an altered filling pattern with an increase in early-to-late filling (E/A) ratio in male rats (WT: 1.14 ± 0.01 ; Tg β_3 : 1.32 ± 0.04 ; $p < 0.01$), with a preserved EF but without cardiac remodeling. Females did not show any echographic alteration. Interestingly, E/A ratio was similar between WT and Tg β_3 male rats at 15 weeks, showing that diastolic dysfunction appeared with ageing. At this stage, lung and kidney showed no remodeling in Tg β_3 rats.

Conclusion: Our results showed that Tg β_3 male rats presented with ageing a restrictive cardiac filling, representative of HFpEF phenotype. In our model, early stage of cardiac dysfunction is not associated with pulmonary and renal injuries, which could allow us to understand the underlying mechanisms of HFpEF development. Now we must determine the effect of stress and comorbidities on Tg β_3 male rats phenotype.

Abstract n° P-11-06

The Role of Fibroblast NADPH Oxidase-2 in the Development of Cardiac Fibrosis

Daniel RICHARDS; Craig Harrison; Ajay M Shah

King's College London British Heart Foundation Centre, The James Black Centre, 125 Coldharbour Lane, London SE5 8NU, UK

Background NADPH oxidase-2 (NOX2) has previously shown to be elevated in patients with heart failure. Global NOX2 knockout (KO) mice have reduced cardiac fibrosis vs. wild-type (WT) following angiotensin-II (Ang-II) infusion or transverse aortic constriction (TAC). These effects of NOX2 could be mediated by several different cell types. Owing to their central role in extracellular matrix synthesis and remodelling, we hypothesised that NOX2 activation in fibroblasts contributes to the development of cardiac fibrosis in response to chronic stress.

Methods Novel mice deficient in fibroblast NOX2 were generated using the Cre-LoxP system. These mice have NOX2 exons 1 and 2 flanked by LoxP sites, with Cre Recombinase driven by an inducible Col1a2 promoter for fibroblast specificity. Ang-II infusion (1.1 mg/kg/day; 2 weeks) or TAC surgery were used to generate chronic pressure overload. Successful TAC was confirmed by echocardiographic estimation of aortic peak pressure gradient.

Results Daily treatment with 1 mg tamoxifen for 10 days induced a 60% reduction in cardiac NOX2 protein levels. Ang-II infusion led to the development of significant cardiac fibrosis in WT littermate mice, but not in KO mice (1.38% vs. 0.42% increase in total collagen, respectively; $p < 0.05$). Mice were hypertensive after 2 weeks of