

fibronectin and lysyl oxidase. Therefore, finerenone may represent a novel substance to prevent maladaptive cardiac structural remodelling.

BASIC SCIENCE: HFpEF - HEART FAILURE WITH PRESERVED EJECTION FRACTION

P1774

Effect of neuregulin-1 on angiotensin II-induced ventricular inflammation, fibrosis and stiffening

FWO (Application number, G0C5214), a grant from the European Commission (FP7-HEALTH-F2-2010-261409), IOF POC of the University of Antwerp Z Zarha Vermeulen¹; L. Vandekerckhove¹; VFS Segers¹; AS Hervent¹; GW De Keulenaer¹

¹University of Antwerp, Antwerp, Belgium

Purpose: Heart failure mitigating effects of the endothelium-derived growth factor Neuregulin-1 (NRG-1) are currently tested in clinical trials. Surprisingly, however, NRG-1's underlying mechanisms of cardiac protection remain poorly understood. Here, we hypothesized that NRG-1/ErbB4 signaling attenuates left ventricular (LV) fibrosis and stiffening, and regulates cardiac fibroblast function.

Methods: LV fibrosis and stiffening were induced by treatment of mice with Angiotensin II (Ang II, osmotic mini-pumps, 1000 ng.kg⁻¹.day⁻¹, 4 weeks). NRG-1/ErbB4 signaling was either activated by co-treatment with rhNRG-1 (20 µg.kg⁻¹.day⁻¹, i.p. injection 5 days/week), or inhibited by fibroblast-specific deletion of ErbB4 (by crossing C57BL/6-ErbB4F/F mice and BALB/c-S100a4-Cre+ mice). The effect of rhNRG-1 on fibroblast gene expression was studied in cultured primary fibroblasts by cDNA MicroArray analysis with the Illumina MouseRef-8 v2.0 Expression BeadChip. Results In wild type mice, rhNRG-1 treatment significantly attenuated Ang II-induced LV fibrosis (quantified by histology and molecular analysis) and prevented Ang II-induced LV passive stiffening (quantified by invasive hemodynamic recordings). Blood pressure was not affected. Consistently, in ErbB4^{-/-}; Cre+ mice, LV fibrotic response to Ang II-treatment was robustly enhanced. cDNA MicroArray comparison of PBS- and rhNRG-1-treated primary fibroblasts showed 960 differentially expressed genes of which 450 were down-regulated and 510 were up-regulated. Network and pathway analysis using the Ingenuity Pathway Analysis (IPA) software confirmed that rhNRG-1 significantly inhibited the pathway of connective tissue development, but also unmasked that rhNRG-1 significantly downregulated several inflammatory pathways. Upstream regulator analysis identified the downregulation of several cytokines (mostly from the interleukin family), cytokine receptors and transcription factors of cytokine signaling (mostly from the IRF and STAT family) hence generating the hypothesis that rhNRG-1 also mediates anti-inflammatory effects. To further test this hypothesis, wild type mice were exposed to Ang II for 3 days to induce a myocardial inflammatory response. As expected, co-treatment with rhNRG-1 significantly abrogated myocardial infiltration of both neutrophils and macrophages. Conclusion This study shows a prominent role for NRG-1/ErbB4 signaling in the control of LV fibrosis during Ang II-induced LV remodeling. Both direct anti-fibrotic effects and indirect anti-inflammatory effects seem to underlie this effect. These data contribute to the understanding of the therapeutic effects of rhNRG-1 in heart failure.

BASIC SCIENCE: ANIMAL MODELS AND EXPERIMENTATION

P1775

Distinct myocardial expression of mitochondrial regulators is associated with characteristic differences of in vivo hemodynamics in physiological and pathological left ventricular hypertrophy

Hungarian Scientific Research Fund (OTKA 105555) to Bela Merkely A Olah¹; BT Nemeth¹; C Matyas¹; A Lux¹; M Ruppert¹; D Kellermayer¹; AA Sayour¹; L Szabo¹; B Merkely¹; T Radovits¹

¹Semmelweis University, Heart and Vascular Center, Budapest, Hungary

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

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 P-V analysis. In addition histological and molecular biological 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 only 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, $p < 0.01$). LV mechanical efficiency and ventriculo-arterial coupling were improved in PhyH, whereas remained unchanged in PaH. Myocardial gene expression of mitochondrial regulators showed marked differences between PaH and PhyH (peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α): +19.1±10.3% PhyH vs. -37.8±7.2% PaH, $p < 0.01$), while markers of oxidative stress and inflammation did not differ between the groups.

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 mitochondrial differences.

P1776

An allogeneic bioengineered myocardial graft limits infarct size and improves cardiac function: pre-clinical study in the porcine myocardial infarction model

SAF201459892; PI14/0168; RD12/0042/0047; RD12/0019/0029; Beca SEC 2015; Beca de Recerca Bàsica de l'Acadèmia 2015; SGR 2014.

I Isaac Perea Gil¹; C Prat-Vidal¹; C Galvez-Monton¹; S Roura¹; A Llucia-Valldeperas¹; C Soler-Botija¹; I Diaz-Guemes²; V Crisostomo²; FM Sanchez-Margallo²; A Bayes-Genis³

¹Health Research Institute Germans Trias, Cardiology, Badalona, Spain; ²Jesus Usón Minimally Invasive Surgery Centre, Cáceres, Spain; ³Germans Trias i Pujol University Hospital, Cardiology, Badalona, Spain

Background: Cardiac tissue engineering combines scaffolds and cells, aiming to renew myocardium and restore cardiac function after myocardial infarction (MI).

Purpose: Herein, we developed a scalable engineered myocardial graft (EMG) and evaluated its impact on cardiac function and scar dynamics in the swine MI model.

Methods: EMG, comprising a decellularized porcine myocardial scaffold repopulated with GFP-labeled porcine adipose tissue-derived progenitor cells (pATDPCs), was engrafted to the myocardial surface of allogeneic swine after MI induction. Cardiac function was assessed using magnetic resonance imaging. Infarct size, scar healing, and vascularization were evaluated using quantitative morphometry and histopathology. Animals were sacrificed one month post-MI.

Results: Compared to control-MI animals, EMG-treated animals exhibited significantly higher left ventricular ejection fraction relative to baseline (3.26±2.85 vs. -7.97±4.29; $P = 0.047$) and post-MI (61.30±3.07% vs. 50.76±2.62%; $P = 0.001$). Relative to control-MI animals, EMG-treated animals had a 68% smaller infarct size (2.46±0.60% vs. 7.63±2.26%; $P = 0.048$) and significantly lower type I/III collagen ratio (2.26±0.72 vs. 13.01±6.85; $P = 0.032$). GFP+ pATDPCs migrated to underlying ischemic myocardium and expressed cardiac lineage markers (GATA4, ME2, SERCA2, connexin43, and cTnI) and endothelial makers (IsoB4 and CD31). Newly-formed blood vessels were connected to host myocardium. EMG promoted increased infarct myocardium vascularization, with blood vessel densities of 3.64±0.50% for EMG-treated animals and 1.72±0.12% for control-MI animals ($P = 0.011$).

Conclusions: In the pre-clinical swine MI model, the newly developed EMG improved cardiac function and injured myocardium neovascularization, reduced infarct size, and limited fibrosis progression. This scalable allogeneic EMG is ready for clinical translation.

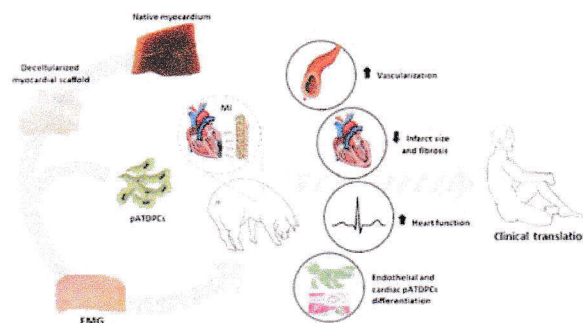


Figure 1. Effects promoted by the EMG