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Poster session 1

Group 2 - Growth/death, Regeneration and Stem cells

Session held on 4 July 2014

Abstract: P74

Citation: Cardiovascular Research, Volume 103, Supplement 1, 15 July 2014

Reversible cardiac hypertrophy and left ventricular functional changes after exercise training in a rat model

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Purpose: Long-term exercise training is associated with characteristic structural and functional cardiac adaptation termed athlete's heart. However the effect of discontinuation of the training (detraining) on left ventricular (LV) function is still unclear. Our aim was to evaluate the development characteristics of athlete's heart and the reversibility of morphological and functional changes during detraining.

Methods: Rats were divided into trained (n=15) and control (n=17) groups. Trained rats swam 200 min/day for 12 weeks, while control rats were taken into the water for 5 min/day. Detrained rats remained sedentary for 8 weeks after completion of the training protocol. We regularly performed echocardiographic measurements to investigate development and regression of exercise-induced cardiac changes. LV pressure-volume analysis was performed to calculate cardiac functional parameters. LV samples were harvested for histological examination. Myocardial gene expression analysis was performed using qRT-PCR.

Results: Echocardiographic examinations showed rapidly developing LV hypertrophy in the trained group according to wall thickness values (LVmass index after training period: 2.45 ± 0.09 vs. 2.07 ± 0.07 g/ttkg, $p < 0.05$). This adaptation regressed after detraining (LVmass index: 1.94 ± 0.02 vs. 2.05 ± 0.05 g/ttkg, $p = 0.0634$), which was confirmed by post-mortem measured heart weight and histological morphometry. Unchanged myocardial expression of TGF- β and β -MHC and unaltered amount of LV collagen confirmed the physiologic nature of the observed cardiac hypertrophy. Hemodynamic measurements indicated decreased LV end-systolic volume (LVESV: 75 ± 5 vs. 100 ± 7 μ l, $p < 0.05$) along with unchanged end-diastolic volume (EDV), improved systolic function and contractility (slope of the dP/dtmax-EDV relationship: 35.9 ± 2.6 vs. 25.8 ± 2.8 Hgmm/s/ μ l, $p < 0.05$), ameliorated active relaxation and mechanoenergetics (mechanical efficiency: 53 ± 2 vs. $45 \pm 2\%$, $p < 0.05$) after long-term exercise training. After the detraining period regression of exercise-induced cardiac functional changes were observed: LVESV (117 ± 5 vs. 115 ± 6 μ l, $p = 0.7846$), active relaxation, LV contractility (slope of the dP/dtmax-EDV relationship: 30.5 ± 1.7 vs. 28.4 ± 4.3 Hgmm/s/ μ l, $p = 0.5871$) and mechanoenergetic (mechanical efficiency: 50 ± 2 vs. $48 \pm 5\%$, $p = 0.7760$) enhancement reverted completely to control values. Training and detraining did not affect myocardial stiffness.

Conclusions: Our results confirm that the morphological and functional properties of exercise-induced physiologic LV hypertrophy completely regressed after an eight week detraining period.

Poster session 1

Group 11 - Thrombosis & Hemostasis

Session held on 4 July 2014

Abstract: P229

Citation: Cardiovascular Research, Volume 103, Supplement 1, 15 July 2014

Tranexamic acid and aprotinin: antifibrinolytics in cardiac surgery

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Purpose: Anti-haemorrhagic drugs are being used to prevent and treat haemorrhagic complications in cardiac surgery. The serine-protease-inhibitor aprotinin is an antifibrinolytic agent that had been used in clinical practice for decades. In 2008, the BART-study revealed its unfavourable effects on postoperative mortality, which led to its withdrawal from the market. Today, the lysine-analogue tranexamic acid (TA) is available for the clinical routine.

We compared the effects of aprotinin and TA on postoperative blood loss, hemodynamic, hemostaseologic and inflammatory parameters, using a canine model of cardiopulmonary bypass (CPB).

Methods: Beagle dogs were randomized into three groups (n=8/group). Control dogs received placebo, treated groups were given aprotinin or TA. All animals received heparin and underwent 90min of CPB. The weaning from the heart-lung-machine was followed by administration of protamine and 130min of observation. We regularly determined blood loss and coagulation parameters, while hemodynamic parameters were continuously monitored. To assess the systemic inflammatory response induced by CPB, plasma levels of IL-6, IL-8 and TNF- α were determined by ELISA.

Results: Compared to control, aprotinin significantly reduced blood loss (105 $\pm$ 22ml vs. 41 $\pm$ 8ml), while TA was found to be less effective (65 $\pm$ 16ml). Regarding hemodynamic and coagulation parameters, no significant difference was detected among the groups. The elevation of proinflammatory cytokine levels during CPB was tendentially decreased by aprotinin, while a significant anti-inflammatory effect was observed in the TA group (TNF α 90min after starting CPB: 5.2 $\pm$ 1.2ng/ml control vs. 3.7 $\pm$ 0.9ng/ml aprotinin vs. 0.8 $\pm$ 0.3ng/ml TA).

Conclusions: Compared to aprotinin, TA is less effective in reducing blood loss, but has a stronger anti-inflammatory effect. Our work points out the need for the development of novel pharmacological tools for effective and safe postoperative blood loss reduction.

Poster session 2

Group 13 - Pathophysiology, Signaling

Session held on 5 July 2014

Abstract: P508

Citation: Cardiovascular Research, Volume 103, Supplement 1, 15 July 2014

Pharmacological activation of the soluble guanylate cyclase inhibits pressure overload-induced cardiac hypertrophy

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Purpose: Pathological cardiac hypertrophy is observed in pressure overload of the left ventricle. Elevated intracellular cGMP-levels have been reported to prevent the development of pathological myocardial hypertrophy. We investigated the effects of chronic activation of the cGMP producing enzyme, soluble guanylate cyclase (sGC) by cinaciguat in a rat model of pressure overload-induced cardiac hypertrophy.

Methods: We performed aortic banding (AB) to evoke pressure overload-induced cardiac hypertrophy in our rats. Sham operated animals served as controls. Experimental groups were treated with 10 mg/kg/day cinaciguat (Cin) or with placebo (Co) p.o., respectively. Development of cardiac hypertrophy was investigated by echocardiography. We performed left ventricular (LV) pressure-volume analysis with a pressure-conductance microcatheter to assess cardiac function. In addition to our functional experiments, histological and molecular biological measurements were carried out.

Results: Echocardiography showed marked myocardial hypertrophy in the AB-Co group (left ventricular mass index (LVMI): 3.15 ± 0.09 AB-Co vs. 2.13 ± 0.04 g/ttkg Sham-Co) which was verified by post mortem investigation of the hearts (heart weight/tibial length ratio (HW/TL): 0.384 ± 0.015 AB-Co vs. 0.293 ± 0.008 g/cm Sham-Co) and by histology (cardiomyocyte diameter (CD): 17.37 ± 0.04 AB-Co vs. 14.55 ± 0.12 µm Sham-Co). Increased left ventricular dimensions (left ventricular end-diastolic volume: 414 ± 19 AB-Co vs. 341 ± 19 µl Sham-Co) were observed while ejection fraction and fractional shortening remained unchanged. Cinaciguat did not alter blood pressure but effectively attenuated left ventricular hypertrophy (LVMI: 2.64 ± 0.06 g/ttkg, HW/TL: 0.339 ± 0.009 g/cm, CD: 15.08 ± 0.10 µm, $p < 0.05$ vs. AB-Co).

Conclusions: Our results demonstrate that chronic stimulation of the NO-cGMP signalling by pharmacologically activating soluble guanylate cyclase might be a novel therapeutic approach in the prevention of pathological myocardial hypertrophy.

Poster session 3

Group 3 - Signalling - Hormones and reactivities oxygen species on cardiomyocytes

Session held on 6 July 2014

Abstract: P604

Citation: Cardiovascular Research, Volume 103, Supplement 1, 15 July 2014

Cardiac effects of exhaustive exercise induced oxidative stress in a rat model

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Purpose: The role of physical exercise in the prevention and treatment of cardiovascular diseases has been well-described, even though elevations in cardioneurotic biomarkers after prolonged exercise (i.e. ultramarathon running) were observed. We aimed to establish and validate a rat model of acute exhaustive exercise and determine the biochemical, molecular biological, structural and functional alterations in the heart.

Methods: Rats of the exercise group were forced to swim for 3h with 5% body weight (workload) attached to the tail, control rats were taken into the water for 5 min. 2 hours after completion of swimming we performed left ventricular (LV) pressure-volume analysis using a pressure-conductance microcatheter to investigate LV function and mechanoenergetics. Additionally, blood and myocardium samples were harvested for biochemical and histological examination. Alterations of gene expressions were detected using qRT-PCR.

Results: When compared to controls, elevated plasma levels of cardiac troponin T (0.131 ± 0.022 vs. 0.025 ± 0.006 ng/ml, $p < 0.001$), creatine kinase, transaminases and lactate dehydrogenase were detected after exhaustive exercise. Histological analysis showed sporadic fragmentation of myocardial structure, tissue edema and leukocyte infiltration. Myocardial gene expression analysis showed a significant increase of endogenous antioxidants (thioredoxin-1: 1.24 ± 0.07 vs. 1.01 ± 0.04 , $p < 0.05$) and dihydroethidium staining indicated robust generation of superoxide anions after exhaustive exercise. We found a markedly significant augmentation of Bax/Bcl-2 ratio (1.80 ± 0.18 vs. 1.04 ± 0.03 , $p < 0.01$) and the proapoptotic activity was confirmed by semiquantitative analysis of TUNEL staining. Dysregulation of the matrix metalloproteinase (MMP) system (MMP-2/TIMP-2 (tissue inhibitor of matrix metalloproteinase-2) ratio: 1.46 ± 0.08 vs. 1.05 ± 0.03 , $p < 0.01$) was observed after exhaustive swimming. We observed increased end-systolic volume, decreased ejection fraction (48 ± 5 vs. $59 \pm 3\%$, $p < 0.001$), impaired contractility (end-systolic elastance: 0.70 ± 0.07 vs. 0.95 ± 0.07 mmHg/ μ l, $p < 0.05$) and mechanoenergetics (mechanical efficiency: 48 ± 2 vs. $59 \pm 2\%$, $p < 0.001$) of LV in the exercise group.

Conclusions: Excessive physical activity has an adverse effect on the heart. Enhanced oxidative stress and apoptotic signalling as well as MMP dysregulation could underly the elevation of myocardial necrotic markers. The characteristic molecular and histological alterations are associated with impairment of LV systolic function, contractility and mechanoenergetics.

Poster session 3

Group 13 - Cardiac pathophysiology

Session held on 6 July 2014

Abstract: P758

Citation: Cardiovascular Research, Volume 103, Supplement 1, 15 July 2014

Cinaciguat prevents diabetes mellitus related cardiac alterations in rats

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Purpose: Diabetes mellitus (DM) is associated with severely impaired nitric oxide (NO) signalling which leads to development of diabetic cardiomyopathy. The second messenger cyclic guanosine monophosphate (cGMP), generated by soluble guanylate cyclase (sGC), plays crucial role in DM related cardiovascular alterations. Improvement of NO - cGMP signalling have been reported to have cytoprotective effects. We investigated the effects of chronic activation of sGC by cinaciguat in diabetic cardiomyopathy in a rat model of type 1 DM.

Methods: Type 1 DM was induced by a single i.p. injection of streptozotocin (60mg/kg) in Sprague-Dawley rats. Rats were treated with 10 mg/kg/day cinaciguat (treatment groups) or with placebo (control groups) orally for 8 weeks. Left ventricular (LV) function was assessed using a pressure-volume (PV) conductance microcatheter system in vivo. In addition to our functional experiments, gene expression analysis was performed by qRT-PCR, expression of proteins were assessed by Western blotting (WB). TUNEL assay was carried out to evaluate degree of apoptosis. Cardiac remodelling and fibrosis were investigated by histology and immunohistochemistry.

Results: DM was associated with significantly elevated endothelial nitric oxide synthase (eNOS) myocardial expressions while WB proved elevated phosphodiesterase-5 (PDE5) and protein kinase G (PKG) levels and decreased phosphorylated vasodilator-stimulated phosphoprotein - vasodilator-stimulated phosphoprotein (p-VASP/VASP) ratio. We observed increased atrial natriuretic factor (ANF), transforming growth factor- β (TGF- β) and matrix metalloproteinase 9 (MMP-9) levels and fibrotic remodelling of the diabetic heart as evidenced by Masson's trichrome staining. TUNEL assay showed increased apoptosis in DM. Impaired LV contractility (preload recruitable stroke work (PRSW): 49.5 ± 3.3 vs. 83.0 ± 5.5 mmHg, $p < 0.05$) and diastolic function (time constant of LV pressure decay (τ): 17.3 ± 0.8 vs. 10.3 ± 0.3 msec, $p < 0.05$) were found in the untreated DM group. Cinaciguat treatment prevented DM associated molecular changes and cardiac remodelling and significantly improved systolic (PRSW: 66.8 ± 3.6 vs. 49.5 ± 3.3 mmHg, $p < 0.05$) and diastolic (τ : 14.9 ± 0.6 vs. 17.3 ± 0.8 msec, $p < 0.05$) function compared to untreated DM. It had no effect in non-diabetic control animals.

Conclusions: Our results demonstrate that cinaciguat prevents DM associated myocardial alterations and improves diabetic cardiac dysfunction in rats. Pharmacological activation of sGC might be a novel therapeutic approach for diabetic cardiomyopathy.

Poster session 3

Group 13 - Cardiac pathophysiology

Session held on 6 July 2014

Abstract: P765

Citation: Cardiovascular Research, Volume 103, Supplement 1, 15 July 2014

Diabetic cardiomyopathy: a comparative investigation in diabetic rat models

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Purpose: Diabetic cardiomyopathy, a cardiac manifestation of diabetes mellitus (DM), is characterised by specific structural, molecular and functional alterations of the myocardium. Upon this concept we investigated whether type-1 or type-2 diabetes lead to different alterations in cardiac function or histological and molecular changes.

Methods: Our experiments were carried out in a rat model of type-1 (streptozotocin induced) and type-2 DM (Zucker Diabetic Fatty rats). Left ventricular (LV) function was characterised using a pressure-volume (P-V) conductance catheter system. Load independent indices of LV contractility (preload recruitable stroke work (PRSW)) and indices of LV relaxation (time constant of LV pressure decay(Tau)) and stiffness (LV end-diastolic pressure (LVEDP)) were calculated, respectively. In addition to our functional measurements TUNEL assay was performed to evaluate degree of apoptosis. Myocardial gene expression analysis was performed by qRT-PCR, expression of proteins was investigated by western blot and immunohistochemistry.

Results: In comparison to the control, type-1 DM resulted in decreased LV systolic performance: decreased systolic pressure, maximal dP/dt and PRSW (45.39±2.45 vs 76.44±4.06 mmHg). Type-2 DM was associated with increased LV stiffness (LVEDP: 9.4±0.5 vs 7.7±0.4 mmHg) while systolic indices were altered only to a lower extent. We observed cardiac hypertrophy and degeneration with histomorphological examination. More pronounced nitro-oxidative stress resulted in more severe DNA-damage. Overexpression of c-fos and c-jun and downregulation of eNOS were observed in type-1 diabetic rats. On the other hand TGF-β1 and ANF mRNA-levels were significantly higher in type-2 diabetic model.

Conclusions: Diabetic cardiac alterations are characterised by decreased systolic performance and impaired relaxation in type-1 diabetic rats, while diastolic dysfunction was more pronounced in type-2 DM. In the background of diabetic cardiomyopathy different processes can be identified in the two models.



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