Characteristic distinction of energy-dependent hemodynamics in physiological and pathological left ventricular hypertrophy is related to different myocardial expression of mithocondrial regulators

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Background and purpose: Left ventricular (LV) hypertrophy is a physiological (athlete's heart) or pathological response of LV myocardium to increased cardiac load. To date, a direct comparison of functional consequences of PhyH and PaH and possible underpinning mechanisms is missing. We aimed at comparing hemodynamic alterations in well established rat models of physiological (PhyH) and pathological hypertrophy (PaH) by using LV pressure-volume analysis and investigating underlying molecular mechanisms (oxidative stress, inflammatory markers, mitochondrial regulators).

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 pressure-volume analysis. In addition histological and molecular biological (gene expression analysis) 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 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, $p<0.01$). Mechanical efficiency and ventriculo-arterial coupling were improved in PhyH, whereas remained unchanged in PaH (mechanical efficiency: +20.8±4.7% PhyH vs. +4.7±4.9% PaH, $p<0.05$). Myocardial gene expression of regulators related to mitochondrial biogenesis showed marked differences between PaH and PhyH (peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α): +19.1±10.3% PhyH vs. -37.8±7.2% PaH, $p<0.01$; nuclear respiratory factor 1 (NRF1): -4.5±2.8% PhyH vs. -27.4±7.6% PaH, $p<0.05$). Alterations in myocardial expression of oxidative stress and inflammatory markers did not differ between the two models.

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 differences in expression of key regulators related to mitochondrial biogenesis.