

levels were not significantly altered. In samples with a truncating MYBPC3 mutation (n=9), HSP27, but not HSP60, was increased in the myofilament fraction.

Conclusion: Levels of small HSP27, the mitochondrial HSP60, and LC3B-II are increased in HCM only when a sarcomere mutation is present, implying that mutant-mediated alterations in PQC may play a role in HCM pathology.

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Poster session 1

Name of presenter: Roy Kalfon

Abstract # 29

The role of dual loss-of-function mutations in the bZIP-repressor proteins, ATF3 and JDP2, in cardiac remodeling and hypertrophy

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Background: The Activating Transcription Factor 3 (ATF3) and the c-Jun dimerization protein 2 (JDP2) are members of the basic leucine zipper protein (bZIP) superfamily of transcription factors. Despite their high functional homology, the loss of JDP2 expression promotes, while ATF3 loss of expression prevents cardiac remodeling and hypertrophy. Interestingly, the loss of either ATF3 or JDP2 expression results in increased expression of the other gene. Therefore, we hypothesized that increased ATF3 expression in the absence of JDP2 results in a maladaptive cardiac response.

Methods and results: We used transverse aortic constriction (TAC) in C57Bl/6 mice with whole body ablation of both JDP2 and ATF3 (dKO) and assessed the cardiac pathological, physiological, and molecular consequences following intervention. In the absence of cardiac stress, the hearts derived from dKO mice display a relatively higher ventricles/body weight ratio (4.4) and superior cardiac function in comparison to Wt mice (3.7). Following 4 weeks of TAC, dKO hearts remained fully functional while Wt mice exhibited reduced cardiac function. Following 8 weeks of TAC, all mice showed deterioration in cardiac function. However, dKO mice exhibited preserved systolic function, resulting in attenuation of cardiac dysfunction in comparison to Wt mice. Consistently, the hearts of Wt mice showed significant elevation in hypertrophic, fibrosis, and inflammatory cytokine gene markers in comparison to dKO mice.

Conclusion: hearts derived from male and female dKO mice display amelioration in contractile function in the absence of stress; and are resistant to maladaptive cardiac remodeling processes with preserved contractile function following chronic pressure overload.

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Poster session 1

Name of presenter: Jessica Sabourin

Abstract # 30

Orai1 channels inhibition protects the heart from pressure overload-induced ventricular dysfunction

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Background: Despite uncertain role for store-operated Ca²⁺ entry (SOCE) in adult cardiac physiology, studies reported strong evidences that SOCE dysfunction is a key contributor to cardiac hypertrophy and development of failure. However, the pathophysiological role of Orai1 channels, the archetypical store-operated channels is not elucidated.

Methods and results: Adult mice subjected to transverse aortic constriction (TAC) developed cardiac hypertrophy and reduced ventricular function that is associated with increased Orai1 expression and activity. We generated a mouse model with cardiac-specific expression of a dominant-negative Orai1R91W mutant (DT). At baseline, DT mice displayed normal cardiac electromechanical function even if Orai1-dependent SOCE is reduced.

Compared to control littermates, after TAC, DT mice, which were prevented from exacerbated SOCE, showed cardiac hypertrophy with protection from systolic dysfunction and less interstitial fibrosis deposition. At cellular level, TAC-induced Ca²⁺ signaling alterations observed in control ventricular cardiomyocytes, namely depressed cellular contractility, Ca²⁺ transients amplitude and decay decreases, lower SR Ca²⁺ load and decreased level of SERCA2a expression, were prevented in myocytes from DT mice. Moreover, 3 weeks treatment of mice with the selective Orai1 inhibitor, JP111, after establishment of TAC-induced alterations, prevented ventricular dysfunction deterioration, as revealed by recovering of ejection fraction without affecting hypertrophy and by reversion of cellular Ca²⁺ handling alterations.

Conclusion: Our findings highlighted a key role of Orai1 channels in pressure overload-induced ventricular dysfunction and their blockade is beneficial for the ventricular function by improving Ca²⁺ cycling and reducing fibrosis. Thus, targeted inhibition of Orai1 might be a promising inotropic therapy for maintaining contractility reserve after hypertrophic stresses.

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Poster session 1

Name of presenter: Tamás Radovits

Abstract # 31

Characterization of left ventricular morphological and functional changes during the development and regression of exercise-induced cardiac hypertrophy

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Background: Although exercise-induced cardiac hypertrophy has been intensively investigated, consecutive evaluation of its development and regression dynamics is not fully described. We aimed to characterize the effects of regular exercise training and detraining on myocardial mechanics by speckle-tracking echocardiography (STE) in a rat model.

Methods and results: Rats were divided into exercised and control groups ($n=12/\text{group}$). Trained rats swam 200min/day for 12 weeks. After completion of the training protocol, rats remained sedentary for 8 weeks (detraining period). Echocardiographic follow-up was performed regularly using a 13MHz linear transducer to obtain LV long- and short-axis recordings for STE analysis. Global longitudinal and circumferential strain and systolic strain rate (CSr, LSr) were measured. LV pressure-volume analysis was performed using also additional groups to obtain hemodynamic data.

Echocardiography showed the development of LV hypertrophy in the exercised group (exercised vs. control; LVmass index: 2.4 ± 0.1 vs $2.0 \pm 0.1 \text{ g/kg}$, $p < 0.05$), which was followed by improvement of systolic function. These differences disappeared during detraining (2.3 ± 0.1 vs $2.4 \pm 0.1 \text{ g/kg}$, n.s.). Strain and strain rate values were increased after the training period (exercised vs. control; CSr: -5.6 ± 0.3 vs $-4.0 \pm 0.31/\text{s}$; LSr: -4.6 ± 0.2 vs $-3.9 \pm 0.21/\text{s}$, $p < 0.05$), whereas supernormal values rapidly reversed to the control level after training cessation. Load-independent hemodynamic indices, e.g. preload recruitable stroke work, confirmed the exercise-induced systolic improvement and complete regression after detraining.

Conclusion: Our study provides the first comprehensive data to describe the development and regression dynamics of morphological and functional aspects of physiological myocardial hypertrophy in detail. Speckle-tracking echocardiography has been proven to be feasible to follow-up changes induced by exercise training and detraining.

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Poster session 1

Name of presenter: Mihály Ruppert

Abstract # 32

The role of gender in the regression of pressure overload-induced left ventricular myocardial hypertrophy

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Background: Sex-related disparities were identified during the development of pressure overload (PO)-induced left ventricular (LV) myocardial hypertrophy (LVH). However, it is less clear whether gender also affects the regression of LVH after pressure unloading. Thus, we investigated the effect of sex on myocardial reverse remodeling in a rat model of banding and debanding of the abdominal aorta.

Methods and results: Abdominal aortic banding (AB) was performed to induce PO in male and female rats for 6 or 12 weeks. Sham operated animals served as controls. Pressure unloading was evoked by debanding the aorta at week 6. Cardiac morphology and function

were assessed by echocardiography and LV pressure-volume analysis. Additionally, molecular and histological markers of cardiac hypertrophy and fibrosis were measured.

In both genders, PO induced the development of LVH as confirmed by increased LV mass, heart weight-to-tibial length ratio (HW/TL), cardiomyocyte diameter and enhanced fetal gene expression. Similarly, enhanced myocardial collagen accumulation was observed in male and female AB groups as well. The extent of LVH was greater among females, while fibrosis was more severe in male animals. In both genders, LVH was associated with diastolic dysfunction. However, systolic function only impaired in males. Contrary to the sex-dependent differences in LVH, debanding the aorta resulted in morphological (decreased LV mass, HW/TL), histological (decreased cardiomyocyte diameter and fibrosis), molecular (decreased fetal genes) and functional (restored diastolic and systolic function) reverse remodeling in both genders.

Conclusion: Pressure unloading leads to myocardial reverse remodeling at a comparable degree in male and female rats.

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Poster session 1

Name of presenter: Marta Vigil-Garcia

Abstract # 33

Gene expression profiling of hypertrophic and failing cardiomyocytes identifies new players in pathological remodeling

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Background: Pathological cardiac remodeling induced by pressure overload triggers cardiomyocyte hypertrophy and fibroblast activation, and ultimately leads to heart failure. So far, to study the mechanisms behind these processes, genome wide expression analysis on full heart tissue led to the identification of molecular mechanisms at play. However, these data were based on signals derived from all cardiac cell types. To date, the progression from cardiomyocyte hypertrophy to failure remains insufficiently understood and as a result there is a lack of therapies to reverse maladaptive remodeling.

Methods and results: Here, we generated a cardiomyocyte-specific reporter mouse Myh6-Cre-tdTomato line which we exposed to pressure overload by transverse aortic banding (TAB). Using Fluorescence-activated Cell Sorting (FACS) we collected both hypertrophic (one week after TAB) and failing (eight weeks after TAB) cardiomyocytes. Using these cells we performed RNA sequencing and identified subsets of genes and pathways differentially regulated and specific for either the hypertrophic and failing stages, such as Col3a1 and Nppb, respectively. Moreover, we identified a group of genes that yet have not been linked to cardiomyocyte hypertrophy and failure. A subset of these novel genes, we also found to be upregulated during human end stage heart failure. To validate the