

Methods: The investigation was approved by the local ethical committee. Informed consent was obtained from patient's parents. Target sequencing of 108 cardiomyopathy-associated genes was performed to uncover the genetic background of dilated cardiomyopathy followed by molecular-cytogenetic analysis using oligonucleotide array-based comparative genomic hybridization (CGH-array) on a 180K microarray platform with 13 kb median probe spacing.

Results: Target next generation sequencing did not identify any pathogenic, likely pathogenic variant, or variant of unknown significance in a gene segregating with the observed phenotype. High-resolution array-CGH analysis allowed to identify a ~4.8 Mb microdeletion of a 15q11.2-q13.1 locus known as the Prader-Willi/Angelman syndrome critical region. Indeed, 15q microdeletion of the paternal chromosomal copy is the most common genetic cause of Prader-Willi syndrome. A subsequent clinical examination of the patient at the age of 2.5 revealed development of typical features of PWS such as severe hypotonia, global developmental delay, excessive weight gain and hip dysplasia, which supported our genetic finding.

Conclusion: Here we demonstrate a rare case of Prader-Willi syndrome presenting with systolic heart failure due to dilated cardiomyopathy. Our data support the utility of not only next generation sequencing, but also array-CGH screening in patients with heart failure of unknown etiology and complex clinical phenotype.

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Polymorphisms in the CYP11B2 and AGT genes related to the renin-angiotensin-aldosterone system and their correlation with ischemic and non-ischemic phenotypes in patients with chronic heart failure.

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Background: The renin-angiotensin-aldosterone system represents a target for understanding the mechanisms involved in the development of heart failure (HF). Despite the therapeutic advances in this area, HF still represents one of the main causes of mortality. Association studies are commonly used to identify the genetic basis of quantitative traits as well as susceptibility to complex diseases.

Purpose: To determine the allelic and genotypic frequencies distribution of 8 polymorphisms, supposedly deleterious, associated with the production of aldosterone and angiotensinogen in samples of patients with HF. Ancestral information markers of insertion/deletion polymorphisms were also determined in the samples to better identify the ancestralities of the individuals.

Methods: A cross-sectional study of 326 individuals of both genders followed-up at a HF outpatient clinic. They were 220 DNA samples from peripheral blood of patients with HF, 102 with ischemic HF (caucasians= 70; blacks= 16; others= 16), 119 with non-ischemic HF (niHF) (caucasians= 53; blacks= 32; others= 30), and 106 samples from healthy volunteers. The genomic DNA samples were extracted by the salting-out technique and genotyped by the PCS and SnapShot Multiplex systems for polymorphisms rs3802228 (UTR-3 region), rs309 (UTR-3), rs72554626 (T498A), rs5317 (F487V), rs146655862 (V129M) and rs5315 (V403E), located in the CYP11B2 gene, which encodes the enzyme aldosterone synthase, in addition to the polymorphisms rs699 (M235T) and rs3789678 (intronic region NM_000029.3) of the angiotensinogen gene. Their allele and genotype frequencies were calculated by the SnapStats Software and compared between the two groups separated by etiology.

Results: The mean age of patients with HF was 64.09±12.67 y.o. and the mean age of the healthy subjects was 42.71±12.68 y.o. The polymorphism rs3802228 demonstrated a possible influence on both HF etiologies when the results were adjusted for age, gender and ethnicity, assuming the co-dominance models ($p = 0.013$) (genotype frequencies of iHF group were: G/G: 44.9%; G/A: 50%; A/A: 5.1%; and niHF group were: G/G: 30.1%; G/A: 57.3%; A/A: 12.6%; dominance model ($p = 0.014$) (genotype frequencies of iHF group were: G/G: 44.9%; G/A-A/A: 55.1%; and niHF group were: G/G: 30.1%; G/A: 57.3%; A/A: 12.6%) and recessivity model ($p = 0.029$) (genotype frequencies of the iHF group were: G/A-A/A: 94.4%; A/A: 5.1%; and niHF group were: G/A-A/A: 87.4%; A/A: 12.6%). The genotypes and alleles of the other polymorphisms studied did not show any significant association with the parameters evaluated in the study population.

Conclusion: these preliminary results suggest a possible link between polymorphism rs3802228, located in the UTR-3 region of the aldosterone synthase gene, and a higher susceptibility to HF, although it has not been possible to identify if this SNP can influence to a higher or lower degree the ischemic and non-ischemic phenotypes of HF.

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Investigation of atrial remodeling induced by exercise training in a rodent model of athlete's heart

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Introduction Atrial fibrillation and heart failure share common risk factors and frequently coexist as atrial fibrillation leads to impaired myocardial function. Although regular exercise training is associated with cardiovascular benefits, the increased risk of atrial arrhythmias has been observed, with differences in prevalence between genders. While multiple mechanisms are likely, the atrial alterations induced by long-term physical exercise still need to be elucidated.

Purpose We aimed at investigating exercise-induced atrial remodeling in a rat model of athlete's heart and determining sex-specific differences.

Methods Age-matched young adult rats were divided into female exercised (FEX), female control (FCO), male exercised (MEX) and male control (MCO) groups. After exercised animals completed a 12-week-long swim training protocol, echocardiography was used to describe atrial alterations. In vivo electrophysiologic investigation was performed by programmed stimulation with an octapolar catheter inserted into the right atrium and atrial gene expression analysis was carried out. We used two-way ANOVA for statistical evaluation.

Results Post-mortem atrial weight data confirmed marked atrial hypertrophy (atrial weight to tibial length: 18.6±2.7g/cm FEX, 10.3±1.0g/cm FCO, 23.7±2.2g/cm MEX, 15.8±1.9g/cm MCO, $p < 0.01$), while echocardiography data showed slight atrial dilatation and improved contraction in both exercised groups. Exercise training was associated with bradycardia, P-wave enlargement and prolonged right atrial effective refractory period (RAERP: 45.7±4.3ms FEX, 40.2±5.9ms FCO, 49.8±4.2ms MEX, 43.1±4.6ms MCO, $p < 0.01$). Sinus node recovery time (SNRT) did not differ between groups and we could not induce significant number of arrhythmias by programmed stimulation (double extrastimulation, burst pacing) in any groups. We found increased atrial gene expression of antioxidant enzymes (e.g. NADPH oxidase 2, superoxide dismutase 2) in both genders. Despite the marked atrial hypertrophy, no gene expression alteration was found regarding markers that describe pathological remodeling (atrial natriuretic factor), proinflammatory (tumor necrosis factor- α) and profibrotic [e.g. transforming growth factor- β (TGF- β), matrix metalloproteinase-2 (MMP-2)] processes. While exercise training did not affect on the expression of profibrotic markers, female gender was associated with lower TGF- β and MMP-2 expression. We found altered expression of ion channels participating in atrial depolarization and repolarization.

Conclusions Our data suggests that long-term exercise-induced atrial hypertrophy is not associated with harmful electrical remodeling and no inflammatory or profibrotic response was observed in the atrium of exercised rats.

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Human cardiac precursor cell secreted exosomes improved cardiac function of cardiomyopathic myocytes

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Background: The global heart failure is growing and the ominous prognosis is still a socioeconomic burden. Cardiometabolic dysfunction may contribute to the pathogenesis of certain cardiomyopathy and heart failure. The exosomes secreted from human cardiac precursor cell (hCPC-Exo) were reported to have cardioprotective actions. However, it is unclear whether hCPC-Exo can rescue cardiometabolic dysfunction in cardiomyopathic myocytes.

Purpose: This study aimed to examine whether hCPC-Exo could recover cardiometabolism in cardiomyopathic myocytes and to investigate the underlying mechanism.

Methods: Monolayer culture method was used to culture hiPSCs derived from healthy and left ventricular cardiomyopathy patients (LVNC). Cardiomyogenic differentiation of hiPSC was conducted by sequential Wnt modulation (CHIR99021 in the initial day 1-2 and followed by IWP4 in day 3-10). The culture medium in day 3-10 was collected to purify the exosome by ExoQuick-TC. The vesicle size was further measured by Nanosight. The exosomal miRNA profile was characterized by RNA seq. Mitochondrial function of human cardiomyocyte derived from left ventricular non-compaction patient's iPSC (LVNC-hiPSC-CM) was examined by Agilent Seahorse XF24 analyzer.

Results: The significant decrease of oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) was detected in LVNC-hiPSC-CM as compared to those in healthy hiPSC-CM. In the presence of hCPC-Exo (500 ng total exosomal RNA per 104myocytes) for consecutive 7 days, both of OCR and ECAR were prominently increased. The velocity of cell shortening was also increased in hCPC-Exo-treated group. Mirpath analysis shows the possible involvement of the regulated pathways including fatty acid metabolism and glucose metabolism.

Conclusions: The present study demonstrated hCPC-Exo possesses therapeutic potential to improve cardiometabolic dysfunction in LVNC.