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Detailed characterization of atrial remodeling induced by exercise training in a rodent model of exercise-induced cardiac hypertrophy

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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 regarding 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.

Results: Post-mortem atrial weight data revealed marked atrial hypertrophy (atrial weight to tibial length: 18.6 ± 2.7 g/cm FEx, 10.3 ± 1.0 g/cm FCo, 23.7 ± 2.2 g/cm MEx, 15.8 ± 1.9 g/cm MCo $p < 0.01$), while echocardiography data showed slight atrial dilatation and improved contraction in both ex-

ercised groups. Exercise training was associated with bradycardia, P-wave enlargement and prolonged right atrial effective refractory period (RAERP: 45.7 ± 4.3 ms FEx, 40.2 ± 5.9 ms, FCo, 49.8 ± 4.2 ms MEx, 43.1 ± 4.6 ms 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.