

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

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Introduction Although regular exercise training is associated with cardiovascular benefits, the increased risk of atrial arrhythmias has been observed after vigorous exercise, with differences in prevalence between sexes. While multiple mechanisms are likely, exercise-induced atrial alterations 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 confirm cardiac hypertrophy. In vivo electrophysiologic investigation was performed by programmed stimulation with an octapolar catheter inserted into the right atrium. Additionally, atrial histological examinations and atrial gene expression analysis were carried out.

Results Post-mortem atrial weight data and histological examination confirmed marked atrial hypertrophy. Exercise training was associated with bradycardia, P-wave enlargement and prolonged right atrial effective refractory period (RAERP: 43.1±4.6ms MCo, 49.8±4.2ms MEx, 40.2±5.9ms FCo, 45.7±4.3ms FEx). Sinus node recovery time did not differ between groups and we could not induce arrhythmias by programmed stimulation in any groups. We found increased atrial gene expression of antioxidant enzymes (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)] processes. While exercise training did not effect on the expression of profibrotic markers, female gender was associated with lower TGF- β and MMP-2 expression. We found decreased expression of potassium channels participating in atrial repolarization and connexin 43. Female gender was associated with lower profibrotic expression and collagen density.

Conclusions Long-term, balanced exercise training 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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Effect of lysophosphatidylcholine on osteoclast development

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Introduction Osteoclasts are multinucleated bone-resorbing cells of myeloid origin. Their differentiation is regulated by macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor- κ B ligand (RANKL) and can be divided into a biochemical maturation phase followed by the fusion of mononuclear preosteoclasts. Osteoclasts play a crucial role in physiological bone homeostasis, as well as in pathological changes of bone resorption during osteopetrosis, osteoporosis, or rheumatoid arthritis. Despite their critical role in various disease states, the molecular mechanisms of osteoclast development and the potential differences between its two phases (biochemical maturation and intercellular fusion) are poorly understood.

Aim Our aim was to characterize the effect of lysophosphatidylcholine (LPC) as a putative fusion-blocking agent on osteoclast development in vitro.

Methods Bone marrow cells were isolated from C57Bl6/J mice and cultured in the presence of M-CSF and RANKL. Varying (100-500 μ M) concentrations of LPC were added from day 2 of culture. After the indicated time, the cells were fixed and stained for the osteoclast-specific Tartrate-resistant acid phosphatase (TRAP) enzyme. Hoechst 33342 dye was used to stain the nuclei. The plates were imaged with a LEICA fluorescence microscope, followed by image quantification and analysis, aided by the ImageJ program.

Results Initial analysis of the kinetics of osteoclast development indicated the emergence of TRAP-positive cells on days 2-3 and the first fusion events during days 3-4 after RANKL treatment. Osteoclast maturation peaked on day 5 followed by increasing apoptosis of the cells from day 6. Increasing concentrations of LPC reduced the number of osteoclasts (multinucleated TRAP-positive cells) and resulted in spindle-shaped cellular morphology with long cytoplasmic processes. Importantly, though the number of nuclei per cell was strongly reduced by LPC, the cells remained TRAP-positive. The optimal concentration for inhibition of multinucleation without a substantial effect of TRAP-positivity or overall cell number proved to be around 300-400 μ M.

Conclusion LPC inhibits the formation of multinuclear osteoclasts, primarily through inhibiting intercellular fusion, rather than blocking biochemical differentiation of the cells.

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