

Beneficial Effects of Moderate Exercise in Arterial Hypertension

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Never go to excess, but let moderation be your guide.

—Cicero

Exercise and cardiorespiratory fitness have long been associated with reduced cardiovascular mortality and overall longevity in apparently healthy individuals and also in patients with pre-existing cardiovascular diseases.^{1,2} It is part of the general recommendations for lifestyle modifications in patients with early forms of cardiovascular disease and has been associated with changes in multiple cardiac risk factors, such as lipid metabolism, insulin resistance, weight, inflammation, and psychosocial variables.^{3,4} Effects of exercise on blood pressure are mild to moderate, with an average reduction of -10 mm Hg systolic and -8 mm Hg diastolic. However, exercise as a specific therapeutic intervention is difficult to evaluate and dose.³

Controversy exists on the specific form of exercise, such as aerobic versus resistance training, as well as the intensity, duration, and training intervals of the specific form of exercise chosen as a lifestyle intervention regimen.⁴ Experimental evidence from animal models and clinical data in individuals with hypertension suggest that cardiac and vascular remodeling in hypertension are positively influenced by exercise but also showed detrimental results associated with excessive exercise in an animal model of hypertension.⁵

Miyachi et al⁶ studied the effects of moderate exercise on cardiovascular remodeling and function in an established animal model of hypertension with resulting heart failure (male salt-sensitive Dahl rats). Rats were exercised by swimming for 1 hour per day, 5 days per week, for 9 weeks, and sedentary animals on a high-salt diet served as controls, whereas a second control group consisted of Dahl rats on a low-salt diet (that do not develop hypertension). The exercise regimen started at the relatively young age of 9 weeks and lasted for 9 weeks. Animals in the exercise group had similar blood pressure as measured by tail cuff compared with the sedentary control group with progressive increase over the study period. Exercise lowered the resting heart rate of animals with salt-induced hypertension in the early phase of the exercise regimen, a potentially beneficial effect that was, however, lost over time. Overall mortality was high in the

sedentary group of animals with salt-induced hypertension (56%) and was dramatically reduced in the exercise arm of the study (12%). This exciting finding alone argues for strong beneficial effects of exercise in this animal model of hypertension and heart failure. Through their careful and focused analysis of cardiac function, structure, histomorphology, and molecular signaling pattern, the authors provide several answers to the questions that triggered their investigation of exercise as an intervention to prevent the onset of heart failure in hypertension.

Animals in the exercise group also had less hypertrophy indicated by smaller wall thickness of both the left and the right ventricle but slightly enlarged left ventricles compared with their sedentary counterparts. Most notably, left ventricular end-diastolic pressure increased in the sedentary group as an indicator of the development of heart failure but remained at the same level in both the exercise group and in the control group. This was accompanied by normal lung mass in the exercise group, with significantly increased lung mass in the sedentary group.

Exercise Affects Myocardial Angiogenesis

A relative reduction in capillary density has been proposed in left ventricular hypertrophy and heart failure resulting from higher relative increases in myocyte volume with impaired angiogenesis.⁷ The state of physiological cardiac hypertrophy, as found in the athletes heart, is characterized by a normal or increased number of myocardial capillaries, whereas pathological hypertrophy, such as in hearts with aortic stenosis, hypertension, or after myocardial infarction, is associated with a reduction in capillary density.⁷ In pathological hypertrophy, therefore, there is an imbalance of oxygen supply and myocyte demand for oxygen. Areas of interstitial myocardial ischemia, myonecrosis, and progressive fibrosis are evident in long-standing hypertension and might contribute to the development of heart failure in both animal models of heart failure and patients with hypertension-induced heart failure.⁸

The ratio of capillaries:myocytes increased in the heart failure group and further increased in the exercise group. This ratio can be misleading, because it does not account for the increased volume of myocytes in left ventricular hypertrophy. It is, therefore, important to consider capillary density in the interpretation or to perform an analysis that adjusts for myocyte volume through either cross-sectional area assessment or a 3D analysis.

The current study showed the expected reduction of capillary density in sedentary animals with complete normalization in the exercise group. Through gene expression analysis by RT-PCR, the authors also show an increased angiogenic

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potential in the myocardium of animals in the exercise group. Higher mRNA levels of hypoxia-inducible factor 1 α , vascular endothelial growth factor, and endothelial NO synthase in the exercise group compared with sedentary animals are consistent with increased angiogenesis and increased capillary density in response to exercise. Notably, expression levels of these angiogenic factors nearly normalized to the expression pattern seen in nonhypertensive animals. This implicates the potential for a reversal of impaired molecular signaling in left ventricular hypertrophy and heart failure through physiological stimuli, such as exercise. In addition, it identifies angiogenic myocardial signaling as a potential target of antihypertrophic interventions in hypertension.

Moderate Exercise Preferentially Activates Phosphatidylinositol 3-Kinase/Akt/Mammalian Target of Rapamycin Signaling and Inhibits Fibrosis

The authors further investigated the underlying molecular signaling cascades in their model of cardiac hypertrophy and the impact of exercise. Myocardial hypertrophy is associated with a multitude of adaptations in cardiac structure, metabolism, signaling, and inflammation that have been linked to fundamental changes in gene expression and a switch to a fetal transcriptional program. Physiological hypertrophy is characterized by a preferential activation of the phosphatidylinositol 3-kinase/Akt signaling cascade. Pathological hypertrophy has been linked to increased activation of the p38/mitogen-activated protein kinase cascade, pronounced interstitial fibrosis, and higher rates of cardiomyocyte apoptosis.⁸ The concerted action of these maladaptive mechanisms is associated with the transition from cardiac hypertrophy to failure.⁸ The current study shows inhibition of phosphatidylinositol 3-kinase/Akt signaling as indicated by lower levels of phosphatidylinositol 3-kinase and Akt phosphorylation, as well as reduced phosphorylation of mammalian target of rapamycin, a target of Akt, and p70S6K, a downstream target of mammalian target of rapamycin, in the sedentary group of animals with hypertension compared with controls. Sedentary animals with hypertension also showed higher levels of both phosphorylated p38 mitogen-activated protein kinase and ERK indicating activation of signaling cascades implicated in pathological forms of cardiac hypertrophy. Notably, exercise corrects activation of the phosphatidylinositol 3-kinase/Akt cascade, as well as p38 mitogen-activated protein kinase and extracellular signal-regulated kinase, to levels seen in the control group. These findings indicate correction of cellular signaling in this animal model of hypertension by a moderate exercise regimen.

Finally, the authors documented increased myocardial fibrosis in the sedentary group of animals with salt-induced hypertension, which was reduced but not completely inhibited by exercise. Excessive long-term exercise was shown to enhance cardiac fibrosis and to have deleterious effects on cardiac remodeling in a previous experimental animal study of hypertension.⁵ Although the authors did not compare different levels of exercise intensity, the superior outcome of their exercise regimen might support the idea of moderate exercise as a safe and effective nonpharmacological intervention in hypertension.

The findings of the current study indicate that controlled and moderate exercise in the hypertensive state is safe and positively affects cardiac remodeling and may inhibit the progression to cardiac failure in rats. Clearly, we need further studies to better define the fine line between beneficial and detrimental effects of exercise. Nevertheless, the current study is reassuring and supports the concept of exercise as a valuable nonpharmacologic intervention in hypertension. Again, our approach should be guided by moderation and not excess.

Disclosures

None.

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