Moderate Exercise Decreases Inflammation and Oxidative Stress in Hypertension
But What Are the Mechanisms?

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Extensive epidemiological, clinical, and experimental data indicate that physical exercise slows the progression of vascular disease and reduces cardiovascular morbidity and mortality. Physical inactivity is believed to be an independent risk factor for the development of coronary heart disease, stroke, and peripheral vascular disease. As such, regular exercise is rapidly gaining widespread advocacy as a measure for preventing cardiovascular diseases, diabetes mellitus, cancer, and other chronic illnesses. In fact, major clinical guidelines for the management of hypertension suggest that exercise, together with other lifestyle modifications, should be the first line of antihypertensive management. In support of this, a comprehensive meta-analysis showed that aerobic endurance training reduces systolic blood pressure by 2 to 7 mm Hg with the greatest reduction in hypertensive participants but with blood pressure–lowering effects as well in prehypertensive patients.

Positive cardiovascular effects of exercise are associated with beneficial changes in cholesterol levels, antioxidant systems, blood pressure, adipogenesis, and inflammation. Myriad factors have been implicated, whereby exercise induces protective cardiovascular actions, including decreased sympathetic activity, reduced angiotensin II levels, increased NO bioavailability, increased antioxidant capacity, modulation of K+ channels, and expression of cardioprotective factors, such as apelin. In addition, growing evidence indicates that exercise prevents oxidative damage by reducing oxidative stress, an important factor in inflammation and hypertension. What remains unclear is exactly how exercise modulates redox status and how it influences proinflammatory processes.

In the present issue of Hypertension, Agarwal et al further highlight the benefits of exercise in reducing blood pressure and focus on the role of ameliorating oxidative stress and inflammation as putative mechanisms for beneficial effects of exercise. By using the spontaneously hypertensive rat (SHR) model and a moderate training program, they demonstrate that exercise delays the progression of hypertension, a response associated with decreased plasma levels of proinflammatory cytokines and norepinephrine, reduced oxidative stress, and diminished activation of the nuclear factor κB (NF-κB) system.

Despite the many studies demonstrating that exercise reduces oxidative stress, which probably impacts on cardiovascular status, there is a paradox relating to interactions between exercise and the generation of reactive oxygen species. For example, exercise protects against atherosclerosis but also induces oxidative stress as a result of the inefficiency of the mitochondrial respiratory chain and the increase in fluid shear stress on the endothelium. Human and experimental studies showed that repeated exposure to mild oxidant stress that occurs with exercise may initiate adaptive processes to reduce oxidative stress by decreasing superoxide anion (O2−) production and/or upregulating antioxidant enzymes. This, together with the exercise-induced increase in shear stress, might contribute to increased NO availability and improvement of vasodilator responses observed during exercise.

Some studies have queried how exercise impacts on the source of O2−, focusing especially on the expression and/or activity of NADPH oxidase, a major enzymatic contributor of O2− in the cardiovascular system. However, these studies were conducted primarily in normotensive exercising models, with little information available in hypertension. In fact, it is unclear whether exercise actually influences NADPH oxidase activity and NADPH oxidase subunits expression in hypertension. A recent study in humans indicated that exercise had significant effects on oxidative stress and blood pressure in hypertensive patients independent of polymorphisms in p22phox. In the study of Agarwal et al, exercise training clearly normalized the increased expression of gp91phox and the increased production of reactive oxygen species in the heart of SHRs, as well as induced upregulation of antioxidant enzymes, promoting a low redox milieu.

In keeping with other studies, Agarwal et al demonstrated that exercise reduces inflammation. As suggested in the article, mechanisms for this may relate to decreased oxidative stress, changes in IL-6 production and decreased activation of NF-κB. Physiological concentrations of interleukin (IL) 6 stimulate the appearance in the circulation of the anti-inflammatory cytokines IL-1 receptor antagonist and IL-10 and inhibit the production of the proinflammatory cytokine tumor necrosis factor-α. In addition, a role for the Toll-like receptor 4 in mediating the anti-inflammatory properties of
exercise has been suggested. This is based on the fact that Toll-like receptor 4 expression is decreased in physically active versus sedentary older women. It is also possible that the decrease in reactive oxygen species generation reduces NF-κB activation and consequent cytokine production (Figure). To what extent these phenomena participate in exercise-induced reduction of inflammation in the context of hypertension remains unclear, and unfortunately the study by Agarwal et al leaves many unanswered questions as to exactly how exercise actually influences cardiovascular function.

A limitation of the study under discussion is the fact that Toll-like receptor 4 expression is decreased in physically active versus sedentary older women. It is also possible that the decrease in reactive oxygen species generation reduces NF-κB activation and consequent cytokine production (Figure). To what extent these phenomena participate in exercise-induced reduction of inflammation in the context of hypertension remains unclear, and unfortunately the study by Agarwal et al leaves many unanswered questions as to exactly how exercise actually influences cardiovascular function.

A limitation of the study under discussion is the fact that the data are essentially associative. It is not possible to conclude anything definitive about mechanisms whereby exercise influence molecular/cellular events and signaling pathways. Moreover, the changes observed in oxidative stress and inflammatory biomarkers in the study may be independent, because there is a circuital relationship and positive feedforward relationship between free radicals and inflammation/NF-κB (Figure). In fact, these data pose the question of whether exercise-induced reduction in oxidative stress is responsible for the anti-inflammatory properties of exercise and/or whether the reduction of cytokines explains the antioxidant properties of exercise. The authors attempt to unravel this issue, in part, by exploring the relationship between the sympathetic nervous and oxidative stress/inflammation system in exercising SHRs.

Plasma norepinephrine levels with associated increased sympathetic activation in SHRs may lead to cardiomyocyte hypertrophy, cardiac damage, and apoptosis. It is generally accepted that, in both humans and experimental models, exercise training reduces sympathetic activity and/or increases parasympathetic tone, which are correlated with reduced heart rate and blood pressure. It is also known that increased sympathetic activity is strongly related to cardiac oxidative stress through the formation of reactive oxygen species by catecholamine oxidation but also by stimulating its generation through activation of NADPH oxidase. Interestingly, this catecholamine induced-ROS production participates in cardiomyocyte hypertrophy. In addition, norepinephrine induces proinflammatory cytokines in the cardiomyocytes. To what extent these reduced norepinephrine levels participate in the decrease in proinflammatory cytokines and reactive oxygen species reported by Agarwal et al is not addressed but
probably does play a role, because exercise is a powerful modulator of sympathetic activity, which, in turn, influences NADPH oxidase–derived generation of $O_2^−$.

A particularly important and clinically relevant question posed by Agarwal et al. is "How much exercise is actually needed to confer cardiovascular benefits?" These investigators clearly demonstrate that even moderate exercise training is enough to activate molecular pathways leading to decreased inflammation and oxidative stress in SHRs and to attenuate the development of hypertension. In fact, low-to-moderate–intensity exercise appears to be as beneficial as higher-intensity exercise for reducing blood pressure. Interestingly, the authors did not find beneficial effects of this training program in normotensive animals, suggesting differential responsiveness between Wistar-Kyoto rats and SHRs. Such data provoke the question as to whether there are different levels of exercise benefits in pathological and physiological conditions. This is an important issue, because Schultz et al. reported the provocative findings that excessive exercise, in the untreated hypertensive state, can have deleterious effects on cardiac remodeling and may actually accelerate progression to heart failure. The study by Agarwal et al has clinical significance because it highlights the fact that even moderate exercise improves cardiac function and attenuates the development of hypertension, possibly by decreasing oxidative stress and inflammation through modulation of the sympathetic nervous system. Although these findings are interesting and support clinical studies, they are still essentially associative. Until we have a greater understanding of exactly how exercise influences the fundamental process at the gene, molecular, and cellular levels, we cannot make any conclusions regarding antihypertensive mechanisms of exercise. Much research is still needed to address these important clinically relevant aspects.

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None.

**References**


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