Hypertension Research (2016) 39, 61–63

www.nature.com/hr

COMMENTARY

Exercise is a double-edged sword for endothelial function

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Hypertension Research (2016) **39,** 61–63; doi:10.1038/hr.2015.127; published online 12 November 2015

Several lines of evidence have shown that aerobic exercise reduces cardiovascular morbidity and mortality in the general population, including hypertension.[1,2] Although the mechanisms underlying the antiatherogenic and antihypertensive effects of exercise remain unclear, exercise-induced improvement of endothelial function should contribute to reduction in cardiovascular events. Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis.[3] Hypertension is also associated with alteration in endothelial function mediated through reduced nitric oxide (NO) bioavailiability.[4] Exercise is expected to prevent cardiovascular events through an augmentation of endothelial function in patients with hypertension. Indeed, it is well known that aerobic exercise improves endothelial function both in animal models of hypertension and in patients with hypertension.[5,6] A balance between ambient levels of reactive oxygen species (ROS) and released NO has a critical role in the maintenance of normal endothelial function. A number of mechanisms of improvement in endothelial function during exercise have been postulated. Regular aerobic exercise has beneficial effects on blood pressure, lipid metabolism, glucose metabolism, neurohormonal factors and shear stress. Although the precise mechanism of exercise-induced improvement in endothelial function has not been fully clarified, it has been shown that regular aerobic exercise increases NO production with upregulation of endothelial NO synthase (eNOS) gene expression and vascular endothelial growth factor-induced angiogeneisis and it decreases NO inactivation with augmentation of activity of components of the antioxidant defense system, such as superoxide dismutase (SOD), glutathione peroxidase and catalase, and attenuation of NADH/NADPH oxydase activity, leading to an increase in NO bioavailiability.[7] These findings suggest that exercise increases NO production and decreases NO inactivation, leading to an increase in NO bioavailiability. However, not all types of exercise improve endothelial function. It is clinically important to select the appropriate intensity, duration, frequency and kind of exercise, as high-intensity exercise can be hazardous to human vessels.[8] In general, the guidelines for management of hypertension recommend exercise at an intensity of ~50% of maximum oxygen consumption, such as walking, jogging, cycling or swimming, for 30 min per time and 5 to 7 times per week, for patients with mild-to-moderate essential hypertension.[9–11]

Although the mechanisms by which moderate-intensity exercise induces improvement of endothelial function have been investigated in detail, there is little information on the mechanisms by which high-intensity exercise impairs or does not alter endothelial function. In this issue, Battault *et al.*[12] reported that high-intensity exercise training had no beneficial effects on endothelial function in spontaneous hypertensive rats (SHR). In this animal model of hypertension, high-intensity exercise training induced an increase in oxidative stress, resulting in eNOS uncoupling related to increase in ROS generation and leading to a vicious circle of decrease in NO bioavailiability and increase in ROS. Oxidation of tetrahydrobiopterin (BH_4) has a critical role in oxidative stress-induced eNOS uncoupling during high-intensity exercise. Under conditions of BH_4 deficiency other than oxidation of BH_4, eNOS produces ROS, which inactivate NO.[13] Dysfunctional eNOS with insufficient BH_4 causes generation of ROS, resulting in decreased NO activity in prehypertensive SHR.[14] It has been reported that the degradation of BH_4 by ROS, including peroxynitrite, superoxide and hydrogen peroxide, is associated with downregulation of eNOS.[15] These findings suggest that BH_4 deficiency-induced decrease in eNOS activity cause endothelial dysfunction in hypertension through an increase in oxidative stress. There is a possibility that high-intensity exercise activates oxidative stress through exacerbation of BH_4 deficiency, as well as oxidation of BH_4.

Interestingly, exercise increases not only ROS but also NO in relation to its intensity (Figure 1). An unbalance between NO and ROS, especially the condition of excess ROS compared with NO, so called 'oxidative stress', under the condition of high-intensity exercise. We cannot deny the possibility that the action of increased ROS that inactivates NO is removed by increased NO production, resulting in maintenance of endothelial function. Moderate-intensity exercise may predominately increase NO production compared with ROS production, leading to augmentation of endothelial function. It is likely that mild-intensity exercise does not alter either NO or ROS, resulting in no change in endothelial function. Exercise is a double-edged sword for endothelial function.

On the other hand, attention should also be paid to the effects of high-intensity exercise on the antioxidant defense system, too. It is thought that hypertension is associated with diminished activity of the antioxidant defense system. Steady laminar shear stress upregulates the gene expression of

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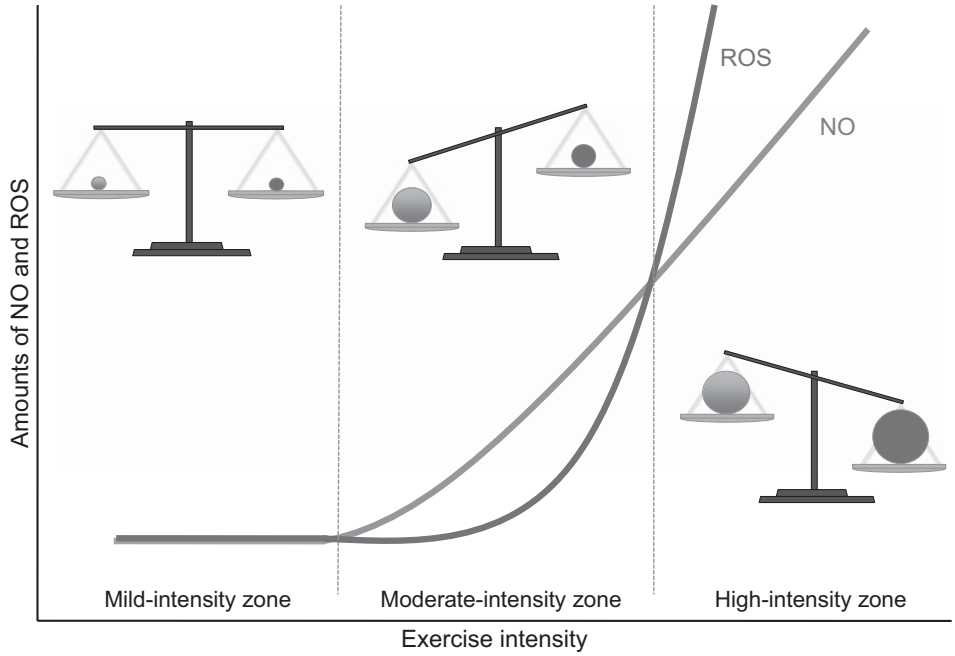

Figure 1 Production of nitric oxide (NO) and reactive oxygen species (ROS) in response to different exercise intensities. During mild-intensity exercise, NO and ROS are constant, resulting in no change in endothelial function. Production of NO and that of ROS are greater during moderate-intensity exercise than during mild-intensity exercise. During moderate-intensity exercise, production of NO is greater than production of ROS, resulting in augmentation of endothelial function. Production of NO and that of ROS are greater during high-intensity exercise than during moderate-intensity exercise. During high-intensity exercise, production of ROS is greater than production of NO, resulting in diminished endothelial function.

Cu/Zn SOD and Mn SOD in endothelial cells.[16] Exercise training enhances the protein level and enzymatic activity of SODs, such as Cu/Zn SOD and Mn SOD, in pig coronary artery endothelial cells.[17] A physiological level of shear stress upregulates glutathione peroxidase mRNA levels and glutathione peroxidase enzymatic activity in cultured bovine aortic endothelial cells.[18] Adaptive changes in glutathione peroxidase and catalase gene expression in skeletal muscle in response to various types of exercise have been reported.[19] However, it is not clear whether high-intensity exercise severely impairs the antioxidant defense system or does not alter the system.

We have shown that a 12-week period of exercise of high-intensity increases the indices of oxidative stress, including plasma concentration of 8-hydroxy-2′-deoxyguanosine and serum concentration of malondialdehyde-modified low-density lipoprotein, and decreased endothelium-dependent vasodilation in forearm circulation in healthy men.[20] Davies *et al.*[21] reported that the massive increase in oxygen uptake that occurs in skeletal muscle during exercise is associated with an increase in ROS. These findings suggest that high-intensity exercise increases oxidative stress in humans. Therefore, it is thought that increased oxidative stress induced by high-intensity exercise diminishes endothelium-dependent vasodilation in humans. At present, there is no information on the role of high-intensity exercise in the BH_4/eNOS/NO pathway in moderation of endothelial function in humans with hypertension. Future studies are needed to evaluate the effects of high-intensity exercise on endothelial function and confirm the precise mechanisms of high-intensity exercise-induced changes in endothelial function in a general population, including humans with hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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