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Pathophysiological mechanisms underlying the beneficial effects of physical activity in hypertension

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Prevention and management of hypertension represent a global public health challenge. Therefore, the identification of new therapeutic strategies is of growing interest. The American Heart Association defines as "alternative approaches", the non-pharmacological treatments able to lower blood pressure, classifying them into three categories: behavioural therapies, non-invasive procedures, and exercise-based regimens[1]. In the last decades, several studies have revealed that exercise and fitness produces beneficial effects in the general population, reducing the relative risk of death by 20–35%[2,3], particularly death caused by cardiovascular disease[4,5].

The definition of "*exercise*" given by the American College of Sports Medicine reads *"Any and all activity involving generation of force by the activated muscle(s) that results in disruption of a homeostatic state"*. Behind this general definition, different categories of exercise are recognized, which differ for type, intensity and duration. As the success of pharmacological therapies is linked to the optimal dose, also for "exercise" the potential therapeutic effect strongly depends on the "dose", resulting from optimal intensity and duration. This critical point has opened an extensive research aimed at considering exercise training in therapeutic plans for the management of systemic disorders like diabetes and hypertension. Substantial evidence in literature supports the efficacy of fitness on hypertension, suggesting that physical activity lowers blood pressure, thereby preventing the development and progression of hypertension.

In this issue of the Journal, Wellman and colleagues have shown in an elegant study performed in adolescents that engaging in physical activity is associated with lower odds of

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CONFLICT OF INTEREST

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having blood pressure in the hypertensive range[6]. The exact molecular basis of the beneficial effects that physical activity produces on blood pressure are not completely understood, probably because the regulation of blood pressure is complex and multifactorial, including neuro-hormonal, hemodynamic, and metabolic mechanisms. Starting from this multifaceted substrate, exercise training can affect blood pressure acting on different processes (Figure 1), only in part known.

Physical activity and endothelial function

A foremost mechanism by which physical exercise can affect blood pressure is the regulation of endothelial function. Indeed, vascular homeostasis depends on the activity of the endothelium, which is a fundamental regulator of the vasomotor responses, modulating the health and resistance of the vessels. Nitric oxide (NO) is a key mediator of endothelial function, and both clinical and preclinical studies have confirmed the ability of exercise to improve NO-dependent endothelial vasodilation[7–12]. Physiologically, high NO production occurs in response to increased blood flow to compensate the shear stress by vasodilation[13–15]. Exercise training results in repeated exposure to shear stress, thus improving the bioavailability of NO[16]. In rats, a 2–4-week exercise training not only stimulates the NO production in the arterioles of the skeletal muscle, but also markedly improves the vasodilator response to acetylcholine[17]. A regular aerobic exercise can improve endothelial function also in aged population, in which the endothelium is compromised. Indeed, exercise training has been shown to attenuate endothelial dysfunction during aging[18], probably increasing NO synthesis to counteract ROS generation[19]. A direct evidence of the improvement of endothelial function as a pivotal mechanism underlying the anti-hypertensive effect of physical exercise comes from the SEFRET study (*Study of endothelial function response to exercise training in hypertensive individuals*)[20]. In this report, the Authors unveil two crucial points: i) physical activity ameliorates the endothelium-dependent vasodilation in a hypertensive population; ii) the magnitude of the improvement of endothelial function depends on the type of exercise training (aerobic, resistance, or concurrent training). This evidence strengthens the proof of concept that the prescription of a specific exercise program is fundamental in the therapeutic approach of hypertensive patients.

Exercise training and angiogenesis

Hypertension is characterized by microvascular rarefaction caused by impaired angiogenesis[21]. Constant physical exercise has been shown to induce vessel adaptation, augmenting blood flow reserves[22]. These morphological changes in the vascular tree result from exercise-induced angiogenesis, which increases the size and number of blood vessels[23]. The formation of new microvessels and the increase of vessel networks are processes regulated by vascular endothelial growth factor (VEGF) and other mediators; released in response to exercise training, VEGF produces a mitotic effect on endothelial cells, induces endothelial cell migration, and promotes chemotaxis[24]. Other factors able to regulate angiogenesis are released in response to exercise, including angiopoietins and metalloproteinases, which initiate the degradation of the extracellular matrix, a process essential for the formation of vascular networks[25]. An interesting research by Oliveira and

colleagues demonstrated that exercise training prevents the microvascular rarefaction in hypertensive rats[26]. Interestingly, this effect seems to be mediated by specific microRNAs implicated in angiogenetic process[27,28]. This new mechanism again supports the potential therapeutic application of exercise training in vascular disease, mainly in hypertension.

Physical activity and insulin sensitivity

A seminal study demonstrated that the hypertensive phenotype induced by high-fructose diet was strongly attenuated by spontaneous physical activity in rodents, accompanied by a significant attenuation of insulin resistance[29], strongly suggesting a pathophysiologic link between essential hypertension and hyperinsulinemia[30].

More recently, in an animal model of metabolic syndrome, exercise training of moderate intensity has been shown to play a preventive role, playing an important role on the regulation of blood pressure and insulin sensitivity[31]. The recurrent association between exercise training and recovery of insulin sensitivity strongly supports the hypothesis that physical activity may prevent hypertension development and progression through its action on insulin responsiveness. Direct evidence about such a link comes from a number of studies: Chisholm and colleagues demonstrated that exercise training induces a significant increase in whole body insulin sensitivity, in particular acting on glucose uptake and oxidation by the skeletal muscle[32]. The increased glucose uptake in response to exercise is essentially due to GLUT4 translocation on the membrane, which is independent from insulin receptor; indeed, insulin receptor knockout animals displayed the same response to exercise in terms of muscular glucose uptake[33]. Other not fully understood pathways could be involved in the increased glucose uptake during muscle contraction: epigenetics, oxidative stress, intracellular Ca^{2+} dynamics[34–38].

Exercise training as effective therapeutic tool in hypertensive patients

One of the first clinical studies showing the antihypertensive effect of physical activity was published in 1968. The research demonstrated that in men that self-reported more than 5 hours/week of physical exercise the incidence of hypertension was significantly reduced[39]. In five decades this finding has been reproduced by large prospective studies, confirming that physical activity inversely correlates with hypertension[40–42].

Interventional studies have corroborated the direct effects of physical activity on blood pressure, providing information about the more responsive target populations. A training program of 2 days for week lowered blood pressure both in hypertensive and normotensive subjects[43]; another study demonstrated that the effect of physical exercise on blood pressure is more pronounced in hypertensive patients than in normotensive individuals[44]. Nevertheless, if on one hand the major effect of exercise training is recorded in hypertensive conditions, on the other hand the training inhibits the progression from normal to pre-hypertension and from pre-hypertension to hypertension[43,45–48]. Therefore, physical exercise represents a powerful therapeutic tool to prevent the development of hypertension, especially in high-risk populations like diabetic patients or individuals with family history of hypertension.

Conclusions

Physical exercise has been shown to have beneficial effects on blood pressure, through means of adaptation mechanisms which culminate in both hemodynamic and metabolic changes. Several studies demonstrate that the effects of physical exercise on blood pressure are dose-dependent[49–51]. Moreover, the beneficial effects depend on the type of exercise training[52–58]. Importantly, resistance training is contraindicated in presence of instable cardiovascular conditions, including uncontrolled severe hypertension[59,60]. Therefore, it is imperative to emphasize that a specific training plan including the specific type and dose of exercise training has to be delineated for each individual. Accordingly, a stress testing before starting exercises should be performed. Physical activity remains a potential therapeutic and prevention tool, which needs further investigations to support a fully personalized therapeutic program.

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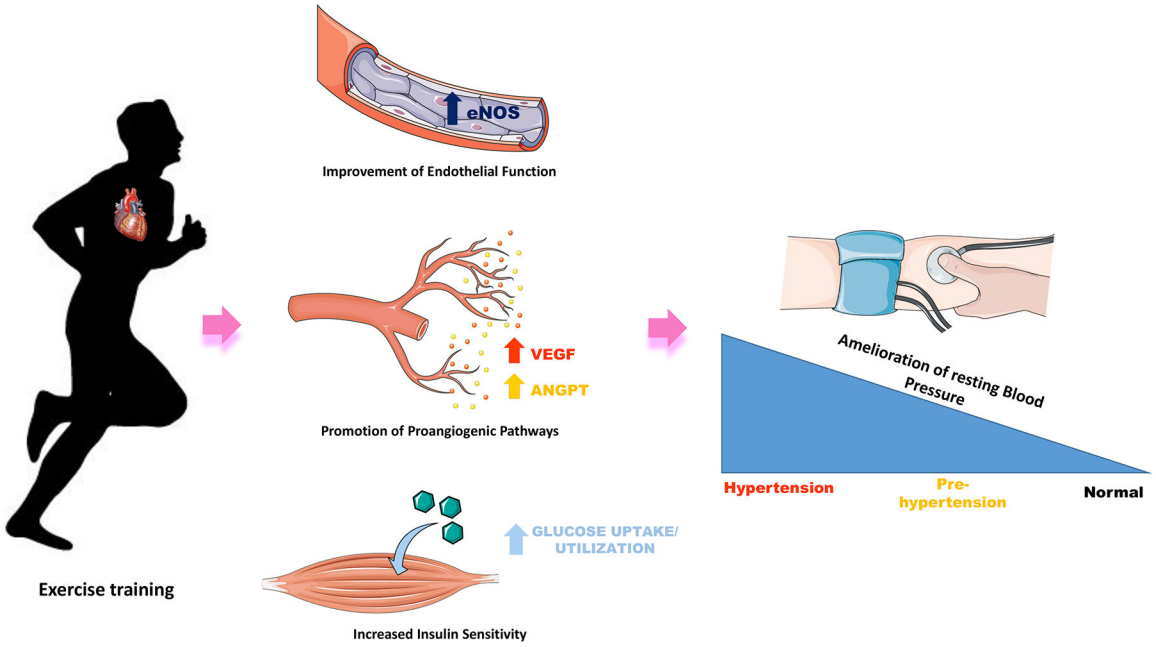

Figure 1.

Exercise training activates adaptive mechanisms: i) Improvement of endothelial function increasing NO production, ii) Induction of pro-angiogenic pathways, iii) Increased insulin sensitivity. These mechanisms produce a significant reduction in blood pressure. The beneficial effects are more pronounced as higher is the starting blood pressure.