

Mini Review

Impact of Exercise Training on Blood Pressure and Endothelial Function in Individuals with Systemic Hypertension

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Ischemic heart diseases are largely determined by multifactorial risk factors that are associated with systemic arterial hypertension. Furthermore, high levels of total cholesterol, high body mass index, and high fasting glucose are also major risk factors that can lead to atherosclerosis. Endothelial dysfunction is a characteristic feature of systemic arterial hypertension and an early marker of atherosclerosis. Evidence shows that high blood pressure can result in vascular remodeling and damage to vascular endothelial cells and may partly explain endothelial dysfunction found in hypertensive individuals. There is a consensus that regular exercise can help control blood pressure levels in hypertensive individuals and all leading health organizations consider it the first-line non-pharmacological strategy for blood pressure control. Moreover, regular exercise has shown to improve endothelial function in different populations. However, different modalities of exercises, i.e. aerobic, resistance or combined (aerobic + resistance), could have different effects on blood pressure and endothelial response and they need to be further investigated. Thus, this review aims to better understand the behavior of blood pressure and endothelium-dependent vasodilator capacity in hypertensive individuals engaging in different forms of exercise training.

Keywords: Exercise; Endothelium; Hypertension**Abbreviations**

SAH: Systemic Arterial Hypertension; CVD: Cardiovascular Disease; NOS: Nitric Oxide Synthase; NO: Nitric Oxide; eNOS: endothelial Nitric Oxide Synthase; LDL-C: Low-Density Lipoprotein Cholesterol; EPCs: Endothelial Progenitor Cells; BP: Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; NOx: Nitrate/Nitrite; 1 RM: One Repetition Maximum

Introduction

Systemic Arterial Hypertension (SAH) is characterized by high Blood Pressure (BP) resulting in a failure of vascular regulation due to malfunction in pressure control mechanisms [1,2]. It is likely that a large number of interrelated factors contribute to increased blood pressure in hypertensive subject, and their relative roles may differ between individuals. Factors associated with SAH are excess sodium intake [3], elevated levels of circulating angiotensin-converting enzyme [4], increased sympathetic nervous system activation [5], genetic factors [6], and endothelial dysfunction [7,8]. It is estimated that, by 2025, approximately 29% of the world population will have hypertension, accounting for about 1.56 billion individuals affected, mostly in developing countries [9]. These data are concerning given the high incidence of coronary artery disease, peripheral artery disease, stroke, and heart failure in this population [10,11]. Of all risk factors for developing coronary artery disease, hypertension is described as the most important, followed by high levels of total cholesterol, high body mass index, and high fasting glucose [12].

Obesity [13,14], physical inactivity [15], and insulin resistance [16] are all risk factors closely associated with SAH. These risk factors may individually contribute to the development of atherosclerosis and consequent mortality from ischemic Cardiovascular Disease (CVD) [17].

The vascular endothelium has an important function in modulating angiogenesis, inflammatory responses, homeostasis as well as and vascular tone and permeability [18]. This important vascular protection function results from a balance of factors released by vascular endothelium that determine vasodilation or vasoconstriction [19]. Vasodilation is primarily mediated by factors such as prostacyclin, Endothelium-Derived Hyperpolarizing Factor (EDHF), and Nitric Oxide (NO), whereas a vasoconstrictor state is mediated by factors such as angiotensin II, Endothelin-1 (ET-1), thromboxane A₂, and prostaglandin H₂ [20,21]. Among these factors, NO is considered to be the most potent endogenous vasodilator [22,23]. NO is produced from L-arginine and released by the activity of endothelial NO Synthase (eNOS) through the action of chemical agonists that act on specific endothelial chemoreceptors or respond to mechanical forces on mechanoreceptors such as shear stress [24]. A decrease in NO production, low local bioavailability, and inadequate vasomotor response characterize endothelial dysfunction, [19] a hallmark of diabetes mellitus type 2 [25], SAH [26] and dyslipidemia [27] and an early marker of atherosclerosis [28].

Evidence exists that clearly shows that physical exercise can improve the endothelium-dependent vasodilatory capacity in

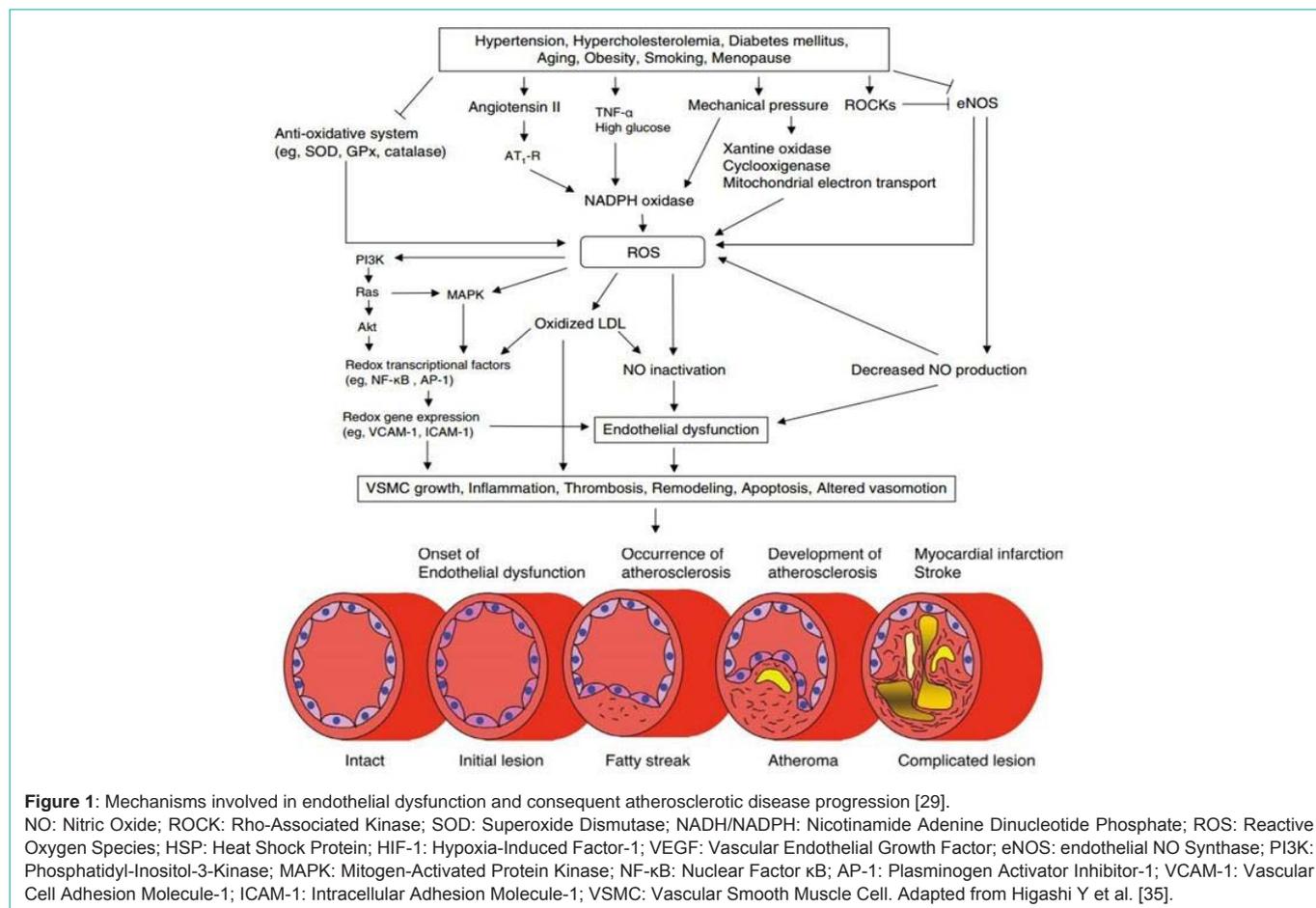


Figure 1: Mechanisms involved in endothelial dysfunction and consequent atherosclerotic disease progression [29].

NO: Nitric Oxide; ROCK: Rho-Associated Kinase; SOD: Superoxide Dismutase; NADH/NADPH: Nicotinamide Adenine Dinucleotide Phosphate; ROS: Reactive Oxygen Species; HSP: Heat Shock Protein; HIF-1: Hypoxia-Induced Factor-1; VEGF: Vascular Endothelial Growth Factor; eNOS: endothelial NO Synthase; PI3K: Phosphatidy-Inositol-3-Kinase; MAPK: Mitogen-Activated Protein Kinase; NF-κB: Nuclear Factor κB; AP-1: Plasminogen Activator Inhibitor-1; VCAM-1: Vascular Cell Adhesion Molecule-1; ICAM-1: Intracellular Adhesion Molecule-1; VSMC: Vascular Smooth Muscle Cell. Adapted from Higashi Y et al. [35].

different populations [29]. Increasing physical activity levels and/or physical exercise is a recommended treatment for SAH in major guidelines [30]. Accumulated evidence supports exercise as a non-pharmacological strategy for the prevention of CVD including ischemic heart disease as endothelial dysfunction precedes the development of these conditions and has a major role in the pathogenesis of atherosclerosis [28].

Regular exercise is a non-pharmacological intervention recommended by all leading health organizations because it provides the most comprehensive benefits among modifiable risk factors [31]. Thus, considering that regular exercise is part of antihypertensive therapy and has shown to improve endothelial function in different populations, this review seeks to provide an overview of the effects of different types of physical exercise on BP levels and endothelial function in hypertensive patients.

Endothelium

The endothelium is a single layer of cells lining the tunica intima of blood vessels and it plays a major role in the modulation of vascular angiogenesis, inflammatory responses, and vascular tone and permeability [18,32]. Endothelial protection particularly involves the activity of eNOS, an enzyme involved in the production of NO.

Endothelium-dependent NO release can be stimulated by different physiological factors including physical stress (shear stress), circulating hormones (catecholamines, vasopressin, and aldosterone),

platelet agonists (serotonin and adenosine diphosphate), autacoids (histamine and bradykinin), and prostaglandins [33]. The NO dilates all types of blood vessels by stimulating soluble guanylyl cyclase and increasing cyclic GMP in smooth muscle cells [34]. A decreased production of NO, low local bioavailability, and/or insufficient vasomotor response characterize endothelial dysfunction evidenced in patients with SAH, [19] which has an important role in the pathogenesis of atherosclerosis (Figure 1) [28,35].

In the pathogenesis of atherosclerosis, there is first a qualitative change of the monolayer of endothelial cells lining the inner surface of the arteries when exposed to irritating stimuli such as high BP, dyslipidemia or pro-inflammatory mediators. This change induces endothelial cells to express adhesion molecules that recruit leukocytes to the surface. At the same time there are changes in the permeability and extracellular matrix composition of the endothelium promoting the entry and retention of Low-Density Lipoprotein Cholesterol (LDL-C) [36]. Chemically modified particles in these components may induce leukocyte adhesion, and modified intact particles are endocytosed by macrophages leading to intracellular accumulation of cholesterol. During the progression of an atherosclerotic plaque, leukocytes directly migrate into the intima the innermost layer of an artery, where monocytes differentiate into macrophages that engulf lipoprotein particles and become foam cells [37]. The recruitment of smooth muscle cells of the tunica media to the intima is also involved in the formation of atherosclerotic plaque (atheroma) [37].

After migrating from the middle layer to the intima, smooth muscle cells proliferate in response to mediators such as platelet-derived growth factors, and produce extracellular matrix molecules, including interstitial collagen and elastin, to form a fibrous cap covering the plaque [37]. The atherosclerotic plaque is generally rich in foam cells, dead smooth muscle cells, and released lipids that accumulate at its center. Ineffective release of dead cells can promote the accumulation of cellular debris and extracellular lipids creating a lipid-rich necrotic core (Figure 1) [38].

Atherosclerotic plaques can produce the clinical manifestation of angina pectoris with a positive exercise stress test and perfusion defects at imaging studies [39]. Blood flow restriction and stenosis lead to tissue ischemia or thrombus formation which may disrupt blood flow or break loose and become lodged in distal arteries causing acute thrombotic vascular disease including myocardial infarction, cerebral vascular accident, and sudden death [36].

The balance between endothelial injury and recovery is critical to continuously maintaining endothelial function [40]. The bone marrow releases a progenitor cell subtype called Endothelial Progenitor Cells (EPCs) that migrate to the peripheral circulation and differentiate into mature endothelial cells to maintain vascular integrity [27]. EPC levels have been associated with cardiovascular risk factors [41], endothelium-dependent vasodilation [42], and clinical outcomes including hospitalization and cardiovascular death rates [43]. In patients with cardiovascular risk factors such as SAH [44], smoking [45], metabolic syndrome and diabetes mellitus [46,47] circulating levels of EPCs can be reduced compared with healthy individuals of matching age and sex. Endothelial dysfunction has been associated with decreased number and impaired function of EPCs in patients with SAH, diabetes mellitus and metabolic syndrome, and thus increased risk of atherosclerosis would be expected [48].

There is good evidence in the literature of the role of regular exercise in healthy individuals. Regular aerobic exercise is able to improve endothelial function [29], reduce arterial stiffness [49], increase the number of EPCs [50], reduce blood pressure levels [51], and improve cardiopulmonary fitness [52] in health individuals. Resistance training for healthy individuals can improve endothelial function [29] and reduce blood pressure levels [51]; however, it does not appear to have positive effects on arterial stiffness [53]. Compared to aerobic exercise, resistance training stands out by increasing muscle mass [54], bone density [55], and muscle strength [56].

Considering that regular exercise is part of antihypertensive therapy and that it improves endothelial function in healthy subjects, an overview of the effect of exercise on endothelial function in patients with SAH is required.

Exercise in Hypertensive Individuals

Factors associated with potential antihypertensive effects of long-term exercise are not yet fully understood; although it has been proposed exercise can reduce the sympathetic activity [57] and promote a balance between vasodilation and vasoconstriction [58]. Regular exercise, also known as exercise training, produces effects on the cardiovascular system and has a proven action restoring endothelial function even in the presence of cardiovascular disease [59]. It promotes changes in cholesterol and its subfractions; accelerates the

removal of chylomicrons and LDL-C from circulation; increases the release of NO that seems to generate increased expression of NOS; increases the number of circulating EPCs in healthy individuals as well as in individuals with established cardiovascular disease [50,60], and improves plasma glucose [61], which has a direct link to impaired endothelial function [62].

This assumption is consistent with findings in healthy individuals [63], individuals with diabetes mellitus type 2 [64] and patients with CVD showing that exercise training improved vascular function and overall health [65]. Particularly aerobic exercise can contribute to reducing mortality due to CVD by about 30%. There is evidence that regular aerobic exercise can prevent loss in endothelium-dependent vasodilation and restore previous levels in middle-aged men, the elderly, and physically inactive individuals [66,67].

The relationship between aerobic exercise and SAH has been widely investigated. Studies have showed a reduction in BP with exercise in the short and long term [31,68]. In a meta-analysis of studies conducted between 1976 and 2012 Cornelissen et al. (2013) provided a recent comprehensive view of the effects of aerobic training as an intervention on BP reduction [51]. They found a mean reduction of 4.7 mmHg in the Systolic Blood Pressure (SBP) and 2.8 mmHg in the Diastolic Blood Pressure (DBP) among males and a lower reduction among females of 0.8 mmHg in SBP and 0.5 mmHg in DBP. Regarding exercise frequency per week, no differences in BP reduction were seen when exercise frequency was less than three times a week (3.9 mmHg in SBP; 2.8 mmHg in DBP) compared to 3 to 4 times (3.5 mmHg in SBP; 2.4 mmHg in DBP) or more than 4 times (3.2 mmHg in SBP; 2.4 mmHg in DBP). These authors also assessed the relationship between BP reduction and exercise duration and found a difference in DBP reduction only for 30 to 45 minute (3.8 mmHg in SBP; 3.3 mmHg in DBP) and more than 45-minute sessions (2.8 mmHg in SBP; 1.9 mmHg in DBP). The magnitude of BP reduction in response to exercise intensity was similar in moderate (4.8 mmHg in SBP; 2.3 mmHg in DBP) and vigorous exercise (3.6 mmHg in SBP; 3.1 mmHg in DBP) [51].

Cross-sectional studies have shown that individuals that exercise regularly have lower arterial stiffness when compared to sedentary ones [62]. A prospective study of 18 healthy young volunteers who followed an aerobic training program on a treadmill for eight weeks found reduced arterial stiffness, which returned to baseline values after a four-week period of detraining [69]. Higashi et al. (1999) assessed forearm blood flow in 17 patients with mild SAH in response to an aerobic training program [66]. After a 12-week training, forearm blood flow values were greater post-training compared to pre-training. This beneficial effect on endothelium-dependent vasodilation is mediated by an increase in endothelial NO. In another study 13 middle-aged sedentary men underwent a 12-week running program (45-min sessions, 5-6 days a week, with gradual intensity increase up to 75% of maximum heart rate) [69]. There was an increase in forearm endothelial function by approximately 30% [70].

Aerobic exercise performed for one hour on an exercise bike, three times a week, for six months at an intensity of 50% of heart rate reserve was shown to increase plasma concentrations of nitrate/nitrite (NOx), which are metabolites used to indirectly measure NO levels in postmenopausal women with hypertension [71].

Interestingly, increased nitric oxide negatively correlated with BP changes [71]. It is thus evident aerobic exercise training plays an important role in reducing BP and this benefit is associated with improved endothelium-dependent dilation. However, low-intensity aerobic exercise performed on an upper body ergometer, three times a week for 12 weeks, was shown to reduce BP levels without changes in endothelium-dependent dilation in hypertensive subjects [72]. This same response has been described in other studies after moderate-intensity aerobic training on a treadmill [58] which confirms that multiple factors are involved in reducing BP in individuals with SAH.

Unlike aerobic training, few studies have investigated the effects of resistance training on SBP and DBP with inconsistent results. Bermudes et al. (2004) did not find any differences in SBP and DBP 24 hours after circuit sessions of resistance training compared to the group who did not exercise [67]. Nascimento et al. (2014) evaluated hypertensive elderly women after a resistance training program [73]. The training sessions were held twice a week for 14 weeks and consisted of six types of exercises, three sets of 8-12 repetitions with a rest period of two minutes at moderate intensity based on Borg's rating scale of perceived exertion [6-20 point scale]. The authors found reduced SBP and DBP compared to pre-exercise values, which remained after up to 14 weeks of detraining [73].

To assess whether resistance training can be used for SAH prevention and treatment, a meta-analysis reviewed 29 studies and compared normotensive, pre-hypertensive, and hypertensive patient groups [51]. Overall, the analysis showed that resistance training could lead to a mean reduction of 1.8 mmHg in SBP and 3.2 mmHg in DBP. However, no reduction in BP was found when they analyzed in hypertensive patients [51].

Stensvold et al. (2010) have shown that a three-month program of resistance exercises, three times a week, with three sets of 8-12 repetitions at vigorous intensity (80% of One Repetition Maximum - 1 RM) improved endothelial function in patients with metabolic syndrome [74]. This response was independent of changes in total body weight, fasting glucose, lipid profile and BP levels. Interestingly, this result was similar to those found when the patients exposed to aerobic training or combined aerobic and resistance in the same week [74].

The positive effects of resistance training on BP may also be associated with improved endothelium-dependent vasodilation in healthy subjects [75]. However, the effect of resistance training on endothelial function, as well as its relationship to BP in patients with SAH, still needs further investigation. The European Society of Hypertension and the American College of Sports Medicine guidelines for lifestyle changes recommend regular moderate-intensity dynamic aerobic exercise for a minimum of 30 minutes 5-7 days a week for the treatment of hypertension [30,76]. Strength exercise training is also recommended as part of a weekly program for the prevention and treatment of hypertension. However, since the amount of evidence on this form of training is more scant, [51] aerobic exercise is often a more recommended first choice. There are few reports of the effects of concurrent or combined training that involves a combination of resistance and aerobic exercise in one training session. Keese et al. (2011) investigated the effects of resistance training followed by aerobic training and found a reduction

in SBP that remained for 2 hours after exercise when compared to the control group [77]. A reduction in DBP occurred at 50 minutes post-exercise. Another study assessed the effect of a training program consisting of three concurrent training sessions at different aerobic intensities (50%, 65% and 80% of VO_2 max) [78]. The authors found that post-exercise hypotension was longer after the most intense session. However, after the session at an intensity of 65% VO_2 max, the post-exercise hypotensive effect on SBP lasted for up to 2 hours and on DBP for 40 minutes [78]. Despite its promising findings, a meta-analysis by Cornelissen and Smart did not show any beneficial effects of concurrent training on BP in hypertensive patients [51]. A study by Kawano et al. (2006) reported increased arterial compliance in young healthy men after combined training (resistance training at 80% of maximum load and 30 minutes of aerobic exercise) [79]. In a physical training protocol proposed by Walsh et al. (2003), they noted an increase in endothelium-dependent and endothelium-independent vasodilatation in patients with heart failure after an eight-week circuit-training program [80]. The program consisted of a combination of resistance (55-65% of 1-RM) and aerobic training (70-85% HR peak), lasting 40 minutes per session [80].

Conclusion

This brief review showed that overall exercise training could reduce blood pressure, improve the effectiveness of antihypertensive drugs and decrease cardiovascular risk. Various forms of exercise training at different intensities and durations lead to endothelial vascular modulation in hypertensive individuals. Thus, the review addressed new issues such as the effect of resistance exercise training on endothelium modulators in CVD, especially SAH. In brief, moderate-intensity aerobic exercise (60-75% of heart rate reserve), with an average duration of 40 minutes, seems to be the most suitable for improving endothelium-dependent and hypotensive effects. Resistance training at an average intensity of 60-85% of the maximum repetition test (1-RM) also produces significant improvement in endothelial function, although the hypotensive effect is still controversial. Alternatively, an exercise program consisting of a combination of aerobic (60-75% of heart rate reserve) and resistance (50-80% of 1-RM) exercises in a single session (concurrent or combined training) can improve endothelial function and lower blood pressure.

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