REVIEW ARTICLE

Exercise as a preventive tool in the progression of hypertension to cardiovascular disease

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ABSTRACT

Hypertension (HTN) stands as an adjustable risk trait for cardiovascular disease (CVD), the foremost cause of both mortality and morbidity across the globe. Incorporating physical exercise into medical care is important and may aid in treating hypertension and CVD. The frequency and intensity of exercise, particularly moderate levels of physical activity, are closely linked to a decrease in adverse CVD events associated with high blood pressure, as well as improved health outcomes. After physical training, the drop in blood pressure is much higher in hypertension patients, ranging from 6 to 7 mmHg. Additionally, it may help prevent or delay the age-related increase in arterial stiffness. Engaging in physical activity can improve insulin sensitivity, mitigate plasma dyslipidemia, normalize elevated blood pressure, reduce blood viscosity, stimulate the production of endothelial nitric oxide, and enhance leptin sensitivity.

Keywords: Hypertension; Exercise; CVD, Leptin; Dyslipidemia.

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INTRODUCTION

Physical Exercise, Blood Pressure, and Hypertension

The World Health Organization (WHO) has released its inaugural report, shedding light on the extensive worldwide impact of high blood pressure. According to the published report, hypertension affects 1 in 3 adults worldwide, which contributes significantly to cardiovascular disease (CVD) mortality and morbidity.[1] One person dies every 33 seconds in the United States (US) from cardiovascular disease.[2] About 695,000 people in the US died from heart disease in 2021—that's 1 in every five deaths.[2,3] Hypertension places a significant public health burden on cardiovascular well-being and the healthcare system in Asia, with India experiencing a notable impact.[4] Both rural and urban areas of India face significant challenges with hypertension as a public health issue.[5] As published by the Registrar General of India, hypertension affects 25.0% of the urban population and 10.0% of the rural population in the country.[4] While the global incidence of hypertension among adults is well-documented, uncertainties persist regarding hypertension among children and adolescents due to its historically low occurrence and limited epidemiological research in this age group.[6]

Consistent physical exercise is key in primary prevention efforts against hypertension. [7] Its advantages are not restricted to individuals with high blood pressure but also to those with conditions such as type 2 diabetes,[8] chronic kidney disease,[9] and depression.[10] Consistent exercise, such as walking, yoga, aquatic sports, and football, is are effective health or medical management option in addressing hypertension or cardiovascular disease. [11] The frequency and intensity of physical exercise, especially moderate-intensity physical activities (30 minutes of exercise, 5 times a week), significantly reduce the occurrence of adverse cardiovascular events related to blood pressure.[12] Furthermore, Vigorous-intensity physical activities had a better protective effect on cardiovascular health than moderate-level activity in both genders, while moderate-level physical activities could only affect patients younger than 60 years old.[13] According to a research report, individuals who engaged in high-intensity physical activity for an average of 2.29 MET h/week (30 min/week) had an 18% (95% CI 0.72–0.93) reduced risk of cardiovascular mortality compared with non-participants and no further risk reductions were observed at higher levels.[14]

Regular moderate physical exercise employs various physiological effects on the body's circulatory system, including enhancing vascular endothelial function through improved flow-mediated vasodilatation (FMD), reducing the resting heart rate (RHR) by enhancing parasympathetic tone, stimulating vasculogenesis through endothelial progenitor cells, and enhancing tolerance for ischemia and reperfusion injury. [15]

Hypertension (HTN) has emerged as a substantial health issue, contributing to compensatory pathological hypertrophy and impacting cardiac function. Modifications of lifestyle, including physical exercise, are encouraged for hypertensive

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patients. While some studies imply that exercise training can reverse pathological hypertrophy, studies on hypertensive animal models have shown increased cardiac growth with exercise practice. [16]

In normotensive individuals, chronic physical training typically results in an approximate 3-4 mmHg reduction in resting blood pressure.[17-19] Hypertensive patients experience an even greater reduction in blood pressure, with a decrease of 6-7 mmHg following training.[19] Despite the promotion of hypertrophy, engaging in physical exercise offers protection against cell death. It could potentially enhance cardio-myocyte replication, leading to the progression of a presumed characteristic. One of the hallmark beneficial effects of exercise in hypertension is the enhancement of myocardial β-adrenergic responsiveness.[20]

Pathophysiology of Hypertension

Alteration of vascular structure, endothelial dysfunction, and sympathetic overstimulation are leading contributing factors to the pathophysiology of hypertension (HTN).[21] Physical conditioning has been demonstrated as an effective and essential aspect of non-drug interventions for controlling blood pressure.[22] Various exercise regimen options (including aerobic, resistance, and concurrent training) have shown differential contributions to reducing and controlling blood pressure, sparking scientific debate on the optimal exercise training regimen (including modality, volume, and intensity) for achieving these effects. Exercise training induces a variety of physiological alterations, with vascular and autonomic adaptations playing crucial roles in managing blood pressure.[21]

In the context of standard therapy for hypertension, the benefits of exercise on hypertension and CVD have been well established.[23] Engaging in regular physical exercise is related to decreased blood pressure, thereby lowering the risk of cardiovascular disease and promoting cardiac remodeling.[24] Although both exercise and hypertension may lead to the progression of left ventricular hypertrophy (LVH), the cardiac alteration resulting from HTN is pathological, characterized by an increase in myocyte hypertrophy, fibrosis, and heightened risk of heart failure and mortality. In contrast, LVH observed in athletes is typically non-pathological and devoid of the fibrosis commonly seen in hypertension.[25] Treating hypertension can halt the progression or onset of LVH and diminish cardiovascular risk.[26] In HTN patients, physical activity has been linked to a paradoxical regression or prevention of LVH, indicating a mechanism through which aerobic exercise can benefit hypertensive individuals.

Regular physical activity (PA) is widely considered beneficial for cardiovascular health. Regular exercise is strongly linked with a reduction in cardiovascular mortality and the likelihood of developing cardiovascular disease.[27] Individuals who engage in physical exercise experience lower BP, increased insulin sensitivity, and a more favorable plasma lipoprotein profile. The connection between blood lipids and cardiovascular health is greatly impacted by systemic insulin sensitivity, and resistance to insulin signaling is recognized as a factor in promoting heart disease, partly through alterations in the blood lipid profile.[28] Studies in animal models revealed that PA on a regular basis inhibits the progression of atherosclerosis and enhances the presence of vasodilatory mediators like nitric oxide.[29] Exercise has also been found to have positive impacts on the heart.

During exercise, the elevation in cardiac stroke volume and heart rate raises cardiac output. This, coupled with a temporary rise in systemic vascular resistance, leads to an elevation in mean arterial blood pressure.[30] Changes in vascular function and cardiac exercise have been connected with various alterations in tissue metabolism and signaling pathways. However, our understanding of the underlying mechanisms of these changes remains incomplete. While moderate levels of exercise consistently demonstrate a reduction in cardiovascular disease risk, the earlier finding suggests that maintaining high levels of exercise, such as marathon running, could have unfavorable effects on cardiovascular health.[31] Engaging in physical activity throughout life enhances cardiovascular fitness, leading to improved blood pressure and a decreased prevalence of hypertension and coronary heart disease.[32] It may also delay or prevent age-related increases in arterial stiffness.[33]

Type of Exercise

The effect of specific exercise types (aerobic, resistance, or a combination) on blood pressure and vascular function remains uncertain. Engaging in aerobic exercise, typically involving 30 to 40 minutes of training at 60 to 85% of the predicted maximal heart rate on most days of the week, demonstrates significant improvement in blood pressure and reduction in augmentation index. [33] Resistance training, typically consisting of three to four sets of eight to 12 repetitions at 10 repetitions maximum, performed three days a week, demonstrates significant improvement in blood pressure. Conversely, combination exercise training, involving 15 minutes of aerobic and 15 minutes of resistance exercises, performed five days a week, appears to provide beneficial effects on vascular function, albeit to a lesser extent. Aerobic exercise appears to produce greater benefits for both blood pressure and vascular function.[32]

Exercise offers numerous advantages, such as heightened mitochondrial function, revitalization and enhancement of the vasculature, and the secretion of myokines from skeletal muscle, which helps to maintain or enhance cardiovascular function.[34]

Overwhelming evidence supports the association between lifelong exercise and an extended healthspan, resulting in the delayed onset of 40 chronic conditions or diseases.[35] Regarding molecular mechanisms, the effects of endurance exercise training on cardiovascular fitness and its correlation with enhanced health outcomes, along with the emerging molecular links between endurance training and mental

health, are key considerations in sustaining and enhancing quality of life.[35]

The global prevalence of hypertension (HTN) continues to rise, highlighting the significance of prioritizing primary prevention as a crucial global public health initiative.[36,37] Promoting physical activity is frequently essential for lifestyle adaptation that can help prevent hypertension. Epidemiological findings consistently illustrate a temporal and dose-dependent correlation between physical activity and hypertension development. In recent years, the favorable effects of exercise on lowering BP have been well established, elucidating the relationship between physical activity and hypertension.[38] Although substantial evidence supports the role of physical activity in preventing hypertension, numerous questions remain unanswered. These include inquiries into the protective benefits of physical activity for high-risk individuals, factors that could moderate the relationship between physical activity and hypertension, and determining the optimal prescription for hypertension prevention.[38]

The prevalence and risk predictors associated with cardiovascular disease (CVD) underscore the significance of PA, which is advised to improve leptin sensitivity, reduce blood viscosity, normalize high BP, improve insulin sensitivity, reduce plasma dyslipidemia and elevate endothelial nitric oxide production, all of which thereby safeguard the heart and blood vessels. 39 Furthermore, the protective effects of exercise extend beyond laboratory animal models to clinical studies, as highlighted by WHO recommendations. The American Heart Association advises moderate exercise of 30 minutes, 5 times a week, as a general intensity for preventing CVD in humans. However, standard exercise regimens may not suit everyone, leading to an inevitable trend toward tailored approaches that maximize benefits while minimizing inefficient physical activities.[39]

There is a strong association between hypertension and CVD. Additionally, aerobic exercise training has proven effective in reducing blood pressure both during exercise and ambulation.[40,43] Acute aerobic exercise has been demonstrated to induce relative hypotension during the post-exercise recovery phase.[44] Therefore, the overall decrease in BP resulting from aerobic exercise training helps alleviate the afterload on the heart, forming the theoretical foundation for exercise's potential in mitigating cardiac hypertrophy in hypertension. Chronic hypertension adversely affects myocardial structure and function, leading to pathological concentric hypertrophy. This hypertrophic cardiac response to elevated pressure overload is believed to be an adaptation aimed at normalizing left ventricular wall stress, thereby aiding in maintaining cardiac function despite increased hemodynamic load. This phenomenon is known as compensatory hypertrophy. In hypertension, compensated left ventricular hypertrophy encompasses cardiomyocyte hypertrophy, apoptosis, and proliferation. Exercise impacts each of these pathways, although the precise role of individual signaling pathways remains unclear.

Hypertension and Development of Cardiovascular Diseases

Mechanical loading factors govern the development of compensated hypertrophy alongside the activation of endocrine, paracrine, and autocrine growth factors. These factors stimulate the hypertrophic growth of cardiomyocytes by signaling through specific G-protein coupled ligand receptors. [45,46] These signaling tracts also regulate Ca^{2+} transients, particularly in response to the increased afterload observed in hypertensive hearts. However, persistent activation of these pathways and consequent chronic rises in intracellular Ca^{2+} concentrations prompt cardiomyocyte growth through mechanisms related to Ca^{2+}-calmodulin.[46,47] Specifically, the Ca^{2+}-calmodulin-activated protein phosphatase, calcineurin, plays a pivotal role in mediating hypertension-induced compensatory hypertrophy. Upon activation, calcineurin dephosphorylates members of the nuclear factor of activated T-cells (NFAT) transcription factor family within the cardiomyocyte cytoplasm, facilitating their nuclear translocation and initiating a fetal gene program. [45-50] Overexpression of calcineurin through transgenic means has been demonstrated to significantly augment heart size and trigger heart failure, whereas inhibition of calcineurin prevents these pathological developments. [46,47] While calcineurin inhibition halts cardiac hypertrophy in response to pressure overload, it does not lead to short-term hemodynamic compromise.[48] Various methods of calcineurin inhibition have also been effective in attenuating the development of agonist-induced cardiac hypertrophy induced by phenylephrine and angiotensin II infusions. [49,50]

Beneficial Effects of Exercise in Cardiovascular Disease

Exercise training reduces calcineurin expression, yet in animal studies, exercise induces cardiomyocyte hypertrophy while decreasing apoptosis and fibrosis. However, high volume/intensity exercise in hypertension may pose risks to the heart by increasing apoptosis and cardiac dysfunction. Human studies on exercise training yield mixed morphometric results, with some indicating a decrease in left ventricular mass and others showing no change. Conversely, exercise training in hypertensive animal studies has been demonstrated to mitigate or postpone the onset of hypertension. [51] Research findings indicate that voluntary activity wheel running reduces sympathetic tone, leads to resting bradycardia, and diminishes the tachycardic response during progressive exercise in spontaneously hypertensive rats.[52,53] This effect can be partly attributed to a notable reduction in adrenergic tone that regulates heart rate during exercise.[54] Exercise enhances the overall heart phenotype in humans and animals, a benefit unrelated to hallmark exercise-induced blood pressure reduction. Among the shifts associated with hypertension is the downregulation of the adrenergic receptor (AR) system. Exercise training enhances β-adrenergic receptor (βAR) responsiveness in

the heart, potentially by elevating βAR binding affinity or through downstream effects such as suppressing G Protein-Coupled Receptor Kinase 2 and calcineurin. Regardless of the underlying mechanisms, exercise and physical activity engagement is crucial for prehypertensive and hypertensive patients, preferably at low intensities. Patients should closely cooperate with their medical professionals to tailor an appropriate exercise regimen.

CONCLUSION

Incorporating physical exercise into medical care is important and may aid in the treatment of hypertension and cardiovascular disease (CVD). The frequency and intensity of physical exercise, particularly moderate exercise, are strongly linked to positive health outcomes and a reduction in unfavorable cardiovascular events associated with high blood pressure. Additionally, it may prevent or delay the age-related increase in arterial stiffness. Regular physical exercise can improve leptin sensitivity, reduce blood viscosity, boost endothelial nitric oxide production, enhance insulin sensitivity, lower plasma dyslipidemia, and restore elevated blood pressure to normal levels.

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PEER-REVIEWED CERTIFICATION

During the review of this manuscript, a double-blind peer-review policy has been followed. The author(s) of this manuscript received review comments from a minimum of two peer-reviewers. Author(s) submitted revised manuscript as per the comments of the assigned reviewers. On the basis of revision(s) done by the author(s) and compliance to the Reviewers' comments on the manuscript, Editor(s) has approved the revised manuscript for final publication.