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Brief Review

Hypertension: Protective Effects of Physical Exercise on Cognition Function, Arterial Function and Brain Health

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ABSTRACT

Systemic Arterial Hypertension (SAH) is a chronic condition that requires clinical treatment and is associated with increased risk of cognitive impairment and dementia. Therefore, strategies with fewer side effects and less invasive procedures are required. Evidence supports that Physical Exercise (PE) has antihypertensive effects and has proven to be an efficient and complementary tool for managing hypertension, reducing cardiovascular disease risk factors, and improving cerebral perfusion in the majority of healthy populations. Much of this cardiovascular-protective effect of PE is probably due to pluripotent effects on the vasculature, including regulation of vascular tone, energy metabolism, microvascular recruitment, and endothelial function (reducing oxidative stress and preserving NO availability). These factors are speculated to work synergistically, thereby reducing systolic and diastolic blood pressure and are directly related to improved cerebrovascular function. However, few studies have specifically examined the potential positive effects of PE on the brain in hypertensive individuals. In this brief review, we discuss the potential effect of different PE modalities (aerobic, resistance, and combined) that may act as an effective preventive or therapeutic strategy for reducing blood pressure in hypertensives and, consequently, mitigate the association between hypertension, cognitive impairment and risk of dementia.

1. INTRODUCTION

1.1. Systemic Arterial Hypertension and Cognitive Function

It is estimated that Systemic Arterial Hypertension (SAH) affects more than 40% of adults worldwide [1] and is strongly associated with coronary artery disease, stroke, and heart failure [2]. Blood Pressure (BP) rises with age; High BP (HBP) affects 50% of adults aged ≥60 years, and has a lifetime prevalence of 90% [3]. The World Health Organization estimates that suboptimal BP (>115 mmHg systolic BP) is responsible for 62% of cerebrovascular disease [4]. Numerous studies have demonstrated that SAH increases the risk of cognitive impairment, Alzheimer's Diseases (AD) and vascular dementia [5–16], contributing to the increased burden of the disease worldwide, whose prevalence is achieving alarming figures [17]. Dementia in high-income countries ranks mainly between 3rd and 6th place as a cause of disability adjusted life years over the last 25 years [18].

The Atherosclerosis Risk in Communities Cohort (ARIC) study [19] has followed 13.476 individuals for 20 years, trying to understand the influence that increased BP, registered in mid-life (48–67 years old), might have in the development of cognitive dysfunction in later stages of life. The investigators were able to show that subjects exposed to SAH and pre-hypertension in mid-life had a higher (6.5% and 4.8%, respectively) cognitive function in various domains using a complete neurocognitive assessment (especially executive dysfunction). In fact, the trajectories of cognitive function in individuals with SAH demonstrated faster decline in global cognition and several cognitive domains [20], including worse performance in the executive function and information processing speed [21].

Furthermore, SAH is associated with subtle neurocognitive deficits [22,23] which may be potentiated by one's lifestyle, like obesity

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[24], smoking [25], sedentary behavior [26], stress [27] and may further increase the risk of dementia [28]. Taken together, this background is associated with an increased chance SAH individuals have for developing vascular dementia, especially those who have been exposed to this condition for years [29].

A more comprehensive understanding of modifiable dementia risk factors should be based on interventions that can potentially prevent or delay the onset of the condition, and the possible target periods for intervention would extend from prenatal period to old age [30]. The Lancet Commission on dementia concluded that up to 35% of all cases may be attributable to potentially modifiable risk factors including physical inactivity, SAH, obesity, diabetes, smoking, hearing loss, education, depression and social isolation [31]. As such, there is strong, ongoing demand for evidence-based strategies that prevent, delay, or reverse age-associated increases in BP and cognitive decline [32–38]. Indeed, the need for new approaches is expected to grow as the burden of age- and accelerated aging-associated cardiovascular dysfunction and disease continues to rise [39]. An alternative therapeutic approach to HBP [35–38,40], vascular health [41–45] and cognitive dysfunction [29,46], is physical exercises [39].

Physical Exercises (PEs), in particular, has pluripotent effects on the vasculature, including regulation of the vascular tone [47], Cerebral Blood Flow (CBF) [48], endothelial function [42,49], microvascular recruitment [50], energy metabolism [51], vessel insulin actions [52], and antihypertensive effects [36–38,53], all important factors for brain health. PE might be an effective intervention to mitigate the association between SAH and cognitive impairment. In this brief review, we discuss the potential of PE to act as an effective preventive or therapeutic strategy for preventing or restoring SAH, and link it to cognition function and brain health. The focus will be primarily on studies in humans.

2. PHYSICAL EXERCISE AS A MEDIATOR IN SYSTOLIC ARTERIAL HYPERTENSION

Guidelines [54–56] recommend that SAH individuals perform at least 30 min of moderate intensity Aerobic Exercise (AE) ≥3–5 days a week (but preferably every day), supplemented by dynamic Resistance Training (RT). Cornelissen and Smart [57] showed that AE training [moderate to high intensity, <210 min/week or 40–60% Hear Rate (HR) reserve] contributed to reduce Systolic BP (SBP) and Diastolic BP (DBP) (8.5 and 5.1 mmHg, respectively; $p < 0.001$ for both comparisons) in hypertensive subjects. Wen and Wang [58] have observed decreased SBP (by 7 mmHg) and DBP (by 5 mmHg) in essential hypertensive patients. The study conducted by Moriguchi et al. [59] found that AE training at 50% VO_2max twice a week over a period of 3 months promoted benefits in Flow-Mediated Dilatation (FMD) from 5.2% (pre-training) to 8.7% (post-training; $p < 0.001$) in hypertensive individuals. Also, there was a reduction in SBP (14.5 mmHg) and DBP (9.6 mmHg) in the study. Vigorous AE training intensities may be considered in patients with HBP. Molmen-Hansen et al. [60] observed that AE performed by hypertensive individuals for 12 weeks improved FMD (before: 6.5 ± 3.7 and after: 10.7 ± 5.0%; $p < 0.001$) only in the group that practiced AE in high intensities (alternating between 60–70% and 90–95% of HR reserve). Ashor et al. [61] showed significantly reduced Pulse Wave Velocity (PWV) in hypertension subgroups analyses −0.66 (−1.23 to −0.10 m/s; $p < 0.02$). A significantly higher reduction in PWV after AE intervention in participants with stiffer arteries (PWV > 8 m/s) was also shown.

Cornelissen et al. published a set of meta-analyses on the effects of RT on BP in 2005 [36], 2011 [38], and 2013 [37]. In the 2005 publication, data from nine Randomized Clinical Trials (RCTs) 110 were pooled, and the investigators concluded that RT reduced SBP (by 3.2 mmHg and DBP at 3.5 mmHg). Subsequent meta-analysis (2011) showed that isometric RT (handgrip) may be more effective in reducing BP levels (SBP: 13.5 mmHg and DBP: 6.1 mmHg) than dynamic RT (SBP: 2.8 mmHg and DBP: 2.7 mmHg). In 2013, the meta-analysis confirmed the superiority of isometric RT in reducing SBP (10.9 mmHg) and DBP (6.2 mmHg); however, only four studies for isometric training were analysed [57]. Similar findings for the efficacy of isometric exercise were reported in another meta-analysis [62,63]. A reduction in SBP of 3.0 mmHg and DBP of 3.0 mmHg was observed. MacDonald et al. [63] conducted a meta-analysis with 64 controlled studies (71 interventions) to determine the efficacy of dynamic RT as a stand-alone antihypertensive therapy. Participants (N = 2344) were white (57%), middle-aged (47.2 ± 19.0 years), and overweight (26.8 ± 3.4 kg/m^2) adults with SAH (126.7 ± 10.3/76.8 ± 8.7 mmHg); 15% were on antihypertensive medication. Overall, moderate-intensity dynamic RT [65–70% of One-Repetition Maximum (1RM)] was performed 2.8 ± 0.6 days/week for 14.4 ± 0.9 weeks and elicited small-to-moderate reductions in SBP (3.0 mmHg) and DBP (2.1 mmHg) compared with controls ($p < 0.001$). HBP reductions occurred among samples with higher resting SBP/DBP: ≈6/5 mmHg for hypertension, ≈3/3 mmHg for prehypertension, and ≈0/1 mmHg for normal BP ($p < 0.023$) [63]. On the other hand, study conducted by Moraes et al. [64] show that middle-aged, stage 1 hypertensive patients without antihypertensive medication (reaching 153 ± 6/93 ± 2 mmHg SBP/DBP after a 6-week medication washout period), submitted to a 12-week conventional RT program (3 sets of 12 repetitions at 60% 1 RM, 3 times a week on nonconsecutive days) reduced SBP (16 mmHg; $p < 0.001$), DBP (12 mmHg; $p < 0.01$) and mean BP (13 mmHg; $p < 0.01$) to prehypertensive values. Moreover, the benefits of BP reduction achieved with RE training remained unchanged for up to 4 weeks without exercise. Similarly, in the study Beck et al. [65] observed reduction in SBP (9.6 mmHg) and DBP (8 mmHg), in young unmedicated prehypertensive after 8 weeks dynamic RT protocol (2 sets of 8–12 repetitions at 60% 1 RM, 3 times a week) and improvement in FMD from 6.2% to 8.30%, concomitant with reduction in the Endothelin-1 level (ET-1). Thus suggesting the effectiveness of the RT in improving the endothelial artery function and oxidant/antioxidant balance in young prehypertensive. Both studies demonstrate the potential usefulness of conventional moderate-intensity (60% 1RM,) RT in the treatment of stage 1 hypertensive patients.

The evidence discussed earlier suggests the antihypertensive effects of isolated AE training (5–8 mmHg) and dynamic RT training (≈2–3 mmHg) for the same population [35–38,63]. Thus, it would be logical to think that combined exercises (AE + RT) performed in a single session or within a couple of hours one from another, which is referred to as concurrent [66] exercise or combined aerobic and resistance exercise [67], could enhance the antihypertensive effect. The Combined Training (CT) conferred the antihypertensive benefit to SAH individuals ≈15–9 mmHg [68] compared with prehypertension ≈2–7–4 mmHg [69], older men with SAH (12–24 mmHg) from BP at rest, respectively. Stewart et al. [70] reported average reductions of 5.3 and 3.7 mmHg for SBP

and DBP, respectively, in hypertensive older adults who completed a concurrent training protocol for 6 months. When the training frequency amounted to three weekly sessions, the training intensity ranged from 50–80% of 1RM and 60–90% HRmax and training duration per session averaged 40–90 min. However, the aortic stiffness, indexed by aortofemoral PWV, was unchanged [70]. Son et al. [71] showed that 12 weeks of combined moderate (60–70% HR reserve) aerobic and resistance exercise training is a useful exercise modality for improving brachial-ankle PWV (Δ1.11 ± 0.63 m/s, $p < 0.05$), both SBP (Δ13.5 ± 1.58 mmHg, $p < 0.05$) and DBP (Δ11 ± 1.34 mmHg, $p < 0.05$), and functional capacity (Δ4.4 ± 3.89, $p < 0.05$) in postmenopausal women with stage 1 hypertension.

3. PHYSICAL EXERCISE, COGNITION FUNCTION, ARTERIAL FUNCTION AND BRAIN HEALTH

Lifestyle habits, including PE, associated with 35% reduction in CVD risk factors and mortality [72] are promising approaches for the prevention of neurocognitive decline [33,73], and physically active (PA) individuals are less likely to develop dementia [74,75]. Evidence suggests that AE improves brain structural integrity – brain volume [76], neurocognitive performance [34] associated with increased attention, executive function, and memory [77]. In addition, PE promotes several molecular and structural adaptations in different neurotrophils in the human brain such as Brain Derived Neurotrophic Factor (BDNF) [78,79], which mediates neuronal survival, plasticity, and synapse reinforcement [79]. It has been observed that PE training is associated with higher CBF, higher metabolic activity in the hippocampus, and better memory compared with the control group that did not exercise [80,81]. Also, PE is associated with increased length, complexity, and density of some types of neuron dendrites [82], and greater integrity of the Blood–Brain Barrier (BBB) [83]. Taking together, it is suggested that PE promotes several molecular and structural adaptations that can improve cognitive functioning [84,85].

Additionally, the cause and effect relationship between PE and cerebral perfusion [86] may be attributed to hemodynamics effects, including BP [35–38,63], endothelial function [41,49,50,65,87,88] and arterial remodeling [42,43,61,89–92]. PE provides benefits not only to the vascular beds that are involved during the session, but also to those in non-working sites or limbs [93,94]. This phenomenon could be explained by the increased shear stimuli in non-working limbs during an exercise bout [95]. The proposed mechanisms through which PE may prevent the development and treatment of SAH are presented in Table 1. It is speculated that these factors work synergistically, thereby reducing systolic and diastolic BP and improvement in vascular function. It is plausible that PE training may contribute to improved CBF in hypertensive individuals.

Summary of mechanisms through which PE promotes vascular adaptation, adapted from Green et al. [96] and Diaz et al. [97].

Table 1 | Proposed mechanisms through which PE may treat and prevent the development of hypertension

Reduction	Improvement
Vascular resistance	Endothelial function
Arterial stiffness	Arterial compliance
Intima-media thickness	Arterial lumen diameter
Renin-angiotensin system activity	Angiogenesis and arteriogenesis
Sympathetic activity	Parasympathetic activity
Oxidative stress	Renal function
Inflammation	Sodium handling
Body weight/body mass	Insulin sensitivity/glucose handling
Psychosocial stress	Baroreflex sensitivity
Vascular responsive to adrenergic- and endothelin-receptor stimulation	Nitric oxide (NO)

4. PERSPECTIVES AND CONCLUSION

Therefore, despite the lack of direct evidence showing a relationship between exercise and cognitive function in hypertensive individuals, drawing upon the available literature, there is evidence to support that exercise has antihypertensive effects and benefits on vascular function. In addition, it is plausible to assume that the role of exercise in modifying cardiovascular risk factors may prevent cognitive decline and potentially reduce the risk of dementia in hypertensive individuals.

Although some studies have shown that PE can improve cerebrovascular function and cerebrovascular structure, RCTs focusing on hypertensive individuals are needed. Further research is needed to show how different modalities of physical training (AE, dynamic RT, isometric RT and combined exercises) and their characteristics (frequency, intensity, type and time) act on cerebrovascular structure and function and their implications for cognitive function in this population. Brain function and structure may be assessed by different techniques such as arterial spin marking or Functional Magnetic Resonance Imaging (fMRI), which provides a noninvasive quantitative measure of BF in specific brain regions. fMRI has been used as an approach to examine CBF in regions of interest associated with cognitive dysfunction and dementia. In addition, it may allow a broader understanding of the potential effect of PE training acting as a preventive or therapeutic strategy as well as preventing or restoring impaired brain perfusion and potentially impaired cognitive function with advancing age in hypertensive patients.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

MLP, EB and PGC conceived and performed the systematic review. MLP, EB and PGC provided physical exercise, hypertension and cognitive function. MLP wrote the manuscript with input from all authors.

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ABBREVIATIONS

SAH, systemic arterial hypertension; BP, blood pressure; AD, Alzheimer's diseases; PE, physical exercise; CBF, cerebral blood flow; AE, aerobic exercise; RT, resistance training; SBP, systolic blood pressure; DBP, diastolic blood pressure; VO_2max, maximum volume of oxygen; FMD, flow-mediated dilation; HR, heart rate; PWV, pulse wave velocity; 1RM, one-repetition maximum; CT, combined training; CVD, cardiovascular disease; PA, physically active; BDNF, brain derived neurotrophic factor; BBB, blood-brain barrier; ON, nitric oxide; METs, metabolic equivalent of task; RCTs, randomized clinical trials; ASL, spin marking; fMRI, functional magnetic resonance.

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