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The protective role of regular aerobic exercise on vascular function with aging

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Aging is the primary risk factor for cardiovascular diseases (CVD), the leading cause of death in developed and developing societies. Much of this age-associated increase in CVD risk is due to arterial dysfunction, characterized by stiffening of the large elastic arteries and endothelial dysfunction. Aerobic exercise is an evidence-based healthy lifestyle strategy for improving arterial function with aging, in part, by suppressing oxidative stress and chronic inflammation. Here, we summarize the effects of exercise on arterial function and aging, highlighting recent advancements regarding estrogen-deficient postmenopausal women, cerebrovascular function and healthy lifestyle-inspired interventions that work through similar mechanisms as aerobic exercise.

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Introduction

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in men and women in the United States and other developed societies [1,2]. Advancing age is the strongest risk factor for CVD, with >90% of CVD occurring in adults 50 years of age and older [3]. The number of middle-aged and older adults is rapidly increasing, leading to projections for a significant increase in CVD prevalence [4]. Therefore, effective treatment and prevention strategies are needed to reduce CVD risk in middle-aged and older adults [38,110–112].

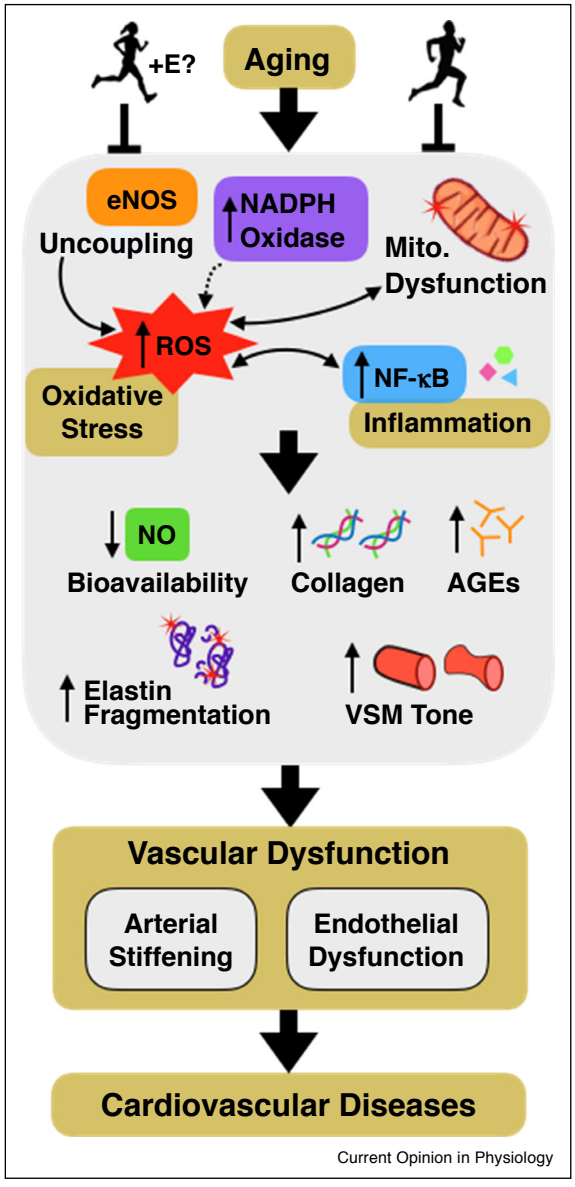
Much of the age-associated increase in CVD risk is mediated by arterial dysfunction, largely characterized by stiffening of the large elastic (aorta and carotid) arteries and vascular endothelial dysfunction [6] (Figure 1). Aerobic exercise is the most well studied and evidence-based healthy lifestyle strategy for preserving and improving arterial function with aging [7]. This review will cover the beneficial effects of regular aerobic exercise on arterial function with aging. Attention will be paid to recent findings regarding the efficacy of aerobic exercise in estrogen-deficient postmenopausal women, exercise and cerebrovascular function, and interventions inspired by exercise and other healthy lifestyle strategies for improving arterial function.

Exercise and arterial stiffness

Aging is associated with stiffening of the large elastic arteries [6]. Increased arterial stiffness is an important risk factor for CVD [1], hypertension [8], cognitive decline/dysfunction [9] and chronic kidney disease [10]. In humans, arterial stiffness is measured with carotid-femoral pulse wave velocity (CFPWV), a measure of aortic stiffness that increases with aging [11,12], and carotid artery compliance, which measures the change in diameter and pressure of the carotid artery through the cardiac cycle and decreases with aging [13]. The age-related increase in arterial stiffness is mediated, in part, by structural changes to the arterial wall including degradation of elastin fibers, compensatory deposition of collagen, and formation of advanced glycation end products (AGEs), which mediate the cross-linking of structural proteins [6] (Figure 1). Functional changes in vascular smooth muscle tone (i.e. increased vascular smooth muscle contraction) also contribute to elevated arterial stiffness. Increased functional stiffness may be linked to abnormal smooth muscle signaling and endothelial dysfunction [6,14,15]. Overall, these structural and functional changes in arteries are likely related to age-related increases in vascular oxidative stress and chronic low-grade inflammation [16,17,108,109].

Regular aerobic exercise counteracts increases in arterial stiffness with aging (Figure 1). Cross sectional studies demonstrate regularly active middle-aged and older adults exhibit lower CFPWV and higher carotid compliance than their sedentary counterparts [13,18–20]. Similarly, moderate intensity aerobic exercise interventions decrease CFPWV in middle-aged and older men and improve carotid artery compliance in middle-aged and older men and women [13,19,21]. Cumulatively, these data suggest that aerobic exercise can be viewed as both a preventive strategy and a therapeutic intervention for arterial stiffening with age. Studies in aging adults suggest aerobic exercise decreases arterial stiffness by reducing oxidative stress [22] (Figure 1), whereas studies in mice suggest reductions in oxidative stress in response to aerobic exercise lower

Figure 1



An overview of the mechanisms mediating age-related arterial dysfunction and how aerobic exercise can improve vascular function by decreasing oxidative stress and inflammation. Estrogen (E), reactive oxygen species (ROS), nuclear factor-κB (NF-κB), advanced glycation end products (AGEs), nicotinamide adenine dinucleotide phosphate (NADPH), nitric oxide (NO), endothelial NO synthase (eNOS), vascular smooth muscle (VSM), mitochondria (Mito).

arterial stiffness by reducing vascular expression of the fibrosis-stimulating cytokine, transforming growth factor β1, which, in turn, reduces collagen content, and also by reducing arterial calcification [23].

Unlike aerobic exercise, resistance exercise does not improve arterial stiffness. In fact, middle-aged and older adults who perform vigorous resistance training alone exhibit similar or lower carotid artery compliance compared to inactive peers [24]. However, training programs that include both aerobic and resistance exercise suppress age-related stiffening of the large elastic arteries [25]. Interestingly, the order one performs resistance and aerobic exercise may be important. It has recently been reported that aerobic exercise is only effective at decreasing arterial stiffness when performed after a bout of resistance exercise, but not before [26•].

Recently, research has focused on understanding how different types or doses of exercise influence arterial stiffness. Several studies suggest middle-aged and older adults need to meet or exceed current aerobic exercise guidelines (≥150 min of moderate intensity aerobic exercise per week) to minimize age-related arterial stiffening [27,28,29•]. Studies on aerobic exercise-based high-intensity interval training (HIIT), that is, repeated bouts of intense exercise interspersed with low-intensity recovery periods, have reported inconsistent results [30•,31,32]. Therefore, the efficacy of HIIT for decreasing arterial stiffness remains to be established. However, the HIIT protocols studied to date have used widely varying interval lengths and intensities. Further investigation may elucidate optimal HIIT protocols for decreasing arterial stiffness with human aging (Figure 2).

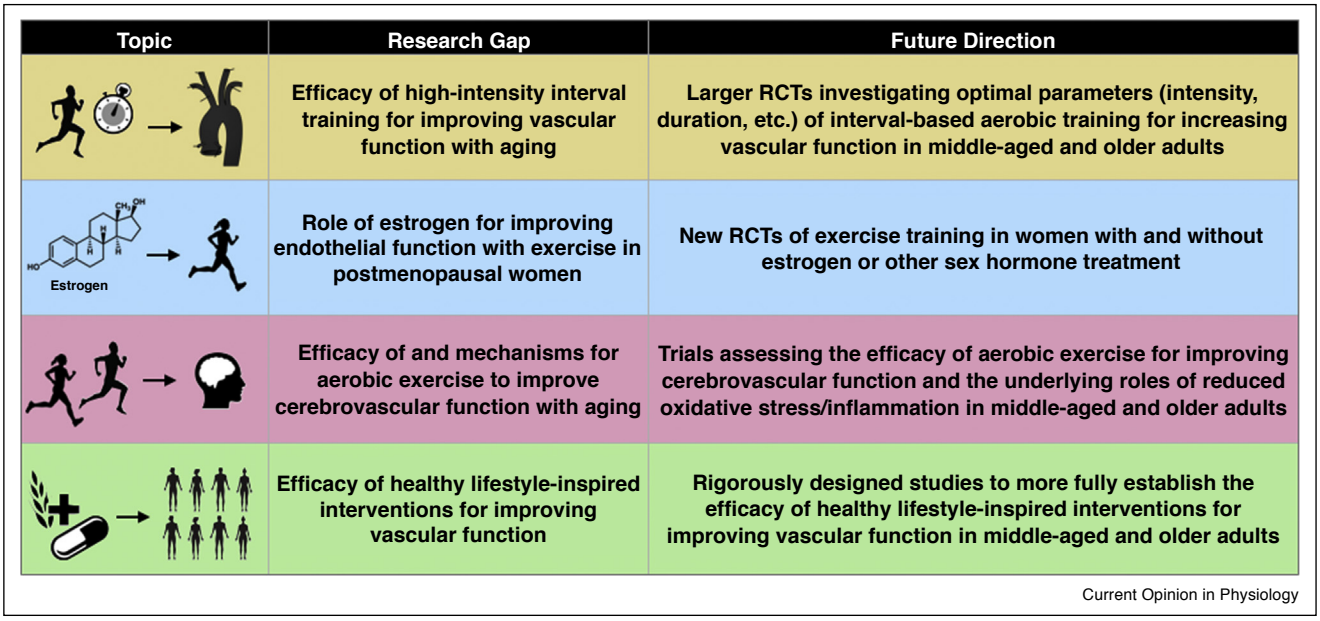
Exercise and endothelial function

The endothelium is a single layer of cells located on the inner lining of blood vessels which synthesizes molecules that influence blood vessel health and function. The most important of the endothelium-derived compounds for vascular health is nitric oxide (NO), which acts as a potent vasodilator and has anti-coagulative, anti-proliferative, and anti-inflammatory effects as well. Endothelial dysfunction occurs with aging due in large part to inadequate NO bioavailability driven by increased oxidative stress and chronic low-grade inflammation [7,34] (Figure 1).

Endothelial function is commonly assessed by the magnitude of endothelium-dependent dilation (EDD), whereby either a chemical (e.g., acetylcholine) or mechanical (i.e. blood flow/shear rate) stimulus evokes NO synthesis/release from the vascular endothelial cells. Evaluating responses in forearm blood flow to increasing concentrations of brachial artery-infused acetylcholine, or cutaneous blood flow responses to thermal stress, can be used to assess endothelial function in the microvasculature of human subjects [34,35]. Macrovascular (conduit artery) endothelial function can be determined by assessing blood flow-mediated dilation (FMD) of the brachial artery (FMD_{BA}) via ultrasound vascular imaging [34].

Older, sedentary, otherwise healthy adults demonstrate impaired endothelial function, assessed with either acetylcholine infusion or FMD_{BA} [36,37]. This age-related decline in EDD is linked to excessive superoxide-

Figure 2



Research gaps and future directions for investigating age-related arterial dysfunction and potential healthy lifestyle interventions. Randomized controlled trial (RCT).

induced oxidative stress mediated by some combination of increased expression and activity of the oxidant enzyme nicotinamide dinucleotide phosphate (NADPH) oxidase, uncoupling of the NO-producing enzyme endothelial NO synthase (eNOS) and increased mitochondrial superoxide synthesis and release (Figure 1). In the face of unchanged or even reduced antioxidant defenses, suggesting a lack of appropriate compensatory responses [34,38,39]. The prevalence of pro-inflammatory proteins also increases in the arteries of animals and endothelial cells of humans with aging, suggesting a role for increased inflammation in mediating age-related endothelial dysfunction as well [7,114,115].

Aerobic exercise protects against the age-related decrease in endothelial function. EDD in regularly exercising middle-aged and older men and male master's endurance athletes generally does not differ significantly from healthy young adults, likely because aerobic exercise maintains endothelial function by decreasing oxidative stress and inflammation [36,37,40,41]. Specifically, aerobic exercise decreases oxidative stress by reducing expression and activity of, and superoxide production from NADPH oxidase [37,42]. Aerobic exercise also reduces whole artery mitochondrial superoxide production [39,42], improving antioxidant defenses by increasing superoxide dismutase expression [37,42], upregulating eNOS expression [42] and improving eNOS coupling [43] (Figure 1). Exercise also inhibits inflammation, in part by decreasing activation of the major proinflammatory transcription factor, nuclear factor-κB (NF-κB) [44,113].

Age-related impairments in endothelial function occur in both men and women [36,34,45–47]. However, unlike middle-aged and older men, aerobic exercise does not consistently improve endothelial function in postmenopausal women [7,48,50]. Specifically, in several cross-sectional and intervention studies, estrogen-deficient postmenopausal women have not demonstrated enhanced vascular endothelial function in response to aerobic exercise [49–51]. Indeed, FMD_{BA} is reported to decline across the menopausal transition even in highly fit women [52]. Taken together, these findings suggest that aerobic exercise may not consistently slow or prevent declines in endothelial function during menopause in women who are estrogen deficient. Consistent with these observations, unlike results in regularly exercising middle-aged and older men [40,41], oxidative stress-related suppression of EDD is observed in *both* sedentary and endurance exercise-trained estrogen-deficient postmenopausal women [53], although systemic markers of oxidative stress and inflammation may be lower in some postmenopausal estrogen-deficient women who regularly exercise [54••].

In contrast to the results of the studies described above, improvements in vascular endothelial function in estrogen-deficient postmenopausal women following aerobic exercise training also have been reported [55,56•,57,58]. The disparate results regarding aerobic exercise-

mediated improvements in endothelial function in postmenopausal women may be due to a number of factors differing among studies, including, but not limited to, exercise intensity, specific vascular beds studied, and number of years postmenopausal [48,59]. Another possibility is differences in circulating estrogen status of the postmenopausal women who served as subjects. This factor was interrogated with a double-blind, randomized, exercise intervention study in which healthy, sedentary, estrogen-deficient postmenopausal women underwent a 12-week aerobic exercise intervention while receiving estrogen supplementation or placebo. At the end of the exercise intervention, endothelial function (FMD_{BA}) was improved in the estrogen-replaced, but not in the placebo-treated group, suggesting sufficient circulating estrogen may be requisite for improvements in vascular endothelial function in postmenopausal women [53]. However, more research is needed on postmenopausal women and the role of estrogen in facilitating exercise-induced improvements in endothelial function (Figure 2) [48].

Exercise and cerebrovascular function

Advancing age is associated with cognitive decline and an increased risk of dementia [60]. Cerebrovascular dysfunction, characterized by elevated cerebrovascular pulsatility, decreased total cerebral blood flow and lower cerebrovascular reactivity (CVR), is also closely linked to cognitive decline and may be a mediator of age-related cognitive dysfunction [61–65]. Aerobic exercise may be one way to slow or delay cognitive decline, as both high cardiorespiratory fitness and high levels of physical activity are associated with better performance on measurements of cognitive function in older adults [60,66,67].

Overall cerebral blood flow decreases [68•] with aging. CVR (i.e. the change in cerebral blood flow in response to a stimulus such as exercise or hypercapnia), in turn, either decreases [69] or remains unchanged while becoming more dependent on an augmented blood pressure response and increased pulsatile blood flow [70] with aging, indicative of cerebrovascular dysfunction. Importantly, pulsatile blood flow in the cerebrovasculature is believed to damage the brain [71].

The mechanisms contributing to age-related cerebrovascular dysfunction are thought to be the same as those contributing to systemic vascular dysfunction, namely increased inflammation and oxidative stress [72–74], though mechanistic studies linking these processes to cerebrovascular function are currently lacking. Systemic inflammation is clearly related to cognitive function [75•,76••]; however, the relation between inflammation and cerebrovascular function has not been fully investigated. Similarly, markers of oxidative stress are associated with cognitive decline in humans [77], and results from studies using animal models suggest a relation between oxidative stress and cerebrovascular dysfunction [78], though more preclinical and clinical research is needed (Figure 2).

Regular aerobic exercise may be beneficial for cerebrovascular health, as higher cardiorespiratory fitness has been associated with better measures of cerebrovascular function in some studies [79–82]. Similarly, some exercise intervention studies in older adults and patients with heart disease have shown improvements in cerebrovascular function [83–86]. Although the findings of these studies support aerobic exercise as a promising intervention for improving cerebrovascular function, there is a need for larger trials with established measures of cerebrovascular function to determine the efficacy of exercise for cerebrovascular benefits and the associated mechanisms of action (Figure 2).

Emerging 'Healthy Lifestyle-Inspired' strategies for vascular aging

Despite clear evidence for vascular and other health benefits, adherence to aerobic exercise guidelines remains low (<40%) in middle-aged and older adults [87]. Therefore, investigating alternative lifestyle or pharmacological therapies that activate some of the same pathways and provide similar benefits to aerobic exercise, but promote better adherence, is warranted (Figure 2).

Passive heat therapy

Recent evidence suggests regular elevations in body core temperature are associated with improved vascular function and decreased CVD risk. A large study in Finland found higher frequency and duration of sauna bathing has a strong inverse association with CVD risk in middle-aged and older adults [88••]. Similarly, regular hot water immersion increases endothelial function and arterial compliance, decreases blood pressure and protects against ischemia-reperfusion injury in healthy young adults [89]. The latter improvements were similar in magnitude to aerobic exercise training [89]. The mechanisms mediating the beneficial effects of passive heat therapy likely involve upregulated expression of heat shock proteins and decreased oxidative and inflammatory stress [90]. These findings suggest heat therapy may be effective at improving arterial function with aging; a clinical trial to address this (NCT03264508) is underway.

Mitochondrial antioxidant therapy

Vascular mitochondrial function declines with age, resulting in increased mitochondrial-derived superoxide production and oxidative stress (mtROS). In old mice, voluntary wheel running exercise improves artery resistance to mtROS-associated stress [39]. Similarly, chronic treatment with MitoQ, a mitochondrial-targeted antioxidant, reduces aortic mtROS production and improves vascular endothelial function and large artery stiffness in both old mice [91,92] and middle-aged and older adults [93••].

Rapamycin

Inhibition of the mammalian target of rapamycin (mTOR) enzyme results in multiple health benefits in model organisms [94]. Rapamycin inhibits mTOR, and rapamycin supplementation has been shown to reverse age-related vascular dysfunction, decrease oxidative stress, and ameliorate markers of arterial senescence (the process by which cells stop dividing) in old mice [95]. These results make rapamycin an intriguing potential therapy for improving vascular function with aging.

Sirtuin activators

Sirtuins are a class of enzymes that help regulate cellular energy homeostasis by stimulating lipid oxidation and other metabolic functions for producing energy (ATP) during low energy states [96]. As a result, sirtuin activation evokes complementary changes in signaling pathways that ensure coordinated increases in dilation and blood flow to provide nutrient support for increases in cellular energy production. Nicotinamide adenine dinucleotide (NAD^+) is an essential substrate for sirtuins and increasing NAD^+ bioavailability can increase sirtuin activity [97]. Nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) are NAD^+ precursors that increase NAD^+ bioavailability. In old mice, supplementation with NMN decreases arterial stiffness and improves vascular endothelial function [98]. In an initial pilot study in middle-aged and older adults, six-weeks of supplementation with NR decreased arterial stiffness and systolic blood pressure compared to placebo [99]. A larger clinical trial is being initiated to follow-up on the results of this pilot study (NCT03821623).

Curcumin

Curcumin is a naturally occurring phenol found in the curry spice turmeric. In mice, supplementation with curcumin decreases arterial stiffness and improves endothelial function [100]. These vascular benefits are linked to decreased oxidative stress and reduced arterial collagen and AGEs [100]. Similarly, in humans, dietary supplementation with curcumin improves endothelial function in middle-aged and older adults by increasing NO bioavailability and decreasing oxidative stress [101].

Nitrate/Nitrite supplementation

Nitrate and nitrite represent sources of NO that can be produced independent of eNOS via reduction of nitrate to nitrite and then to NO [102]. In old mice, sodium nitrite supplementation in the drinking water reverses vascular endothelial dysfunction and large elastic artery stiffness [103]. These effects are likely mediated by reductions in oxidative stress, inflammation, and AGEs [104]. In middle-aged and older adults, oral supplementation with sodium nitrite improves vascular endothelial function by 45–60% and increases carotid artery compliance [105]. Nitrate supplementation also improves endothelial function and arterial stiffness in aged mice [106,107]. However, the efficacy of nitrate supplementation, including dietary nitrate-boosting using foods high in nitrate such as beetroot juice, for improving vascular function in middle-aged and older adults remains to be established.

Conclusion

Age-related arterial dysfunction, including stiffening of the large elastic arteries and impaired vascular endothelial function, is a major risk factor for CVD. Regular aerobic exercise remains the most evidence-based healthy lifestyle strategy for maintaining/improving vascular function with aging. Aerobic exercise can decrease large elastic artery stiffness in middle-aged and older men and women and improve vascular endothelial function in aging men. However, aerobic exercise may not consistently improve endothelial function in estrogen-deficient postmenopausal women, though benefits are likely dependent on a combination of exercise history and use (or disuse) of hormone replacement therapy. Exercise may also improve cerebrovascular function and, if so, this may represent a key mechanism by which regular exercise slows/minimizes age-related cognitive decline. Recent efforts have been made to establish healthy lifestyle-inspired strategies that work through some of the same pathways and promote similar benefits as aerobic exercise; the efficacy of many of these interventions for improving arterial function is yet to be determined, though early results are promising. Given the public health importance of preventing CVD, additional research on the beneficial effects of exercise and healthy lifestyle-inspired strategies on arterial function in both men and women is needed.

Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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