Arterial stiffness and lifestyle modification

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Abstract

Previous research has established that both aging and obesity trigger elevation of arterial stiffness and that such elevation is an independent risk factor for cardiovascular morbidity and mortality. Changes in arterial stiffness are known to be caused by alterations in the balance of hormones, inflammatory, nervous system-related, and endothelium-derived vasoactive factors, and levels of oxidative stress—all of which are known to strongly affect vasoconstriction and vasodilation. Lifestyle modifications that promote the restriction of energy intake, maintenance of nutrient balance, and performance of regular aerobic exercise, can decrease arterial stiffness in elderly and obese individuals. In this review, we discuss the lifestyle strategies found effective in decreasing arterial stiffness in elderly and obese individuals via improvement of vasoactive functional factors.

Keywords: aging, arterial stiffness, diet, exercise, obesity

Introduction

Increased arterial stiffness is known to be an independent risk factor for cardiovascular morbidity and mortality¹. Many previous studies have found that dietary modification and regular exercise can decrease arterial stiffness in elderly and obese individuals, in whom arterial stiffness tends to be higher compared to young and non-obese individuals²-⁷. Here we discuss the findings regarding the mechanisms underlying arterial stiffness, and propose the implementation of several lifestyle modifications that have been found to decrease arterial stiffness in elderly and obese individuals.

Regulators of arterial stiffness

The arterial vascular wall is composed of the intima, media, and adventitia layers. The majority of the intima layer is composed of endothelial cells, which produce several types of vasoactivators affecting arterial stiffness. The intima layer is composed of endothelial cells that produce endothelin-1 (ET-1), a vasoconstrictor substance, and nitric oxide (NO), a vasodilator substance, both of which modulate arterial stiffness by altering smooth muscle tone⁴-⁶. It has been reported that increases in levels of circulating angiotensin II (AT-II), another potent vasoconstrictive hormone produced from angiotensin I with an angiotensin-converting enzyme (ACE), increase arterial stiffness⁸.

Endothelial-cell dysfunction is caused by the production of pro-inflammatory cytokines and oxidative low-density lipoproteins (oLDL)⁹. It has been demonstrated that arterial stiffness is positively correlated with the production of pro-inflammatory cytokines and oxidative stress markers, including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), and oLDL⁹, but negatively correlated with production of pentraxin 3 (PTX3), an anti-inflammatory factor mainly produced in arterial wall components (i.e., endothelial and smooth muscle cells and macrophages)⁹. The extent of arterial wall stiffness is determined by the ratio of collagen to elastin, both of which are components of the vascular wall¹⁰. Synthesis and degradation of these fibers is regulated by the level of advanced glycation end products (AGEs), which are irreversible cross-linkers between collagen and matrix metalloproteinase 9 (MMP-9). As MMP-9 promotes degradation of mature elastin fibers, depending on the functional factors present¹¹, increased levels of AGEs and MMP-9 result in increased arterial wall stiffness. Thus, levels of both AGEs and MMP-9 are significantly positively correlated with the extent of arterial stiffness¹². Compared to functional changes that occur within vessels, the organic change resulting in the production and degradation of the molecular contents of the vasculature is of long duration, but, nevertheless, greatly affects arterial stiffness. Together, these findings indicate that increased arterial stiffness is induced by acute endothelial dysfunction resulting from increases in levels of inflammatory and oxidative substances and the maintenance of such adverse vascular functioning in a manner that may alter structures abnormally (Fig. 1).

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Aging, obesity, and arterial stiffness

Aging and obesity are known to cause disturbances in endothelial functioning and to increase the level of systemic pro-inflammatory and oxidative stress factors. Exposure to these factors may lead to elevated arterial stiffness in elderly or obese individuals. In elderly and obese women, dramatic decreases in estrogen with menopause or obesity-induced menstrual disorder may decrease NO bioavailability and activate AT-II production, leading to significant increases in arterial stiffness with the onset of menopause or menstrual disorder. Thus, multiple factors may be related to increases in arterial stiffness in elderly and obese individuals.

Regular exercise and arterial stiffness

Aerobic exercise training at any intensity can decrease arterial stiffness. On the other hand, and in spite of its utility in preventing the development of lifestyle diseases (i.e., diabetes mellitus and sarcopenia), high-intensity resistance exercise may elevate arterial stiffness. These different types of exercise likely induce such contradictory affects on arterial stiffness by altering functional and/or vasculature components in vasculature tissue in a differential manner.

Aerobic exercise training and arterial stiffness

Previous research has established that arterial stiffness decreases within 2 to 4 weeks of beginning a program of regular aerobic exercise training but that this positive effect disappears soon after cessation of the program. Such a decrease in arterial stiffness with regular aerobic exercise is likely induced by the activity of several vaso-activators. It has been demonstrated that regular aerobic exercise increases NO activity and decreases ET-1 activity, both of which decrease arterial stiffness. In previous studies, we demonstrated that levels of plasma ET-1 decrease while levels of plasma nitrite/nitrate (NOx), the stable end product of NO, increase after aerobic exercise training in elderly and obese individuals. Furthermore, using a pharmacological approach, we found that endogenous ET-1 plays a role in the mechanism underlying the decrease in arterial stiffness induced by aerobic exercise training. Together, our findings indicate that ET-1 and NO may strongly affect the extent of arterial stiffness.

The production of pro-inflammatory factors is known to increase with aging and/or fat accumulation. Several researchers have found that their production can be decreased with physical activity. Kondo et al., demonstrated that circulating levels of CRP and IL-6 decreased in obese individuals after initiation of a program of regular aerobic exercise. However, other researchers found no evidence of such a decrease, including van Guilder et al., who observed that circulating levels of CRP and IL-6 did not change after initiation of a program of regular aerobic exercise. The mixed nature of these results may have been due to differences in the lengths of the interventions; More specifically, the obese subjects in Kondo et al.’s study participated in a 7-month intervention, whereas the obese subjects in van Guilder et al.’s study participated in a 3-month intervention. Similarly, discrepant results have been observed in studies of oxLDL levels.

On the other hand, levels of PTX3, an anti-inflammatory factor, can be altered after participation in even a short-term course of aerobic exercise training. In a previous study, we found that plasma PTX3 levels in healthy postmenopausal women increased after participation in an 8-week course of moderate aerobic exercise training. However, Fukuda et al. found that PTX3 levels in individuals with chronic heart failure decreased after participation in a 3-month course of mild aerobic exercise. Such mixed findings indicate that further study is necessary to uncover and clarify the mechanism underlying PTX3 alteration by exercise training.

It has been observed that participation in 10 to 16 weeks of regular aerobic exercise decreases production of collagen fibers and increases production of elastin fibers in the central arteries of animals, which may lead to a decrease in arterial stiffness. Improvement in endothelial functioning caused by participation in a program of regular aerobic exercise may partly stimulate the alteration of arterial wall components, which decreases arterial stiffness. It was also reported that dosing the inhibitor of AGEs, an irreversible cross-linker between collagens, increased peak oxygen uptake and improved cardiac function in heart failure patients. Taken together, these findings indicate that participation in a program of regular aerobic exercise decreases arterial stiffness by improving arterial function and then modifying arterial function in a manner that leads to the development of a well-balanced arterial wall structure (Fig. 2).
In healthy middle-aged and elderly individuals after participation in a 10- to 12-week course of mild or moderate resistance exercise\(^{48,49}\). In obese individuals, participation in a 12-week course of moderate strength training resulted in a decrease in levels of systemic inflammatory cytokines\(^{50}\). Together, these findings indicate that participation in moderate resistance exercise training may be an effective lifestyle modification for elderly and obese people.

Okamoto et al., devised a means for combining resistance exercise with aerobic exercise in a manner that cancels the adverse effects of resistance exercise on artery, and have suggested that aerobic exercise should be done in combination\(^{51}\). We recently found that participation in whole body vibration (WBV), a novel form of resistance training, can be an effective means of decreasing fat-free mass without increasing arterial stiffness in overweight and obese women\(^{52}\). We must continue to gain greater understanding of the forms of resistance training that improve the health and fitness of elderly and obese individuals.

**Dietary modification and arterial stiffness**

To lose weight, obese individuals must ensure that their energy consumption exceeds their caloric intake. Previously, we demonstrated that arterial stiffness in middle-aged obese men decreased after participation in a 12-week course of dietary modification\(^{53}\). Specifically, it was observed that plasma ET-1 levels decreased and plasma NOx levels increased after dietary modification. Another study found that participation in a 20-week course of dietary modification decreased circulating oxLDL levels in obese postmenopausal women\(^{54}\). Bosutti et al. reported that maintenance of an equal energy balance increased levels of pro-inflammatory factors (i.e., CRP and IL6) while maintenance of a negative energy balance increased levels of anti-inflammatory substances (i.e., PTX3 and IL-10) in healthy young men\(^{55}\). Taken together, these results indicate that maintenance of a positive energy balance increases levels of pro-inflammatory factors, oxidative stress, and endothelial vasoactive substances, which may elevate the risk of arterial stiffening.

**Nutrition and arterial stiffness**

The consumption of well-balanced meals is an important factor in arterial stiffness, as it affects endothelial function and vascular structure\(^{56}\). Several studies that investigated the effect of consumption of specific nutrients on arterial stiffness found that consumption of high-fat, high-sucrose, and high-salt foods increases arterial stiffness while consumption of fish oil and wine decreases stiffness\(^{56-58}\). It has been demonstrated that consumption of high-fat foods increases levels of pro-inflammatory factors and vasoconstrictors while decreasing the expres-
sion level of the NO synthesis enzyme, NO bioavailability, and anti-oxidant capacity\textsuperscript{50}. Mercier et al. has shown that consumption of a 7% NaCl diet decreases longevity in spontaneously hypertensive animals by promoting elevation in arterial stiffness, but that such a lethal elevation can be reduced by blocking production of AT-II\textsuperscript{57}.

Ingestion of polyphenols, substances known to have anti-inflammatory and anti-oxidative effects\textsuperscript{60}, via wine consumption for 4 weeks, is known to decrease circulating TNF-α and isoprostane levels. Several studies have revealed that eicosapentaenoic acid (EPA), a type of fish oil, is an all-round healthy substance because of its multiple functions, including anti-inflammatory and anti-oxidant effects and improvement of endothelial function\textsuperscript{59,61}. These findings have led to the development of several of these nutrients as supplements for health enhancement. It has been observed that supplementation with vitamins C and E decreases arterial stiffness via the anti-oxidant effects of these substances\textsuperscript{62,63}. In a previous study, we demonstrated that 8 weeks of supplementation with lactotripeptide (LTP), a substance found in dairy products, decreases arterial stiffness in postmenopausal women\textsuperscript{64}. It is known that LTP inhibits ACE activity, which decreases AT-II levels. As these studies indicate, many nutritional factors can decrease arterial stiffness by improving endothelial function, hormonal levels, and inflammatory and oxidative conditions.

Conclusion

Aging and obesity clearly increase arterial stiffness. In this review, it was explained how lifestyle modifications, particularly changes in diet and participation in habitual aerobic exercise, can decrease arterial stiffness by improving endothelial function and vascular wall composition, and reducing levels of inflammatory and oxidative stress factors. We recommend lifestyle modification as the best strategy for reducing arterial stiffness and cardiovascular risk factors in elderly and obese individuals.

References


