Influence of Lifestyle Modification on Arterial Stiffness and Wave Reflections

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Arterial stiffness and wave reflections exert a number of adverse effects on cardiovascular function and disease risk and are associated with a greater rate of mortality in patients with end-stage renal failure and essential hypertension. Accordingly, the prevention and treatment of arterial stiffness are of paramount importance. Because arterial stiffening is being recognized as a critical precursor of cardiovascular disease (CVD), it is essential to understand the role of lifestyle modifications on preventing and reversing arterial stiffening. Available evidence indicates that lifestyle modifications, in particular aerobic exercise and sodium restriction, appear to be clinically efficacious therapeutic interventions for preventing and treating arterial stiffening. Thus, sufficient evidence is available to recommend lifestyle modifications as part of a first-line therapeutic approach for arterial stiffening. However, more information is needed for a full understanding and optimal use of lifestyle modifications in the management of arterial stiffening. Am J Hypertens 2005;18:137–144 © 2005 American Journal of Hypertension, Ltd.

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Large elastic arteries expand and recoil with cardiac pulsation and relaxation. During systole, a significant portion of the ejected stroke volume is stored by arterial distention, which acts to buffer the rise in systolic pressure and to convert pulsatile cardiac ejection into continuous blood flow in capillary beds. Reductions in arterial compliance and increases in arterial stiffness are believed to contribute to the pathophysiology of cardiovascular disease (CVD) and have recently been identified as powerful and independent risk factors for CVD.1,2 Increased arterial stiffness can contribute to the development and progression of hypertension, left ventricular hypertrophy, myocardial infarction, and congestive heart failure.1

For most risk factors for CVD, the first-line approach for prevention and treatment for development of CVD is lifestyle modification (Fig. 1). Given the role of arterial stiffness as a critical precursor of CVD,2 it is important to recognize the effects of lifestyle modifications for the prevention and treatment of arterial stiffening. An emerging body of evidence supports the concept that lifestyle modifications can prevent and reverse arterial stiffening. This article reviews the evidence regarding the influence of lifestyle modifications on arterial stiffening and wave reflections. The focus will be placed on increased physical activity, weight loss, a reduced salt intake, other dietary modifications, and smoking cessation. Much of the confusion in the field of arterial stiffness arises from the different terminologies and methodologies used to express the elastic properties of an artery.3 In this review, we specified the methodology used in each study so that readers can assess each study with their own judgments. Interested readers may refer to a recent consensus report that reviewed various methodologies to assess arterial stiffness.3

Regular Exercise

Aerobic (Endurance) Exercise

A cross-sectional study from the Baltimore Longitudinal Study of Aging found that older men who performed endurance exercise on a regular basis demonstrated lower levels of aortic pulse wave velocity (PWV) and carotid augmentation index (AI; an indicator of the magnitude of arterial wave reflection and arterial stiffness) than did their sedentary peers.4 We also reported that significant age-related increases in central arterial stiffness (aortic PWV and carotid augmentation index) were absent in physically active postmenopausal women and that aerobic fitness was strongly associated with arterial stiffness.5 Physically active individuals often demonstrate resting bradycardia, which could act on wave reflections and pulse pressure.


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amplifications. However, there are no consistent associations between resting heart rate and arterial stiffness in these studies involving endurance-trained adults. In contrast to the effects on central elastic artery, peripheral arterial stiffness (leg PWV and arm PWV) was not different between sedentary and physically active adults. These cross-sectional findings provide support for the role of regular aerobic exercise in the primary prevention of central arterial stiffening and wave reflections. However, athletic and sedentary adults may differ in terms of many constitutional factors. To demonstrate the direct effect of regular exercise on arterial stiffness, interventional studies are required.

Unknown to most, the first intervention study to determine the influence of exercise training on arterial stiffness was conducted in Japan. After 9 months of physical training incorporating a variety of exercises including jogging, soccer, handball, and judo, Ikegami et al found a small but significant reduction in aortic PWV in 80 healthy young Japanese men. We recently completed an exercise intervention study involving previously sedentary but healthy middle-aged and older men, and reported that a relatively brief period (3 months) of aerobic exercise can increase carotid arterial compliance as measured with a simultaneous application of high-resolution ultrasound and applanation tonometry (Fig. 2). This improvement was not associated with changes in body weight, adiposity, blood pressure (BP), plasma cholesterol, or resting heart rate, indicating a direct effect of exercise on arterial compliance. Importantly, this was accomplished with an intensity (moderate) and type (walking) of physical activity that can be performed by most, if not all, healthy older adults. In contrast to central elastic arteries, the compliance of the peripheral muscular artery did not change with exercise training, indicating that the effect of resistance training involves only central elastic arteries, which have a cushioning function that dampens fluctuations in pressure and flow. Because the effects of exercise training were observed only on the central elastic artery (carotid artery) but not on the peripheral muscular artery (ie, femoral artery), it is possible to hypothesize that some mechanical/physical (local) factors may have interacted with structural or functional mechanisms to improve arterial compliance. We recently prescribed an identical aerobic exercise program...
to middle-aged and older women and found that women appear to benefit from regular aerobic exercise to a greater extent than do men (40% v 25%).7 Taken together, these results suggest that habitual aerobic exercise may be an effective lifestyle intervention for augmenting central arterial compliance in healthy adults.

Available evidence indicates that short-term aerobic exercise intervention may not be as effective in reducing arterial stiffness in a patient population as in healthy adults. For example, we recently reported that 3 months of exercise intervention produced only small reductions in aortic PWV and augmentation index in postmenopausal women with elevated systolic BP.10 In another study, short-term aerobic exercise training was unable to increase systemic arterial compliance in patients with isolated systolic hypertension.11 It is possible that the plasticity of the arterial function to adapt to exercise training may diminish as arteries are exposed to chronically elevated BP. Because hypertensive patients are arguably the greatest beneficiaries of destiffening therapy, larger scale studies are warranted to investigate the potential efficacy of long-term aerobic exercise intervention on arterial stiffness in this population.

**Resistance (Weight) Training**

In recent years, statements on physical activity by various health organizations have recommended weight training as part of a preventive and rehabilitative program of physical activity.12 These recommendations are based primarily on the documented impact of weight training on the attenuation of osteoporosis and sarcopenia as well as on the emerging beneficial effects on metabolic risk factors. Given this, it is reasonable to hypothesize that weight training would be associated with reduced arterial stiffness. However, the currently available evidence does not support this.13,14 In our recent study,13 sedentary and resistance-trained men were carefully matched for age, height, BP, heart rate, and metabolic risk factors to isolate the influence of resistance training as much as possible. Additionally, in an attempt to isolate the effect of long-term resistance training per se, we excluded those who had been concurrently performing endurance training and those taking anabolic steroids or other performance enhancing drugs. However, middle-aged men who performed resistance training on a regular basis demonstrated greater levels of arterial stiffness compared with their sedentary peers.15 It is possible that the marked elevations in arterial BP, as high as 320/250 mm Hg,15 during weight lifting, may result in long-term increases in the smooth muscle content of the arterial wall and the load-bearing properties of collagen and elastin, thereby increasing arterial stiffness. Indeed, carotid arterial compliance was modestly but significantly associated with carotid wall thickness. Given the well known limitation of cross-sectional study design and the conflicting results between aerobic and strength training, these cross-sectional study findings should be confirmed prospectively with the interventional approach.

**Weight Reduction**

Obesity is a major public health problem with markedly increased morbidity and mortality risks from nearly all of the common CVD. In particular, obesity is closely linked with the development of hypertension.16 Several studies have investigated the relation between obesity and large arterial functions with contradictory results. In some studies, obese subjects have been found to have higher degrees of arterial stiffness,17,18 and in other studies lower degrees.19,20 These discordant results may be due to the method used to describe mechanical wall properties of arteries. For example, obese subjects are expected to have larger stroke volume and cardiac output simply because of the larger body size, and this could influence some measures of arterial distensibility (such as systemic arterial compliance and stroke volume/pulse pressure ratio) that rely on stroke volume. These methodologic artifacts could explain, at least in part, the paradoxically smaller degree of arterial stiffness reported in obese subjects. Similarly, the estimation of arterial length required for the PWV measurements may not be accurate in obese individuals. Moreover, arterial compliance measurements using ultrasound may be limited by decreased acoustic penetration and its dependence on lumen diameter, which tends to be greater in obese individuals. Studies using the measures of arterial stiffness that are relatively free of these methodologic issues (eg, MRI) have consistently demonstrated that obese as well as overweight individuals have increased levels of arterial stiffness17,21 and that measures of adiposity are closely and positively associated with arterial stiffness.18,21 Interestingly, a recent study reported that brachial artery distensibility was associated with fasting serum leptin concentration.22 Because obesity is closely associated with the development of insulin resistance and the metabolic syndrome, it is not surprising that arterial stiffness is found to be increased in these disease states.23

Few interventional studies have investigated the effects of weight loss on arterial stiffness, and most of them are short-term studies lasting between 4 and 16 weeks.21,24,25 In one of the first studies to address this, a group of investigators from Paris reported that 4 weeks of caloric restriction, which aimed to achieve a 10% to 15% reduction in body weight, induced significant reductions in BP and aortic PWV in nine obese hypertensive subjects.21 Moreover, in normotensive obese men, 3 months on an energy-restricted diet induced a significant reduction in body weight, which was associated with reductions in large artery stiffness.25 The improvement in the elastic properties of arteries observed in this study, however, appears to be dependent on the accompanied reductions in arterial BP, because no change in arterial stiffness was observed when it was measured under isobaric condi-
tions. In obese women, a 16-week weight loss program achieved ~10% reduction in body weight and induced ~30% increase in systemic arterial compliance. The increase in arterial compliance was significantly but modestly associated with the reduction in BP, suggesting that the effect of weight reduction on arterial distensibility may be mediated indirectly by the concomitant decreases in BP. However, there was a subgroup of women who achieved significant reductions in arterial stiffness without any changes in arterial BP. Thus, the available evidence indicates that weight reduction may decrease arterial stiffness in obese subjects. However, currently it is not clear whether the reduction in arterial stiffness is due to weight reduction per se or whether it is an epiphenomenon of BP reductions accompanying weight loss. The direct effects of weight reduction on arterial stiffness should be investigated in the future in obese subjects in general and in obese hypertensive subjects in particular.

Dietary Modifications

There is now overwhelming evidence that dietary factors influence the risk of cardiovascular disease, and emerging data indicate that arterial stiffness is markedly influenced by dietary factors. Red wine containing alcohol induced small but significant reductions in BP, PWV, and AI obtained at the radial artery. These effects were not observed when dealcoholized wine was consumed. Although part of the effect of alcohol appears to be BP dependent, the reduction in arterial stiffness remained significant even after adjusting for BP changes. Recent studies indicate that caffeine intake, in the form of a tablet or in coffee, produces a short-term increase in AI obtained at the radial artery in normotensive and hypertensive subjects. No such changes were seen with placebo or decaffeinated coffee intake. Taken together, these studies suggest that arterial stiffness can be changed acutely with commonly consumed dietary factors.

Sodium Restriction

Salt intake is being recognized as an important factor determining the BP differences between and within populations and is a major cause of the rise in arterial BP with advancing age. Increased salt intake is thought to raise BP by increasing plasma volume, blood volume, and subsequently cardiac output. Although this could be true in short-term experiments involving saline infusion, the evidence that the chronic increase in cardiac output is responsible for salt-induced increase in BP is not convincing, because increased blood volume is associated with increased venous compliance with little change in central venous pressure and cardiac output. Alternatively, there is increasing evidence supporting the link between sodium intake and arterial stiffness. The INTERSALT Study indicates that excess intake of sodium, as reflected in 24-h urinary sodium excretion, is associated with an increase in systolic BP but not in diastolic BP. Additionally, aortic PWV was measured in groups of individuals living in a rural or an urban community in China. Aortic PWV was significantly lower in the rural community with low salt intake, and the group difference persisted even when subgroups of subjects with the same BP and age were compared. Cross-sectional findings in normotensive adults varying in age indicate that subjects who follow a diet low in sodium demonstrate lower levels of PWV than age- and BP-matched controls with higher salt intake. Moreover, borderline hypertensive subjects who are sodium sensitive with regard to BP have decreased arterial distensibility compared with sodium-resistant subjects. Plasma volume, cardiac output, and BP were not different between sodium-sensitive and sodium-resistant subjects and could not have been responsible for observed differences in arterial stiffness. Taken together, these cross-sectional findings support the hypothesis that sodium intake influences arterial stiffness long term, independent of BP.

There have been only a few intervention studies that determined the effects of salt restriction on arterial stiffness. We reported that in postmenopausal women with elevated BP, 3 months of moderate dietary sodium restriction reduced both casual and 24-h BP. The changes in resting and 24-h systolic BP and pulse pressure were consistently correlated with the corresponding changes in both aortic PWV and carotid AI. Importantly, the reductions in carotid AI were not associated with changes in body weight, mean BP, plasma volume, and heart rate, indicating a direct effect of sodium restriction on arterial stiffness. An interesting observation in this study is that sodium restriction was more efficacious in reducing BP and arterial stiffness than a moderate aerobic exercise program in postmenopausal women. We recently followed-up this previous study using carotid arterial compliance measured with a simultaneous application of ultrasonography and applanation tonometry. A novel finding of this study is that arterial compliance increased very rapidly at the end of week 1 of sodium restriction, attaining peak levels by week 2 (Fig. 3).
Other Dietary Modifications

To date, a number of short-term dietary modifications have been shown to change the elastic properties of large arteries, although most studies have involved a relatively small number of subjects. A comparison of aortic PWV between inhabitants of fishing and farming villages in Japan revealed that the population with higher fish consumption demonstrated lower arterial stiffness.\(^{38}\) In an Australian cross-sectional study involving both healthy and diabetic subjects, fish eaters demonstrated a greater arterial compliance compared with non–fish eaters who were matched for age, BMI, and BP.\(^{39}\) These cross-sectional study findings were confirmed by interventional studies. In placebo-controlled studies, several weeks of fish oil supplementation with n-3 fatty acid significantly improved arterial wall characteristics in obese subjects\(^{40}\) as well as in diabetic subjects.\(^{41}\) Collectively, these findings are consistent with the hypothesis that fish oils, more specifically n-3 fatty acids, may reduce arterial stiffness.

The antioxidant vitamins, in particular ascorbic acid and \(\alpha\)-tocopherol, have been reported to reduce arterial stiffness. In a placebo-controlled, double-blind, randomized study, AI measured at the radial artery was reduced 6 h after oral intake of vitamin C in healthy subjects.\(^{42}\) The results of this short-term study are in agreement with a recent intervention study involving diabetic patients.\(^{43}\) After 4 weeks of oral intake of ascorbic acid, aortic AI estimated from the radial artery waveform decreased significantly.\(^{43}\) It should be noted, however, that reductions in peripheral resistance, which could be induced by vitamin C intake, may be responsible for the reduction in AI. Similarly, 8 weeks of vitamin E intake induced 44% increase in systemic arterial compliance in middle-aged men and women.\(^{44}\) These results suggest that the antioxidant vitamin may be beneficial in reversing arterial stiffening, presumably through its effect as free radical scavenger. Although the available data regarding the effects of vitamins on arterial stiffness are encouraging, there appears to be little evidence that supplements of vitamin C or E are sufficiently effective in preventing and controlling high BP or cardiovascular disease (that is, sequelae of arterial stiffening).\(^{45,46}\) Thus, the clinical significance of the short-term effects of vitamins on arterial stiffness remains to be determined. In fact, a recent well-controlled study involving both short-term and long-term administration of ascorbic acid failed to affect carotid arterial compliance in healthy young and older men.\(^{47}\) Similarly, homocysteine lowering therapy with folic acid-based treatments have been shown to be ineffective in improving carotid artery compliance.\(^{48}\) Thus, available information is not encouraging in terms of recommending antioxidant vitamins for the prevention and treatment of arterial stiffening and subsequent CVD.

Smoking Cessation

Smoking is a major and independent risk factor for development and progression of cardiovascular disease. Despite the strong evidence linking cigarette smoking and cardiovascular disease, the mechanisms by which smoking causes cardiovascular disease remain poorly understood. In addition to smoking-induced endothelial dysfunction, emerging evidence indicates that smoking may exert its effects, at least in part, through decreasing arterial compliance. Short-term cigarette smoking was found to increase arterial stiffness in nonsmokers\(^{49,50}\) and smokers,\(^{49,51,52}\) and the magnitude of increases in arterial stiffness after smoking was similar between the two groups.\(^{49}\) The greatest effects of short-term smoking on arterial stiffness seem to occur in the first 5 minutes after smoking,\(^{49,53}\) and ambulatory BP measurements indicate that smoking increases pulse pressure during day but not at night (that is, when subjects do not smoke).\(^{54}\) A recent study has demonstrated that “passive” or environmental smoking is also associated with acute deterioration in the elastic properties of the aorta.\(^{52}\)

Consistent with the short-term effects of smoking, the majority of studies to date have reported that long-term smoking is associated with arterial stiffening,\(^{55,56}\) although there are some conflicting reports.\(^{57}\) The effects of long-term smoking on arterial stiffness have been observed both in normotensive and hypertensive individuals\(^{55,56}\) and appear to be independent of BP levels.\(^{56}\) Long-term exposure to environmental tobacco smoke (ie, passive smoking) also is associated with carotid arterial stiffening in a dose-dependent manner.\(^{58}\) These results indicate that some chemicals in the gas may be a cause of smoking-induced arterial stiffening. In this context, exposure to oxidizing gases may be a primary suspect, as blood levels of nicotine and carbon monoxide are quite low in passive smokers\(^{59}\) who also demonstrate arterial stiffening.

To the best of our knowledge, there has been no study to determine directly whether smoking cessation would reduce stiffness in large elastic arteries. However, because several weeks of smoking cessation reduces systolic BP in hypertensive patients,\(^{60}\) it is reasonable to hypothesize that arterial stiffness would be reduced with smoking cessation. Nonetheless, the information regarding the influence of smoking cessation on arterial stiffness should be derived in future studies.

Physiological Mechanisms Underlying Arterial Destiffening

The three primary elements of the arterial wall that determine its stiffness are as follows: 1) the amount/proportion of elastin and collagen (quantitative structural elements); 2) fracture/fragmentation of elastic lamellae and the cross-linking of collagen and advanced glycation end-products (qualitative structural elements); and 3) the vasoconstrictor tone exerted by its smooth muscle cells (functional elements) (Fig. 1). Although different lifestyle modifications would likely act on different physiologic mechanisms to change arterial stiffness, any favorable influences of lifestyle modifications should involve an attenuation or...
reversal of one or more of the mechanisms contributing to arterial stiffening.

It is thought that structural changes, in particular elastin and collagen content, play a major role in determining central arterial stiffness. However, the elastin–collagen composition of the arterial wall represents a more long-term component of the stiffness of the artery and changes only over a period of years. As such, it is unlikely that this may be a physiologic mechanism underlying reductions in arterial stiffness induced by short-term lifestyle modifications described above. In fact, in an animal experiment, we recently demonstrated that the influence of regular aerobic exercise on arterial stiffness does not appear to be mediated by the quantitative changes in arterial wall elastin and collagen.

In addition to the “quantitative” changes, the constituents of arterial wall undergo “qualitative” changes with age, hypertension, and diabetes (for example, fracture and fragmentation of elastic lamellae as well as changes and remodeling of extracellular matrix, including fibronectin and integrin). In particular, there is an accumulation of additional interstitial collagen in the arterial wall, which can react nonenzymatically with glucose, link them together, and produce advanced glycation end-products. These end-products accumulate slowly on long-lived proteins to stiffen arteries. It is plausible to hypothesize that some lifestyle interventions, such as exercise, may act to break these links to reduce arterial stiffness. In this context, the agents that break these protein cross-links reduce arterial stiffness in aged monkeys as well as in aged adults. Because this favorable effect can be induced in several weeks, it is reasonable to hypothesize that some lifestyle modifications may act on arterial stiffness via this mechanism.

In marked contrast to the prevailing thought that arterial stiffness is a relatively static measure, arterial stiffness has a large “reserve” and can be altered—even acutely—over a much shorter period. The ability to modify arterial stiffness over the short term is thought to be due to modulation of the contractile states of the vascular smooth muscle cells in the arterial wall. As such, it is possible that the reduction in vasoconstrictor tone exerted by smooth muscle cells may be a potential mechanism underlying improvements in arterial stiffness with lifestyle modifications. Another related and plausible mechanism contributing to the reduction in arterial stiffness is reduced vascular endothelium mediated vasoconstrictor tone. The augmented nitric oxide bioavailability should tonically suppress vascular smooth muscle cell tone, thereby reducing arterial stiffness. In this context, nitric oxide was recently shown to regulate brachial artery elasticity in humans.

Perspectives
Arterial stiffening and increased pulse pressure are being recognized as predictors of CVD, in particular myocardial infarction. Because reduced pulse pressure involves a decrease in systolic BP, which acts to reverse cardiac hypertrophy, and an increase in diastolic BP, which improves coronary circulation, treatments that reduce pulse pressure and arterial stiffness may further reduce cardiovascular risks. It is a matter of debate as to whether a direct measurement of arterial stiffness would provide a greater increment in cardiovascular risk stratification over an indirect index, including systolic and pulse pressure. However, systolic and pulse pressure lose their predictive power for cardiovascular events after adjustment for arterial stiffness, and arterial stiffness exerts the stronger independent predictive power. As such, arterial stiffness should be considered as a marker of cardiovascular risk independent of brachial BP levels.

Current guidelines recommend that to prevent and treat most cardiovascular risk factors, lifestyle modifications be used for an initial period of 3 to 6 months, followed by pharmacological intervention if necessary to achieve normalization. Available evidence indicates that lifestyle modifications—in particular, aerobic exercise and sodium restriction—appear to be clinically efficacious therapeutic interventions for preventing and treating arterial stiffening. Thus, sufficient evidence is available to recommend lifestyle modifications as part of a first-line therapeutic approach for arterial stiffening. However, more information is needed for a more complete understanding and optimal use of lifestyle modifications in the management of arterial stiffening.

References


