

Effects of exercise and angiotensin-converting enzyme (ACE) on aortic stiffness in the elderly

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Senescence is a complex process involving many variables including genetics, lifestyle factors, and chronic diseases, the interaction of which significantly influences the manner in which we age (2). In particular, hypertension and genes of the rennin-angiotensin-aldosterone system have been associated with functional and structural changes of the large arteries, which are thought to contribute to age-related increases in the incidence of cardiovascular disease. Despite mounting evidence implicating sedentary behavior as a significant risk factor in chronic-disease morbidity and mortality among the elderly, there is a limited amount of information on the role of exercise in promoting optimal health and function in older people (27). The purpose of the present review is to discuss the effects of exercise training and angiotensin-converting enzyme (ACE) on aortic stiffness in the elderly.

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INTRODUCTION

The high prevalence of hypertension in our society imposes a considerable public health issue; therefore, the prevention of hypertension is a major public health objective. Hypertension is a serious problem that increases the risk of aortic stiffness (77), which is thought to contribute to age-related increases in the incidence of cardiovascular disease (77). Arterial stiffness may predict coronary heart disease beyond classic risk factors. In a longitudinal study (14), the predictive value of arterial stiffness on coronary heart disease in patients with essential hypertension and without known clinical cardiovascular disease was assessed. It was found that measurements of arterial stiffness correlated significantly with those of endothelial function, mainly influenced by the relationship of the angiotensin converting enzyme (a key component in the rennin-angiotensin system) and bradykinin. Data show that different molecular mechanisms are responsible for the hypertension and aortic stiffness seen in elderly and in cardiac patients. Moreover, there is growing evidence for a genetic

contribution to the pathophysiology of hypertension and aortic stiffness. In particular, genes of the rennin-angiotensin-aldosterone system have been associated with functional and structural changes of the large arteries, which are thought to contribute to age-related increases in the incidence of cardiovascular disease. Genetic studies may help us to understand the mechanisms underlying the involvement of the rennin-angiotensin system in arterial regulation. There is mounting evidence implicating sedentary behavior as a significant risk factor in chronic-disease morbidity and mortality among the elderly, though there is a limited amount of information on the role of exercise in promoting optimal health and function in older people (27). The purpose of the present review is to discuss the effects of exercise training and angiotensin-converting enzyme (ACE) on aortic stiffness in the elderly.

Ageing considerations

Many cross-sectional studies have demonstrated a significant relationship between age and aortic

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stiffness, although the age-related changes observed in peripheral arteries appear to be less marked (62). However, age is the main clinical determinant of the large artery stiffness seen in elderly persons with isolated systolic hypertension. This condition is characterized by fissuring and fracturing of the elastin protein, collagen proliferation, and calcium deposition, and is frequently associated with a widened and torturous aorta (69, 85). As large arteries dilate, wall tension and pulsatile stresses increase and exacerbate artery wall degeneration, thus initiating a feedback loop whereby increased hypertension leads to further degeneration (69). In response to a stress, the age-related reduction in physiological reserves causes a loss of regulatory or homeostatic balance. This, combined with another consequence of age-related changes—an increased perception of effort associated with sub-maximal work—establishes a vicious cycle especially in patients unbeknown to the above. This vicious cycle leads to decreased exercise capacity, which results in an elevated perception of effort and subsequently causes avoidance of activity, resulting in an exacerbation of the age-related declines secondary to disuse.

Age-related, environmental, and genetic factors are responsible for structural and functional changes of the arterial wall, leading to decreased elasticity and increased stiffness (52, 53, 82). Aging is also associated with structural and functional changes of the vessel wall, which result in decreased vascular distensibility and elevated arterial stiffness (4). There are several possible explanations for the influence of aging on the loss of elasticity of central arteries. The most likely explanation appears to be age-associated structural changes in the arterial wall, such as a decrease in elastin and an increase in collagen and connective tissues (90). The aorta stiffens during senescence, as indicated by an increase in arterial pulse wave velocity (45, 93). Pulse pressure, measured as the difference between systolic and diastolic blood pressure, rises markedly after the fifth decade due to arterial stiffening with age, which results in a progressive rise in systolic blood pressure and a fall in diastolic blood pressure as the elastic capacity of the aorta diminishes (31). Pulse pressure may be increased because of a larger forward pressure wave or an earlier or larger wave reflection (63).

The Baltimore Longitudinal Study of Aging (93) found that aortic arterial-pulse wave velocity increased progressively with age in 50 healthy females from 26 to 96 years old, in whom only modest age-related increases in blood pressure were observed. This is noteworthy since the elastic properties of arteries are not necessarily uniform (45). Aging has been reported to have different effects on the stiffness of peripheral (e.g., brachial and radial) and central arteries in men (71). This may increase cardiovascular morbidity and

mortality because of an elevation of systolic blood pressure, which raises left ventricular afterload, and because of a decrease in diastolic blood pressure, which alters coronary perfusion (60, 82).

Aortic stiffness considerations

Arteries serve the dual purposes of conducting blood to the peripheral tissues and buffering the pressure pulsations that are a necessary accompaniment of intermittent ventricular pumping (64). Isolated systolic hypertension may increase arterial stiffness, especially in older subjects, but not peripheral artery stiffness, although the underlying mechanisms are somewhat unclear (7).

Aortic elasticity is an important determinant of left ventricular performance and coronary blood flow. As a consequence of arterial stiffness, left ventricular workload is increased, and myocardial oxygen demand, leading at times to left ventricular hypertrophy (19, 88, 98), impairs ventricular relaxation (32, 47, 55), causing subendocardial ischemia in the presence or absence of coronary artery stenosis (53, 97). In addition, when aortic stiffness is followed by significantly elevated afterload, end-diastolic filling pressure rises and diastolic dysfunction develops, presumably due to incomplete relaxation and impaired left ventricular filling (56, 57)

It is well appreciated that the aorta is not only a conduit, but also plays an important role in regulating left ventricular performance, coronary blood flow, and normal arterial function throughout the entire cardiovascular system (49). Loss of vascular distensibility reduces the buffering function of the aorta and is manifested as elevated pulse pressure, which adds to load on the heart and likely damages the large and small vessels as well. Several studies have shown that disease states, aging, and pharmacological agents may alter the elastic properties of the aorta, and that stiffening of the aorta may be associated with an increased incidence of cardiovascular events (49). These effects may increase the susceptibility of the aging heart to ischemia and ventricular dysfunction. An increase in the stiffness of the large conduit vessel may represent either a cause or a consequence of endothelial dysfunction and may explain why elevated pulse pressure is a new cardiovascular risk factor (70).

The rennin-angiotensin system

Clinical and experimental studies have demonstrated a major role of the rennin-angiotensin system (RAS) in the functional and structural changes of the large arteries in hypertension. The RAS is important for regulating blood pressure and extracellular fluid. The concept of the RAS has recently evolved from a classical systemic endocrine system to the idea of local

RASs functioning in a paracrine manner, including in the vascular wall (81). Angiotensin-converting enzyme (ACE) is a key component in the RAS system, generating the vasoconstrictor angiotensin II, and degrading vasodilator kinins (22). ACE is widely expressed in human tissues, including skeletal muscle, and may play a metabolic role during exercise (41). Angiotensin II, the predominant biological product of RAS, has been known for its effects on metabolism (15) and is a recognized growth factor necessary for the hypertrophy of skeletal muscle in response to mechanical load (35). Most of its known physiological and pathophysiological activities are mediated through the angiotensin II type 1 receptor (AT1R), the dominant receptor in the cardiovascular system (36). Higher levels of ACE have been observed in human subjects with increased carotid wall thickness. Clinical and experimental pharmacological studies have shown that ACE inhibitors can prevent and/or beneficially affect hypertension-induced structural and functional alterations of the arterial wall independent of blood pressure changes (6).

Growing evidence supports a role for the involvement of genetic factors in the development of hypertension and aortic stiffness. Recent genetic studies (5, 99) focused on the RAS and on the identification of RAS candidate genes. These studies may help us to understand the mechanisms underlying the involvement of RAS in arterial regulation. A functional polymorphism of the human ACE gene has been identified in which the absence (deletion - D allele) rather than the presence (insertion - I allele) of a 287-bp Alu repeat element in intron 16 is associated with higher enzyme activity in both serum and tissue (25, 78), resulting in greater production of angiotensin II and aldosterone and a decreased half-life of bradykinin (5, 99). The polymorphism in the AT1R gene that has been most extensively studied is the A1166C variant. This polymorphism has been linked to enhanced physiological responses of angiotensin II resulting in increased vasoconstrictor activity (94). Because RAS activity plays a major role in the regulation of vascular tone, the ACE ID genotype associated with ACE activity could be a candidate gene for large-artery stiffness (92). It has been suggested that in hypertensive but not normotensive subjects, the AT1R and ACE genotypes are involved in the regulation of aortic rigidity (1). The ACE genotype has been shown to affect exercise and glucose load responses (33). The AT1R genotype appears to predispose to favorable anthropometric and metabolic traits relative to cardiovascular risk (1), and has previously been associated with the development of hypertension and coronary disease.

Exercise benefits

There is increasing evidence that regular exercise training initiated as early as young adulthood, but even during old age, can result in a high level of activity, thereby influencing the aging process. Thus, it is appropriate to perceive physical activity as a medical prescription for the aging population (54). Regular physical activity is associated with reduced risk of cardiovascular disease (11). In the Baltimore Longitudinal Study of Aging (93), it was found that aortic arterial pulse wave velocity increases progressively, but that older adult males who performed endurance exercise on a regular basis demonstrated lower levels of aortic arterial pulse wave velocity than their sedentary peers did.

Previous studies have reported that, in endurance athletes, arterial stiffness is decreased by prolonged endurance training (17, 43) while aortic distensibility is increased, particularly in those with the ACE II genotype. In addition, it has been found that moderately intense exercise as brief as 10 minutes in duration is needed to elicit a decrease in resting blood pressure; this may have potential benefits as a non-pharmacological aid to hypertension (58). These effects represent an extracardiac adaptation to chronic prolonged training in athletes (92).

Arterial compliance is an important therapeutic target in older individuals in whom stiffening of the proximal aortic blood flow is thought to underlie systolic hypertension and increased cardiac work. This indicates a positive association between systemic arterial compliance and fitness levels in healthy older people, and an inverse association between systemic arterial compliance and systolic blood pressure. These findings are consistent with either the acquisition of a more compliant circulation and lower blood pressure due to enhanced physical activity, or with the idea that a more compliant arterial circulation and lower blood pressure permit greater athletic performance (18). For healthy subjects between the ages of 25 and 65 years, there is an interactive effect between age and gender and an independent effect of physical training on peripheral vascular function (59). It was suggested that interventions to improve aerobic capacity alleviate the stiffening of the arterial tree that accompanies normative aging (93).

Exercise in hypertension

The relationship between arterial stiffness and hypertension is complex. Elastic artery stiffening, an age-related process, can be accelerated in the presence of hypertension. Hypertension may produce arterial stiffening by both functional and structural mechanisms. Therefore, the distending, or mean,

arterial pressure is an important confounder of measurements of arterial stiffness (62).

Physical activity has been recommended for the prevention and treatment of hypertension (8, 30). A large body of data demonstrates that changes towards a more physically active lifestyle positively affect blood pressure response in both normotensive and hypertensive individuals (10, 34, 75). A meta-analysis of longitudinal aerobic training studies (37) in mild essential hypertensive subjects demonstrates an average reduction in resting systolic and diastolic blood pressures of 10.8 and 8.2 mmHg, respectively (34). Therefore, participation in an exercise-training program may be viewed as a non-pharmacological approach for preventing and treating mild hypertension.

Previous studies (37, 80) have shown that a supervised exercise program leads to a decrease in blood pressure in humans with essential arterial hypertension. Men in a high fitness group with resting systolic blood pressure above or equal to 140 mmHg had a lower death rate than their low-fitness, below-140-mmHg-resting-systolic-pressure counterparts. Nevertheless, even though a reduction in blood pressure due to exercise training was detected in normotensive and hypertensive patients, the magnitude of reduction in systolic and diastolic blood pressure at rest and during submaximal exercise was greater in hypertensive subjects (9, 16).

How does physical activity produce a decrease in blood pressure in elderly and borderline hypertensive patients? The mechanisms responsible for the reduction in arterial pressure have not been investigated, although a reduction in sympathetic nerve activity resultant from exercise training has been suggested as a cause of lower arterial pressure (77). However, the lack of change in muscle sympathetic nerve activity after training indicates that the lower arterial pressure is unrelated to a reduction in central sympathetic outflow. The failure of muscle sympathetic nerve activity to change at rest with isometric training is also typically observed with either forearm or leg dynamic exercise training (76, 86). Therefore, reductions in sympathetic outflow to skeletal muscles do not appear to be a prerequisite to lower arterial pressure in humans. However, it cannot be excluded that sympathetic outflow to other vascular beds (e.g., visceral regions) may be reduced and may contribute to a reduction in arterial pressure at rest (77).

Another possible mechanism for the reduction in arterial pressure is peripheral vascular adaptation. Aerobic and isometric exercises elicit marked increases in muscle sympathetic nerve activity and norepinephrine release. Thus, vascular sensitivity to norepinephrine may be decreased with aerobic and isometric training (46, 68).

Exercise and arterial-ventricular coupling

In healthy subjects, the arterial system and the left ventricle (LV) are closely matched to optimize left ventricular performance (20). The interaction between the arterial system and the left ventricle is referred to as arterial-ventricular coupling and is a central determinant of cardiovascular performance and energy (44). Age-related arterial stiffening is typically accompanied by changes in the left ventricle that exacerbate end-systolic chamber stiffness (44). These changes, aggravated by common disorders such as hypertension, may disrupt the coupling between the ventricle and the arterial system and reduce cardiovascular mechanic efficiency, cardiovascular reserve and exercise capacity (72). Resting arterial-ventricular coupling is generally maintained within a range that maximizes the efficiency of the heart (67). However, the arterial-ventricular coupling changes during exercise, manifested by a decrease in the arterial-ventricular coupling index, due to a greater increase in the ventricular contractility than in the arterial load (67). Thus, arterial-ventricular interaction favors the maximization of left ventricle performance at the expense of energy efficiency in conditions of physiological stress.

In older populations, however, this arterial-ventricular coupling index decreases to a lesser extent during exercise, possibly due to decreased arterial capacitance or lower cardiovascular reserve (67). Moreover, it has been reported that this change in arterial-ventricular coupling during exercise is additionally restricted by hypertension (21).

The mechanisms that mediate the association between aging, hypertension and the impairment of arterial-ventricular coupling are not yet completely understood. Nevertheless, it seems clear that these mechanisms differ in men and women. One previous study reported that women exhibit a greater age-related increase in proximal aortic stiffness than men (96). Later, another study found that arterial load during exercise is higher in older than in younger women, but no age-differences were found in men (67). Recently, Chantler et al. (21) reported that hypertensive women had blunted arterial-ventricular coupling index responses during exercise, but that there were no differences between hypertensive and normotensive men.

Although age-related arterial stiffness impairs arterial-ventricular coupling, there is growing evidence suggesting that exercise training may play an important role in restoring mechanical efficiency. A previous study demonstrated that resting end-diastolic volume increased and the effective arterial load decreased after exercise training, thereby improving arterial-ventricular coupling (79). These data suggest that exercise training may improve arterial-ventricular

coupling by shifting from left ventricle efficacy to the optimization of ventricular mechanical efficiency.

Exercise and ACE

Angiotensin-converting enzyme (ACE) is a key component in the RAS system, generating the vasoconstrictor angiotensin II and degrading vasodilator kinins within cardiovascular tissue (22). ACE is widely expressed in human tissue, including the skeletal and cardiac muscles (41, 83), and may play a metabolic role during exercise (41). In the human ACE gene, an insertion/deletion gene polymorphism has been identified, characterized by the presence (Insertion, I allele) or absence (Deletion, D allele) of a fragment of 287 bp in the intron 16. In this polymorphism the D allele was found to be associated with higher plasma and tissue ACE activity in animals (24), healthy subjects (78) and athletes (13). In addition, Faure-Delanef (29) demonstrated that in centenarians the ACE DD genotype had much higher circulating ACE activity than the ID and II genotypes did. The increased ACE activity associated with the DD genotype may lead to enhanced production of angiotensin II (24), which is the predominant biological product of RAS that mediates many of the local effects of ACE on several tissues.

Angiotensin II is a necessary factor in mediating vascular smooth muscle growth (41), and it has a direct hypertrophic effect on skeletal muscle (35). In addition, there is evidence that the ACE D allele is associated with ventricular hypertrophy (84) and increased left ventricular mass (28, 39, 68, 102). Angiotensin II also increases collagen production, perhaps by up-regulating TGF- β (100, 101). As a result, the increased ACE activity associated with the DD genotype may up-regulate the production of angiotensin II and TGF- β , favoring cellular hypertrophy and proliferation and synthesis of the extracellular matrix. Individuals with the DD genotype would therefore be more prone to vascular smooth muscle hypertrophy and would be at greater risk of arterial stiffness.

Additional effects attributable to angiotensin II may involve the regulation of body fluid balance via increased aldosterone secretion. This in turn results in the retention of sodium and water, leading to increased venous return, larger end diastolic volume, and subsequently to an increase in stroke volume due to Starling's law. It has been demonstrated that after exercise training sodium excretion is significantly increased in the ACE II but not in the ID or DD individuals (42). Moreover, increases in sodium excretion were inversely associated with changes in diastolic blood pressure (42). Therefore, the lower ACE activity associated with the II genotype may up-regulate sodium excretion, leading to lower venous

return and stroke volume. The net result is lower diastolic blood pressure. However, a number of studies have shown no differences in the levels of rennin, angiotensin II or aldosterone between ACE insertion/deletion genotypes (29, 50). These data suggest that other mechanisms, parallel to angiotensin II, mediate the association between the ACE gene and cardiovascular tone.

There is evidence suggesting that increased ACE activity leads not only to augmented production of angiotensin II, but also to a reduction in angiotensin (1-7) peptide, which is known to cause vasodilating effects (41). A recent study demonstrated that patients with hypertension who have the II genotype (lower ACE activity) have much higher circulating levels of angiotensin (1-7) than do those patients with hypertension who have the DD genotype (higher ACE activity) (40). Thus, it is conceivable that the ACE genotype positively contributes to vascular response to exercise by its involvement in the fine tuning of the levels of both angiotensin II and angiotensin (1-7).

Another explanation for increased arterial distensibility following exercise may be the effect of ACE on endothelin-1 (ET-1), a potent vasoconstrictor peptide produced by vascular endothelial cells (65). It has been reported that systemic administration of an endothelin receptor antagonist significantly decreased systemic blood pressure and peripheral vascular resistance in healthy humans, strongly suggesting that endogenously generated ET-1 contributes to basal vascular tonus in humans (38). In animals, the enhanced response of angiotensin II in the vasculature is mediated by both an increased binding capacity for the hormone and facilitation of the ET-1 action (23). Furthermore, it has been reported that arterial stiffness was increased by an intra-arterial infusion of ET-1 and decreased by the administration of an ET-1 receptor antagonist (61, 95). These findings suggest that endogenous ET-1 also participates in the regulation of arterial stiffness. Therefore, individuals with the DD genotype may be more prone to develop arterial stiffness due to higher ACE activity and increased generation of ET-1. Indeed, it has been demonstrated that hypertensive subjects who are homozygous for deletion (DD) have significantly less endothelium-dependent vasodilatation than subjects who were homozygous for insertion (II) and heterozygous (ID) (74).

Environmental and genetic factors may also influence the magnitude of the effects of age on large artery stiffness. AT1 receptor genotypes may influence arterial aging in hypertensive subjects; this shows that the association between genotypes and arterial stiffness may manifest itself later in life (51). The explanation for decreased arterial stiffness following endurance and isometric training may be due to the improvement in endothelial function. The increased

exposure to shear stress on the vessels throughout the entire body by the systolic blood pressure response during aerobic and isometric exercises may up-regulate the production of nitric oxide synthase and increase the release of endothelium-derived nitric oxide (26, 48, 87, 89). This is a potentially important effect because essential hypertension is associated with an impairment of endothelium-derived vasodilation related to nitric oxide production (73). During exercise, with the increased demand for oxygen by the working muscles, it is crucial to increase blood flow to the working muscles. Therefore, during exercise vascular smooth muscle tone plays a fundamental role in regulating blood pressure, blood flow, microcirculation, and other cardiovascular functions. The cellular and molecular mechanisms by which vascular smooth muscle contractility is regulated are not completely elucidated (91). It has been suggested that kinins may play a major role in the vasodilatation needed during exercise. Kinins are very potent vasodilating peptides that reduce blood pressure by lowering peripheral vascular resistance. Plasma and vascular kinins regulate and modulate the control of blood flow by the endothelium of vascular smooth muscles. The role of kinins in vasomotion is determined by the rate of peptides production by kininogenases and their degradation by kininases. ACE splits bradykinin into inactive fragments, thereby reducing the action of kinins. Therefore, acute increases in plasma kinin levels during exercise indicate that the metabolism of the peptides is fine-tuned to the systemic or local metabolic demands (12, 66). In addition, levels of growth-inhibitory kinins, induced by increased ACE activity, may act as a secondary mechanism by which the ACE genotype regulates left ventricular and vascular growth in response to exercise. Together, these findings suggest that the D allele (and thus higher tissue ACE activity) favors the development of aortic stiffness. Nevertheless, it is at present unclear whether subjects with hypertension and the DD genotype benefit more from exercise training than the respective subjects with either the ID or II genotype.

Conclusions and recommendations

These observations suggest that habitual low-to-moderate-intensity exercise—30 minutes per day on most days of the week in activities such as walking, biking, running, and swimming—does not only elicit a favorable blood pressure response that contributes to healthy aging, but also may prevent or at the very least delay increased aging-associated stiffness in central arteries. The absence of evidence-based data on corresponding endurance-trained young adults precludes a conclusive assessment as to preventative efficacy. However, the fact that aerobic and isometric

training have proven effective in reversing or at least decelerating the age-related stiffening process and concomitant morbidity of central arteries by lowering arterial stiffness in aged normotensive subjects does suggest that both modes of exercise training may offer an effective non-pharmacological intervention for the prevention of hypertension, and could be a treatment for hypertensive adults. In addition to their preventative and rehabilitative properties, aerobic and isometric forearm exercises are easily available, simple to set-up, and easily and quickly performed. These advantages give them a competitive edge in the recruitment of elderly participants, their compliance with the prescribed training, and their retention in the program, thereby overcoming non-adherence to a regimen or, worse yet, dropping out of such programs altogether. These are problems that have notoriously hampered positive clinical outcomes of such programs, particularly for the elderly. Furthermore, in being financially affordable, aerobic and isometric training programs may offer an inexpensive and effective therapeutic treatment to a large number of sedentary elderly people, as well as an inexpensive and effective preventative measure for chronic diseases in the public at large, with the goal of a longer, healthier life for everyone.

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