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Aortic stiffness in older persons, determinants and consequences

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Abstract

Vascular aging is an age-related process characterized by stiffening of the arteries, a process which is accelerated by cardiovascular risk factors such as hypertension and diabetes mellitus.
Arterial stiffness can deeply influence short- and long-term blood pressure profiles, influences the patterns of hypertension in older subjects and increases the risk of primary and secondary cardiovascular events. Also, arterial stiffness, seems to play a role in determining functional and cognitive decline in older age.

KeyWords: Arterial stiffnees, older adults, arteriosclerosis

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Introduction

The structural elements of the vessel wall that are particularly important in determining the vessel's stiffness are elastin and collagen. Elastin is very stretchable and is important to pulsatile behavior, but not of great importance in determining vessel wall strength. When elastin fibers are stretched and released, they return promptly to their original state. Collagen fibers are much stiffer and can resist stresses > 100 times the fracture stress of elastin fibers but are less extensible. The vessel wall is considered to act in a biphasic manner with the elastin fibers important in determining stiffness at low distending pressures, and collagen in determining stiffness at high distending pressures. In the normal arterial tree, the large arteries act as a buffering system that is dependent on vessel compliance. During systole, the stroke volume is rapidly infused into the arterial tree, with only 30% to 40% resulting in forward flow, whereas the rest is stored in the large arteries and subsequently released into the periphery during diastole. This buffering action essentially converts the pulsatile flow at the level of the aorta to continuous flow in the capillaries (the Windkessel effect). With aging, there is a thinning and fracturing of elastin and increased collagen deposition in the tunica media and therefore an increased vessel wall stiffness. Alterations in the buffering capability of the large arteries, mediated through

changes in arterial compliance, have hemodynamic consequences and important effect on organ function. The increase in arterial stiffness is responsible for earlier wave reflections and changes in pressure wave contours. The arterial pressure waveform is derived from the complex interaction of the left ventricular stroke volume, the physical properties of the arterial tree, and the characteristics of the fluid in the system. At the time of left ventricular ejection, a pressure wave is initiated that is propagated forward in the blood as well as by the aortic and arterial walls. When arteries are compliant and pulse wave velocity is relatively slow, reflected waves return to the central aorta in diastole, augmenting diastolic blood pressure and, therefore, coronary blood flow, which occurs predominantly during diastole. When arteries are stiffer and pulse wave velocity is higher, reflected waves arrive earlier and augment central systolic blood pressure, rather than diastolic blood pressure, increasing left ventricular workload and compromising coronary blood flow. Because left ventricular ejection remains stable or even decreases with age, arterial stiffness is the principal factor responsible for increased systolic blood pressure, decreased diastolic blood pressure and, therefore, high pulse pressure during aging.

Arterial stiffness has been exiguously investigated in large population-based studies. The studies presented in this review are based on the Rotterdam Study and focus on two measures of arterial stiffness: carotid-femoral pulse wave velocity as measure of aortic stiffness and the distensibility coefficient of the common carotid artery as measure of carotid stiffness. The Rotterdam Study is a population-based cohort study among subjects aged 55 years and older at baseline. In total, 7983 subjects agreed to participate and were included in the study. Baseline data were collected from March 1990 to July 1993. During the third examination phase (from 1997 until 1999) measurements of arterial stiffness were obtained. Of the 4148 subjects who were eligible for physical examination, carotid-femoral pulse wave velocity was measured in 3550 subjects and distensibility of the common carotid artery was measured in 3098 subjects.

Determinants

Age is the main determinant of changes in the viscoelastic vessel wall properties and is associated with vascular stiffness. However, the extent of these changes may depend on several cardiovascular risk factors. Besides age, hypertension and diabetes mellitus can alter arterial structure and reduce vascular elasticity. In subjects with hypertension, the principal structural modification of the vessel wall is hypertrophy of the media with a considerable development of extracellular matrix, mainly at the site of the central but not peripheral arteries. Nonenzymatic glycation due to raised blood glucose and consequent collagen cross linkage lead to alterations in the mechanical arterial properties in diabetes mellitus. It has been reported that high cholesterol

levels alter the endothelial function, leading to a decreased relaxation of the arterial vessels but at the moment the results of the literature are controversial. However, within the Rotterdam study, a high-density lipoprotein cholesterol was found to be associated with carotid stiffness, whereas no association was found between serum cholesterol levels and measures of pulse wave velocity.

Traditional risk factors can only explain part of the incidence of cardiovascular events. Many studies have focused on the role of inflammation in the development of atherosclerosis and cardiovascular disease. C-reactive protein (CRP), a marker of acute inflammation, is associated with atherosclerosis, whereas results on the predictive value of CRP are not consistent. A study in healthy US adults found that increases in pulse pressure, which reflect a gradual increase in stiffness of the large arteries, are associated with elevated CRP levels. In the Rotterdam study, it was found that high CRP levels were independentely associated with increased arterial stiffness. Increased levels of CRP have been found to be associated with major determinants of arterial stiffness as insulin resistance variables, diabetes mellitus, and high blood pressure levels. Therefore, it could be speculated that CRP levels would contribute to increased arterial stiffness, by being associated with metabolic and hemodynamic changes that lead to arterial stiffness. However, since associations remain after taking these factors into account in statistical models, other mechanisms might be involved. High CRP levels are associated with endothelial dysfunction. The vascular endothelium releases nitric oxide, a substance that has a major influence on basal arteriolar tone and blood pressure inducing arterial distensibility. Moreover, agonists that stimulate endothelial nitric oxide release, such as acetylcholine, also reduce muscular artery stiffness in vivo. It may be that high CRP levels impairs endothelial function and subsequently alters the mechanical properties of the vessel walls leading to increased arterial stiffness.

Increased arterial thickness, the presence of plaques and decreased carotid distensibility often coexist in the same subjects and the relationships among different alterations of the arterial wall, that is, hypertrophy (increased media thickness), atheromatosis (plaques) and stiffness (decreased compliance), remain to be explored. Atherosclerosis and arterial stiffness are both related to an unfavourable cardiovascular risk profile and it has been speculated that arterial stiffness may play a role in the development of atherosclerosis or vice versa. Studies evaluating the relation between arterial stiffness and atherosclerosis have reported conflicting results. The observed difference in the impact of independent determinants of these vascular entities, as body mass index and high levels of cholesterol that are strongly associated with atherosclerosis but not clearly associated with vascular stiffness, may suggest that the two alterations are at least partly independent entities of vascular damage.

The genetic background of arterial stiffness is also explored and several studies have suggested that arterial mechanisms are influenced by genes, as those related to the renin-angiotensin aldosterone system. The angiotensin-converting enzyme (ACE) gene has been implicated in structural changes of the vessel wall. The ACE gene has an I/D polymorphism in intron 16, which has been previously found to be associated with cardiovascular diseases and atherosclerosis. However, results between the ACE I/D polymorphism and vascular stiffness are not consistent. It has been found that aortic stiffness was similar among the three ACE I/D genotypes in normotensive subjects whereas it was slightly higher among hypertensive subjects with the II genotype. In another study the I allele of the ACE gene was associated with stiffening of the large arteries in patients with diabetes mellitus type 2 compared with subjects without diabetes mellitus. The results of the Rotterdam study are in contrast with these two previous studies but in agreement with a study in a small group of young adults which showed that higher stiffness of the common carotid artery was associated with the ACE D allele In participants in the Rotterdam study, higher stiffness of the common carotid artery was present in subjects with the ACE D allele. Higher circulating levels and tissue ACE activity are present in subjects with the D compared to the I allele. ACE catalyzes the conversion of angiotensin I to angiotensin II and the breakdown of bradykinin to kinin degradation products. Both angiotensin II and bradykinin are potent peptide hormones that play a role in vascular wall homeostasis reducing vascular tone, vascular smooth muscle cell growth and production of extracellular matrix. These processes may lead to progressive degeneration of arterial media as fractures and fragmentation of elastic lamellae, increased collagen and calcium content and dilation and hypertrophy of the large arteries with subsequent increased arterial stiffness. Other candidate genes related to cardiovascular aging, particularly those related to elastin, collagen and telomere length may offer new insights into genetic patterns influencing the pathogenesis of arterial stiffness. More recently, genome-wide linkage studies were conducted to investigate common genetic variants unconstrained by prior knowlegde, in which only weak associations have been found. Future studies are needed to help in the identification of candidate genes, since techniques are evolving rapidly.

Different lifestyles may also influence arterial elastic properties. Cigarette smoking is a known risk factor for cardiovascular disease however data on arterial compliance are less consistent. Reduced small vessels compliance has been demonstrated in smokers compared to non-smokers, whereas others were only able to demonstrate short-term changes in arterial distensibility, but not long-term effects. Physical exercise has also been shown to influence arterial functional properties. Senior endurance-trained athletes demonstrated less stiff arteries than sedentary men of the same age. Light to moderate alcohol consumption seems to have a protective effect on the

cardiovascular system. However, few studies investigated the relation between alcohol consumption and arterial stiffness and it is not clear whether alcohol consumption has an association with elastic properties of the vessel wall. Alcohol consumption increased pulse wave velocity in middle-aged Japanese men, whereas other authors showed that alcohol consumption was associated with lower arterial stiffness. Previous studies found a J-shaped association between alcohol consumption and arterial stiffness in men aged 40-80 years and an inverse association in healthy postmenopausal women. In the Rotterdam study, an U-shaped association was also found between alcohol consumption and arterial stiffness in women, independent of cardiovascular risk factors and atherosclerosis. In men, the same trend was observed, although the estimates lacked statistical significance. The association seems to be stronger for wine consumption. However, we do not believe that these results should encourage alcohol consumption.

Prognostic value of arterial stiffness

In the past, vascular stiffening and the increase in systolic and pulse pressure have been considered a part of normal aging. Besides its strong relation with age, arterial stiffness is also associated with hypertension, diabetes mellitus and atherosclerosis. Changes in the arterial walls, which lead to reductions of arterial compliance, may precede the onset of clinically apparent disease, and identify individuals at risk before disease onset (symptoms due to disease are, in general, late manifestations of alterations in organ function). The ability to predict alterations in vascular structure and function before the onset of clinical diseases has potential advantages. Aortic stiffness has been found to be a predictor of cardiovascular disease in selected groups of patients with hypertension, and patients with end-stage renal disease. Previous studies have also shown that measures of aortic stiffness can be linked to cardiovascular events in diverse study populations, such as in patients with diabetes mellitus, but also in elderly subjects, patients without prevelant cardiovascular disease and in the general population. In the Rotterdam study, it was found that aortic pulse wave velocity is a strong predictor of cardiovascular disease among apparently healthy subjects. The association is present both in men and women and in younger and older subjects. The measure of aortic pulse wave velocity improves the prognostic value above cardiovascular risk factors and carotid intima media thickness, which is a measure of atherosclerosis. These results show the additional information of arterial stiffness in risk stratification also in older age and indicate that arterial stiffness should no longer be considered as an innocent expression of vascular aging but as a sign of increased cardiovascular risk. Controversely, no association was found between carotid stiffness and incident cardiovascular disease. Age- and sex adjusted risk estimates for carotid stiffness were increased but the

estimates attenuated after further adjustment.

Clinical implications and future research

Vascular stiffening and the subsequent increase in systolic and pulse pressure have been considered in the past as a part of normal aging. To date, determinants of arterial stiffness and its clinical consequences have been exiguously investigated in large population-based studies. Besides aging, also hypertension, diabetes mellitus, atherosclerotic lesions and, specific genes have been found to be associated with structural changes of the vessel wall that lead to stiffer arteries. However, a large part of the variability in arterial stiffness is yet unknown. Large populations based studies should investigate whether age-related hormonal changes, nutritional patterns, physical activity and possible interactions of genetic and environmental factors can influence the functional vascular properties.

It is not completely clear whether vascular stiffening is a generalized process or whether several measures of stiffness obtained in different vascular territories may provide distinct information. In the Rotterdam study different associations were found, when studying stiffness measured at various sites of the arterial tree. In the proximal aorta and its main branches, elastin is the main component, whereas in the distal muscular arteries the collagen to elastin ratio is reversed and in peripheral arteries collagen predominates. Differences in elastic and muscular contents of the arterial wall could lead to differences in vascular stiffening at various sites. This, in combination with the different methods used in these studies, could also partially explain the results obtained. The measure of the carotid distensibility is a local measure of stiffness that provides information on the functional properties at a specific site of the arterial tree and may be strongly influenced by the presence of atherosclerotic plaques near the site of measurement. The measure of the pulse wave velocity provides information on generalized stiffness; however, this measure combines measurements of elastic and muscular arteries, making it impossible to evaluate differences in functional properties between the two types of arteries. Future research should investigate the relation between risk factors and structural and functional modifications at different sites of the arterial tree.

Different non-invasive measures of atherosclerosis are currently used in stratification of cardiovascular risk. The ankle- arm index, which is the ratio between systolic blood pressure of the tibial posterior artery and systolic blood pressure of the brachial artery, predicts cardiovascular disease. Carotid intima media thickness is a predictor of coronary heart disease in the general population, independent of traditional risk factors and other measures of atherosclerosis. In addition, the prognostic value of coronary calcification has been investigated within the framework of the Rotterdam Coronary Calcification Study and has been shown to be a

strong and independent predictor of cardiovascular disease. However, both measures of intima media thickness and coronary calcification require expensive devices and may require extensively trained personnel. Aortic pulse wave velocity, can measure non-invasively and in the Rotterdam study it was found that this measure is predictive of cardiovascular disease in the general population, with an additive value above other known risk factors also in older age. The strength of the associations with incident cardiovascular disease, the relatively low cost, ease of use, and acceptability to patients may suggest the measurements of arterial stiffness to identify individuals at higher cardiovascular risk. However, the role of aortic pulse wave velocity in the prediction of primary cardiovascular disease, in relation with other risk factors and co-morbid situations as atherosclerosis, needs to be confirmed further in other studies including different populations.

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