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Arterial stiffening: Causes and consequences

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Abstract Increased arterial stiffness, as measured by pulse wave velocity, is increasingly recognised as an important predictor of future cardiovascular events. At present, the mechanisms leading to stiffening of large arteries and the processes underlying the association between arterial stiffness and cardiovascular disease remain unclear. One suggestion is that stiffening may be a caused by atherosclerosis along the aorta, explaining its association with cardiovascular disease. However, age-related stiffening of large arteries can occur independently of atherosclerosis and development of atherosclerosis does not necessarily contribute to increased aortic stiffness. Vascular calcification, extracellular matrix degradation and inflammation are likely to contribute to arterial stiffening. One consequence of increased large artery stiffness is an increase in pulse pressure, which, in older subjects, is the blood pressure components most closely correlated with cardiovascular events. The association between arterial stiffness and cardiovascular events may be explained, at least in part, by the adverse haemodynamic consequences of increased stiffness. This review summarises the potential mechanisms of arterial stiffening and its haemodynamic consequences.

Introduction

Cardiovascular disease is a major cause of morbidity and mortality in Western populations.[1] The majority of cardiovascular events occur from complications of atherosclerosis.[2] Over the last decade, arterial stiffness has emerged as an important predictor of cardiovascular events including atherosclerotic coronary events.[3] The prognostic importance of pulse wave velocity (PWV), a measure of arterial stiffness, was first highlighted in renal patients where the probability of remaining free of a cardiovascular event is greatly reduced in patients with high PWV.[4] These findings have been replicated in other cohorts including hypertensive, diabetic and elderly subjects where PWV is a predictor of cardiovascular morbidity and mortality independently of other more established cardiovascular risk factors including blood pressure.[3]

At present, the mechanisms leading to arterial stiffening and the processes underlying the association between arterial stiffness and cardiovascular disease remain unclear. The aim of this review is to summarise potential mechanisms of arterial stiffening and its haemodynamic consequences.

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Mechanisms of arterial stiffness

Does atherosclerosis cause arterial stiffness?

One of the earliest studies to highlight an association between atherosclerosis and arterial stiffness was by Hirai et al.[5]; they showed abdominal aortic and carotid artery stiffness to be significantly higher in patients with coronary vessel disease when compared to age-matched controls. Furthermore, large artery stiffness increased linearly with progressively higher degrees of coronary disease.[5] More recently, these findings have been replicated by large epidemiological studies. The Rotterdam study included >3000 participants and showed a stepwise increase in PWV with progressively higher plaque burden when measured in the carotid artery and abdominal aorta.[6] One explanation proposed for these findings is that atherosclerosis causes arterial stiffness and that the prognostic importance of PWV is explained by it being a marker for the degree of atherosclerosis along the aorta. In support of this, both atherosclerosis and age-related artery stiffness are localised to large and medium sized arteries and increase in prevalence after 50 years of age.[7,8] However, early work by Avolio et al.[9] suggests that this may not be the case. In a Northern Chinese community which is known for its low serum cholesterol, incidence of atherosclerosis and coronary artery disease, age-related increase in PWV was comparable to and even more marked than that of western communities where atherosclerosis is prevalent.[9] This suggests that age-related stiffening of large arteries can occur independently of atherosclerosis.

At a histological level, arteriosclerosis the stiffening and dilation of the arterial wall is distinct from atherosclerosis. Arteriosclerosis is mainly localised to the medial part where there is an abundance of elastin[10] which becomes fragmented with age, showing a disorganised structure that may become calcified.[10] By contrast, atherosclerosis is primarily a disease of the intimal part of the wall which is characterised by accumulation of lipids accompanied by inflammation, fibrosis and calcification at the most advanced stages.[10] Furthermore, arteriosclerosis and atherosclerosis are likely to have different regulatory processes. Although established cardiovascular risk factors including hypercholesterolemia, diabetes mellitus, male sex and smoking have been associated with increased arterial stiffness, we recently showed in a systematic review that adjustment for age and blood pressure in cross-sectional studies often renders these associations non-significant.[11] These findings have been substantiated by the limited number of longitudinal follow-up studies. Benetos et al. [12] found a significant increase in PWV in both hypertensive and normotensive subjects over a 6-year follow-up period. However baseline measures of serum cholesterol, triglycerides, glucose or body mass index were not significant predictors of PWV progression. More recently, data from the Caerphilly prospective study showed only a modest relationship between PWV and cardiovascular risk factors measured over a 20 year follow-up period.[13] In animal studies of atherosclerosis, early deposition of plaque does not necessarily lead to increased arterial stiffening[14] and autopsy studies show only a modest relationship between arterial stiffness and plaque burden.[15] In postmenopausal women, we have shown a lack of association between PWV and lipid-rich non-calcified plaque assessed by ultrasound[16] or total aortic plaque burden as measured by magnetic resonance imaging.[17] Moreover, Paini et al.[18] observed increased local arterial compliance at the level of carotid plaques when compared to adjacent plaque free areas. These findings suggest that development of atherosclerotic plaque alone does not necessarily contribute to increased stiffness of arteries and that measures of arterial stiffness are unlikely to accurately reflect the extent of atherosclerosis along the aorta.

Calcification and arterial stiffness

Calcification within the central arteries can occur at two distinct sites: in the media of the arterial wall where it associates with elastin fibers or in the intima where it localizes within atherosclerotic plaque. In animal models, induced medial calcification leads to increased arterial stiffening independently of atherosclerotic plaque.[19] In humans, vascular calcification is increased in diabetic and end-stage renal disease patients, and in these patients arterial stiffness is greater compared to control subjects.[20–22] In healthy subjects, arterial stiffness relates to intimal calcification independently of non-calcified plaque assessed using ultrasound.[16,23] Furthermore, aortic calcification as measured by computed tomography is associated with increased aortic stiffness, independently of total aortic plaque burden.[17] As there is often an overlap between medial and intimal calcification, and because current imaging techniques are not able to distinguish between the two types of calcification, their individual associations to arterial stiffness are unknown. Indeed, intimal calcification may simply be a marker for minor degrees of medial calcification, undetectable by CT/ultrasound imaging but which alter the elastic properties of the media. Alternatively, because medial calcification co-localises to areas of elastin fracture, its association to arterial stiffness could be secondary to or it may be a marker for degeneration of elastin.

Extracellular matrix and arterial stiffness

Elastin and collagen are the main loading bearing components of the arterial wall.[10] A rise in blood pressure passively increases wall stiffness by transferring the pressure load from elastin to stiffer collagen fibers[10] and, reduction in arterial pressure leads to a reduction in arterial wall stiffness.[24] Prolonged increase in arterial pressure may additionally lead to structural changes within the arterial wall resulting from increased mechanical stimuli. In this instance, acute blood pressure lowering would not be able to normalise arterial stiffness.[24] The inability to lower arterial stiffness with anti-hypertensive drugs in end-stage renal disease patients is associated with worse prognosis.[25]

Age-related structural change of arterial extracellular matrix includes elastin fragmentation, change in elastin-collagen ratio, matrix cross-links from advanced glycation end-products and calcification.[26–30] Matrix metalloproteinases (MMP) are members of the zinc-dependent