Arterial stiffness

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Summary

Measurements of biomechanical properties of arteries have become an important surrogate outcome used in epidemiological and interventional cardiovascular research. Structural and functional differences of vessels in the arterial tree result in a dampening of pulsatility and smoothing of blood flow as it progresses to capillary level. A loss of arterial elastic properties results a range of linked pathophysiological changes within the circulation including increased pulse pressure, left ventricular hypertrophy, subendocardial ischaemia, vessel endothelial dysfunction and cardiac fibrosis. With increased arterial stiffness, the microvasculature of brain and kidneys are exposed to wider pressure fluctuations and may lead to increased risk of stroke and renal failure. Stiffening of the aorta, as measured by the gold-standard technique of aortic Pulse Wave Velocity (aPWV), is independently associated with adverse cardiovascular outcomes across many different patient groups and in the general population. Therefore, use of aPWV has been proposed for early detection of vascular damage and individual cardiovascular risk evaluation and it seems certain that measurement of arterial stiffness will become increasingly important in future clinical care. In this review we will consider some of the pathophysiological processes that result from arterial stiffening, how it is measured and factors that may drive it as well as potential avenues for therapy. In the face of an ageing population where mortality from atheromatous cardiovascular disease is falling, pathology associated with arterial stiffening will assume ever greater importance. Therefore, understanding these concepts for all clinicians involved in care of patients with cardiovascular disease will become vital.

Introduction

> *In extreme old age, the arteries themselves, the grand instrument of the circulation, by the continual apposition of earth, become hard, and as it were bony, till, having lost the power of contracting themselves they can no longer propel the blood, even through the largest channels, in consequence of which death naturally ensues.*
>
> –John Wesley, 1703–1791

The association of the hardening of human arteries with age and disease, summed up by John Wesley in the quote above, has been known

for many centuries. Indeed early physiology experiments measuring changes in the properties of arteries in different disease states first began over ninety years ago.[1] 'Stiffening' of the central arteries, arteriosclerosis, is associated with adverse cardiovascular outcomes in many different patient groups[2] and in the general population.[3] Aortic stiffening is strongly associated with age and is the driving force of isolated systolic hypertension, the major form of hypertension in older individuals.[4] In the face of an ageing population where the mortality from atheromatous cardiovascular disease continues to fall, pathology associated with arteriosclerosis will assume ever greater importance.

Why have elastic arteries?

Arteries are conduits through which blood is pumped from the heart to organs but in addition they have a smoothing function where large changes in blood pressure and flow resulting from intermittent ventricular ejection are integrated into a more steady flow within peripheral tissues. The aorta, where the artery wall contains a high proportion of elastin fibres, permits significant distension during systole. During diastole, blood is pushed forward through the arterial tree due to elastic recoil ensuring blood flow in one direction and smoothing of blood flow. More distal muscular arteries differ from the aorta in that they have a higher proportion of collagen fibres making them less distensible. The net result is a progressive reduction of pulsatility through the arterial tree to the level of the microcirculation of high-flow cerebral and renal vascular beds, minimizing barotrauma that would result from exposure to peak systolic pressures.

What is arterial stiffness?

Many ways of defining the biomechanical properties of the arterial wall exist. The most commonly used to express the viscoelastic property is *stiffness*, which expresses the relationship between change in pressure (ΔP) and change in volume (ΔV). Stiffness represents the instantaneous slope of the pressure–volume relationship ($\Delta P/\Delta V$).

Due to shared risk factors, disentangling the effect of atherosclerotic plaque formation from arterial stiffening is challenging. However, arterial stiffness increases progressively with age in populations around the world, even where there is a low prevalence of atherosclerosis[5] and occurs in arteries where atherosclerotic plaques rarely develop.[6]

Adverse haemodynamic consequences of increased stiffness

As the aorta stiffens it leads to a range of linked pathophysiological changes within the circulation. It is less able to accommodate the volume of blood ejected by the left ventricle, with greater pressure increment in systole exposing the myocardium to higher systolic pressures and resulting in left ventricular hypertrophy and fibrosis.[7] Reduced aortic elastic recoil and reservoir capacity leads to a fall in diastolic pressure resulting in the widened pulse pressure seen with age. The vasculature of the brain and kidneys are exposed to greater pressure fluctuations linked to an increased risk of stroke and renal impairment.[8] Lower diastolic blood pressure reduces coronary artery perfusion and promotes subendocardial ischaemia which is exacerbated by left ventricular hypertrophy.[9] Finally, changes to arterial pulsatility lead to an increase in shear stress—the dragging frictional force of blood flow against the vessel wall.[10] This affects endothelial production of nitric oxide and may promote the development of atheromatous plaques through vessel wall remodelling.[11]

Assessment of arterial stiffness in clinical practice

As the prognostic importance of the physical properties of the arterial wall have become apparent, many different parameters and measurement techniques have been developed to characterise them. These include using high-fidelity pressure transducers connected to angiographic catheters and non-invasive techniques such as echo-Doppler and pressure-sensing probes. The most commonly-used technique is measurement of the pulse-wave velocity (PWV) which provides a non-invasive method of assessing stiffness along an arterial section. When a pressure pulse generated

by ventricular ejection is propagated along the arterial tree its speed is determined by the geometric and elastic properties of the arterial wall and PWV has been shown to increase in parallel with arterial stiffness.[12] If the time interval between the foot of the pulse wave is measured at two different sites and the distance between the two sites is known, PWV can be calculated as:

$$\text{Velocity (m/s)} = \text{distance (m)}/\text{time (s)}$$

Although PWV can be measured in any arterial segment, PWV of the aorta (aPWV) is considered the 'gold-standard' measurement of arterial stiffness[2] as it has the clearest pathophysiological significance and extensive outcome data.[3]

The vast majority of studies involving aPWV to date have used two techniques; Complior® and Sphygmocor®, both of which involve probes placed on the carotid and femoral arteries. However, the need for operator training and time required to access the femoral artery at the groin has led to the development of new devices such as Vicorder® which measures aPWV using automated cuffs around the neck and mid-thigh. Further cuff-based methods such as Arteriograph® and Mobil-o-Graph® derive values of aPWV from oscillometric measurements of the brachial artery waveform. These simple techniques make widespread clinical measurement of aPWV a realistic possibility in the near future.[13] However, there is concern that these derived values may not accurately represent stiffness of the aorta but are in part determined by local arterial properties.[14]

Measurement of aortic stiffness using PWV provides a single value, giving no insight into regional variation in vessel wall characteristics. Measurement of aPWV using magnetic resonance imaging has demonstrated that velocities differ between separate regions of the aorta and that these progress at different rates with age and disease.[15] Imaging studies are likely to provide additional prognostic and physiological insights in the future.

A major drawback for research in this field until recently has been that variations in the algorithm used to detect the arterial pulse wave, and of distance estimates used to calculate velocity, lead to differences in absolute values obtained. This has limited comparisons between cohorts and recommendations for clinical practice. However recent work has focussed on standardisation of values to enable technique comparisons resulting in the publication of reference values for the general population[16] and new guidelines to categorise levels associated with increased cardiovascular risk.[1]

Factors regulating arterial stiffness

An important factor that has a complex interplay with measurement of arterial wall properties is blood pressure. The PWV of an arterial segment is not constant but depends upon the distending pressure, best represented by the mean arterial pressure (MAP). As MAP rises, the arterial segment experiences increased circumferential pressure with greater recruitment of inelastic collagen fibres.[18] This leads to higher measured stiffness so PWV values must be interpreted in light of MAP at the time of measurement. This difficulty has led to disagreement about whether isobaric arterial stiffness is increased among hypertensives. However, in longitudinal studies increased blood pressure does determine progression of arterial stiffness.[19]

Other than the effect of MAP, arterial elasticity is determined by structural characteristics of the artery wall and by vascular smooth muscle tone. Therefore factors associated with arterial stiffness can be considered in terms of structural and functional changes to the endothelium or the medial layer affecting smooth muscle cells, the elastic lamina or the connective matrix.

Structural changes

Vascular calcification can occur in both the arterial intima and media and the factors underlying it are complex and poorly understood. Recent evidence suggests that it is an active cell-mediated process following transformation of vascular smooth muscle cells into osteoblast-type cells.[20] Calcification is a major driver of the markedly increased arterial stiffness seen in patients with kidney disease where it is strongly associated with cardiovascular mortality.[21] However, aortic calcification is also associated with aPWV in healthy individuals.[22]

Progressive medial elastin fatigue, fracture and degradation, with a consequent increased loading on stiffer collagen fibres also determine arterial stiffness.[23] In addition to promoting arterial stiffening, elastin degradation is associated with changes in the extracellular matrix that may promote vascular calcification and be associated with the pathogenesis of atherosclerotic disease.[24] A further potential cause of arterial stiffening is advanced glycation end products (AGEs), which result from non-enzymatic protein glycation. It has been proposed that these form irreversible cross-links between collagen and elastin molecules, stiffening the vessel wall and altering normal cell-matrix interactions.[25]

There is growing evidence that dietary salt intake affects arterial wall properties. *In vitro* and in animal models, increased sodium concentration leads to vascular smooth muscle cell hypertrophy and increased arterial wall thickness with substantially increased collagen content and abnormal cross-linking.[26,27] However, whether these changes are relevant to humans is unclear. In large cross-sectional studies, populations with a high salt intake have greater progression of arterial stiffness over the life course.[5] Clinical studies have shown fall in aPWV in humans following dietary salt reduction but this may be attributable to blood pressure reduction.[28]

In addition, inflammation is emerging as a potential determinant of arterial stiffness that can result in both structural and functional changes to arterial walls. Inflammatory diseases such as rheumatoid arthritis and vasculitis are associated with increased aPWV which may reflect chronic vascular inflammation driving irreversible changes such as increased arterial calcification.[29] However, aPWV and endothelial function in patients with rheumatoid arthritis improves after anti-inflammatory treatment suggesting that these changes may be in part reversible.[30] Even among the healthy older population, levels of C-reactive protein are associated with aortic stiffness.[31]

Functional changes

By altering smooth muscle tone, endothelial function affects arterial stiffness although in humans the impact is more marked in the smaller arteries than in the aorta which has a smaller percentage of smooth muscle cells within the media. Modulation of nitric oxide levels affect human iliac artery stiffness[32] while infusion of endothelin-1 increases iliac PWV,[33] and it is reduced by the administration of an endothelin-1 blocker.[34] Endothelial function has been associated with aortic PWV in healthy humans[35] and in addition to acute modulation of vessel tone this may be a mechanism by which cardiovascular risk factors cause chronic changes to the vessel wall.

In addition to calcification, it has also been proposed that the high levels of arterial stiffness seen in patients with kidney disease are as a result of impaired endothelial function resulting from reduced renal excretion of toxins. For example, levels of asymmetric dimethylarginine (ADMA), a circulating amino acid which competitively inhibits nitric oxide synthase, are higher in patients with renal failure than controls.[36] Many studies of people with chronic kidney disease have shown a negative relationship between aortic stiffness and renal function[37] but it remains unclear if this is as a result of the uraemic state or shared risk factors between kidney disease and arterial stiffening such as hypertension and diabetes.[38]

Genetic factors

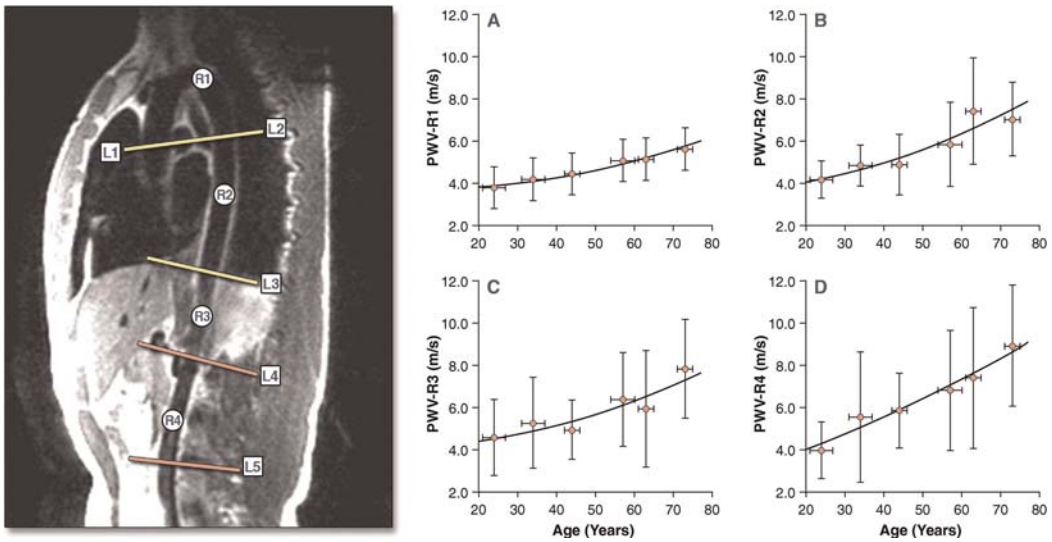
Aortic stiffness is a moderately heritable trait and many possible genetic influences on arterial stiffness have been identified.[39] These include genes affecting the renin-angiotensin-aldosterone system, beta-adrenergic receptors, differentiation of vascular smooth muscle cells, elastic fibre structural components, metalloproteinases, endothelin receptors, the NO pathway and inflammatory molecules. Most recently, a meta-analysis of genome-wide association data in nine community-based cohorts identified a locus on chromosome 14 in the 3-BCL11B gene desert that is associated with aPWV. Importantly, the locus identified is associated with increased risk for cardiovascular disease, consistent with the hypothesis that increased aortic stiffness plays a causal role in the pathogenesis of cardiovascular disease.[40]

Clinical usefulness

Measurements of arterial stiffness have been widely used in large-scale epidemiological

Figure 1

Left hand panel: Sagittal image of the aorta from the aortic root to the level of the bifurcation. L1 through L5 indicate the level of cine phase contrast magnetic resonance imaging image acquisition, and R1 through R4 indicate the region of pulse wave velocity measurement. Right hand panel: Association between age and regional aortic PWV in regions A-R1, B-R2, C-R3, D-R4. Reprinted from Hickson SS, Butlin M, Graves M, *et al*. The relationship of age with regional aortic stiffness and diameter. *JACC Cardiovasc Imaging* 2010;3:1247–55, with permission from Elsevier



studies to provide insight into cardiovascular disease and pathophysiology in a range of different diseases and in the general population. However, to find a clinical role, measurement of aortic stiffness needs to predict cardiovascular risk above conventional risk factors. Within the Framingham Heart Study, aPWV increases risk discrimination for first cardiovascular events [41] although it does not add to existing risk prediction among the elderly.[42] This suggests that measurement of aPWV may help target cardiovascular risk prevention in younger people with few overt risk factors and longitudinal studies are currently underway to establish whether this is the case.

There are several additional roles for measurements of arterial stiffness in the context of clinical trials. Use of surrogate markers of cardiovascular disease as end-points in interventional studies has been criticized but changes can be more quickly observed, are less expensive and can be chosen to be clinically relevant. This is particularly important in trials involving younger people when the time to development of hard cardiovascular outcomes may be long and studies require prohibitive follow-up. Aortic stiffness is a widely-used surrogate marker since it is clinically validated, reproducible and does not require excessive expertise to learn or time to undertake. In addition a validated technique has been used as a non-invasive method of assessing endothelial function.[35]

Therapeutic intervention

Given the strength of data linking arterial stiffness with adverse cardiovascular outcomes, it provides an appealing target for pharmacological intervention. However, despite intensive research, the evidence base for effective treatments remains small. As discussed previously, arterial stiffness is in part determined by MAP so dissecting out effects on stiffness above the effect attributable to blood pressure reduction can be complex. In order to distinguish between passive effects and those due to direct drug actions on arterial structure and function it is important to include positive control agents that reduce mean arterial pressure to a

similar degree as the study drug. Cross-over comparisons of antihypertensive classes have revealed no clear benefit in reduction of aPWV.[43] However, a meta-analysis of double-blind randomized trials showed that in longer studies all classes examined reduced aPWV compared to placebo, suggesting that a sustained unloading of the arterial wall due to a decrease in blood pressure may lead to a further decrease in arterial stiffness.[44]

Reduction of inflammation in patients with auto-immune diseases has been associated with reduction of arterial stiffness. This raised the hypothesis that the pleiotropic anti-inflammatory effects of statins may have similar benefits. Early clinical trials suggest that they may do[45,46] but absence of an antihypertensive effect of statins argues against an important improvement of arterial stiffness.[47] Benefits for statin treatment in reduction of arterial stiffness above general cardiovascular risk reduction have not been demonstrated.

The development of a thiazolium class of drugs that break established AGE cross-links between proteins showed great promise in lowering large artery stiffness in early trials.[48] However, these drugs have not progressed to wider clinical use and their benefits remain unclear.

Patients with chronic kidney disease have both high arterial stiffness and dramatically increased cardiovascular risk. Clinical trials within this population are therefore ideal for demonstrating 'proof of principle' effects. Treatment with both selective endothelin-A receptor antagonists and spironolactone reduced arterial stiffness in patients with chronic kidney disease.[49,50] In addition, treatment with drugs which reduce serum phosphate levels, a specific driver for arterial stiffening in this population, may show some benefit.[51] However, an effect of these drugs in reducing arterial stiffness has not yet been established beyond this high-risk group.

Future directions

Attempts to reduce the morbidity and mortality of cardiovascular disease over recent decades have focused on atherosclerosis. The steady reduction in age-adjusted mortality in high-income countries is a testament to the success of this effort. However, as the population ages, the cardiovascular disease spectrum is changing to one involving considerations of arterial disease beyond those caused by obstruction and ischaemia to the progressive stiffening of the aorta and central elastic arteries. There is extensive evidence to show that arterial stiffening is linked with adverse outcomes independently of atherosclerosis and while the underlying process is manifest as systolic hypertension the pathophysiological mechanisms of harm extend well beyond this.

Arterial stiffness is an important therapeutic target but two areas of research are urgently needed to take the current evidence base forward. Firstly, to identify potential areas for therapy the process underlying arterial stiffening needs to be understood in detail. This requires large, well-characterized prospective cohorts commencing at a young age before the acceleration of stiffness occurs. The recent identification of new genetic markers demonstrates that there is still much to be learnt about what drives the process of stiffening. Secondly, well conducted interventional trials with matched blood pressure reduction between arms are needed. If these demonstrate that modification of stiffness is associated with improved outcomes, measurement of pulse wave velocity will move from the sidelines to an everyday clinical test.

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