Arterial stiffness: clinical relevance, measurement and treatment

Paul K. HAMILTON, Christopher J. LOCKHART, Cathy E. QUINN and Gary E. McVEIGH
Department of Therapeutics and Pharmacology, Queen’s University Belfast, Whitle Medical Building, 97 Lisburn Road, Belfast BT9 7BL, U.K.

ABSTRACT

Most traditional cardiovascular risk factors alter the structure and/or function of arteries. An assessment of arterial wall integrity could therefore allow accurate prediction of cardiovascular risk in individuals. The term ‘arterial stiffness’ denotes alterations in the mechanical properties of arteries, and much effort has focused on how best to measure this. Pulse pressure, pulse wave velocity, pulse waveform analysis, localized assessment of blood vessel mechanics and other methods have all been used. We review the methodology underlying each of these measures, and present an evidence-based critique of their relative merits and limitations. An overview is also given of the drug therapies that may prove useful in the treatment of patients with altered arterial mechanics.

INTRODUCTION

In recent years, many papers have been published detailing different methodologies for the assessment of mechanical properties of arteries. This review provides an update to our review published in 2002 [1]. The focus here is the various technologies that are available for assessing arterial stiffness. The merits and limitations of each technique are assessed, giving a balanced and unbiased overview of what can appear to be a confusing area.

CLINICAL RELEVANCE OF ARTERIAL STIFFNESS

Traditionally, the prevention and treatment of cardiovascular disease has focused on favourably modifying ‘risk factors’, such as hypertension, smoking, hyperglycaemia and dyslipidaemia, that are known to be detrimental to arterial integrity [2–4]. However, a significant number of cardiovascular events occur each year in persons who do not qualify for drug treatment based on such guidelines [5]. A population-wide treatment scheme in which all individuals over a certain age would receive treatment, much like a vaccination programme, could provide a solution to this issue. This would, however, be economically impractical, and would put healthy persons at risk of adverse drug reactions. Much research has therefore focused on developing a method of accurately identifying subgroups of the general population at highest risk. Treatment of such individuals could provide large treatment benefits at a dramatically reduced cost to society [6].

Recent research has resulted in the identification of novel risk factors that are independent of the established risk factors for cardiovascular disease. It would seem plausible that making decisions on risk based upon many risk factors would facilitate much more precise risk stratification and, indeed, this is the case for the established risk factors mentioned above. However, the same may not be true for many recently described ‘circulating’ risk factors. In a recent study involving 3209 subjects, the C-statistic for major cardiovascular events was found to be 0.76 using age, sex and conventional risk factors as predictors [6]. However, the same may not be true for many recently described ‘circulating’ risk factors. In a recent study involving 3209 subjects, the C-statistic for major cardiovascular events was found to be 0.76 using age, sex and conventional risk factors as predictors compared with 0.77 when ten other biomarkers [CRP (C-reactive protein), BNP (B-type

Key words: arterial mechanics, arterial stiffness, augmentation index, cardiovascular risk factor, pulse pressure, pulse wave velocity.

Abbreviations: AASI, ambulatory arterial stiffness index; AGE, advanced glycation end-product; BP, blood pressure; ABPM, ambulatory BP monitoring; C1, large artery compliance; C2, small artery compliance; CRP, C-reactive protein; DBP, diastolic BP; LV, left ventricular; PT/TT, peak time/total time; PWV, pulse wave velocity; SBP, systolic BP; SV/PP, stroke volume/pulse pressure.

Correspondence: Dr Paul K. Hamilton (email pk_hamilton@yahoo.co.uk).
Artery walls are the primary site of disease in atherosclerosis and represent an attractive target for demonstrating functional and structural alterations [8]. Most traditional cardiovascular risk factors alter the structure, properties and function of arterial blood vessels [9–11]. It therefore seems intuitive that a more comprehensive assessment of the cumulative damaging effects of multiple risk factors on arterial wall integrity could improve risk stratification. Furthermore, we may be able to distinguish the beneficial effects of an intervention on an individual’s arterial end organ, rather than simply measuring its effect on intermediate risk markers, such as BP (blood pressure), improvements in which do not confer benefits for all individuals. If, however, a marker of arterial integrity was to serve as a useful indicator of cardiovascular disease or risk, it would have to be shown to have some merit over and above classical cardiovascular risk factors before it could ever conceivably be introduced into routine clinical practice. To establish if this is the case, longitudinal studies are required to demonstrate that an improvement in outcome is related to an improvement in the arterial parameter in question in a strong and graded fashion. Finally, the measure chosen should predict risk for an individual better than traditional measures.

BP is comprised of two components: steady-state and pulsatile. The steady-state component is characterized by the mean arterial pressure, which represents the product of cardiac output and peripheral resistance [12]. This measure allows inferences about the state of the arteriolar and capillary bed to be made, since these sites provide most of the resistance to flow in the circulation [13]. The pulsatile component is determined by LV (left ventricular) ejection and stroke volume, as well as the compliance of the arterial circulation [14]. Compliance may be defined as a change in volume or cross-sectional area of a vessel for a given change in pressure; the compliance characteristics of the entire arterial circulation being largely determined in the proximal vessels.

The elastic wall of the aorta transforms the pulsatile on/off blood flow of the left ventricle into less pulsatile flow in distal vessels that results in a smooth non-pulsatile flow in capillaries [15]. The ability of the aorta and proximal arteries to buffer the pulsatile flow largely depends on the compliance characteristics of the vessels. A benefit of such a system is the fact that the microcirculation is protected from pressure-induced damage, and that the heart receives adequate blood flow in the coronary arteries during diastole to meet its metabolic requirements. Stiffening of the aorta results in an elevation in SBP (systolic BP) and a lowering of DBP (diastolic BP) which, in turn, increases LV afterload and alters coronary artery perfusion [16]. These changes may result in LV hypertrophy [17], worsening of coronary ischaemia [18,19] and increased fatigue of arterial wall tissues [20], all of which substantially increase the risk of cardiovascular events [21]. In addition, increased arterial stiffness stresses vessel walls [22], which can increase the chance of atherosclerotic plaque rupture [23].

As the arterial tree branches and tapers, changes in diameter and stiffness occur, and this results in reflection of a portion of the propagating pressure wave [6]. Reflected waves travel backwards with approximately the same speed as the forward-flowing wave and, at some point through the aorta and its branches, the incident and reflected waves are traditionally thought to summate [23]. Pressure wave reflection may serve at least two beneficial purposes [24]. First, under ideal circumstances, the reflected wave returns to the central aorta in diastole, thereby enhancing the diastolic perfusion pressure in the coronary arteries [16]. Secondly, wave reflection limits the transmission of pulsatile energy to the periphery where damage to the microcirculatory beds might occur [25]. A stiffening of the central circulation relative to the peripheral circulation results in a reduction in the normal impedance-mismatch that exists between these two areas. This may diminish wave reflections [24] or cause wave reflections to occur in systole rather than diastole, thereby reducing diastolic perfusion of the coronary circulation and increasing transmission of pulsatile energy into the microcirculation. This situation is made slightly more complicated by the fact that reflected waves can, in certain circumstances, interact negatively with forward-travelling waves [26]. The phenomenon of wave reflection remains complicated and incompletely understood; much remains to be learned.

**MEASUREMENT OF ARTERIAL STIFFNESS**

Several methods for quantifying arterial mechanical properties have been proposed. These can be divided into techniques which apply propagative models to the circulation and those using non-propagative models [27]. Propagative models assume that the velocity with which a pulse wave travels along a given artery has a finite value [28]. Non-propagative methods include the Windkessel model that likens the circulation to a mechanical device found on old fire engines. A Windkessel pump was designed to transform the intermittent pulsing of a manual water pump into a continuous stream of water from a hose [16]. Similarly, modelling the circulation in this way separates its functions into conduit and cushioning functions. The Windkessel model has been criticized, however, since the arterial tree does not have separate conduit and cushioning functions, and because...
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Figure 1 Summary of the methods available for assessing stiffness

AIx, augmentation index.

the model makes the assumption that PWV (pulse wave velocity) has infinite velocity [28]. Inferences can be made about the mechanical properties of arteries by measuring pulse pressure or by measuring a variety of ‘stiffness indices’ in the form of outputs recorded from one of several commercially available devices. Such devices usually measure one of three possible types of arterial stiffness: systemic stiffness (i.e. a measure of the stiffness of the entire circulation); regional or segmental stiffness (i.e. a measure of the stiffness of a segment of the arterial tree); or local stiffness (i.e. a measure of the stiffness in a small section of one blood vessel under study) [29]. They can, however, provide information about more than one aspect of the circulation and can thus be classified as devices that: quantify pulse transit time; analyse the pressure pulse waveform; or provide direct estimation of vessel stiffness by the simultaneous assessment of arterial diameter and a corresponding distending pressure (Figure 1).

When an article describes the ‘stiffness’ of a blood vessel, one must ask what is actually being referred to. This is because the term arterial ‘stiffness’ lacks a precise definition and has no mathematical relationship to the mechanical properties of arteries [30]. As such, arterial stiffness cannot be directly quantified [31]. The terms ‘compliance’ and ‘distensibility’ are often used interchangeably with ‘stiffness’ [32]. However, compliance (a change in volume or cross-sectional area for a given change in pressure) and distensibility (a fractional change in volume or cross-sectional area for a given change in pressure) are parameters that can be quantified and have units of measurement [1], unlike arterial stiffness that is a purely descriptive term that cannot be measured or quantified. Stiffness represents a convenient shorthand term for alterations in the mechanical properties of blood vessels.

**Pulse pressure**

The measurement of pulse pressure is the simplest surrogate measure of arterial stiffness. Pulse pressure is calculated by subtracting DBP from SBP. It is determined by cardiac stroke volume and arterial stiffness [33].

\[
\text{Pulse pressure} = \text{SBP} - \text{DBP}
\]

This simple parameter, which indicates the degree of impairment of the buffering function of larger arteries, has been shown in several studies to have predictive value for cardiovascular events. Pulse pressure has been shown to be a predictor of cardiovascular disease in general populations [34], healthy individuals [35–37], untreated hypertensive patients [38], treated hypertensive patients [39] and patients with Type 2 diabetes mellitus [40,41]. In patients with Type 1 diabetes mellitus, age is significantly associated with pulse pressure, particularly in patients with albuminuria or retinopathy [42]. Elevated pulse pressure can also independently predict congestive cardiac failure in healthy elderly individuals [43].

Some authors report that pulse pressure is more meaningful if measured centrally [44], and this has been shown to relate more strongly to endothelial function than pulse pressure measured at the brachial artery [45]. It has also been suggested that the measurement of pulse pressure over a 24 h period is a better predictor of mortality than a single office measurement [41], and it has been shown that, after an acute stroke, patients with elevated 24 h pulse pressure have a higher risk of stroke recurrence [46].

Pulse pressure is affected by a number of physiological factors and is difficult to interpret in the presence of aortic valve insufficiency or the presence of arteriovenous fistulae [47]. \(\beta\)-Adrenergic activation has been shown to increase pulse pressure, but without changing the aortic PWV [48], demonstrating that a change in pulse pressure does not always indicate a change in aortic stiffness. The predictive value of pulse pressure can be affected by medical therapy. Greenberg [49] has shown that pulse pressure only had significant predictive value for cardiovascular/coronary disease in treated hypertensive subjects, but this was not the case for untreated individuals.

Because conduit arteries display a non-linear pressure–volume relationship, pulse pressure is directly related to the mean arterial pressure. Lowering BP will therefore reduce pulse pressure without necessarily exerting a direct effect on the arterial wall [47]. With this in mind, a more refined index involving pulse pressure is the SV/PP (stroke volume/pulse pressure) ratio. This index should
allow for the fact that the usefulness of pulse pressure depends on its ability to provide an estimate of the pressure-volume relationship, but that the volume increment during systole is determined by stroke volume and systolic run-off [47]. The SV/PP ratio has been shown to be a predictor of cardiovascular events in the general population [50] and in patients with hypertension [51].

Devices that quantify pulse transit time

PWV

The recent expert consensus document on arterial stiffness describes carotid–femoral PWV as the ‘gold standard’ measurement of arterial stiffness [28]. The principal determinants of PWV are described by the Moens–Korteweg equation that was derived in the 1920s, and relates the velocity of pulse wave travel in a vessel to the distensibility of that vessel [52,53]:

\[ c_o = \sqrt{\frac{Eh}{2\rho R}} \]

where \( c_o \) is the wave speed, \( E \) is Young’s modulus in the circumferential direction, \( h \) is the wall thickness, \( R \) is the vessel radius and \( \rho \) is the density of fluid.

In a given blood vessel filled with blood of fixed density, PWV is proportional to the square root of the Young’s modulus of elasticity of the vessel. In other words, the stiffer the vessel, the faster the PWV. However, the square root relationship between PWV and Young’s modulus means that changes in PWV are not a particularly sensitive measure of changes in the mechanical properties of an artery.

PWV is usually obtained by measuring the time taken for a pulse wave to travel a specified distance; the distance being divided by the time to give velocity. Distance measuring is usually estimated using a tape measure over the body surface; timing is performed by measuring the interval between fiduciary points on a pressure or flow waveform using a proximal and distal sensor [47]. Usually timing is made using the ‘foot’ of a waveform, since this is the part that is least affected by wave reflection. There are various devices on the market for measuring PWV. Some simultaneously measure pulse waveforms in multiple sites using several transducers. In others, the time between a defined point on an ECG and a defined point on the pulse waveform is compared between different sites. Another technique employs an oscillometric BP cuff and an electrocardiography recorder [29]. The time between the QRS complex and the corresponding diastolic phase, as measured in the brachial artery by the cuff, gives an estimate of PWV from the heart to this site.

Errors in PWV estimation can be introduced in the two measures required: distance between pulse assessment points and time taken for the pulse wave to travel between the sites. In measuring the distance between two arterial sites such as the carotid and femoral arteries, no allowance is made for differences in body shape between subjects. This distance will obviously be greater in a subject with central obesity than in a lean subject of the same height. Distance measures may also be inaccurate, since an assumption is made that the aorta is straight. The software supplied with some systems requires distance between sensors to be entered in centimetres, whereas other devices require millimetre accuracy. Thus there may be a tendency to round measurements when using the former set-up. When measuring the time taken for the pulse wave to travel between the two points of interest, a controversial area relates to the identification of the start of a pulse cycle in the recorded waveform. Similar points between waveforms must be identified to enable timing to be made of the speed of wave travel. However, determination of the wavefront is difficult because of changes in the pressure pulse contour that occur as the wave propagates, due to the visco-elastic properties of the transmission path and wave reflections [54]. Typically, four different points can be chosen to mark the onset of the pressure pulse. These are: (i) when the pulse height is at a given percentage of the maximum pulse height (e.g. 10 %); (ii) when the first derivative of the pressure waveform is maximal; (iii) when the second derivative of the pressure waveform is maximal; and (iv) the point formed by the intersection of a line tangent to the initial systolic upstroke of the pressure waveform and a horizontal line through the minimum point. Chiu et al. [54] studied the effects of using four similar methods of identifying a wavefront on the calculation of PWV. PWV results obtained using the second derivative and intersecting tangent methods were most correlated, with a correlation coefficient of 0.90. However, when the point of minimum DBP was used and correlated with the first derivative, the correlation was weak at 0.09. In one subject, PWV was calculated as 14.11 ms⁻¹ using the former method and 7.00 ms⁻¹ using the latter: a difference of over 50 %. Reports detailing PWV results should therefore stipulate the method used for identifying the start of a wavefront, and caution should be applied when comparing results between studies where different techniques have been used.

PWV varies from vessel to vessel. For a middle-aged adult, a typical velocity in the ascending aorta would be of the order of 4 ms⁻¹ compared with 5 ms⁻¹ in the abdominal aorta and carotid arteries, 7 ms⁻¹ in the brachial artery and 8 ms⁻¹ in the iliac arteries [55,56]. PWV measured along the aortic or aorto-iliac pathway is felt to be the most clinically relevant [16], since the aorta and its first branches are responsible for most of the pathophysiologic effects of arterial stiffness [57]. This idea is supported by data from Cameron et al. [58], who measured PWV in various locations, but showed that only carotid-femoral PWV was associated with age in non-diabetic subjects. Furthermore, Paini et al. [59] demonstrated that, when aortic stiffness was estimated using PWV and
carotid stiffness by measuring diameter change, the aorta stiffened more than the carotid artery with age and other cardiovascular risk factors in patients with hypertension and/or diabetes mellitus. PWV may also be estimated by simultaneously recording the pulse through the finger and toe by way of dual-channel photoplethysmography [60].

There are multiple trials that show that increased aortic PWV is associated with poor cardiovascular outcome. Increased aortic stiffness, as evidenced by measurement of aortic PWV, is associated with mortality in patients with end-stage renal disease [22], essential hypertension [61] and Type 2 diabetes mellitus [62]. Meaume et al. [63] studied rehabilitation patients in a Paris hospital and showed that, between the ages of 70 and 100 years, PWV could predict cardiovascular death. These findings were extended by the demonstration that, even among healthy older adults in their eighth decade, PWV was associated with cardiovascular mortality [64]. In a multivariate analysis with adjustment for pulse pressure and other variables, PWV remained associated with all end points, except congestive heart failure.

In addition to its predictive value for mortality, PWV can also predict primary cardiovascular events. Boutouyrie et al. [57] studied over 1000 subjects with hypertension, and showed that a 1 S.D. rise in PWV was independently associated with a relative risk of a coronary event or cardiovascular event of 1.42 and 1.41 respectively. This compared with a relative risk of a cardiovascular event of 1.16 that was associated with a 10 mmHg rise in pulse pressure.

Blacher et al. [65] studied subjects with atherosclerosis, as defined on the basis of clinical events, and concluded that aortic PWV was associated with the presence and extent of atherosclerosis. It is well-recognized that atherosclerotic plaques are heterogeneous and that the type of plaque present could have a bearing on clinical relevance. Plaques can be divided into echoluent and echogenic types depending on their appearance on ultrasound. The former tend to be lipid-rich, whereas the latter have a higher content of fibrous tissue and calcification [66]. The presence of echogenic plaques in the carotid artery is associated with higher aortic PWV when compared with the presence of echoluent plaques, suggesting that the presence of this type of plaque is associated with increased aortic stiffness [67]. It has also been suggested, however, that aortic stiffness can occur in the absence of atherosclerosis [68].

When interpreting results from studies in which PWV has been measured, it is critical that the characteristics of the population under investigation have been adequately assessed. This is because of the enormous potential for confounding, since many differing factors have been shown to affect PWV. For example, in renal disease, increasing PWV is linked with falling renal function, as evidenced by a falling creatinine clearance [69] or by stage of chronic kidney disease [70]. Abnormalities in PWV seem particularly common in rheumatological conditions, with raised PWV being found in rheumatoid arthritis [71], systemic lupus erythematosus in association with elevated serum homocysteine levels [72] and Takayasu’s arteritis [73]. Metabolic disease is also associated, with increased PWV being found in untreated overt [74] and subclinical [75] hypothyroidism, as well as with increasing numbers of component parts of the metabolic syndrome [76–78]. An interesting, and relatively recent finding, is the association between PWV and mental dysfunction. PWV is significantly higher than normal in patients with vascular or Alzheimer’s dementia [79]. It is significantly associated with the score obtained in a mini-mental state examination [80], as well as degree of personal dependency [81].

Within subjects, PWV can also be influenced by many factors, any of which could affect result interpretation. Tobacco smoking acutely increases PWV, particularly in black subjects [82], as does acute consumption of coffee [83]. These authors also showed that long-term consumption of coffee is associated with a PWV 13% higher than persons who do not consume coffee. Moderate alcohol consumption is associated with lower PWV, particularly in women [84]. Acute mental stress can also increase PWV significantly [85], and PWV has been shown to be higher in persons with type A behaviour [86]. The presence of Helicobacter pylori seropositivity is also related to high PWV, although there is no association in males aged over 50 years [87]. Antioxidant status may also influence PWV. For example, there is an inverse association between the levels of β-carotene and β-cryptoxanthin and PWV [88]. Drugs, such as protease inhibitors [89] and triptans [90], can also affect PWV. Furthermore, female sex hormones can affect PWV measures. In normal pregnancy, PWV falls in the second semester, increases in the third semester and falls after delivery [91].

It should also be remembered that aortic PWV is solely a measure of large artery segments [92] and offers no insight into the status of smaller blood vessels.

**Devices that analyse the pressure pulse waveform**

Although it is eminently feasible to study large central and peripheral arteries using catheterization techniques or surface tonometers, it is currently impossible to use such technologies for the direct study of small vessels. Small blood vessels constitute a considerable part of the vascular network and are preferential targets in diseases such as diabetes mellitus and hypertension. Diabetic microvascular disease includes retinopathy [93], nephropathy [94] and neuropathy [95], and accounts for considerable morbidity and mortality in affected patients.

Small arteries and resistance vessels can also influence the behaviour of larger more central arteries. Evidence of this comes from the fact that vasodilatory drugs reduce central arterial stiffness by unloading central arteries,
increasing the buffering capacity of peripheral arteries and by reducing pulse wave reflections [23]. Although aortic stiffening is a marker of advanced disease and may serve as a predictor of morbid events in the next 5–10 years, assessment of smaller arteries may allow much earlier identification of disease [8].

Small vessels with a diameter between 100 and 350 µm in the gluteal region were biopsied in healthy subjects and patients with mild hypertension [96]. It was found that subjects with the highest BP had significantly higher vessel media-to-lumen ratios. Thus structural remodelling in small arteries may precede clinically detectable target organ damage, at least in patients with hypertension. Studying only the large vessels in such individuals may potentially miss important manifestations of disease in the microvasculature. It must be acknowledged, however, that large vessels were not examined in that study, and that only LV hypertrophy was assessed as evidence of target organ damage. A further study assessing the predictive value of media-to-lumen ratios in small resistance arteries in hypertensive subjects revealed a significant association with the occurrence of fatal or non-fatal cardiovascular events [97]. The idea that changes in small arteries or end organs can have powerful predictive value for disease in large arteries is of great interest at present.

The characteristics of small blood vessels may be inferred by analysing pulse waveforms obtained in larger, more proximal, feeding vessels. Stiffening of small arteries alters the magnitude and timing of reflected waves that can often be identified visually in late systole or more reliably by computer analysis of the diastolic pressure decay part of the pressure waveform [8]. Indices derived from analysis of the diastolic decay component of a waveform have been shown to identify disease-related alterations in the mechanical properties of microcirculatory beds. A cohort of 870 subjects who underwent assessment of their small vessel stiffness in this way has been performed [98]. Although only 48 % of the cohort were followed up, 41 % had at least one cardiovascular event. A measure of small microcirculatory arterial stiffness was a significant predictor of such an event.

Identification of abnormalities in the reflected components of waveforms obtained from large arteries should therefore enable analysis of the downstream microvascular network to be made. An experiment in which dogs’ aortas were clamped at different levels successfully utilized these techniques to identify occlusions and characterize them in terms of amplitude and distance from the heart [99]. Employing computer analysis of the diastolic decay part of the arterial pressure waveform and using a Windkessel model, an assessment of C1 (large artery compliance (capacitative compliance)) as well as C2 (small artery compliance (reflective or oscillatory)) is possible [10].

A study involving patients with Type 1 diabetes mellitus without overt microvascular complications was carried out to compare C1 and C2 with a healthy control population [100]. Both measures were significantly lower in the diabetic group, showing that changes were apparent before any clinical complications had developed.

Another approach that may provide insight into the mechanical properties of small vessels is the PT/TT (peak time divided by total time) ratio of the pressure curve. This has been used to study the microcirculation in the finger in patients with Raynaud’s phenomenon [101]. This technique has, however, been criticized. A change in elasticity may not change the time to peak; the theoretical validity of correcting for total time is uncertain; peak time can be influenced by reflections from arterial endings; and the PT/TT ratio in digital arteries cannot distinguish between arterial stiffness and early wave reflections [23]. This index may therefore be prone to error in the same manner as the augmentation index in the aorta. Studies have also been carried out utilizing waveforms obtained by finger plethysmography [102,103].

As with other measures of arterial stiffness, techniques that provide information about small artery properties must be evaluated with caution. Izzo et al. [104] investigated the correlation between three measures of arterial stiffness: systolic pulse contour analysis, diastolic pulse contour analysis and cuff plethysmography. The study showed absent or weak correlations between these variables. A further study investigated agreement between different measures of vascular mechanics [27]. Although good agreement was noted between some variables (‘stiffness index’, augmentation index, and central and brachial pulse pressure) and central PWV, poor agreement was noted between other variables (C1, C2 and SV/PP ratio) and central PWV. A further source of error in pulse waveform analysis relates to the fact that frequency components of pressure and flow below the heart rate should generally be studied in order to obtain a valid estimate of compliance [105]. Since a single cardiac cycle does not contain these frequencies, the practice of estimating total arterial compliance from a single cardiac cycle is suspect under most circumstances. Unfortunately, since it is not currently possible to directly measure the mechanical properties of small vessels in vivo, results obtained by model-based analysis of arterial waveforms remain inconclusive [23] and more long-term data about the prognostic capabilities of such techniques are eagerly awaited. Pulse waveform analysis permits the identification of changes in waveforms and attempts to interpret that change in relation to a change in the mechanical properties of arteries. However, it must be remembered that this technique does not provide any direct assessment of the mechanical properties of blood vessels.

**Transfer functions**

Because of its size and elasticity, the aorta is the principal determinant of systolic arterial compliance and therefore arterial stiffness [106]. Studying the mechanical
properties of this major vessel is therefore of primary importance. However, the aorta is inaccessible to applanation tonometry, meaning that invasive techniques are necessary for accurate pressure acquisition.

It is much easier to obtain a pressure waveform from a peripheral artery such as the radial artery than from a central artery, since this can be achieved by placing a tonometer on the surface of the vessel. Mathematical processes can, however, be applied to peripherally measured waveforms in order predict the waveform in the more proximal aortic circulation. Such models, or ‘transfer functions’, have been used with some success [107–109]. The rationale for such functions is that, if the relationship between pressure waveforms in two parts of the circulation is known, the pressure waveform at one site may be deduced from data collected at the other site [110]. The mathematical functions correct for the linear filter properties of the segment of vasculature between the recorded site and the site of interest [111].

If a transfer function is to be useful, it must yield accurate and reproducible data and should be reliable on an individual as well as a group basis [112]. Unfortunately, the validity of such transfer functions has been questioned. At the site of pressure assessment, the waveform will be modified by both the pressure-dependent filter characteristics of the arterial segments through which the blood has already passed and by reflections from the distal arterial bed [111]. Thus application of the transfer function to the radial artery pressure waveform to estimate the aortic pressure waveform causes reflection to appear earlier in the cardiac cycle than is to be expected.

Transfer functions are generally derived in healthy subjects; however, it has been shown that such an approach is inappropriate for the derivation of central waveforms in Type 2 diabetes mellitus [110]. These authors report that in subjects with diabetes, there is a shorter time to the inflection point on the waveform and a trend toward a greater augmentation index. These findings would suggest that a transfer function specific to the population being studied is required.

Tonometry at peripheral arterial sites is not without its problems either. ‘Pressure bounce’ describes the phenomenon whereby the tonometer moves outwards in late systole, thus underestimating pressure and causing a trailing of the diameter of the vessel with respect to pressure in late systole and early diastole [111]. Furthermore, compression of the artery by the probe can result in reflections. Perhaps the most criticized aspect of peripherale vessel tonometry relates to calibration. Pressure calibration of tonometers is generally performed by assuming that the SBP and DBP measured by the device is equal to the BP at the brachial artery, which is usually measured non-invasively using a sphygmomanometer. Such measures are, however, notoriously unreliable at accurately assessing true BP [113]. Hope et al. [114] assessed the differences between radial waveforms calibrated to non-invasive and invasive BP, and the effect of the method of calibration on reconstruction of central waveforms by application of a generalized transfer function [114]. Non-invasive calibration resulted in a significant underestimation of central BP, making waveform analysis unreliable. This was not the case when invasively calibrated BPs were used. The authors concluded that when only non-invasive pressures are accessible, analysis of untransformed radial waveforms produces smaller errors in the estimation of central aortic pressure, and other waveform parameters, than using a generalized transfer function. A study involving 84 subjects assessed the worth of untransformed radial waveforms [115]. It was found that there was a close correlation between the augmentation index calculated from the radial artery waveform directly and that calculated from a transformed radial artery waveform ($R = 0.96$). This finding would imply that, if one is prepared to predict an aortic waveform from a radial artery waveform, there may be no worth in using a transfer function at all.

The problems with transfer functions are not restricted to waveforms obtained from the radial artery. For example, the applicability of finger–aorta transfer functions has also been questioned [116].

Augmentation index

The phenomenon of pulse wave reflection has been described in an earlier section and is fundamental to understanding the concept of the augmentation index. Near the aortic root, the initial rise in pressure following LV ejection is rapidly superimposed with a reflected pressure wave returning from the periphery [6]. These authors report that the start of this reflected wave is visible on the measured waveform as an inflection point, which has been named the augmentation point. The augmentation index is a mathematical expression of the augmentation point in the pressure domain, whereby the increment in pressure after the first systolic shoulder to the peak of the aortic pressure is calculated as a percentage of pulse pressure [117]. The augmentation index depends on the shape of the forward wave, which is influenced by LV outflow and the elasticity of the ascending aorta, as well as the timing of the reflected wave, a factor influenced by gender, height, reflected wave amplitude and vessel stiffness [6]. It must be calculated from a central arterial pressure waveform either measured directly or estimated by transforming a pressure waveform obtained from the periphery (see the previous section).

There is a positive correlation between the augmentation index and PWV, albeit a modest correlation ($r = 0.29$, $r^2 = 0.08$) [118]. This is to be expected, since a higher aortic PWV will result in faster transmission of pressure waves to the peripheries and, in turn, a faster return of reflected waves that determine the augmentation index.

Alterations in the augmentation index with disease have been investigated. A study investigating vascular
function in Type 1 diabetes mellitus revealed an increased augmentation index in tandem with elevated PWV [119], although this finding has not always been duplicated [120]. The augmentation index was found to be elevated in subjects with hypercholesterolaemia [121]. The ARYA (Atherosclerosis Risk in Young Adults) study measured the augmentation index in young men and found that heavy alcohol intake, smoking and elevated LDL (low-density lipoprotein) levels were significantly related to the augmentation index [122,123]. A combined assessment of vascular function using the augmentation index and a measure of carotid artery intimal-medial thickness has been shown to be associated with a high cardiovascular risk, as predicted by the Framingham risk score [124]. The augmentation index is significantly and inversely related to endothelial function, as assessed using brachial artery flow-mediated dilatation [45], and a significant correlation exists between hsCRP (high-sensitivity CRP; a possible marker of subclinical atherosclerosis) and the augmentation index [125].

McEnierie et al. [45] studied normal vascular aging and found that, although both the augmentation index and aortic PWV increased significantly with age, these changes were non-linear [45]. Thus the augmentation index increased more in younger individuals, meaning that it may be more sensitive than a measure of PWV at delineating arterial stiffness in younger (< 50 years old) individuals.

The prognostic significance of the augmentation index was assessed in patients with end-stage renal failure [126]. After adjustment for confounders, each 10% increase in the augmentation index was associated with a risk ratio for all-cause mortality of 1.51 and 1.48 for cardiovascular mortality. However, measurement of the augmentation index is not without its difficulties. The effects of alterations in heart rate on the augmentation index have been investigated. A significant linear relationship between the two parameters has been reported (r = -0.76) [127]. In other words, for every 10 beats/min increase in heart rate, the augmentation index fell by approx. 4%. This finding has been replicated in several studies. In patients with chronic heart failure, the augmentation index also depends on LV ejection fraction and the duration of ejection [128]. Lemogoum et al. [48] administered isoprenaline to healthy volunteers to stimulate β-adrenoceptors and studied the effects on the augmentation index. Although administration of the study drug resulted in a significant reduction in the augmentation index and peripheral PWV, the aortic PWV did not change. Thus, in this study at least, the augmentation index failed as a surrogate measure of aortic stiffness determined by PWV, presumably because drug-induced changes in the peripheral circulation, not the aorta, influenced wave reflections.

As mentioned above, the augmentation index must be calculated from a central arterial waveform. If a transfer function is used to predict the central waveform from a peripheral waveform, it is questionable as to whether there is any merit at all in calculating the augmentation index. Hope et al. [112] calculated the augmentation index both directly and from a transfer function-derived waveform. They showed that the scatter between directly measured and indirectly predicted augmentation indices was so marked that the measures were not significantly correlated.

Since the augmentation index can be affected by multiple factors (LV ejection, PWV, timing of reflection, arterial tone, structure at peripheral reflecting sites, BP, age, gender, height and heart rate) and the concern over the accuracy and validity of central augmentation index derivation from pulse waveform analysis, it is difficult to see how it can provide clinically useful data in the assessment of intervals with hypertension or cardiovascular comorbidity [129].

Local assessment of mechanical properties
Arterial compliance is defined as the change in arterial blood volume for a given change in arterial BP.

\[
C = \frac{\Delta V}{\Delta P}
\]

where C is compliance, \(\Delta V\) is the change in arterial blood volume and \(\Delta P\) is the change in arterial BP. By simultaneously measuring the diameter of a blood vessel and the BP in that area, compliance can be directly calculated. Diameters can be measured using ultrasound or MRI (magnetic resonance imaging). The so-called β-index is derived from a logarithmic transformation of the curvilinear relationship between pressure and diameter, as measured using an oscillometric arm cuff and an ultrasound probe [130].

The measurement of distending pressure is more difficult. This is because (i) it is difficult to physically place a pressure sensor next to an ultrasound probe; (ii) invasive pressure catheters probably influence local flow and are not suitable for routine use; and (iii) the use of pressure waveforms taken elsewhere in the circulation can introduce pressure errors and phase delay [131]. Accurate measurement of compliance has been carried out using an intravascular ultrasound device with pressure transducer [132]. The addition of an external cuff allows investigators to vary transmural pressure and, thus, calculate wall stress. Pressure waveforms can also reliably be extrapolated from diameter waveforms [131]. Thus a measure of compliance can be obtained by tracking the diameter change in a vessel wall.

It is important to appreciate that arteries are not homogenous tubes, and compliance can vary in different parts of the same vessel. For example, in older subjects and in those with borderline hypertension, the loss of distensibility of the carotid artery is most pronounced in the carotid artery bulb [133].
Other methods for assessing arterial stiffness

AASI (ambulatory arterial stiffness index)

ABPM (ambulatory BP monitoring) is commonly used to assess an individual’s BP over a 24 h period. It has been suggested that data obtained in this way can better predict cardiovascular risk and target organ damage than any solitary measure of BP measured at a clinic [134]. ABPM involves measuring BP at regular intervals over a 24 h period and typically approx. 70 readings are recorded. It has been postulated that the relationship between SBP and DBP over a range of values might provide information about the stiffness of the arterial tree. ABPM provides a simple method of obtaining multiple measures of BP.

AASI describes, in a single number, the dynamic relationship between DBP and SBP over 24 h [135]. The index may principally reflect the mechanical properties of small arteries [136]. The technique is an extension of the hypothesis proposed in 1914 that loss of arterial elasticity influences the height of DBP and its relationship to SBP [137]. AASI is calculated by plotting a scatter diagram of SBP against DBP readings. A regression line is drawn and the AASI calculated as 1 — the gradient of this line [138]. The authors report that, as arterial stiffness increases, the gradient approaches 0 and the AASI approaches 1.

In healthy volunteers, a significant correlation was found between AASI and aortic PWV \( r = 0.51, P < 0.0001 \) [138]. The Dublin Outcome Study assessed the predictive value of AASI for cardiovascular mortality [139]. In a regression analysis, AASI predicted cardiovascular mortality after adjustment for traditional risk factors. When adjusted for pulse pressure, however, AASI lost predictive power for cardiac or cardiovascular mortality; it continued to predict fatal stroke. In a separate study, Leoncini et al. [140] studied untreated patients with primary hypertension. After statistical adjustment, each S.D. increase in AASI conferred approx. a 2-fold increased risk of microalbuminuria, carotid intimal-medial thickness or LV hypertrophy.

The measurement of AASI appears to be a straightforward method of assessing arterial stiffness. It utilizes readily available equipment with which most physicians are familiar. It has, however, come under criticism [141]. The simple fact that AASI is correlated with PWV does not necessarily mean that the two variables are linked mechanistically as (i) AASI may not remain significantly correlated to PWV after full adjustment for confounders; (ii) the predictive value of AASI is lower than the predictive value for PWV; and (iii) measurement of aortic PWV is much less time-consuming and less distressing for patients. At present, further studies are required before reliance should be made on AASI for robust assessment of arterial stiffness.

THERAPIES TARGETING ARTERIAL VESSELS

At present, there are few published studies that directly assess the effects of therapeutic intervention on arterial stiffness and no outcome studies on the long-term efficacy of such agents. There is some evidence that arterial mechanics can be improved by treatment with statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) [142–145], inhibitors of the renin–angiotensin system [146–150] and \( \beta \)-adrenoceptor antagonists [151]. When interpreting the results from such studies, one must ensure that adequate care has been taken to allow for potential confounding factors, such as other haemodynamic actions of the drugs concerned. Current best practice for managing cardiovascular risk would be the most appropriate therapeutic strategy in such patients. A pragmatic approach should be adopted, however. For instance, a common clinical manifestation of arterial stiffening is isolated systolic hypertension. Current guidelines for the treatment of this diagnostic entity rely on conventional antihypertensive drugs which, by lowering DBP, could paradoxically result in adverse clinical consequences due to a reduction in coronary perfusion [21]. A study of the effect of antihypertensive therapy in patients with end-stage renal failure revealed a worse prognosis for patients with arterial stiffening, if the antihypertensive therapy failed to improve stiffness [152].

Non-enzymatic glycation of protein is a process involving the modification of tissue proteins by physiological sugars in vivo [153]. The sugar-derived modifications are called AGEs (advanced glycation end-products), and these form a heterogeneous group of glycated structures which are found in plasma and accumulate in blood vessel walls and other tissues [154]. It has been hypothesized that AGEs play a role in the development of arterial stiffening [21], and therapies targeting AGEs have recently been developed. AGE-modifying drugs are only one example of how assessment of vascular stiffness could add value to clinical outcome trials in novel therapeutic agents. Since drugs affecting AGEs target arterial walls without affecting systemic haemodynamic parameters, their true effects on arterial mechanics can confidently be assessed.

Two main classes of drugs can attenuate the effects of AGEs. Inhibitors of AGE formation, such as aminoguanidine, have been used with some effect in animals. For example, treatment of normotensive rats with aminoguanidine resulted in a 20 % reduction in PWV [155]. Human studies have, however, been somewhat less hopeful. ACTION I (the first Aminoguanidine Clinical Trial in Overt Type 2 Diabetic Nephropathy) studied the effects of administration of pimagedine, another inhibitor of AGE formation, for between 2 and 4 years in patients with Type 1 diabetes mellitus with nephropathy and retinopathy [156]. The primary end point of the study was...
the time to doubling of serum creatinine, and this was not significantly altered by pimagedine. The drug did, however, significantly reduce proteinuria, and patients taking it had less progression of retinopathy. The follow-on ACTION II study was unfortunately halted prematurely due to drug toxicity [157]. The results of clinical testing of less toxic inhibitors of AGE formation, such as pyridoxamine, ALT-946 and OPB-9195, are awaited with interest [21].

The second class of compound are agents which break down established AGE crosslinks. Animal studies of the thiazolium derivative ALT-711 (3-phenacyl-4,5-dimethylthiazolium chloride) have shown promising results, linking the drug to an improvement in arterial stiffness [158], LV stiffness [159], erectile dysfunction [160], SBP and proteinuria [161]. Human studies with these drugs are few. In one study, 92 humans with evidence of vascular stiffening (pulse pressure $\geq 60$ mmHg, SBP $\geq 140$ mmHg and large artery compliance $\leq 1.25$ ml/mmHg) were given ALT-711 or placebo for 56 days. ALT-711 treatment resulted in a significant rise of 15% in total arterial compliance and a significant 8% reduction in PWV [162]. Treatment of patients with diastolic heart failure resulted in significant improvements in LV mass, LV diastolic filling and quality of life [163].

CONCLUSIONS

Alteration of the mechanical properties of arteries is, without doubt, of considerable prognostic significance for many patients. Attempts to quantify deviations from normality have been made, but none of the methods currently available is perfect. The fact that there is a confusing array of devices on the market, each producing results pertaining to different aspects of vascular structure and function, should not discourage clinicians [164]. No measure currently represents a complete description of wall properties and all techniques have theoretical, technical and practical limitations [1]. Devices which aim to detect changes in more than one section of the circulation simultaneously have, to date, not been successful.

A complete understanding of the ‘stiffness’ of the circulation might only be made possible by interrogating the vasculature at various levels using several devices. The concept of a total stiffness index, which might take into account, for example, PWV in the aorta and pulsewave-analysis-derived indices of the small vessels, may allow this to be done.

The development of therapies specifically designed to target the arterial wall is welcomed. Whether or not such treatments can affect the long-term prognosis of patients with stiff arteries remains to be seen. Much more research is required in this exciting and challenging area of medicine.

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