Assessment of arterial stiffness in clinical practice

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Introduction

There has been much recent interest in the relationship between arterial stiffness and cardiovascular disease. Pulse pressure and pulse wave velocity, surrogate measures of arterial stiffness, indicate that arterial stiffness increases both with age and in certain disease states that are themselves associated with increased cardiovascular risk, including hypertension, diabetes mellitus, hypercholesterolaemia and end-stage renal failure. As changes can be detected before the appearance of clinically apparent vascular disease, arterial stiffness may act either as a marker for the development of future atherosclerotic disease, or may be more directly involved in the process of atherosclerosis. Arterial stiffening has been particularly implicated in the development of isolated systolic hypertension, a disease mainly affecting the elderly population and associated with considerable excess morbidity and mortality.

Arterial stiffness may be measured using a variety of different techniques, although at present the majority of measurements are made for experimental and physiological studies rather than in clinical practice. However, it is likely that over the next few years measurement of arterial stiffness will become an increasingly important part of the process of risk assessment, and may possibly also improve the monitoring of therapy in patients with conditions such as isolated systolic hypertension. Therefore, it will become necessary for physicians both in primary care and hospital practice to understand the importance of arterial stiffness and the techniques available for its clinical assessment, which will be the focus of this review.

Historical perspectives

Assessment of the arterial pulse has always been an important part of clinical examination, and the ancients recognized that changes in the character of the pulse indicated the presence of disease. However, the ‘golden era’ of the pulse was the 19th century. With the development of the sphygmograph by Marey and its refinement over the next few years by Mahomed, Broadbent and Mackenzie, the art of interpreting the shape of the arterial waveform, or sphygmcadiography, began. Mahomed noted important differences in the shape of the waveform with age and the pre-albuminuric stage of Bright’s disease (now thought to be essential hypertension), with a late systolic peak and little or no diastolic fluctuation. However, stiffening of the arteries was thought to be an inevitable consequence of ageing, and its clinical significance was not fully appreciated by many. Nevertheless, Roy commented as early as 1880 that with increasing age the stiffness of the arteries changed, and that this might have significance for the health of the individual: ‘Only in the case of young children do we find that the elasticity of the arteries is so perfectly adapted to the requirements of the organism as it is in the case of the lower animals.’
However, when the modern mercury sphygmomanometer was developed by Riva-Rocci in 1896, clinicians began to concentrate more on the absolute values of systolic and diastolic blood pressure rather than on the shape of the waveform, thereby disregarding important qualitative information in favour of information covering only the extremes of pressure. Indeed, as Lord Kelvin suggested, sphygmomanometry was considered far more scientific: ‘When you can measure what you are speaking about, and can express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind’ (Lord Kelvin, 1891).

Thus, by the early 20th century, sphygmocardiography was in rapid decline and the sphygmomanometer has dominated ever since. Only recently have clinicians re-discovered the importance of the arterial waveform and arterial stiffness, hence spawning a variety of different measurement techniques.

Definitions

The terminology used in the field of arterial stiffness can be confusing. Terms are often used interchangeably when in fact they have slightly different meanings. Therefore, the generic term ‘arterial stiffness’ is used in the present review to avoid confusion. In simple terms, arterial stiffness describes the rigidity of the arterial walls. Other terms used to describe the properties of vessel walls are defined in Table 1. Important indices include compliance, elasticity (or elastic modulus), distensibility and vascular impedance. However, interpretation of these indices can be complicated, especially

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<tr>
<td>Elastic modulus**</td>
<td>The pressure change required for theoretical 100% stretch from resting diameter ((\Delta P \times D)/\Delta D) (mmHg)</td>
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<tr>
<td>Young’s modulus**</td>
<td>Elastic modulus per unit area ((\Delta P \times D)/(\Delta D \times h)) (mmHg/cm)</td>
<td>Ultrasound* MRI</td>
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<tr>
<td>Arterial distensibility**</td>
<td>Relative change in diameter (or area) for a given pressure change; inverse of elastic modulus (\Delta D/(\Delta P \times D)) (mmHg(^{-1}))</td>
<td>Ultrasound* MRI</td>
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<tr>
<td>Arterial compliance**</td>
<td>Absolute diameter (or area) change for a given pressure step (\Delta D/\Delta P) (cm/mmHg) or (cm(^2)/mmHg)</td>
<td>Ultrasound* MRI</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>Velocity of travel of the pulse along a length of artery Distance/(\Delta t) (cm/s)</td>
<td>Pressure waveform* MRI</td>
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<td>Augmentation index</td>
<td>The difference between the second and first systolic peaks as a percentage of pulse pressure</td>
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<td>Stiffness index ((\beta))**</td>
<td>Ratio of (\ln(\text{systolic/diastolic pressures})) to (relative change in diameter) (\beta = \frac{\ln(P_s/P_d)}{(D_s - D_d)/D_d})</td>
<td>Ultrasound*</td>
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<td>Relationship between oscillating pressure change and oscillating volume change around the exponential pressure decay during diastole (\Delta V/\Delta P) (cm(^3)/mmHg)</td>
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P, pressure; D, diameter; V, volume; h, wall thickness; t, time; v, velocity; s, systolic; d, diastolic. *Most common method of measurement; **Also requires pressure measurements.
because many are dependent on blood pressure. In this respect, the stiffness index ($\beta$) may be more useful because it is less dependent on blood pressure.

Vascular impedance relies on consideration of the circulation as an electrical circuit. Impedance describes the relation of forces acting in the circulation to the motion of blood. However, in order to calculate impedance, it is necessary to measure pressure and flow simultaneously at one point in the circulation, which has limited its widespread usage. Different types of impedance values can be calculated. Characteristic impedance is probably the most useful, and describes the ratio of pressure to flow, assuming no reflected waves are present. In contrast, input impedance describes the impedance in the whole of the vascular bed distal to the catheter, and thus is influenced by wave reflection. Terminal impedance approximates to peripheral vascular resistance, and longitudinal impedance is the ratio of the pressure gradient to flow and describes the impedance only in the local segment of artery being studied.

**Methods of measuring arterial stiffness**

There are several different methods of assessing arterial stiffness, some of which are more widely applicable in the clinical setting than others. Several techniques give information on systemic arterial stiffness, while others only give information on local stiffness of the vessel being studied.

**Pulse pressure**

The pulse pressure is simply the difference between systolic and diastolic pressures, and depends on the cardiac output, large-artery stiffness and wave reflection. Indeed, pulse pressure is a valuable surrogate marker for arterial stiffness, as recognized in 1922 by Bramwell and Hill: 'Hence the difference between systolic and diastolic pressure, that is the pulse pressure, other things being equal will vary directly as the rigidity of the arterial walls.'

Both systolic and diastolic blood pressures tend to increase with age (Figure 1). However, beyond the age of 50–60 years there is no further increase in diastolic blood pressure and, in many cases, it actually declines. Thus, with increasing age, the pulse pressure widens.

Pulse pressure can be measured using a standard sphygmomanometer. It is one of the simplest measures of arterial stiffness, and easily practicable in the clinical setting. However, some oscillometric sphygmomanometers may be unreliable in older subjects. Moreover, pulse pressure alone is inadequate to assess arterial stiffness accurately. Problems include the ‘normal’ amplification of the pressure wave as it travels from the aorta to the periphery, although this effect becomes less pronounced with increasing age. Thus, measurements of pulse pressure made in the periphery, for example in the upper arm, do not always accurately reflect the actual central pulse pressure. Indeed, there can be differences of up to 20 mmHg between central pressures of patients with identical brachial blood pressure readings. Interestingly, exaggerated amplification is thought to account for the phenomenon of pseudohypertension in the young. Central pressure may, therefore, be a more accurate predictor of risk than peripheral blood pressure. Moreover, it is central pressure that contributes most to the development of left ventricular hypertrophy, itself an independent predictor of cardiovascular mortality, and changes in left ventricular geometry. Also, carotid intimal medial thickness, a marker of cardiovascular risk, is dependant on carotid but not brachial pulse pressure.

A number of studies have shown that pulse pressure is an important predictor of risk. Data from the Framingham study in the US demonstrate that in hypertensive patients, the pulse pressure is a better predictor of coronary heart disease risk than either systolic or diastolic pressure alone, in the over-50s. This finding was confirmed in the MRC mild hypertension trial and a long-term follow-up study of normotensive and hypertensive French men. Further data in subjects post-myocardial infarction and with impaired left ventricular function support this view. In addition, pulse pressure predicted
both stroke and all-cause mortality in the SHEP (Systolic Hypertension in the Elderly Program) population.\textsuperscript{23} Aortic pulse pressure also predicts restenosis after percutaneous transluminal coronary angioplasty\textsuperscript{24} and aortic dilatation in subjects with Marfan's syndrome.\textsuperscript{25} Conversely, in the under-50s, diastolic pressure is probably the best predictor of coronary heart disease risk, suggesting that peripheral vascular resistance rather than arterial stiffening is the dominant pathophysiological mechanism regulating risk.

**Pulse wave velocity**

The pulse wave velocity is the speed at which the forward pressure wave is transmitted from the aorta through the vascular tree. It is calculated by measuring the time taken for the arterial waveform to pass between two points a measured distance apart, and involves taking readings from the two sites simultaneously, or gating separate recordings to a fixed point in the cardiac cycle, usually the R wave of the ECG. Various different methods have been used, both invasive and non-invasive, and can be applied to either flow or pressure waves. The important point is the reference point on the waveforms. Indeed, foot-to-foot methodology is usually used, as it avoids the confounding influence of wave reflection.

Problems with this technique include the inaccessibility of the central arteries, necessitating compromise by using the nearest superficial arteries. There can also be some difficulty in estimating the actual arterial distance between recording sites using only surface measurements.\textsuperscript{26} The pulse wave velocity becomes less accurate if the recording points are very close together, and the technique is, therefore, limited to use on the larger arteries. Pulse wave velocity provides information on the distensibility of the local vessel being studied, rather than on systemic arterial stiffness; distensibility being inversely related to stiffness. The Moens Korteweg equation can be used to calculate the pulse wave velocity (PWV):

\[
PWV = \sqrt{\frac{EH}{2\rho}}
\]

where \(E\) = Young’s modulus of elasticity of wall material, \(h\) = wall thickness of vessel, \(r\) = inside radius of vessel and \(\rho\) = density of blood).

A more useful version of this equation is the Bramwell and Hill equation, which relates PWV to distensibility:

\[
PWV = \frac{\Delta PV}{\Delta PV \rho} = \frac{1}{\rho D}
\]

where \(\Delta PV/\Delta V\) = relative volume elasticity of vessel segment, \(\rho\) = density of blood, and \(D\) = distensibility.

The technique of pulse wave velocity is valid and reproducible, and has been widely applied in both normal volunteers and patients in the research setting. The principle is relatively simple and the technique can be learned fairly easily. Moreover, outcome data show that pulse wave velocity is an independent predictor of cardiovascular risk in both hypertensive patients and patients with end-stage renal disease.

More recently, an alternative method of measuring pulse wave velocity has been described that uses a Magnetic Resonance Imaging technique.\textsuperscript{27} This allows accurate path length to be assessed and measurements to be made from ‘inaccessible arteries’, but is expensive, time-consuming and can only be applied to relatively large arteries at the present time.

**Ultrasound-derived indices (Figure 2)**

Ultrasound can be readily used to measure arterial stiffness (distensibility and compliance), but its use is limited to the larger and more accessible arteries. Hence this technique has been used mainly on the brachial, femoral and carotid arteries and the abdominal aorta. Several images of the vessel wall are obtained per cardiac cycle, and the maximum and minimum areas of the vessel are calculated by wall tracking and computerized edge-finding software. Distensibility and hence compliance (inverse of stiffness) can be calculated using the following formulae if blood pressure is also recorded:

\[
\text{Distensibility} = \frac{\Delta V}{\Delta P \sqrt{V}}
\]

\[
\text{Compliance} = \frac{\Delta V}{\Delta P}
\]

where \(\Delta V\) = change in volume, \(\Delta P\) = change in pressure, and \(V\) = volume.

Problems with the use of ultrasound to assess arterial stiffness include the limited resolution, which can make the detection of very small changes in vessel diameter difficult. The technique also relies heavily on the ability of the operator to image the walls of the vessel being studied accurately, and there have been some concerns about the reproducibility of the technique, although with an experienced operator this can be improved. The technique can be made less operator-dependent by introducing measures such as fixing the ultrasound transducer in a robotic arm, and maintaining the arm of the subject in a fixed position using a groove or brace.
It is necessary to measure blood pressure simultaneously. This is usually done in the brachial artery or finger, which may not be appropriate if distensibility is being assessed in a more central artery, for example the aorta, due to the normal phenomenon of pressure wave amplification towards the periphery. Moreover, finger blood pressure is not necessarily a reliable measure of brachial blood pressure. It is unclear whether information obtained from one particular site can be generalized to the rest of the vasculature.

Although ultrasound has the advantage of being non-invasive, the imaging equipment required is not easily portable, and is expensive. Thus the use of ultrasound in determining arterial stiffness has been largely confined to the research setting to date. However, in the ARIC study, ultrasonic determination of carotid arterial distensibility showed that a lower carotid distensibility increased the risk of developing hypertension in the future.28

MRI-derived indices

Magnetic resonance imaging (MRI) techniques have been used to measure vascular distensibility and compliance. Most of the human studies have been based on measurements of the aorta. MRI has been used to demonstrate the inverse relationship between aortic distensibility and age, that aortic distensibility is reduced in hypertensive patients,29 and that arterial compliance is reduced in patients with coronary artery disease but increased in athletes.30 Although MRI has the advantage of being non-invasive, it remains expensive, and the availability of scanning facilities is limited. Therefore, the place of this technique in clinical practice is doubtful, although it continues to be used in research.

Waveform analysis

The pressure waveform was first recorded and analysed at the end of the 19th century using the sphygmograph, and since then numerous other methods of analysing the arterial waveform have been developed including the vasculograph,31 various invasive devices and, more recently, non-invasive applanation tonometry. The arterial pressure and volume waveforms differ, and it is important to note that some methods record the pressure waveform whilst others record the volume waveform (Figure 3).

The arterial waveform

The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave. Waves are
reflected from the periphery mainly at branch points or sites of impedance mismatch. Therefore, the arterial waveform varies throughout the arterial tree. The velocity at which the pressure wave travels through the vasculature is influenced by the stiffness of the vessel walls—the stiffer the walls, the higher the velocity. In elastic vessels, the reflected wave tends to arrive back at the aortic root during diastole, serving to augment diastolic pressure and hence improve coronary artery perfusion. In the case of stiff arteries, the reflected wave arrives back at the central arteries earlier, causing augmentation of the systolic pressure and a consequent decrease in diastolic pressure. High central systolic pressures hasten the development of left ventricular hypertrophy, whereas low diastolic pressures reduce coronary artery perfusion. The amplitude of the reflected wave also increases as the arterial stiffness increases, further augmenting central systolic pressure.

The O’Rourke Pulse Wave Analysis (PWA) system is a simple, non-invasive, validated method of measuring arterial stiffness. Applanation tonometry (Figure 4) is used to record pressures at the radial or carotid artery, and a validated generalized transfer factor is then applied to derive the corresponding central waveform. From this, the augmentation index, which is the difference between the first and second systolic peaks expressed as a percentage of the pulse pressure, and a measure of systemic stiffness, can be derived. It is also possible to estimate the central arterial pressure from the peripheral waveform. The estimation of augmentation index using this technique is more reproducible than blood pressure as assessed by some automated sphygmomanometers. The tonometer is the size of a pen; the system is easily portable and, therefore, useful in both hospital and clinic settings.

Tonometers consisting of an array of pressure transducers are also available. The sensor is placed over the radial artery and held in place by a strap around the wrist. The system automatically readjusts itself to detect the best possible pressure waveform. The advantages of such systems include less operator dependency than with a hand-held tonometer, and continuous measurements for dynamic investigational studies.

Pressure waveform analysis has also been performed more distally on the digital artery using a servocontrolled pressure cuff. One such example is the Finapres system, which has been successfully used to measure the arterial waveform. However, there are some reservations about this method, in that the recorded waveform may be significantly damped and, therefore, any derivations of central pressure may be less accurate.

Pressure pulse contour analysis is another method which has been used to estimate arterial stiffness non-invasively. This technique involves tonometry, again at the radial artery, but the compliance is derived differently, using a modified Windkessel model of the circulation and an assessment of diastolic pressure decay. This method calculates large-vessel and peripheral compliance. Augmentation index and peripheral compliance, as calculated by pulse contour analysis, are related.
but augmentation index more accurately reflects drug-induced haemodynamic changes. Pressure pulse contour analysis requires estimation of cardiac output from an algorithm. The technique does not provide any information on central pressures or augmentation index. Also, it may be less accurate than the techniques described above, as the theoretical model depends on the diastolic component of the waveform, which tends to be less reliably recorded than the systolic component. Most of wave reflection occurs in systole rather than diastole. Also, the point at which diastole is assumed to start and the point in diastole from which the exponential decay is calculated may be affected by the reflected wave, leading to further inaccuracies.

Photoplethysmography has been used to record the digital volume pulse. This technique resembles that of pulse oximetry, and measures the transmission of infrared light through the finger, thus detecting changes in flow and producing a volume waveform. It has been used to develop a stiffness index and a reflection index that are thought to reflect systemic arterial stiffness, and is now commercially available. Problems include the damping of the peripheral pulse, and temperature-dependant changes in the peripheral circulation. A study that compared photoplethysmography of the digital volume pulse with pulse wave velocity, found that pulse wave velocity correlated more closely with the expected influences on vascular compliance, namely age and atherosclerosis. However, the technique has the advantages of being relatively simple and easily portable. If it were to be validated, it would have potential uses in the clinical setting.

**Other methods**

Arterial stiffness can also be estimated from oscillometric blood pressure measurement. As the cuff is deflated, oscillations are increased, reaching a peak at mean arterial pressure. The pattern of oscillations depends on arterial stiffness, therefore, by coupling this to a computer algorithm, an index of arterial stiffness can be calculated. This method has been shown to be reproducible, and is currently being evaluated in outcome studies and clinical practice.

**Conclusions**

Over 100 years ago, arterial stiffness was recognized as important in predicting cardiovascular disease. In recent years, there has been a rediscovery of this insight. Methods of measurement have been refined since the early attempts at analysis, and we now have several relatively simple non-invasive methods of measuring the arterial waveform and arterial stiffness. Some of these methods simply assess local stiffness in the particular vessel being studied, while other methods are more generalizable to the systemic circulation. Others even allow estimation of central pressures. Outcome studies are now underway to assess the importance of arterial stiffness. Pulse wave analysis is included in the ASCOT study in hypertension, the SEARCH study in hypercholesterolaemia and the FIELD study in type II diabetes mellitus, to assess whether arterial stiffness measurements can predict future cardiovascular events. The results of these studies should help to clarify the position of assessment of arterial stiffness in clinical practice. At present, measurements are being used in the research setting and also as part of cardiovascular risk prediction clinics. There is scope for using these techniques to assess the response to different classes of antihypertensive medications, particularly in the case of isolated systolic hypertension, which is largely a disease of arterial stiffening. As the various techniques become simpler, less expensive and more widely available, it is conceivable that the measurement of arterial stiffness could become an important part of the routine assessment of patients, both in the primary-care setting and in hospital practice.

**Acknowledgement**

We would like to thank Mrs Carole Turner, Radiographer, Addenbrooke’s Hospital, Cambridge for Figure 2.

**References**


