Evaluation of mechanical arterial properties: clinical, experimental and therapeutic aspects

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ABSTRACT

Ageing and disease states associated with an increase in cardiovascular events alter the physical characteristics of blood vessel walls and impair the pulsatile function of arteries. An accumulating body of evidence indicates that impaired pulsatile function of arteries provides important prognostic and therapeutic information beyond that provided by traditional blood pressure measurements. A variety of techniques are currently employed to evaluate the mechanical properties of arteries. All techniques have theoretical, technical and practical limitations that impact on their widespread application in the clinical setting and use as measurement tools to improve cardiovascular risk stratification. A detailed discussion of these issues forms the basis of this review.

INTRODUCTION

The complications of cardiovascular disease represent the leading cause of morbid and mortal events in Western society [1]. A number of expert panels have published classification schemes and guidelines designed to aid diagnosis, assess severity and determine prognosis in patients with risk factors for cardiovascular disease [2,3]. The recommendations emphasize the role of high blood pressure, cholesterol and glucose as examples of major risk factors that exhibit strong, positive and continuous relationships with the risk of cardiovascular disease, even within defined normal ranges. Clearly the definition of what constitutes a target requiring intervention is somewhat arbitrary given the continuous graded relationship between these risk factors and the occurrence of cardiovascular events, but deemed necessary for practical reasons relating to patient assessment, treatment and cost.

RATIONALE FOR ASSESSING ARTERIAL MECHANICAL PROPERTIES

The development and progression of arterial vascular disease is a multifactorial process and abnormalities in individual risk factors, viewed in isolation, are poor predictors of risk [4,5]. Whereas the relative risk of cardiovascular events increases with the magnitude of disturbance in each of these risk factors, the population attributable risk, a function of relative risk and the percentage of the at-risk population, is greater for the vast majority of individuals who exhibit relatively minor alterations in traditional risk factors [6,7]. Thus the majority of the at-risk population have normal or only minor abnormalities in classical risk factors that would be below present thresholds for intervention, but nevertheless act in concert to detrimentally impact on arterial wall integrity and accelerate the development of atherosclerosis. Risk factors for cardiovascular disease mediate their effects by altering the structure, properties and function of wall and endothelial components of the arterial blood vessels that vary between different vascular beds [8–10]. The ability to detect and monitor sub-clinical damage, representing the cumulative and integrated influence of risk factors in impairing arterial wall integrity, holds potential to further refine cardiovascular risk stratification and enable early intervention to prevent or attenuate disease progression [11].

The importance of assessing arterial wall integrity has been highlighted by studies demonstrating that a reduction in the pulsatile function of large arteries represents
an independent risk factor for future cardiovascular events [12–18]. Accumulating evidence suggests that abnormalities in the pulsatile characteristics of arteries occur early in the disease processes associated with increased cardiovascular risk, and can be favourably modified by therapeutic interventions [19–21]. Impaired pulsatile arterial function is recognized as an independent predictor of risk for vascular events with ageing and various disease states, including coronary heart disease, congestive heart failure, hypertension and diabetes mellitus [12–18]. For example, Vaccarino et al. [15] found a 10 mmHg increase in pulse pressure, employed as a measure of arterial stiffness (generic term to describe the resistance to deformation of an artery), was associated with a 12% increased risk of coronary heart disease and a 14% increased risk of congestive heart failure. The association with pulse pressure persisted after incorporation of other blood pressure variables into the statistical model [15]. An increase in the pulsatile component of haemodynamic load can detrimentally impact on ventricular performance and may limit coronary perfusion [22]. Changes in the mechanical behaviour of blood vessels can also influence growth and remodelling of all sections of the arterial vasculature, and potentially influence the development and progression of arterial disease [23]. Emerging results support the concept that the cardioprotective actions of drug interventions may, at least in part, be dependent on favourably influencing these processes in blood vessels and not simply changing arterial blood pressure [24]. Measures that provide more direct information in relation to changes in arterial wall integrity with ageing and disease clearly hold predictive and therapeutic potential [25,26]. The pathophysiological consequences of impaired pulsatile characteristics of the arterial circulation are outlined in Figure 1.

**PULSATILE AND STEADY-STATE HAEMODYNAMICS IN THE ARTERIAL SYSTEM**

The arterial system is composed of a branching network of elastic conduits and high resistance terminals, which constitutes a hydraulic filter converting the intermittent output from the heart into steady capillary flow [27]. For maximal efficiency this function should be achieved with the least possible energy expenditure. To minimize cardiac work during systole in this pulsatile system, the normal arterial bed provides a low input impedance (impedance input is described as the ratio of pressure and
flow at a given site, which is considered to be the input to the vascular tree distal to that site) or opposition to left ventricular ejection [28,29]. This is accomplished in the periphery by desirable arterial elastic properties and geometric proportions to achieve optimal coupling between the left ventricle and the peripheral circulation. Therefore the peripheral circulation impart an impedance (described as the total opposition to flow offered by the arterial system) load on the heart, which physiologists and clinicians have attempted to quantify by analysing altered pressure–flow relationships and the pulse contour parameters produced through the effects of ageing and disease on the structural and functional components of the arterial system [30].

Traditionally, the arterial circulation has been considered a steady-flow system characterized by mean arterial pressure that represents the product of cardiac output and total peripheral resistance [31]. Diastolic pressure has often been regarded as a surrogate measure of peripheral resistance that is viewed as an approximation of the steady-flow load. The resistance calculation reflects changes in tone, capillary density or in the wall thickness-to-lumen ratio in the media of the microvasculature [32]. The measure provides information about a change in calibre, principally of the arteriolar and capillary bed where most of the resistance to flow in the circulation resides [33]. By acting as a variable resistor, this section of the vasculature serves the function of regulating blood flow to meet tissue requirements. The steady-state haemodynamic approach views the heart as a continuous pump ejecting a constant output into a lumped resistance. Although this model describes a stable perfusion pressure and continuous blood flow, it ignores the pulsatile component of the haemodynamic load buffered by the elastic properties of the arterial blood vessels [34].

The arterial pulse waveform is derived from the complex interaction of the left ventricular stroke volume, the physical properties of the arterial tree and the characteristics of the fluid in the system [35]. The principal components of blood pressure comprise both a steady component (mean arterial pressure) and a pulsatile component (pulse pressure) [36]. The pulsatile component of pressure is determined by the pattern of left ventricular ejection, the stroke volume and the compliance characteristics of the arterial circulation [37]. Arterial compliance is defined as a change in area, diameter or volume of an artery or arterial bed for a given change in pressure [38]. Arterial compliance estimates, therefore vary with alteration in the physical properties and geometry of blood vessels [39]. Pulse pressure for any given ventricular ejection and heart rate will depend on arterial compliance, and the timing and magnitude of peripheral pulse wave reflection. A reduction in arterial compliance or an increase in systemic resistance will increase the systolic blood pressure. By contrast, diastolic blood pressure rises with an increase in systemic resistance, but falls with impaired compliance characteristics of central arteries; the relative contribution of each parameter determining the ultimate diastolic blood pressure [36]. The fall in diastolic blood pressure associated with a decrease in arterial compliance is explained by the greater peripheral run-off of the stroke volume during systole and impaired elastic recoil of the aorta, which buffers the drop in blood pressure during the diastolic interval. An appreciation of pulsatile and steady-state haemodynamics provides a pathophysiological explanation for the paradox of coronary heart disease risk being directly related to diastolic blood pressure when considered alone, and inversely related when systolic and diastolic blood pressure are analysed together [40].

**BLOOD VESSEL STRUCTURE**

Although the concepts related to the direct assessment of mechanical wall properties of blood vessels are gaining wider recognition in the research community, important barriers remain to be overcome before general acceptance is gained in the clinical arena. The lack of a ‘gold standard’ has fostered the growth of a variety of techniques and methodologies to derive measures of mechanical wall properties. This diversity makes the comparisons of results from different laboratories difficult if not impossible [41,42]. The descriptive terms representative of the mechanical properties of arteries are generally unfamiliar to physicians, and the constitutive relationships between the descriptors and their physiological counterparts in the circulation can be abstract and difficult to grasp. Individual descriptors representative of mechanical wall properties are conceptually related but not synonymous [43], and have been the subject of debate and dispute even amongst experts in the field [44-48]. For example, arterial stiffness has been employed as an all encompassing term to include arterial compliance, arterial distensibility (change in diameter or area \((\Delta A/A)\) for a given change in pressure \((\Delta P)\)), elastic modulus (the change in stress for a given change in strain of the wall materials), volume-elastic modulus, Young’s modulus, pulse-wave velocity (speed of travel of a pressure or flow pulse along an arterial segment), characteristic impedance (the ratio of pressure and flow in an artery when pressure and flow waves are not influenced by wave reflection), stiffness index \((\beta)\), capacitative compliance and oscillatory compliance as measures representative of the mechanical properties of arteries [48]. These issues further confound interpretation of studies that employ different techniques to measure aspects of local, segmental or global properties of arterial vessels associated with ageing or disease, or changes in response to therapeutic interventions. Techniques that can provide quantitative estimates of arterial wall properties are outlined in Table 1.
Table 1 Methods used to estimate the mechanical properties of arteries

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<td>TTE/TEE</td>
<td>TTE non-invasive, reasonable availability</td>
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Anatomically the arterial wall is composed of three concentric zones: the tunica intima, tunica media and tunica adventitia. The tunica media forms the largest part of the arterial wall and is the principal determinant of the vessels’ mechanical properties. It comprises the elastic materials collagen and elastin, in addition to smooth muscle. The distribution of collagen, elastin and smooth muscle differs strikingly between the central and peripheral arteries [49]. Elastin fibres play a major role in determining the mechanical strength of blood vessels at lower pressures, with collagen fibres bearing most of the mechanical stress (stress is described as the force per unit area that produces a change in arterial cross-sectional area) at higher pressures [50]. Arterial blood vessels are complex three-dimensional structures whose components exhibit strongly non-linear, anisotropic and visco-elastic behaviour [51–53]. The mechanical behaviour of anisotropic materials vary with the direction of the applied stress, and visco-elastic materials display a time dependency in response to a stress or strain [strain is defined as the ratio of change in area (ΔA) to the initial area (A)]. Furthermore, wall properties vary in different vessels, differ in the same vessel at various distending pressures and alter with activation of smooth muscle in the vessel wall [54]. The complex nature of the biological materials in the arterial walls means no single descriptor or combination of descriptors can provide a comprehensive characterization of the mechanical behaviour of the arterial blood vessels [38].

Recently, the potential role of the endothelium in buffering pulsatile pressure in the arterial system has been emphasized [55]. As a single monolayer of cells, the endothelium possesses little tensile strength, but can profoundly alter the mechanical characteristics of blood vessels through the elaboration of vaso-active substances that influence arterial tone, structure and growth [56,57]. An imbalance that favours a pro-coagulant, vaso-constrictive and growth promoting state is found with risk factors for, and disease states associated with, an increase in vascular events [58,59]. Impaired pulsatile arterial function and defective endothelium-derived NO-mediated control of arterial tone are common accompaniments to the disease states associated with an increase in cardiovascular events [55,58,59]. Experimental
MODELLING THE ARTERIAL CIRCULATION

The use of models to represent the circulation or arterial walls has proved useful for data interpretation and helps facilitate understanding of the relationships between physical phenomena occurring in the arterial tree [62]. Investigators have used analogue models to explain the behaviour of the human arterial system under varying conditions. Analogues of the circulatory system are models that replace real body compartments, such as vessel walls, with mechanical or electrical analogies for which constitutive relations are well established [30]. The reason one employs analogues, rather than dealing with the actual arterial system, stems from the large number of variables that affect the properties, responses and control of the human circulation. It is impossible to study all of these factors at the same time or to even clearly define the contribution that a specific variable may make to a specific observed phenomenon. The problem becomes even more complex when one appreciates that the variables can interact with each other and the outcome of the interaction is often poorly understood. In an analogue model, it is possible to either eliminate or maintain at fixed levels most of the parameters and include only a few variables of interest at a time [63]. Two basic classes of models employed in the study of arterial dynamics are transmission-line or wave-propagation models and reduced-lumped-parameter models, such as the Windkessel, which can be shown to be a special case of propagation models [64,65]. The most simple Windkessel model describes the circulation as a chamber with parallel capacitance (compliance) and resistance components as lumped entities in the arterial system. This Windkessel model cannot account for the effects of wave reflection in contrast with distributive models that allow for wave travel in the system. However, each approach has limitations, and the derived relations cannot represent a complete description of physical phenomena occurring in the arterial tree. Although improved representation of the arterial tree can be achieved by increasing the number of elements and complexity of the models, the cost is a clouding of the relationship between physical processes in the circulation and their respective model counterparts [66].

GLOBAL ASSESSMENT OF ARTERIAL PROPERTIES

Impedance assessment in the frequency domain

Impedance, a term borrowed from electrical engineering theory, describes the opposition to flow presented by a system. The impedance load of the arterial tree can be quantified by analysing pressure–flow relationships, and pulse contour parameters produced through the effects of disease on the structural and functional components of the arterial system [30,67]. Input impedance relates simultaneously recorded pressure and flow waveforms under specific mathematical conditions. The haemodynamic properties of the system can be quantified, since the impedance concept permits the heart and arteries to be considered separately, and their interaction to be understood as a function of pump and load properties. As pressure and flow waves are periodic and continuous, Fourier-series methods can be used to generate the impedance function [68,69]. Fourier analysis involves decomposing recorded pressure and flow waveforms into a spectrum of single frequency components, each having its own associated amplitude and phase. The modulus at each harmonic is the ratio of the pressure modulus to the flow modulus at that harmonic, and the phase at each harmonic is the difference between pressure phase and flow phase at the same harmonic. As the impedance of a vascular bed varies with frequency (heart rate), complete specification of pulsatile pressure and flow relationships must take the form of a spectrum of moduli and phase angles versus frequency [70]. Characteristic impedance (the inverse of arterial compliance) defines the relationship between pressure and flow in an artery or arterial network when pressure and flow waves are not influenced by wave reflections [70,71]. These conditions do not exist in the arterial system, and the input impedance values oscillate around the characteristic impedance value because of wave reflection. Wave reflections are known to exert their greatest influence on impedance moduli at low frequencies. At higher frequencies, the input impedance approaches the characteristic impedance, which has been estimated in previous haemodynamic studies [69–71] as the arithmetic mean of the input impedance moduli above 2–4 Hz.

The aortic impedance spectrum contains a great deal of information about the physical state of the arterial circulation, and had been considered the reference standard for studying the opposition to left ventricular
ejection. The utility of the technique is limited by its invasive nature, which generally requires placement of a catheter in the aortic lumen making it unsuitable for clinical studies. Recorded moduli values are often close to the noise level of the recording instruments, and the characteristic impedance, which is not a standardized parameter, has provided conflicting results regarding evaluation of the status of the cardiovascular system in health and disease [71, 72]. Finally, the input impedance does not necessary represent specific physical characteristics of the system, as the impedance moduli can be modelled by an infinite number and combination of elements [42].

**Pulse-contour analysis**

A natural progression from the impressive array of results indicating that elevated systolic blood pressure represents an important determinant predicting future cardiovascular risk was the realization that pulse pressure may provide additional information beyond that provided by systolic blood pressure alone [73]. Increased stiffness or loss of compliance of large arteries serves to widen the pulse pressure. Although brachial artery pulse pressure is an imperfect surrogate for aortic pulse pressure, it has been shown to represent an independent predictor for myocardial infarction and recurrent infarction in patients with impaired left ventricular function [14, 15, 17]. It acts also as an independent determinant of cardiovascular risk in the elderly population [74]. Clinical investigators have also determined the ratio between stroke volume and pulse pressure as a crude global measure of arterial compliance based on the principal that the arterial tree can be modelled as a two-element Windkessel. Total arterial compliance changed in a predictable way with ageing in patients with arterial hypertension, and predicted the occurrence of future cardiovascular morbid events independently of age and left ventricular mass index [18].

The systolic and diastolic pressures represent the limits of pressure fluctuations during the cardiac cycle. A more complete description of the complex interaction between the left ventricle and the physical properties of the arterial system is provided by the descriptive or quantitative analysis of the arterial-pulse contour. For the analysis to be meaningful, the arterial-pulse contour should change in a consistent and predictable way with ageing and disease states associated with an increase in vascular events. Consistent and predictable morphological change has been repeatedly identified by many investigators in the arterial pressure [75–80] and, to a lesser extent, the digital volume pulse [81–84]. In particular, loss of the oscillatory waveform, which distorts the proximal part of the diastolic decay from a pure exponential, represents an early and sensitive marker for altered structure of tone in the vasculature with ageing and disease states associated with an increase in vascular events [85–87]. This morphological feature probably arises from wave reflection and a damped resonance, which occurs in the arterial tree, with the major of site of reflected waves originating in smaller arteries and arterioles [29, 64, 88]. A second characteristic age-related change in the arterial pressure pulse contour, described at the carotid, radial and femoral sites and recorded by transthoracic tonometry, involved a steepening of the diastolic decay [78]. Progressive morphological change in the arterial pulse contour eventually results in the forward incident pressure wave summating with backward reflected pressure wave to augment systolic blood pressure [80]. These changes in the arterial pressure pulse and volume pulse contours can be presented in a descriptive way, but the derivation of quantitative relationships to alteration in the mechanical properties of arteries requires modelling of the arterial system.

Increased peripheral resistance has long been regarded as the haemodynamic hallmark to describe vascular adaptations accompanying sustained hypertension and is employed as the parameter of choice to monitor the effect of drug interventions [31, 32, 89]. This steady-state approach ignores the pulsatile phenomena occurring in the arterial circulation, and a logical progression to account for this Windkessel or cushioning function of arteries was the introduction of a capacitance in parallel with a terminal resistance to model the arterial tree. Although the Windkessel concept has been criticized in some quarters [48], many physiologists and bioengineers continue to successfully exploit the usefulness of simple reduced models of the circulation to represent a load on the heart, or to interpret the load in terms of the mechanical properties of the arterial circulation [30, 64–66, 90–94].

We and others [9, 30, 58, 95–97] have employed a modified Windkessel (Figure 2) to interpret changes in arterial waveshape during diastole in terms of compliance, inerterance and resistance in the arterial system. The Windkessel concept represents a lumped parameter non-propagative approach to interpret changes in arterial mechanical properties, and cannot account for wave travel in the arterial system [64–66, 98]. The simple Windkessel with a capacitor in parallel with a terminal

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**Figure 2** Modified Windkessel model of the arterial system

Abbreviations: C1, proximal compliance; C2, distal compliance; i_in, systemic inflow; L, inerterance; R, systemic vascular resistance.
resistance cannot therefore account for wave amplification or a secondary diastolic wave that results from pulse wave reflection in the arterial circulation. Some investigators have chosen to minimize the effects of distortion in the diastolic pressure pulse waveform by employing an area method to derive compliance estimates [99]. However, the energy contracts between all the elements in an expanded modified Windkessel model can account for distortions in pressure-pulse contour produced by wave reflection, interpreting these changes in terms of altered compliance, resistance and inertance elements in the model.

No unique solution exists for the calculation of the model-based parameters (compliance, inertance and resistance values that describe the pressure decay in diastole), and the non-invasive approach derives the cardiac output estimate using an algorithm incorporating the radial pressure-pulse waveform [58]. A strength of this approach is that the derived model-based parameters change in a consistent and expected fashion with the ageing and disease states associated with an increase in vascular events [9,30,58,95]. In particular, a reduction in the small artery compliance estimate, which reflects a diminished amplitude, duration and frequency of the secondary diastolic wave, represents an early marker for vascular abnormalities in the arterial system. With age, gender, heart rate and blood pressure controlled as confounding variables, this measure identified altered vascular structure or tone in diabetes mellitus and with cigarette smoking, which was not identified by changes in cardiac output or peripheral resistance [86,87]. Whether analysed qualitatively or quantitatively, analysis of the radial artery pressure-pulse waveform, derived by applanation tonometry or the digital volume pulse waveform obtained by photoplethysmography, provide valuable tools for studying the haemodynamic actions of drug interventions [55,84].

A number of techniques have been described in an attempt to determine central aortic pressure from peripheral arterial waveforms [100–103]. A feature of the central aortic waveform is a late systolic pressure peak that may represent a manifestation of pulse-wave reflection and its transit time from peripheral reflecting sites to the aortic root [104]. With ageing, the late systolic peak eventually augments the peak pressure of the incident wave in early systole, and results in an increased impedance load to left ventricular ejection [80]. Previously [105], estimation of the central aortic pressure and augmentation of the incident pressure waveform was limited to analysis of carotid pulse contours obtained by applanation tonometry. This artery is difficult to apperate effectively, and in elderly patients an inflection point on the systolic upstroke was difficult to identify. Recently, estimation of central aortic waveforms has been derived from brachial and radial artery pressure, and this was based on the determination of a pressure transfer function between the peripheral and central artery locations [102].

A number of investigations using this approach [106–109] have reported expected changes in this index with ageing and disease. However, the use of a general transfer function can show bias and a significant amount of variation in predicting the centrally obtained augmentation index [44,103,110]. This may be due to the need to filter data at low frequencies in order to reduce noise in the general transfer function. Whereas the average transfer function appears useful in predicting aortic pressure for estimation parameters, such as the augmentation index, individual patient transfer function differences make this measure less robust [46,110]. Simultaneous assessment of the augmentation index derived using the pressure transfer function and pulse-wave velocity, used as an estimate of aortic stiffness, revealed a positive but modest correlation ($R = 0.29$) [111]. In this study, only 9% of the variation in pulse-wave velocity was explained or accounted for by variation in augmentation index. Invasive studies examining the haemodynamic consequences associated with the administration of sublingual glyceryl trinitrate demonstrated marked changes in the central aortic pressure waveform and a significant drop in blood pressure without any change in the aorto-femoral pulse-wave velocity [112,113]. These and other data derived from analysis of digital volume waveforms showed that marked changes in arterial waveform morphology, which would profoundly influence the augmentation index, can occur without a change in pulse transit time, indicative of a change in aortic stiffness. The results are explained by improved impedance matching at peripheral reflecting sites in response to glycercyl trinitrate that occur independently of a change in the mechanical properties of the aorta. Unfortunately, recent publications [107–109] unequivocally identified an increased augmentation index as being synonymous with an increase in arterial stiffness. Although in some circumstances this may be the case, it must be emphasized this is a speculative assumption based solely on a descriptive change in waveform morphology.

**REGIONAL ASSESSMENT OF ARTERIAL PROPERTIES**

**Pulse-wave velocity**

The principal that a pulse wave will travel faster in a rigid compared with a distensible tube enables estimates of regional mechanical wall properties be determined [114]. To measure pulse-wave velocity, two pressure or flow waveform measurements are recorded at a known distance apart to accurately determine the time delay between the recorded waveforms [115]. The measurement of the transmission delay is complicated by the
small magnitude of the delay, and the dissimilar nature of the proximal and distal waveforms due to the wave reflection in the arterial system [65]. The ‘foot’ of the waveform, which is least prone to distortion by wave reflection, is often used as the landmark for determining the transit time delay. The lack of a precise definition of what constitutes the foot of the waveform can lead to errors in accurately calculating the pulse-wave velocity [116]. Accurate recording of the path length between the pressure transducers can also introduce errors into the measurement. Pulse-wave velocity is sensitive to changes in heart rate and blood pressure [65,116,117], and small changes in arterial wall properties may not be detected between individuals, as data generated can often show considerable scatter for a given age range [118].

Many studies relate changes in pulse-wave velocity as reflecting a change in the stiffness of wall materials in arterial segments. Arterial stiffness, or the opposition to deformation presented by wall materials, is a generic and less precisely defined term compared with elastic modulus [39]. Mathematical equations are employed to quantitatively express the relationship between pulse-wave velocity and elastic modulus that represents a change in stress for a given change in the strain of arterial wall materials. The Moens–Korteweg formula assumes that the pulse-wave velocity depends only on vessel diameter, blood density and local arterial wall properties [65]. As pulse-wave velocity is proportional to the square root of the elastic modulus, it is not particularly sensitive to changes in the mechanical properties of the wall materials and no study has related changes in elastic modulus estimates with clinical outcome. Nevertheless, pulse-wave velocity is a long established technique employed in the study of arterial wall properties, and to date is the only non-invasive measure shown to be an independent predictor of outcome in high risk populations [119–121]. Unfortunately, the utility of further refining risk stratification in patients already designated as high risk, who should be receiving optimal therapy for risk reduction, will have limited clinical value.

LOCAL ASSESSMENT OF ARTERIAL PROPERTIES

Echo-tracking techniques

A number of techniques have been described to determine mechanical wall properties by measuring simultaneous pulsatile pressure and diameter (or area) changes within an artery [35]. Some of the techniques are invasive and therefore not suitable for clinical studies [122]. Ultrasound techniques have been employed to study local arterial wall properties at the radial, brachial, carotid, femoral and aortic segments. Non-invasive echo-tracking techniques employ ultrasound measurement of the separation of the anterior/posterior walls of an artery plotted against time during the cardiac cycle [123,124]. Blood pressure waveforms can be recorded simultaneously, although from a different site from the diameter measurements. Alignment of the contours is achieved by matching the foot of the pressure waveform with the foot of the diameter of the waveform. The relative contribution of arterial wall components to the physical properties of the vessel are determined by employing models of the arterial wall [50]. A further innovation has been the use of a fluid-filled cuff that enables measurement of brachial artery mechanics over a range of transmural pressures [123]. These elegant physiological studies, which have shed light on the complex relationship between smooth muscle tone and arterial wall mechanics, have been the subject of much controversy and dispute in the literature [54,123,125,126]. However, even with this degree of sophistication, changes in the derived parameters describing the mechanical properties of arteries do not necessarily change in the same way in response to drug interventions that alter smooth muscle tone. Studies by Bank et al. [123] reveal that population characteristics, the type of artery studied, the amount of vasodilation induced by the drug intervention and the method employed to study mechanical wall properties play important roles in influencing derived parameters. The techniques require expensive equipment, a high degree of technical expertise, are time consuming and therefore are not suitable for large population studies. Furthermore, in muscular arteries descriptors of mechanical wall properties do not change (and may paradoxically improve) with ageing and hypertension; disease states associated with increased cardiovascular risk. Obviously, measures relating to the pulsatile function of arteries derived from these sites will provide limited information with regard to disease detection or in monitoring the effects of therapeutic interventions.

RISK FACTOR ASSOCIATIONS AND THERAPEUTIC ASPECTS

Age

Understanding age-related physiological changes in the arterial system is crucial in order to appreciate the influence of age on the development of cardiovascular disease and its response to treatment. A major problem in studying effects of age on the cardiovascular system relates to separating age-related from disease-related changes [35]. Ageing effects on the arterial vasculature are heterogeneous, and the mechanical properties of blood vessels vary depending on the vascular territory studied [58,118]. Localized examination of mechanical wall properties using echo-tracking technology reveal that age-related changes are inhomogeneous within arterial segments of elastic and muscular arteries [127–129]. It
is generally agreed that age-related structural changes in the aorta serve to stiffen or decrease distensibility (an intrinsic property of wall materials) in this arterial segment [130]. This contrasts with findings from the muscular radial and brachial arteries that indicate compliance, not necessarily decreased with age, may be increased in females, and that no relationship exists between age and distensibility in this vessel [127–129].

**Atherosclerosis and hypercholesterolaemia**

Atherosclerosis alters the morphology of diseased arterial tissue in a highly variable and complex fashion that defies straightforward characterization [51,53]. In elderly subjects, aorto-femoral pulse-wave velocity is increased in subjects with atherosclerosis detected at various sites in the vascular tree. Some studies [131–134], but not all [135], support a relationship between coronary artery disease and aortic stiffness, and aortic pulse-wave velocity estimates have been proposed as a useful surrogate for atherosclerosis in the coronary bed [136]. However, the localized interrogation of mechanical wall properties of vessels around predominantly lipid-laden plaques reveals a decrease, rather than an increase, in arterial wall stiffness [51,53]. Therefore vulnerable lipid-laden plaques that are prone to fissuring and rupture are unlikely to be identified by changes in pulse-wave velocity. Atherosclerosis is a patchy disease, and an increased pulse-wave velocity, which represents a composite measure of the entire arterial segment under evaluation, probably identifies a more extensive calcific disease distributed throughout the aorta [53,83].

Pressure pulse-wave reflections occur at any impedance mismatch and are thought to originate mostly in the peripheral arterial bed, as the magnitude of reflection alters markedly with changes in vascular tone [64,77,137]. Vasodilation causes wave reflection to decrease due to improved impedance matching, whereas vasoconstriction produces the opposite effect [29,88]. Altered vascular tone and reactivity characterizes disease states such as hypertension, heart failure, diabetes and atherosclerosis. Whereas the relationship between hypercholesterolaemia and changes in mechanical properties of the large arteries is controversial [20,138–140], a defect in endothelium-mediated vasodilation in response to physical or pharmacological stimuli is a uniform finding [141]. The vast surface area of endothelium in the microvasculature compared with conduit vessels means that the consequences of altered vascular reactivity are most apparent in this section of the circulation [142]. Impaired microvascular reactivity that manifests as an early ‘downstream’ feature of hypercholesterolaemia and subclinical atherosclerosis, may alter impedance matching and the pattern of wave reflection. Therefore changes in the arterial waveform may identify altered tone, predominantly in the smaller arteries and arterioles, as a consequence of the endothelial dysfunction that accompanies traditional cardiovascular risk factors. The administration of NO donors and inhibitors of endothelium-derived NO synthesis, which act predominantly on small arteries and arterioles to produce vasodilatation and vasoconstriction respectively, profoundly influences wave reflection, producing characteristic changes in the pressure pulse morphology [55].

**Hypertension**

By passively increasing the distending pressure on vessel walls, high blood pressure will impair the compliance characteristics of the arterial system [143]. Therefore a reduction in arterial compliance is a well-accepted finding in hypertension, whatever the site and method of measurement [38]. Whether the reduction in compliance is merely a consequence of elevated blood pressure or represents an alteration in wall properties in hypertension remains the subject of considerable controversy [19,43]. Growth and remodelling of the vasculature in hypertension would intuitively be expected to alter mechanical descriptors of arterial wall properties [35,144]. Paradoxically, this may not necessarily be the case, as a reduction in the elastic modulus of wall constituents may serve to normalize wall stress, despite an increase in wall thickness [145]. The situation becomes even more complex when one considers that high blood pressure frequently co-exists with other cardiovascular risk factors that may independently alter the structure and tone of arterial blood vessels [96,97]. A recent study [146] also indicates that the mechanical properties of arteries may differ in patients with isolated systolic hypertension in comparison with systo-diastolic hypertension.

The therapeutic benefits of antihypertensive drugs on the cardiovascular system comprises two major effects: the effect due to blood pressure lowering, and the direct effect of the drug in the vessel wall [43]. Most studies cannot differentiate change in arterial mechanical properties attributable to the drug effect on blood pressure from the direct effect of the drug on the vessel wall [54]. Animal work suggests that drug therapy, which favourably influences blood vessel function directly, may improve the mechanical properties of the vasculature independently of changes in blood pressure. In a rat model of hypertension, a direct vasodilator and angiotensin-converting-enzyme inhibitor lowered mean arterial pressure and peripheral resistance comparably, but only the angiotensin-converting-enzyme inhibitor significantly reduced left ventricular mass [147]. The differential regression of left ventricular hypertrophy was attributed to a favourable effect on pulsatile load exhibited solely by the converting enzyme inhibitor. A variety of cardiovascular and non-cardiovascular factors modulate left ventricular mass [148–150]. Whereas some studies suggest a relationship between impaired pulsatile arterial function and left ventricular mass [151], other
the endothelium and wall properties), remains to be influencing the arterial wall (through the direct effects on and steady-state haemodynamics), or by favourably blood pressure is lowered (by influencing both pulsatile further improvements in outcome depend on how the patients improves clinical outcome [160–162]. Whether Drug therapy that lowers blood pressure in hypertensive these compounds in large-scale clinical outcome studies. [153,159]. The disappointing effect of antagonists, in particular, appear to exhibit little beneficial effect on the mechanical wall properties in hypertension [153,159]. The disappointing effect of β-blockers, in this regard, has to be weighed against the proven benefits of these compounds in large-scale clinical outcome studies. Drug therapy that lowers blood pressure in hypertensive patients improves clinical outcome [160–162]. Whether further improvements in outcome depend on how the blood pressure is lowered (by influencing both pulsatile and steady-state haemodynamics), or by favourably influencing the arterial wall (through the direct effects on the endothelium and wall properties), remains to be established [163].

Diabetes mellitus and insulin resistance
Although diabetes mellitus is characterized by an elevation in blood glucose, this abnormality represents one component of a complex metabolic syndrome. Given the heterogeneous nature of the disease, it is not surprising that differences in vascular structure and function have been described in Type I and Type II diabetes mellitus [164,165]. An increasing number of investigators employing a variety of techniques have studied the mechanical properties of arteries in type I and type II diabetes mellitus [86,166–174]. Pulse-wave velocity has been the method most commonly employed in earlier studies to investigate the effect of diabetes mellitus on the properties of large arteries. Most, but not all, studies show an increase in pulse-wave velocity in patients compared with the controls [35]. Using ultrasound techniques, localized changes in the mechanical wall properties in diabetes mellitus have been reported in different vascular territories [168,173,174], but this is not a universal finding [169,171,172]. In contrast, consistent abnormalities have been recognized in the arterial pressure contour in Type I and Type II diabetes mellitus for many years [85,175,176]. Described originally by Lax and Feinberg [175], the principal morphological change reflects a diminution in the amplitude and duration of the oscillatory wave in proximal diastole that identifies an early vascular abnormality in diabetes, as it is found prior to the detection of vascular complications of the disease [85,86]. The clustering of cardiovascular risk factors accompanying Type II diabetes mellitus can also be found in non-diabetic subjects with normal glucose tolerance. Previous studies indicate that variables of the insulin resistance syndrome can be associated with measures of arterial stiffness in Type II diabetes mellitus [177] and in healthy non-diabetic subjects [178].

Heart failure
The failing heart is exquisitely sensitive to arterial loading conditions [179]. These loading conditions have generally been assessed in terms of the non-pulsatile left ventricular load, with less information available on the effects of the pulsatile load faced by the failing heart [180,181]. Pulse pressure employed as an index of arterial stiffness has been shown to be a powerful independent predictor of the risk for congestive cardiac failure in elderly patients [15,17]. Invasive studies employing aortic impedance measurements have shown reduced [182] and normal impedance values in patients with heart failure [72,183]. A decrease in the compliance characteristics of the carotid and brachial arteries [184,185] has been documented in chronic heart failure, but this has not been a uniform finding when studied at the radial artery [186,187]. Studies in animal models of left ventricular dysfunction suggest that abnormalities in pulsatile arterial function may precede changes in peripheral vascular resistance, but these require confirmation [188]. With respect to the effect of pharmacological interventions, improvement in pulsatile loading conditions in patients with heart failure have been demonstrated with nitroprusside, dobutamine and angiotensin-converting-enzyme inhibition [35].

Hormone replacement therapy
A number of studies have investigated the effect of hormonal replacement therapy on arterial wall properties [189–195]. Hormone replacement therapy has been shown to influence favourably the mechanical properties of blood vessels in post-menopausal women [190,191, 195]. However, female sex hormones do not appear to influence the arterial wall properties during the normal menstrual cycle [193], and invasive cardiovascular studies reveal no significant benefit of the acute administration of oestrogen on arterial wall dynamics [189].

Exercise
A variety of techniques have been employed to study the effect of exercise on mechanical wall properties [196–199]. Most reports suggest that mechanical wall properties are favourably influenced in endurance-trained compared with sedentary individuals [196–198]. Aerobic exercise training may also blunt the age-
associated stiffening of large arteries [196]. However, the situation may be different in muscle strength-trained athletes, where increased stiffness in the arterial circulation has been reported in comparison with sedentary individuals [199].

**Cigarette smoking**

Few studies have investigated the effects of long-term cigarette smoking on arterial wall properties [200,201]. The results are contradictory and may depend on the method employed to describe changes in mechanical wall properties. The changes in waveform morphology found in chronic cigarette smokers compared with subjects who have never smoked would appear to designate the smaller arteries and arterioles as the predominant site of the vascular abnormality in these subjects [87].

**Dietary interventions**

Short-term dietary modifications have been shown to alter the pulsatile characteristics of the arterial circulation [61,202–206]. The changes in mechanical wall properties appear to represent direct effects on the arterial wall, as traditional haemodynamic measures were largely unaltered by the dietary interventions in these studies. In normotensive subjects, dietary sodium restriction has been associated with improvement in arterial stiffness [202]. Reduced arterial distensibility and compliance estimates have been documented in salt-sensitive compared with salt-resistant hypertensive subjects [203]. We have previously shown that the dietary supplementation with ω-3 fatty acids improves the compliance characteristics of the arterial circulation independent of a change in steady-state haemodynamic variables [61]. Subsequently other groups have shown that n-3 fatty acids derived from flaxseed oil also improve measures of arterial compliance [204]. In perimenopausal and menopausal women, administration of isoflavones derived from soya bean or red clover also has a favourable impact on the pulsatile characteristics of arterial blood vessels [205,206].

**SUMMARY**

Ageing of arteries is the substrate on which risk factors act to alter arterial structure and function, and influence the development of disease and the occurrence of vascular events. The usefulness of employing any measure of mechanical wall properties to further refine risk stratification is based on the assumption that ageing and cardiovascular risk factors alter arterial wall properties at an early stage, in a consistent, progressive and predictable fashion. This is far from certain, and an increasing number of studies testify to the heterogeneity in wall properties that are dependent in part upon patient demographics, the duration of disease, disease state and the vascular territory studied. Given the complexities of the arterial circulation, compromises are made by all investigators when studying the physical properties of arteries, since no measure represents a complete description of wall properties and all techniques have theoretical, technical and practical limitations.

Despite these caveats, relatively crude measures that reflect impaired pulsatile function of arteries can provide important prognostic information in the clinical setting. The recognition that pulse pressure predicts future cardiovascular risk independently of systolic and diastolic blood pressure attests to the pathophysiological importance of impaired pulsatile arterial function, but also raises the bar for the application for all non-invasive methodologies in further refining risk. The pulse-pressure measurement requires no special training, is simple to calculate and can be obtained by regular staff in routine clinic or outpatient settings. This suggests that the predictive value of the measurement appears generalizable across at-risk populations.

A widening of the pulse pressure marks the presence of arterial wall damage and acts as a risk factor for accelerated disease progression. However, the measure provides limited information about the ventricular–vascular interaction, and represents a relatively late manifestation of impaired arterial wall properties. Recent advances in technology have facilitated the development and refinement of a variety of non-invasive approaches to study pulsatile arterial function. To date, only pulse-wave velocity has been shown to be an independent predictor of cardiovascular outcome, albeit in high-risk populations. The measure is likely to be dominated by changes in the structural components of the aortic wall, which probably reflect established and advanced disease.

The early and consistent changes that occur in pulse-waveform morphology, suggests that descriptive representation of the pulse contour may hold potential to further refine risk stratification. In youth, this waveform describes optimal coupling between the left ventricle and the arterial circulation. It would appear intuitively appealing to restore this favourable situation, altered through the effects of ageing and disease on arterial properties, by employing therapeutic interventions that influence both steady-state and pulsatile arterial dynamics. Additional information derived by transforming or modelling waveform data adds a layer of complexity to the descriptive analysis of arterial pulse waveforms. Parameters derived using these approaches may have clinical use, but this assertion requires testing in large-scale outcome studies.

Physicians need to know that measures of the mechanical properties of arteries will provide valid information for guiding the clinical decision making process. Will measures of arterial wall properties aid clinical risk stratification and guide therapeutic interventions? Will improvement in the measurements represent valid sub-
REFERENCES


73 Black, H. R., Kuller, L. H., O’Rourke, M. F. et al. (1999) The first report of the systolic and pulse pressure (SYPP). J. Hypertens. (Suppl. 5) 17, S3–S14

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114 Branwell, J. C. and Hill, A. V. (1922) Velocity of transmission of the pulse wave and elasticity of arteries. Lancet i, 891–892
115 McDonald, D. A. (1968) Regional pulse-wave velocity in the arterial tree. J. Appl. Physiol. 24, 73–78
124 Hayoz, D., Rutschmann, B., Perret, F. et al. (1992) Conduit artery compliance and distensibility are not necessarily reduced in hypertension. Hypertension 20, 1–6
125 Dobrin, P. B. (1978) Mechanical properties of arteries. Physiol. Rev. 58, 397–460
178 Emoto, M., Nishizawa, Y., Kawagishi, T. et al. (1998) Stiffness indexes β of the common carotid and femoral arteries are associated with insulin resistance in NIDDM. Diabetes Care 21, 1178–1182
188 Eaton, G. M., Cody, R. J. and Binkley, P. F. (1993) Increased aortic impedance precedes peripheral vasoconstriction at the early stage of ventricular failure in the paced canine model. Circulation 88, 2714–2721


