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Ultrasonography and Tonometry for the Assessment of Human Arterial Stiffness

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1. Introduction

The structure and function of the human vasculature is integral to the efficacy of the cardiovascular system. In particular, arteries function as both a reservoir to dampen oscillations from the pumping heart, as well as a conduit to transport blood to the periphery. With age and disease, alterations in the composition of the arterial wall can occur. This can result in arteries becoming more resistant to wall deformation, referred to as arterial stiffness, which can have significant implications for the development of cardiovascular disease. Due to the emergence of arterial stiffness as a measure of cardiovascular disease risk, a number of non-invasive techniques have been developed, which include the use of ultrasonic assessment. These techniques are highly effective, reliable, and well validated, and consider stiffness both locally (most commonly measured at the carotid artery) as well as regionally (most commonly measured through the aorta) in the arterial tree. The assessment of arterial stiffness is critical to our understanding of the overall vascular health, and is the focus of this chapter.

2. Anatomy and physiology of the blood vessel

2.1 Anatomy of the artery

The human artery is comprised of a lumen surrounded by a series of concentric layers, which work together cohesively to assist in propagating blood from the heart to the periphery. The arterial wall itself is divided into 3 major regions: the tunica intima, media, and adventitia (Figure 1). The intima is comprised in part by the vascular endothelium, which lines the interface with the lumen. The vascular endothelium is a single layer of simple squamous epithelial cells that play a critical role in the regulation of smooth muscle tone through the release of several vasoactive substances. Adjacent to the endothelium lies a thin layer of elastin and collagen fibers, which attach to the internal elastic lamina, an elastic tissue that forms the outermost layer of the intima region. The tunica media is a more complex structure, and contains smooth muscle amidst a structure of elastin and collagen, which together act as a homogenous unit (Dobrin, 1999). A surrounding structure of thicker elastin bands wraps circumferentially with finer bands of elastin connecting them, and

collagen dispersed in the intervening spaces with some inherent slack. The collagen also attaches to the smooth muscle, which lies internal to the surrounding structure. This latticework provides a flexible “safety net” for the blood vessels to prevent damage to the wall of the artery, especially at high transmural pressures. Finally the outermost region, the tunica adventitia, is separated from the tunica media by the outer elastic lamina, and is a layer of elastin and collagen that merges with the surrounding tissues.

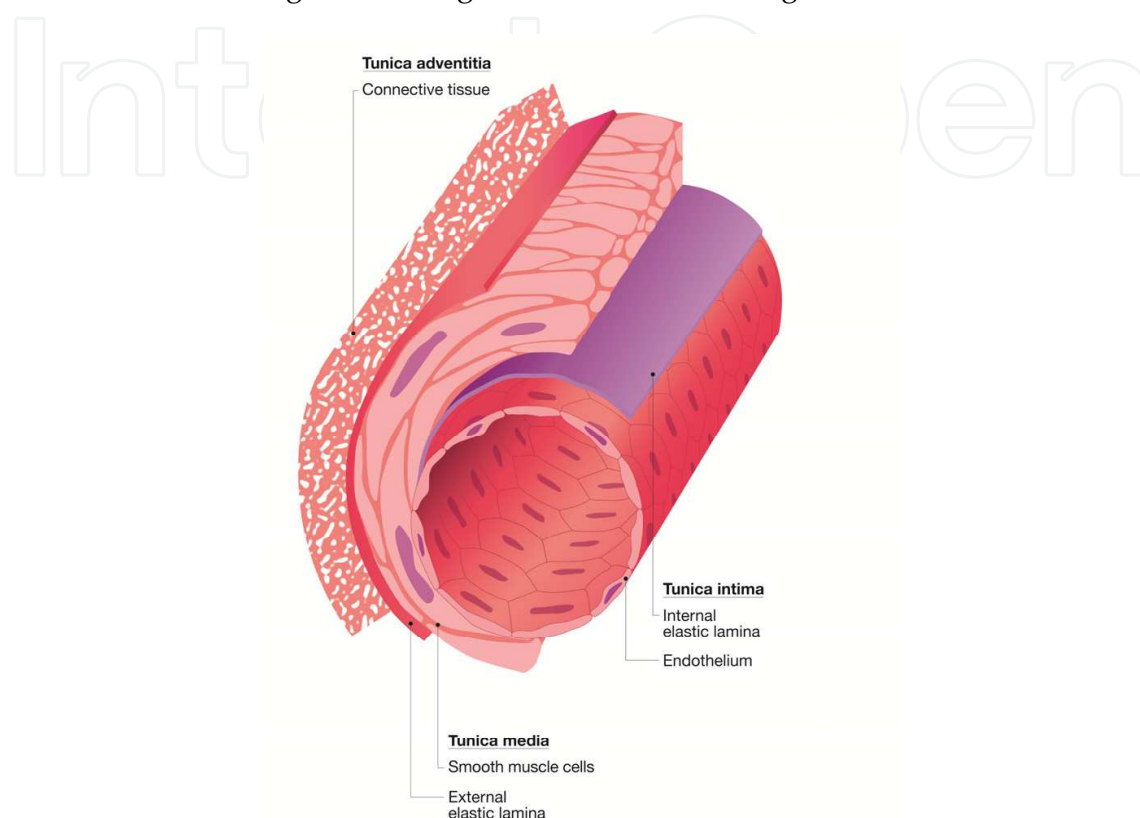


Fig. 1. Anatomy of a blood vessel

2.2 Functions of the arterial system

Arteries act as a conduit system to transport blood through the body, and dampen oscillations from the pulsatile ejection of blood to provide steady flow throughout the arterial tree. There are 3 separate anatomical arterial regions addressing these functions (Nichols & O'Rourke, 2005). First, large elastic arteries such as the aorta provide the predominant cushioning reservoir for blood flow. Second, large muscular arteries act as the conduit for blood to the periphery and actively modify wave propagation through smooth muscle tone regulation. Finally, arterioles function to alter peripheral artery resistance, and subsequently aid in the maintenance of mean arterial pressure and delivery of a continual flow to required systems and subsequent capillary beds.

Several models have been proposed for the functioning of the arterial system, with the propagative/distensible tube model considered superior (Laurent et al., 2006; O'Rourke et al., 2002). The propagative/distensible tube model consists of a single distensible tube with one end representing peripheral resistance, and the other receiving blood in pulses from the left ventricle (Nichols & O'Rourke, 2005). The pressure wave generated from the heart

travels down the tube and is propagated and dampened by the viscoelastic wall of the vessel. When applying this theory to the entire arterial tree several phenomena need to be considered. As the pulse travels down the arterial tree it becomes amplified. This amplification is caused by the progressive increase in stiffness of the arteries distally from the heart (Learoyd & Taylor, 1966) and the branching, bifurcations, and non-linearity in the vascular tree that produce sites where the pressure wave can be reflected. These reflections return in the opposite direction and amplify the pressure signal. Reflection sites are closer to the pulse wave in the periphery (greater branching) than in the central arteries, and amplification is therefore greater (known as the 'amplification phenomena') (Laurent et al., 2006). Thus, the pressure wave at any given location is the result of the summation of the incident and reflected wave (Figure 2) (Davies & Struthers, 2003; O'Rourke et al., 2002), and depending on the elasticity of the vasculature, can create various pressure waveforms.

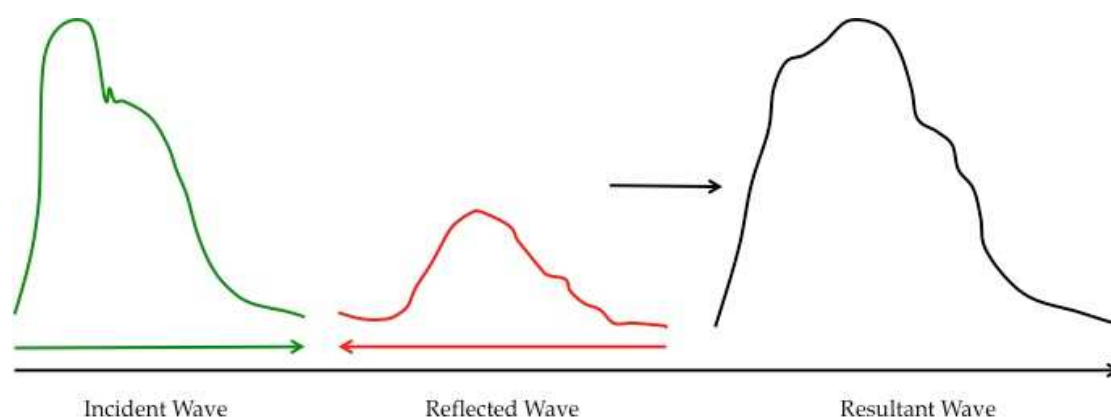


Fig. 2. The pressure waveform is a result of the summation (right) of the incident wave (left) travelling toward the periphery and combining with the reflected wave (middle) returning from the periphery.

The composition of the arterial wall, in particular the elastin and collagen content, changes from central to peripheral arteries. Starting in the proximal aorta, elastin is the dominant component. At the abdominal aorta the content of collagen and elastin appears similar, and by the periphery collagen becomes dominant (Harkness et al., 1957). As collagen is 300 times stiffer than elastin (elastic modulus 1000×10^6 dyne/cm² vs. 5×10^6) (Armentano et al., 1991), the altering arterial wall composition causes an increasing 'stiffness gradient' down the arterial tree. For example, in the central arteries, up to 50% of the stroke volume ejected from the heart is momentarily stored in the aorta and large elastic arteries. Approximately 10% of the energy produced by the heart is used to distend the arteries during systole. The elastic walls of the artery store the energy, and subsequently use it to recoil the vessel wall during diastole (London & Pannier, 2010), thus ensuring continuous flow to the stiffer, more collagen based, peripheral arteries. For this dampening in the central arteries to be most efficient, the energy needed to distend the wall needs to be as low as possible (London & Pannier, 2010), which not only depends on elasticity (and high elastin content), but also the geometry of the vessel walls.

Elastin and collagen cause the pressure-diameter relationship at any specific area on the arterial tree to be non linear (Figure 3) (Armentano et al., 1991). At low distensions, pressure

is mainly governed by elastin fibers, which are quite compliant and the resulting curve is more linear, where at higher tensions it is governed by the supporting latticework of collagen content, which is much stiffer, resulting in a steeper slope (a greater required pressure for a given diameter change) (Lanne et al., 1992).

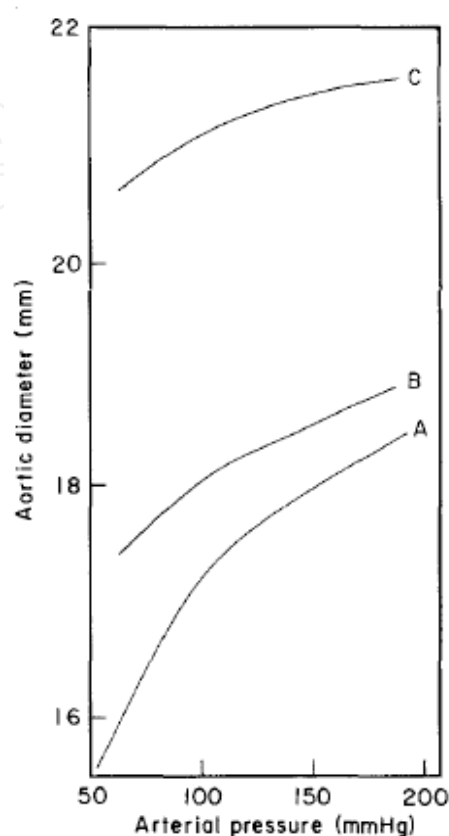


Fig. 3. Pressure-diameter relationship of the abdominal aorta in (A) young (mean 25 yrs), (B) middle aged (mean 51 yrs) and (C) elderly (mean 70 yrs) humans. Reprinted with permission (Lanne et al., 1992)

3. Arterial stiffness

3.1 Development of arterial stiffness

Considerable research supports the measurement of arterial stiffness as a highly relevant tool in the assessment of vascular structure. Degenerative stiffness of the arterial wall is considered arteriosclerosis, and is distinguishable from atherosclerosis, which is the occlusive result of endovascular inflammatory disease, lipid oxidation and plaque formation (Cavalcante et al., 2011). Even in healthy, young individuals, arterial stiffness is heterogeneous throughout the arterial tree, as amplification and the natural stiffness gradient result in more elastic central and stiffer peripheral arteries (London & Pannier, 2010). Arteries in humans, however, also stiffen with healthy ageing and disease (discussed later in the chapter), affecting predominately the aorta and proximal elastic arteries, and to a lesser degree the peripheral arteries (O'Rourke et al., 2002), and can even result in a minimization or reversing of the stiffness gradient (Benetos et al., 1993; Boutouyrie et al., 1992; Laurent et al., 2006). This regional age associated stiffening has been attributed to

longstanding pulsation that induces greater cycles of stress in the central arteries (Adji et al., 2011; Lee & Oh, 2010).

With age and disease, degeneration of the media in the central arteries appears to be the primary structural change associated with chronic increases in arterial stiffness. Fatigue and fracture of elastin and collagen fibers occur. These structural changes to the elastin and collagen functional unit are determined by the extent of circumferential strain, which is greater centrally, and length of strain exposure (number of cardiac cycles) (McEniery et al., 2010). The orderly arrangement of elastic lamellae disappears, and is replaced by thinning, fragmented elastin, greater foundations of collagen (Laurent & Boutouyrie, 2007; Najjar et al., 2005; Zieman et al., 2005) and medial calcification (elastocalcinosis) (Atkinson, 2008). Other age and disease associated changes in the arterial wall include specific changes in the smooth muscle cell connections (Laurent et al., 2005), and inflammation in the form of acute systemic (Vlachopoulos et al., 2005) and chronic (Roman et al., 2005) inflammatory disease.

A stiffer artery propagates a pulse wave faster than a more compliant vessel. This leads to earlier return of the reflected wave, which amplifies systolic pressure and decreases diastolic pressure (Figure 4). Increased systolic pressure places a greater stress (distending pressure) on the wall of the vessel, which over time can accelerate the stiffening and remodeling process. A decrease in diastolic pressure can reduce coronary perfusion pressure, reducing coronary blood flow reserve, which may be a possible link to increase cardiac event risk in

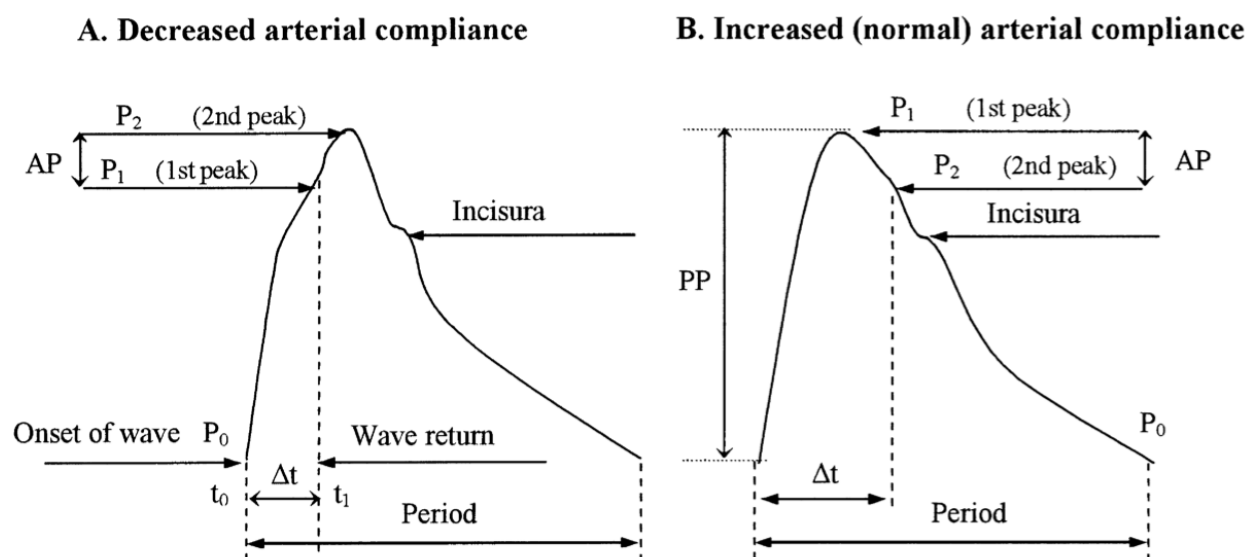


Fig. 4. Effect of decreased (A) and normal (B) arterial compliance on the pulse waveform. P₀: end-diastolic pressure; P₁: early systolic peak; P₂: late systolic peak (from reflected wave); Δt: time from onset of pressure wave (t₀) to return of reflected wave (t₁); PP: pulse pressure. Reprinted and modified with permission AP: augmentation of systolic aortic pressure (Papaioannou et al., 2004)

subjects with elevated arterial stiffness (Saito et al., 2008). Increased arterial stiffness also results in failure to suppress the pulse oscillations downstream from the central arteries. Decreased pulse suppression potentially increases the risk for damage to micro vascular beds in highly perfused organs such as the brain and kidneys (O'Rourke & Safar, 2005), and has important implications for risk of stroke and renal failure.

Increased arterial stiffness with age and disease is partially compensated for by remodeling of the arteries, through luminal enlargement (Boutouyrie et al., 1992) and wall thickening (Cheng et al., 2002; Ziemann et al., 2005). It appears that endothelial dysfunction, which can occur from a decrease in nitric oxide (NO) release, increase in oxidative stress, and/or a decrease in antioxidant capacity with age or disease, is the earliest change in the vasculature that can lead to advancing vascular disease (Taddei et al., 2001; Widlansky et al., 2003). Decreased NO leads to increasing vascular tone of the small arteries responsible for major changes in total peripheral resistance (arterioles). Increasing vascular tone leads to structural and functional changes upstream in the larger arteries, resulting in stiffening and remodeling, increasing blood pressure (in particular pulse pressure), as well as atherosclerotic plaque development and additional functional abnormalities (Folkow, 1995). However, this temporal sequence in the manifestation of arterial disease is not always present, as structural changes can present without obvious functional changes, and these structural changes are not always homogenous across the vascular tree (Naghavi, 2009).

Arterial stiffness is emerging as one of the most important determinants of increased systolic blood pressure and pulse pressure in ageing and disease. It is the root cause of a number of cardiovascular complications including left ventricular hypertrophy, left ventricular failure, aneurism formation and rupture, and is a major contributor to atherosclerotic and small vessel disease, which can lead to stroke, myocardial infarction and renal failure (Nichols & O'Rourke, 2005). Central artery stiffening, in particular aortic stiffening, is strongly related to cardiovascular events, independent of age, arterial pressure, and conventional risk factors for cardiovascular disease (Adji et al., 2011), as well as future hypertension risk after correcting for systolic blood pressure, age, sex, body mass index, heart rate, total cholesterol, diabetes, smoking, alcohol and physical activity (Dernellis & Panaretou, 2005). In fact, stiffening of the aorta rather than left ventricular myocardial abnormalities appears to be the predominant cause of cardiac failure with age (Levy & Brink, 2005) as it produces higher systolic pressures in the aorta and left ventricle. These elevated systolic pressures present a high load on the ventricle, predisposing it to increased systolic wall stress and remodeling, which can progress to dysfunction and failure (Adji et al., 2011).

A variety of techniques for measuring arterial stiffness have been developed. In particular, with the use of ultrasonography, two techniques have been utilized extensively and have been validated for measuring central arterial stiffness non-invasively. In the measurement of regional arterial stiffness, pulse wave velocity has emerged as the gold standard (Laurent et al., 2006) for the noninvasive assessment of arterial stiffness, while local arterial stiffness measures, specifically at the carotid artery, have emerged as an important tool for the mechanistic study of vascular structure and function. Although researchers and clinicians extensively use arterial stiffness measures, a number of potential limitations to these techniques have been identified (Laurent et al., 2006; O'Rourke et al., 2002). Assumption of a homogenous vascular wall when it is heterogeneous in nature, the use of different locations for measures of pressure and arterial diameter, and failing to account for the altering effects

of heart rate (which affects the rate that pulse pressure amplifies) (Wilkinson et al., 2002) and cardiac contractility (O'Rourke et al., 2002) are common oversights in measurement. Furthermore, nervous system activity, fluctuations in autonomic control, vasoactive substances such as nitric oxide, and hormones influence vascular smooth muscle, which can also influence arterial stiffness. Muscular arteries, particularly smaller arteries (O'Rourke et al., 2002), are also subject to spontaneous vasomotor changes that affect both diameter and stiffness (Hayoz et al., 1993). Despite these limitations, measures of arterial stiffness are considered an integral tool in the noninvasive assessment of vascular structure and function, and are an important determinant for cardiovascular risk.

3.2 Local arterial stiffness and measurement

3.2.1 Viscoelastic properties of the arterial wall

The arterial wall is considered to be viscoelastic, as it contains both elastic and viscous properties (Nichols & O'Rourke, 2005). When a stress is applied (a force that produces deformation) to a perfectly elastic material, it will regain its original form when the stress is removed. In an artery, however, wall viscosity is present, which leads to the wall retaining part of the deformation (London & Pannier, 2010). This is partially responsible for hysteresis seen in the pressure-diameter loop (Figure 5). Unfortunately the viscosity of the wall is difficult to measure in humans, and therefore the elasticity component of the arterial wall is what has been extensively evaluated.

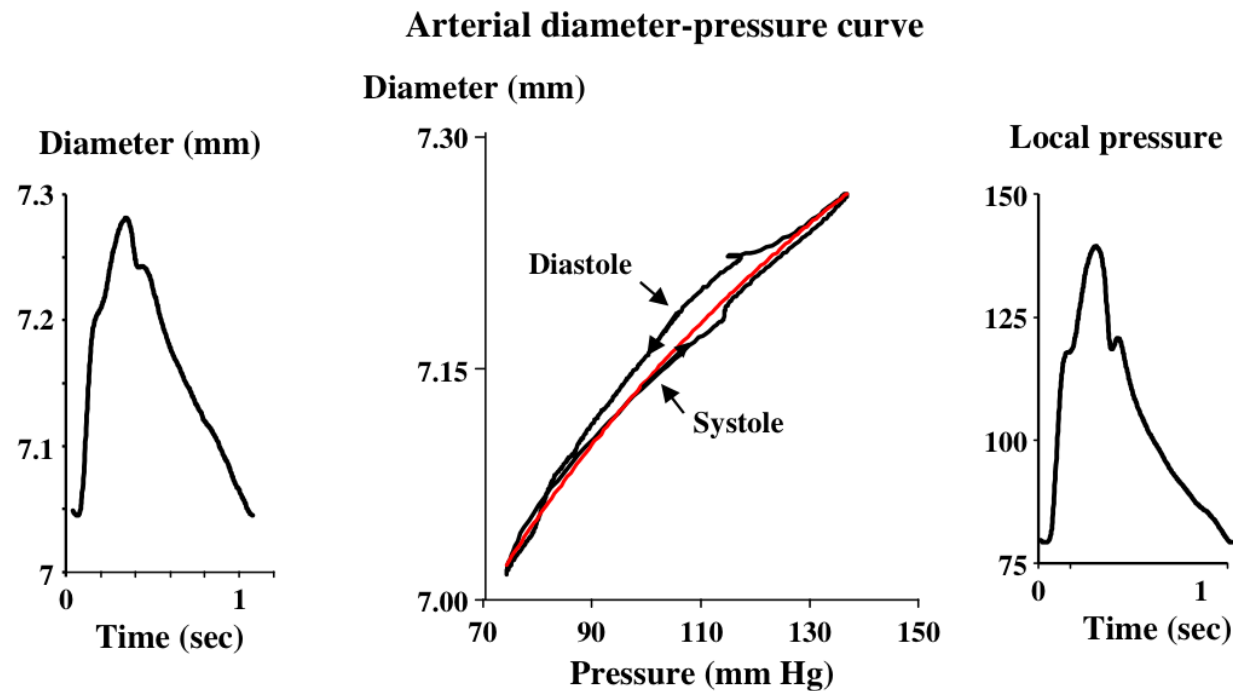


Fig. 5. Diameter-pressure curve (middle) derived from the diameter (left) and local pressure (right) of the common carotid artery. Differences in systole and diastole represent the energy dissipation due to viscous properties of the arterial wall. The red line is the averaged pressure-diameter curve. Reprinted and modified with permission (London & Pannier, 2010)

3.2.2 Calculations of local arterial stiffness

The elasticity of the arterial wall can be gauged by understanding the stress/strain relationship. While stress is the force producing deformation, strain is the resulting deformation incurred as a percentage change in length (Cavalcante et al., 2011). Strain therefore is dimensionless, and the stress/strain ratio is known as the elastic modulus, or Young's modulus (O'Rourke et al., 2002). In an artery, assuming the segment is a cylindrical tube with a circular luminal cross-section (Pannier et al., 2002; Reneman et al., 2005), compliance is considered the absolute change in volume (strain) due to a change in pressure (stress). Distensibility takes into account the initial dimensions of the artery, and is considered the relative change in volume for a given pressure. The equations are as follows:

$$\text{Compliance} = \frac{\Delta \text{CSA}}{\text{PP}} = \frac{\Pi r^2 - \Pi r^2}{\text{PP}} = \frac{\Pi \left(\frac{d_{\max}}{2} \right)^2 - \Pi \left(\frac{d_{\min}}{2} \right)^2}{\text{PP}} \quad (1)$$

$$\text{Distensibility} = \frac{\Pi \left(\frac{d_{\max}}{2} \right)^2 - \Pi \left(\frac{d_{\min}}{2} \right)^2}{\Pi \left(\frac{d_{\min}}{2} \right)^2 \times \text{PP}} \quad (2)$$

where d_{\max} is the maximum systolic diameter, d_{\min} is the minimum diastolic diameter, and PP is the carotid pulse pressure. Compliance and distensibility can both be estimated as a change in radius, diameter, flow, or cross sectional area for a given change in pulse pressure, measured at the same site (Nichols & O'Rourke, 2005). The resistance to deformation is known as stiffness, which in turn is the reciprocal of compliance.

Local arterial stiffness of the central arteries is directly determined, as denoted from a change in pressure producing a given change in volume (Laurent et al., 2006) (Figure 6). In the large elastic arteries (i.e. the carotid artery or aorta) the relationship between lumen cross sectional area and change in pressure is linear (Meinders & Hoeks, 2004) and the error from this assumption is quite small (Reneman et al., 2005). In stiffer peripheral muscular arteries this error can be large (Reneman et al., 2005), therefore direct measures done at the carotid artery and aorta for determining local stiffness have been extensively explored.

Young's modulus, or the incremental elastic modulus (E_{inc}), outlined in equation [3], has been used extensively (Nichols & O'Rourke, 2005). It estimates the elastic properties of the arterial wall by taking into account its thickness. Current measuring techniques unfortunately cannot differentiate the load bearing section of the wall (media/adventitia) from the non-load bearing portion (intima). Intima-media thickness (IMT) is used as a surrogate for wall thickness, as the adventitia is indistinguishable from surrounding structures with ultrasound imaging techniques. The assumptions are that the IMT is load bearing, and that the arterial wall is homogeneous (Adji et al., 2011; O'Rourke et al., 2002). Thus caution should be exercised in using Young's modulus as current measurements can be imprecise and unrealistic (O'Rourke et al., 2002).

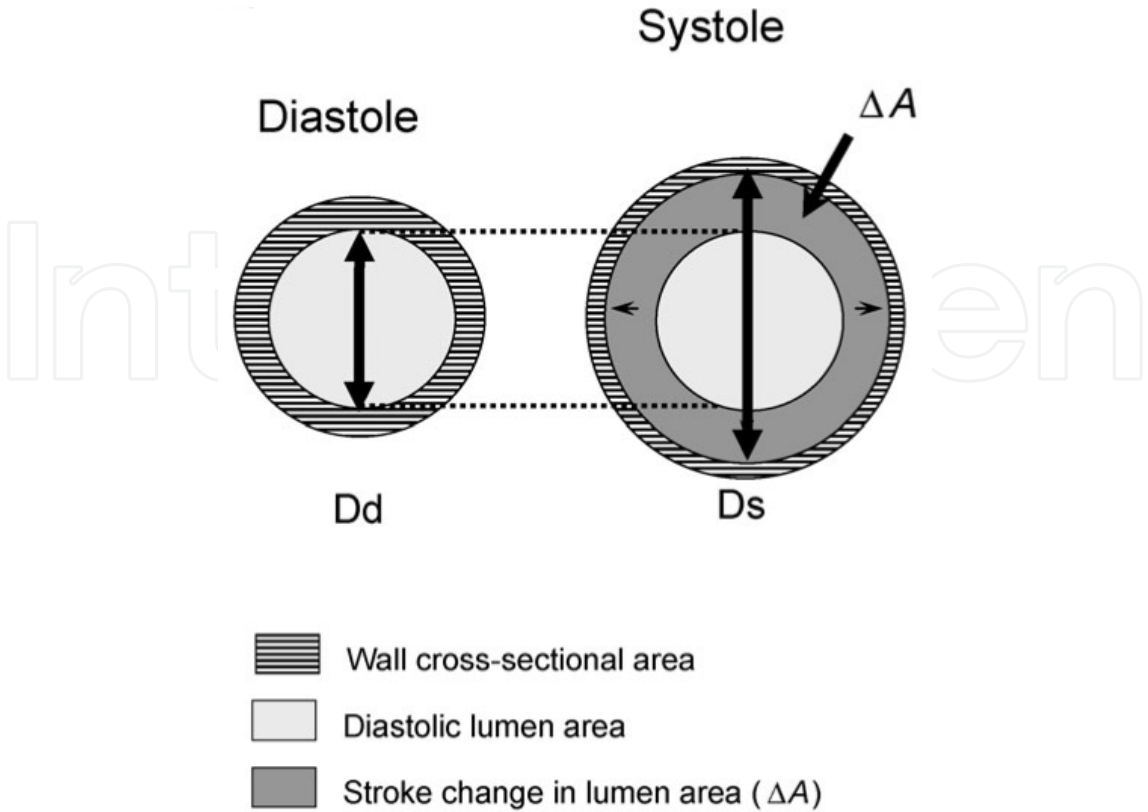


Fig. 6. Measurement of local arterial stiffness: change in luminal cross sectional area (ΔA) for a given change in pressure (diastole to systole). Reprinted and modified with permission (Laurent et al., 2006)

$$E_{inc} = \frac{3 \left(\frac{1 + \Pi \left(\frac{d_{min}}{2} \right)^2}{\Pi \left(\frac{d_e}{2} \right)^2 - \Pi \left(\frac{d_i}{2} \right)^2} \right)}{\frac{CSA}{\Pi \left(\frac{d_{min}}{2} \right)^2 \times PP}} \quad (3)$$

where d_e is the external diameter and d_i is the internal diameter, measured in diastole.

Peterson's elastic modulus (Peterson et al., 1960), outlined in equation [4], is different from Young's elastic modulus. It assumes a linear stress strain relationship, is inversely related to arterial distensibility, and needs to be specified at a given blood pressure (Cheng et al., 2002). In turn, an equation that provides an index of arterial compliance independent of distending pressure is the β stiffness index (Hirai et al., 1989), outlined in equation [5], where SBP is systolic blood pressure, and DBP is diastolic blood pressure.

$$\text{Peterson} = \frac{\Pi \left(\frac{d_{\min}}{2} \right)^2 \times PP}{\Pi \left(\frac{d_{\max}}{2} \right)^2 - \Pi \left(\frac{d_{\min}}{2} \right)^2} \quad (4)$$

$$\beta = \frac{\ln \left(\frac{\text{SBP}}{\text{DBP}} \right)}{\left(\frac{d_{\max} - d_{\min}}{d_{\min}} \right)} \quad (5)$$

3.2.3 Measurement of local arterial stiffness with ultrasound and tonometry

Ultrasound is a common tool used in the non-invasive assessment of the elastic properties of the arterial wall. Many devices have been developed to determine vascular diameters and IMT. These include echo tracking software (Hoeks et al., 1990; Tardy et al., 1991), which use radiofrequency signals to obtain a high precision image, as well as B-mode ultrasound equipped with a high-resolution linear array transducer (Currie et al., 2010; Nualnim et al., 2011; Redheuil et al., 2010; Tanaka et al., 2000) in combination with various edge detection and image analysis software. Both methods have been shown to have high agreement for assessing vessel diameter (A. S. Kelly et al., 2004). Measurement of IMT using non-invasive ultrasound systems is also an important tool and is used as a surrogate measure for wall thickness in measures of elasticity of the arterial wall such as Young's modulus. IMT is also often used as an indicator for cardiovascular disease (O'Leary et al., 1999) and has been employed in clinical studies (Molinari et al., 2010; Simon et al., 2002).

Most commonly, B-mode ultrasound images are collected at a minimum of 10 frames/sec with a 7.5-11 MHz linear array transducer positioned longitudinally to the common carotid artery with collection ~1-2 cm below the bifurcation of the external and internal carotid arteries. Analysis of time points associated with the maximal diameter in systole and the minimum diameter in diastole are selected and diameters are determined by measurement of the far wall from the interface of the lumen and intima to the near wall interface of the adventitia and media (Tanaka et al., 2000). Imaging of media-adventitia interface of the near wall is used, as the intima-lumen interface can be difficult to obtain. Determination of arterial diameters can be made manually using calipers, or with edge-detection software. Most edge-detection software determines the arterial diameter by identifying the arterial wall within a selected region of interest, based on the contrasting intensity of brightness between the arterial wall boundary and the lumen (Currie et al., 2010; Peters et al., 2011). Measurements are made at numerous points within the region of interest (typically ≥100 points), thereby increasing the precision of the measurement. Other software uses the radiofrequency signals generated from the tissue echo reflections to detect boundaries in tissue density. The radiofrequency detection has the added advantage of not being

dependent on the post-processing of the B-mode images but is less commonly available (Woodman et al., 2001).

Local arterial measures also require measurement of local blood pressure. Applanation tonometry has been shown to produce near-identical pulse waveforms as those performed invasively (R. Kelly et al., 1989). Applanation tonometry uses a probe that incorporates a high fidelity strain gauge transducer which records continuous pressure waveforms in an artery. It is placed over the greatest area of pulsation, and requires support from solid structures (bone, bone plus ligaments) to flatten the artery slightly to produce a consistent and reproducible signal (R. Kelly et al., 1989). Based on the assumption that diastolic and mean blood pressure are constant through the arterial tree (Nichols & O'Rourke, 2005), Kelly and Fitchett developed a system of approximation of local arterial pressure using a tonometer (R. Kelly & Fitchett, 1992), which has been shown to provide the highest accuracy compared to invasive methods (Van Bortel et al., 2001). As baseline levels acquired by the tonometer are subject to hold down pressure, diastolic and mean blood pressures are equated to brachial blood pressures. Local systolic blood pressure is then determined by the extrapolation of the maximal tonometer signal and calibrated pressures, due to the amplification in systolic blood pressure (Nichols & O'Rourke, 2005). An example of this is provided in Figure 7. Ideally carotid artery pressures should be calibrated to concurrent brachial blood pressures measured continuously using various automated oscillometric blood pressure devices (Ex. Finometer (Finapres Medical Systems B.V.; Amsterdam, The Netherlands), Nexfin (BMEYE; Amsterdam, The Netherlands), CMB-700 (Colin Medical Instruments; San Antonio, TX, USA)), which correct to brachial blood pressure from either finger or radial artery waveforms. When this is not possible, carotid artery pressures can

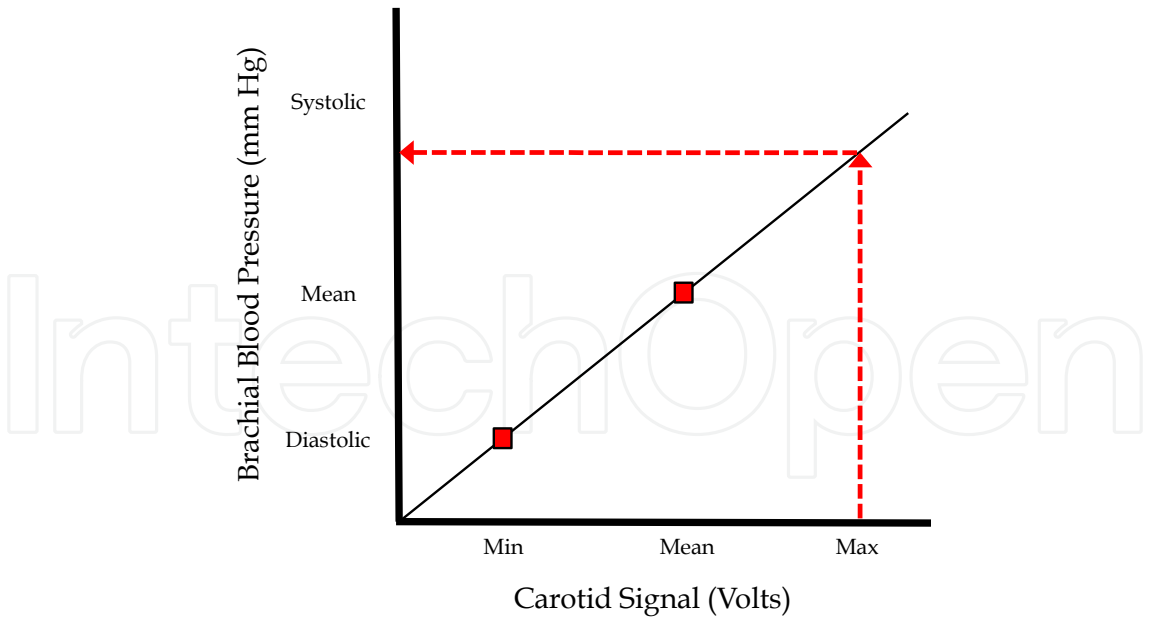


Fig. 7. Approximation of carotid systolic pressure. Minimum and mean carotid artery tonometry values are equated to the diastolic and mean brachial artery blood pressures (red squares), and the equation of the line connecting the points is generated. The pressure (y-axis) at which the maximum carotid artery tonometry value intersects with this line is identified as the predicted carotid artery systolic blood pressure.

also be calibrated to discrete brachial blood pressures collected using a manual sphygmomanometer or an automated oscillometric device. It should be mentioned that previous investigations (Barenbrock et al., 2002; Dijk et al., 2005; Tsivgoulis et al., 2006) have used brachial pulse pressures in the calculation of arterial stiffness measurements when the collection of localized pulse pressure is not available; however, this is not recommended.

Common carotid artery diameter and simultaneous carotid artery blood pressures are collected for 10 cardiac cycles (Currie et al., 2010) in the supine position following at least 10 minutes of quiet rest. Assessments should be performed in a temperature-controlled room, at the same time of day (for repeated measures), and individuals should abstain from caffeine, food consumption, and smoking for at least 3 hours, and alcohol consumption for at least 10 hours prior to testing (Laurent et al., 2006). Section 4 will discuss the association between local measures of carotid artery stiffness and disease; however, it has been suggested that local measures of arterial stiffness be used in mechanistic studies in pathophysiology, pharmacology, and therapeutics, rather than epidemiological studies moving forward (Laurent et al., 2006).

3.2.4 Validity, reliability, and reproducibility of local arterial measurements

Carotid measurements have been validated in clinical studies (Boutouyrie et al., 1999), as both ultrasound imaging for detection of lumen diameter and IMT (Gamble et al., 1994; Hoeks et al., 1990; Hoeks et al., 1997; A. S. Kelly et al., 2004) and use of applanation tonometry (R. Kelly et al., 1989) has been shown to be accurate and reproducible. Between visit coefficient of variation for distensibility measures using B-mode ultrasound imaging techniques is approximately 10% (Kanters et al., 1998; Liang et al., 1998), whereas IMT measures have a coefficient of variation of 2.6-2.8% (Currie et al., 2010; Liang et al., 1998).

3.2.5 Limitations of local arterial measurements

There are several limitations when measuring local arterial stiffness. Applanation of an artery requires a firm background surface to flatten the artery and low levels of subcutaneous fat to avoid dampening of the pulse (Reneman et al., 2005), therefore acquiring a pulse can be an issue in obese individuals. Local stiffness measures using ultrasound are also less sensitive than MRI measures of age-related ascending aortic stiffness in individuals free of cardiovascular disease (Redheuil et al., 2010). However, ultrasound is still a highly accessible clinical tool, and its use for determination of stiffness in the carotid artery is an accepted technique in the assessment of central artery stiffening. Finally, the predictive capacity of carotid stiffness measures for vascular events in patients with manifest arterial disease has been shown to be limited (Dijk et al., 2005). Although, brachial pressures were used in this study as a surrogate of local carotid pressure, therefore caution should be used when considering this result (see Figure 7).

3.3 Regional arterial stiffness and measurement

Regional arterial stiffness can be assessed using pulse wave velocity (PWV), which is commonly defined as the speed of the arterial pulse wave throughout the vasculature (O'Rourke et al., 2002). As previously described, ventricular ejection produces an incident pressure wave, which moves away from the heart and towards the peripheral vasculature at

a finite speed. The assessment of how fast the incident wave travels, or its PWV, can provide information about the stiffness of different arterial segments. The faster the PWV, the stiffer the artery, which is addressed by the Moens-Korteweg equation (O'Rourke, 2006):

$$PWV = \sqrt{\frac{Eh}{2Rp}} \quad (6)$$

where E represents the intrinsic elastic properties of the vessel (Young's modulus in the circumferential direction), p is the blood density, and (h/2R) is the ratio of arterial wall thickness to vessel diameter. However, PWV can be determined practically and non-invasively using a variety of pulse detection tools including continuous wave or pulsed wave Doppler ultrasound.

3.3.1 Measurement of regional arterial stiffness

The assessment of PWV involves recording pulse waves at two different arterial sites, for a minimum of 10-15 seconds, to ensure measurement across at least one respiratory cycle (Van Bortel et al., 2002). Traditionally PWV is separated into central and peripheral measurements to account for differences in vascular composition of different portions of the vascular tree. Central PWV, also referred to as aortic PWV, provides an index of stiffness of the large elastic arteries, and is commonly measured as the PWV between the carotid and femoral arterial sites. Peripheral pulse wave velocity provides an index of stiffness of the medium sized muscular arteries, and can be separated into upper limb and lower limb measures. Upper limb assessments typically involve pulse detection at the carotid and brachial or radial arterial sites, where as lower limb PWV can be measured from the femoral artery to either the dorsalis pedis or posterior tibial arterial sites. Doppler ultrasound can be used to collect blood velocity signals at any of the sites listed above. However, aortic PWV can also be determined by collecting blood velocity signals at the suprasternal notch (root of the left subclavian artery), and the umbilicus (near the bifurcation of the abdominal aorta) (Lehmann et al., 1998).

3.3.2 Calculations of regional arterial stiffness

PWV is calculated using the following equation:

$$PWV = \frac{D}{\Delta t} \quad (7)$$

where D is the distance between measurement sites, and Δt is the pulse transit time.

Distance is measured along the surface of the body with anthropometric measuring tape, using specific anatomical landmarks. Central PWV measurements can be made using one of the following pathways: 1) total distance between carotid (carotid artery site to sternal notch) and femoral (sternal notch to inferior border of the umbilicus + inferior border of the umbilicus to the femoral artery site) arterial sites, 2) subtracting the distance of the carotid artery site from the total distance, or 3) subtracting the distance of the carotid artery site

from the femoral artery site, which has recently been shown to have the best agreement with invasive measures (Weber et al., 2009). When standardization between distance measurement pathways is needed, central distance values can be converted to the total distance between carotid and femoral arterial sites (The Reference Values for Arterial Stiffness' Collaboration, 2010). PWV can then be multiplied by 0.8 to correct for the overestimation (The Reference Values for Arterial Stiffness' Collaboration, 2010). For upper limb PWV, the distance between the carotid artery site to the sternal notch is subtracted from the distance between the sternal notch and the upper limb site (brachial or radial artery site), which is measured when the arm is abducted 90 degrees. Lower limb measurements are made from the femoral artery site along the leg to either the dorsalis pedis or posterior tibial artery site.

The pulse transit time is determined as the time delay between the arrival of the pulse wave at the two arterial sites, and is calculated using the following equation:

$$\Delta t = T_2 - T_1 \quad (8)$$

where T_2 is the pulse arrival time at the distal site, and T_1 is the pulse arrival time at the proximal site. Time at each site can be determined online or offline. Online analysis uses the ECG trace and manual calipers to determine the time at the R-spike and at the arrival of the blood velocity waveform, which is commonly identified as the foot of the waveform. By subtracting the two values, you can determine time for that arterial site (either T_1 or T_2). To perform offline analysis, the raw audio signal from the color wave or pulsed wave Doppler ultrasound is outsourced to an external data collection system. The most reliable techniques include identifying, 1) the intersecting point between the tangent to the initial systolic upstroke of the blood velocity signal, and the horizontal line through the minimum point, and 2) the second derivative of the blood velocity signal, where the arrival of the waveform is identified as the maximum value (Figure 8) (Chiu et al., 1991). However, identification of the arrival of the pulse wave using derivatives has been criticized, since the shape of the waveform changes with heart rate fluctuations (Nichols & O'Rourke, 2005), altering where the peak of the derivative identifies. The arrival of the waveform can also be identified based on the phase velocity theory, which suggests the foot of the waveform is primarily composed of frequencies between 5 and 30 Hz, near the 30 Hz value (McDonald, 1968; Munakata et al., 2003). By filtering out the lower and higher frequencies from the signal using a band-pass filter (<5Hz, >30Hz), the foot of the waveform can be identified as the minimum value of the filtered signal. Unlike the derivative method, fluctuations in heart rate do not influence analysis since the frequencies are unaffected (Nichols & O'Rourke, 2005). When blood velocity signals are collected simultaneously using more than one Doppler probe, time at each site can easily be identified using the maximum or minimum value. When signals are collected sequentially, time at each site is determined using an ECG trace, similar to the online analysis.

3.3.3 Additional devices for the assessment of regional arterial stiffness

The assessment of PWV using Doppler ultrasound has been shown to be valid and reliable (Jiang et al., 2008; Sutton-Tyrrell et al., 2001). However, there are several other techniques available for the detection of the pulse wave in the determination of PWV including

applanation tonometry (as previously described), photoplethysmographic sensors, and magnetic resonance imaging (MRI). Photoplethysmographic sensors contain an infrared emitting diode (peak wavelength 880nm), and a phototransistor detector. The infrared light is either absorbed by the blood and vascular tissue, scattered by other tissues, or reflected back to the detector. The arterial waveform is generated based on how much infrared light is reflected back to the detector (Loukogeorgakis et al., 2002). Flow measurements can also be made using MRI. This technique is capable of providing accurate PWV assessments since distance can be measured along the anatomical segment (Mohiaddin et al., 1993).

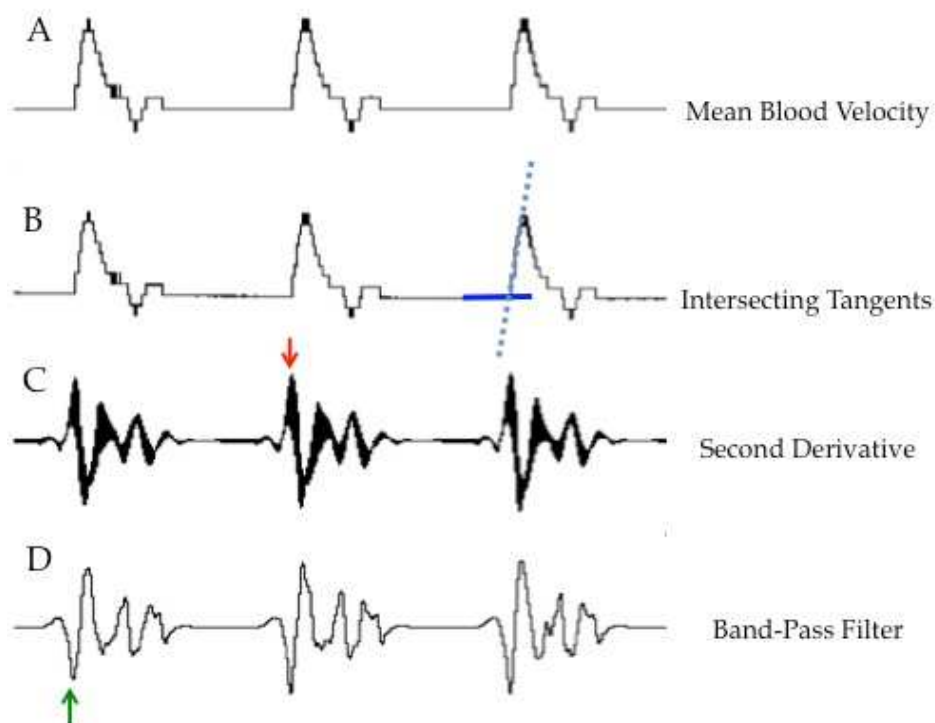


Fig. 8. Various analysis methods for identifying pulse transit time. The arrival of the mean blood velocity waveform (A) is identified with a red arrow. The intersecting tangent (B) analysis locates the point of intersection between the tangent to the initial systolic upstroke of the signal (dotted line), and the horizontal line through the minimum point (closed line). Pulse arrival can also be identified as the maximum value of the second derivative (C), or the minimum value of the band-pass filter (D).

3.3.4 Limitations of regional arterial stiffness measurements

PWV does have its limitations. The measurement of distance along the surface of the body is not a true anatomical representative of the arterial segment and therefore can introduce error into the PWV calculation. Pulse wave measurements at the two arterial sites should be collected simultaneously; however, equipment limitations may not permit this. While the collection of sequential measurements is sufficient, caution should be exercised when interpreting results. While MRI assessments of PWV are not subjective to these limitations, the technique is not that widely used given the lack of available equipment and high cost per use.

3.3.5 Local versus regional assessment of arterial stiffness

Aortic stiffness measures (via carotid-femoral PWV) and local carotid measures of distensibility have been compared (Paini et al., 2006). Strong correlations exist between the two measures in healthy subjects, but decrease with an increasing number of comorbidities (hypertension; hypertension and type 2 diabetes), as the aorta stiffens disproportionately to the carotid artery with age and other cardiovascular risk factors (Paini et al., 2006). Stiffness measures at the carotid artery, therefore, seem to provide a strong estimation for aortic stiffness in less diseased individuals, but aortic and carotid stiffness measures should not be used synonymously in higher risk populations.

4. Arterial stiffness in health and disease

Indices of arterial stiffness provide a non-invasive assessment of the health of the vasculature, and can provide relevant information about an individual's future risk of morbidity and mortality. While arterial stiffening is primarily attributed to modifications to the intrinsic structure of the vessel, several lifestyle factors can transiently augment or attenuate arterial stiffness. Caffeine consumption (Mahmud & Feely, 2001), smoking (Mahmud & Feely, 2003), and resistance exercise (DeVan et al., 2005) have been shown to temporarily increase arterial stiffness, whereas alcohol consumption (Mahmud & Feely, 2002), food consumption (Ahuja et al., 2009), and aerobic exercise (Kingwell et al., 1997) transiently decrease arterial stiffness. Chronic exposure to these factors, however, can lead to more permanent changes in arterial stiffness. Elevated resting arterial stiffness is observed in habitual smokers and individuals who consume excess caffeine and alcohol. Conversely, individuals who are habitually active, or who undergo an exercise training program are capable of attenuating or reversing age associated increases in arterial stiffness (Tanaka et al., 2000). Resting arterial stiffness is also affected by time of day, with larger arterial diameters and lower blood pressures reported at night (Kool et al., 1992).

Arterial stiffness increases naturally with age (O'Rourke & Hashimoto, 2007), and the rate of arterial stiffening is often associated with lifestyle factors (discussed above) and disease. Arterial stiffness is present in individuals with congenital diseases such as Marfan syndrome (Hirata et al., 1991), congenital heart diseases including coarctation of the aorta (de Divitiis et al., 2001) and tetralogy of Fallot (Cheung et al., 2006), as well as non-congenital conditions including but not limited to Kawasaki disease (Senzaki et al., 2005) and end-stage renal disease (Blacher et al., 1999). Traditional risk factors for cardiovascular disease are associated with increased arterial stiffening in adults, including obesity (Danas et al., 2003), type 2 diabetes (Henry et al., 2003), hypertension (Ting et al., 1986), and hypercholesterolemia (Wilkinson et al., 2002). Additionally, the presence of atherosclerosis is associated with arterial stiffening at various sites within the vascular tree (van Popele et al., 2001; van Popele et al., 2006). Not surprisingly, elevated arterial stiffness is present in individuals with cardiovascular diseases including coronary artery disease (Weber et al., 2004), heart failure (Kawaguchi et al., 2003), and stroke (Mattace-Raso et al., 2006).

Adolescents and children with cardiovascular disease risk factors including familial hypercholesterolemia (Aggoun et al., 2000), obesity (Tounian et al., 2001), and type 1 diabetes (Heilman et al., 2009) demonstrate greater arterial stiffness than their age and

gender matched peers. While these studies are cross-sectional in design, and provide no information about their future outcomes, the research suggests children and adolescents with impaired arterial compliance are at a greater risk for disease development in adulthood.

Several investigations have examined the association between indices of arterial stiffness and future risk of cardiovascular morbidity and mortality and all-cause mortality. Aortic (carotid to femoral) PWV is considered the non-invasive gold standard measure of arterial stiffness. In apparently healthy men and women, higher aortic PWV (≥ 11.8 m/s) is associated with a 48% increased risk of first major cardiovascular disease event including myocardial infarction, unstable angina, heart failure and/or stroke (Mitchell et al., 2010). According to a meta-analysis on aortic PWV, an increase of 1 m/s corresponds to an age, gender, and risk factor adjusted risk increase of 15% for cardiovascular and all-cause mortality (Vlachopoulos et al., 2010). This systematic review included a variety of populations and measurement techniques and therefore provides a comprehensive examination of the risk associated with elevated aortic stiffness. However, there are numerous other studies demonstrating increased risk of mortality in clinical populations with elevated aortic PWV including but not limited to end-stage renal disease (Blacher et al., 1999), hypertension (Laurent et al., 2001), and type 2 diabetes (Cruickshank et al., 2002).

The literature on the relationship between other indices of arterial stiffness and future risk of morbidity and mortality is not as well defined. Some investigations demonstrate no association between decreased carotid artery compliance and distensibility and future risk (Leone et al., 2008; van Dijk et al., 2001), whereas other studies demonstrate elevated risk in individuals with carotid artery stiffness (Barenbrock et al., 2002; Tsivgoulis et al., 2006). Additionally, not all of these investigations used local carotid pulse pressure in the calculation of arterial stiffness; therefore the findings should be interpreted with caution.

5. Future directions and conclusions

Efforts have recently been made to establish reference values of arterial stiffness for carotid-femoral PWV (The Reference Values for Arterial Stiffness' Collaboration, 2010). This is an important first step in understanding the baseline changes that occur with arterial stiffness in the healthy person as they age. Furthering these attempts will continue to elucidate the role of stiffness in aging, and will significantly contribute to understanding the role of stiffness in disease. Furthermore, even though stiffness measures have been shown to be strong prognostic indicators for the occurrence of cardiovascular events, work has yet to be done to show if the reduction or attenuation of arterial stiffness is associated with a reduction of cardiovascular events, independent of other risk factors (Laurent & Boutouyrie, 2007). Indeed, more immediate changes such as reductions in blood pressure, hyperglycemia, and lipids do show reductions in cardiovascular risk scores. However, improvements in the wall of the vessel (stiffness) may in fact suggest more long lasting reductions in cardiovascular risk, but this remains to be seen (Laurent & Boutouyrie, 2007).

Despite these future considerations, measurement of arterial stiffness is critical in understanding changes in the vascular tree, as its indices can be transiently and chronically altered by aging, disease, and lifestyle factors. Aortic PWV is considered the gold standard for non-invasive assessments of arterial stiffness, and can provide the most relevant

information about an individual's future risk of cardiovascular morbidity and mortality, and all-cause mortality. Measurement of local arterial stiffness, while requiring more expertise and time, has also emerged as an important tool for the mechanistic study of vascular structure and function, especially in less diseased populations. In combination, these ultrasonic techniques provide a simple, comprehensive, and non-invasive approach to understand arterial structure and function. They should therefore be considered in the study of overall vascular health.

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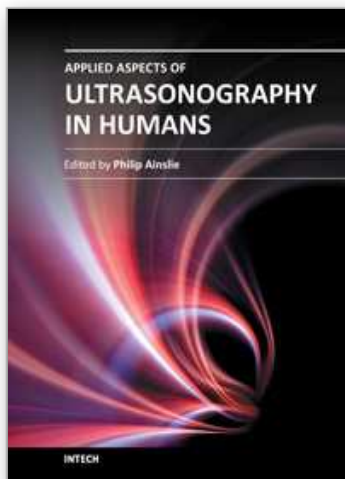
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