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INVITED REVIEW

Assessment of arterial stiffness using applanation tonometry

David H. Kim and Branko Braam

Abstract: Augmentation index (AIx) and pulse wave velocity (PWV) assess functional and structural aspects of the vascular wall and are independent markers of cardiovascular morbidity and mortality. Like blood pressure, many factors, genetic, structural, and physiological, affect AIx and PWV. AIx and PWV can be assessed noninvasively using applanation tonometry. The technique is simple, but comes with a number of practical and technical limitations that have not been well documented and (or) explored. This review considers pulse wave analysis in the context of cardiovascular disease, and considers its limitations. Data are presented indicating that the placement of the probe is critical, and that the amplitude of the obtained signal is related to the variability in measurements. On a more theoretical note, issues are discussed regarding the applied transfer functions that are built in the devices to assess central AIx from peripheral waveforms. Altogether, PWV and its analysis are useful additions to the arsenal of parameters that can be used to assess vascular health and to estimate vascular risk. Yet, our analysis underscores the necessity for precise operating procedures, and calls for transparency regarding the applied transfer functions of commercial devices.

Key words: arterial stiffness, augmentation index, pulse wave velocity, applanation tonometry.

Résumé : L'index d'augmentation (IA) et la vitesse de l'onde pulsatile (VOP) évaluent les aspects fonctionnels et structurels de la paroi vasculaire et constituent des marqueurs indépendants de la morbidité et de la mortalité cardiovasculaires. Comme la pression sanguine, plusieurs facteurs — génétiques, structurels et physiologiques — affectent l'IA et la VOP. L'IA et la VOP peuvent être évaluées de manière non invasive à l'aide de la tonométrie à aplanation. La technique est simple mais elle s'accompagne d'un certain nombre de limitations pratiques et techniques qui n'ont pas encore été bien documentées et (ou) explorées. Cet article de revue examine l'analyse de l'onde pulsatile dans le contexte de la maladie cardiovasculaire et examine ses limites. Les données présentées indiquent que le positionnement de la sonde est critique et que l'amplitude du signal obtenu est reliée à la variabilité des mesures. Sur un plan plus théorique, les problèmes relatifs aux fonctions de transfert appliquées qui sont construites dans les dispositifs afin d'évaluer l'IA central à partir de la forme de l'onde périphérique sont discutés. Ensemble, la vitesse et l'analyse de l'onde pulsatile sont des ajouts utiles à l'arsenal de paramètres pouvant être utilisés pour évaluer la santé vasculaire et évaluer le risque vasculaire. Notre analyse souligne encore la nécessité d'avoir des procédures d'opération précises, et appelle à la transparence relativement aux fonctions de transfert appliquées des dispositifs commerciaux. [Traduit par la Rédaction]

Mots-clés : rigidité artérielle, index d'augmentation, vitesse de l'onde pulsatile, tonométrie à aplanation.

Introduction

Structural abnormalities in arterial properties, such as increased intima–media thickness and presence of atherosclerotic plaques are important indicators of developing cardiovascular disease. Similarly, functional abnormalities, such as impaired vasodilation and increased arterial stiffness, are significantly associated with future cardiovascular events in healthy, hypertensive, or chronic kidney disease (CKD) subjects (Blacher et al. 1999; Nishiura et al. 2008; Song et al. 2009; Gomez Marcos et al. 2010). Arterial stiffness can be assessed by determining the augmentation index (AIx) and pulse wave velocity (PWV) (Laurent and Boutouyrie 2007) via simple and noninvasive applanation tonometry. This technique has been validated in many studies (Sharman et al. 2006; Hope et al. 2007; Zuo et al. 2010) and is now applied in large studies that relate arterial stiffness and outcomes. Nevertheless, some of its practical aspects have not been studied in depth, like seemingly trivial operator aspects such as the angle at which the tonometer is applied on the vessel that may influence the AIx and PWV measurements. This review explores the basis of applanation tonometry to assess AIx and PWV and discusses several practical aspects, illustrated using original data and those from other studies. Without a doubt, applanation tonometry can support early diagnosis of vascular dysfunction and guide effective treatment strategies, if used with thought. This review specifically does not address more recently developed interpretations of the arterial pulse wave. It also does not cover the details of applying tonometry to assess left ventricular afterload (Chirinos and Segers 2010*a*, 2010*b*).

Definition and determinants of AIx and PWV

Arterial pressure waveform develops from the forward pressure wave created by the cardiac contraction combined with the wave reflected from the periphery. The augmentation index (AIx) is the ratio of the augmented pressure, which is the difference between the second peak (P_2, due to reflected wave) and the initial peak or (P_1, due to forward wave) of a pressure waveform, and the pulse pressure (PP) (Shimizu and Kario 2008) (Fig. 1). Assessing AIx is performed by so-called pulse wave analysis (PWA). Pulse wave

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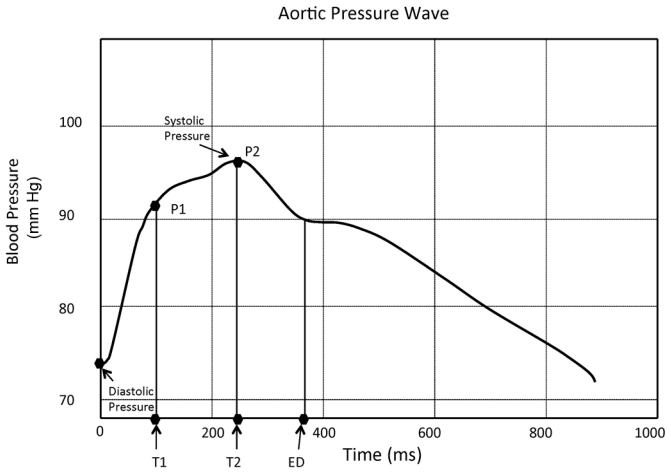
Fig. 1. Aortic pressure waveform. T1, time to 1st peak; T2, time to 2nd peak (reflected pressure wave arrives at heart); ED, ejection duration (the duration of mitral valve closure).

$$\text{AIx} = \frac{P_2 - P_1}{\text{pulse pressure}} \times 100$$



velocity (PWV) is the speed at which the pressure wave travels between 2 sites in an arterial tree (DeLoach and Townsend 2008). PWV is the transmission of energy in the form of pulse waves in blood. Normal PWV varies between 6 and 10 m/s (The Reference Values for Arterial Stiffness Collaboration 2010).

Arterial stiffening increases AIx: if the reflected wave arrives earlier in a cardiac cycle, it superimposes on the initial systolic peak and AIx increases, resulting in increased and (or) prolonged cardiac afterload, which is obviously associated with development of left ventricular hypertrophy (LVH). If arterial stiffness is low, the reflected wave arrives later in a cardiac cycle, the ascending aortic pressure increases during diastole and AIx decreases, and this improves perfusion of the coronary arteries (Davies et al. 2003). Increased arterial stiffness also increases PWV. The difference between these parameters is that PWV assesses the arterial stiffness between 2 recording sites, whereas AIx indicates systemic arterial stiffness (Riggio et al. 2010). Yet, AIx depends on the cardiac cycle (including heart rate), PWV, and also on the amplitude of the reflected wave. Thus, AIx provides more complex information about the qualities of systemic vasculature than PWV (Shirwany and Zou 2010).

AIx and PWV versus SBP, DBP, and PP in the evaluation of cardiovascular status

Until late in the 20th century, diastolic blood pressure (DBP) was predominantly used to identify cardiovascular risk. Subsequently, the Framingham Heart Study researchers found significant correlations between elevated systolic blood pressure (SBP), coronary events (Kannel et al. 1971), and stroke (Kannel et al. 1981). Subsequently, a meta-analysis reported that SBP was a stronger predictor than DBP of cardiovascular events (Lewington et al. 2002). Soon after, pulse pressure (PP) was reported to have significant predictive value for cardiovascular events (CHD, stroke, myocardial infarction) in both normotensive and hypertensive populations (Madhavan et al. 1994; Benetos et al. 1997; Franklin et al. 1997, 1999). SBP and DBP both increase with advancing age, but at around 50 years of age DBP stabilizes and subsequently decreases, while SBP continues to increase (Franklin et al. 1997). As a result, PP increases, which is likely related to arterial stiffening with age, and becomes a predictive factor for CVD (Benetos et al. 2000).

Not surprisingly, when noninvasive equipment became available for the assessment of PWA and PWV, it was reported that PWV is a more potent independent predictor of cardiovascular events than PP (Laurent et al. 2001; Meaume et al. 2001). Aortic PWV (aPWV) was shown to predict future cardiovascular events in hypertensive (Laurent et al. 2001), CKD (Wimmer et al. 2007), end-stage renal disease (ESRD) (Blacher et al. 1999), and diabetic (Cruickshank et al. 2002) patients and in elderly hospitalized subjects (Meaume et al. 2001). Even after adjusting for sex, age, body mass index (BMI), and MAP, aPWV shows a better association with coronary artery disease (CAD) stroke, and heart failure than PP in normotensive, hypertensive, or diabetic patients (Willum-Hansen et al. 2006). aPWV can significantly improve the risk stratification for cardiovascular complications beyond other traditional risk factors, including mean arterial pressure (MAP), SBP, DBP, PP, age, BMI, current smoking, and alcohol intake (Willum-Hansen et al. 2006). AIx is affected by the cardiovascular risk factor profile. Radial AIx (rAIx) was increased in patients with impaired glucose metabolism (IGM) and more severely in those with diabetes mellitus 2 (DM-2) compared with healthy subjects when controlled for age, sex, MAP, heart rate (HR), BMI and other factors (Schram et al. 2004). AIx is also increased in patients with hypercholesterolemia (Matsuo et al. 2005). Moreover, AIx is an independent predictor of CVD (London et al. 1994; Chirinos et al. 2005; Qureshi et al. 2007; Weber et al. 2007), particularly in younger and middle-aged patients (Weber et al. 2004). rAIx was positively correlated with development of cardiovascular disease such as CAD and cerebrovascular accident (CVA) in healthy subjects and in hemodialysis patients (Nishiura et al. 2008). Together, PWA and PWV seem to extend the prediction of cardiovascular events beyond blood pressure.

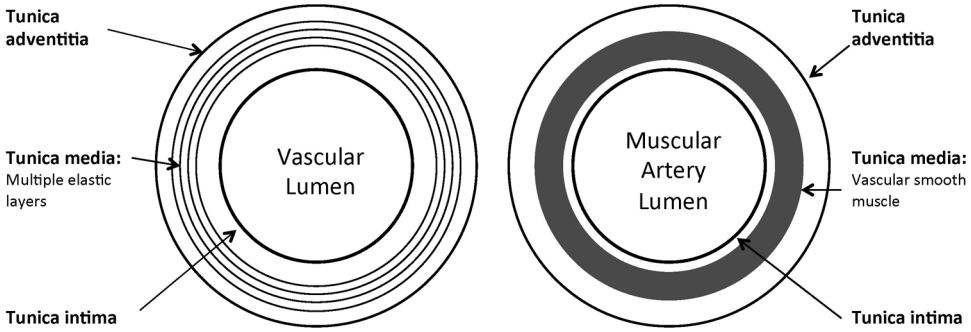
Of note, ambulatory arterial stiffness index (AASI) can also be used to assess arterial stiffness that considers the dynamic relationship between SBP and DBP. AASI can be assessed by ambulatory SBP and DBP measurements made over 24 h: the slope of the linear regression between DBP and SBP is defined as the arterial compliance, and 1 minus the slope as the AASI. In stiffer arteries, SBP increases substantially more with increases in DBP than in arteries that are less stiff, leading to greater AASI. AASI is closely correlated with aPWV and AIx (Li et al. 2006). Renal disease, left ventricular hypertrophy (LVH), and increased carotid intima–media thickness (Leoncini et al. 2006) are all associated with increased AASI. Although AASI has been reported to be a better predictor of stroke than aPWV in both hypertensive and normotensive subjects, the latter better predicts cardiovascular events (Hansen et al. 2008). Thus, AASI has some prognostic value by itself; however, because it requires 24 h blood pressure measurements, it takes longer to measure than PWA and PWV.

Carotid-femoral PWV (cfPWV) measures the aPWV (or central PWV) while carotid-radial PWV (crPWV) evaluates peripheral PWV. aPWV is considered the best standard so far for assessing arterial stiffness, presumably since it resembles best the dynamics of the pressure wave close to the heart itself. Age and DM are associated with increased aPWV, and only modestly associated with peripheral PWV (Kimoto et al. 2003). However, both aPWV and crPWV were independently associated with arterial stiffness in Chinese populations with DM-2 (Zhang et al. 2011). Nevertheless, crPWV is frequently used because of the more comfortable site of measurement. One could argue though that central PWV is more relevant than peripheral PWV in assessing the pathophysiology of CVD (Safar et al. 2003).

Vascular wall structure and the location of arterial pressure wave reflection

The aorta and pulmonary trunks are low resistance elastic arteries. Their thick media is composed of many layers of elastin fibres, which make the arteries more distensible to accommodate the blood pressure created by cardiac contraction (Fig. 2). The muscular layer of resistance arteries, on the other hand, enables

Fig. 2. Composition of the wall of an elastic artery (left) and a muscular artery (right).



the arteries to adapt to local and systemic factors (Shirwany and Zou 2010). Key for the current discussion is that pressure waves created by the systole of the left ventricle are transmitted to the aorta and to the resistance arteries as forward waves, and then become reflected to return to the heart. This reflection of pressure waves in the arterial tree occurs at sites of "impedance mismatch." Arterial impedance is the impediment of the flow of pressure waves determined by the geometry of a vessel (radius and wall thickness), elastic properties of the vascular wall, and blood viscosity. Impedance mismatch occurs where there is an abrupt change in vascular impedance, causing partial reflections of the pressure wave flow while the rest of the waves continue to propagate forward (Del Rio et al. 2003). Major sites of impedance mismatch are located at bifurcations or arteriolar branching between the aorta and the femoral artery and at the interface where the low resistance elastic arteries meet high resistance muscular arteries (Benchimol-Barbosa and Barbosa-Filho 2010). The reflected waves from many sites of impendence mismatch combine with each other to form a backward pressure wave returning to the heart. However, these reflection sites shift away from the heart as one ages; this predominantly happens in men over 65 years of age (Sugawara et al. 2010).

Peripheral amplification of SBP and PP

SBP and PP increase from proximal to peripheral arteries while diastolic pressure remains virtually constant; this is known as "peripheral amplification." This is explained as follows. Arterial stiffness progressively increases from proximal elastic arteries to distal muscular (resistance) vessels. Initially, when blood is transmitted through the arteries from the heart, the elastic properties of the large vessels lead to arterial wall distension, which dampens the pressure waves generated by cardiac contraction. When the pressure wave travels further into the muscular resistance vessels, which are less elastic, this augments the pressure wave. DBP is similar in both types of arteries because the heart is at rest during diastole and does not generate additional pressure for vascular wall distension. Thus, as the arteries become stiffer, SBP increases and DBP remains the same, which elevates PP (London and Pannier 2010). However, with increasing age, the peripheral amplification effect is reduced as the aortic stiffness increases substantially, compared with peripheral stiffness, and the stiffness gradient from centre to periphery is decreased (Mitchell et al. 2004). Another factor for peripheral amplification is the overlap between forward and reflected pressure waves in the periphery. The forward and reflected waves are in phase at the site of impedance mismatch, and 100% overlap occurs, which leads to maximum augmented pressure. However, at locations in central arteries distant from the site of reflection, the forward and reflected waves are out of phase and less overlap occurs, leading to a smaller augmented pressure (London and Pannier 2010). This decreased overlap results in lower SBP and PP in central arteries compared with peripheral arteries.

Factors affecting arterial stiffness

Many factors influence PWV and AIx. These can be divided into genetic, structural, and functional factors.

Genetic factors

SNPs in genes coding for vascular proteins, components of the renin–angiotensin system (RAS), and inflammatory enzymes have all been shown to influence arterial stiffness (Mitchell et al. 2007). Specific examples are SNPs in the *FAS* inflammatory pathway (Schnabel et al. 2008), mutations in the *FBN1* gene that encodes Fibrillin-1 and leads to Marfan syndrome (Kingwell and Boutouyrie 2007), and allele deletion in the elastin gene, causing Williams syndrome (Lacolley et al. 2002; Kingwell and Boutouyrie 2007). All of these lead to abnormalities in vascular function and stiffness.

Structural factors

Intima–media thickness (IMT) is the combined arterial thickness of intimal and medial layers. Elevated IMT is associated with increased arterial stiffness and a surrogate marker of atherosclerosis (Bots et al. 2005). The extracellular matrix (ECM) is a major component of the vascular wall and is crucial for controlling vascular remodelling, which is a dynamic process that involves changes in the luminal diameter and in the tunica media mass, and thereby also affects IMT in response to hypertension and changes in HR (Touyz 2005). ECM is a home for many growth factors, substrates for cell adhesion, and factors involved in vascular remodelling. The latter are mainly metalloproteinases (MMPs) and their inhibitors (TIMPs). MMPs and TIMPs are regulated via growth factors stored in the ECM. Immune cells such as neutrophils secrete MMPs that degrade ECM by decreasing collagen and elastin fibre production, whereas TIMPs counteract these reactions, thereby providing a dynamic balance of ECM (Shirwany and Zou 2010). People with prolonged inflammation, increased blood pressure, and old age have overproduction of collagen and decreased elastin synthesis, leading to increased arterial stiffness (Shirwany and Zou 2010). Consequently, diversity in the ECM components and their regulators lead to differences in arterial stiffness between individuals (Kingwell and Boutouyrie 2007).

Functional effects by key physiological systems in systemic hemodynamic regulation

Angiotensin II (AngII), likely via the AT1 receptor (Rehman et al. 2002), leads to collagen formation, elastin degradation, and decreased nitric oxide production (Raij and Gonzalez-Ochoa 2011) in the vascular wall, ultimately leading to an increase in arterial stiffness (Mahmud and Feely 2004). AngII action also increases PWV, independent of the change in brachial blood pressure (Rehman et al. 2001). Activation of the sympathetic nervous system (SNS) induces smooth muscle cell (SMC) hyperplasia, increases collagen production (Nichols and Epstein 2009), and thereby also increases arterial stiffness. Endothelin 1 (ET-1), a po-

tent vasoconstrictor, elevates PWV by binding to the ET_A receptor subtype, leading not only to structural changes in the SMC, in the form of hyperplasia, but also to the accumulation of ECM and inflammation, all of which contribute to vascular stiffness (Nichols and Epstein 2009). Vuurmans et al. showed that infusing ET-1 in healthy volunteers increased their PWV and aortic SBP, which were reversed upon administering ET_A receptor blockers (Yuan et al. 2006), indicating a functional response. Conversely, prostaglandins, via the prostaglandin E_2-sensitive receptors (EP receptors) EP2 and EP4, cause vascular smooth muscle cells (VSMC) to relax and decrease arterial stiffness (Maeda et al. 2005). Also, people with volume overload have increased arterial stiffness. Increased extracellular fluid volume causes arterial distension, which increases stiffness. Ultrafiltration of hemodialysis patients improved their arterial compliance (Ie et al. 2005).

The subject of the relationship between heart rate (HR) and arterial stiffness is complex. HR has a significant positive association with arterial stiffness (Park et al. 2010). Higher HR usually indicates greater sympathetic activity and metabolic rate. This is associated with increased vascular tone and oxidative stress, respectively (Shankar et al. 2004), and can contribute to increased arterial stiffness. However, there are technological considerations as to how the relationship between HR and PWV functions. Increased HR leads to reduced cardiac ejection time, and also alters the predicated aortic waveform. Whether HR is a determinant of central PWV depends on whether one measures the peak of the upstroke of the pulse wave, or the peak derivative of the upstroke. When the lowest point before the rapid increase in upstroke is used to denote pulse arrival time, PWV is not influenced by HR (Hayward et al. 2002).

HR reportedly is negatively correlated with AIx. Many studies have not accounted for arterial stiffness (radial-carotid PWV) (Stefanadis et al. 1998; Wilkinson et al. 2000; Gatzka et al. 2001). After accounting for arterial stiffness, there is a stronger relationship between AIx and HR for people with high arterial stiffness than those with low arterial stiffness (Papaioannou et al. 2008). Thus, it is preferable to correct AIx for an HR of 75 bpm, based on the levels of aortic stiffness (Wilkinson et al. 2000; Gatzka et al. 2001). This could cause a paradox with respect to antihypertensive treatment, since drugs that lower HR to reduce BP may increase AIx in patients with high arterial stiffness, which would offset decreased cardiovascular risk due to the BP reduction. Exercise not only increases HR but also BP, which make PWV changes hard to interpret (Siche et al. 1989; Lantelme et al. 2002). An increase in PWV upon higher HR is likely due to the reduced time for vascular recoil (Mangoni et al. 1996). In sum, increased HR decreases Aix but elevates PWV. Therefore, PWV and AIx are not interchangeable, and AIx reflects arterial stiffness as well as other factors such as ventricular ejection pattern, vascular tone, and the absolute duration of systole (Lantelme et al. 2002).

Vascular applanation tonometry

Invasive and non-invasive assessment of pulse waveforms

The measurement of arterial pressure waveforms began in the 19th century with the sphygmograph, a mechanical instrument used to detect pulse, amplified with a lever and springs (Fig. 3).[1] In the early 20th century, vascular catheterization was invented, which allowed central pressure waveform measurements by inserting a fluid-filled femoral artery catheter that was advanced into the ascending aorta (Wang et al. 2004). These days, pulse waveforms can also be assessed with a catheter with a pressure transducer on its tip. Although accurate, invasive measurement comes with risks that include potential blood vessel damage, cholesterol emboli, and infection (Sakurai et al. 2007; Sokolski et al. 2011). In the 1960s, the idea of arterial applanation tonometry was further developed to measure arterial waveforms noninvasively (Nelson et al. 2010).

Applanation tonometry and measurement of AIx and PWV

Applanation tonometry records arterial pressure waveforms and can be used to calculate AIx, PWV, and other cardiovascular parameters (Nelson et al. 2010). When the rounded surface of a columnar chamber is gently flattened, the intramural pressure can be transmitted to and detected by the sensor that presses on the chamber (Tsai and Yucha 2001). We expand briefly on the SphygmoCor system as one of the prototypical system that is widely used. This device measures aortic AIx via applanation tonometry by recording peripheral waveforms at the peripheral artery. However the peripheral pressure is not the same as central aortic pressure, which has greater prognostic value. By application of a mathematical function called (generalized) transfer function (TF), the central pressure waveform is calculated from the peripheral pressure waveform. This method of aortic AIx measurement is called pulse wave analysis (PWA).

PWV is the pulse wave transit distance between those sites, divided by the pulse wave transit time between 2 recording sites (radial and carotid arteries for peripheral PWV; femoral and carotid arteries for central PWV). The transit time is calculated by assessing the delays between the R wave of recorded ECG and the foot of the pressure waveform at site A or B is the wave transit time of ECG-site A or ECG-site B, respectively (Frimodt-Moller et al. 2006).

Other devices that can measure AIx and PWV noninvasively use piezoelectric and oscillometric sensors; however, the general principles are similar. Complior (ALAM Medical) evaluates AIx, PWV, and central pressure via a piezo-electric method, and allows stationary pressure signals at the carotid and femoral arteries to be recorded simultaneously (Amar et al. 2001). Arteriograph (TensioMed) measures brachial pressure waveforms, oscillometrically, on the subject's upper arm with a blood-pressure cuff. The pulsatile pressure in the artery causes oscillations or periodic pressure changes in the inflated cuff that are recorded as pressure curves. Arteriograph uses commercial algorithms to determine central blood pressure and AIx from peripheral measurements (Horvath et al. 2010; Rezai et al. 2011) (Table 1).

Quality control indices of AIx and PWV measurements

Devices provide quality assessment algorithms; however, the validity of the algorithms is not entirely transparent. For AIx, Sphygmocor quality assessment incorporates average pulse height, pulse height variation, pulse length variation, and diastolic variation into an operator index. Diastolic variation is the fluctuation in the DBP across waveforms. SphygmoCor recommends that the average pulse height be greater than 100 units, pulse height and diastolic variation be <5%, and the operator index be >80 for optimal AIx measurements. The underlying data for this are not transparent. For PWV, quality control indices are present for both pressure waveforms and ECG signal. Both measurements are evaluated in terms of their average pulse height, pulse height variation, pulse length variation, and baseline variation (the amount of variation in the base line drift). However, an operator index is not calculated for PWV measurements. Another quality index for PWV is the SD of mean time difference between sites A and B, which should be below 6% for optimal PWV values, according to SphygmoCor.

[1]Figure 3 is a reproduction of a previously published figure (E.J. Marey. 1876. La Méthode Graphique dans les Sciences Expérimental. Partie 2. *Edited by* G. Masson. Libraire de l'Académie de Médecine, Paris, France. p. 208). It was not possible to obtain permissions for this figure.

Fig. 3. Illustration of the sphygmograph invented by Etienne Jules Marey in 1860 (reproduced from Marey, E.J. 1878. La méthode graphique dans les sciences expérimentales. p. 208; permissions were not applicable for this image).

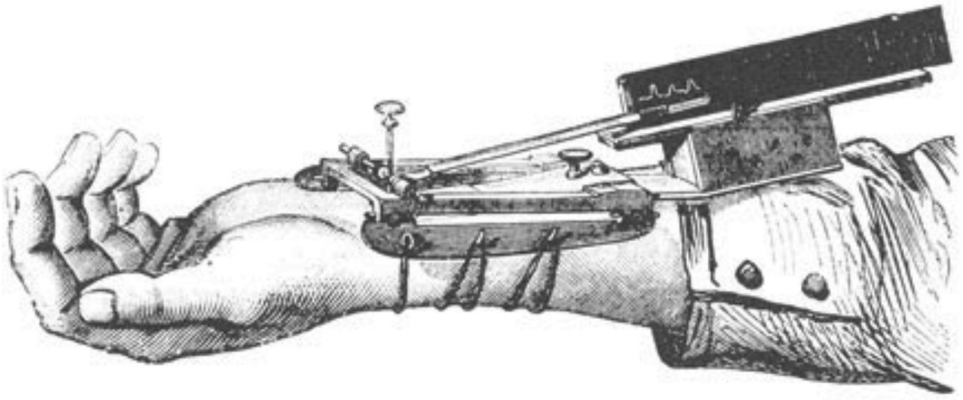
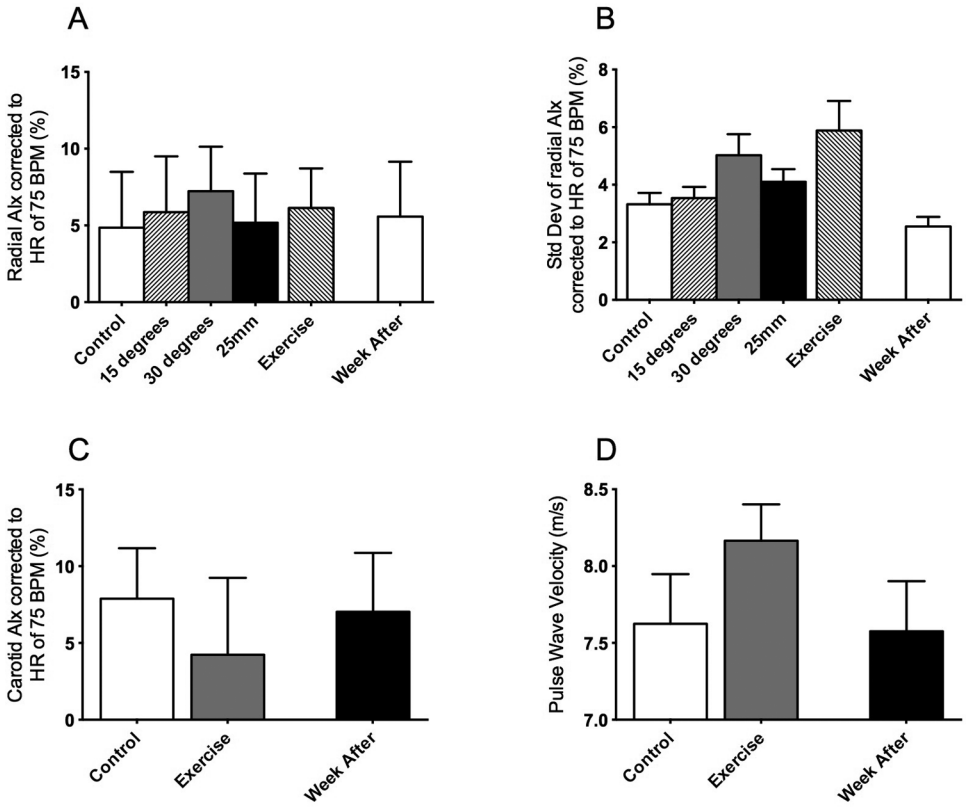


Table 1. Different noninvasive methods of assessing arterial stiffness (AIx and PWV), and their advantages and disadvantages.

Method	What is measured	Measurement site	Advantages	Disadvantages
Applanation tonometry (SphygmoCor)	aAIx, PWV	Radial, carotid and femoral	Non-invasive, easy to use	Requires multiple measurements, probe placement is critical
Piezo-eletric (Complior)	aAIx, PWV, aortic pressures (from carotid artery without GTF)	Radial, carotid, femoral and distal arteries	Non-invasive, no ECG required, simultaneous measurement at 2 sites, probe fixed at site	Digitized waveform cause difficulty in distinguishing the arrival time of wave.
Oscillometric (Arteriograph)	aAIx, PWV, aortic pressures (from commercial algorithms)	Brachial artery	Locating exact position of artery not required	Pressure cuff may be uncomfortable

Note: aAIx, aortic augmentation index; PWV, pulse wave velocity.

Fig. 4. (A) Comparison of an individual's radial augmentation index (AIx) at a heart rate (HR) of 75 bpm (AIx_{75}). The differences are not statistically significant ($P > 0.05$). (B) Comparison of the SD for AIx_{75} under different technical conditions: just after exercise, and a week after exercise. The differences are statistically significant ($P < 0.05$). (C) Comparison of carotid AIx_{75} under different technical conditions. The differences are not statistically significant ($P > 0.05$). (D) Comparison of pulse wave velocity under different technical conditions: before exercise, just after exercise, and a week after exercise. The differences are statistically significant ($P < 0.05$).



Technical considerations of AIX and PWV

To obtain more insight into technical and biological variation of the AIx and PWV measurements, we assessed the technical variation in radial AIx and intra- and inter-individual variability of radial and carotid AIx in 17 healthy subjects (mean age 29 [19–50] years; 8 males, 9 females). The studies were approved by the Health Research Ethics Board at the University of Alberta. Under control conditions, subjects were asked to rest in a supine position for 5 min and their AIx and PWV were measured using a SphygmoCor to assess inter-individual variability. Technical variability was assessed by varying the tonometer angle and its location of placement on the right radial artery. Subjects were re-measured a week later to assess intra-individual variability at rest. Carotid AIx and PWV remained constant after one week (Fig. 4; 1-way ANOVA; all $P > 0.05$). Significant inter-individual variation in radial AIx, carotid AIx, and PWV was observed (Table 2). In other studies, radial applanation tonometry has shown high within- and between-observer repeatability when measuring healthy and hypertensive subjects (Wilkinson et al. 1998; Crilly et al. 2007). However, PWV measurements have been less reproducible (both aortic and brachial PWV) owing to the difficulty of recording pressure waveforms accurately at the femoral and carotid arteries (Wilkinson et al. 1998). The reproducibility of carotid tonometry remains unclear.

The angle of the tonometer and the exact placement on the radial artery seem relevant for the reproducibility of the results. In our hands, consecutive measurements of the radial AIx tended to vary, even if they had high operator indices. This was a result of the slightest movement of the hand-held tonometer while recording, which would shift the amplitude of pressure wave and thus affected the arterial pressure waveforms. Also, the subject's HR varied during the 10 s period of measurements, which may change the shape of each pressure waveform. As a result of these variations, it seems preferable to obtain several measurements of AIx in an individual, rather than a single measurement. We have been unable to find consistently in the literature whether multiple measurements are indeed performed by other investigators.

Angle and position of the probe relative to the radial artery

The angle at which the tonometer was applied on the radial artery did not significantly affect the average of radial AIx measurements ($P > 0.05$). However, the variability of AIx increased by decreasing the angle of the tonometer to the skin (Fig. 4), and the average pulse height and the operator index of the arterial pressure waveforms tended to decrease. Increasing the distance of tonometer placement from the radial artery did not significantly affect the AIx measurements per se, but again decreased the amplitude and the operator index of the pressure waveforms (Fig. 4). It became more difficult to locate the radial artery as the distance increased from the wrist moving up the arm, as the thickness of subcutaneous layer that covers the artery increases. For optimal measurements, it seems that the tonometer should be placed close to 90° on the radial artery and close to the wrist.

The radial AIx is negatively correlated with average pulse height (PH_{avg}). Recording waveforms with higher amplitude tended to measure lower radial AIx (Fig. 5A). The SphygmoCor software guideline states that for AIx, values for PH_{avg} greater than 100 mm Hg are optimal (1 mm Hg = 133.322 Pa). However, when only values of PH_{avg} greater than 100 mm Hg (values range from 100 to 250 mm Hg) and operator index greater than 80 were considered, there was still a significant negative correlation between radial AIx and PH_{avg} (Fig. 5B). Carotid AIx and PWV were not significantly correlated with PH_{avg}. Since only the foot of the arterial waveform is important during PWV measurement, other quality indices such as average pulse length, pulse height variation, and baseline variation are not significantly associated with PWV.

Table 2. Inter-individual variability of radial and carotid Aix_{75} and PWV.

Parameter	*N*	Range	1-way ANOVA
Radial AIx	17	−26.5% to 31.0%	$P < 0.01$
Carotid AIx	12	−2.0% to 36.5%	$P < 0.01$
PWV	16	6.2% to 9.9%	$P < 0.01$

Note: PWV, pulse wave velocity; AIx, augmentation index.

Heart rate and AIx corrected to a heart rate of 75 bpm

In our small study, radial AIx corrected to HR of 75 bpm ($rAIx_{75}$) was significantly correlated with HR (with a very low r^2 of 0.04 and 0.03, respectively; $P < 0.01$ for both; $n = 606$ measurements in 17 subjects). This was evaluated through exercise-induced increased pulse as subjects were asked do quick sit-ups or running on the spot to elevate their HR (Figs. 6A and 6B). Similarly, HR and both carotid AIx and AIx_{75} were significantly correlated ($r^2 = 0.32$ and 0.04 respectively; P value <0.001 for both; $n = 217$ measurements in 12 subjects; Figs. 6C and 6D).

Validity of radial-aortic generalized transfer function

An intriguing aspect of pulse wave analysis is the radial-aortic transfer function, of which the validity is still questioned by some. The transfer function was constructed by determining the relationship between central aortic waveforms recorded invasively, and radial waveforms measured via applanation tonometry in humans, and by applying various techniques such as Fast Fourier Transform (Hope et al. 2007) and autoregressive-exogenous method (Chen et al. 1997). Many studies that indicate a single generalized transfer function (GTF) can be used to determine central from peripheral waveforms (Karamanoglu et al. 1993; Takazawa et al. 1996; Chen et al. 1997; Sugimachi et al. 1997; Fetics et al. 1999; Pauca et al. 2001). However, the reconstructed AIx (aortic AIx converted from radial AIx via GTF) has a high degree of variability (Davies et al. 2003; Smulyan et al. 2003; Hope et al. 2007). Thus, the published TFs derived from different studies cannot be proven to be different (O'Rourke 2007) owing to a high SD among the errors. Moreover, the subjects from whom the GTFs were derived had clinical indications for cardiac catheterization and, therefore, the relationship between central aortic and radial waveforms may differ in other groups of subjects (Lehmann 1998; Hope et al. 2007). Unfortunately, GTFs incorporated in the software of devices such as SphygmoCor are proprietary. Differences have been reported in the radial-aortic GTF between diabetic and nondiabetic individuals (Hope et al. 2004); men and women (Hope et al. 2002); and subjects before and after exercise (Payne et al. 2007). The dispute has not ended, since critiques of this study emphasize that the GTF for the diabetics does not agree with the food and drug administration (FDA) approved GTF, which seemed to be accurate in diabetic patients (Wilkinson and McEniery 2004). Thus, one would hope that in the next few years, diabetic- and gender-specific GTFs will be further developed to convert radial waveforms into central waveforms.

Inaccurate detection of the 2nd systolic peak of arterial pressure waveform

Software for PWA detects the time to peak 1 (T1 in Fig. 1) due to heart contraction and peak 2 (T2 in Fig. 1) due to reflected waves returning to heart in the pressure waveforms. Sometimes the 2nd peak is not clear in radial pressure waveforms (Figs. 7A and 7B). Since the software may incorrectly identify the 2nd peak in the peripheral waveform, the transform into central aortic waveform using GTF may not be accurate. The exact algorithms used by the different devices are not public, and therefore the consequences of different wave forms for the calculated central aortic waveform is not clear.

Fig. 5. (A) The effect of an average pulse height of aortic pressure waveform on radial augmentation index (AIx) at a heart rate (HR) of 75 bpm (AIx_{75}; n = 606 measurements in 17 subjects) with a significant nonzero slope. (B) The effect of an average pulse height of aortic pressure waveform greater than 100 mm Hg on radial AIx_{75} (n = 172 measurements in 17 subjects) with a significant nonzero slope; 1 mm Hg = 133.322 Pa.

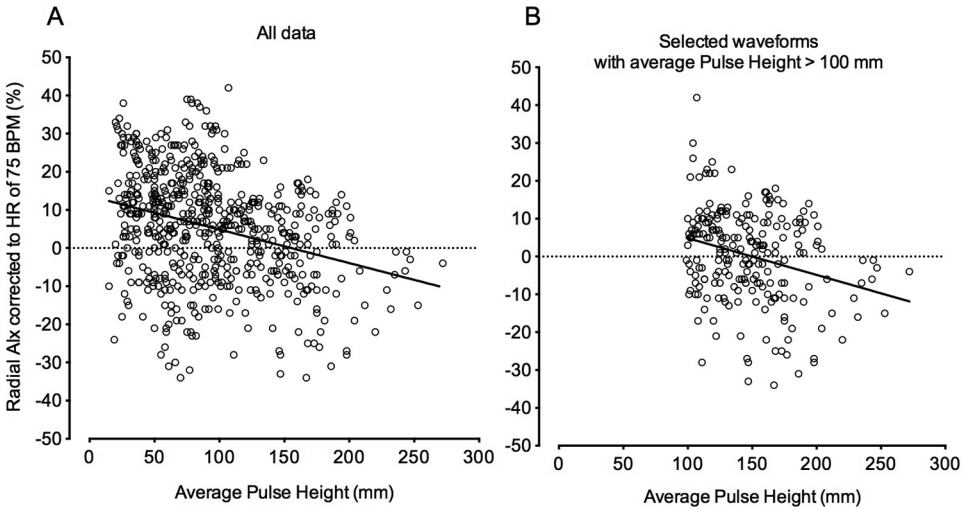


Fig. 6. Linear regression of heart rate vs. (A) radial augmentation index (AIx), (B) radial AIx adjusted for a heart rate of 75 bpm (AIx_{75}), (C) carotid AIx, and (D) AIx_{75}.

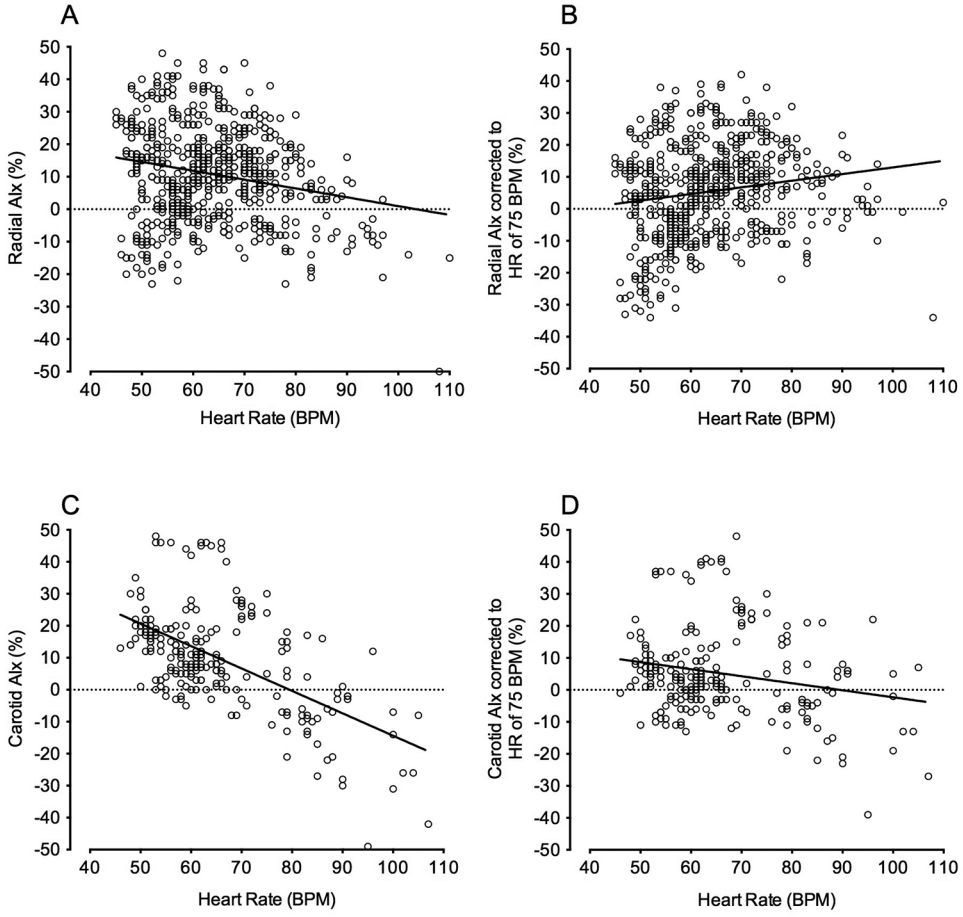
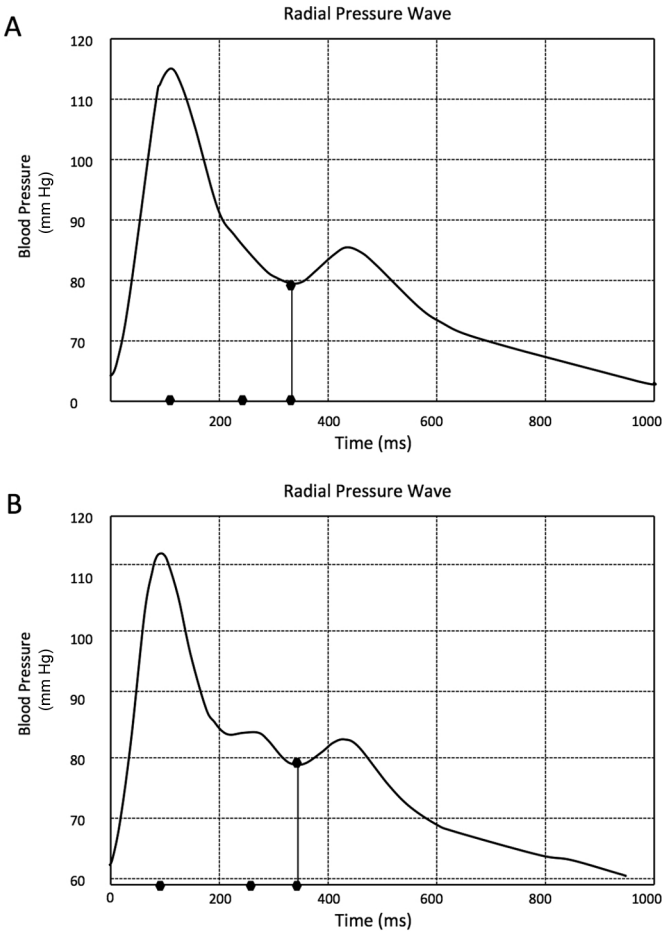


Fig. 7. Comparison of 2 graphs of a radial augmentation index where one has a visible 2nd peak and the other does not.



Limitations and usefulness of carotid applanation tonometry

Carotid applanation tonometry is not a validated technique. Some literature states that it is inaccurate because the overlying subcutaneous fat layers hinder the access to the carotid artery. Thus, locating the carotid artery and accurately recording waveforms can be difficult. Also, a subject's breathing can cause artefacts in the carotid artery waveform. Furthermore, the pressure amplitude recorded at the carotid artery is smaller than that measured at the radial artery, which leads to a lower quality of carotid AIx measurements. As a result, there are greater variations among multiple carotid AIx measurements within a subject compared with radial AIx recordings. It seems particularly important for the carotid waveforms that the operator index is high. In our small study, the average carotid AIx did not correspond with average radial AIx (Student's paired *t*-test; $P < 0.01$), yet radial and carotid AIx within each subject were not different when only curves with an operator index >70 were selected (Student's paired *t*-test; $P = 0.677$). Since carotid AIx requires a high operator index, radial applanation tonometry is simpler for assessing central AIx.

Conclusions

Aortic AIx and PWV have greater prognostic value of cardiovascular events than SBP, DBP, or PP. Therefore, assessment of the arterial pulse wave seems important. Nevertheless, a number of practical and more theoretical issues seem important when using pulse wave analysis. Regarding the practical issues, placement of the electrode seems key, and repetitive measurements are important. We strongly call for more transparency about the transfer functions incorporated in devices assessing PWA, and that would be publication of the GFTs. Altogether, the arterial pulse wave harbours important information about vascular integrity, yet routine application in clinical care should safeguard that the method is used technically appropriately. Moreover, clinical judgement of vascular function by transfer functions that are not public and therefore not testable does not seem be in line with sound clinical research and implementation in care.

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