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COMMENTARY

Pulse wave analysis and pulse wave velocity techniques: are they ready for the clinic?

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INTRODUCTION

In the present issue of *Hypertension Research*, Nürnberger *et al.*[1] interestingly describe an important factor when arterial stiffness is clinically assessed: subject's body position. Although this is an important question, especially if we want to bring this research tool to the clinic in a regular basis, there are several other factors that should be considered. The purpose of the present commentary is to briefly review past, present, and future of Pulse Wave Analysis and Pulse Wave Velocity and to discuss if these techniques are ready for clinical use.

Pulse wave analysis (PWA) was first developed in the nineteenth century by Mohamed.[2] With his sphygmograph, Mohamed was able to differentiate and diagnose several cardiovascular conditions, including rheumatic carditis, dilated left ventricular hypertrophy and 'arterial senility'. In addition, he was able to observe and document the deleterious effects of infectious diseases on the cardiovascular system, such as Bright's disease, irritative fever and typhus. However, it took almost a century to understand the hydro- and hemodynamic mechanisms involved in pressure wave reflection characteristics. Seminal work by McDonald[3], Womersley,[4] and Nichols and Rourke[5] was essential in this understanding,[3–5] but the relationship between central aortic pressures and PWA, via the analysis of pressure wave reflection characteristics, was not well established until late in the twentieth century by Murgo and Westerhof.[6–8]

On the basis of the pressure wave reflection characteristics and their relationship with central aortic pressures, O'Rourke, Safar and others[9–11] went one step forward and used PWA to non-invasively study central hemodynamics, cardiac function and hypertension development. Further technological advances in micromanometers design, expanded the study of pressure wave characteristics to include peripheral vascular scientists.[7,8,12] From this line of research, several vascular factors have been identified that affect PWA, for example, arterial stiffness, location of reflection sites and vessel diameter.[10,13,14] Consequently, early twenty-first century research has focused on determining which of these vascular factors are best chronicled by PWA techniques and, more importantly, what PWA information is useful in the clinical setting. One fact that has emerged from this legacy of research is that pressure wave forms change when arteries become stiff.[9,10] For example, round trip travel time of the reflecting wave (ΔTp) and aortic augmentation index (Aix; Figure 1) provide information on aortic wave reflection and arterial stiffness.[9,15] However, it is the measurement of pulse wave velocity (PWV) that is recognized as the gold standard for arterial stiffness assessment.[16] Although both PWA and PWV are tonometer techniques derived from pressure wave characteristics, PWA cannot be used as a surrogate for actual PWV in the clinic to assess arterial stiffness.[17]

In summary, PWA and PWV are two available research tools that are based on the same principles of pressure wave propagation/reflection characteristics. Both PWA and PWV are powerful research tools supported by ample scientific evidence. The remaining unanswered question is whether PWA and PWV techniques should be introduced in the clinical setting?

PWA AND PWV CHARACTERISTICS

Both PWA and PWV are based on pressure wave propagation/reflection characteristics.[5] Non-invasive PWA represents the aortic pressure waveform derived from the radial or carotid pulse using applanation tonometry and application of a generalized transfer function, which corrects for pressure wave amplification in the upper limb.[5] On the other hand, PWV represents the propagation velocity of pressure waves, and regional measurements can be performed nearly anywhere in the vascular tree. However, aortic PWV is considered the most clinical relevant. A brief description of both PWA and PWV follows. For further details consult Nichols and Singh[15] and Laurent *et al.*,[16] respectively.

Pulse wave analysis

Although new methods to assess PWA have been partially validated,[18–21] non-invasive assessment of aortic wave reflection characteristics is normally performed via applanation tonometry. High-fidelity radial artery pressure waveforms are recorded using a 'pencil type' micromanometer (Millar Instruments, Houston, TX, USA). Then, the aortic pressure waveform is derived from the application of a generalized transfer function, which corrects for pressure wave amplification in the upper limb.[5] Central pressure waveforms are characterized by several components (Figure 1). Among these components, the following PWA variables have been shown to have clinical relevance.

- *Aortic systolic (Ps), diastolic (Pd) and pulse pressures (Ps–Pd)* are derived from the generalized transfer function and recently they have been strongly associated with cardiovascular disease and outcome.[22,23]
- *Aortic incident pressure (Pi)*, defined as the pressure wave exclusively generated by ventricular contraction, has been recently better associated with aortic stiffness and aging than other PWA parameters, for example, aortic AIx.[14,24]

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- *AIx*, defined as the reflected wave amplitude in terms of pulse pressure (AIx=((Ps−Pi)/(Ps−Pd))×100),[6] represents the integration of incident and reflecting pressure waves. AIx has been associated with aging and arterial stiffness.[5,10,12,15,25] However, recent studies have shown that AIx may not be the best way to assess arterial stiffness.[14,24,26]
- *Round trip travel time of the reflecting wave (ΔTp)* is defined as the transit time required by the forward wave to travel from the ascending aorta to the major reflection site and back. Δ*T*p is measured from the foot of the forward traveling pressure wave to the foot of the reflected wave.[15] Although Δ*T*p is a direct component of PWV,[6,15] the relationship between Δ*T*p and measured PWV has not been consistent.[26–28]
- *Wasted left ventricular energy (LVE_W)* represents the extra workload that the ventricle must to generate during the duration of the reflecting wave. This energy is wasted because no gain in blood flow occurs.[15] According to previous studies,[9,29,30] LVE_W can be estimated as one-half of the area of an ellipse, i.e., $LVE_W=((\pi/4)\times(Ps-Pi)\times(ED-\Delta Tp)\times1.333)$, where ED is ejection duration and $2\times(Ps-Pi)$ and $(ED-\Delta Tp)$ are the major and minor diameters, respectively (shaded area in Figure 1b). Recent studies have determined that LVE_W is associated with left ventricular hypertrophy,[29] heart failure,[31] refractory angina syndrome[17] and smokeless tobacco use.[32]

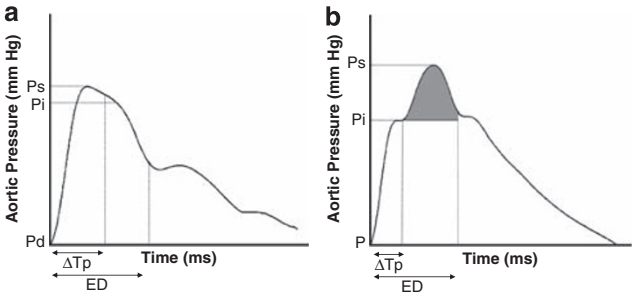

Figure 1 Aortic pulse wave analysis. (**a**) Normal/young pulse waveform. Reflecting wave during late systole, that is, longer Δ*T*p and Pi occurs after Ps, does not increase left ventricular effort. (**b**) Altered/old pulse waveform. Reflecting wave during early systole produces an augmented systolic pressure, which decreases blood flow (not shown), what enhance a wasted ventricular effort (dashed area). Ps, systolic pressure; Pi, incident pressure from reflecting pressure wave; Pd, diastolic pressure; Δ*T*p, round trip travel time of the reflecting pressure wave; ED, ejection duration. Aortic augmentation index (AIx)=((Ps−Pi)/(Ps−Pd))×100. Wasted left ventricular energy (LVE_W)=((π/4)×(Ps−Pi)×(ED−Δ*T*p) ×1.333).

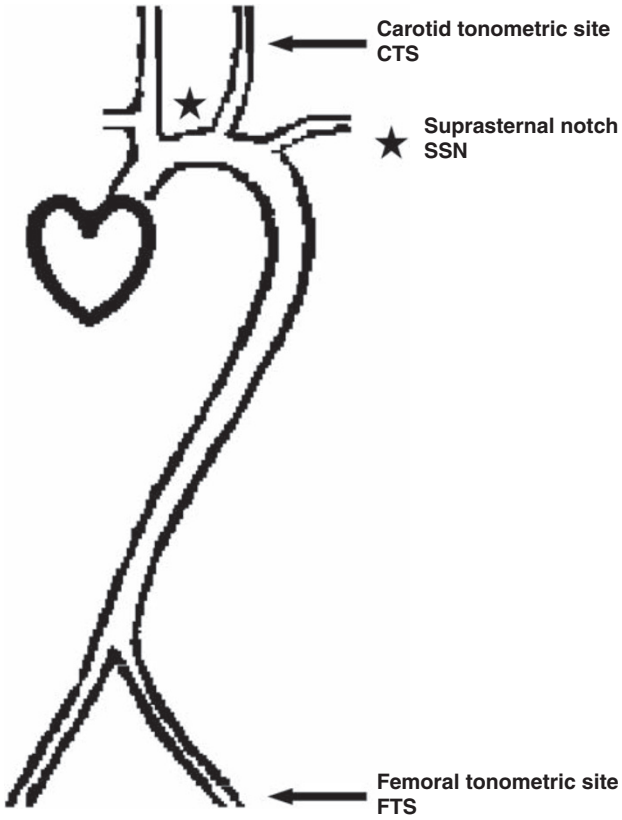

Figure 2 Pulse wave velocity aortic transit distance (ATD) determination to account for parallel transmission in the aorta and common carotid. Tonometric transit distance (TTD)=(CTS−SSN)+(SSN−FTS); ATD=TTD–(2×CTS−SSN) or ATD=(SSN−FTS)–(CTS−SSN). CTS, carotid tonometric site; SSN, suprasternal notch; FTS, femoral tonometric site.

Pulse wave velocity

Arterial stiffness is an important pathogenic factor for hypertension and it increases cardiovascular risk.[5,16,28,33] PWV is considered the gold standard for arterial stiffness assessment.[16,23] Non-invasive assessment of PWV can be performed using magnetic resonance imaging, vascular ultrasound, echotracking, mechanotransducers and tonometric devices. In general, these devices determine the time elapsed between two pressure wave forms from two different anatomical sites, normally between carotid and femoral artery sites. The travel distance used to calculate velocity is normally taken from body surface landmarks on the subject. Although new methods to assess PWV have been partially validated, the gold standard method of non-invasive assessment of PWV continues to be applanation tonometry.[5,10,14,16,18–21] In general, pressure waveforms are gated with simultaneous electrocardiographs and are used to calculate the PWV between the two sites (carotid–femoral). Foot-to-foot PWV is calculated by determining the delay between the appearance of the pressure waveform foot in the carotid and femoral sites (Δ*t*). The measurement of the tonometry transit distance is made using a measuring tape on the surface of the body connecting the carotid measuring site with the suprasternal notch and the suprasternal notch with the femoral measuring site, respectively (Figure 2). The aortic transit distance is estimated by subtracting two times the suprasternal notch–carotid distance from tonometry transit distance, to account for parallel transmission in the aorta and common carotid.[25] Finally, aortic

PWV is estimated by dividing aortic transit distance by Δt, using a validated computerized system.[14,25,26,34]

CLINICAL REFERENCE

In the past 20 years, multiple studies have been published that performed PWA or PWV in clinical populations with a variety of diseases.[10] These studies have ranged from analysis of pulse wave forms in patients with chronic renal disease[27] to studying central pressure in osteoporotic postmenopausal women[35] and in old men during exercise.[36] In aggregate, these studies have provided overwhelming evidence that PWA and PWV are different in various clinical populations when compared with age-matched healthy subjects. Moreover, PWA and PWV are changed by therapeutic interventions. The results of these studies illustrate the potential usefulness of PWA and PWV techniques in non-invasively assessing changes in the vasculature. However, there are two major considerations that must be resolved before PWA and PWV can bridge the gap between the research laboratory and clinical application: (1) the erroneous assumption that PWA and PWV are interchangeable, and (2) the lack of PWV and PWA reference values for 'healthy vasculature'.

PWA and PWV interchangeability

Although both PWA and PWV are derived from pressure wave characteristics, they are not interchangeable. As mentioned previously, PWV is the gold standard for arterial stiffness and it has been associated with cardiovascular mortality.[33] PWA, on the other hand, determines central pressure wave characteristics, where aortic systolic and diastolic blood pressures are the main variables. The clinical benefit of using PWA to determine aortic blood pressure, *vs.* conventional brachial artery spygmomanometry, is supported by two major clinical studies. The Conduit Artery Function Evaluation study[37] and the Strong Heart Study[22,38] both demonstrated that central systolic and pulse pressures are significantly more sensitive than peripheral blood pressure to pharmacological interventions and cardiovascular risk assessment. Another PWA variable with potential clinical relevance is LVE_W.[17,29,31,32] However, larger clinical studies are needed to establish the relationship between increased LVE_W and increased cardiovascular risk.

Reference values for PWA and PWV

Until a couple of years ago, there were no reference values for PWA or PWV. Early studies designed to assess changes in PWA or PWV reported data as the percentage of difference between study and control groups.[12–14,24,25,28,30,31,34,36,39,40] Recent studies have provided some reference values for PWV[41] and PWA.[10,22,38] According to Mitchell *et al.*,[41] there is a significant increase in cardiovascular risk when aortic PWV is $>11.8\,m\,s^{-1}$, compared with a slower aortic PWV ($<7.7\,m\,s^{-1}$). Although reference values for PWA have been reported,[6,10] only one recent study has been able to determine some reference values using PWA.[22,38] According to Roman *et al.*,[22,38] there are four central pulse pressure quartiles (Q) that have a direct relationship to cardiovascular risk: Q-1, $\leqslant$31 mm Hg; Q-2, 32–39 mm Hg; Q-3, 40–49 mm Hg; and Q-4, $\geqslant$50 mm Hg. Further studies are needed to establish the relationship between PWA variables, such as AIx, Pi and LVE_W and cardiovascular morbidity and mortality.

INDUSTRY STATUS

The biomedical industry has made consistent efforts to improve PWA and PWV availability for both the basic scientist and clinicians. Presently, there are three commercially available systems that allow determination of PWA and PWV; (1) tonometric, (2) oscillometric and (3) piezoelectronic.[20] Although the tonometric technique is considered the gold standard, tonometric devices are costly and oriented heavily toward research. More affordable and user friendly devices are those using oscillometric or piezoelectronic technologies. Regrettably, to date, validation studies for the oscillometric and piezoelectronic devices have not generated convincing data.[21]

For example, indwelling catheter validation of an oscillometric device showed a strong linear relationship for AIx, Ps and PWV (R^2=0.813, $P<0.001$; R^2=0.901, $P<0.001$; and R^2=0.833, $P<0.001$, respectively); however, confidence intervals of Bland–Altman agreement tests showed low sensitivity between both methods for AIx and Ps ($\pm$2 s.d.=(−12.1–11.6%), and $\pm$2 s.d.=(−17.6–16.5 mm Hg), respectively), whereas sensitivity improved only for PWV ($\pm$2 s.d.=(−1.6–1.5 $m\,s^{-1}$)).[19] Several other inter-technique validations for PWA and PWV have showed similar results.[18,20,21] In general, significant correlation coefficients between techniques are observed; however Bland–Altman agreement tests showed a lack of sensitivity for PWA variables and moderate sensitivity for PWV. As stated by Jatoi *et al.*[20] and Nemcsik *et al.*,[21] oscillographic devices should not yet be considered as gold standards.

In summary, PWA and PWV are two important non-invasive bioassays for cardiovascular assessment. When used properly, PWA and PWV techniques will provide the clinician with reliable information for cardiovascular screening. However, PWA and PWV devices should be more affordable and they must be carefully validated before they are used by physicians to evaluate individual patients in the clinic.

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