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Review

Brachial-Ankle Pulse Wave Velocity: Myths, Misconceptions, and Realities

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Key Words
Arterial stiffness · Cardiovascular disease · Vascular function

Abstract
A variety of techniques to evaluate central arterial stiffness have been developed and introduced. None of these techniques, however, have been implemented widely in regular clinical settings, except for brachial-ankle pulse wave velocity (baPWV). The most prominent procedural advantage of baPWV is its ease of use, since it only requires the wrapping of blood pressure cuffs on the 4 extremities. There is mounting evidence indicating the ability of baPWV to predict the risk of future cardiovascular events and total mortality. Additionally, the guidelines for the management of hypertension in Japan recommended the measurement of baPWV be included in the assessment of subclinical target organ damage. However, baPWV has not been fully accepted worldwide due to perceived theoretical and methodological issues. In this review, we address the most frequently mentioned questions and concerns regarding baPWV to shed some light on this simple and easy arterial stiffness measurement.

Large artery stiffness increases gradually and progressively with advancing age and is an independent predictor of cardiovascular morbidity and mortality [1]. A compliant aorta and large elastic arteries effectively buffer cardiac pulsations acting to maintain pulse pressure at low levels and to keep blood flow in the capillary circulation smooth and continuous. Arterial stiffness is one of the earliest detectable signs of functional and structural changes in the vascular wall [2]. Thus, the assessment of central artery stiffness has become a focal point of early detection and prevention of vascular diseases [3–5]. As a result, a number of methodologies and indices have been developed and introduced to characterize arterial stiffness

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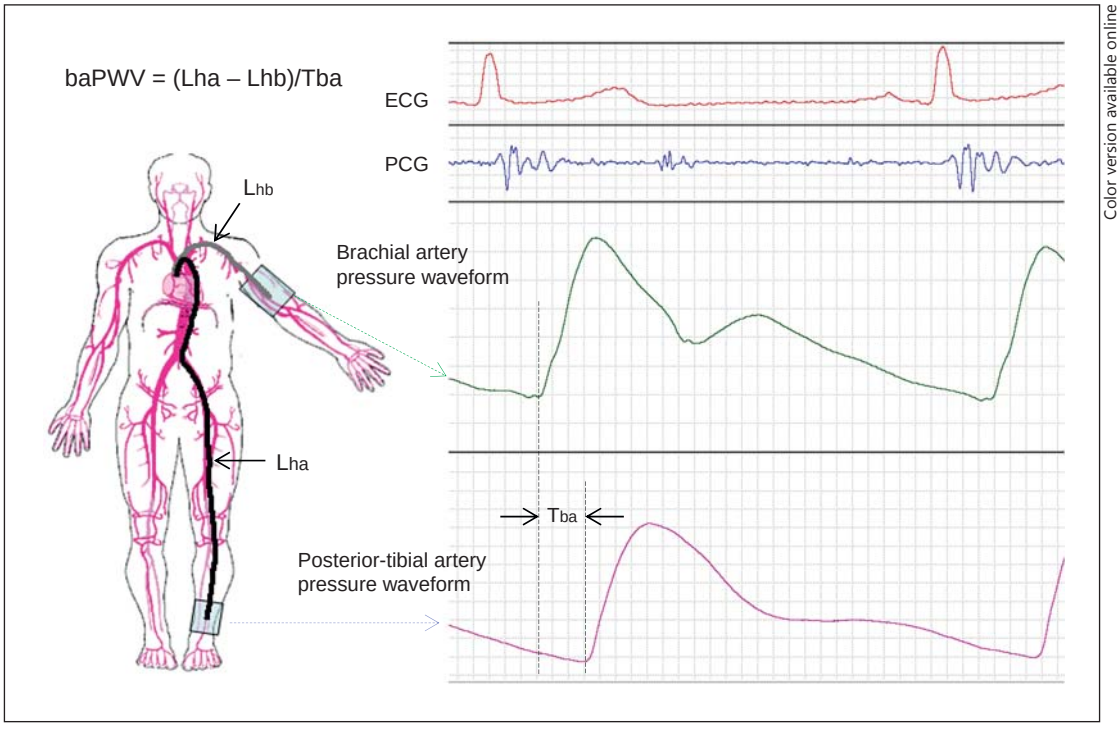

Fig. 1. Measurements of baPWV. The time difference between the commencements of systolic increase in brachial and ankle pressure waves (Tba) is used to calculate baPWV.

[6–8]. Among them, carotid-femoral pulse wave velocity (cfPWV) is the most validated and serves as a reference standard technique to quantify arterial stiffness (as described in consensus statements on arterial stiffness) [3, 4]. A cutoff or prognostic value of cfPWV has been included in the consensus report to facilitate its routine clinical use [4]. Given this, it would be reasonable to assume that the assessment of arterial stiffness may have been incorporated into the daily clinical practice to improve the early detection of cardiovascular and cerebrovascular diseases. However, the primary use of cfPWV remains in research settings and it has not yet been implemented in clinics and hospitals. This methodology is hindered by the technical precision required for carotid pulse acquisition and the intimate nature of femoral pulse acquisition in spite of its accuracy and reproducibility and the strong prediction of clinically relevant outcomes.

Brachial-ankle pulse wave velocity (baPWV) is the notable exception in this regard. baPWV is calculated as the ratio of the virtual arterial path length derived from the subject's height and the time difference between the commencements of systolic increases in brachial and ankle pressure waves (fig. 1). The PWV value can be obtained by simply wrapping blood pressure cuffs on the 4 extremities. The height-based estimation of arterial path length eliminates the need for body surface measurements. Because of the procedural advantage of its ease of use, it has been incorporated into routine clinical settings in Japan with an impressive number of semi-automated machines (~10,000) being placed in various clinics and hospitals. In recent years, the use of baPWV has spread widely throughout East Asian countries and become a popular modality of arterial stiffness measurement in population- or community-based studies [9, 10].

However, baPWV has not been fully accepted worldwide, especially in Western countries, where arterial stiffness assessment using cfPWV dominates in research communities.

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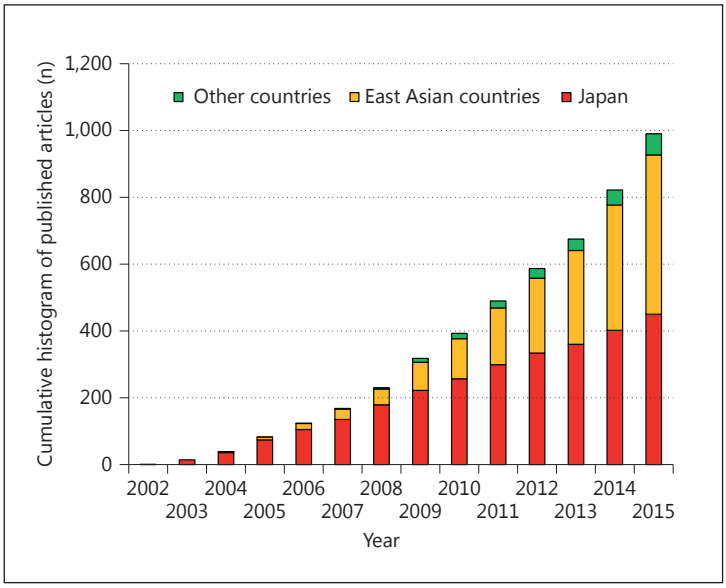

Fig. 2. Yearly increases in the number of publications using baPWV. The data in 2015 (2 months' worth of data) were extrapolated to 12 months.

This is because there are a number of frequently asked questions and concerns and perceived problems associated with the measurements of baPWV. In this review, we addressed some of the common questions, myths, misconceptions, and realities surrounding the assessment of baPWV as a measure of arterial stiffness.

'baPWV Is Used Only in Japan'

The measurement of baPWV was initiated in Japan in 2000, and the first publication using baPWV came from Japanese scientists in 2002 [8]. Since then, the use of baPWV rapidly spread nationwide and to other countries. In order to determine the worldwide spread of baPWV in research use, we conducted a PubMed search using the key word 'brachial-ankle pulse wave velocity'. A total of 850 scientific papers were identified on the PubMed database as of the end of February 2015. The initial years of publication were dominated by Japanese scientists, and to date, 48% of the total publications have come from Japan (fig. 2). The number of publications using baPWV has spread rapidly and widely in other Asian countries, and to date, 46% of the total publications have come from these East Asian countries. The increasing number of publications from Korea and China is particularly remarkable after 2009. Other countries accounted for 6%. The number of publications from non-Asian countries is expected to increase in the future as large-scale studies, including the Atherosclerosis Risk in Communities (ARIC) study and the Bogalusa Heart Study [11] in the US, have adopted the use of baPWV.

'baPWV Has No Research to Indicate Its Clinical Utility'

Similar to other measures of arterial stiffness, there are a number of observational studies demonstrating the association of baPWV with pathological conditions. High baPWV is observed in aged populations [12, 13] and in patients with hypertension [13], diabetes [14], chronic kidney disease [15], and metabolic syndrome [16]. Additionally, baPWV is associated with left ventricular hypertrophy [9], severity of coronary calcification [17], and carotid atherosclerosis [18].

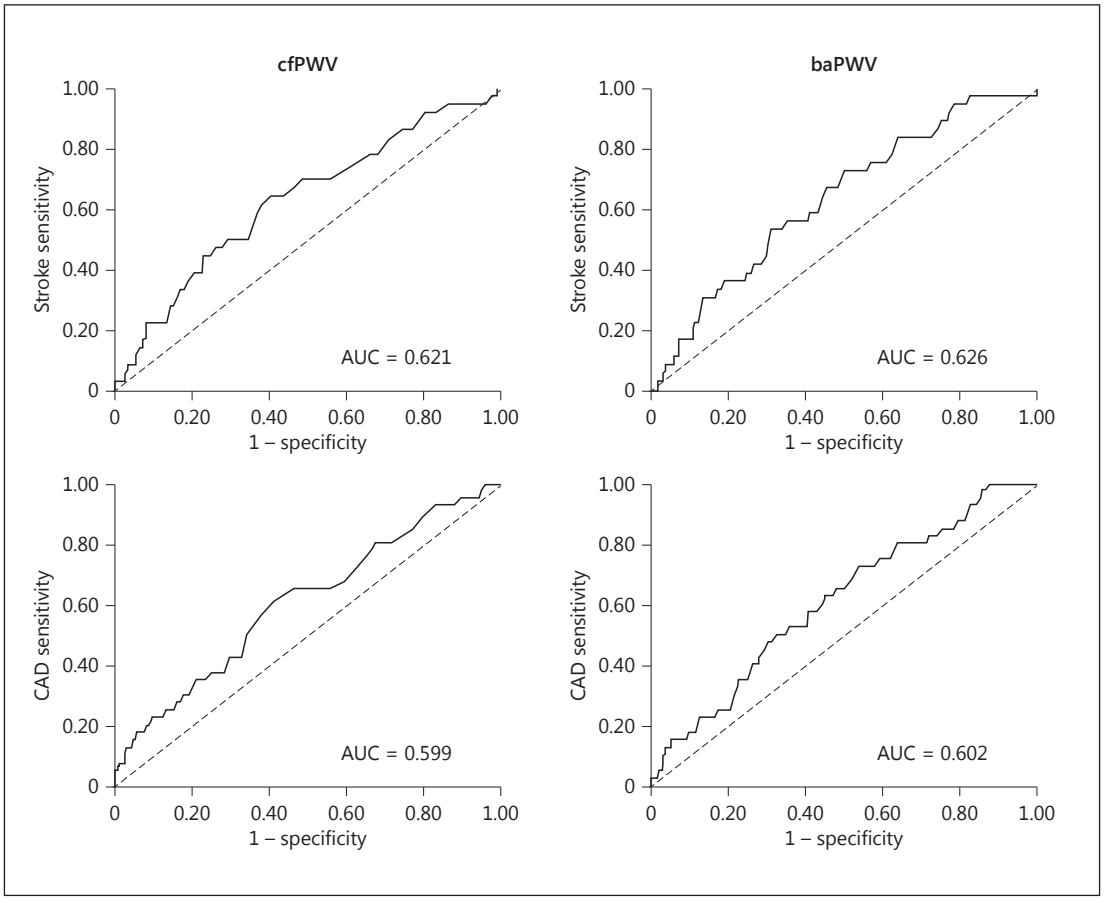

Fig. 3. Receiver operating characteristic curves of stroke and coronary artery disease (CAD) [12, 13]. Reproduced with permission from Lippincott Williams & Wilkins.

The measurement of baPWV has shown to be predictive of cardiovascular events as well as mortality in a number of different populations. In a cohort study of a general population, a 20% increase in baPWV was associated with a 1.3-fold increase in the risk of cardiovascular events [19]. The J-TOPP (Japanese Trial on the Prognostic Implication of Pulse Wave Velocity) study examining patients with untreated hypertension found that patients with high baPWV had a 2.8-fold increase in the risk of cardiovascular events compared to patients with low baPWV, even after the adjustments for traditional risk factors were applied [20]. In another population-based prospective cohort study, the risk of cardiovascular events in subjects with baPWV ≥1,800 cm/s was 2.7-fold higher than in subjects with baPWV <1,800 cm/s [21]. Recently, a systematic review using meta-analyses gathered data from 18 different studies involving 8,169 subjects, who were followed up for a mean of 3.6 years [22]. Subjects with high baPWV demonstrated a 3-fold higher risk of total cardiovascular events, a 5-fold higher risk for cardiovascular mortality, and a 2.5-fold higher risk for all-cause mortality compared to patients with low baPWV. An increase in baPWV by 1 m/s was associated with increases in 12, 13, and 6% in total cardiovascular events, cardiovascular mortality, and all-cause mortality [22]. Moreover, the area under the receiver operating curves of PWV to predict the presence of both stroke and coronary artery disease are comparable between cfPWV and baPWV [12, 13] (fig. 3). Thus, there is sufficient evidence in the literature indicating clinical utilities of baPWV.

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Does the measurement of baPWV have a high reproducibility? Yu et al. [9] reported that the intra- and inter-observer mean percentage errors for baPWV (5.6 ± 4.4 and 6.6 ± 4.7%) were comparable to those for cfPWV (5.0 ± 4.3 and 7.4 ± 5.4%). Additionally, Munakata et al. [23] indicated that the intra- (day-to-day) and inter-observer (on the same day) coefficient of variation for baPWV were 6.5 ± 4.1 and 3.6 ± 3.9%. Thus, the repeatability for baPWV appears to be good.

'Arterial Pulse Does Not Travel from the Brachial Artery to the Ankle'

Clearly, the pulse wave does not travel directly from the brachial arteries to the posttibial arteries (ankle) in the same arterial tree. Accordingly, some investigators propose that the nomenclature of PWV is inappropriate [22]. However, the same argument can be made for the well-established cfPWV. In its initial years, aortic PWV was frequently measured from the ascending aorta (suprasternal notch) to the femoral artery, both of which are located in the same arterial tree [24, 25]. But in more recent years, most investigators have performed measurements of PWV from carotid to femoral arteries. These 2 arteries are not connected directly in the same arterial tree. This violation is accepted in cfPWV, presumably because the length of the arterial segment on the carotid artery is shorter, and no criticism has been raised. If the nomenclature should be changed for baPWV, the same change needs to be made for cfPWV.

'baPWV Is a Measure of Peripheral Artery Stiffness'

The stiffness of central elastic arteries increases with advancing age [26] and is closely associated with cardiovascular and all-cause mortality [27]. But such a relationship is much weaker or even absent for peripheral muscular arteries [26]. Accordingly, the stiffness of central elastic arteries is considered clinically important, whereas that of peripheral muscular arteries may not be relevant for the cardiovascular risk assessment. There is a prevalent notion that baPWV predominantly reflects peripheral arterial stiffness and therefore should not be recommended for risk assessment. Indeed, in the measurement of baPWV, the majority of the central elastic segment of the aorta does not seem to be included when one looks at the projection of pulse waves traveling from the abdominal aorta at the level of the brachial artery to the posttibial artery on the ankle. However, the available research indicates that a major determinant of baPWV is the arterial stiffness of central elastic arteries as there are strong associations between baPWV and cfPWV. In a Japanese population, baPWV was strongly correlated with invasively measured aortic PWV ($r = 0.87$) [8]. A similarly strong correlation has been reported between baPWV and noninvasively measured cfPWV among US and Japanese adult populations varying widely in age ($r = 0.76$) [12], and this association does not seem to be affected by race [28]. If baPWV and cfPWV reflect similar properties of vascular wall function, decreases in cfPWV induced by an intervention should be accompanied by corresponding changes in baPWV. In a regular aerobic exercise intervention study, reductions in cfPWV observed with the exercise intervention were significantly and positively associated with corresponding decreases in baPWV ($r = 0.74$), and changes in baPWV were explained by changes in cfPWV, explaining 55% of the total variance [28]. Thus, baPWV may provide qualitatively similar information to those derived from central arterial stiffness though some portions of baPWV may be determined by peripheral arterial stiffness.

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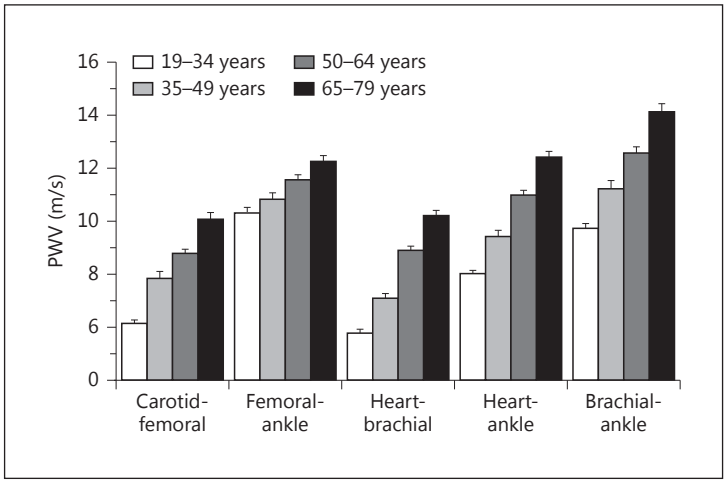

Fig. 4. Age-related increases in various segments of PWV measures (modified and adapted from Sugawara et al. [28]).

'The Height-Based Formula to Estimate Arterial Path Length Is Invalid'

PWV is calculated by a simple equation of the distance between the measurement sites divided by the pulse transition time. A prominent feature of baPWV is the height-based estimation of arterial path length eliminating the need for body surface measurements. A recent study using 3D MRI arterial tracing [29] reported that, compared to the MRI-based measurement, the height-based arterial path length formula for baPWV grossly overestimated the actual effective arterial path length because of a greater underestimation of arterial path lengths towards arms (approx. 30%) and legs (approx. 2%). However, baPWV derived from height-based formulas was linearly correlated with baPWV recalculated using the MRI-based path length ($R^2 = 0.96$). Given this, the height-based formula can easily be converted to the actual arterial path length with an adjustment factor. Given that East Asians are known to have shorter leg lengths compared to other races [30, 31], could the height-based formula derived primarily from Japanese populations be applicable to other races? The height-based formula can be applicable to different racial and ethnic populations as the ratio of the distance from the suprasternal notch to the ankle is strongly correlated with height irrespective of races and ethnicities (i.e. Asians, Whites, African-Americans) [32]. Additionally, the ratios of the upper arm length and height are 0.20 in Asians, 0.21 in Whites, and 0.21 in African-Americans. Similarly, the ratios of the distance from the suprasternal notch to the ankle and height are all 0.89 in these racial groups [30]. Even though the height-based estimation of the arterial path length is often considered a weakness of the technique, by cramping the arterial path length constant in a given patient, this could be a strength in clinical settings where individual small changes in PWV over time should be carefully monitored.

'Absolute baPWV Values Are Greater than PWV of Any Other Arterial Segments'

The values of PWV are lowest in cardiothoracic arteries and increase gradually toward more distal or peripheral locations in the arterial tree [29, 33]. The normative values of baPWV are substantially higher than other PWV values reported in the literature [12, 13]. If baPWV is associated with central artery stiffness (as indicated above), why are absolute baPWV values greater than cfPWV and even higher than PWV of peripheral muscular arteries in the extremities (fig. 4)? This is in part due to the overestimation of arterial path lengths

used to calculate baPWV. A recent study using 3D MRI tracing demonstrated that the effective path length used in baPWV was substantially shorter than the height-based path length used in the baPWV calculation [29], and the recalculation of baPWV by the MRI-based arterial path lengths reduced baPWV more than 10%. However, the adjusted baPWV values were still greater than cfPWV and remained higher than PWV of the leg in the majority of individuals. These results suggest that the high absolute values of baPWV are attributed not only to the overestimation of arterial path lengths from height-based formulas, but also to other experimental and/or methodological issues. One possible reason might be the different velocities of pulse waves that travel towards the arms and legs. In the calculation of baPWV, the proximal portion of the arterial path length is eliminated through subtractions involving the aorta. This assumption is valid only if pulse waves travel at the same rate from the aorta to the brachial artery and to the posttibial artery. However, the aforementioned MRI study demonstrated that PWV from the aortic annulus to the ankle was approximately 26% faster than PWV from the aortic annulus to the brachial artery [29]. This difference could produce a shorter projected time span between the pulse travelling to the 2 arterial sites and contribute to the overestimation of baPWV. Interestingly, this particular problem is also inherent in the measurement of cfPWV, as pulse waves travel at different rates to the carotid artery and to the femoral artery [4].

Perspectives

Arterial stiffness assessment is becoming a focal point in the efforts of early detection and prevention of cardiovascular and cerebrovascular diseases. Despite the well-established clinical significance of arterial stiffness, the measurement of arterial stiffness has not been incorporated in routine clinical settings. In order to implement the measurement of arterial stiffness in daily clinical practice, an accurate, reproducible, and simple measurement that does not require technical expertise is needed.

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