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Expert Consensus on the Clinical Use of Pulse Wave Velocity in Asia

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Keywords
Arterial stiffness · Pulse wave velocity · Cardiovascular disease · Asia

Abstract
Arterial stiffness is a progressive aging process that predicts cardiovascular disease. Pulse wave velocity (PWV) has emerged as a noninvasive, valid, and reliable measure of arterial stiffness and an independent risk predictor for adverse outcomes. However, up to now, PWV measurement has mostly been used as a tool for risk prediction and has not been widely used in clinical practice. This consensus paper aims to discuss multiple PWV measurements currently available in Asia and to provide evidence-based assessment together with recommendations on the clinical use of PWV. For the methodology, PWV measurement including the central elastic artery is essential and measurements including both the central elastic and peripheral muscular arteries, such as brachial-ankle PWV and cardio-ankle vascular index, can be a good alternative. As Asian populations are rapidly aging, timely detection and intervention of "early vascular aging"

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in terms of abnormally high PWV values are recommended. More evidence is needed to determine if a PWV-guided therapeutic approach will be beneficial to the prevention of cardiovascular diseases beyond current strategies. Large-scale randomized controlled intervention studies are needed to guide clinicians.

Introduction

With increasing age, arteries become stiffened (arteriosclerosis) and this increases linearly with the risk of cardiovascular (CV) disease [1]. However, different genetic background, environmental, and lifestyle factors result in large individual variability in the biological age of arteries, even at the same chronological age. This has led to the notion that accelerated arterial aging may be regarded as a failure of the interaction between genetic and environmental factors [2]. The vascular aging CV continuum has similar final outcome to the classic CV continuum, such as end-stage cardiac, cerebral, and renal diseases, and death may occur, but there exists a distinct difference in the underlying pathophysiology [3, 4]. The mechanism of the classic CV continuum is atherosclerosis and cardiac hypertrophy at the beginning. In contrast, that of the vascular CV continuum is fracture of elastic lamellae, aortic stiffening, and dilatation, which induces pulse wave pathology such as pulse wave encephalopathy, pulse wave nephropathy, renal disease, and dementia [3].

Arterial stiffness with aging increases pulse wave velocity (PWV), the measurement of which is a reliable tool to predict CV disease [5]. Although its impact on outcomes has been widely studied and suggested as a clinical aid for primary and secondary CV prevention [6], there are still large hurdles in applying the concept of PWV in clinical use. Hypertension guidelines pay minimal attention to the clinical use of PWV and with many methods available there is no standard method for measuring PWV [7, 8]. Currently, the main tool of measuring vascular aging is PWV, but there are differences in measurement methods. Europeans favor carotid-femoral PWV (cfPWV) [9]. In contrast, in Asia, there is favor toward brachial-ankle PWV (baPWV) [10] or cardio-ankle vascular index (CAVI) [11]. Main differences between methods are the arterial measurement sites that vary from the central elastic aorta to the aorta and peripheral muscular arteries. This review aims to discuss multiple PWV measurement methods and to provide recommendations on the clinical use of PWV in Asia.

Methodologic Aspects

The original concept of "hardening of arteries" was generally understood as a buildup of atheroma and calcification of the arterial lumen, resulting in regional stenosis and leading to obstruction of blood flow [12]. This effect can be readily measured invasively by detecting a pressure drop across the stenotic lesion, or noninvasively using Doppler devices to detect changes in blood flow velocity. However, this concept has now evolved from alterations in the intimal component of the arterial wall to the medial component [12, 13], with altered mechanical properties affecting arterial wall stiffness, which cannot be measured directly noninvasively. The effect of stiffness of large conduit arteries is to increase pulse pressure, an effect largely responsible for isolated systolic hypertension in the elderly [14], but because pulse pressure is a result of stroke volume and the distensibility of the aorta and large arteries, it is not an explicit measure of arterial stiffness. However, from the biophysical relationship of stress and strain in the arterial wall, it has been shown that PWV can be used as a reliable surrogate measure of arterial stiffness, particularly in large conduit arteries [15].

An important consideration in using PWV as a measure of arterial stiffness is that the arterial wall is a type of "hyperelastic" material, i.e., the stiffness depends on blood pressure (BP) – the higher the pressure, the higher the PWV for the same arterial wall. However, the inherent structural material which alters the mechanical properties does not change with increase in pressure immediately, but what does change is the functional arterial stiffness [16]. Increase in structural stiffness is seen as increase in PWV at the same level of BP [17]. These are important methodological aspects to be considered when measuring PWV and interpreting individual patient or population data with respect to contribution of PWV to CV risk beyond BP. An important example of this was shown in two populations in China with distinct geographical separation (north, Beijing; south, Guangzhou). PWV was markedly higher in the Beijing cohort at similar levels of BP in both groups. This implied a difference in inherent structural arterial stiffness, which was most likely related to a lifelong difference in dietary salt consumption, resulting in a marked difference of the prevalence of hypertension in both groups [18, 19].

The sections that follow describe the specific methods used for PWV measurement that will address the use of PWV as a potential clinical measurement that can be performed together with BP in the context of established guidelines for measurement of arterial stiffness [7]. In ad-

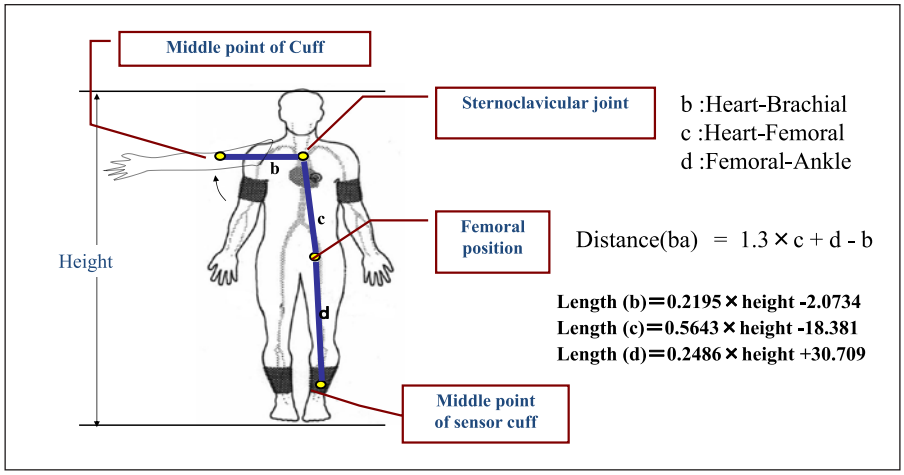

Fig. 1. Path length formula for baPWV (source, see ref. 22).

dition, the innovative application of the pressure dependency of arterial stiffness will be described to obtain a corrected value of PWV, which is independent of BP [20]. The important methodologic advancement with this technique is that the measurement gives information of structural stiffness for an individual patient without the need of statistical information from cohort measurements to correct the measured PWV for the effect of BP.

The measurement of PWV involves a measure of pulse transit time (PTT) obtained from the time delay between two arterial pulses measured simultaneously or sequentially over a given distance. To obtain a reliable measure of PTT, the path length cannot be too short; that is, the longer the distance the smaller the relative error in PTT. In addition, the site of measurement should be convenient and one in which a reliable pulse waveform can be easily recorded. Furthermore, the PTT distance should be applied to cover mainly large conduit arteries. For this, the carotid and femoral sites have been conventionally used as a reasonable compromise which will give meaningful information [7]. However, although these sites have been used extensively in many population cohorts, this measurement method is not favored by investigations among Asian populations, where instead pulses are detected at brachial and ankle sites [21]. Although this methodology offers an unobtrusive form of measurement, the path lengths cover muscular arteries, where the wall stiffness may be modulated by smooth muscle tone and so affect changes of PWV.

Concepts and Clinical Evidence

Brachial-Ankle Pulse Wave Velocity

Concept and Principles

baPWV is calculated by dividing the brachial-ankle distance by the time difference between the brachial and ankle arterial waves. Thus, baPWV is considered as a global measure of arterial stiffness, including the aorto-muscular region. A volume-plethysmographic technique is used to measure baPWV. Pressure cuffs are wrapped at the bilateral brachial and ankle sites to record pulse waves as shown in Figure 1 [22]. The brachial-ankle distance (Distance [ba] in the figure) is determined by the linear equation of height, and the time difference between the brachial and ankle waves is determined by the foot-to-foot method. The height-based path length has been validated by comparing it with the path length determined by magnetic resonance imaging [23]. The unique feature of this equipment is that it simultaneously records the BP at four sites using the oscillometric method, thus also enabling determination of the ankle-brachial pressure index (ABI). This index is critical in confirming the iliotibial circulation and ensuring valid use of baPWV, which becomes invalid if ABI <0.9. The baPWV measurement is easy and reproducible and the generalizability and validity of the methodology have been determined [22]. Thus, this method is suitable for clinical applications.

Clinical Evidence

A recent review summarized that baPWV increases in patients with hypertension, diabetes, metabolic syndrome, chronic kidney disease, sleep apnea syndrome, as well as with aging and conditions such as tachycardia and

Table 1. Reference values and risk associated with PWVs

Method	Reference values	Risk of CV events
baPWV	Normal <14 m/s Borderline ≥14 and <18 m/s Abnormal ≥18 m/s	Every 1-SD increase of baPWV→ 21% increase in the risk of CV disease [26] Every 1 m/s increase of baPWV→ 12%, 13%, and 6% increase in CV events, CV mortality, and all-cause mortality, respectively [27]
CAVI	Normal <8 Borderline ≥8 and <9 Abnormal ≥9	Every 1.0 index increase of CAVI→ 12.6% increase in the risk of future CV events [128] Cut-off values for CVD events→ 9.0–9.2 in Asian patients [129, 130] 5-year overall net reclassification index→ 16.4% and 33.7% for CVD events in patients with obesity and in patients with ACS, respectively [131]
cfPWV	Abnormal ≥10 m/s	Every 1-SD increase of cfPWV→ 30% increase in the risk of CV events after adjustment for traditional risk factors [44] Every 1 m/s increase of cfPWV→ 14%, 15%, and 15% increase in total CV events, CV mortality, and all-cause mortality, respectively [1] 5-year overall net reclassification index→ 14.8% and 19.2% for coronary heart disease and stroke, respectively, in intermediate-risk individuals [44]

ACS, acute coronary syndrome; baPWV, brachial-ankle PWV; cfPWV, carotid-femoral PWV; CV, cardiovascular; PWV, pulse wave velocity; CAVI, cardio-ankle vascular index; CVD, cardiovascular disease.

postmenopause [24]. In hypertension and diabetes, higher baPWV is associated with advanced organ damage. The relationship between baPWV and lipid levels remains unclear. Antihypertensive agents, statins, oral diabetic drugs, weight loss, smoking cessation, and continuous positive airway pressure have all been reported to lower baPWV [25].

The risk of CV events increases linearly with an increase in baPWV. Individual participant data meta-analyses of 14,673 individuals, with no previous history of CV events, demonstrated that baPWV can predict both CV events and all-cause mortality Independent of conventional CV risk factors including BP [26]. Every 1-SD increase in baPWV was associated with a 21% increase in the risk of CV disease. Moreover, a 1 m/s increase in baPWV was associated with an increase of 12%, 13%, and 6% in CV events, CV mortality, and all-cause mortality, respectively [27]. Importantly, patients at intermediate risk were reclassified into a higher or lower CV risk category when baPWV was added to a model incorporating the Framingham risk score; net reclassification improved by approximately 25%.

Clinical Use

To implement baPWV measurement in everyday clinical practice, it is necessary to determine reference values. Recently, the expert committee of the Japanese Society of Vascular Failure proposed a physiological diagnostic criterion for various vascular function tests, including baPWV [Table 1] [28]. baPWV was positioned as an arterial stiffness measure to examine the medial layer function of the aorto-muscular region. The measurement of baPWV was categorized as normal (<14 m/s), borderline (14–18 m/s), and abnormal (>18 m/s). These thresholds may be used by health practitioners to individualize nonpharmacological or pharmacological interventions. However, future studies need to verify the clinical significance of these criteria. The inclusion of leg artery stiffness has been long considered a critical limitation of baPWV, but the accumulated data are not fully supportive [28]. This suggests that aorto-muscular artery stiffness is involved more in the modulation of central hemodynamics than initially considered [29, 30]. This topic is the new frontier for future studies.

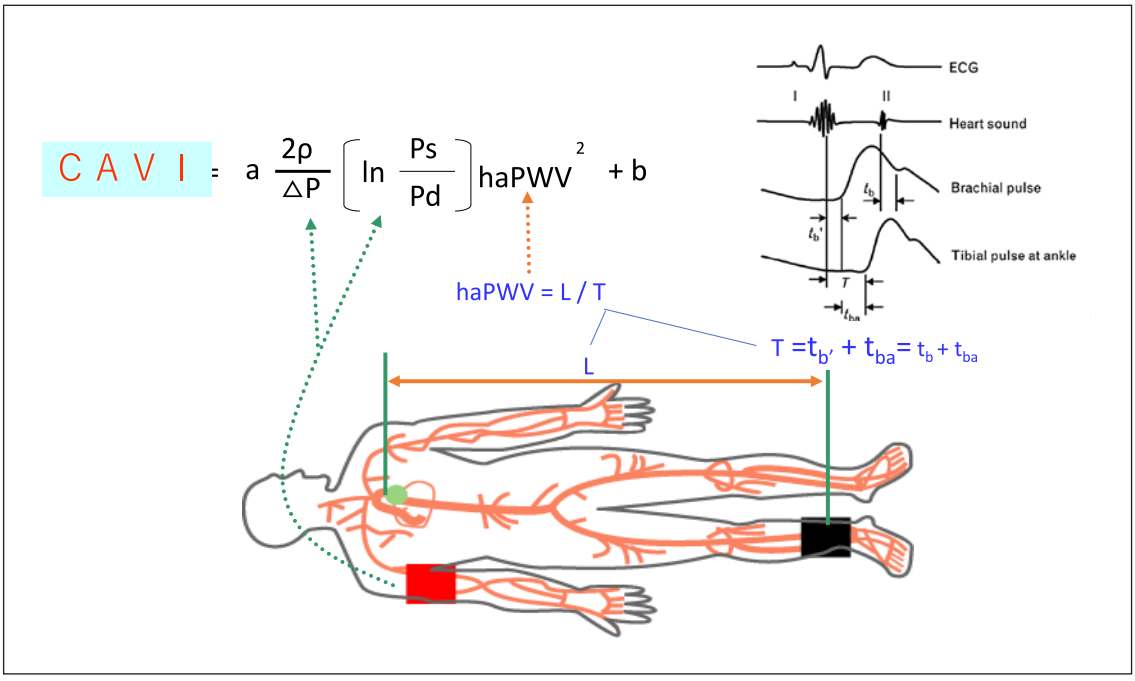

Fig. 2. Determination of the cardio-ankle vascular index (CAVI). Ps, systolic blood pressure of brachial artery; Pd, diastolic blood pressure; haPWV, pulse wave velocity from the origin of the aorta to the ankle at mid pressure; ΔP, Ps-Pd; ρ, blood density; a and b, constants to convert the values of CAVI to those of Hasegawa's hfPWV; T, time of the pulse from aortic valve to the ankle; L, length of the arterial tree from the origin of aorta to the ankle.

Limitations

baPWV measurement becomes unreliable if the circulation is disturbed in any part from iliac to tibial arteries. In patients with ABI <0.9, therefore, baPWV cannot be used as a metric for clinical decisions [25]. In addition, up to now the evidence of baPWV is derived mainly from Asian populations. For global application of baPWV, evidence from non-Asian populations is needed.

Cardio-Ankle Vascular Index

Concept and Principles

CAVI reflects the arterial stiffness of the arterial tree from the origin of the aorta to the ankle. CAVI is theoretically derived from stiffness parameter β, and the Bramwell-Hill's equation, and is obtained by systolic and diastolic BPs and PWV [20]. The equation and measuring methods are shown in Figure 2. CAVI is measured in the supine position using the VaSera system (Fukuda Denshi, Tokyo, Japan). A feature of CAVI is that it purports to be a measure that is independent of BP at the time of measurement. It is therefore theoretically possible that the effect of antihypertensive drugs on structural arterial stiffness can be evaluated as well as the effect of BP change in chronic phase. The cut-off value of CAVI is proposed to be 9.0 for predicting CV diseases [31].

Clinical Evidence

Cross-sectional studies report that CAVI is higher with older age, among men and with arteriosclerotic diseases (coronary artery disease, cerebral infarction, chronic kidney disease) as well as most coronary risk factors such as metabolic syndrome, visceral fat accumulation, hypertension, diabetes mellitus, and dyslipidemia (see Fig. 3) [31]. In vasculitis such as collagen diseases (systemic lupus erythematosus, rheumatoid arthritis) and polymyalgia rheumatica, CAVI is also increased.

CAVI also reflects functional stiffness. CAVI decreases in sepsis [32] and rises in hypovolemia [33]. These facts indicate that CAVI reflects the effect of contraction of arterial smooth muscle cells. Administration of nitroglycerin and the α-blocker, doxazosin acutely decreases CAVI [34, 35]. Patients with sleep apnea syndrome showed high CAVI, probably due to enhanced sympathetic nervous system activation. CAVI was also reported to be elevated after an earthquake [36], indicating a potential influence of mental or physical stress. Prospective studies showed

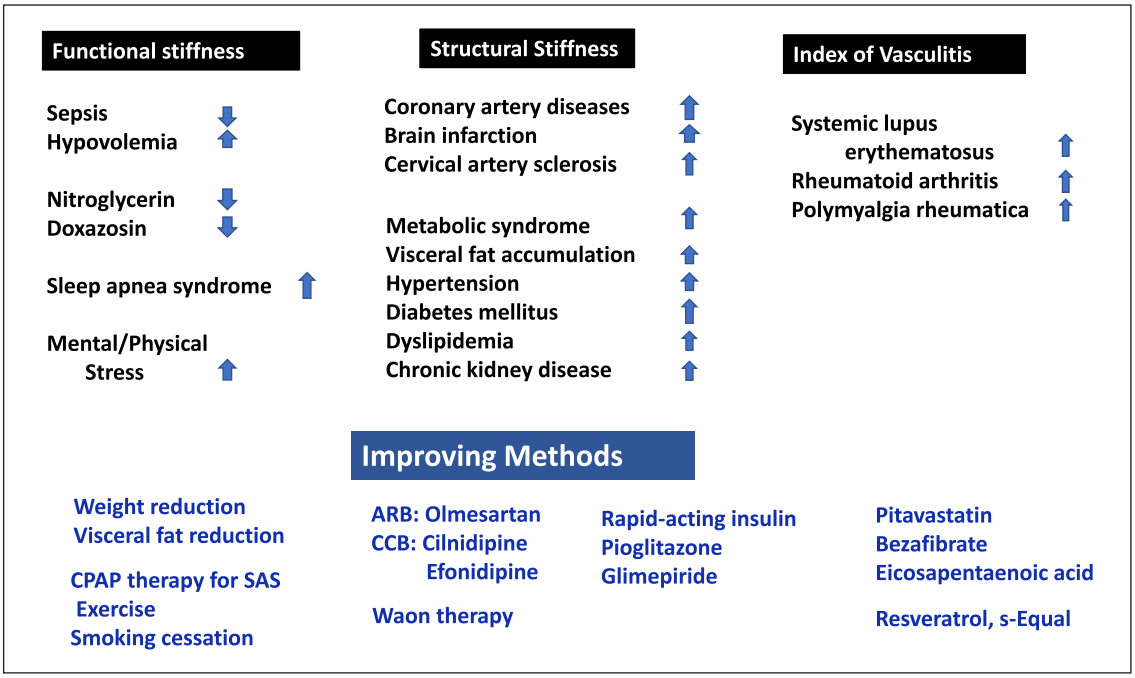

Fig. 3. Clinical implications of CAVI and improving methods. ARB, angiotensin receptor antagonist; CCB, calcium channel blocker; CPAP, continuous positive airway pressure; SAS, sleep apnea syndrome.

that high CAVI is predictive for mortality and morbidity of coronary artery diseases [31], for the incidence of atrial fibrillation [37] in the general population, and also for deterioration in kidney function [38, 39].

Clinical Use

In routine clinical practice and medical checkup, measuring CAVI gives important information in terms of structural arterial stiffness, functional stiffness, and indices of vasculitis as stated above. When CAVI shows abnormally high value for one's age, the risk factors should be intensively examined, and treatments to address risk factor burden and decrease CAVI are recommended. Reported methods for improving CAVI are listed in Figure 3 [31]. Body weight reduction in metabolic syndrome, especially visceral fat reduction, and continuous positive airway pressure therapy for OSAS decreased CAVI. Exercise, smoking cessation, and Waon therapy also decreased CAVI. BP control with angiotensin receptor II blockers, such as olmesartan, calcium channel blockers such as cilnidipine, efonidipine decreased CAVI. Glucose control with rapid-acting insulin, pioglitazone, or glimepiride improved CAVI. Lipid control with pitavastatin, bezafibrate, and eicosapentaenoic acid also decreased CAVI. Resveratrol improved CAVI. Furthermore, a rapid rise of CAVI in persons with high CAVI might a harbinger of impending CV events. The mechanism is thought to be ischemia of vulnerable plaque due to arterial smooth muscle contraction [36]. Periodic monitoring of CAVI might be useful to predict impending CV events. In summary, measuring CAVI might be useful for a quantitative assessment of vascular aging and the degree of arteriosclerosis, and also for control of risk factors.

Limitations

The CAVI value may not be correct when ABI is less than 0.9 because the pulse at the ankle is too weak to be detected, and PWV which constitutes CAVI cannot be properly obtained with the VaSera system. In patients with aortic valve stenosis, CAVI shows low values [40]. It is suggested that this is due to the PWV decrease associated with the lowered blood flow from the left ventricle to the aorta. Abnormally low age-related CAVI value might indicate the presence of severe aortic valve stenosis.

Carotid-Femoral Pulse Wave Velocity

Concept and Principles

Aortic stiffness can be estimated noninvasively by measuring PWV between the right carotid and right femoral artery (cfPWV) [7, 41]. cfPWV (expressed in m/s) is

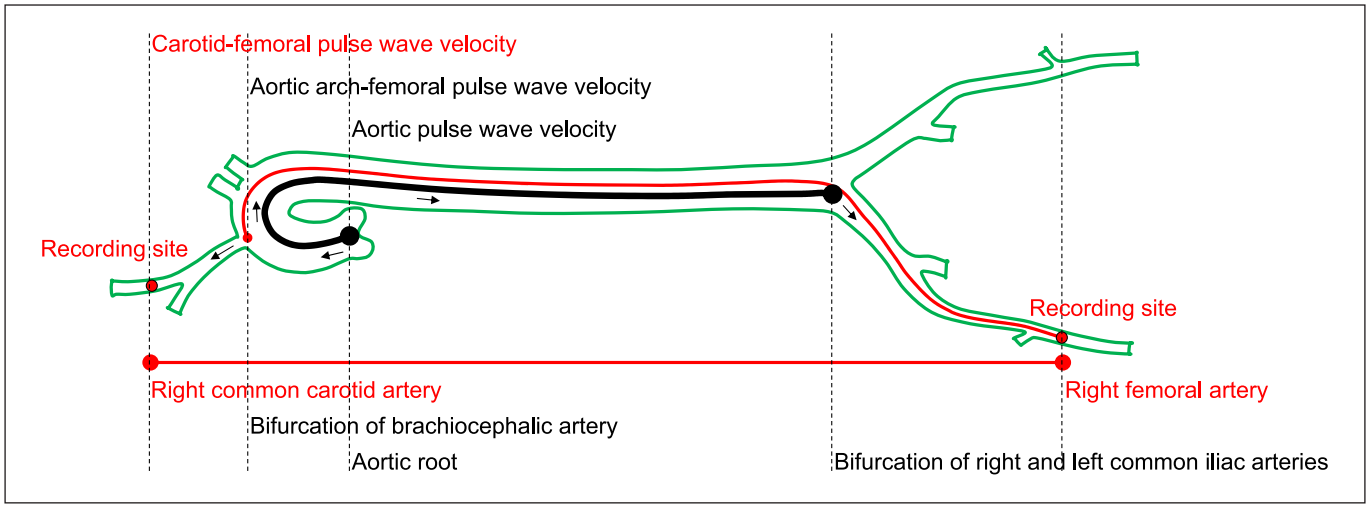

Fig. 4. Measurement schematic diagram of carotid-femoral pulse wave velocity, aortic arch-femoral pulse wave velocity, and aortic pulse wave velocity. The surface distance between the recording sites of right common carotid artery and right femoral artery is depicted as the straight red line. The path of the pulse wave travelling from the aortic arch (near the bifurcation of the brachiocephalic artery) to the recording site of right femoral artery is depicted as the red curved line. The path of the pulse wave travelling from the aortic root to the end of abdominal aorta (near the bifurcation of the right and left common iliac arteries) is depicted as the thick black curved line.

calculated as the surface distance divided by the PTT between the two arterial sites. The PTT can be measured using the foot-to-foot method from pressure, flow, or volume waveforms recorded with tonometry, Doppler, mechanical sensor, or pulse volume recording device. It should be noted that both the surface distance and the PTT are only crude estimates because physiologically the pulse wave does not actually propagate from the recording site of right carotid artery via aortic arch to the recording site of right femoral artery (Fig. 4) [7].

Clinical Evidence

It has been recommended that arterial stiffness should be determined noninvasively by measurement of cfPWV [7] and cfPWV is considered as the "gold-standard" measurement of aortic stiffness [41]. However, cfPWV is actually a crude estimate of aortic arch to femoral artery PWV and does not directly measure stiffness of the ascending aorta (Fig. 4) [42].

cfPWV is a sensitive marker of vascular aging [43] and has been validated as an independent, strong marker for future CV events in patients with hypertension, diabetes, and renal failure, and in the general population and apparently healthy subjects [42]. cfPWV is predictive of coronary heart disease, stroke, systolic hypertension, atrial fibrillation, aortic aneurysm formation, heart failure, and CV mortality events [42, 44–47]. cfPWV improves model fit and reclassifies risk for future CV disease events in models that include standard CV disease risk factors [44]. cfPWV may enable earlier identification of high-risk populations that might benefit from earlier CV disease risk factor management [44]. Therefore, it is reasonable to measure cfPWV to provide incremental information beyond standard CV disease risk factors in the prediction of future CV disease events [7].

Clinical Use

Age- and sex-specific normal reference values and thresholds have been established in a European population, and this may facilitate the clinical application of cfPWV for this demographic [48]. The generalizability of these cfPWV reference values to Asian populations is yet to be known. cfPWV may be clinically useful to identify medium and high-risk CV disease groups, but the prognostic value of arterial stiffness in older adults may be limited [46]. cfPWV is considered as a surrogate target for prevention and intervention [42]. However, large-scale randomized controlled intervention studies are needed to guide clinicians [42].

Limitations

Regarding cerebral structure and function, increased cfPWV has been associated with an increased risk of brain structural abnormalities and worse performance in

various subdomains of cognitive function but negative results were also observed [49]. Since cfPWV does not cover the ascending aorta, which may play a critical role in generating aortic pressure/flow pulsatility, it is probably not an ideal parameter to evaluate the association between vascular aging and cognitive function [49].

Measures of PWV vary with age, sex, BP, ethnicity, and measurement techniques and devices [10]. Standardization of the techniques, the validation of devices, and arterial stiffness studies have been recommended [7, 50].

Estimated Pulse Wave Velocity

Concept and Principles

cfPWV by applanation tonometry is one of the widely used methods for the assessment of aortic stiffness. Despite its popularity as a well-standardized and noninvasive measure of aortic stiffness, the routine assessment of cfPWV still requires sophisticated technical skills and specialized equipment, which may limit its widespread incorporation into routine clinical practice. As a strategy to overcome the restraints concerning the assessment of aortic stiffness using cfPWV, researchers have developed the concept of estimated PWV (ePWV) that can be calculated from age and mean BP (MBP) using a regression equation generated from the Reference Values for Arterial Stiffness Collaboration: $ePWV = 9.587 - 0.402 \times age + 4.560 \times 10^{-3} \times age^2 - 2.621 \times 10^{-5} \times age^2 \times MBP + 3.176 \times 10^{-3} \times age \times MBP - 1.832 \times 10^{-2} \times MBP$ [51].

Clinical Evidence

In the high-risk patients from the SPRINT trial, ePWV predicted all-cause mortality and CVD outcomes beyond traditional risk factors, and improved C-statistics beyond the Framingham Risk Score (from 0.65 to 0.69) [52]. Additionally, ePWV was associated with CV mortality and morbidity independently of the Systematic Coronary Risk Evaluation (SCORE) and Framingham Risk Score, but not independently of traditional CV risk in the MORGAM Project with 38 cohorts from 11 countries [53]. ePWV is associated with all-cause and CVD mortality and slightly improves the C-statistics for the primary outcome in the Chinese Study [54].

By contrast, an addition of ePWV to contemporary CVD risk scores does not improve discrimination of all-cause and CVD mortality risk [55]. Similarly, while ePWV is associated with all-cause mortality and MI, independent of traditional risk factors, discrimination is not improved to a clinically meaningful extent in patients with angina pectoris [56]. Given uncertainty related to the usefulness of ePWV, additional research examining the role of ePWV as a predictor of CVD outcomes is clearly warranted, especially in differing outcomes, populations, and racial/ethnic backgrounds.

Clinical Use

Emerging evidence suggests that ePWV is associated with CVD outcomes and mortality, independent of traditional CVD risk factors in USA and European cohorts [52, 53, 55–59]. The role of ePWV as an independent predictor of CVD outcomes may also extend to Asian populations [54, 60]. Non-device-based estimation of aortic stiffness is rapid, easy, and inexpensive and may be used in clinical practice settings to aid in CVD risk prediction. However, there remains a substantial unexplained variance. Furthermore, the question remains as to whether ePWV can become an alternative for assessment of cfPWV as a marker of vascular aging remains to be determined, and whether ePWV improves CVD risk prediction beyond contemporary CVD risk scores such as Systematic Coronary Risk Evaluation (SCORE) and the Framingham Risk Score, as findings have been sparse and equivocal.

Limitations

To date, only few studies have sought to examine the correlation between ePWV and cfPWV and have reported this correlation to be weak (r ranges: 0.31–0.36) or moderate (r range: 0.52–0.67) [61, 62], but this correlation still remains unexplored in Asian population. It is also unclear whether the current ePWV equation from European cohort data is appropriate to be applied to other populations and racial/ethnic backgrounds. Thus, further validation studies comparing ePWV to other measures of vascular aging are needed in Asian reference populations.

While ePWV is somewhat correlated with cfPWV and an increased risk of CVD outcomes beyond risk scores, it still remains uncertain as to whether ePWV is a sensitive assessment of aortic stiffness and can serve as a substitute for cfPWV. Few studies to date have simultaneously compared the ePWV prediction equation to directly noninvasive or invasive measured aortic stiffness in predicting CVD outcomes. Compared to cfPWV or baPWV, ePWV has been shown to also predict major CV events independently of SCORE and Framingham Risk Score in patients [60, 61]. Interestingly, both ePWV and invasive PWV independently predict CV events and mortality and that ePWV has a similar predictive value for mortality as that of invasive PWV in patients with undergoing coronary angiography [59]. Despite these findings, whether ePWV

can become a substitute for cfPWV as a marker of vascular aging remains to be determined. However, as ePWV reflects an interaction between age and MBP [61], this variable may not be viewed as synonymous with cfPWV [61] and may capture different risk information than cfPWV [56, 61], thereby providing another important prognostic value to the prediction of CV health.

Other Pulse Wave Velocities

Regional PWVs

Devices which measure the cfPWV can also be used to measure other regional PWVs, such as the carotid-radial PWV and femoral-ankle PWV. While the usefulness of these regional PWVs for CV risk assessment may be limited, aortic-brachial arterial stiffness mismatch has been reported to be associated with increased mortality in the dialysis population [63].

Apart from the aforementioned regional PWVs, heart-to-brachium PWV (hbPWV) includes a segment of the proximal aorta, and this measurement can be obtained in the baPWV measurement. PTT for hbPWV can be evaluated fairly easily by simultaneous recordings of the heart sounds or electrocardiography and brachial arterial pulse waves are recorded with a high-fidelity sensor (e.g., air-plethysmography) embedded in the BP cuff. The path length is obtained using an equation derived from the gender and height. hbPWV has been shown to be correlated with the aortic systolic BP and augmentation index. Therefore, the hbPWV may be a marker of proximal aortic stiffness [64].

Finger-toe PWV is a simple noninvasive method for measuring regional arterial stiffness. The finger-toe PWV is determined on the basis of a patented height chart for the distance and the PTT between the finger and the toe pulpar artery signals (ft-PTT). Acceptable correlation has been reported between the finger and the toe pulpar artery signals and carotid-femoral PTT [65].

Recently, based on the pulse waveform recorded at the radial and digital arteries, the radial-digital PWV has become available as a measure of the regional stiffness of small conduit arteries [66]. The clinical implication of this measurement has not yet been clarified.

Local PWVs and Ambulatory PWVs

The use of cuff-based oscillometric devices provides an estimated (local) PWV based on pulse wave analysis and wave separation analysis at a single site such as the carotid, brachial, radial, or femoral arteries [67, 68]. These are simple and relatively operator-independent, and enable ambulatory measurements, and the PWV values are associated with aortic stiffness. Sarafidis et al. [69] reported that ambulatory PWV is a useful marker to predict future CV events. Ambulatory PWV was estimated with an oscillometric ambulatory BP monitoring device. In the future, it may be possible for both ambulatory and home monitoring of stiffness parameters and related hemodynamic abnormalities. It is still not known how these may be applied in clinical practice, and robust validations for such devices are needed.

Aortic PWV by Magnetic Resonance

For measurement of the aortic PWV by magnetic resonance, which is the most reliable noninvasive method to measure the aortic PWV, a fully automatic method has become available [70], although this measurement is limited to research use because of its cost and availability in limited institutions. In patients with hypertrophic cardiomyopathy, the aortic strain of the descending aorta assessed by magnetic resonance was significantly decreased as compared with that in control subjects and correlated with the native T1 values. Aortic strain may be a marker of myocardial fibrosis in patients with hypertrophic cardiomyopathy [71].

Standardization of PWV Measurement

Validation is a crucial step for standardization. For the validation of devices, performance in terms of precision (i.e., repeatability/reproducibility) and accuracy (i.e., closeness to real value) must be assessed [72] because these features determine the reliability and validity of a device in clinical practice. Validation is a fundamental prerequisite for a device to be clinically useful. For this reason, structured standardized protocols providing evidence of the performance of a system need to be implemented in the development of any medical device. Currently, available guidelines provided by the Artery Society in 2010 [73] have been used in the last 10 years for validation of devices measuring carotid-femoral cfPWV. However, since 2010, many devices measuring PWV on arterial paths other than carotid-femoral have been developed, raising many methodological and clinical questions. A detailed evaluation of these issues is beyond the scope of this article: an international working group is now working to provide an updated document including those cases. However, it is worthwhile to mention some open issues posed as questions and answers below:

- Q1: Are PWV values from different arterial segments directly comparable in a single individual?

- A1: baPWV is systematically higher than cfPWV [74], even when correction formulas are used [23]. This is a consequence of different arterial segments containing different distributions of elastic and muscular arteries. One possible standardization could be to make reference to normal percentiles, or vascular age calculation, for each technique, noting that validation of such approach is still needed.
- Q2: Are PWVs from different arterial segments to be validated against the same reference standard (i.e., invasive aortic PWV)?
- A2: As elaborated in Q1, PWVs differ quantitatively between arterial beds. As far as baPWV is concerned, the brachial-ankle arterial bed cannot realistically be assessed invasively using catheters. As an alternative, new baPWV devices can be validated against existing (noninvasive) baPWV devices that have shown prognostic relevance beyond classical risk factor assessment [26]. Thus, new baPWV devices can be validated against these proven devices. For arterial beds other than brachial-ankle, the answer is less clear.
- Q3: Do PWVs from different arterial segments provide similar prognostic information/risk stratification in a single individual?
- A3: cfPWV and baPWV predict CV events beyond classical CV risk assessment and improve risk reclassification [26, 44]. To the authors' knowledge, a formal head-to-head comparison between cfPWV and baPWV in terms of risk prediction is not available at present. International collaborations are encouraged to address this important gap. However, in 2005, Pannier et al. [75] directly compared the ability of cfPWV, carotid-radial PWV, and femoral-tibial PWV to predict CV events in end-stage renal disease and found only cfPWV to significantly predict CV events.

Other devices, measuring finger-to-toe PWV by finger plethysmography or heart-to-foot PWV by a combination of ballistocardiography and foot impedance measurement [65, 76], have demonstrated agreement with noninvasive cfPWV, but only in small samples; no information on prognostic value is available. Furthermore, an increasing number of approaches claim to evaluate arterial stiffness by use of machine learning algorithms applied mostly to arterial waveforms, but sometimes also using clinical variables such as age, sex, or BP [77]. Though promising given their ease of use and with the potential of evaluating beat-to-beat PWV for some methods, these techniques cannot be recommended for clinical use to date.

The standardization of PWV measures must also consider the standardization of how these measures should be recorded in clinical practice. This is crucial given the dependence of PWV measurements on the hemodynamic status of the patient. We recommend standard operating procedures which are similar to those of BP measurements [78] or ECG, and that are summarized in the 2012 paper about measurement of cfPWV in daily practice [9]. Most importantly, we recommend that the measurement is taken in a quiet and stable-temperature environment after 10 min rest, avoiding smoking, caffeine, alcohol, and eating in the hours preceding the measurement, and not speaking during the measurement. Noteworthy, each technique may have specific contraindications (e.g., carotid stenosis for cfPWV, peripheral arterial disease for baPWV). With an increasing number of devices allowing out-of-office, self-measurement of arterial stiffness [79], the issue of measure standardization will become even more critical.

Clinical Implication of PWV Measurement

Arterial stiffness is the primary parameter to detect age-related CV risk before CV risk factors and organ damage become clinically overt. In addition, even after clinically overt risk factors, organ damage, and/or CV disease developed, arterial stiffness is closely associated with these risks and is useful for the management [80]. Thus, arterial stiffness is a useful parameter across the broad scope of healthcare and medicine [28, 81].

CV Risk Stratification for Medical Use

A clinical implication of arterial stiffness is the risk stratification for CV events from the community-dwelling population to outpatients with CV risk factors and/or CV diseases. The hypertension guidelines or expert consensus documentation include measures of arterial stiffness for risk stratification and better management of hypertension [82].

There is ample evidence which demonstrates that increased arterial stiffness, assessed by different measures such as cfPWV, baPWV, and CAVI, is associated with organ damage and CV events [28]. Although arterial stiffness is closely associated with high BP, all arterial stiffness measures are associated with CV event risk even after controlling for BP.

First, cfPWV is a well-established measure of arterial stiffness, independently associated with organ damage and CV event risk. Theoretically, it is the measure of stiff-

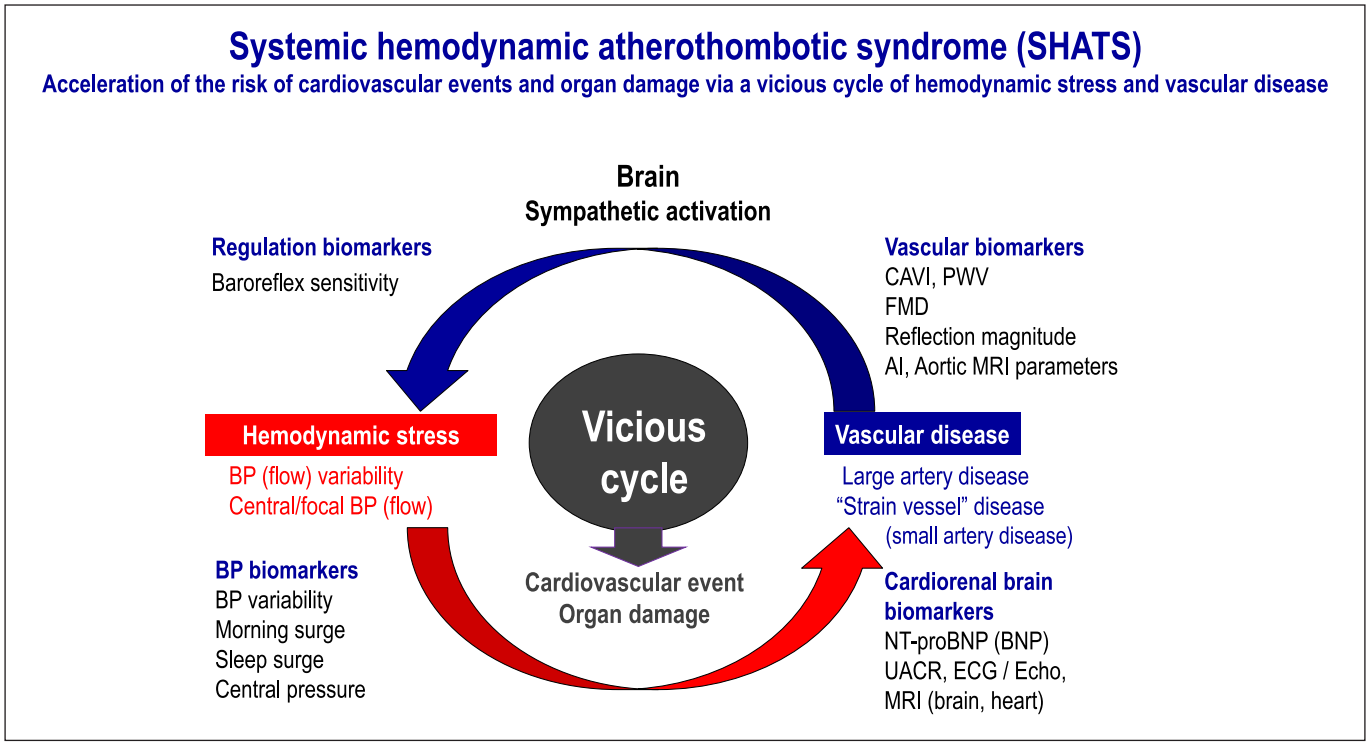

Fig. 5. Concept and biomarkers of the systemic hemodynamic atherothrombotic syndrome. AI, augmentation index; BNP, B-type natriuretic peptide; CAVI, cardio-ankle vascular index; FMD, flow-mediated dilation; UACR, urinary albumin/creatinine ratio. (Source: Kario. Nat Rev Nephrol. 2013;9:726–738 and Kario. Prog Cardiovasc Dis. 2016;59:262–281.)

ness of large arteries, however, to detect the pulse at the femoral site limits its clinical use. Second, compared with cfPWV, baPWV included the arterial properties of muscular peripheral artery distal to the femoral site. Thus, this indicator is more closely affected by BP. baPWV is associated with CV risk factors and a risk predictor of CV events, and it is useful for the risk stratification [83–85]. Third, CAVI is a new measure of arterial stiffness that reflects the stiffness from the ascending aorta to the ankle arteries and demonstrates less dependence on BP during the evaluation [20]. The systematic review to assess the association between CAVI and CV diseases (9 prospective studies (n = 5,214) and 17 cross-sectional eligible studies (n = 7,309), with most enrolling high CVD risk populations in Asia), demonstrated a modest association between CAVI and incident CVD risk [86]. A recent prospective study, CAVI-J, demonstrated that CAVI is predictive of stroke and heart failure in outpatients with CV risk [87].

The challenges of arterial stiffness are to demonstrate the benefit of arterial stiffness-guided management of risk factors on future CV prognosis. To address this issue, the Coupling study, a nationwide-prospective study, is now ongoing to demonstrate the association of serial change of CAVI and CV risk [88, 89]. A recent prospective study on the serial cfPWV change in patients with resistant hypertension, reducing, or preventing progression of aortic stiffness was associated with significant CV protection in patients with resistant hypertension [90].

Prediction of Hypertension in Healthcare

In healthy subjects, arterial stiffness may predict the future development of hypertension and hypertension-related organ damage. In subjects without hypertension, increase in CAVI or baPWV predicted hypertension [91]. Stress and obesity per se could accelerate the age-related arterial stiffening [92–94]. Other age-related diseases, such as cognitive dysfunction-associated small artery disease and atrial fibrillation are also associated with increased arterial stiffness [95, 96].

Challenges and Concept of Systemic Hemodynamic Atherothrombotic Syndrome

There is the vicious cycle between arterial stiffness and BP variability to facilitate the organ damage and CV events. The concept of systemic hemodynamic atherothrombotic syndrome (SHATS) has been proposed, describing an age-related and synergistic vicious cycle of hemodynamic stress and vascular disease [97]. This was presented and discussed at the 2018 Scientific meeting of Pulse of Asia, Kyoto (Fig. 5) [98]. The importance of SHATS is based on the assumption that the assessment of BP variability and arterial disease is likely to provide an effective opportunity to intervene early to reduce progression to hypertension in younger patients or to CV disease events and organ damage in older patients. We propose a new SHATS score to diagnose and assess the severity of SHATS. The score includes two components – a BP score and a vascular score – which are multiplied to generate the SHATS score [98]. This reflects the synergistic, rather than additive, effects of BP and vascular disease on target organ damage and CV disease events. Recently, we demonstrate the interaction of arterial stiffness with the association between home BP variability and CV risk in the prospective J-HOP study [99, 100]. First, the regression line of levels of BNP, a measure of cardiac overload, against home BP variability was steeper in those with baPWV >1,800 cm/s than those with baPWV <1,800 cm/s in the cross-sectional analysis [100]. Second, in the prospective analysis, the regression lines of CV events against the home BP variability were also steeper in those with baPWV >1,800 cm/s than those with that <1,800 cm/s [100]. Although it requires refinement and validation in future studies and in other populations, early detection of SHATS using tools such as the proposed score, combined with population-based stratification and technology-based anticipation medicine incorporating real-time individual data, has the potential to contribute to meaningful reductions in rates of CV disease events and target organ damage.

Perspective of PWV Measurement

Methodology Perspectives

There is no methodologic consensus for PWV in risk prediction models of CV disease. Japan Brachial-Ankle Pulse Wave Velocity Individual Participant Data Meta-Analysis of Prospective Studies (J-BAVELs) suggested the steno-stiffness approach improved CV risk assessment in primary prevention using the inter-arm BP difference, the ABI, and baPWV [83]. Asian population might have different responses in PWV profiles to vascular aging or BP lowering treatment. Vascular aging or hypertension-related medial degeneration is the dominant factor associated with increased arterial stiffness (arteriosclerosis) more than the narrowing of the artery (atherosclerosis) in Asian populations [18]. Asian populations also have a particular predisposition to increased central aortic pulse pressure because of the relatively larger diameter and thinner media at the proximal aorta that modulates the interaction between ventricular ejection and arterial load than other ethnicities [101]. Still, there are no specific indications for the vascular markers in most Asian CV prevention guidelines. However, recently the Japanese Society of Hypertension Guidelines introduced the implication of PWV analysis [102]. Both cfPWV and baPWV could improve the prediction of existing risk models; however, with the improvement of the prognostic ability being larger when baPWV was used in the low-risk group [26], cfPWV may perform better when used in cases of moderate or higher risk [44]. Also, the guideline recommended to conduct vascular evaluation upon stabilization of BP after the initiation of antihypertensive treatment rather than before treatment. One of the fundamental limitations of PWV measurement is that BP change substantially influences its value, namely "functional stiffness." Therefore, after BP lowering, the PWV values are reduced rapidly within weeks before the vascular rigidity is actually reversed. There is little possibility that any advances in PWV methodology might completely remove functional components from the PWV values. However, the standard method of PWV evaluation after BP lowering treatment, e.g., taking stable doses of medication for 2–3 months to minimize the effect of BP lowering or antihypertensive medications, will be necessary to remove the functional component, thus solely evaluating the vascular structural changes.

Clinical Perspectives

Modern clinical practice stresses the importance of basing healthcare practices and health policy on the best available clinical evidence. However, it is a long journey to translate research evidence into routine clinical practice through closing fundamental translational gaps [103]. There have been numerous studies and meta-analyses demonstrating the prognostic value of arterial stiffness beyond established CV disease risk factors, including age and BP [1, 44]. Nevertheless, clinical practice guidelines rarely recommend the routine use of arterial stiffness in daily care [104, 105]. To facilitate the routine use

of arterial stiffness measurements, the corresponding translational gaps in the clinical application should be analyzed and addressed with appropriately designed clinical trials.

To justify the routine clinical use of any biomarkers, several criteria must be met. For the many methodologies to estimate arterial stiffness, their reliability, and reproducibility in a standard clinical setting should be firstly demonstrated [106]. Moreover, in a busy clinical environment, a less complicated measurement procedure with operator independence is more welcomed [105]. Second, these techniques must carry the ability to add additional risk discrimination beyond the conventional risk prediction systems such as Framingham risk score or SCORE and should be cost-effective. Not only the independent prognostic value but also the significant reclassification ability should be shown [44]. Lastly, clear indication of the implementation of arterial stiffness techniques should be provided including but not limited to being used for risk stratification, treatment monitoring, or as a therapeutic target.

Previous studies pertaining to arterial stiffness have endeavored to address most but not all the above requirements. The independent value of arterial stiffness in predicting CV events have been presented [1, 44, 107]. Moreover, its ability to predict incident hypertension [108] and target organ damage, including brain [109, 110], heart [111], and kidney [112] have also been confirmed. In an individual patient, data meta-analysis of cfPWV for subjects at intermediate risk [44] adding cfPWV into standard risk factors rendered a net reclassification of 15% and 27% for coronary heart disease events and CVD death, respectively. Such analysis provided justification to apply arterial stiffness measurements in routine clinical practice. They can make risk prediction more accurate by reclassifying subjects with intermediate CV risk into a higher risk level, in which treatment is indicated, or into a lower risk level, in which further therapy could be safely avoided. In subjects with intermediate risk such as white coat hypertension [113], isolated diastolic hypertension [114], or borderline hypertension, the uncertainty in risk prediction may be further reduced by measuring arterial stiffness.

Of the techniques for estimating arterial stiffness, advantages and disadvantages of each technique are observed. Although cfPWV has the strongest evidence base supporting clinical value [7], the operator dependence limits its widely use in routine practice [105]. Cuff-based devices require less training but may be less accurate [106]. Further research is required to address this important unmet need. Besides, recommendation of the routine use of arterial stiffness techniques could be further supported by conducting randomized controlled trials adopting arterial stiffness as a treatment target, a treatment monitoring instrument, or as a tool incorporated in the intervention strategies such as risk stratification for subjects with intermediate risk profiles. To obtain health insurance reimbursement, cost-effectiveness analysis accompanied with the prospective studies for arterial stiffness is also warranted to support its routine clinical implement.

The distinctive clinical value of arterial stiffness techniques relies on the ability to provide important information regarding BP progression and susceptibility to end organ damage. The most useful scenario seems to be the more accurate risk classification for subjects at intermediate CVD risk, in which condition the need for treatment is uncertain, such as patients with masked or white coat hypertension. Therefore, arterial stiffness can be seen as complimentary to current BP measurement, and both should be considered when risk assessment is required for making timely and relevant treatment decisions. The role of arterial stiffness as a treatment target, treatment monitoring strategy in response to therapy, or a tool in the intervention strategy should be further uncovered in prospective studies or randomized controlled trials.

Research Perspectives

Comparison between Various PWVs and Exploration on Structural Stiffness

Irrespective of the cfPWV or baPWV, the PWV measurements are highly dependent on BP, which often makes the interpretations of separate interventional effects on structural and functional stiffness difficult [16]. CAVI is less dependent on BP, but it reflects not only aortic stiffness but also stiffness of the femoral and tibial arteries, similar to baPWV [20]. cfPWV, baPWV, and CAVI were all associated with target organ damage and predictive of adverse clinical outcomes. However, comparisons between these parameters in their associations with target organ damage are inconsistent [115, 116]. It remains to be determined whether the predictive value would be different between various PWVs, and what values are added on each other. Furthermore, there is still a need to develop new methods for the calculation of PWV-derived values independent of BP, especially for interventional research.

Asian-Specific Reference Values

In addition to age and BP, the two major determinants of PWV, other factors include sex, body height, body

weight, heart rate, blood glucose, and lipids. Populations of different ethnicity or environmental background may share similar major risk profiles of PWV but may be different in risk factors and strengths of associations between these risk factors and PWV [117]. Indeed, Europeans and Asians are different in body height, heart rate, and metabolic risk profiles [117]. It is therefore necessary to explore whether the currently proposed reference values of PWV fit the Asian population.

New Devices and Parameters

Recent advanced techniques make it possible to monitor the diurnal PWV changes during ambulatory BP monitoring [118]. In normotensive volunteers, the 24-hour PWV follows a similar circadian pattern as BP [119]. However, the clinical significance of 24-hour, daytime, and nighttime PWVs remains to be elucidated. It is expected that the "white-coat" effect and the "masked" phenomenon also exist for the PWV measurement because of its BP-dependent nature. Indeed, in patients with chronic kidney disease, 24-hour PWV increased only in patients with masked uncontrolled hypertension and sustained uncontrolled hypertension, but not those with controlled hypertension [120].

Emerging newly developed smart wearable devices can estimate PWV via signals of electrocardiography and photoplethysmography in a tracing of 30 s [121]. Such a device (Huawei Watch GT2/3 Pro) has been recently commercialized in China. According to the results of a validation study in adults, the mean difference in comparison with the estimation by the Complior device (France) was within the acceptable pass criteria [121]. It remains to be determined what this new and convenient measurement of PWV can add on the management of arterial stiffness in populations.

During PWV measurement, PTT varies in a beat-to-beat manner. In the Chinese and Swedish elderly populations, the beat-to-beat variation of PTT within a 10-s measurement period independently predicted all-cause and CV mortality outcomes and improved risk prediction beyond PWV and other conventional risk factors [122]. Further studies are warranted to address whether the longer term variation of PWV or PTT could add to risk stratification and would be modifiable by lifestyle modifications and drug treatment.

New Strategies and Drugs

In most of the previous research, PWV has been used as a risk predictor. The SPARTE trial was the first to investigate whether a PWV-guided therapeutical strategy would be better than conventional antihypertensive treatment in improving CV outcomes [123]. Although the PWV normalization driven strategy, compared with usual BP driven therapeutic strategy, did not result in a statistically significant reduction in the risk of CV events because of inadequate power, it resulted in significant treatment intensification, reduction in office and ambulatory BP, and prevention of vascular aging. The research hypothesis is warranted to be tested in future adequately powered trials.

The lack of effective interventions to improve arterial stiffness is a major barrier for the clinical application of PWV measurement. Conventional lifestyle improvement and RAS inhibitors, especially in high doses, such as 40 and 80 mg olmesartan, were able to significantly remodel or destiffen the arterial wall material during long-term treatment, partly independent of BP lowering effects [124, 125]. Selective sodium-glucose cotransporter inhibitors were recently demonstrated to reduce PWV independent of change in systolic BP and CV risk factors [126], although not CAVI [127]. However, it is important to look for new therapeutic targets. The promising effect of several new agents on the pathways of caloric restriction, inflammation, and fibrosis, such as the mTOR inhibitors, AMPK, sirtuin and PPAR-γ activators, and TNFα antagonism, is anticipated to be tested in future clinical research [125].

Conclusion

Arterial stiffness, as a marker of subclinical target organ damage, is an important and independent predictor for CV mortality and morbidity. PWV is a noninvasive and reliable tool for the assessment of arterial stiffness. Various methods of PWV measurement, depending on which arterial sites are involved, are now available. PWV measurement including the central elastic artery is essential and measurements including both the central elastic and peripheral muscular arteries can be a good alternative, as PWVs, with either measurement methodology, are predictive of outcomes. As Asian populations are rapidly aging, timely detection and intervention of "early vascular aging" are recommended. Convenient and wearable devices may facilitate the application of PWV measurement in diverse settings; nonetheless, the validation of devices is also necessary pending the development of consensus on the validation protocol. More evidence is urgently needed to prove a PWV-guided therapeutic approach will be beneficial to the prevention of CV diseases beyond current strategies.

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Author Contributions

Jeong Bae Park, James E Sharman, and Yan Li contribute to the design of this review. Jeong Bae Park contributes to the writing of the Introduction and Conclusion. Alberto P Avolio contributes to the writing of Methodologic aspect. Masanori Munakata, Kohji Shirai, Chen-Huan Chen, Sae Young Jae, Hirofumi Tomiyama, and Hisanori Kosuge contribute to the writing of baPWV, CAVI, cfPWV, ePWV, and others, respectively. Rosa Maria Bruno, Bart Spronck RM, and James E Sharman contribute to the writing of how to standardize the methods. Kazuomi Kario contributes to the writing of clinical implication. Hae Young Lee, Hao-Min Cheng, Jiguang Wang, and Yan Li contribute to the writing of perspectives on methodologic, clinical, and research aspects. Matthew Budoff and Raymond Townsend contribute to the final version of the manuscript as external reviewers. All authors discussed and commented on the manuscript.

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