

## Review

# The Noninvasive Assessment of Vascular Aging

Stéphane Laurent, MD, PhD, Louise Marais, BS, and Pierre Boutouyrie, MD, PhD

*Université Paris-Descartes, Assistance-Publique Hôpitaux de Paris, Paris, France; INSERM U970, Paris, France; Department of Pharmacology and Hôpital Européen Georges Pompidou, Paris, France*

### ABSTRACT

The growing interest in the clinical measurement of arterial aging through the noninvasive assessment of arterial stiffness is associated with important developments in novel methods and apparatus. In this review, we aimed to describe the major principles of the measurement of arterial stiffness and to critically review the advantages and limitations of the different methods. The measurement of regional stiffness is recommended by international guidelines for routine clinical practice. It is most often determined through pulse wave velocity (PWV) between 2 arterial sites. Methods using a single-site cuff-based measurement are promising. Local determination of arterial stiffness, obtained either with the well-established, high-resolution echo tracking systems or more recently with magnetic resonance imaging, is indicated for pathophysiological and pharmacologic studies. Novel apparatus that were developed for determining arterial stiffness claimed superiority over pioneering methods either through greater simplicity of use, better repeatability, or a more pertinent arterial pathway. However, the true additive value of measuring arterial aging with a given apparatus had to be translated into the predictive value of arterial stiffness as an intermediate end point, ie, the higher the arterial stiffness the higher the number of cardiovascular (CV) events. Thus, another important aim of this review was to analyze the amount of epidemiologic evidence obtained with a given method regarding the predictive value of arterial stiffness for CV events.

### RÉSUMÉ

L'intérêt grandissant pour la mesure clinique du degré de vieillissement des artères par l'évaluation non invasive de la rigidité artérielle a donné lieu à une multiplication des nouvelles méthodes et des nouveaux dispositifs. Dans cet article, nous passons en revue les principales méthodes d'évaluation de la rigidité artérielle et nous examinons les avantages et les limites propres à chacune. Les lignes directrices internationales recommandent la prise de mesures locales de la rigidité artérielle en pratique clinique courante, ce qui s'effectue habituellement à l'aide de la vitesse de l'onde pulsatile (VOP) entre deux points de repère artériels. Les méthodes de mesure en un seul point avec manchon sont particulièrement prometteuses. Les mesures locales de la rigidité artérielle à l'aide soit de l'échographie à haute résolution, soit de la résonance magnétique sont pour leur part indiquées dans le cadre d'études physiopathologiques et pharmacologiques. Les nouvelles méthodes de mesure ont appuyé leur supériorité par rapport aux anciennes sur leur plus grande facilité d'utilisation, la répétabilité des mesures ou encore sur la pertinence des voies artérielles utilisées. Cependant, la valeur réelle de la mesure du vieillissement artériel à l'aide d'une méthode donnée doit être évaluée sous l'angle de la valeur prédictive de la rigidité artérielle en tant que paramètre intermédiaire (c.-à-d. nombre d'événements cardiovasculaires augmentant avec le degré de rigidité artérielle). C'est pourquoi cet article avait également pour objectif d'analyser la teneur des preuves épidémiologiques obtenues pour chacune des méthodes de mesure en ce qui a trait à leur valeur prédictive de la rigidité artérielle et d'événements cardiovasculaires.

The aging of the large artery wall is characterized by a progressive reduction in the elastin content, in parallel with an increased amount of collagen, and changes in the cell-matrix interactions, leading to increased arterial stiffness.<sup>1</sup> In recent years, a better comprehension of these processes has led to the proposal of a condition called “early vascular aging” (EVA) in patients with increased arterial rigidity for

their age and sex.<sup>2-5</sup> More generally, EVA indicates a pronounced effect of aging on the vascular tree and especially on arterial function. In parallel, the cross-talk between the microcirculation and the macrocirculation promotes a vicious circle of increased resistance in small arteries,<sup>6,7</sup> leading to increased mean blood pressure (BP) and then to increased large artery stiffness, which leads to an increased wave reflection, leading, in turn, to a disproportionately increased central BP, mean BP levels, and excessive variability of 24-hour ambulatory brachial BP, and ultimately to target organ damage.<sup>6-8</sup> EVA also represents an altered capacity for repairing arterial damage in response to aggression such as mechanical stress and metabolic and chemical (oxidative) stresses.<sup>4</sup>

Vascular aging in general, and EVA more specifically, can be monitored noninvasively by measuring arterial stiffness,

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Corresponding author: Dr Stéphane Laurent, Department of Pharmacology and INSERM U 970, Hôpital Européen Georges Pompidou, Assistance Publique—Hôpitaux de Paris, 56 rue Leblanc, 75015 Paris, France. Tel.: 33-1-56-09-39-91; fax: 33-1-56-09-39-92.

E-mail: [stephane.laurent@egp.aphp.fr](mailto:stephane.laurent@egp.aphp.fr)

See page 677 for disclosure information.

central BP, carotid intima-media thickness (IMT), endothelial dysfunction, and small artery disease.<sup>3,7</sup> These parameters can be considered arterial “tissue biomarkers.” They may be more specific and more integrative of cardiovascular (CV) risk factors than “circulating” biomarkers such as high-sensitivity C-reactive protein and show better additional prediction ability when coupled with classic CV risk scores.<sup>9</sup> In particular, arterial stiffness measures the cumulative influence of CV risk factors with time, because age represents both the aging process and the duration of exposure to risk factors. Indeed, arterial stiffness represents true arterial wall damage, whereas other risk factors such as BP, glycemia, and lipid levels vary during patient follow-up and thus may not be representative enough of the cumulative effects of CV risk factors on the arterial system. Classic and sophisticated CV risk factors (ie, circulating biomarkers) can be considered “snapshots,” and arterial stiffness can be considered an integrator of the long-lasting effects of identified and nonidentified CV risk factors. Arterial stiffness can be considered a tissue biomarker.<sup>7</sup>

In this review, we focus on arterial stiffness, a simple and robust parameter that is able to estimate vascular aging, and particularly EVA. Indeed, although small arteries play a role in vascular aging, mainly through the cross-talk between the microcirculation and the macrocirculation in response to their inward eutrophic remodelling and increased total peripheral resistance,<sup>6</sup> their clinical investigation most often needs invasive methods and thus is not recommended by international guidelines.

The phrase “arterial stiffness” is a general term that refers to the loss of arterial compliance or changes in vessel wall properties, or both. Compliance of large arteries—including the thoracic aorta, which has the major role—represents their ability to dampen the pulsatility of ventricular ejection and to transform pulsatile pressure (and flow) at the site of the ascending aorta into continuous pressure (and flow) downstream at the site of arterioles to lower the energy expenditure during organ perfusion.

The predictive value of arterial stiffness for CV events has been well demonstrated. The largest amount of evidence has been seen for aortic stiffness, measured through carotid-femoral pulse wave velocity (cfPWV). This was initially reported in the late 1990s to early 2000s.<sup>10,11</sup> Currently, as many as 19 studies have consistently shown the predictive value of aortic stiffness for fatal and nonfatal CV events in various populations having different levels of CV risk: the general population, hypertensive patients, elderly individuals, patients with type 2 diabetes, and patients with end-stage renal disease.<sup>12</sup>

Because there is both a growing interest in the clinical measurement of arterial aging through arterial stiffness and an increasing number of novel methods and apparatus, we aimed to describe the major principles of measurement and to critically review the advantages and limitations of the various methods. Another important aspect is the amount of epidemiologic evidence obtained with a given method regarding the predictive value of arterial stiffness for CV events.

### Clinical Measurements of Arterial Stiffness

Arterial stiffness can be evaluated at different levels: systemic, regional, and local. Systemic arterial stiffness can only

be estimated from models of the circulation, whereas regional and local arterial stiffness can be measured directly and non-invasively at various sites along the arterial tree. Regional and local arterial stiffness measurements have the advantage that they are based on direct measurements strongly linked to wall stiffness. Reviews have been published on methodological aspects.<sup>13-15</sup> Table 1 gives the principal features of the various methods currently available.

### Regional measurements of arterial stiffness

The aorta is the principal vessel of interest when measuring regional arterial stiffness because (1) the thoracic and abdominal aorta are the principal sites for the arterial buffering function and (2) aortic PWV has proved to be an independent predictor of outcome in various populations.<sup>10-12,14,15</sup> However, all accessible arterial territories are potentially interesting. For instance, the forearm circulation corresponds to BP measurement, and the lower limb arteries are a classic site for atherosclerosis. The measurement of local carotid stiffness also carries important prognostic information, because the carotid artery is also a possible site for atherosclerosis.

**Two-site PWV measurements.** The measurement of PWV is generally accepted as the most simple, noninvasive, robust, and reproducible method with which to determine arterial stiffness. PWV between the common carotid artery (CCA) and the common femoral artery (cfPWV) is measured directly and corresponds to a well-accepted propagative model of the arterial system.<sup>14</sup> Because it includes the aortic and aortoiliac pathway, it is clinically relevant, because the big thoracic arteries (aorta and its first branches) represent the hemodynamic load that the left ventricle “sees” and are therefore responsible for a large part of the pathophysiological influence of arterial stiffness. Most epidemiologic studies demonstrating the predictive value of aortic stiffness for CV events have used carotid-femoral PWV. CfPWV is considered the gold standard for measuring arterial stiffness.<sup>13</sup> By contrast, PWV measured outside the aortic track, for instance on the upper (brachial-radial PWV) or lower limb (femoral-tibial PWV), does not provide any additional predictive value in patients with end-stage renal disease.<sup>32</sup>

PWV is usually assessed using the foot-to-foot velocity method from various waveforms. These are obtained transcutaneously at the right CCA and the right femoral artery (ie, cfPWV), and the time delay ( $\Delta t$ , or transit time) is then measured between the feet of the 2 waveforms (Fig. 1).<sup>13,17</sup> The “foot” of the wave is defined as the transition between the end of diastole and the steep rise of pressure during early systole. The transit time is the time of travel of the foot of the wave over a known distance.

Different waveforms can be used, including pressure,<sup>17,18</sup> distention, and Doppler waveforms.<sup>22</sup> The distance (D) travelled by the waves is approximated by the surface distance between the 2 recording sites, ie, the CCA and the common femoral artery (CFA), respectively. The direct distance DD is (CFA to CCA). PWV is calculated as  $PWV = D \text{ (m)} / \Delta t \text{ (seconds)}$ .

However, because waves travel in diverging directions in the carotid artery and the descending aorta, it has been recommended to calculate the distance between the suprasternal

**Table 1. Device and methods used for determining regional, local, and systemic arterial stiffness**

Year of first publication	Device	Method	Measurement site	Reference	Predictive value for CV events (year 1 <sup>st</sup> publication)	Ease of clinical utility	Approval by FDA*
<b>Regional stiffness</b>							
1984 <sup>†</sup>	Complior	Mechanotransducer	Aorta, cf PWV	Asmar et al. <sup>17</sup>	Yes (1999)	++	No
1990 <sup>†</sup>	Sphygmocor	Tonometer	Aorta, cf PWV	Pauca et al. <sup>18</sup>	Yes (2011)	++	Yes
1991	WallTrack	Echotracking	Aorta, cf PWV	Bussy et al. <sup>19</sup>	No	+	?
1994	QKD	ECG +	Aorta, cf PWV	Gosse et al. <sup>20</sup>	Yes (2005)	++	Yes
1997 <sup>†</sup>	Cardiovasc. Eng. Inc	Tonometer	Aorta, cf PWV	Mitchell et al. <sup>21</sup>	Yes (2010)	+	NA
2002	Artlab	Echotracking	Aorta, cf PWV	Bussy et al. <sup>19</sup>	No	++	Yes
2002	Ultrasound systems	Doppler probes	Aorta, cf PWV	Cruickshank et al. <sup>22</sup>	Yes (2002)	+	NA
2002	Omron VP-1000	Pressure cuffs	Aorta, ba PWV	Sugawara et al. <sup>23</sup>	Yes (2005)	+++	Yes
2007	CAVI-Vasera	ECG + pressure cuffs	Aorta, ca PWV	Shirai et al. <sup>24</sup>	Yes (2014)	+++	Yes
2008	Arteriograph	Arm pressure cuff	Aorta, aa PWV	Baulmann et al. <sup>25</sup>	Yes (2013)	++	No
2009	MRI, ArtFun	MRI	Aorta, aa PWV	Herment et al. <sup>26</sup>	Yes (2014)	+	NA
2010	Mobil-O-Graph	Arm pressure cuff	Aorta, cf PWV <sup>‡</sup>	Wassertheurer et al. <sup>27</sup>	No	++	Yes
2010	Ultrafast	Echography	Common carotid	Couade et al. <sup>28</sup>	No	-	No
2013	pOpmetre	Photoplethysmography	Aorta, ft PWV	Hallab et al. <sup>29</sup>	No	+++	No
<b>Local stiffness</b>							
1991	WallTrack	Echo-tracking	CCA <sup>§</sup> , CFA, BA	Bussy et al. <sup>19</sup>	No	+	No
1992	NIUS	Echo-tracking	RA		No	+/-	No
2002	Artlab, Mylab	Echo-tracking	CCA <sup>§</sup> , CFA, BA	Bussy et al. <sup>19</sup>	Yes (2014)	++	Yes
	Ultrasonography	Echography	CCA <sup>§</sup> , CFA, BA		No	+	?
2009	MRI, ArtFun	Cine-MRI	AA, DA	Herment et al. <sup>26</sup>	No	+	NA
<b>Systemic stiffness</b>							
1989	Area method	Diastolic decay		Simon et al. <sup>30</sup>	No	+/-	NA
1995	HDI PW CR-2000	Modified Windkessel		Cohn et al. <sup>31</sup>	No	+	Yes
1997 <sup>†</sup>	Cardiovasc. Eng. Inc	Tonometer/Doppler/echo		Mitchell et al. <sup>21</sup>	Yes (2010)	+/-	NA
2009	MRI, ArtFun	Cine-MRI	AA, DA	Herment et al. <sup>26</sup>	No	+	NA

AA, ascending aorta; aa, aortic arch; ba, brachial-ankle; BA, brachial artery; ca, cardiac-ankle; CCA, common carotid artery; cf, carotid-femoral; CFA, common femoral artery; CV, cardiovascular; DA, descending aorta; ECG, electrocardiogram; ft, finger-toe; MRI, magnetic resonance imaging; NA, not applicable; PWV, pulse wave velocity; RA, radial artery.

\* FDA refers to agreement by the US Food and Drug Administration to release device for the market, which is necessary for use in routine clinical practice but is not necessary for use in research centres. All apparatus have CE agreement by the European Community.

<sup>†</sup> Apparatus used in pioneering epidemiologic studies showing the predictive value of aortic stiffness for CV events.

<sup>‡</sup> Estimated, not measured.

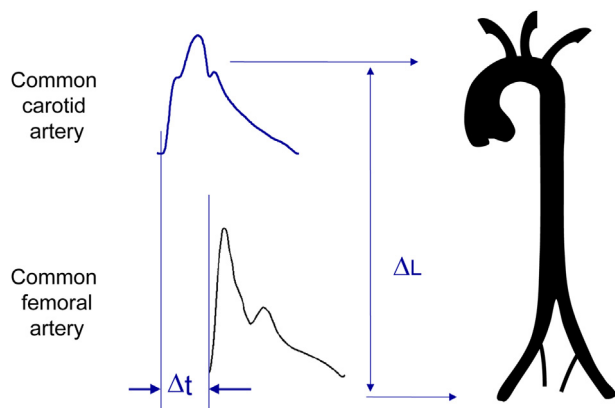
<sup>§</sup> All superficial arteries, including particularly those mentioned.

notch (SSN) and the CFA and to subtract from this distance the small length between the carotid transducer and the SSN. The “subtracted distance” is (SSN to CFA) – (SSN to CCA).<sup>33</sup> Although a consensus statement stated that the investigator could use the subtracted distance, the recommended method is to measure the direct distance and apply a

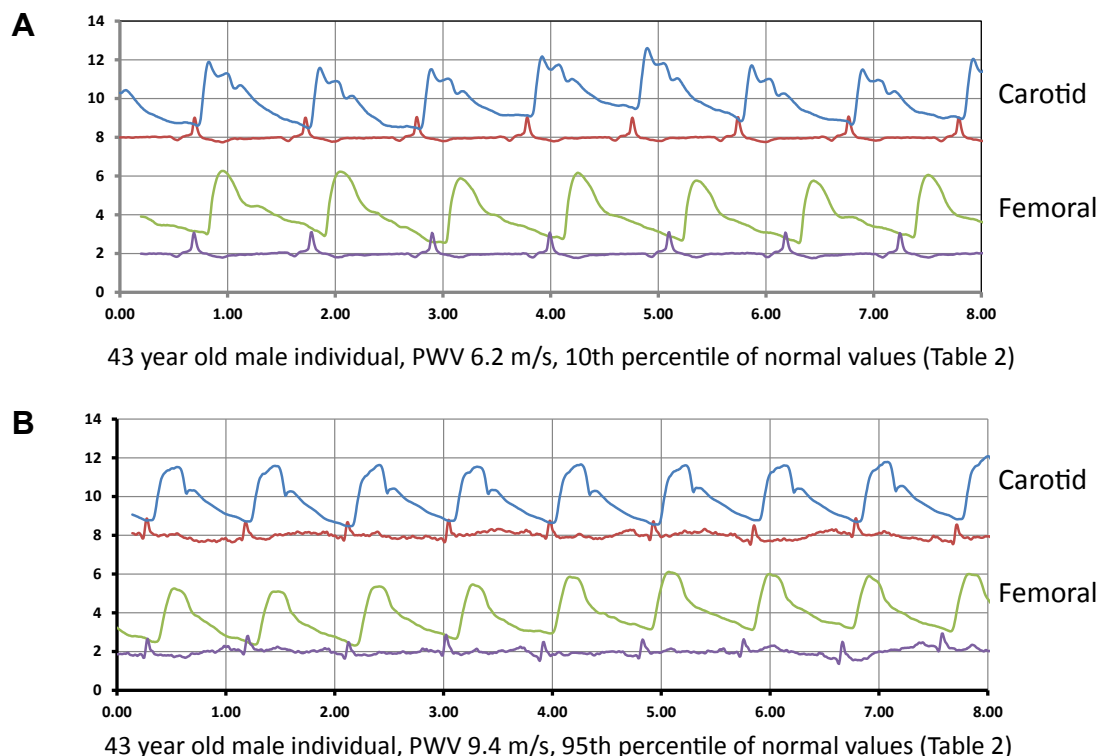
0.8 coefficient.<sup>34</sup> Indeed, the direct carotid-femoral distance largely overestimates the real travelled distance measured by magnetic resonance imaging (MRI) by more than 25%, whereas the subtracted distances (using the distances from suprasternal and sternal notch to CFA and CCA) substantially underestimate the real travelled distance by 10%-30%.<sup>34</sup> Besides, the later formulas are approximations and introduce additional error. Of all currently used distances, the 80% of the direct carotid-femoral distance (CCA to CFA × 0.8) appeared the most accurate, only slightly overestimating the real travelled distance by 0.4%.<sup>34</sup>

Some limitations should be underlined. The femoral pressure waveform may be difficult to record accurately in patients with metabolic syndrome, obesity, diabetes, or peripheral artery disease.<sup>34,35</sup> In the presence of aortic, iliac, or proximal femoral stenosis, the pressure wave may be attenuated and delayed. Abdominal obesity and large bust size can make distance measurements inaccurate with measuring tapes, but this can be avoided by using calipers to measure the distances instead.<sup>34,35</sup>

**Methods based on pressure sensors.** Multiple devices using pressure waveforms recorded simultaneously have been validated as providing automated measurement of PWV. The Complior System (Artech-Medical, Pantin, France) uses



**Figure 1.** Measurement of carotid-femoral pulse wave velocity with the foot-to-foot method. Reproduced from Laurent et al.<sup>13</sup> with permission from the European Society of Cardiology.



**Figure 2.** Measurement of carotid-femoral pulse wave velocity (cfPWV) in 2 age-matched male individuals. **(A)** Individual with hypernormal aging and **(B)** individual with accelerated aging.

dedicated mechanotransducers.<sup>1</sup> The transit time is determined at the foot of the wave using the second derivative algorithm (or now the intersecting tangent algorithm) between each simultaneous recorded wave. The operator can visualize the recorded arterial waves and validate them. Different arterial sites can be evaluated, mainly the aortic trunk (carotid-femoral), and the upper (carotid-brachial) and lower (femoral-dorsalis pedis) limbs.

Pressure waves can also be recorded successively from different sites and transit time determined from the R wave of the electrocardiogram (ECG). In the SphygmoCor system (ArtCor Medical, Sydney, Australia) a single high-fidelity piezoelectric transducer (Millar; ADInstruments Inc, Colorado Springs, CO) is used to obtain a proximal (ie, carotid artery) and distal pulse (ie, radial or femoral), recorded successively, and calculates PWV from the transit time by using the R wave of the ECG as time reference (Fig. 2).<sup>36</sup> Quality controls are built in to check for the variability of measurement over acquisition. Because the measurements are made in immediate succession, the change in contractility of the left ventricle or the change induced by heart rate (HR) variability has no quantifiable effect on pulse transit times. Generally speaking, methods using mechanotransducers or high-fidelity applanation tonometers are well accepted for cfPWV measurement.

To increase ease and acceptability, automatic cuff-based methods have been developed. Brachial ankle PWV (baPWV) (VP-1000 Vascular Profiler; Omron, Kyoto, Japan) is calculated from travelled distance and transit time, as described earlier. The travelled distance is automatically calculated based on the patient's height. Transit time is the

time delay between the proximal and distal foot waveforms. Brachial and post-tibial arterial pressure waveforms are simultaneously detected by cuffs connected to a plethysmographic sensor and an oscillometric pressure sensor wrapped around both arms and ankles.<sup>23</sup> The measurement of baPWV includes a much longer trajectory of the pressure wave along the muscular arteries of the upper and lower limbs than along the aortic pathway and thus may not reflect the true aging of the aorta. However, the main assumption of the developers of the baPWV method was that the transit times of the pressure waves in the upper and lower limbs were comparable. Thus, the net transit time that is measured mainly reflects the aortic pulse transit time. However, although aortic PWV was the primary independent correlate of baPWV, leg PWV also played a role.<sup>37</sup>

Using a similar cuff-based methodology for detecting the pressure waveforms and an electrocardiographic recording, a cardio-ankle PWV can be calculated. A feature of the cardio-ankle PWV (CAVI VaSera; Fukuda-Denshi, Tokyo, Japan) is that it bypasses the subclavian and brachial artery pathways compared with baPWV. Cardio-ankle PWV reflects the stiffness of the aorta, femoral artery, and tibial artery.<sup>24</sup> A cardio-ankle vascular index (CAVI), derived from the Bramwell and Hill equation, has been calculated by Shirai et al.<sup>24</sup> as a BP-independent stiffness parameter. However, the true BP independency of CAVI is still debated.<sup>16</sup>

**Other methods.** The transit time that is required for the determination of PWV can be determined from distention waveforms obtained successively within a short time interval at 2 arterial sites (CCA and femoral artery for instance) with

high-resolution echo tracking systems, using the R wave of the ECG for calculating the time delay.

The transit time can also be measured between 2 flow pulses simultaneously recorded by continuous Doppler probes or again sequentially with electrocardiographic gating.<sup>22</sup> Measurements are made at the left subclavian artery (ie, suprasternal notch on the skin) and the termination abdominal aorta (ie, umbilicus level). Transit time is automatically tracked.

The pOpmetre (Axelife SAS, Saint Nicolas de Redon, France) is based on assumptions similar to those used with the brachial-ankle devices. To further increase feasibility and acceptability, it extends the concept to the finger-toe arterial pathway.<sup>29</sup> It takes advantage of 2 photodiode sensors, similar to pulse oximeters, which are positioned on the finger and the toe so that the pulpar arteries are in the scope of the infrared ray. The pOpmetre measures the transit time between the foot of the pulse wave of the finger and that of the toe, approximating the aortic pulse transit time if the transit times in the upper and lower limbs are comparable.<sup>38</sup> A height chart gives the travelled distance.

**Single-site PWV measurements.** An increasing number of methods calculate PWV over a given arterial pathway from the analysis of the brachial pressure wave, which is determined with a brachial cuff. PWV is thus referred to as “single-site” or brachial cuff–derived PWV, and the apparatus are referred to as brachial cuff–based devices. As detailed further on, PWV is *estimated* from various parameters, themselves either measured or estimated, but PWV is not *directly* measured between 2 arterial sites.

**The QKD method.** Two decades ago, Gosse et al.<sup>20</sup> proposed to take advantage of an ambulatory measurement of BP and continuous monitoring of the ECG over 24 hours (Diasys; Novacor, France) to calculate the QKD interval. QKD is the time between the Q wave on the ECG and the last Korotkoff sound by the microphone in the cuff over the brachial artery. The QKD interval has 2 components: the pre-ejection time, which is influenced by HR and contractility of the left ventricle, and the pulse transmission time, which is inversely related to PWV and thus arterial stiffness. In practice, BP and the QKD interval are measured repeatedly in ambulatory conditions, and a stiffness parameter is derived from the linear regression of all the measurements of the QKD interval, HR, and systolic BP over 24 hours. The QKD interval is estimated for a standardized pressure of 100 mm Hg BP; thus, it gives an estimation of pressure-independent (isobaric) arterial stiffness for a 60-bpm HR.

The arterial pathway studied by the QKD interval is important to consider. The pressure pulse wave travels first along the ascending aorta and the aortic arch—ie, a short pathway of elastic arteries—and then along the subclavian and brachial arteries—ie, a much longer pathway of muscular arteries. This pathway is markedly different from the reference method, ie, the carotid-femoral pathway of the cPWV.<sup>13,34</sup> Since the stiffness of muscular arteries is influenced little by age and hypertension, Gosse et al.<sup>20</sup> attributed the difference in QKD interval duration to the ascending aorta and aortic arch. However, the length of the aortic pathway represents a

very small part of the total pathway, which casts doubt about the validity of the QKD interval. Conversely, even if short, the aortic pathway represents the larger part of the time delay because the aorta is 10 times more distensible than the brachial artery. MRI studies have shown that the transit time of flow wave along the aortic arch (average 120-mm length) is often found to be about 35 ms in young healthy individuals,<sup>39</sup> a value that is far less than the mean QKD interval duration.<sup>20</sup> Thus, part of that QKD interval duration has to be further explained by both the pre-ejection period and the transit time within muscular arteries.

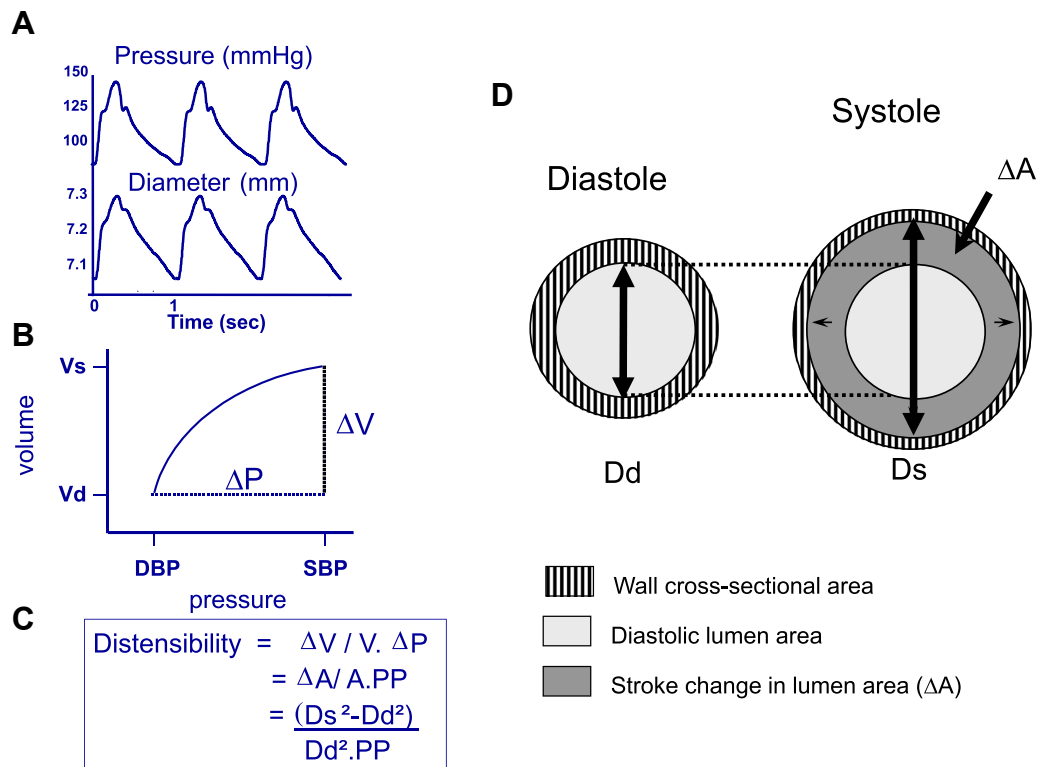
**The Arteriograph method.** The Arteriograph system (TensioMed Kft, Budapest, Hungary) estimates PWV from a single-site brachial-cuff oscillometric determination of the suprasytolic waveform at the brachial artery site. Because the cuff is pressurized at least 35 mm Hg over the actual systolic BP, hemodynamic measurements are performed under “stop-flow/occluded artery” conditions. The inventor of the apparatus claims that pure pressure waves are thus recorded under these conditions and allow precise determination of time delays.<sup>25</sup> The Arteriograph measures the time separating the first wave (left ventricular ejection) from the second wave (alleged to be its reflection from the bifurcation), with additional subtraction of the brachial artery transit time.<sup>25</sup> The final transit time corresponds to the travel of the pressure wave on the thoracic and abdominal aorta.

Although PWV measured with the Arteriograph has been validated against gold standards, there is still a controversy in the literature concerning the arterial pathway followed by the pressure wave. However, a recent study with MRI showed that the arterial pathway covered by the Arteriograph overlapped most of the aortic root bifurcation length, omitting only a few centimetres of the proximal ascending aorta.<sup>40</sup>

**The Mobil-O-Graph method.** The Mobil-O-Graph system (IEM, Rheinland, Germany) takes advantage of oscillometric recording of the brachial artery pressure waveform to synthesize the central pulse wave by applying a transfer function.<sup>27</sup> Central pulse wave is then decomposed into forward and backward waves, and PWV is estimated. More specifically, to estimate PWV, the ARCSolver method (Austrian Institute of Technology) uses sources of different origin: peripheral BP is measured and aortic blood flow is estimated from a model based on the higher-order Windkessel theory. Both are combined for estimating aortic impedance using a proprietary mathematical model and demographic data such as age and central pressure.<sup>41</sup> Aortic characteristic impedance, which is calculated from an *estimated* pressure waveform and an *estimated* flow waveform, is then used to marginally modify the PWV value, which is *estimated* mainly from invasive PWV. There is no direct measurement of PWV.

### Local determination of arterial stiffness

Local arterial stiffness of superficial arteries can be determined directly using ultrasonographic devices. Carotid stiffness may be of particular interest because atherosclerosis is frequent in that artery. All types of classic bidimensional vascular ultrasonographic systems can be used to determine diameter at diastole and stroke changes in diameter, but most



**Figure 3.** Local arterial distensibility. **(A)** Simultaneous recording of stroke changes in blood pressure and diameter. **(B)** Pressure-diameter curve. **(C)** Calculation of distensibility. **(D)** Schematic representation of the stroke change ( $\Delta A$ ) in lumen cross-sectional area (LCSA).  $\Delta A$ , stroke change in lumen area;  $\Delta P$ , stroke change in pressure, ie pulse pressure (PP);  $\Delta V$ , change in volume; DD, diastolic diameter; DPB, diastolic blood pressure; DS, systolic diameter; PP, pulse pressure, calculated as (SBP - DBP); SPB, systolic blood pressure; Vd, diastolic volume; Vs, systolic volume. Reproduced from Laurent S, et al.<sup>13</sup> with permission from the European Society of Cardiology.

of them are limited in the precision of measurements because they generally use a video image analysis. Measuring arterial stiffness from MRI is increasingly popular. However, most pathophysiological and pharmacologic studies have used echo tracking techniques.

**High-resolution echo tracking methods.** A major advantage of echo tracking techniques is that local arterial stiffness is derived directly from the change in pressure related to the change in volume, a procedure that does not imply any model of the circulation (Fig. 3). The drawback is that it requires technical skills and takes longer than measuring PWV. Because of this, local measurement of arterial stiffness is reserved for mechanistic analyses in pathophysiology, pharmacology, and therapeutics, rather than for epidemiologic studies.<sup>13</sup> Ultrasonography (echo tracking or ultrafast echo) is currently the only method to noninvasively determine the stiffness of the arterial wall material (Young's elastic modulus),<sup>19,42</sup> investigate the relationship between IMT and elastic properties, or assess the influence of remodelling patterns (inward or outward) on arterial distensibility.<sup>19,42,45</sup>

Echo tracking devices were developed to measure diameter and beat-to-beat changes in diameter with very high precision. These apparatus use the radiofrequency (RF) signal for improving the precision by a factor of 6-10 compared with video image systems. These systems are

limited by the spatial resolution of pixel analysis. With echo tracking systems, the precision in determining the beat-to-beat changes in diameter is lower than 1  $\mu\text{m}$ , whereas it is 1 pixel (approximately 150  $\mu\text{m}$ ) with classic video image analyzers.<sup>42</sup> For absolute distance, pitch ranges from 9-25  $\mu\text{m}$  with echo tracking systems and from 54-60  $\mu\text{m}$  with video image analyzers. Recent multiarray echo tracking systems having 128 RF lines (ArtLab and MyLab; Esaote Pie Medical Imaging, Maastricht, the Netherlands) are able to determine both IMT and pulsatile changes in diameter along a 4-cm-long arterial segment.<sup>44</sup>

Echo tracking systems have other major advantages over video image systems: from the same ultrasonographic data, the IMT can be extracted, which allows the Young's elastic modulus to be determined. The pressure-diameter curve of the artery allows the determination of arterial stiffness for any given level of BP. Local PWV can be assessed from the time delay between 2 adjacent distention waveforms. Studying changes in stiffness and remodelling patterns gives insight into the pathophysiological and therapeutic changes of micro-constituents within the arterial wall.

The measurement of BP is required whichever technique is used. It should be local pressure, preferably brachial pressure. Local pressure is usually obtained by applanation tonometry.<sup>13</sup> The tonometric waveform is calibrated using brachial mean and diastolic pressures,<sup>45</sup> and a transfer function is then applied to obtain central pressure (if necessary). All the

superficial arteries are suitable for the geometric investigation, particularly the common carotid, common femoral, and brachial arteries.

A new ultrasonographic imaging technique called Ultrafast echography (Supersonic Imagine, Aix-en-Provence, France) has been developed recently for the assessment of local arterial stiffness without resorting to pressure measurement. This innovative approach consists of generating shear waves in the arterial wall through the acoustic radiation force of a focused ultrasonic beam and imaging their transient propagation with a very high frame rate (>2000 images/s). The calculated shear wave propagation speed is linked directly to the tissue stiffness (shear and Young's moduli) and can be evaluated during a cardiac cycle.<sup>28</sup> Moreover, the very high temporal resolution enables the tracking of the pulse wave along a localized arterial segment. Local PWV can be measured directly at the beginning and end of systole, therefore allowing characterization of the arterial diastolic-systolic stiffening.<sup>46</sup>

**Magnetic resonance imaging.** MRI of the aortic system has considerably improved the precision of the anatomic localization of arterial stiffness measurements and added simultaneous investigation of arterial geometry and cardiac function. The determination of arterial stiffness follows the classic laws of physics, as seen earlier regarding echo tracking. Generally, a 3.0-Tesla scanner is used to visualize the aorta on sagittal oblique views. The delimitations of the ascending, proximal, and distal (diaphragmatic) descending aorta are automatically determined during the cardiac cycle on the modulus images of the phase contrast acquisition (for flow analysis) and the cine images (for aortic area analysis) using proprietary software (ArtFun, Paris, France).<sup>26</sup> The maximal ( $A_{\max}$ ) and minimal ( $A_{\min}$ ) aortic lumen areas are used for averaging diameters of the ascending and proximal and distal descending aorta. Relative changes in area [aortic strain, defined as  $AS = (A - A_{\min})/A_{\min}$ ] are used to calculate aortic distensibility in each individual:  $\text{distensibility} = AS/cPP$ , where  $cPP$  is the central pulse pressure obtained by tonometry. PWV (m/s) at the level of the aortic arch is obtained, as described earlier, by measuring the distance between the ascending and proximal descending aortic locations of flow ( $\Delta L$  in micrometers), determining the transit time ( $\Delta t$ , seconds) of the flow curves on the aortic segment, and then calculating the  $\Delta L/\Delta t$  ratio. In that respect, MRI is able to determine not only *local* but also *regional* arterial stiffness.

A major advantage of MRI is that arterial stiffness can be measured on the whole thoracic aorta, whereas  $cPWV$  measures arterial stiffness on an arterial pathway that may not include the ascending aorta. In addition, the analysis of arterial stiffness can be coupled with the analysis of aortic geometry (aortic diameter and arch length, widening, and curvature).<sup>47</sup> MRI, however, suffers from limited time resolution.

### Systemic arterial stiffness

Methods used for the noninvasive determination of systemic arterial stiffness are based on analogies with electrical models combining capacitance and resistance in series. Because of that, they rely on several theoretical approximations after direct assessment of peripheral, and often distal, physical properties.

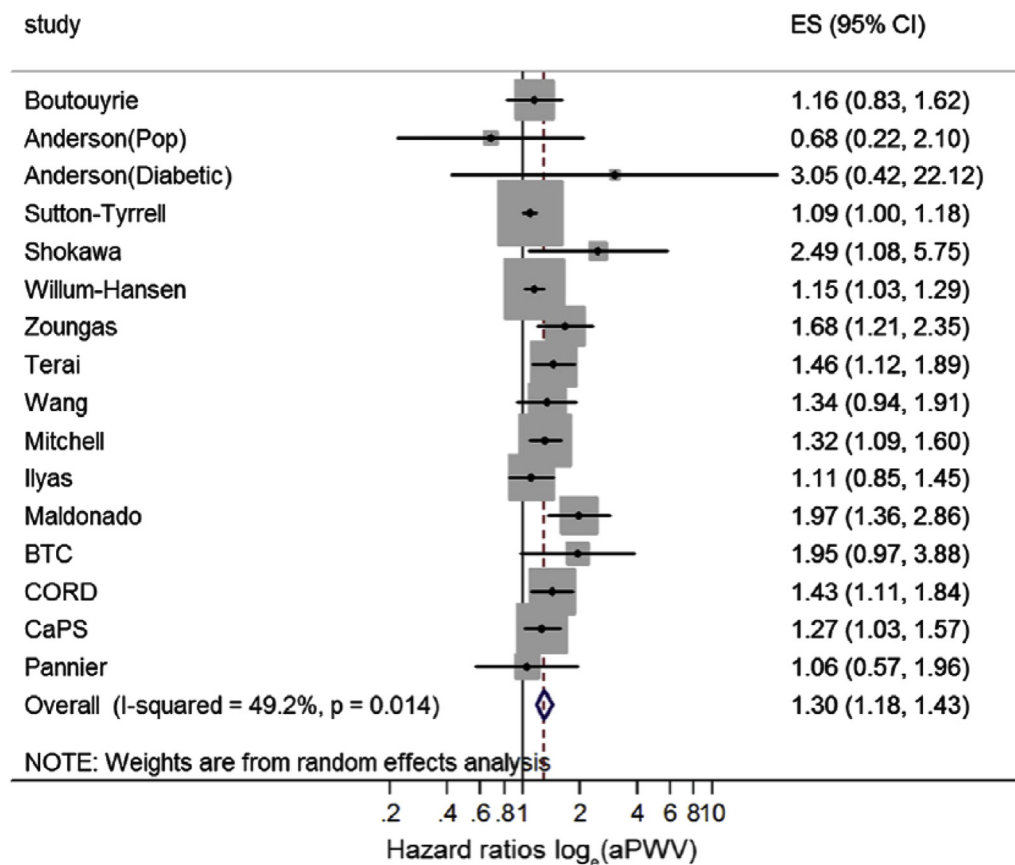
In the early 1980s, the concept of systemic arterial compliance was introduced. It represents the global accommodation of stroke volume by the arterial system (resulting in pulse pressure), assessed by dividing stroke volume by pulse pressure. It was determined by measuring and integrating aortic blood flow (using a velocimeter at the suprasternal notch) and pulse pressure (measured by applanation tonometry) at the CCA site. Systemic arterial compliance was obtained from the formula:  $SAC = Ad/[R(Ps - Pd)]$ , where  $Ad$  is the area under the BP diastolic decay curve from end systole to end-diastole,  $R$  is the total peripheral resistance,  $Ps$  is the end-systolic BP, and  $Pd$  is the end-diastolic BP (calibrated against brachial arterial pressure).<sup>30</sup>

In the 1990s, a methodology based on electrical circuitry using a modified Windkessel model was developed to determine a proximal capacitive compliance and a distal oscillatory compliance (HDI/PulseWave, Hypertension Diagnostics, Minneapolis, MN).<sup>31</sup> This technique was based on the arterial pulse recording at the level of the radial artery and identified the reflections in diastole as a decaying sinusoidal wave.

In the early 2000s, Mitchell et al.<sup>21</sup> estimated characteristic impedance ( $Z_c$ ) in the time domain as the ratio of changes in pressure and flow during early systole before return of the reflected pressure wave (Cardiovascular Engineering, Norwood, MA). This methodology was used in a large number of studies in the Framingham population.<sup>48</sup> Pressure and flow waves were simultaneously recorded by carotid tonometry and pulsed Doppler of the left ventricular outflow tract from an apical 5-chamber view. Pressure waveforms were decomposed into their forward ( $P_f$ ) and backward ( $P_b$ ) or reflected wave components in the time domain after identification of the inflection point between the peaks of the forward and reflected pressure waves. The ratio of their amplitudes ( $P_b/P_f$ ) was taken as an index of global reflection. Proximal aortic compliance per unit length ( $C_l$ ) was calculated using an equation derived by combining the Bramwell-Hill and waterhammer equations:  $C_l = 1/(Z_c \times c_o)$ , where central PWV ( $c_o$ ) was assumed to be equal to  $cPWV$ . Combining the determination of systemic arterial stiffness to that of regional stiffness allows for overcoming some limitations (see further on). For instance, it is possible to show parallel changes in characteristic impedance and  $cPWV$  and to calculate proximal aortic stiffness that is not measured by  $cPWV$ .

In the early 2010s, MRI was used to determine aortic flow in the ascending aorta and was combined with central pressure waveforms (measured with applanation tonometry) to determine impedance indices in frequency domains, such as  $Z_c$ .<sup>49</sup>

The determination of systemic arterial stiffness has limitations. Indeed, these models generally suffer from the theoretical imprecision intrinsic to physics assumptions of the hemodynamic model of the circulation. In addition, they can cumulate measurement errors in the determination of the various parameters used in complex mathematical equations and calculation of the final parameter, for instance  $Z_c$ . By contrast, the determination of regional arterial stiffness, performed through the direct measurement of  $cPWV$ , is subject to less imprecision and error. In this case, although there is imprecision in the measurement of the traveled distance, the calculation of the time delay between the feet of the pressure waves is performed precisely by computers, and a simple equation is used. Direct



**Figure 4.** Forest plot for aortic pulse wave velocity (aPWV) and combined cardiovascular events adjusting for various risk factors. Reproduced from Ben-Shlomo et al.<sup>50</sup> with permission from Elsevier.

measurements have demonstrated their robustness and repeatability. In addition, cfPWV is relatively insensitive to geometry, in contrast to Zc, and is a good measure of wall stiffness.

### Predictive Value of Arterial Stiffness for CV Events

The predictive value is of major importance at the present time, because several novel apparatus, which were developed for determining arterial stiffness, claimed superiority over pioneering methods through greater simplicity of use, better repeatability, or a more pertinent arterial pathway. However, the true additive value of measuring arterial aging with a given apparatus had to be translated into the predictive value of arterial stiffness as an intermediate end point, ie, the higher the arterial stiffness the higher the number of CV events. Table 1 shows which of the well-established or novel methods have been shown to have an independent predictive value for CV events up until now.

#### Aortic stiffness measured by cfPWV

The largest amount of evidence has been given for aortic stiffness, measured through cfPWV. Aortic stiffness has independent predictive value for all-cause and CV mortality, fatal and nonfatal coronary events, and fatal strokes, not only in patients with uncomplicated essential hypertension but

also in patients with type 2 diabetes or end-stage renal disease,<sup>10,11</sup> in elderly individuals, and in the general population. Currently, as many as 19 studies (some were included in an aggregate meta-analysis and an individual participant meta-analysis) consistently showed the independent predictive value of aortic stiffness for fatal and nonfatal CV events in various populations (Fig. 4).<sup>12,50</sup> Aortic stiffness measured through cfPWV is now considered an intermediate end point for CV events and is included in the 2013 European Society of Hypertension and of the European Society of Cardiology guidelines for the management of hypertension.<sup>13,51</sup> High aortic PWV may thus represent target organ damage, which needs to be detected during estimation of CV risk in hypertensive patients.

Although the relationship between aortic stiffness and events is continuous, a threshold of 12 m/s has been suggested as a conservative estimate of significant alterations of aortic function in middle-aged hypertensive patients.<sup>13</sup> However, this cutoff value of 12 m/s was based on the 100% direct “CCA-CFA” distance measurement. Adapted to the new standard distance ([CCA-CFA] × 0.8), to take into account the real travelled distance as seen earlier, it became 9.6 m/s. Ten metres per second was proposed as the new standard cutoff value for cfPWV, because this is an easy figure to use in daily practice.<sup>34</sup>

Reference values for PWV have been established in 1455 healthy individuals and a larger population of 11,092



**Table 2. Distribution of carotid-femoral pulse wave velocity (m/s) according to the age category in the normal value population (1455 individuals)**

Age category (y)	Mean ( $\pm 2$ SD)	Median (10-90 pc)
<30	6.2 (4.7-7.6)	6.1 (5.3-7.1)
30-39	6.5 (3.8-9.2)	6.4 (5.2-8.0)
40-49	7.2 (4.6-9.8)	6.9 (5.9-8.6)
50-59	8.3 (4.5-12.1)	8.1 (6.3-10.0)
60-69	10.3 (5.5-15.0)	9.7 (7.9-13.1)
>70	10.9 (5.5-16.3)	10.6 (8.0-14.6)

pc, percentile.

Reproduced from The Reference Values for Arterial Stiffness' Collaboration<sup>5</sup> with permission from the European Society of Cardiology.

individuals with CV risk factors (Table 2).<sup>5</sup> It is thus possible to be more specific for a given individual and to determine the extent of EVA according to the value of arterial stiffness in a given age and sex category (Fig. 2).

The independence of risk prediction provided by aortic stiffness has been established after adjustment for usual CV risk factors (eg, BP and cholesterol) but also for brachial pulse pressure. Even integration of risk factors in risk scales such as the Framingham risk score does not abolish the predictive value of aortic stiffness, further proving that aortic stiffness has an added value over a combination of CV risk factors.<sup>11</sup> The main reason, previously evoked, is that aortic stiffness integrates the cumulative damages induced by CV risk factors on the aortic wall over a long period, whereas individual risk factors such as BP, glycemia, and lipid levels fluctuate over time, and their snapshot values do not reflect the true values damaging the arterial wall. Another explanation is that arterial stiffness integrates risk factors difficult to measure (eg, oxidative stress, inflammation, and a family or genetic context), or even unknown risk factors.

### Other regional measures of arterial stiffness

The QKD interval has recently been showed to retain its predictive value for CV events after adjustment for left ventricular hypertrophy.<sup>52</sup> Aortic stiffness measured by MRI has demonstrated predictive value for CV mortality and hard CV disease events in the Multi-Ethnic Study of Atherosclerosis (MESA).<sup>53</sup> Arterial stiffness measured through brachial-ankle PWV has also demonstrated predictive value for CV events,<sup>23</sup> as has cardio-ankle PWV, although to a lower extent for the latter.

Data are less consistent regarding arterial stiffness measured at other arterial sites. Because of their particular pathophysiology, upper and lower limb territories may not reflect aortic, cerebral, and coronary artery damage. Indeed, by contrast to cfPWV or baPWV, neither carotid-radial PWV nor femoral-tibial PWV were able to predict CV outcome in patients with end-stage renal disease.<sup>32</sup>

Arterial stiffness measured with the Arteriograph system predicted CV events in patients with myocardial infarction.<sup>54</sup> Brachial-cuff estimated PWV, using the Mobil-O-Graph system, has been shown to complement tissue Doppler echocardiography in diagnosing heart failure with preserved ejection fraction.<sup>55</sup>

### Local and systemic measures of arterial stiffness

Carotid stiffness, measured with high-resolution echo tracking systems, predicted stroke, total CV events, and CV

and total mortality but not coronary heart disease events, independent of traditional CV risk factors in a meta-analysis aggregating 10 studies and more than 20,000 participants.<sup>56</sup>

Until now, methods used for the noninvasive determination of systemic arterial stiffness did not provide evidence in a longitudinal study that systemic arterial compliance or characteristic impedance ( $Z_c$ ) have independent predictive value for CV events.

### Clinical Utility and Potential for Routine Clinical Use

From the various characteristics detailed in Table 1, it can be concluded that regional stiffness is best determined in individuals and patients with a method that is easy to use in the clinical setting and has consistently demonstrated a significant predictive value for CV events in several epidemiologic studies. Thus, cfPWV measured with the pioneering devices Complior and SphygmoCor has generally been considered a gold standard.<sup>13</sup> Brachial-ankle PWV measured with the Omron VP-1000 device can also be considered for routine clinical use; although less pathophysiological and epidemiologic data are available for this device than for the previous devices, the simplicity of use is higher. When enough epidemiologic data is available for cardiac-ankle PWV measurement with the CAVI-Vasera, this method may represent a useful alternative to the brachial-ankle PWV measurement. As detailed earlier, additional epidemiologic data are required before recommending the Arteriograph, Mobil-O-Graph, and pOpmetre for routine clinical use. Other methods and devices are instead indicated for clinical research.

### Conclusions

This review described the major principles of measurement of arterial stiffness used as a noninvasive estimate of vascular aging, critically reviewed the advantages and limitations of the various methods, and highlighted those that showed the largest amount of epidemiologic evidence for predicting CV events.

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