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How to assess vascular aging?

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Abstract

The aging of the large artery wall is characterized by a reduction in the elastin content, as well as an increased content of collagen, and changes in cell-matrix interactions, leading to increased arterial stiffness. In recent years a better understanding of these processes has led to the concept of Early Vascular Ageing (EVA), which indicates a pronounced effect of ageing on the vascular tree and especially on arterial function. In brief, EVA subjects have a higher arterial stiffness than expected for their age and gender. In parallel with an important development of novel methods and apparatus for measuring arterial stiffness during the last decades, a large number of methodological and conceptual issues occurred, which sometimes lead to more confusion than standardisation and simplification. We aimed in this review at describing the major principles of the measurement of arterial stiffness and at critically reviewing the advantages and limitations of the different methods. Arterial stiffness is most often determined through pulse wave velocity between two arterial sites. Methods using a single-site cuff-based pulse wave velocity measurement are promising. The true additive value of measuring arterial aging with a given apparatus had to be translated into the predictive value of arterial stiffness as intermediate end-point, i.e. the higher the arterial stiffness the higher the number of CV events. Thus, another important aim of this review was to analyse the amount of epidemiological evidence obtained with a given method concerning the predictive value of arterial stiffness for CV events.

Keywords: hypertension, aging, arterial stiffness

Introduction

The ageing of the large artery wall is characterized by a reduction in the elastin content, as well as an increased content of collagen, and changes in cell-matrix interactions, leading to increased arterial stiffness (1). In recent years a better understanding of these processes has led to the concept of Early Vascular Ageing (EVA) (2-4) in subjects with higher arterial stiffness than expected for their age and gender (5). More generally, EVA indicates a pronounced effect of ageing on the vascular tree and especially on arterial function. EVA can be seen as an inadequate ability for repairing arterial damage in response to various mechanical, metabolic and chemical stresses (4). Vascular aging in general, and EVA more specifically, can be investigated

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non-invasively through the measurement of a number of parameters, including arterial stiffness (i.e. arteriosclerosis), central blood pressure, carotid intima media thickness (i.e. atherosclerosis), endothelial dysfunction, and abnormalities of small arteries (3,6,7). In this review, we will focus on arterial stiffness, as simple and robust parameter to estimate vascular ageing, and particularly EVA.

In parallel with an important development of novel methods and apparatus for measuring arterial stiffness during the last decades, a large number of methodological and conceptual issues occurred, which sometimes lead to more confusion than standardisation and simplification. Thus, the aim of this review is to describe the major principles of the measurement of arterial stiffness and critically review the advantages and limitations of the different methods. Another important aspect is the amount of epidemiological evidence obtained with a given method concerning the predictive value of arterial stiffness for CV events.

Arterial ageing, arterial stiffness and cardiovascular events

As underlined above, EVA subjects have higher arterial stiffness than expected for their age and gender. The wording "arterial stiffness" is a general term that refers to the loss of arterial compliance and/or changes in vessel wall properties. Compliance of large arteries, including the thoracic aorta that has the major role, represents their ability to dampen the pulsatility of ventricular ejection and to transform a pulsatile pressure (and flow) at the site of the ascending aorta into a continuous pressure (and flow) downstream at the site of arterioles, in order to lower the energy expenditure during organ perfusion.

The popularity of arterial stiffness measurement is largely due to the predictive value of arterial stiffness for CV events. The largest amount of evidence has been given for aortic stiffness, measured through carotid-femoral pulse wave velocity (cfPWV). This has been initially reported in the late 1990s - early 2000s (8,9). Currently, as many as 19 studies consistently showed the predictive value of aortic stiffness for fatal and non-fatal CV events in various populations having different levels of CV risk: general population, hypertensive patients, elderly subjects, type 2 diabetic patients and patients with end-stage renal disease (10). As we will see below, other methods for arterial stiffness measurement have shown predictive value for CV events. An important aspect is that the predictive value of arterial stiffness for CV events was observed independently of classical CV risk factors, including age, BP, gender, cholesterol, diabetes and smoking. Thus, with a simple measurement of arterial stiffness, it is possible to determine the CV risk beyond traditional risk factors.

Clinical measurements of arterial stiffness

Arterial stiffness can be evaluated at the systemic, regional and local levels. In contrast to systemic arterial stiffness, which can only be estimated from models of the circulation, regional and local arterial stiffness can be measured directly, and non-invasively, at various sites along the arterial tree. A major advantage of the regional and local evaluations of arterial stiffness is that they are based on direct measurements of parameters strongly linked to wall stiffness. Reviews have been published on methodological aspects (11-14). Table 1 gives the main features of the various methods currently available.

1. Regional measurements of arterial stiffness

The aorta is a major vessel of interest when determining regional arterial stiffness for at least two reasons: the thoracic and abdominal aorta makes the largest contribution to the arterial buffering function (12-14), and aortic PWV is an independent predictor of outcome in a variety of populations (11,13-14). However, all arterial sites have potential interest. Indeed, the forearm circulation is where blood pressure is commonly measured, and the lower limb arteries are specifically altered by atherosclerosis. Measurement of local carotid stiffness may also provide important prognostic information, since the carotid artery is a frequent site of atheroma formation.

Two-sites pulse wave velocity measurements

The measurement of pulse wave velocity (PWV) is generally accepted as the most simple, non-invasive, robust, and reproducible method with which to determine arterial stiffness. The measurement of PWV between the common carotid artery and the common

Table 1. Device and methods used for determining regional, local, and systemic arterial stiffness (adapted from ref 13, 14, and 26).

Year of first publication	Device	Method	Measurement site	ref.	Predictive value for CV events (year 1st publication)	Ease of clinical utility
Regional Stiffness						
1984*	Complior®	Mechanotransducer	Aorta, cf PWV[1]	16	Yes (1999)	++
1990*	Sphygmocor®	Tonometer	Aorta, cf PWV[1]	17	Yes (2011)	++
1991	WallTrack®	Echotracking	Aorta, cf PWV[1]	37	No	+
1994	QKD	ECG +	Aorta, cf PWV[1]	54	Yes (2005)	++
1997*	Cardiovasc. Eng. Inc ®	Tonometer	Aorta, cf PWV[1]	50	Yes (2010)	+
2002	Artlab®	Echotracking	Aorta, cf PWV[1]	39	No	++
2002	Ultrasound systems	Doppler probes	Aorta, cf PWV[1]	18	Yes (2002)	+
2002	Omron VP-1000®	Pressure cuffs	Aorta, cf PWV[1]	24	Yes (2005)	+++
2007	CAVI-Vasera®	ECG + Pressure cuffs	Aorta, cf PWV[1]	25	Yes (2014)	+++
2008	Arteriograph®	Arm pressure cuff	Aorta, cf PWV[1]	32	Yes (2013)	++
2009	MRI, ArtFun®	MRI	Aorta, cf PWV[1]	45	Yes (2014)	+
2010	Mobil-O-Graph®	Arm pressure cuff	Aorta, cf PWV[2]	34	No	++
2013	pOpmetre®	Photoplethysmography	Aorta, cf PWV[1]	27	No	+++
2017	Withings bathroom scale®	Ballistocardiography + impedance plethysm.	Aorta, cf PWV[1]	36	No	+++
Local stiffness						
1991	WallTrack®	echo-tracking	CCA[3], CFA, BA	39	No	+
1992	NIUS®	echo-tracking	RA		No	+/-
2002	Artlab®, Mylab®	echo-tracking	CCA[3], CFA, BA	39	Yes (2014)	++
	Various ultrasound syst.	echography	CCA[3], CFA, BA			
2009	MRI, ArtFun®	cine-MRI	AA, DA	45	No	+
Systemic stiffness						
1989	Area method	Diastolic decay		49	No	+/-
1995	HDI PW CR-2000®	Modif. Windkessel		48	No	+
1997*	Cardiovasc. Eng. Inc ®	Tonometer/Doppler/Echo		50	Yes (2010)	+/-

* apparatus used in pioneering epidemiological studies showing the predictive value of aortic stiffness for CV events; PWV = Pulse Wave Velocity; cf=carotid-femoral, ba=brachial-ankle, ca=cardiac-ankle, aa=aortic arch, ft=finger-toe, af=aortic-foot; 1measured; 2 estimated, not measured; 3 all superficial arteries, including particularly those mentioned; Ao.= aorta; CCA = common carotid artery; CFA = common femoral artery; BA = brachial artery; RA = radial artery; AA=ascending aorta; DA=descending aorta.

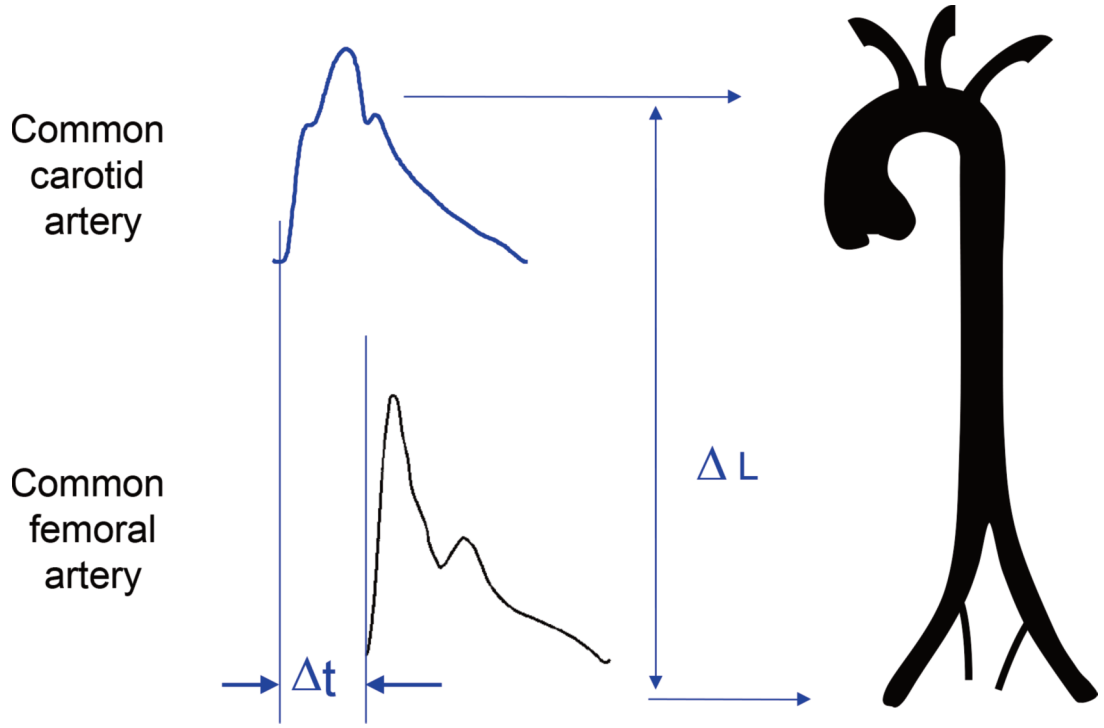

Figure 1: Measurement of carotid-femoral pulse wave velocity with the foot to foot method. (From ref 11 with permission).

femoral artery (carotid-femoral PWV) is a direct measurement, and it corresponds to the widely accepted propagative model of the arterial system (12). Measured along the aortic and aorto-iliac pathway, it is the most clinically relevant, since the aorta and its first branches are what the left ventricle 'sees', and are thus responsible for most of the pathophysiological effects of arterial stiffness. Carotid-femoral PWV has been used in most epidemiological studies demonstrating the predictive value of aortic stiffness for CV events. By contrast, PWV measured outside the aortic track, at the upper (brachial PWV) or lower limb (femoro-tibial PWV), had no predictive value in patients with end-stage renal disease (ESRD) (15).

PWV is usually measured using the foot-to-foot velocity method from various waveforms. These are usually obtained, transcutaneously at the right common carotid artery and the right femoral artery (i.e. "carotid-femoral" PWV - cfPWV), and the time delay (ȁt, or transit time) measured between the feet of the two waveforms (11,14-16) (Figure 1). The "foot" of the wave is defined at the end of diastole, when the steep rise of the wavefront begins. The transit time is the time of travel of the "foot" of the wave over a known distance.

A variety of different waveforms can be used including pressure (16,17), distension and Doppler (18). The distance (D) covered by the waves is usually assimilated to the surface distance between the two recording sites, i.e. the common carotid artery (CCA) and the common femoral artery (CFA). The direct distance DD is (CFA to CCA). PWV is calculated as PWV = D (meters) /Δt (seconds).

However, since the descending thoracic aorta is reached by the pressure wave at the time another pressure wave, originating from the same cardiac contraction, arrives at the carotid site, it has been recommended to calculate the distance between the supra-sternal notch (SSN) and the common femoral artery (CFA), and to subtract from this distance the small length between carotid transducer and SSN. The so-called "subtracted distance" is (SSN to CFA) – (SSN to CCA) (19). A recent consensus paper (20) stated that investigator should use either the subtracted distance, or, best, measure the direct distance and apply a 0.8 coefficient, to take into account the different pathways of the pressure wave described above. Indeed, the direct carotid-femoral distance largely overestimates the real traveled distance measured by magnetic resonance imaging (MRI) by more than 25%, whereas the subtracted

distances (using the distances to common femoral artery and common carotid artery from suprasternal and sternal notch) substantially underestimate the real traveled distance by 10 to 30% (20). Besides, the later formulas are approximations and introduce additional error. Of all currently used distances, the 80% of the direct carotid-femoral distance (common carotid artery to common femoral artery x 0.8) appeared the most accurate, only slightly overestimating the real traveled distance by 0.4% (20).

Some limitations should be underlined. The femoral pressure waveform may be difficult to record accurately in patients with metabolic syndrome, obesity, diabetes and peripheral artery disease (20,21). 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 (20,21).

Methods based on pressure sensors

Pressure waveforms can be recorded simultaneously to provide automated measurement of PWV using a number of devices (Table 1). The Complior® system (Colson, Les Lilas, France) employs dedicated mechanotransducers directly applied on the skin (16). The transit time is determined by means of a correlation algorithm between each simultaneous recorded wave. The operator is able to visualize the shape of the recorded arterial waves and to validate them. Three main 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 sequentially from different sites, and transit time calculated using registration with a simultaneously recorded ECG. In the SphygmoCor® system (ArtCor, Sydney, Australia) a single high-fidelity applanation tonometer (Millar®) to obtain a proximal (i.e. carotid artery) and distal pulse (i.e. radial or femoral), recorded sequentially a short time apart, and calculates PWV from the transit time between the two arterial sites, determined in relation to the R wave of the ECG (17). The time between the ECG and the proximal pulse is subtracted from the time between ECG and distal pulse to obtain the pulse transit time. The initial part of the pressure waveform is used as a reference point. It is also possible to check offline the variability of measurement over a range of pulses, according to each algorithm (22). Since the measurements are made a short time apart, the change in the isovolumic period of the left ventricle or heart rate variability have little or no effect on measured pulse transit times. Methods using mechanotransducers or high-fidelity applanation tonometers are well accepted for carotid-femoral PWV measurement.

In order to increase easiness and acceptability, automatic cuff-based methods have been developed. Brachial-ankle PWV - baPWV (Omron, Japan) is calculated from travelled distance and transit time, as described above. The travelled distance is automatically calculated based on patient's height. Transit time is the time delay between the proximal and distal "foot waveforms". Bilateral brachial and post-tibial arterial pressure waveforms are simultaneously detected by extremities cuffs connected to a plethysmographic sensor and an oscillometric pressure sensor wrapped on both arms and ankles (23). 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 ageing of the aorta. However, the main assumption of developers of the baPWV method was that the transit times of the pressure waves in the upper and lower limbs were comparable. Thus, the transit time that is measured reflects the aortic pulse transit time. However, although aortic PWV was the primary independent correlate of baPWV, leg PWV also played a role (24).

Using a similar cuff-based methodology for detecting the pressure waveforms and an ECG recording, a cardio-ankle PWV can be calculated. A feature of the cardio-ankle PWV (Fukuda Denshi, Japan) is that it shortcuts the subclavian and brachial artery pathways, compared to baPWV. Cardio-ankle PWV reflects the stiffness of the aorta, femoral artery and tibial artery (25). A cardio-ankle vascular index (CAVI), derived from the Bramwell and Hill equation, has been calculated by Shirai et al. (25), as a BP-independent stiffness parameter. However, the true BP-independency of CAVI is still debated (26).

Other methods

The transit time, required for the determination of PWV, can be determined from distension waveforms, successively obtained at a short time interval at two ar-

terial sites (common carotid and femoral artery for instance) with high resolution echotracking systems, using the R wave of the ECG for calculating the time delay.

The transit time can also be measured between two flow pulses simultaneously recorded by continuous Doppler probes (18), or again sequentially with ECG gating. Measurements are usually made at the root of the left subclavian artery (i.e. suprasternal notch on the skin) and near the bifurcation of the abdominal aorta (i.e. umbilicus level on the skin). The transit time is automatically calculated following automatic recognition of the foot of the pulse.

The pOpmetre® (Axelife SAS, Saint Nicolas de Redon, France) is based on similar assumptions as brachial-ankle devices. To further increase feasibility and acceptability, it extends the concept to the finger-toe arterial pathway (27). It takes advantage of two 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, since the timing in the upper and lower limbs are comparable (28-30).

Single-site pulse wave velocity measurements

An increasing number of methods calculate PWV over a given arterial pathway from the analysis of the brachial pressure wave, determined from a brachial cuff. PWV is thus referred as "single-site" or "brachial cuff" derived PWV, and apparatus as "brachial cuff" based devices. As detailed below, PWV is estimated from various parameters, themselves either measured or estimated, but PWV is not directly measured between two arterial sites.

The QKD method

Gosse et al. (31) proposed, two decades ago, to take advantage of an ambulatory measurement of BP and continuous monitoring of ECG over 24 h (Diasys®, Novacor, France), to calculate the QKD interval. QKD is the time between the onset of the QRS on the ECG and the detection of the last Korotkoff sound by the microphone placed upon the brachial artery. It has two components: the pre-ejection time, which is influenced by heart rate (HR) and the pulse transmission time, which is inversely related to PWV, thus arterial stiffness. BP and QKD are measured repeatedly and a stiffness parameter is derived from the linear regression of all the measurements of QKD, HR and SBP over 24 h. The QKD interval is calculated for a 100 mmHg BP, thus it gives an isobaric value of arterial stiffness, and for a 60 beats/min HR in order to reduce the influence of the pre-ejection time.

The Arteriograph® method

The Arteriograph® system (TensioMed Kft., Budapest, Hungary) estimates PWV from a single-site brachial-cuff oscillometric determination of the suprasystolic waveform at the brachial artery site. Because the cuff is pressurized at least 35 mmHg 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 (32), and allow precise determination of time delays. Indeed, the Arteriograph® measures the time elapsed between the first wave ejected from the left ventricle to the aortic root, and its reflection from the bifurcation as the second systolic wave, with subtraction of the brachial artery transit time (32). 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 aortic root-bifurcation length, omitting only a few centimetres of proximal ascending aorta (33).

The Mobil-O-Graph® method

The Mobil-O-Graph® (IEM, Germany) system uses oscillometric recording of brachial artery pressure waveform and reconstructs the central pulse wave by applying a transfer function (34). Central pulse wave is then decomposed into forward and backward waves, and PWV is estimated. More specifically, to estimate PWV, the ARCSolver method uses an aortic blood flow model based on higher order Windkessel theory, and determines several parameters from pulse wave analysis and wave separation analysis combined in a

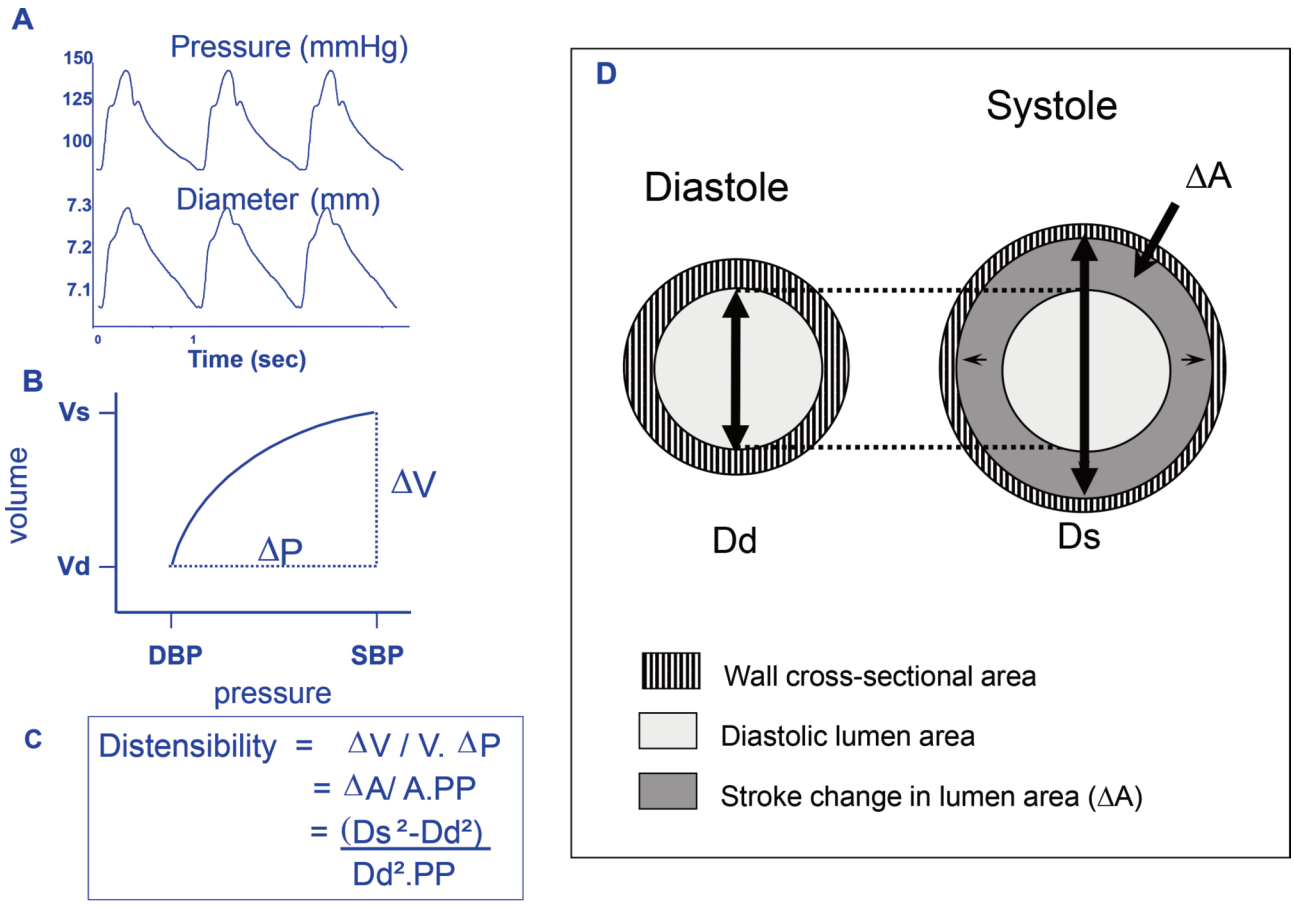

Figure 2. Local arterial distensibility. A: Simultaneous recording of stroke changes in BP and diameter. B: Pressure-diameter curve. C: Calculation of distensibility. D: Schematic representation of the stroke change (DA) in lumen cross-sectional area (LCSA). (From ref 11 with permission).

proprietary mathematical model, whereby the major determinants are age, central pressure, and aortic characteristic impedance, but not timings of brachial suprasystolic wave reflections (35). Aortic characteristic impedance, which is calculated from an estimated pressure waveform and an estimated flow waveform, marginally modifies the PWV value which is mainly estimated from invasive PWV. There is no direct measurement of PWV.

The WITHINGS bathroom scale® method

A new technology company (WITHINGS) specialized in connected devices developed an innovative device (bathroom scale) allowing measurement of pulse transit time between the heart and the foot, through a combination of ballistocardiography and impedance plethysmography. The device has been validated against cfPWV (36).

2. Local determination of arterial stiffness

Local arterial stiffness of superficial arteries can be directly determined using ultrasound devices. Carotid stiffness may be of particular interest, since in that artery atherosclerosis is frequent. All types of classical, bidimensional vascular ultrasound systems can be used to determine diameter at diastole and stroke changes in diameter, but most of them are limited in the precision of measurements because they generally use a video-image analysis. An increasing number of researchers also measure local arterial stiffness of deep arteries like the aorta using cine magnetic resonance imaging (MRI). However, most of pathophysiological and pharmacological studies have used echo-tracking techniques.

High resolution echotracking methods

A major advantage of echotracking techniques is that local arterial stiffness is directly determined from

the change in pressure driving the change in volume, i.e. without using any model of the circulation (Figure 2). However, because it requires some degree of technical expertise, and takes longer than measuring PWV, local measurement of arterial stiffness is only really indicated for mechanistic analyses in pathophysiology, pharmacology and therapeutics, rather than for epidemiological studies (11). Nevertheless, ultrasound is currently the only means to determine, non-invasively, the elastic properties of the arterial wall material (Young's elastic modulus) (37,38), and the relationship between intima-media thickness and elastic properties, or the influence of inward or outward remodelling on arterial distensibility (37-39).

Echotracking devices were developed to measure diameter in end-diastole and stroke change in diameter with a very high precision. These apparatus use the radio-frequency (RF) signal to obtain a precision 6 to 10 times higher than with video-image systems, which are limited by the spatial resolution of pixel analysis. Indeed, the precision in determining stroke change in diameter is as low as 1 micron for echotracking systems, whereas it is around 150 microns (i.e. the size of the pixel) with video-image analysers (37). For absolute distance measurement, the standard deviation extends from 9 to 25 microns for echotracking systems, and from 54 to 60 microns with video-image analysers. Recent multi-array echotracking systems having 128 RF lines (ArtLab® and MyLab®, Esaote Pie Medical, Italy and The Netherlands) are able to determine both IMT and pulsatile changes in diameter along a 4 cm long arterial segment (40).

Echotracking systems have other major advantages over video-image systems: from the same ultrasound data, the intima-media thickness (IMT) can be extracted (41), which allows the Young's elastic modulus to be determined (37); it is possible to determine the pressure-diameter curve of the artery, thus to determine arterial stiffness for any given BP; from the time delay between two adjacent distension waveforms, it is possible to calculate local PWV; and pathophysiological and therapeutic changes in arterial stiffness can be related to geometrical changes (lumen area and IMT).

Most of these parameters require measurement of blood pressure. This should be local pressure, which is usually obtained by applanation tonometry of the vessel in question (11) and calibration of the waveform to brachial mean and diastolic pressures obtained by integration of the brachial or radial waveform (42), or automatic calculation using transfer function processing. All the superficial arteries are suitable for the geometrical investigation, and particularly the common carotid, common femoral and brachial arteries.

A new ultrasound imaging technique, named Ultrafast® echography (Supersonic Imagine, France) has been recently developed for local arterial stiffness assessment without resorting to pressure measurement. The innovative approach consists in generating shear waves in the arterial wall via 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 directly linked to the tissue stiffness (shear and Young's moduli) and over 10 values can be evaluated during a cardiac cycle (43). Moreover, the very high temporal resolution enables the tracking of the pulse wave along a localized arterial segment. Local PWV can be directly measured at the beginning and end of systole, therefore allowing characterization of the arterial diastolic-systolic stiffening (44).

Magnetic Resonance Imaging

MRI of the aortic system has considerably improved the precision of the anatomical localisation of arterial stiffness measurements and added simultaneous investigation of arterial geometry and cardiac function. The determination of arterial stiffness follows the classical laws of physics, as seen above concerning echotracking. Generally, a 3.0 Tesla scanner is used to visualize the aorta on sagittal oblique views. The contours of the ascending, proximal, and distal (diaphragmatic) descending aorta are automatically traced for all phases of the cardiac cycle on both the modulus images of the phase contrast acquisition for flow analysis and on the cine images for aortic area analysis using dedicated software (ArtFun®, Paris, France) (45). The maximal (Amax) and minimal (Amin) aortic lumen areas enter into the calculation of average aortic diameters of the ascending and the proximal and distal descending aorta. Relative changes in area [aortic strain, defined as AS=(Amax-Amin)/Amin] are used to calculate aortic distensibility in each subject: distensibility = AS/cPP, where cPP is the central pulse pressure obtained by tonometry. Aortic arch PWV can be calculated by using the transit time of the flow curves and the distance between the ascending and proximal de-

scending aortic locations of the phase contrast acquisition. 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 cfPWV measures arterial stiffness on an arterial pathway which may not comprise 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) (46,47). MRI however suffers from limited time resolution.

3. Systemic arterial stiffness

Methods used for the non-invasive determination of systemic arterial stiffness are based on analogies with electrical models combining capacitance and resistance in series. As such they rely on numerous theoretical approximations following direct measurement of one peripheral, and often distal, parameter.

Early 1980's, systemic arterial compliance was determined using the "area method" which required measurement of aortic blood flow (velocimeter at the suprasternal notch) and associated driving pressure by applanation tonometry over the proximal right common carotid artery. Systemic arterial compliance was then calculated from the formula: SAC = Ad/[R(Ps-Pd)], where Ad is the area under the blood pressure diastolic decay curve from end-systole to end-diastole, R is the total peripheral resistance, Ps is the end-systolic blood pressure and Pd is the end-diastolic blood pressure (calibrated against brachial arterial pressure) (48).

In the 1990's, a methodology based on an electrical circuit using a modified Windkessel model (49) was developed to determine a proximal capacitive compliance and a distal oscillatory compliance (HDI/PulseWave, Hypertension Diagnostics Inc, Eagan, MN, USA). 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 2000's, Mitchell et al. (50) estimated characteristic impedance (Zc) in the time domain as the ratio of change in pressure and change in flow during early systole before return of the reflected pressure wave (Cardiovascular Engineering Inc, USA). This methodology was used in a large number of studies in the Framingham population (51). 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 (Pf) and backward (Pb) 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 (Pb/Pf) was taken as an index of global reflection. Proximal aortic compliance per unit length (Cl) was calculated using an equation derived by combining the Bramwell-Hill and water-hammer equations: Cl=1/(Zc x co), where central pulse wave velocity (co) was assumed to be equal to cfPWV. Combining the determination of systemic arterial stiffness to that of regional stiffness allows overcoming some limitations (see below) thus strengthening the findings. It is thus possible to show a parallel reduction in characteristic impedance and carotid-femoral PWV, and other measures of pulsatile load, including reduced first modulus of impedance, increased proximal aortic compliance, and delayed timing of wave reflection.

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 Zc. By contrast, the determination of regional arterial stiffness, performed through the direct measurement of carotid-femoral PWV, is subjected to less imprecision and error. In that 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 measurements have demonstrated their robustness and repeatability.

Predictive value of arterial stiffness for CV events

This issue is of major importance at the present time, since several novel apparatus, which were developed for determining arterial stiffness, claimed superiority over pioneering methods either through higher simplicity of use, better repeatability, or more pertinent arterial pathway. However the true additive value of measuring arterial aging with a given apparatus had to be trans-

Table 2. Distribution of carotid-femoral pulse wave velocity (cfPWV, m/s) according to the age category in the normal values population (1455 subjects). From ref 5 with permission.

Age category (years)	Mean (±2SD)	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)

lated into the predictive value of arterial stiffness as intermediate end-point, i.e. the higher the arterial stiffness the higher the number of CV events. Table 2 shows which of the well-established or novel methods have published an independent predictive value of CV events until now.

Aortic stiffness measured by cfPWV

The largest amount of evidence has been given for aortic stiffness, measured through carotid-femoral PWV. Aortic stiffness has independent predictive value for all-cause and CV mortality, fatal and non fatal coronary events, and fatal strokes not only in patients with uncomplicated essential hypertension (8,9), but also in patients with type 2 diabetes or end-stage renal disease, in elderly subjects and in the general population. Currently, as many as 19 studies - some of them were included in an aggregate meta-analysis (11) and an individual participant meta-analsyis (52) - consistently showed the independent predictive value of aortic stiffness for fatal and non fatal CV events in various populations. Aortic stiffness measured through cfPWV is now considered as an intermediate end-point for CV events (11) and included in the 2013 ESH-ESC Guidelines for the management of hypertension (53). High aortic PWV may thus represent target organ damage, which needs to be detected during estimation of CV risk in hypertensives.

Although the relationship between aortic stiffness and events is continuous, a threshold of 12 m/sec has been suggested (11) as a conservative estimate of significant alterations of aortic function in middle age hypertensives. However, this cut-off value of 12 m/s was based on the 100% direct "common carotid artery - common femoral artery" distance measurement. Adapted to the new standard distance ([common carotid artery - common femoral artery] x 0.8), in order to take into account the real traveled distance as seen above, it became 9.6 m/s. Ten m/s was proposed as new standard cut-off value for cfPWV, because this is an easy figure to use in daily practice (20).

Reference values for pulse wave velocity (5) have been established in 1,455 healthy subjects and a larger population of 11,092 subjects with CV risk factors (Table 2 and Figure 3). It is thus possible to be more specific for a given subject, and to determine the extent of Early Vascular Ageing (EVA) according to the value of arterial stiffness in a given age and gender category.

The independent predictive value of aortic stiffness has been demonstrated after adjustment to classical cardiovascular risk factors, including brachial pulse pressure. This indicates that aortic stiffness has a better predictive value than each of classical risk factors. In addition, aortic stiffness retains its predictive value for coronary heart disease events after adjustment to the Framingham risk score, suggesting that aortic stiffness has an added value to a combination of CV risk factors (9,10,52). One reason may be that aortic stiffness integrates the damage of CV risk factors on the aortic wall over a long period of time, whereas BP, glycemia, and lipids can fluctuate over time and their values, recorded at the time of risk assessment, may not reflect the true values damaging the arterial wall. Another explanation may be that arterial stiffness shows the patients in which arterial risk factors were translated into real risk.

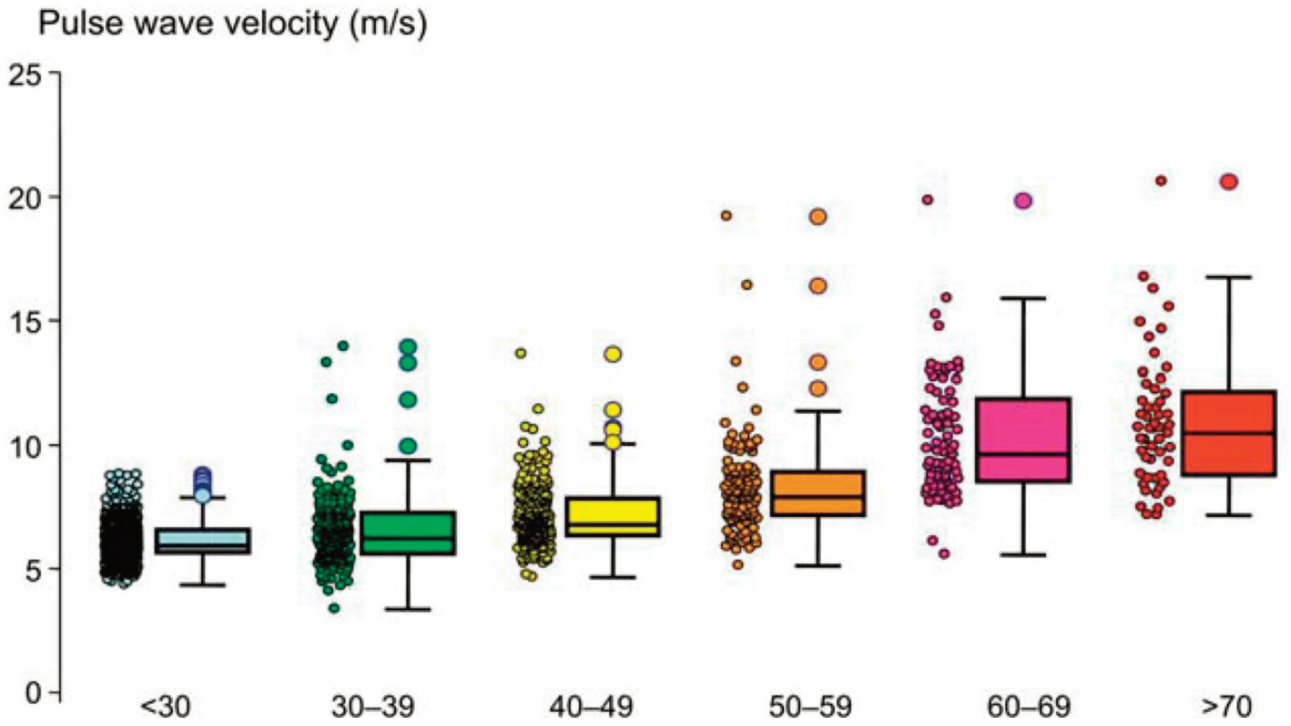

Figure 3. Normal values for pulse wave velocity: average according to age (1455 subjects). Boxes contain 50% of the data and bars contain the remainder; horizontal lines indicate medians and the circle indicates outliers (From ref 5 with permission).

Other regional measures of arterial stiffness

QKD has recently been showed to retain its predictive value for CV events after adjustment to left ventricular hypertrophy (54). Aortic stiffness measured by MRI has demonstrated predictive value for CV mortality and hard cardiovascular disease events in the Multi-Ethnic Study of Atherosclerosis - MESA (55). Arterial stiffness measured through brachial-ankle PWV has also demonstrated predictive value for CV events (24), as well as cardio-ankle PWV, although to a lower extent for the later.

Data are less consistent concerning arterial stiffness measured at other arterial sites. Upper and lower limb territories, due to their particular pathophysiology, may not reflect aortic, cerebral and coronary artery damage. Indeed, by contrast to cfPWV or baPWV, neither carotid-radial PWV nor femoro-tibial PWV were able to predict cardiovascular outcome in ESRD patients (15). Although preliminary meeting reports indicated predictive value of arterial stiffness, measured by the Arteriograph system, for CV events, no study has yet been published. 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 (56).

Local and systemic measures of arterial stiffness

Carotid stiffness, measured with high resolution echotracking systems, predicted stroke, total CV events, CV and total mortality but not coronary heart disease events, independently of traditional CV risk factors in a meta-analysis aggregating 10 studies and more than 20 000 subjects (57).

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

Conclusion

This review described the major principles of measurement of arterial stiffness, used as a non-invasive estimate of vascular ageing, critically reviewed the advantages and limitations of the various methods, and highlighted those which showed the largest amount of

epidemiological evidence for predicting cardiovascular events.

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