Nephrol Dial Transplant (2014) 29: 232–239
doi: 10.1093/ndt/gft309
Advance Access publication 30 September 2013

ndt
Nephrology Dialysis Transplantation

NDT Perspectives

Assessment of arterial stiffness for clinical and epidemiological studies: methodological considerations for validation and entry into the European Renal and Cardiovascular Medicine registry

Pierre Boutouyrie[1], Danilo Fliser[2], David Goldsmith[3], Adrian Covic[4], Andrzej Wiecek[5], Alberto Ortiz[6], Alberto Martinez-Castelao[7], Bengt Lindholm[8], Ziad A. Massy[9], Gultekin Suleymanlar[10], Rosa Sicari[11], Luna Gargani[11], Gianfranco Parati[12], Francesca Mallamaci[13], Carmine Zoccali[13] and Gerard M. London[14]

[1]Hopital Européen Georges Pompidou, Assistance Publique, Université Paris Descartes, Hôpitaux de Paris, Paris, France, [2]Department of Internal Medicine IV, Saarland University Medical Centre, Homburg/Saar, Germany, [3]Renal Unit, Guy's and St Thomas' NHS Foundation Hospital, King's Health Partners, London, UK, [4]Clinic of Nephrology, C. I. Parhon University Hospital, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania, [5]Internal Medicine and Nephrology, and Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia, PL-40-027 Katowice, Poland, [6]IIS-Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Fundación Renal Iñigo Alvarez de Toledo, REDINREN, Madrid, Spain, [7]Hospital Universitario de Bellvitge, IDIBELL, REDINREN, L'Hospitalet de Llobregat, Barcelona, Spain, [8]Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden, [9]INSERM, Unit 1088, and Jules Verne University of Picardie, Amiens, Division of Nephrology, Ambroise Paré Hospital, Paris-Boulogne Billancourt, France, [10]Nephrology Division, Department of Medicine, Akdeniz University Medical School, Antalya, Turkey, [11]CNR Institute of Clinical Physiology Via G. Moruzzi, Pisa, Italy, [12]Department of Clinical Medicine and Prevention, Dept of Cardiology, University of Milano-Bicocca, S.Luca Hospital, IRCCS Istituto Auxologico Italiano, 20149 Milano, Italy, [13]Nephrology, Dialysis and Transplantation Unit, CNR-IBIM Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension, Reggio Calabria, Italy and [14]Hopital Manhes, Fleury-Merogis, INSERM U970, Paris, France

Correspondence and offprint requests to: Gerard M. London; E-mail: glondon@club-internet.fr

ABSTRACT

Epidemiological studies have highlighted the role of arterial stiffness as a risk factor for development of cardiovascular (CV) diseases. Moreover, aortic stiffness has been shown to be a significant predictive factor of all-cause and CV mortality in different populations including patients with end-stage renal disease. Pulse-wave velocity (PWV) is the most widely used technique to assess arterial stiffness. Although PWV can be measured on any artery or between any arterial sites, only carotid-to-femoral PWV, representing stiffness of the aorta and iliofemoral axes, has been shown to have predictive value for morbidity and mortality. The several available commercial devices differ according to the type of signal (pressure, distension, flow) or by recording both sites simultaneously or using ECG synchronization. It is also possible to directly measure arterial diameter changes during the cardiac cycle and link them to local pulse–pressure changes, which provides the pressure–diameter relationship and stress–strain relationship if arterial wall thickness is also measured. These techniques are based on high-precision vascular echo tracking or magnetic resonance imaging and applanation tonometry. This paper summarizes the basic principles of arterial haemodynamics and various methodologies to assess stiffness and the latest consensus recommendations for clinical applications.

Keywords: aortic pressure, arterial stiffness, elastic modulus, pulse-wave velocity

© The Author 2013. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved.

Downloaded from https://academic.oup.com/ndt/article/29/2/232/1911298 by Akdeniz University user on 20 September 2021

INTRODUCTION

Cardiovascular (CV) disease is one of the most frequent causes of morbidity and mortality in industrialized countries, and their major cause in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1, 2]. The main CV complications are heart failure, myocardial infarction, stroke and peripheral artery disease. The CV-disease continuum of these morbid events progresses through target-organ damage including left ventricular hypertrophy (LVH), atherosclerotic plaque formation, arterial stiffening, endothelial dysfunction and inflammation [3]. These mechanisms present early as subclinical organ damage, can be identified before overt clinical manifestations and can be used as surrogate markers significantly associated with the future risk of clinical events, as they are reliable substitutes for a clinical event endpoint [3]. Several markers of CV organ damage have been associated with the risk of all-cause or CV mortality in patients with ESRD; the most relevant being LVH, carotid artery intima media thickness, endothelial dysfunction, arterial stiffness, arterial calcifications and ankle–brachial systolic blood pressure (BP) ratio [4–8]. To individualize risk assessment and risk-reduction strategies, organ damage should be sought. Ideally, such methods need to be safe, noninvasive, rapid, inexpensive, reliable and reproducible with good sensitivity and specificity (Table 1) [3]. Although very appealing, identification of early vascular damage through these surrogate markers has not been validated versus more conservative approaches.

Epidemiological and clinical results demonstrated that damage of large conduit arteries is a major contributing factor associated with the high incidence of CV diseases [4–7]. Many studies emphasized the impact of arterial stiffness on the development of these CV complications, and as a strong and independent predictor of CV and all-cause mortality [9–20] (Table 2). Premature vascular ageing, characterized by aortic and large central artery stiffening associated with arterial outward remodelling, is observed with progression of CKD and in ESRD [7, 21–24].

The roles of arterial stiffness in physiology and pathophysiology were recently detailed in several reviews [23, 25, 26] and herein the basic principles are only briefly summarized. This review focuses on the methodological issues of standardization of arterial stiffness parameters, as a basis for establishing high-quality systematic data collection in the framework of the European Renal and Cardiovascular Medicine (EURECA-m) registry. To guarantee high-quality measurements, the EURECA-m registry created a data validation centre at Hôpital Manhès, France, where all measurements are to be sent by registry-participating investigators.

Table 1. Principal techniques for clinical use and evaluation of CV end-organ damage in CKD/ESRD

- Heart structure and function
  Echocardiography: detection of LV hypertrophy; left atrial dilation; valves dysfunction; systolic and diastolic dysfunction (Doppler). ECG should be part of the assessment (arrhythmias, blocks, ischaemia), calcium score (CT scan)
- Arterial structure and function
  Ultrasound scanning of carotid arteries: detection of vascular hypertrophy (intima media thickness >900 μm), or the presence of atherosclerotic plaques and stenosis (Doppler).
  Doppler unit and blood pressure manometer for ankle-brachial systolic pressure index (A/Bix): A/Bix < 0.9 reflects occlusive peripheral artery disease and advanced atherosclerosis; A/Bix >1.4 is associated with incompressible calcified arteries.
  Arterial stiffness: aortic stiffness [carotid–femoral pulse-wave velocity, the gold standard >12 m/s (in 2007), >10 m/s (in 2013)]; regional and local stiffness via changes in vessel diameter as a function of local pressure changes (ultrasound scanning coupled with tonometry).
  Central pulse-wave analysis and determination of central BP pressure and wave reflections: High fidelity Millar strain gauge transducer and transfer function (Sphygmocor®).
- Several other methods difficult to use for clinical and routine investigation, or not methodologically standardized are available: MRI, endothelial dysfunction, coronary calcifications.

DEFINITIONS OF STIFFNESS PARAMETERS

The arterial system has two main functions: to assure adequate blood flow to tissues and organs, i.e. 'conduit function'; and a 'cushioning or dampening function'. The latter has two facets: transforming cyclic blood flow in the aorta into a continuous capillary flow; and dampening arterial pressure oscillations, thereby limiting their transmission to the microcirculation [23, 27, 28]. The efficiency of these functions depends on the stiffness and geometry of the aorta and central arteries, and

Table 2. Principal longitudinal studies reporting the predictive value of aortic (Aor) and common carotid artery stiffness for cardiovascular or all-cause mortality

First author (year)	Sites	References	Events	Type of patients
Blacher (1999)	AorPWV	[8]	CV mortality	ESRD
Laurent (2001)	AorPWV	[11]	CV mortality	Hypertensive
Shoji (2001)	AorPWV	[12]	CV mortality	ESRD
Meaume (2001)	AorPWV	[13]	CV mortality	Elderly >70 years
Cruickshank (2002)	AorPWV	[14]	All-cause mortality	Diabetic
Laurent (2003)	AorPWV	[15]	Fatal stroke	Hypertensive
Sutton-Tyrrell (2005)	AorPWV	[16]	CV mortality	Elderly
Willum-Hansen 2006)	AorPWV	[18]	CV mortality	General population
Mattace-Raso (2006)	AorPWV	[17]	CV mortality	Elderly
Inoue (2009)	AorPWV	[19]	CV mortality	General population
Verbeke	AorPWV	[20]	CV mortality and CV events	Renal transplant recipients
Blacher (1998)	CCa stiffness	[7]	All-cause mortality	ESRD
Karas (2012)	CCa stiffness	[21]	All-cause mortality	CKD

AorPWV, aortic pulse-wave velocity; CV, cardiovascular; ESRD, end-stage renal disease; CCa, common carotid artery; CKD, chronic kidney disease.

Downloaded from https://academic.oup.com/ndt/article/36/2/232/4841298 by Akdeniz University user on 20 September 2021

rigidity of successive arterial segments. Both functions are linked, since efficient flow distribution to organs is dependent on energy storage during diastole as artery distends, i.e. their elastic properties, which, in return, buffer pressure and flow.

Arteries are distensible, i.e. they expand during systole as a consequence of increased stroke volume, and recoil during diastolic runoff. These geometric–volume transformations are caused by arterial BP changes with stiffness expressing the vasculature (total or segmental) volume as a function of a given transmural pressure (pressure–volume relationships). The ability of arteries to accommodate the stroke volume can be described in terms of compliance, distensibility or its reciprocal, arterial stiffness. Compliance (C) is defined as a volume change (ΔV, strain) for a given pressure change (ΔP, stress): $C = \Delta V/\Delta P$. To compare structures with different initial dimensions, compliance can be expressed relative to the initial volume (V) as distensibility (D): $D = \Delta V/V \times \Delta P$. The reciprocal value of distensibility is stiffness ($V^{*}\Delta P/\Delta V$). Unlike compliance or distensibility, which provide information about the 'elasticity' of the artery as a hollow structure, the elastic incremental (Young's) modulus (E_{inc}) provides information on the intrinsic elastic properties of the biomaterials that compose the arterial wall independent of vessel geometry, because it is normalized to vessel-wall thickness [23, 27, 28].

The pressure–volume relationship is nonlinear: at low distending pressure, the tension is borne by distensible elastin fibres, whereas at a high distending pressure, the tension is progressively transferred and borne by much stiffer collagen fibres. Thus, the arterial wall gets stiffer and more 'resistant' to distension with increased arterial BP. Obviously, the function reflecting this phenomenon is to avoid excessive distension of vessels due to increased BP. The most typical clinical consequence of arterial stiffening is a steep pressure–volume relationship, with increased systolic BP (SBP) during ventricular ejection and decreased diastolic BP (DBP) during diastolic runoff, resulting in high pulse pressure (PP) [25] and excessive variability [23, 29].

During ventricular contraction, part of the stroke volume is momentarily stored in the aorta and central arteries, stretching their walls because of rising local BP. The arterial pressure wave generated in the aorta (forward or incident wave) is propagated to arteries throughout the body and is partly reflected back towards the aorta (reflected pressure wave). Arterial stiffness determines the propagation velocity of the pressure wave [pulse-wave velocity, $PWV = (1/D)^{0.5}$]. PWV propagates bidirectionally, from the proximal aorta towards peripheral vessels and back. When aortic stiffness is low, the reflected pressure wave is delayed enough to impact on central arteries during end-systole and diastole, thereby increasing the aortic pressure during early diastole but not systole. This situation is physiologically advantageous, because the higher DBP boosts coronary perfusion, without increasing the LV pressure load. Increased arterial stiffening disrupts the desirable timing. With faster PWV, the reflected waves return earlier, impacting on the central arteries during systole rather than diastole, amplifying aortic and ventricular systolic pressures and reducing aortic diastolic pressure. By favouring early wave reflections, arterial rigidity increases peak- and end-systolic pressures in the ascending aorta, thereby raising myocardial pressure load (LVH) and oxygen consumption, and decreasing DBP and subendocardial blood flow [25, 27, 30, 31].

The arterial system is heterogeneous. First, the most elastic arteries are close to the heart, and stiffness increases with increasing distance from the heart. As a consequence, PWV increases progressively from the ascending aorta to the peripheral muscular conduit arteries, generating an arterial stiffness gradient of great physiological importance because it acts as a selective filter that regulates pulsatile pressure transmission to the microcirculation. The stiffness gradient, together with aortic geometry changes (tapering), local arterial branching and lumen narrowing, creates an impedance mismatch causing partial pressure-wave reflections generated at the transition between these segments, limiting pulsatile energy transmission downstream to the microcirculation that is not designed to bear it [23, 28, 32–34].

Thus, arterial stiffness enables the arterial tree to cope with the systolic ejection volume due to the distension of compliant large arteries during systole and to relay cardiac contraction during diastolic runoff, when the large arteries return to their initial dimensions and help maintain blood flow. The aorta is the major capacitive element of the arterial system, and a major determinant of the amplitude of the incident/forward pressure wave. Aortic stiffening also influences the reflected pressure-wave return and the overlap of incident and reflected pressure waves. Thus, aortic stiffening, through its direct effects on the forward pressure-wave amplitude and reflected wave timing, has multiple effects on LV structure and function. Aortic stiffness is a major determinant of increased SBP and PP, thereby increasing LV afterload and contributing to LVH, increased oxygen consumption and impaired ventricular relaxation. The lower DBP, which is another consequence of arterial stiffening and modified wave reflection timing, is responsible for decreased coronary perfusion pressure. Increased aortic stiffness also diminishes the stiffness gradient causing pressure overload to smaller arterial segments and microcirculation with concomitant perturbations (capillary rarefaction, inward remodeling of small arteries) [23, 28–34].

MEASUREMENT OF ARTERIAL STIFFNESS

Because the methodological issues concerning the measurement of various stiffness indices and their clinical applications were recently published and updated in detail [23, 25, 26, 35–38], herein we only briefly mention the most relevant for arterial stiffness measurements in clinical practice and research.

Several direct or indirect methods have been proposed to quantify arterial stiffness. Among the former, the most widely used is the propagative model based on PWV measurement, introduced in engineering in the late 19th century and to physiology in 1922 by Bramwell and Hill [39]. The 'elastic' properties of the arterial wall determine the velocity of pulse-wave propagation, $PWV = (V^{*}\Delta P/\Delta V^{*}\rho)^{0.5,}$ derived from Moens–Korteweg equation $PWV = (E^{*}h/D^{*}\rho)^{0.5}$, where ρ is the density, E is the elastic modulus, h is the wall thickness and D is the diameter [27]. PWV determination implies measuring

Downloaded from https://academic.oup.com/ndt/article/29/2/232/1911298 by Akdeniz University user on 20 September 2021

pulse-transit time. The principal elements used to assess PWV are pressure or flow waves, and distension waves, which are essentially equivalent. The most used is the pressure wave obtained by the application of a pressure transducer on the artery of interest. A crucial point is the reference part of the curve, for which time is calculated. The general consensus is to use the systolic upstroke as the reference point: the foot of the wave. The latter's identification relies on different algorithms, with the intersecting tangent method being the most popular and the most reliable [35, 40, 41]. As an alternative to pressure wave, any other physiological wave can be used, with special attention given to the time and amplitude response, which conditions the accuracy of the pulse-transit time. As typical transit time is 30–80 ms, 2 ms (500 Hz) precision represents 2–8% of transit time. Ranked by order of their precision, pressure transducers, Doppler flow and distension by echo tracking can be considered relatively equivalent.

To express transit times as PWV, it is necessary to measure the distance between recording sites. The preferred sites are the common carotid artery and the femoral artery in the groin, and the direct carotid-to-femoral distance was used in almost all epidemiological studies. Usually, the pathway is measured transcutaneously, using a tape measure or caliper. Because the pulse wave travels in opposite directions once it bifurcates at the brachiocephalic trunk, direct measurement between sites leads to a systematic PWV overestimation. Many corrections have been proposed, such as subtracting carotid site to sternal notch distance from the overall distance, which provides values closer to invasive measurements but increases errors due to duplicate distance measurements (Figure 1). Using Doppler probes positioned at the suprasternal notch and close to the umbilicus to measure aortic PWV targets a more linear vessel segment with no curvatures or bifurcations and avoids the above-mentioned difficulties, but is less precise concerning flow signal acquisition site.

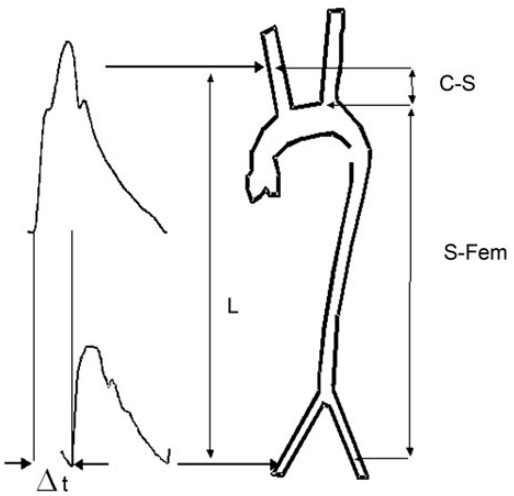

FIGURE 1: Measurements of pressure-wave travelling distance. *L*: direct distance; Δ*T*: transit time; C-S: carotid-sternal notch distance; S-Fem: sternal notch- femoral artery distance. PWV = *L*/Δ*T* (noncorrected distance), PWV = (S-Fem – C-S)/Δ*T* (subtracted distance), PWV = 0.8**L*/Δ*T* (standardized distance).

To overcome these ambiguities, the scientific community has accepted a standard definition of distance, combining the better precision of carotid–femoral site distance measurement, and the better accuracy compared with invasive techniques. The formula is PWV = 0.8**L*/Δ*T* where *L* is direct distance and Δ*T* is transit time (Figure 1). Of all currently used distances, 80% of the direct carotid-femoral distance (*L**0.8) is apparently the most accurate, as it generates fewer errors by measuring distance only once [38, 42].

MRI appears to be the gold standard for measurement of PWV and has been used for absolute PWV calibration [42]. Indeed, it can detect both distension and/or flow with impressive image reconstruction, and allows precise measurement of true path length. Nevertheless, MRI is limited with 20-ms imprecision concerning transit time. Although partial compensation is obtained by repeated measurements on many cycles, it is an important limitation when the examined arterial path is short or PWV very high.

Relative values of different PWV-assessment methods. Carotid–femoral PWV is the most widely used index of arterial stiffness, which has demonstrated predictive value for CV outcomes, independent of and better than classical risk factors in several longitudinal, follow-up studies, conducted in different geographical locations and including various populations (Table 2) [43, 44]. PWV can also be measured on carotid–radial or femoral–tibial arterial segments. However, the predictive values of those more peripheral PWV measurements are unknown, nor is there any epidemiological evidence for derivative technique, e.g. brachial–ankle PWV or single-point PWV measurements.

Prerequisites for PWV measurements. The guidelines for measuring PWV are the same as for any other physiological measurement to obtain the best reproducibility. The subject must rest in supine position for at least 5–10 min, in a room maintained at a standardized temperature (ideally temperature-controlled), and to better interpret PWV measurements, BP must be accurately measured within minutes of recording PWV. Baseline PWV should be the mean of at least two consecutive measurements necessary to appreciate spontaneous variations. Excellent ECG and carotid and femoral pulse records are mandatory. Repeated measurements over the time must be obtained under the same conditions, e.g. at the same time of day, before a meal and without any stimulant (coffee or tobacco) [26, 45, 46], and adjusted for similar BP. Under good conditions, time-repeated PWV measurement is good (8–10% of the mean value) [35, 46, 47]. These constraining requirements are mandatory for haemodynamics studies but are rarely met in clinical settings. To what extent deviations from these optimal conditions affect the validity of measurement has not yet been studied.

Several devices are commercially available and extensively used worldwide (Table 3). The first marketed was the Complior System® (Artech, Les Lilas, France), which simultaneously records arterial pulse waves at carotid and femoral sites, through mechanotransducer probes [46]. The

Downloaded from https://academic.oup.com/ndt/article/36/2/232/4841298 by Akdeniz University user on 20 September 2021

Table 3. Methods and devices to estimate arterial stiffness

Techniques	Manufacturer	Signal	Probe	Remarks
Direct PWV measurement				
Complior	Alam Medical, Fr	Pressure	Standard	Simultaneous
Sphygmocor	AtCor Medical, Au	Pressure	High fidelity	ECG-triggered
PulsePen	Diatechne, It	Pressure	High fidelity	ECG-triggered
PulseTrace	Micromedical, UK	Flow	Doppler	ECG-triggered
Vicorder	Skidmore Medical, UK	Pressure	Cuff	Simultaneous
Ankle–Brachial PWV				
Omron VP-1000	Omron Medical, Jp	Plethysmography	Cuff	Simultaneous
Q-KD	Novacor, Fr	Korotkov sounds	Cuff	ECG-triggered
Echo-tracking techniques				
Artlab System	Esaote, It	128 lines		Online
E-Traking	Aloka, Jp	4 lines		Online
HDI-lab	Philips, NL	NA		Offline
Indirect techniques				
CVProfilor	HDI, US	Pressure	Cuff	
Arteriograph	Tensiomed, Hu	Pressure	Cuff	Suprasystolic inflation
Mobilograph	IEM healthcare, De	Pressure	Cuff	

SphygmoCor® system (ArtCor, Sydney, Australia) [47] has become popular because it also measures central (aortic or carotid) BP, and has been used in large clinical trials and population surveys [48]. It uses a large-band piezoelectric probe and successively records arterial pulse (carotid then femoral), with both signals being synchronized to the same ECG R wave, which imposes verifying that the heart rate is similar at the moment of each recording to avoid any heart rate-induced disturbance. The most recent device is the Pulsepen® (Diatecne, Milano, Italy) [49], which uses successive recordings of arterial pulse waves synchronized to ECG. It also allows carotid artery pulse-wave analysis (proxy for aortic BP), directly measured without any transfer function.

Related techniques warrant being mentioned, notably brachial-ankle PWV (baPWV), based on oscillations in cuffs placed on the brachial artery and calf, measuring the time delay between both signals. This method is popular in Asia because it avoids exposing the groin. The pulse-wave pathway is still being discussed, and the validity of baPWV is still contested [50]. The Qkd, based on ambulatory BP measurements (ABPM) (Diasys®, Novacor, Rueil Malmaison, France) [51], and the speed of Korotkoff sound propagation compared with the ECG R-wave were validated in one large population for its predictive value, but it is very sensitive to heart rate and the precise relationships between QKD interval (Q: QRS complex on ECG; K: Korotkoff sound and D: diastole) and aortic PWV are still being debated.

Single-point PWV based on oscillometric measures (Arteriograph) [52], and many other astute recent techniques (Vicorder) making use of different ingeniously developed concepts are based on assumptions that require further investigation before being recommended (Table 3).

PWV directly measures regional arterial stiffness for the territory located between the two measurement sites. In this respect, it differs from indirect methods relying on circulation models, e.g. the 'Windkessel' model which is based on exponential DBP decay with its exponential proportional to stiffness. This model can be made more complex by using two exponential functions: one for large arteries (C1) and the other for small arteries (C2) [53, 54].

Another indirect technique, uses aortic characteristic impedance, is the minimal impedance for higher frequencies of pressure-and-flow harmonics which is proportional to PWV. It requires flow-and-pressure measurements at the aortic root. Characteristic impedance is rarely used alone, as it is hampered by the difficulty of obtaining reliable noninvasive data for aortic flow and pressure [55].

Also available are rigidity estimates derived from BP measurement, e.g. ABPM-derived arterial stiffness index (1/slope of the SBP–DBP relationship) [56] or crude brachial PP. Although these values reflect arterial stiffness, they are not surrogates for direct artery-stiffness measurements and aortic (carotid–femoral) PWV, which is considered the gold standard [35, 42].

Measurements of local arterial stiffness. While PWV is a measure of arterial stiffness over given segment, it is also possible to directly measure arterial dimension changes during the cardiac cycle and link them to local PP oscillations: local stiffness. This approach is straightforward and provides the pressure–diameter relationship, the stress–strain relationship if wall thickness is also measured and, thus, provides stiffness indexes at any given BP level. These techniques are based on high-precision vascular echo tracking and applanation tonometry [21, 57] (Figure 2). It is mandatory that BP be measured locally at the echo-tracking site of diameter changes because it may differ from brachial BP because of wave reflection [57, 58]. Measurement of stiffness using the pressure–diameter relationship is not as validated equally well as PWV in terms of predicting CV events. Multiple reasons may explain the lack of validation: first it was introduced later; second, it is more technically challenging, and thus, cohorts are smaller; and third, because stiffness is the ratio of BP-to-dimension changes, measurement errors of BP and arterial diameter changes are amplified. Nevertheless, measurement of local stiffness using echo-tracking devices remains a useful tool for

Downloaded from https://academic.oup.com/ndt/article/29/2/232/1911298 by Akdeniz University user on 20 September 2021

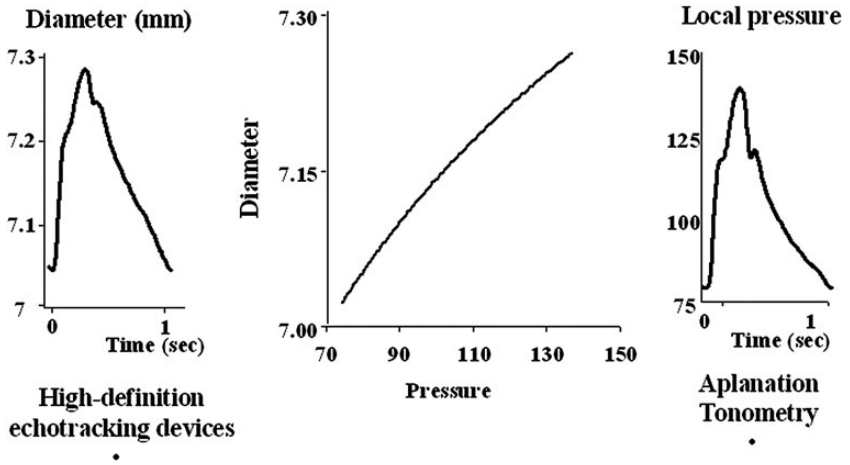

FIGURE 2: Direct measure of local stiffness by diameter–pressure relationship.

clinical research, especially because these values take into account other very important parameters, e.g. artery diameter and thickness [36].

Measurements of central BP. Analysis of the central BP waveform and amplitude (in the carotid artery or proximal aorta) is a further method frequently used to assess arterial stiffness indirectly. Aortic rigidity together with stroke volume and ejection velocity is determinants of arterial pressure-wave amplitude, influencing SBP, DBP and aortic PP. While pressure-wave analysis represents an important advancement in the assessment of large artery properties, its interpretation as a measure of stiffness is an oversimplification. The principal 'stiffness' parameter assessed concerns the effect of reflected pressure waves on pressure waveform shape and amplitude, estimated in absolute terms, i.e. augmented PP in mm Hg or in relative terms, i.e. Augmentation index (Aix in % of PP) [57, 58]. Considered to be a stiffness index, the relationships of Aix with arterial rigidity are more complex, depending on the overlap between forward and reflected pressure waves. That overlap is influenced by the relationships between transit time of pressure waves from the aorta to reflecting sites and back (depending on PWV and traveling distance) and duration of LV ejection (heart rate) [23, 43, 58].

CONCLUSION

Arterial stiffness measurements are obtained with numerous methods and devices but they differ largely according to their physical bases, simplicity of use and characteristics of the measured parameter. A gold standard method would require (i) direct parameter measurement without any intermediate model; (ii) providing a precise image of the patient's physiological condition and of independent predictive value for events; (iii) being easily performed in routine and being accepted by numerous research groups worldwide and based on a broad range of patients in different populations.

As previously noted by the European Expert Consensus on Arterial Stiffness [35, 36], the 'gold standard' method remains carotid–femoral PWV, mainly because it has been validated based on clinical and epidemiological studies on different populations, whose reference values were been published [35, 36, 42]. Much work remains to be done to demonstrate that patient care including PWV measurement provides better protection than standard care, as claimed once [59].

Because PWV measurement still requires technical expertise, many manufacturers have proposed alternative techniques based on assumptions. The techniques are not interchangeable and agreement limits among them are wide. One very important point is the possibility to replace gold standard methods by novel techniques. The usual way to compare techniques is to provide correlations and Bland and Altman plots. New alternative approaches are usually based on additional assumptions (leading to oversimplifications), that are usually related to gold standard PWV with R^2 values of 0.4–0.7, which reflect very imperfect agreement. Most are currently pending epidemiological validation and lack solid results, whereas gold standard PWV has constantly been independently associated with outcomes [35, 36, 60]. Weak correlations with gold standard values are not sufficient to assert equivalence. Even epidemiological evidence is not qualifying, because the parameter's significance is often debatable, interpretation is complex and it is never comparable to the gold standard for predictive value. Independent assessment of the abilities of devices to measure arterial stiffness accurately will be unavoidable in the future.

ACKNOWLEDGEMENTS

We thank Ms Janet Jacobson for her editorial help. This work was supported by G.E.P.I.R (Groupe d'Étude de la Physiopathologie de l'Insuffisance Rénale).

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part.

Downloaded from https://academic.oup.com/ndt/article/23/2/482/1841298 by Akdeniz University user on 20 September 2021

REFERENCES

1. Cheung AK, Sarnak MJ, Yan G *et al.* Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int 2000; 58: 353–362
2. Go AS, Chertow GM, Fan D *et al.* Chronic kidney disease and the risk of death, cardiovascular events, and hospitalisation. N Engl J Med 2004; 351: 296–1305
3. Guidelines for the management of arterial hypertension. The Task–Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and European Society of Cardiology (ESC). Eur Heart J 2007; 28: 1465–1536
4. London GM, Guérin AP, Marchais SJ *et al.* Cardiac and arterial interactions in end-stage renal disease. Kidney Int 1996; 50: 600–608
5. Nitta K, Akiba T, Uchida K *et al.* Left ventricular hypertrophy is associated with arterial stiffness and vascular calcification in hemodialysis patients. Hypertens Res 2004; 27: 47–52
6. Zoungas S, Cameron JD, Kerr PG *et al.* Association of intima–media carotid thickness and indices of arterial stiffness with cardiovascular disease outcome in CKD. Am J Kidney Dis 2007; 50: 622–630
7. Blacher J, Pannier B, Guérin AP *et al.* Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. Hypertension 1998; 32: 570–574
8. Blacher J, Guérin AP, Pannier B *et al.* Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999; 99: 2434–2439
9. Blacher J, Guérin AP, Pannier B *et al.* Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension 2001; 38: 938–994
10. Pannier B, Guérin AP, Marchais SJ *et al.* Postischemic vasodilation, endothelial activation, and cardiovascular remodeling in end-stage renal disease. Kidney Int 2007; 57: 1091–1099
11. Laurent S, Boutouyrie P, Asmar R *et al.* Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001; 37: 1236–1241
12. Shoji T, Emoto M, Shinohara K *et al.* Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. J Am Soc Nephrol 2001; 12: 2117–2124
13. Meaume S, Benetos A, Henry OF *et al.* Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arterioscler Thromb Vasc Biol 2001; 21: 2046–2050
14. Cruickshank K, Riste L, Anderson SG *et al.* Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an index of vascular function. Circulation 2002; 106: 2085–2090
15. Laurent S, Katsahian S, Fassot C *et al.* Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 2003; 34: 1203–1206
16. Sutton-Tyrrell K, Najjar SS, Boudreau RM *et al.* Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation 2005; 111: 3384–3390
17. Mattace-Raso FU, van der Cammen TJ, Hofman A *et al.* Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006; 113: 657–663
18. Willum-Hansen T, Staessen JA, Torp-Pedersen C *et al.* Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation 2006; 113: 664–670
19. Inoue N, Maeda R, Kawakami H *et al.* Aortic pulse wave velocity predicts cardiovascular mortality in middle-aged and elderly Japanese men. Circ J 2009; 73: 549–553
20. Verbeke F, Maréchal C, Van Laecke S *et al.* Aortic stiffness and central wave reflection predicts outcome in renal transplant recipients. Hypertension 2011; 58: 833–838
21. Briet M, Collin C, Karras A *et al.* Arterial remodeling associates with CKD progression. J Am Soc Nephrol 2011; 22: 967–974
22. Karras A, Haymann JP, Bozec E *et al.* Large artery stiffening and remodelling are independently associated with all-cause mortality and cardiovascular events in chronic kidney disease. Hypertension 2012; 60: 1451–1457
23. Briet M, Boutouyrie P, Laurent S *et al.* Arterial stiffness and pulse pressure in CKD and ESRD. Kidney Int 2012; 82: 388–400
24. London GM, Pannier B, Marchais SJ. Vascular calcifications, arterial aging and arterial remodeling in ESRD. Blood Purif 2013; 35: 16–21
25. London GM, Pannier B. Arterial functions: how to interpret the complex physiology. Nephrol Dial Transplant 2010; 25: 3815–3823
26. Tomlinson LA. Methods for assessing arterial stiffness: technical considerations. Curr Opin Nephrol Hypertens 2012; 21: 655–660
27. O'Rourke MF. Principles and definitions of arterial stiffness, wave reflections and pulse pressure amplification. In: Safar ME, O'Rourke MF (eds). Handbook of Hypertension. Vol. 23. Arterial Stiffness in Hypertension. Philadelphia: Elsevier, 2006, pp. 3–19 (Series eds. Birkenhäger WH, Reid JL)
28. Mitchell GF, Vita JA, Larson MG *et al.* Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. Circulation 2005; 112: 3722–3728
29. Schillaci G, Bilo G, Pucci G *et al.* Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from two large cohorts. Hypertension 2012; 60: 369–377
30. Buckberg GD, Towers B, Paglia DE *et al.* Subendocardial ischemia after cardiopulmonary bypass. J Thor Cardiovasc Surgery 1972; 64: 669–687
31. Watanabe H, Ohtsuka S, Kakihana M *et al.* Coronary circulation in dogs with an experimental decrease in aortic compliance. J Am Coll Cardiol 1993; 21: 1497–1506
32. Avolio AO, Chen SG, Wang RP *et al.* Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. Circulation 1983; 68: 50–58
33. Mitchell GF. Effects of central artery aging on the structure and function of the peripheral vasculature: implication for end-organ damage. J Appl Physiol 2008; 105: 1652–1660
34. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension 2005; 46: 200–204
35. Laurent S, Cockcroft J, Van Bortel L *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27: 2588–2605
36. Van Bortel LM, Segers P. Direct measurement of local arterial stiffness and pulse pressure. In: Safar ME, O'Rourke MF (eds). Handbook of Hypertension. Vol. 23. Arterial Stiffness in Hypertension. Philadelphia: Elsevier, 2006, pp. 35–52 (Series eds. Birkenhäger WH, Reid JL)
37. Laurent S, Boutouyrie P. Determination of systemic and regional arterial stiffness. In: Safar ME, O'Rourke MF (eds). Handbook of Hypertension. Vol. 23. Arterial Stiffness in Hypertension. Philadelphia: Elsevier, 2006, pp. 53–62 (Series eds. Birkenhäger WH, Reid JL)
38. Van Bortel LM, Laurent S, Boutouyrie P *et al.* Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens 2012; 30: 445–448
39. Bramwell JV, Hill AV. Velocity of transmission of the pulse wave and elasticity of arteries. Lancet 1922; 1: 891–892
40. Millasseau SC, Steward AD, Patel SJ *et al.* Evaluation of carotid-femoral pulse wave velocity: influence of timing algorithm and heart rate. Hypertension 2005; 45: 222–226
41. The Reference Values for Arterial Stiffness' Collaboration. Reference values for carotid-femoral pulse wave velocity in the reference values for Arterial Stiffness' Collaboration Database. Eur Heart J 2010; 31: 2338–2350
42. Huybrechts SA, Devos DG, Vermeersch SJ *et al.* Carotid to femoral pulse wave velocity: a comparison of real travelled aortic path length determined by MRI and superficial measurements. J Hypertens 2011; 29: 1577–1582
43. Pannier B, Guérin AP, Marchais SJ *et al.* Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients. Hypertension 2005; 45: 592–596
44. Kimoto E, Shoji T, Shinohara K *et al.* Regional arterial stiffness in patients with type 2 diabetes and chronic kidney disease. J Am Soc Nephrol 2006; 17: 2245–2252
45. Van Bortel LM, Duprez D, Starmans-Kool MJ *et al.* Clinical applications of arterial stiffness, Task Force III: Recommendations for user procedures. Am J Hypertens 2002; 15: 445–452
46. Asmar R, Benetos A, Topouchian J *et al.* Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 1995; 26: 485–490

Downloaded from https://academic.oup.com/ndt/article/29/2/232/1911298 by Akdeniz University user on 20 September 2021

47. Wilkinson IB, Fuchs SA, Jansen IM *et al.* Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998; 16: 2079–2084
48. Williams B, Lacy PS, Thorn CM *et al.* Different impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of Conduit Artery Function Evaluation (CAFÉ). Circulation 2006; 113: 213–225
49. Salvi P, Lio G, Labat C *et al.* Validation of a new non-invasive portable tonometer for determining arterial pressure wave and pulse wave velocity: the PulsePen device. J Hypertens 2004; 22: 2285–2293
50. Kubo T, Miyata M, Minagoe S *et al.* A simple oscillometric technique for determining new indices of arterial distensibility. Hypertens Res 2002; 25: 351–358
51. Gosse P, Guillo P, Ascher G *et al.* Assessment of arterial distensibility by monitoring the timing of Korotkoff sounds. Am J Hypertens 1994; 7: 28–233
52. Baulmann J, Schillings U, Rickert S *et al.* A new oscillometric method for assessment of arterial stiffness: coparison with tonometric and piezo-electronic methods. J Hypertens 2008; 26: 523–528
53. London GM, Cohn JN. Prognostic application of arterial stiffness task force. Am J Hypertens 2002; 15: 754–758
54. Duprez DA, Jacobs DR, Lutsey PR *et al.* Association of small artery elasticity with incident cardiovascular disease in older adults. Multiethnic study of atherosclerosis. Am J Epidemiol 2011; 174: 528–536
55. Westerhof BE, van den Wijngaard JP, Murgo JP *et al.* Location of a reflection site is elusive: consequences for the calculation of aortic pulse wave velocity. Hypertension 2008; 52: 478–483
56. Adiyaman A, Dechering DG, Boggia J *et al.* Determinants of the ambulatory arterial stiffness index in 7604 subjects from six populations. Hypertension 2008; 52: 1038–1044
57. Karamanoglu M, O'Rourke MF, Avolio AP *et al.* An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. Eur Heart J 1993; 14: 160–167
58. O'Rourke MF, Kelly RP. Wave reflections in systemic circulation and its implications in ventricular function. J Hypertens 1993; 11: 327–337
59. Guérin A, Blacher J, Pannier B *et al.* Impact of aortic stiffness attenuation on survival of patients in end-stage renal disease. Circulation 2001; 103: 987–992
60. Vlachopoulos C, Aznaouridis K, Stefanidis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systemic review and meta-analysis. J Am Col Cardiol 2010; 55: 1318–1327

Received for publication: 2.4.2013; Accepted in revised form: 6.6.2013

Downloaded from https://academic.oup.com/ndt/article/28/2/232/1841298 by Akdeniz University user on 20 September 2021