

Large artery damage in hypertension

Stéphane Laurent, Hélène Beaussier, Cédric Collin, Pierre Boutouyrie

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

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Corresponding author:

Prof. Stéphane Laurent
Department of Pharmacology
and INSERM U 970
Hôpital Européen Georges
Pompidou
Assistance Publique
– Hôpitaux de Paris
20, rue Leblanc
75015 Paris, France
Phone: 33 1 56 09 39 91
Fax: 33 1 56 09 39 92
E-mail:
stephane.laurent@egp.aphp.fr

Abstract

Arterial stiffness and wave reflections, which are now well accepted as the most important determinants of increasing systolic and pulse pressures in ageing societies, reflect large artery damage in hypertension. These parameters are increasingly used in the clinical assessment of patients with hypertension and various cardiovascular (CV) risk factors. This review addresses recent advances in our understanding of the role played by arterial stiffness and wave reflection in the pathophysiology and treatment of hypertension. We also report a large number of longitudinal epidemiological studies demonstrating the independent predictive value of arterial stiffness, carotid pulse pressure and augmentation index, for cardiovascular events, and show that these parameters are now well accepted as intermediate end-points for CV events. We also discuss the effects of pharmacological agents on aortic stiffness and wave reflections. A remaining major issue is to determine whether a reduction in PWV or wave reflection in hypertensive patients is associated with a concomitant reduction in CV events, independently of the normalization of classical CV risk factors.

Key words: large artery, arterial stiffness, wave reflection, hypertension, cardiovascular risk.

In hypertension, large arteries stiffen and pulse pressure increases, due to wave reflections. A major reason for measuring arterial stiffness and wave reflections “routinely” in clinical practice in hypertensive patients comes from the recent demonstration that arterial stiffness and wave reflections have a predictive value for CV events [1, 2]. A recent expert consensus document has reviewed the methodological agreements for measuring arterial stiffness and wave reflections [1]. This chapter will not address the issue of endothelial dysfunction and intima-media thickness.

Pathophysiology of large artery damage in hypertension

Pathophysiology of arterial stiffness and wave reflection

Aortic stiffening accompanying age and cardiovascular risk factors is caused by various phenomena, including breaks in elastin fibres, cross-links of the elastin network, accumulation of collagen, fibrosis, inflammation, medial smooth muscle necrosis, calcifications, and diffusion of macromolecules within the arterial wall [3-6].

In patients with essential hypertension, arterial stiffness is elevated in response to the increased loading of stiff wall materials, such as collagen. Indeed, when BP increases during the cardiac cycle from diastole to systole, distensibility decreases. These short-term changes should not be confounded with long-term changes in structure and function. Particularly, whether the decrease in large artery distensibility observed in middle aged hypertensive patients is due primarily to an increase in distending pressure or to

hypertension-induced changes in structural properties has been much debated [7]. We recently reviewed the various mechanisms explaining that the changes in arterial wall material which accompany arterial wall hypertrophy in animal models of essential hypertension are not necessarily associated with an increased isobaric stiffness and mechanical strength, and concluded that the increase in arterial stiffness observed in patients with essential hypertension was primarily due to an increase in distending pressure [5, 6]. Later, age, metabolic disorders, or renal failure may modify this haemodynamic pattern [2, 8].

The stiffness of large arteries, including the aorta, represents the ability of large vessels to dampen the pulsatility of ventricular ejection and to transform pulsatile pressure (and flow) at the ascending aorta into continuous pressure (and flow) downstream, at the site of arterioles, in order to lower the energy expenditure of organ perfusion. With high blood pressure, aging, and diabetes, the large arteries stiffen, and pulse pressure (PP = systolic minus diastolic) increases at the site of central and peripheral arteries. Indeed, the arterial tree is approximated to a viscoelastic tube with numerous branches. Because the tube's end has a high level of resistance, waves are reflected and retrograde waves are generated. As arterial stiffness increases, transmission velocity of both forward and reflected waves increases, which causes the reflected wave to arrive earlier in the central aorta and augment pressure in late systole, thus increasing PP. This augmentation can be expressed as the aortic augmentation index (AIx), which represents the percentage of the increment pressure of aortic PP caused by the reflected wave.

In peripheral arteries, wave reflections can amplify the pressure wave because reflection sites are closer to peripheral sites than to central arteries, and pulse wave velocity is higher in a peripheral, stiffer artery than in a central, elastic artery. The net result is that the amplitude of the pressure wave is higher in peripheral arteries than in central arteries – the so-called "amplification phenomenon". Thus, because of pulse pressure amplification between central and peripheral arteries, it is inaccurate to use brachial pulse pressure as a surrogate for aortic or carotid pulse pressure, particularly in young subjects, in whom brachial PP overestimates central PP.

Because central SBP, PP, AIx and PWV increase with age, hypertension, diabetes mellitus, and hypercholesterolaemia, and are associated with target organ damage (left ventricular hypertrophy, microalbuminuria, carotid intima-media thickening, and endothelial dysfunction) and clinical outcomes, they are often used interchangeably as indices of arterial stiffness. This is an oversimplification and should not be the case for various reasons. First, their

determinants are different. Central SBP, central PP and AIx are dependent upon the speed of wave travel, the amplitude of the reflected wave, the reflectance sites, and the duration and pattern of ventricular ejection, especially with respect to change in heart rate and ventricular contractility [9, 10], whereas aortic PWV, which is the speed of wave travel (c_0), represents intrinsically arterial stiffness, according to the Bramwell-Hill formula: $c_0 = \sqrt{V \cdot dP / \rho \cdot dV}$, where dV is the change in arterial volume (V), dP is the change in pressure driving the change in volume, and ρ is the density of fluid. Second, pathophysiological conditions and drugs may change the central pulse pressure and augmentation index without changing aortic PWV, suggesting a predominant effect on reflection wave, heart rate or ventricular ejection, and no change in aortic stiffness [11, 12]. Third, AIx is much more sensitive to the effects of heart rate than aortic PWV [13].

Pathophysiology of cardiovascular events

A generally accepted mechanistic view is that an increase in arterial stiffness causes a premature return of reflected waves in late systole, increasing central pulse pressure, and thus systolic BP. Systolic blood pressure increases the load on the left ventricle, increasing myocardial oxygen demand. In addition, arterial stiffness is associated with left ventricular hypertrophy (LVH) [2, 14, 15], a known risk factor for coronary events, in normotensive and hypertensive patients. The increase in central PP and the decrease in diastolic BP may directly cause subendocardial ischaemia. The measurement of aortic stiffness, which integrates the alterations of the arterial wall, may also reflect parallel lesions present at the site of the coronary arteries.

Increased arterial stiffness can increase the risk of stroke through several mechanisms, including an increase in central PP, influencing arterial remodelling at the site of both the extracranial and intracranial arteries, increasing carotid wall thickness and the development of stenosis and plaques [15, 16] and the prevalence and severity of cerebral white matter lesions. As seen above, the measurement of aortic stiffness, which integrates the alterations of the arterial wall, may also reflect parallel lesions present at the site of cerebral vasculature. Another explanation is given by the differential input impedance in the brain compared with other systemic vascular beds. Finally, coronary heart disease and heart failure, which are favoured by high PP and arterial stiffness, are also risk factors for stroke.

Clinical measurements of arterial stiffness and wave reflections

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 [1, 2, 14, 17, 18]. Table I gives the main features of various methods.

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 [2, 14, 29, 30], and aortic PWV is an independent predictor of outcome in a variety of populations [24, 31-38]. 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. Measu-

rement of local carotid stiffness may also provide important prognostic information, since the carotid artery is a frequent site of atheroma formation.

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. Carotid-femoral PWV is a direct measurement, and it corresponds to the widely accepted propagative model of the arterial system. 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 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), has no predictive value in patients with end-stage renal disease (ESRD) [39].

Table I. Device and methods used for determining regional, local, and systemic arterial stiffness, and wave reflections (adapted from ref. [1])

Device	Methods	Measurement site	Ref.
Regional stiffness			
Complior®	Mechanotransducer	Aortic PWV ¹	[19]
SphygmoCor®	Tonometer	Aortic PWV ¹	[20]
Pulsepen®	Tonometer	Aortic PWV	[21]
WallTrack®	Doppler probes	Aortic PWV ¹	[22]
Artlab®	Doppler probes	Aortic PWV ¹	[23]
Ultrasound systems	Doppler probes	Aortic PWV ¹	[24]
Local stiffness			
WallTrack®	Echo-tracking	CCA ² , CFA, BA	[22]
NIUS®	Echo-tracking	RA	[25]
Artlab®	Echo-tracking	CCA ² , CFA, BA	[23]
Various vascular ultrasound syst.	Echo-tracking	CCA ² , CFA, BA	[17]
MRI device	Cine-MRI	Ao	[17]
Systemic stiffness (waveform shape analysis)			
Area method	Diastolic decay	Carotid, aorta	[26]
Pressure flow waveform ratios		Carotid, LV	[14]
HDI PW CR-2000®	Modif. Windkessel	Radial	[27]
Stroke volume/pulse pressure		Carotid, aorta	[28]
Wave reflections			
SphygmoCor®	Augmentation index	All superficial art.	[20]
Pulse trace®	Finger photoplethysmography		[9]

PWV – pulse wave velocity, ¹aorta – carotid-femoral, also carotid-radial and femoro-tibial PWV, ²all superficial arteries, including particularly those mentioned, Ao – aorta, CCA – common carotid artery, CFA – common femoral artery, BA – brachial artery, RA – radial artery, SV/PP – stroke volume/pulse pressure

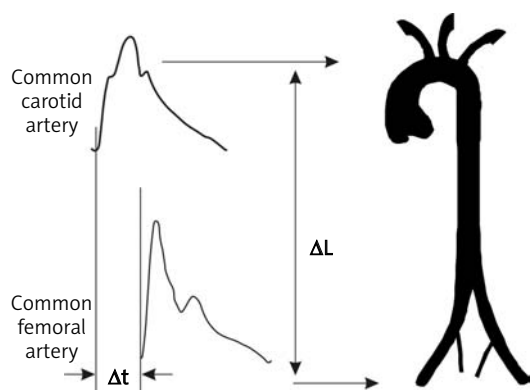


Figure 1. Measurement of carotid-femoral pulse wave velocity with the foot to foot method (from ref. [40] with permission)

Pulse wave velocity 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), and the time delay (Δt , or transit time) measured between the feet of the two waveforms (Figure 1). A variety of different waveforms can be used including pressure [19], distension [41] and Doppler [24]. The distance (D) covered by the waves is usually assimilated to the surface distance between the two recording sites. Some authors subtract from this distance the small length between the carotid transducer and manubrium sterni [2]. Pulse wave velocity is calculated as $PWV = D (m)/\Delta t (s)$.

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 [18]. In the presence of aortic, iliac, or proximal femoral stenosis, the pressure wave may be attenuated and delayed. Abdominal obesity, particularly in men, and large bust size in women, can make distance measurements inaccurate [18].

The most commonly used method for estimating transit time is the “foot to foot” method. 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.

Methods based on pressure sensors

Pressure waveforms can be recorded simultaneously to provide automated measurement of PWV using a number of devices. The Complior System[®] (Colson, Les Lilas, France) employs dedicated mechanotransducers directly applied on the skin [19]. 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. This system was used in most of the epidemiological studies demonstrating the predictive value of PWV for cardiovascular events.

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 [42] (AtCor, Sydney, Australia) a single high-fidelity applanation tonometer (Millar[®]) obtains 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. 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. 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.

Japanese researchers advocated the use of brachial-ankle pulse wave velocity (baPWV), and showed that the aortic PWV was the primary independent correlate of baPWV, followed by leg PWV [43].

Methods based on Doppler probes and other methods

The distension waves obtained from high definition echotracking devices (see below) can be used to calculate PWV. As described above for the SphygmoCor[®] device, PWV is calculated from waves successively obtained at a short time interval at two arterial sites (common carotid and femoral artery for instance), using the R wave of the ECG for calculating the time delay [9, 41].

The transit time required for the determination of PWV can be measured between two flow pulses simultaneously recorded by continuous Doppler probes [24], 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). Transit time is automatically calculated following automatic recognition of the foot of the pulse. This method

was used for showing the predictive value of aortic PWV for cardio-vascular events in diabetic patients [24], and provides a more accurate assessment of "aortic" PWV as compared to carotid-femoral, although whether this has any specific advantage remains to be seen.

Other devices are available to calculate a PWV-based stiffness index [17, 18, 44]. These devices are not so precise as those mentioned above as some propose aberrant transit tracts (i.e. ankle-arm) or estimate distance from height (i.e. height in a sitting position). Some do not correct for electromechanical dissociation of cardiac action or try to correct for it using a model.

Local determination of arterial stiffness

Local arterial stiffness of superficial arteries can be determined using ultrasound devices. Carotid stiffness may be of particular interest, since in that artery atherosclerosis is frequent. All types of classical, bi-dimensional 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. At present some researchers also measure local arterial stiffness of deep arteries like the aorta using cine magnetic resonance imaging (MRI). However, most of the pathophysiological and pharmacological studies have used echo-tracking techniques.

A major advantage of echo-tracking 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 a high 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 [1]. Nevertheless, ultrasound is currently the only means to determine, non-invasively, the elastic properties of the arterial wall material (Young's elastic modulus, see below) [15, 30, 45, 46], and the relationship between intima-media thickness and elastic properties [6], or the influence of inward or outward remodelling on arterial distensibility [41, 45, 47-49].

Echotracking devices were developed to measure diameter in end-diastole and stroke change in diameter with a very high precision. The two first devices were the Wall Track System® [22, 50] and the NIUS O2® [25]. These devices use a 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 [22, 25, 50]

for echotracking systems, and around 150 microns (i. e. the size of a pixel) with video-image analysers. 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 [22, 25, 50]. A novel multi-array echotracking system having 128 RF lines (ArtLab®) is able to determine both IMT and pulsatile changes in diameter along a 4 cm long arterial segment [23]. It also allows one to determine the distension gradient between two adjacent zones, for instance at the level of an atherosclerotic plaque and upstream (or downstream) [23, 51].

Echotracking systems have other major advantages over video-image systems: from the same ultrasound data, the intima-media thickness (IMT) can be extracted, which allows Young's elastic modulus to be determined (see below) [45, 30]; it is possible to determine the pressure-diameter curve of the artery, and thus to determine arterial stiffness for any given BP [30, 45, 46]; from the time delay between two adjacent distension waveforms, it is possible to calculate local PWV [52]; 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 [30, 53] and calibration of the waveform to brachial mean and diastolic pressures obtained by integration of the brachial or radial waveform [53], or automatic calculation using transfer function processing (SphygmoCor®, AtCor, Sydney, Australia). All the superficial arteries are suitable for the geometrical investigation, and particularly the common carotid, common femoral and brachial arteries.

Table II gives the definition of various indices used to describe the elastic properties of blood vessels, non-invasively obtained with ultrasound measurements. For the calculation of wall properties, it is assumed that the cross-section of an artery is circular (Figure 2). The elastic properties of the artery as a hollow structure are assessed through arterial distensibility, determined from the systolic-diastolic variations in arterial cross-sectional area and local pulse pressure [1, 17, 22, 30, 41, 48]. The elastic properties of the arterial wall material are estimated by Young's incremental elastic modulus (E_{inc}), which takes into account the thickness of the arterial wall [1, 30, 54]. The intima-media thickness is taken as a surrogate for arterial wall thickness. Young's elastic modulus, or incremental elastic modulus, which gives information on the wall material, should not be confused with Peterson's elastic modulus, which is inversely related to cross-

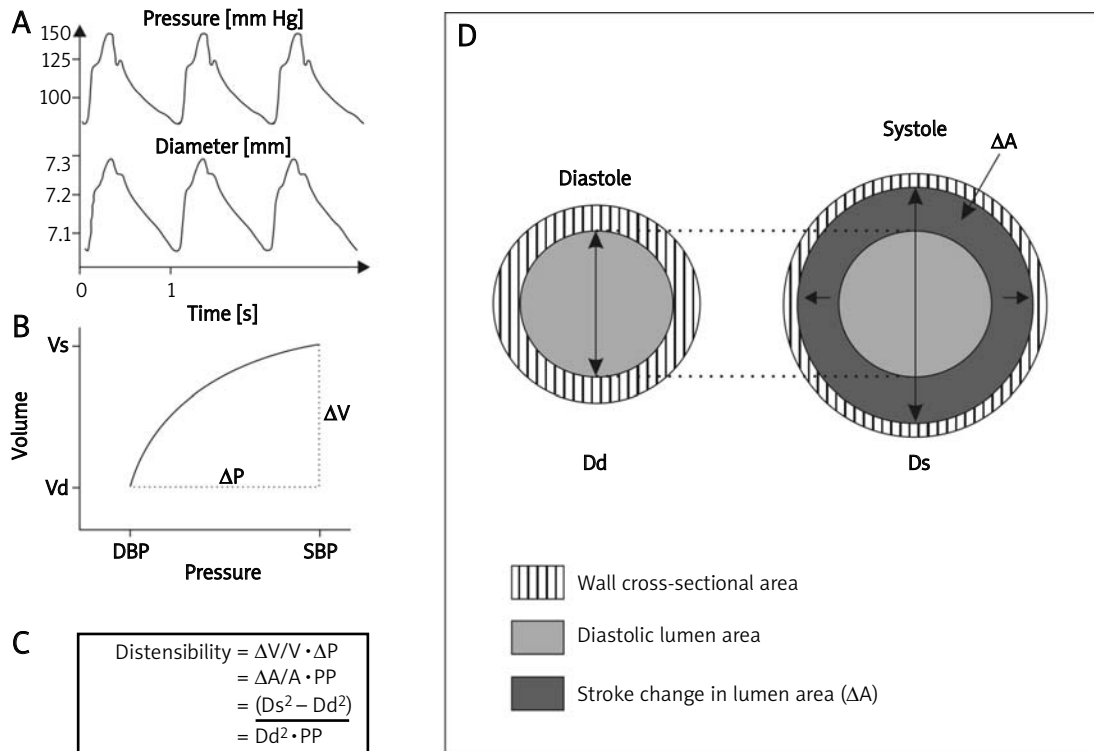


Figure 2. Local arterial distensibility. A – simultaneous recording of stroke changes in BP and diameter. B – pressure-diameter curve. C – calculation of distensibility. D – schematic representation of the stroke change (ΔA) in lumen cross-sectional area (LCSA) (from ref. [40] with permission)

sectional distensibility, and elastic properties of large arteries as hollow structures [1, 54]. Calculation of Young’s modulus from IMT assumes that the wall is homogeneous, and load-bearing, so values may be underestimated.

The relationship between carotid stiffness and aortic stiffness is not obvious. It appears [55] that carotid and aortic stiffness do not differ too much when they are measured in normal subjects. However, as the number of CV risk factors increases, the discrepancies between both measurements increase, suggesting that CV risk factors do not affect the carotid and aortic walls, and consequently their elastic properties, to the same extent (Figure 3) [55].

Systemic arterial stiffness

A methodology based on the simultaneous determination of pressure and flow (at the left ventricle outflow track) allowing calculation of characteristic impedance, has been successfully applied to the characterisation of the Framingham cohort [14]. Another methodology, using an electrical circuit based on a modified Windkessel model [27, 56], has been developed to determine a proximal capacitive compliance and a distal oscillatory compliance (HDI/PulseWave CR-2000 Research CardioVascular Profiling System; Hyper-

tension Diagnostics Inc, Eagan, MN, USA). This technique is based on the arterial pulse recording at the level of the radial artery and identifies the reflections in diastole as a decaying sinusoidal wave [27, 56].

Systemic arterial compliance can also be determined using the “area method” [26, 57], which requires 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 is 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).

In conclusion, some 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. Their theoretical, technical and practical limitations that impact on their widespread application in

Table II. Indices of arterial stiffness applied to geometrical measurements of large arteries with ultrasound (adapted from ref. [1])

Term	Definition [units]
Stroke change in diameter	Change in diameter during systole = systolic diameter (Ds) – diastolic diameter (Dd) [mm]
Stroke change in lumen area	Change in lumen area during systole $\Delta A = \pi(D_s^2 - D_d^2)/4$ [mm ²] with D – internal diameter
Wall cross-sectional area	Surface of a cross-section of the arterial wall WCSA = $\pi(D_e^2 - D_i^2)/4$ [mm ²] with De – external diameter and Di – internal diameter, measured in diastole
Elastic properties of the artery as a whole	
Cross-sectional distensibility	Relative change in lumen area during systole for a given pressure change coefficient (DC) DC = $\Delta A/A \cdot \Delta P$ [kPa ⁻¹] with ΔP – local pulse pressure
Cross-sectional compliance	Absolute change in lumen area during systole for a given pressure change coefficient (DC) CC = $\Delta A/\Delta P$ (m ² · kPa ⁻¹) with ΔP – local pulse pressure
Peterson elastic modulus	Inverse of distensibility coefficient: the pressure change driving an increase in relative lumen area Peterson = $A \cdot \Delta P/\Delta A$ [kPa]
Elastic properties of the arterial wall material	
Young’s elastic modulus or incremental elastic modulus	$E_{inc} = [3(1 + A/WCSA)]/DC$ [kPa]
Elastic properties at the level of the atherosclerotic plaque	
Distension gradient (upstream or “bending strain” plaque) <i>minus</i> distension at the level of the plaque	Calculated as the distension at the adjacent “normal” CCA

the clinical setting have been discussed and compared with methods used for the non-invasive determination of regional stiffness [18, 39, 56, 58]. As yet, they have not provided evidence, in a longitudinal study, that systemic arterial stiffness or systemic arterial compliance has independent predictive value for CV events [26, 28].

Non-invasive determination of wave reflections

Central pulse wave analysis

The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave. Waves are reflected from the periphery, mainly at branch

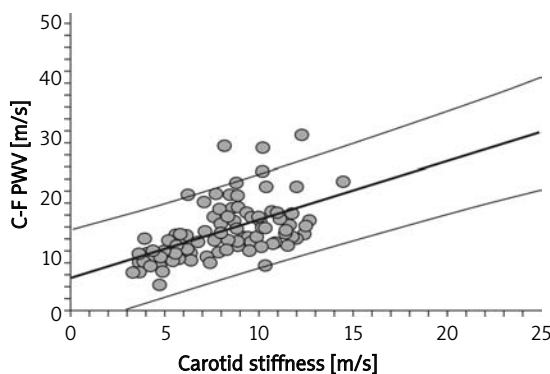
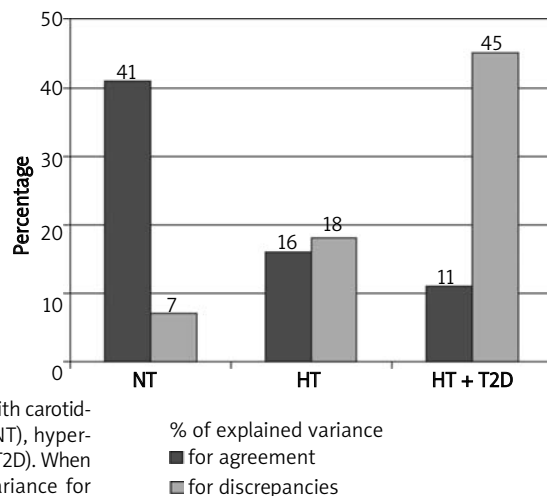


Figure 3. Agreement between aortic stiffness (measured with carotid-femoral PWV) and carotid stiffness, in normotensives (NT), hypertensives (HT) and hypertensives with type 2 diabetes (HT + T2D). When CV risk factors are added, the amount of explained variance for discrepancies increases (from ref. [55] with permission)



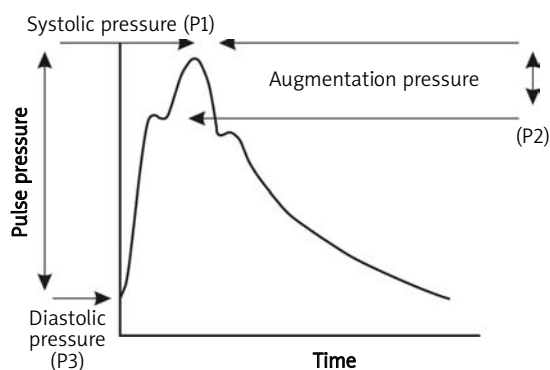


Figure 4. Augmentation index. Carotid pressure waveform is recorded by applanation tonometry. The height of the late systolic peak (P1) above the inflection (P2) defines the augmentation pressure, and the ratio of augmentation pressure to PP defines the augmentation index (Alx, in percent) (from ref. [1] with permission)

points or sites of impedance mismatch. In elastic vessels, because PWV is low, a reflected wave tends to arrive back at the aortic root during diastole. In the case of stiff arteries, PWV rises and the reflected wave arrives back at the central arteries earlier, adding to the forward wave, and augmenting the systolic pressure. This phenomenon can be quantified through the augmentation index (Alx) – defined as the difference between the second and first systolic peaks ($P2 - P1 = AP =$ augmentation pressure) expressed as a percentage of the pulse pressure (Figure 4) [2, 12, 59, 60]. Apart from a high PWV, also changes in reflection sites can influence the augmentation index. In clinical investigation, not only DBP and height, which are related to reflection sites, but also age and aortic PWV are the main determinants of Alx [11].

Arterial pressure waveform should be analysed at the central level, i.e. the ascending aorta, since it represents the true load imposed on the left ventricle and central large artery walls. Aortic pressure waveform can be estimated either from the radial artery waveform, using a transfer function [20, 61], or from the common carotid waveform [17, 18]. In the later case, a transfer function is not necessary. On both arteries, the pressure waveform can be recorded non-invasively with a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments). The most widely used approach is to perform radial artery tonometry and then apply a transfer function (SphygmoCor®, AtCor, Sydney, Australia) to calculate the aortic pressure waveform from the radial waveform [20, 61]. Indeed, in contrast to the carotid artery, the radial artery is well supported by bony tissue, making optimal applanation easier to achieve.

Generalized inverse transfer functions are applied to reconstruct the aortic waveform from radial tonometry [20, 61]. The estimation of central aortic

pressures (PP and SBP) is accepted as more accurate than the estimation of Alx (see below) [9, 11]. Indeed, measurement of Alx is dependent on higher frequency signals than blood pressure measurement and the transfer function appears to be less accurate and to show greater between-subject variability at high frequencies [9, 20, 61]. In addition, brachial artery pressures are used as surrogates of radial artery pressures for the calibration of central pressures, and this may introduce some errors [62]. Despite these limitations, radial tonometry is popular since it is simple to perform and well tolerated.

Carotid tonometry requires a higher degree of technical expertise, but a transfer function is not necessary since the arterial sites are very close and waveforms are similar [1, 61]. Direct measurements obtained at the site of the common carotid artery using applanation tonometry can be calibrated according to the method described by Van Bortel et al. [53, 62].

A transfer function may be useful when applanation tonometry cannot be applied at the site of the carotid artery, for instance in obese subjects, or in patients with major atherosclerotic plaques or calcified arteries, in whom this method may not be free from any risk. However, the use of a transfer function should be limited to the upper limb, where elastic properties remain relatively constant with age and disease, as previously discussed. It would allow assessment of the carotid artery and ascending aorta systolic BP and PP from radial artery PP [20, 53, 62].

The central augmentation index and central pulse pressure have shown independent predictive values for CV events in the hypertensive patients of the CAFÉ study [42] and patients undergoing percutaneous coronary intervention [63], and for all-cause mortality in ESRD patients [10, 59].

Clinical importance

Arterial damage in hypertension and associated clinical conditions

A large number of publications and several reviews [1, 4, 17, 18, 42, 60] have reported the various pathophysiological conditions associated with increased arterial stiffness and wave reflections. Apart from the dominant effect of blood pressure and aging [2, 9, 14, 45, 64], they include (a) physiological conditions [1], such as low birth weight, menopausal status, lack of physical activity; (b) the genetic background such as a parental history of hypertension, diabetes or myocardial infarction, and genetic polymorphisms; (c) CV risk factors such as obesity, smoking, hypertension, hypercholesterolaemia, impaired glucose tolerance, metabolic syndrome, type 1 and 2 diabetes, hyperhomocysteinaemia, and high CRP level; (d) CV diseases such as coronary heart

disease, congestive heart failure, and fatal stroke; and (e) primarily non-CV diseases, such as end-stage renal disease (ESRD), moderate chronic kidney disease, rheumatoid arthritis, systemic vasculitis and systemic lupus erythematosus.

Predictive value of arterial stiffness and wave reflection

A major reason for measuring arterial stiffness and wave reflections “routinely” in clinical practice in hypertensive patients comes from the recent demonstration that arterial stiffness has an independent predictive value for CV events [1, 2].

Arterial stiffness and wave reflection as intermediate end-points

Several longitudinal epidemiological studies have demonstrated the predictive value of arterial stiffness, carotid pulse pressure and augmentation index, as intermediate end-points, i.e. the higher the arterial stiffness the higher the number of CV events. 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 [32, 33, 40], but also in patients with type 2 diabetes [24] or end-stage renal disease [31, 36], in elderly subjects [35, 38] and in the general population [34, 37, 65]. It is now well accepted that aortic stiffness is an intermediate end-point for CV events.

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 the classical risk factors. In addition, aortic stiffness retains its predictive value for CHD events after adjustment to the Framingham risk score, suggesting that aortic stiffness has an added value to a combination of CV risk factors [32]. 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, glycaemia, 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 whom arterial risk factors were translated into real risk.

Data are less consistent concerning arterial stiffness measured at other arterial sites. The predictive value of carotid stiffness has not yet been reported in hypertensive patients. Although carotid stiffness was predictive of CV events in a small number of patients with ESRD [66] or following renal transplantation [67], no predictive value was demonstrated in a larger number of patients with

manifest arterial disease [3]. Upper and lower limb territories, due to their particular pathophysiology [1, 2, 14, 29], may not reflect aortic, cerebral and coronary artery damage. Indeed, in contrast to carotid-femoral PWV, neither brachial PWV nor femoro-tibial PWV was able to predict cardiovascular outcome in ESRD patients [17].

The central augmentation index and pulse pressure, either directly measured by carotid tonometry [10, 59] or estimated using a transfer function from radial artery tonometry [42, 63], are both independent predictors of all-cause mortality in ESRD patients [10, 59], in patients undergoing percutaneous coronary intervention [63], and in the hypertensive patients of the CAFÉ study [42]. In older female hypertensive patients, data from the ANBP2 study showed no benefit in use of carotid applanation tonometry (augmentation index or total arterial compliance) over brachial cuff pressure in prognosis [26].

Pharmacology of arterial stiffness and wave reflection

A large number of publications and several reviews [1, 2, 44, 68] have reported the changes in arterial stiffness and wave reflections after various interventions, either non-pharmacological or pharmacological. Non-pharmacological treatments which are able to reduce arterial stiffness include [1, 2] exercise training, dietary changes (including weight loss, low salt diet, moderate alcohol consumption, garlic powder, α -linoleic acid, and fish oil), and hormone replacement therapy (HRT).

Pharmacological treatments which are able to reduce arterial stiffness include [1, 2] (a) anti-hypertensive treatment, such as diuretics in old people, β -blockers, ACE inhibitors, AT1 blockers, and calcium channel antagonists; (b) treatments of congestive heart failure, such as ACE inhibitors, nitrates, and aldosterone antagonists; (c) hypolipidaemic agents such as statins; (d) anti-diabetic agents, such as thiazolidinediones; and (e) AGE-breakers, such as alagebrium (ALT-711). Whether the reduction in arterial stiffness after antihypertensive treatment is only due to BP lowering, or additional BP-independent effects are involved, is still debated. To our knowledge, some studies unequivocally showed that antihypertensive treatment was able to reduce arterial stiffness and/or wave reflections independently of the reduction in brachial BP, for instance either acutely after a calcium channel blocker [69] or after long-term ACE inhibition [49, 70].

Conclusion

This chapter highlights the importance of arterial stiffness and wave reflection, not only for assessing CV risk, but also for predicting CV outcomes.

Arterial stiffening also provides direct evidence of target organ damage, which is of major importance in determining the overall CV risk of the hypertensive patient. Indeed, measurement of arterial stiffness and wave reflection may avoid patients being mistakenly classified as at low or moderate risk, when they actually have an abnormally high arterial stiffness or central PP, placing them within a higher risk group.

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