Determination of Systemic and Regional Arterial Structure and Function

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Pierre Boutouyrie, Laurent Macron, Elie Mousseaux, and Stéphane Laurent

Abstract

Large artery stiffness can be measured through direct and indirect techniques. Measurement of pulse wave propagation is among the most direct techniques, either through pulse wave velocity or through artificial pressure wave propagation. Measurement of strain and stress through echotracking techniques gives also direct, hypothesis-free measurement of arterial stiffness. Other techniques are derived from models of circulation and can approximate arterial stiffness. Details about techniques, parameter definition, are given here to help researchers and practitioners to make the best choice of technique for their applications.

Keywords

Stiffness • Measurement • Distensibility • Compliance • Echotracking • Remodeling • Arteries

P. Boutouyrie, MD, PhD (✉) • S. Laurent, MD, PhD
Department of Pharmacology and Institut National de la Santé et de la Recherche Médicale U970(Eq7)-PARCC, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Université Paris-Descartes, 20 rue Leblanc, Paris 75015, France
e-mail: pierre.boutouyrie@egp.aphp.fr; stephane.laurent@egp.aphp.fr

L. Macron, MD, PhD • E. Mousseaux, MD, PhD
Radiologie, HEGP, APHP, Inserm U970 Eq7, Université Paris Descartes, Paris, France

Radiology, Hopital Europeen Georges Pompidou, 20 rue Leblanc, Paris 75015, France
e-mail: laurent.macron@egp.aphp.fr; elie.moussseaux@egp.aphp.fr

Arterial stiffness is a generic word covering the way an elastic artery can accommodate changes in blood pressure. This is a key function in physiology and pathology because elastic artery can relay the cardiac contraction during diastole (Fig. 5.1). There are two main techniques to measure arterial stiffness: direct or indirect from circulation models. Because the physical definition of stiffness (Hooke's law) is the relation between a force applied to a material and the deformation of this material, direct measurement of stiffness is only possible through the measurement of both parameters: force and deformation (Fig. 5.2). Arteries are cylindrical structures exposed to pressure. The force applied to the vessel is called stress, which is three dimensional in nature (longitudinal, radial, and circumferential). For the

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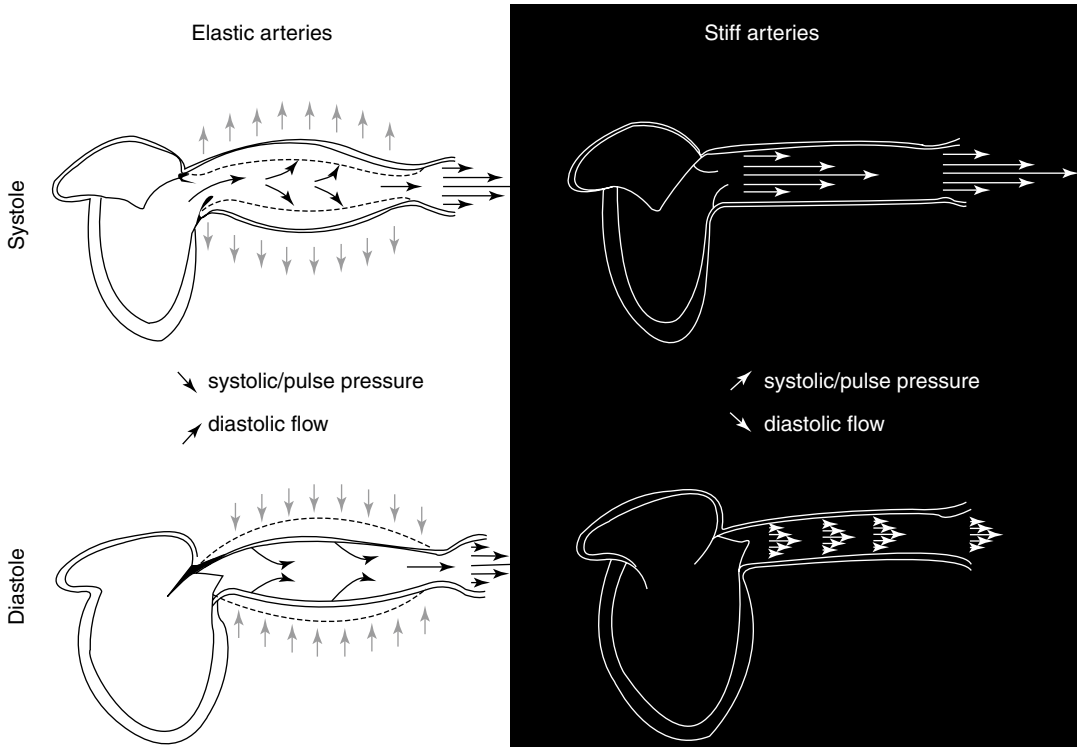

Fig. 5.1 Arterial elasticity and diastolic relay of cardiac contraction

sake of simplicity, circumferential wall stress is usually considered alone and it can only be approximated by the Lamé equation, although arteries are stretched longitudinally by 15–20 % under static conditions [1], and attempts to measure longitudinal stretch variations show significant variations clinically relevant [2]:

$$\sigma_\theta = \frac{P \times R}{h}$$

Because the Lamé equation says that stress is proportional to radius (R) and pressure (P) and inversely proportional to thickness (h), we can understand that it is impossible to interpret stiffness independently of arterial structure. The stress/strain relationship defines the stiffness of the wall material (Einc) (Fig. 5.2). Because the arterial structure is complex, involving smooth muscle cells, elastin, collagen, and many other macromolecules, the mechanical behavior of the arterial wall represents the summation of the individual components behavior, with added complexity due to the distribution of the components and their tridimensional relations [3–5]. Therefore, it is more the 3-D organization of components which can explain the mechanical properties of large arteries [6]. The pressure–diameter or stress–strain relationship is curvilinear; the artery is stiffer at high strain. This is generally associated with the composite nature of the arterial wall and the progressive recruitment of collagen fibers [5]. Whereas technical progress have been outstanding for measuring strain, through ultrasounds or MRI, measurement of stress is still hampered by imprecise noninvasive measurement of blood pressure and the necessity to measure precisely wall thickness. It is also limited by theoretical considerations on which structure in the wall is really carrying the mechanical stress [4]. It remains that the stress–strain relation is considered as the gold standard for assessing arterial stiffness.

Newton's second law of motion implies that the celerity of mechanical waves propagation

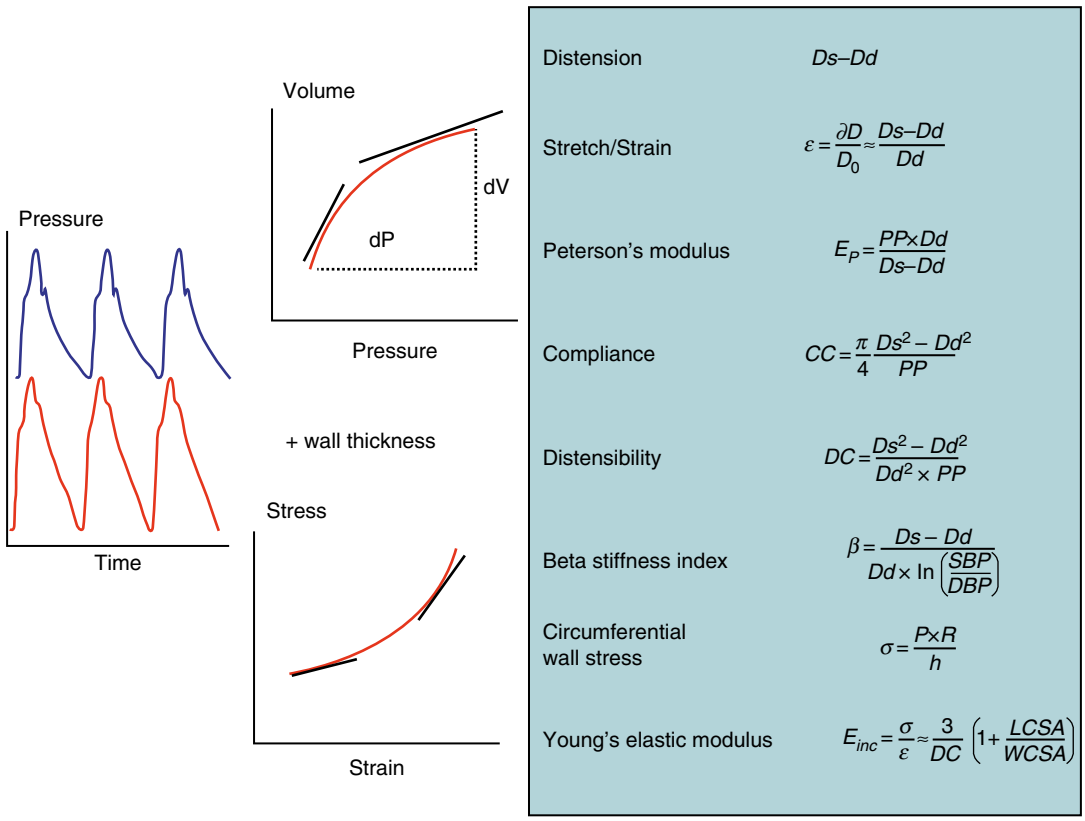

Fig. 5.2 Pressure–diameter and stress–strain relationship: definition of main stiffness parameters

is proportional to its elastic modulus (i.e., stiffness). Moens and Korteweg [7, 8] have derived and simplified this relation into the famous equation

$$PWV = \sqrt{\frac{E_{inc} \bullet h}{2r\rho}}.$$

This equation has been further simplified by Bramwell and Hill [9]:

$$PWV = \sqrt{\frac{dP \bullet V}{\rho \bullet dV}}$$

It is noteworthy that PWV is directly related to characteristic impedance in a pure Windkessel model (Fig. 5.3). The relation between the speed of wave propagation and elastic modulus is also used by very modern techniques such as ultrafast imaging [10].

Direct Measurement of Arterial Stiffness

Pulse wave velocity (PWV) is the most widely used technique that Bramwell and Hill introduced to physiology in 1922 [9]. Briefly, a pressure wave's propagation speed in a solid is proportional to its stiffness. If expressed through the elastic modulus (E_{inc}), PWV can be expressed as $PWV = K \times E^{0.5}$, where K reflects tissue density. Thus, when measuring the pressure wave at different sites along an arterial segment or along the arterial tree (dL), the distal wave is recorded later (dt) than the proximal one and $PWV = dL/dt$. Waveform landmarks, conserved from one site to another, have to be used; the foot of the wave is widely used because it is more clearly identified on all sites. Because early wave reflections can confuse the precise identification of the foot of

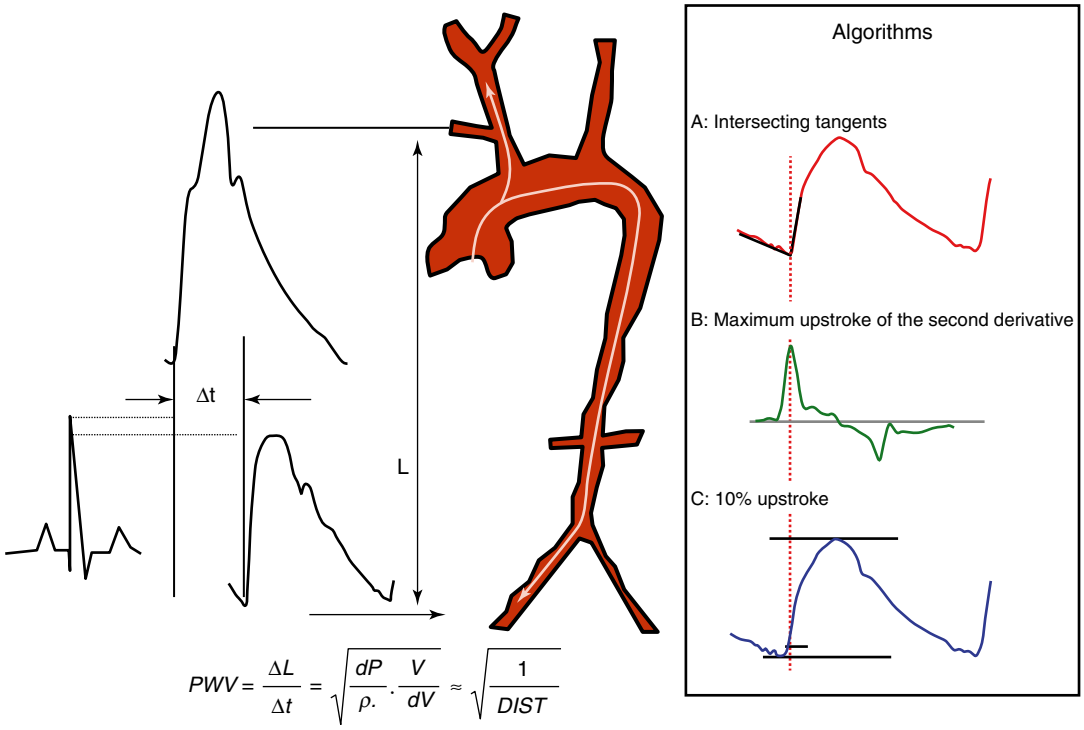

Fig. 5.3 Pulse wave velocity and algorithms for identification of the foot of the wave

the wave, especially if PWV is measured on very short stretches of vessels, it has been proposed to use other landmarks on the pressure wave [11]. The one validated at the site of the carotid is the dichrotic notch, which is not affected by wave reflections [11]. The resulting PWV is nevertheless measured in telesystole and provides higher values than if measured during diastole.

Although PWV can be measured on any artery or between any arterial sites, only carotid-to-femoral [12–15] (or aortic [16], see [17] for meta-analysis) PWV has been shown to have predictive value for morbidity and mortality whereas other arterial pathways have not been associated [18]. Carotid-to-femoral PWV represents stiffness of the aorta and iliofemoral axes. The several commercial devices available differ according to the type of signal (pressure, distension, flow) or whether they simultaneously record both sites or use the ECG for synchronization.
When a high-fidelity pressure transducer is used, they may allow pressure-wave analysis and wave-reflection assessment. PWV reference values determined in a very large population are now available, and measurement standardization based on those values was recently proposed [19].

Distance measurement and identification of the foot of the wave are important issues. To have realistic PWV values, the use of intersecting tangents to measure transit time (*dt*) of the foot of the wave and carotid-to-femoral distance (*dL*) is preferred [20]; PWV is then calculated as $PWV = 0.8 \times dL/dt$ [21]. The reason for this correction has to be explained. Because pulse wave reaching the origin of the carotid bifurcates, the time it reaches the carotid site, it has already progressed in the thoracic aorta. Therefore, measurement of distance between the carotid and the femoral site overestimates the distance. The different options to correct for this have been extensively studied [21, 22]. The most logical is the subtraction method, which unfortunately leads to increased error due to duplicate distance measurements but also to underestimation of the pathway length [22, 23]. The optimal method is

to use the direct distance correct by a factor 0.8, which is now recommended [19, 21]. Since most, but not all epidemiological studies used the direct distance, some authors question the influence of distance measurements on outcome [24]; however, their analysis is biased by the fact that they used the same fixed threshold of 12 m/s for each of the recalculated pathways which do not have the same metrics.

Because measurement of carotid-to-femoral pulse wave velocity necessitates some training, because the patient has to be reclining, and because exposure of the groin is not acceptable in all culture, manufacturers have developed alternative techniques which allow to approximate CF-PWV on different arterial paths, using either multiple or simple cuffs. Several of the implications of this have been discussed in a recent editorial [25]. Although many devices are now on the market (table from Hypertension 2013), there is up to now no validation of such measurements on hard outcome.

The common view for techniques such as the brachial ankle PWV is that much of the aorta is simply ignored by this parameter because the wave is propagating simultaneously in the arm and the aorta and that this might limit its usefulness and reliability. Despite that, agreement between ankle–brachial PWV is better than expected [26], and ankle–brachial PWV is associated with major CV risk factors and outcome, quite similarly to carotid-to-femoral pulse wave velocity [27]. This indicates that the link between aortic stiffness and brachial–ankle PWV is closer than generally considered. An alternative view of the arterial path is that muscular arteries only contribute for a small part to the compliance of large vessels and that it is rather insensitive to aging and hypertension [28, 29], the major contribution to brachial–ankle pulse wave velocity being provided by the aorta.

Another alternative interesting technique is the Q-KD which measures the time interval between the ECG Q wave and the first Korotkov sound during ambulatory blood-pressure monitoring [30]. This technique provides an estimate of stiffness partly dependent on heart rate because of variable electromechanical coupling time, but it has the major advantages of including mostly the ascending aorta, being ambulatory and minimally invasive. Most importantly, it has been shown to be predictive of events, even on top of LV mass [31]. The method developed by Gosse et al. measures the time delay 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. Thus, the pressure pulse wave travels first along the ascending aorta and the aortic arch, i.e., a short pathway of elastic arteries, and then along the subclavian and brachial arteries, i.e., a much longer pathway of muscular arteries. Since the stiffness of muscular arteries is little influenced by age and hypertension, Gosse etal. attributed the difference in QKD duration to ascending aorta and aortic arch. However, a closer look at the figure shows that the length of the ascending and aortic arch pathway represents a very small part of the total pathway and casts doubt about this statement [25]. Furthermore, in MRI studies, the transit time of flow wave along the aortic arch (average 120 mm length) is often found around 35 ms in young healthy subjects [32], a value which is far from the mean 206 ms QKD duration found in the present study. Thus, part of that QFD duration has to be further explained by both the pre-ejection period and the transit time within muscular arteries.

Local Measurement of Arterial Stiffness

It is also possible to directly measure arterial dimension changes during the cardiac cycle and link them to local pulse pressure changes [33–37] (Figs. 5.2, 5.4, and 5.5). This approach is straightforward and provides the pressure–diameter relationship which is the most closely related to the definition of stiffness, the stress–strain relationship if thickness is also measured, and, thus, yields stiffness indexes at any given blood-pressure level (Fig. 5.2). These techniques are based on high-precision vascular echotracking or magnetic resonance imaging [38–40] coupled with applanation tonometry (Fig. 5.4). The advantage of echotracking technique is its ability

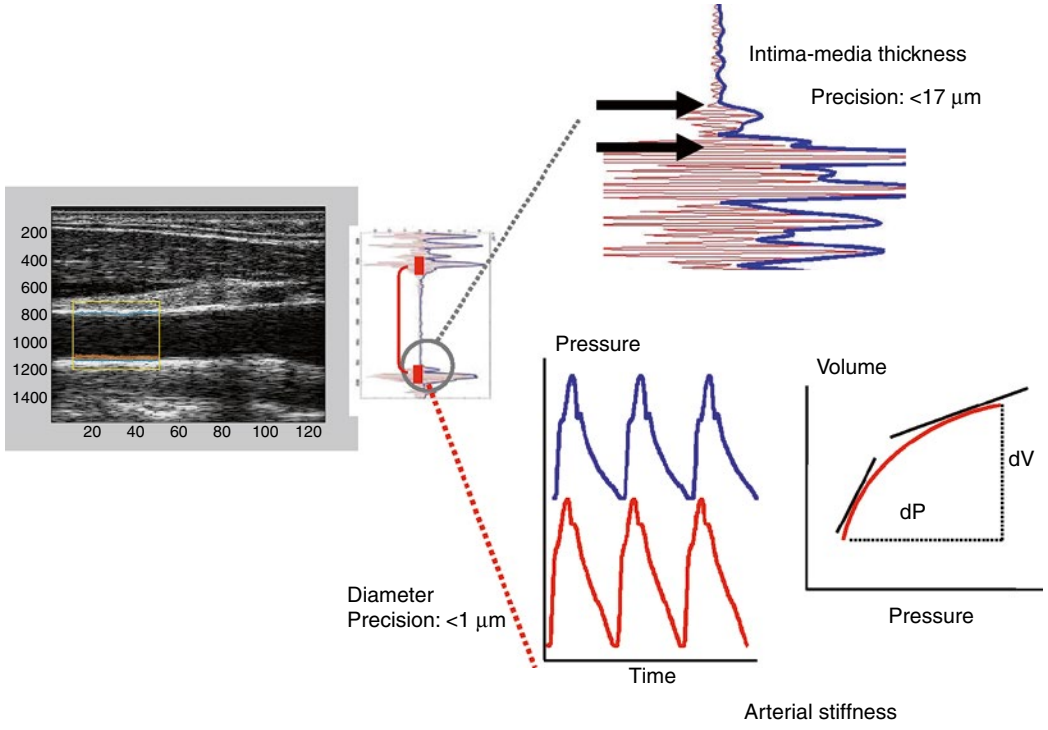

Fig. 5.4 Principle of echotracking

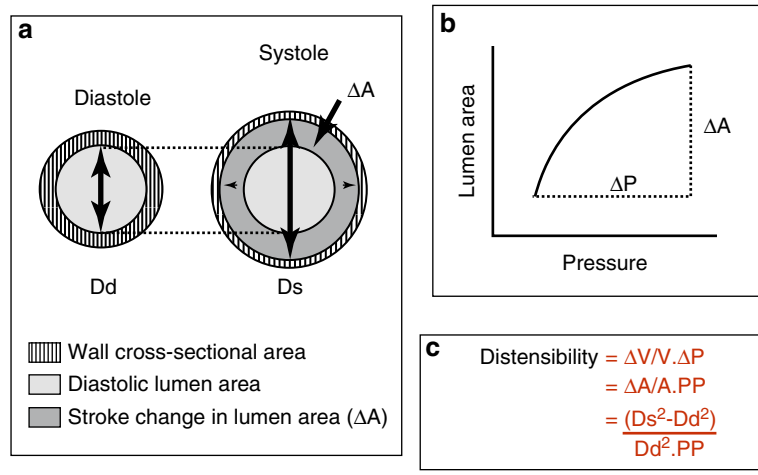

Fig. 5.5 Simplified representation of echotracking of superficial arteries

to track ultrasound radiofrequency signals with a very high time and space resolution. Typically, a 10 MHz probe provides a temporal resolution of 600–1,000 Hz with a spatial resolution of 17 µm for fixed structures and <1 µm for motion [37]. This very high precision is also very useful to quantify arterial structure in terms of diameter, intima media thickness, and related measures. The use of multiframe echotracking makes it possible to assess the heterogeneity of the wall on a segment [37, 41]. We recently applied this approach to the characterization of atherosclerotic plaques, showing that the artery might be more or less distensible at the site of the plaque

than beside and that this characteristic was associated with the kind of remodeling (eccentric or concentric) at the site of the plaque [42]. Recent improvement in ultrasound probe quality and in signal processing allows to use dedicated devices based on image analysis since they show a very good agreement with echotracking techniques [43]. Measurement of local arterial stiffness is still limited by the accessibility of the artery to ultrasound (which practically excludes the thoracic aorta) but most importantly limited by the measurement of local pulse pressure. The advantage of MRI is the accessibility of deep arteries, the possibility to investigate the true arterial geometry and blood flow distribution. Its limits are the low temporal and spatial resolution. Both ultrasound and MRI share the same limits for local pressure assessment. Tonometric techniques have been validated against invasive measurements; however, this validation concerns more populations than measurements for individual patients [44]. Calibration of pressure waves is still highly debated, and inaccuracies may lead to errors in interpretation of data [45–47]. It is also likely that the applanation tonometry by itself induces push–pull artifacts due to the motion of the arterial wall and thus might distort the shape of the curve. This explains why it is very difficult to assess arterial wall viscosity in vivo. Experimental data show that in controlled conditions in vivo in animals [48, 49] and in human [50], viscosity is barely measurable and arteries behave as quasi-pure elastic structures. Opposite to that, human data were all obtained with noninvasive pressure and all exhibited large viscoelastic loops [51]. The most likely explanation is the presence of distortions on the pressure recording with tonometry. Analyses have focused on modeling the pressure–diameter relationship which enables to determine arterial stiffness and all parameter for any given blood pressure or wall stress [52–57]. This is of course the most rigorous method but it is not free of caveats. For instance, the reference condition at 0 stress is necessary for any physical model [3, 5] and is considered of crucial importance for characterizing the arterial wall mechanical behavior [58]. The determination of unloaded dimension is quite impossible in vivo, because even if studied at 0 pressure, the artery is still submitted to quantitatively important residual stresses (longitudinal and circumferential). Parameters have then to be "incremental," which means that they are determined within a narrow range of blood pressure (usually diastolic and systolic). It is not warranted that this mechanical behavior can be extrapolated to blood pressure (wall stress) beyond these boundaries, and it usually does not. Experiments have shown that systolic–diastolic variations of diameter and pressure do not follow the whole range, static pressure–diameter relation [59]. Thus usual models are purely phenomenological and do not help to predict behavior outside the experimental conditions. It is possible to partially circumvent these theoretical problems by applying advanced techniques to solve the energy equation of the wall by the reverse problem solving using diameter and pressure data [3]. This has been successfully used in animal and human [4, 60] research. This approach is still highly demanding in terms of calculation power and cannot be applied in routine. The other caveat is that measuring simultaneously pressure and diameter for the carotid artery in human can be done only on right and left or in immediate succession [54]. The last one is that expression of results is very cumbersome and complex, which does not help.

In order to circumvent the limits of applanation tonometry, an interesting approach is to rescale the distension waveform obtained by echotracking since this is a noncontact, high-fidelity technique [61]. By using and extending this method, it is possible to assess arterial stiffness at different time points either in diastole or during systole [62]. The advantage over modeling the whole pressure/diameter curve is that we deal with discrete number of values instead of a continuum. It has also been shown that systolic stiffness might be more associated with target organ damage than diastolic stiffness [62]. Another application of echotracking is local measurement of local pulse wave velocity. For this we take advantage of the measurement of 14 distension waveforms on 2 cm along the vessel. Using adequate landmarks (the dicrotic notch), PWV can be measured and contrasted with the

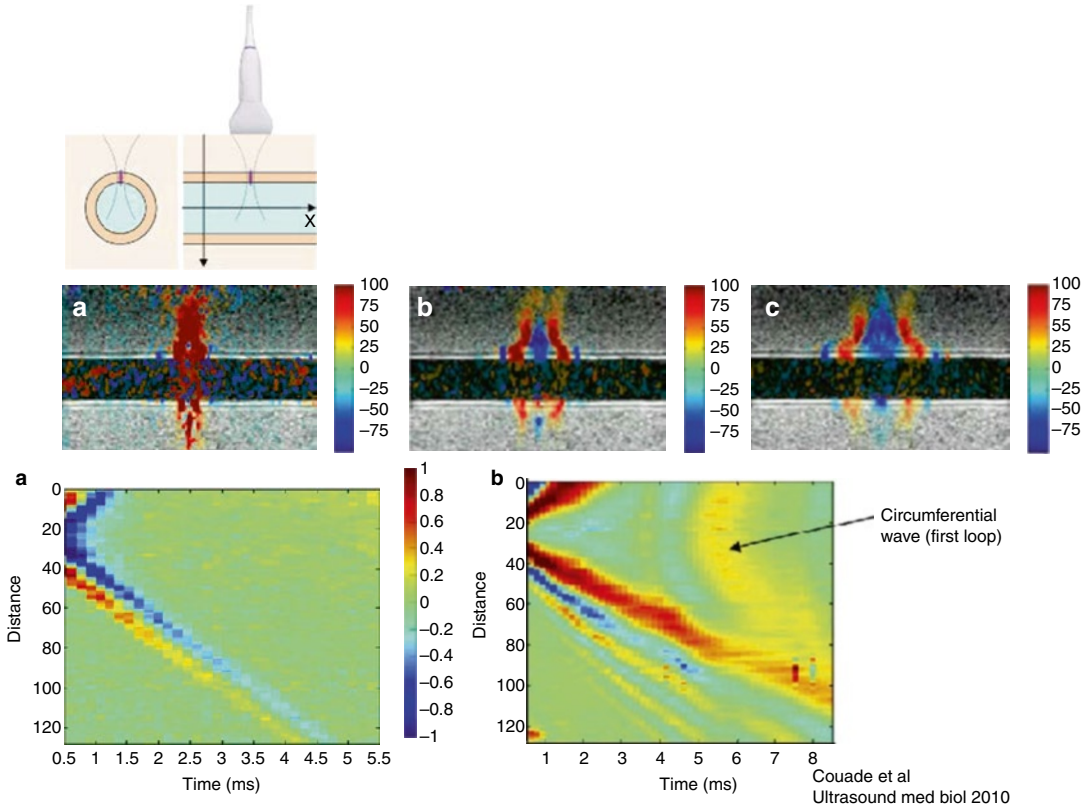

Fig. 5.6 Principles of ultrafast ultrasound scans. Scans are performed on artificial tissues. *Middle panels*: shear wave propagating from the center of the image. *Bottom panels* wave propagation. The slope of each waveform gives the wave speed, i.e., the stiffness of the wall material in a homogenous material (**a**) or in an heterogeneous one (**b**) (Reproduced with permission of Couade et al. [10], Elsevier)

locally measured distensibility from local pressure and distension [11]. To what extent this technique performs better or is complementary to more classical one remains to be determined.

The ultrafast imaging technique is an innovative ultrasound imaging technique. It takes advantage of the very high pulse rate frequency for acquiring plane emission waves [63]. Frequencies up to 20 kHz can be used. At that frequency, it is possible to measure accurately the speed of propagation of spontaneous waves such as the pressure wave. Moreover, it is possible to locally apply short ultrasound impulsion at a very precise place in a tissue and to measure the propagation speed of this pressure wave (Fig. 5.6). By using the Moens–Korteweg equation, propagation speed can be converted into elastic modulus. This method has been applied to the detection of cancer in solid organs and more recently to the heart and the arteries [10]. Because of the complex pattern of pressure wave propagation within laminar structure, there are still some theoretical issues to solve for extracting pressure independent values of elastic modulus. The quality of images obtained from plane wave emission is low, and coupling with echotracking might be necessary for obtaining full potential for this method.

Indirect Estimation of Arterial Stiffness

These techniques rely on simplified circulation models and are being used when a single site for measuring the pressure waveform is required. The most widely used is the Windkessel model [64].

In a "pure" Windkessel, the diastolic blood-pressure decay is exponential, and the constant of this exponential modeling is 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) [65, 66]. To date, only one published study epidemiologically validated this technique in terms of hard clinical endpoints [66], only for small-artery compliance. Sophisticated Windkessel models have been applied to derive PWV from single-point cuff measurements. Although the method takes more than a simple Windkessel [67], the prediction of PWV from a simple brachial cuff waveform seems to provide accurate estimates [68]. Some methods are based on the time flight of the reflected wave. The arteriograph takes advantage of the sharpening of the late systolic peak observed after overinflation of the brachial cuff, which makes it sharper and easier to detect [69–71]. After some assumptions on the pulse wave travel path and distance estimation [72], it is possible to deduce a value for PWV. This method appears to correlate reasonably well with reference techniques [73]. These methods have still to demonstrate their predictive value for hard clinical outcome.

Another indirect technique, aortic characteristic impedance, requires flow and pressure measurement at the aortic root [64, 74, 75]. Characteristic impedance is the minimal impedance for higher frequencies of pressure and flow harmonics. It is proportional to PWV, again if a pure Windkessel model is retained. This technique is rarely used alone, as it is hampered by the difficulty of obtaining reliable noninvasive data for aortic flow and pressure.

Ambulatory Arterial Stiffness Index

On the list are also rigidity estimates derived from blood-pressure measurement, e.g., ambulatory blood-pressure-monitoring-derived ambulatory arterial stiffness index (1/slope of the systolic blood pressure and diastolic blood pressure relationship) or crude brachial pulse pressure [76]. Although these values partially reflect arterial stiffness, they also depend on many other parameters [77], so it is very reductive to interpret them as arterial stiffness. The simple metric of this parameter makes it also difficult to interpret, because it might be confounded by short term variability of blood pressure [78, 79].

Conclusion

There are many techniques to measure arterial stiffness available now. The most validated in terms of association with cardiovascular risk factors, early organ damage, and hard clinical endpoints is carotid-to-femoral pulse wave velocity, measured from tonometry or Doppler. Because they came later than the carotid-to-femoral PWV, for which a tremendous amount of data is available in terms of association with target organ damage and hard clinical endpoints, the alternative techniques will have undergo similar validations and further will have to be scaled against reference techniques, so that thresholds and reference values might be shared. Techniques measuring directly arterial stiffness through the pressure–diameter relationship, although being the most direct, do not have extensive validation in terms of epidemiology; they are limited by measurement of local blood pressure. Learned societies will have to provide clear indications as to which level of agreement is necessary to substitute one technique by another one and finally which alternative technique can be accepted.

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