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Arterial wall elasticity: State of the art and future prospects

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Abstract Peripheral vascular disease is a frequently occurring disease and is most often caused by atherosclerosis and more rarely by anomalies of the collagen or other components of the arterial wall. Arterial stiffness problems form one of the precursor phenomena of peripheral vascular disease, and in the case of atherosclerosis represents an independent risk marker for the occurrence of cardiovascular disease. The first techniques, developed to evaluate arterial stiffness, use indirect measurements such as pulse wave velocity or the analysis of variations in pressure and volume to estimate arterial wall stiffness. Techniques based on the pulse wave lack precision because they assume that arterial stiffness is uniform throughout the path of the pulse wave, and that it is constant throughout the cardiac cycle. Moreover, measuring the velocity of the pulse wave may be less precise in certain pathological situations: metabolic syndrome, obesity, large chest, mega-dolico artery. Techniques based on the analysis of variations in pressure and volume do not accurately measure blood pressure, which can only be taken externally. In addition, these techniques require dedicated equipment, which is not reimbursed by the French health care system, and which is cumbersome to use (especially for techniques based on variation in pressure) in clinical practice. This explains why these two techniques are not used in clinical practice. Ultrafast echography is a new ultrasound imaging method that can record up to 10,000 images per second. This high temporal resolution makes it possible to measure the velocity of the local pulse wave and arterial wall stiffness thanks to the remote palpation carried out by shear wave. The ease of use and the accuracy of these two techniques suggest that these diagnostic applications will play a significant role in vascular pathology in the future. It is possible in real time, using a traditional vascular ultrasound probe, to make an accurate assessment of local arterial stiffness and of its variation during the cardiac cycle. This technological breakthrough will probably improve phenotype evaluation of patients suffering from vascular diseases, to more effectively evaluate the cardiovascular risk for patients, at primary and secondary prevention level, and to carry out broad epidemiological studies on cardiovascular risks.

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Atherosclerosis and non-atherosclerotic peripheral vascular pathologies occur frequently. The first category is often difficult to detect at early stage of development; while it is difficult to come up with a specific diagnosis for the second category. Arterial stiffness modifications constitute one of the precursor phenomena for peripheral vascular disease and represent in the case of atherosclerosis an independent risk marker for the occurrence of cardiovascular disease [1].

Arterial stiffness is more often performed approximately, either by measuring pulse wave velocity (PWV) [2—4], or by analysing local variations in local pressure and volume [5—7]. PWV is directly linked to Young’s modulus, and therefore to the arterial wall elasticity.

To date, the reference techniques for assessing arterial wall stiffness are respectively methods that either measure global PWV, like the Compilor® (Alam Medical, Vincennes, France) or the SphygmoCor (ArtCor Medical, West Ryde, Australia) [3], or measure the variations in the diameter of the arteries and arterial pressure and produces a local measurement of arterial stiffness, called, echo-tracking, which is carried out using the echography system Artlab® (Esaote, Italy) [5,6]. Two novel techniques are currently being evaluated: ultrafast ultrasound imaging or UltraFastEcho (or UltraFast® Imaging) which measures the PWV locally at the beginning and the end of systole [8], and shear wave elastography that measures changes in elasticity of the wall during the cardiac cycle [9,10]. These latter two techniques are currently being validated for various cardiovascular pathologies and are available on the Aixplorer® echography system (SuperSonic Imagine, Aix-en-Provence, France).

**Pulse wave and arterial stiffness**

The opening up of the aortic valve, when the heart contracts, creates a pressure wave that travels along the arteries and propels the blood through them: this is the pulse wave [4]. As the pulse wave passes through the artery it causes the arterial wall to dilate (Fig. 1), a sign of significant fluid-structure interaction.

The velocity with which the pulse wave passes through the artery may be estimated by accurately measuring both the propagation times between various points of the arterial network and the propagation distance. The temporal resolution with which the pulse wave is captured as it travels along the artery is very important because this wave travels at a speed, which ranges from several metres per second to tens of metres per second (depending on age, gender, pathology etc.), therefore, temporal resolution must be to in the order of milliseconds. The velocity at which the pulse wave passes down the artery is directly linked to the thickness, radius and elasticity of the artery along which it is traveling. If we assume that the artery is an elastic, linear and isotropic tube and that mechanical disturbances are low, we can show that the propagation speed of a pressure wave, c, in this tube, is shown by the following formula:

$$c = \sqrt{\frac{Eh}{Z\rho R}}$$

where $R$ is the radius of the tube, $h$ is the thickness, $\rho$ the density and $E$ its Young’s modulus. The Moens and Korteweg formula shows that the pulse wave speed is an indicator of arterial wall stiffness since it is directly related to the Young’s modulus. It is, moreover, used clinically as such. The Moens and Korteweg formula also shows the relationship between the pulse wave speed and the arterial wall diameter and thickness.

**Measurement of the global pulse wave velocity**

The carotid-femoral PWV is generally accepted as the standard for the measurement of aortic stiffness [11,12]. It is a stiffness measurement based on a widely accepted “propagation model” of the arterial tree. The result is an average speed between the carotid artery and the femoral artery, and represents the aortic stiffness and therefore the afterload the left ventricle must withstand during systolic ejection. This pressure then applies directly to the targeted organs (heart, kidneys, brain). It is aortic stiffness that is responsible for the majority of physiopathological phenomena that end up causing cardiovascular complications. This is the reason why carotid-femoral PWV alone has been accepted as the independent value for predicting cardiovascular events. The PWV is usually measured from the recording of the arterial pressure wave “foot”, of Doppler flow, or the distension wave (Fig. 2). The propagation time of the wave is measured and related to the distance, which is usually measured between the sites with a ruler.

Some investigators recommend measuring the distance between the carotid and femoral sites; others advise measuring between the suprasternal notch and the femoral site. The latest recommendations of the European Society of Hypertension (ESH 2007) and more recent recommendations relating specifically to PWV, identifying PWV and an evaluation of arterial wall stiffness as the most significant parameters to establish a cardiovascular prognosis [11,13]. They identified a value of $12 \text{ m/s}$ as the high-risk cutoff. This value is based on the direct carotid-femoral distance measurement. The applicability of this technique is close to 100% while its short-term reproducibility is around ±0.5 m/s [1]. This technique does, however, have several limitations:

- first of all, its little use rate in clinical practice, to a large extent because of the need to purchase a dedicated device and to place sensors on the carotid and femoral arteries of the patient;

Figure 1. Diagram of the propagation of the pulse wave: direction of blood flows and movements of the arterial wall.
Evaluation of local arterial stiffness using echo-tracking

Echo-tracking was, until recently, the only tool available for evaluating the local Young’s modulus, the relationship between intima-media thickness, viscoelastic properties, and the influence of external or internal remodeling on arterial distensibility [5–7]. This technique relies on the direct, local calculation of arterial wall stiffness derived from variations in pressure and volume calculated locally, and overcomes the issue of the circulation model hypothesis. The parameters of local mechanical properties of the vessel walls with echo-tracking are obtained performing the following measurements:

- the diastolic diameter, \( D \), of the artery, to calculate the surface area of the lumen, \( A \);
- the variation in diameter over time (to calculate the systolic/diastolic variation in the section of the lumen, \( \Delta A \));
- the thickness of the wall, \( h \);
- the variation in pressure, \( \Delta P \).

The properties of the vessel wall such as distensibility (DC), compliance (CC), and the Young’s modulus (Y), can then be derived using the following equations [7]:

\[
A = \pi (D/2)^2
\]

where \( \Delta A \) is the change in the transverse section of the vessel between diastole and systole, and \( \Delta P \) is the change associated with local blood pressure. It is assumed that DC and CC are constant throughout the entire range of pulsatile arterial pressure values and that the length of the arterial segment remains constant. A fundamental limitation with local evaluation of vessel wall properties is assessing local intra-arterial blood pressure variations (\( \Delta P \)). The substitution of arterial pressure, taken in the brachial artery is only an approximation, because arterial pressure varies from one site to another. It has been shown, however, that brachial arterial pressure is a good substitute for carotid arterial pressure [14].

In practice, traditional ultrasound scans could evaluate the diameter of the vessel and its systolic/diastolic variation, but in most cases, its spatial resolution is insufficient. The spatial and temporal resolutions required to calculate the variation in arterial diameter come to around a few micrometres and a few milliseconds respectively, while the spatial and temporal resolutions offered by conventional ultrasound diagnostic imaging systems offers a spatial resolution of around a hundred microns (corresponding to the size of a pixel of a video image) and a temporal resolution of few tens of milliseconds (corresponding to maximum image rates of 100 Hz). In recent years, the echo-tracking technique has been developed to carry out high-resolution
ultrasound imaging both spatially and temporally [7,15]. This technique uses a radiofrequency signal that is the result of transforming an acoustic signal into an electric signal by way of the piezoelectric crystals of the probe. It increases spatial resolution from 6 to 10-fold and temporal resolution by a factor of 10 compared to conventional echography. The resolution of the latter is limited temporally and spatially by the processing speed of the acoustic signals that generate the pixels of the video image. This technique can also be used to accurately measure intima-media thickness. By obtaining the pressure volume curve of the scanned artery, arterial stiffness can be calculated for a given arterial pressure value. Using the time lapse between two arterial dilations caused by the pressure wave, it is also possible to obtain the local pulse wave velocity [15].

Echo-tracking can be used to measure many parameters locally connected with arterial wall stiffness, but this technique also has a number of disadvantages which limit its use in routine clinical practice:

- echo-tracking acquisition takes much longer than PWV measurement, such that it is only indicated for mechanical analyses of rare vascular diseases, in pharmacology and for therapy, but it is not used for epidemiological studies, and even less in clinical practice;
- to calculate most of the parameters derived from this acquisition, it is necessary to assess the local pressure, which is most frequently obtained using an aplanation tonometer, which in turn requires the use of a transfer function [16]. This indirect measurement of intra-arterial pressure constitutes one of the major limitations of the use of this technique in clinical practice, because it does not provide a sufficient level of precision;
- this approach does not reflect fine parietal elasticity anomalies of the arterial wall [17].

The evaluation of local arterial wall stiffness is most often performed using superficial arteries such as the carotid. The stiffness of the carotid is useful because this is where atherosclerosis is often located.

Some teams work on the evaluation of local stiffness of deep arteries such as the aorta, using dedicated MRI sequences [18]. However, the compromise required for this method between spatial and temporal resolution is too high. Using MRI for such a simple measurement may seem to be disproportionate compared with a dedicated device (tonometry). Most clinical and pharmacological studies use the ultrasound echo-tracking technique.

Evaluation of local arterial stiffness using ultrafast imaging

A new imaging technique using ultrasound, called UltraFastEcho or UltraFast Imaging [8], has recently been developed. It was initially developed for the analysis of shear wave propagation in elastography imaging for breast cancer and thyroid exploration but is today evaluated as a new diagnostic tool for vascular pathologies. This technique was developed by a French research laboratory, the Institut Langevin (ESPCI, Paris) [8]. Its main innovation is extremely imaging frame rate, which is one hundred times faster than for conventional ultrasound diagnostic imaging devices currently available (the frame rate can reach 10,000 images/s, i.e 10 kHz). This technological breakthrough is based on sending a single plane wave in emission (as opposed to 128 focused lines with conventional echography systems) and focusing on reception only. The received signals are then processed by an acoustic signal-processing device that is extremely powerful, enabling the image to be reconstructed very rapidly (Fig. 3). The speed of acquisition of this system means that it can capture the propagation of the pulse wave (a few m/s to dozens of m/s). Standard echography system image frame rates are at the most in a few hundred Hertz, so

![Image acquisition methods: left: traditional method with focusing at emission reception, requiring 128 shots; right, transmission of a single plane wave, in emission, with focusing at reception only. The image rate corresponds to the pulse repetition frequency (PRF) of the device.](image-url)
it impossible for these devices to capture the propagation of this wave. Once the pulse wave propagation has been captured, the PWV of a localised segment of the arterial wall is calculated at the beginning and end of systole, to identify local stiffness problems of the arterial wall (Fig. 4). The measurement of the local PWV with ultrafast imaging consists of the following stages:

- the clinician optimises the image, in B-mode, of the artery for which the PWV is to be measured. The measurement is taken along the main axis of the artery to be studied (a good view of the intima-media generally indicates that the optimum image quality has been reached);
- once the image has been optimised, the acquisition procedure of the ultrafast imaging device is activated and the system is frozen for a few seconds;
- the system automatically detects the proximal and distal walls of the artery in the region of interest, completes a tissue Doppler analysis of the vessel walls (which shows the propagation of the pulse wave) and deduces from that the propagation velocities of the pulse waves at the beginning of systole (opening of the aortic valve) and at the end of systole (closure of the aortic valve), estimating the speed gradients in the spatial-temporal mode of the tissue Doppler image, then these gradients are displayed on the image. The gradients are also displayed in the spatial-temporal mode of the tissue Doppler function;
- the PWV values at the beginning and end of systole are derived from the gradients and displayed.

A pilot study to evaluate this technique has been carried out by our team. The results of this study are presented at the end of the next section.

Evaluation of local arterial stiffness using shear waves

The second innovative technique currently being evaluated is used to carry out a remote palpation of the arterial wall using another wave called a ‘shear wave’ [9]. The principle of this technique is applied in a well-known field, namely that of shear wave elastography (see chapter on the principles of elastography). This technique entails sending an ultrasonic shear wave into the tissue to be studied, and calculating the propagation velocity of the wave which is directly correlated with the stiffness of the tissue, as represented by the Young's modulus (Fig. 5). This technology, called Shear Wave Elastography, is embedded in the ultrasound device, Aixplorer® (SuperSonic Imagine, Aix-en-Provence, France). The velocity of the shear wave created is directly linked to the elasticity of the arterial wall and does not depend, like the pulse wave velocity, on other parameters such as blood density and intra-arterial pressure.

However, in the shear wave elastography mode implemented for clinical applications such as breast, liver elastography etc., the elasticity map is obtained assuming that the medium is elastically homogeneous, non-viscous and infinite in space. These hypothesis are, however, not valid in the artery (not elastically homogenous and not infinite). Indeed, arteries can be compared geometrically with cylinders that have elastic properties different from the tissue surrounding them. For this geometric and elastic configuration, Couade et al. developed a model for the propagation of shear waves generated by acoustic radiation force [10]. They also demonstrated that the shear wave spreads in a dispersive fashion (depending on the

Figure 4. Example of a Pulse Wave Velocity (PWV) measurement at the beginning of systole (BS) and the end of systole (ES) with display of the standard deviation for each measurement in a healthy subject. Ultrafast imaging acquisition is carried out after optimising the view in B-mode of the artery being studied using an ultrasound system (Aixplorer®, SuperSonic Imagine®). The system is then frozen during acquisition. Once acquisition is complete, the system detects the proximal and distal walls of the artery, completes a tissue Doppler analysis of the vessel walls and deduces from that the propagation velocities of the pulse waves at the beginning of systole, ES (opening of the aortic valve) and at the end of systole, LS (closure of the aortic valve), while calculating the speed gradients on the spatial-temporal Doppler feature displayed under the image. The gradients are also displayed on the spatial-temporal mode of the tissue Doppler function.
frequency), and they established the dispersion relation, making it possible to analytically express the phase velocity according to frequency, \( f \), wall thickness, \( h \) and group velocity of the shear waves, \( c_T \):

\[
\nu(f) = \sqrt{\frac{2fhc_T}{2\sqrt{3}}}
\]

The dispersion curves of the velocity depending on frequency are measured by means of ultrafast imaging, and then used to obtain the shear modulus of the arterial wall by superimposing them on the theoretical propagation curves by calculating the value \( c_T \) minimising the error between the two curves.

This technique can be used to calculate the local elasticity of the arterial wall, without using the pulse wave.

The information obtained using ultrafast imaging combined with the acoustic radiation force or "push mode" provides the viscoelastic properties of the arterial wall, taking into account the non-linearity (stiffness that varies throughout the cardiac cycle as the pulse wave progresses) and the anisotropy of arterial stiffness (stiffness that varies according to the relative position in space) (Fig. 6). So, the high temporal resolution of this technology makes it possible to evaluate PWV in systole and in diastole, and to evaluate via the push mode over ten stiffness values during a cardiac cycle.

**Figure 5.** Principle of virtual palpation or “push mode” of Ultrafast echo.

**Figure 6.** Principle of Ultrafast echo-elastography.
cycle (Fig. 7). This provides stiffness parameters, which had been unknown until now (variation rate of arterial stiffness during the cardiac cycle).

In addition, arterial stiffness, calculated using PWV and the geometric parameters of the arterial wall, corresponds to circumferential stiffness, while that calculated using shear wave velocity corresponds to longitudinal arterial wall stiffness. This means that it is possible to obtain an accurate topographical description both in space and time of the arterial stiffness of the segment being studied, thereby providing a fine characterisation of the viscoelastic properties of the arterial wall.

Our team (vascular medicine at HEGP and PARCC, Inserm U633), working with the Institut Langevin, carried out a clinical study promoted by the Société Française de Cardiologie [French Cardiology Society], supported by the Agence Nationale de Recherche [French National Research Centre] (Ultrafastecho, clinical trials gouv; NCT01096264; PI: E. Messas). Thanks to this study, we have been able to evaluate the technique for measuring local PWV with ultrafast imaging, and the virtual palpation technique with shear waves, on healthy volunteers (n = 30). The aim of this pilot study was to determine the local PWV values, and the local values of the shear modulus of the carotid, by age and by gender, in healthy subjects.

Elasticity values (PWV at the beginning of systole and the end of systole and the minimum and maximum of the shear modulus, \( \mu_{\text{min}} \) and \( \mu_{\text{max}} \)), recorded in healthy subjects, are relatively uniform. Table 1 summarizes the measurements averages taken on 30 volunteers on the left common carotid artery.

An analysis of stiffness according to age was also carried out and showed that ageing of the arteries leads to an increase in arterial stiffness. Of the 30 healthy subjects studied, the estimated pulse wave velocity and the measured shear modulus increase with the age of the volunteers (1st group: average age 28 years (21–36 years); 2nd group: average age 46 years (42–53 years); 3rd group: average age 62 years (55–68 years)). The average values and the standard deviations of the pulse wave velocity and of the shear modulus estimated using elastography are shown for each population in the following figure (Fig. 8).

An analysis of the elasticity of the arterial wall, according to pressure, was also carried out. Fig. 9 shows that there is a strong dependency between elasticity and the pressure values recorded in diastole and in systole. The pressure values

Figure 7. Fifteen measurements in vivo of variations in elasticity of the arterial wall during a cardiac cycle (15 cycle measurements) with ECG recording: top: 15 successive acquisitions of the spatial-temporal field of particle speed in the arterial wall caused by the pulse wave and the shear wave generated by radiation pressure; middle: previous speed field from which are subtracted movements due to the pulse wave (shear wave alone); bottom: shear modulus of the wall (in red) estimated for each acquisition and synchronised ECG (in blue).

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<th>Table 1</th>
<th>Summary table of the results of the clinical study on 30 volunteers from the clinical study.</th>
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<td>PWV (m/s) beginning of systole</td>
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<tr>
<td>Average population</td>
<td>5.7</td>
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<tr>
<td>Average standard deviation</td>
<td>0.6</td>
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<td>Population variance</td>
<td>1.2</td>
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PWV: Pulse Wave Velocity.
they assume that arterial stiffness is uniform throughout the path of the pulse wave, and that it is constant throughout the cardiac cycle. Techniques based on the analysis of variations in pressure and in volume do not allow for inter-arterial pressure, an indirect measure, to be estimated accurately, since this value can only be performed externally. In addition, these techniques require dedicated equipments, which are not reimbursed by the French health system, and which are cumbersome to use (especially for techniques based on variation in pressure). These different reasons explain why these two techniques are used very little in clinical practice, and only for epidemiological studies on cardiovascular risk.

Ultrasound echography is a new ultrasound imaging technique that can record up to 10,000 images per second. This high temporal resolution makes it possible to measure the velocity of the local pulse wave and arterial stiffness thanks to the virtual palpatiation carried out by shear waves.

The ease of use and the accuracy of these two techniques suggest that these diagnostic applications will play a significant role in vascular pathology in the future. It is possible in real time, using a traditional vascular ultrasound probe and a diagnostic ultrasound imaging device, to perform an accurate assessment of local arterial stiffness and of its variation during the cardiac cycle.

This technological leap will probably make it possible to improve the phenotype evaluation of patients suffering from vascular disease, to more effectively evaluate the cardiovascular risk of patients for primary and secondary prevention, and to carry out broad epidemiological studies on cardiovascular risk. The guiding principle for this research will be to use the temporal, spatial and local precision of these new techniques, in order to gain information about the non-linearity and the anisotropy of local arterial stiffness, to more effectively determine the vascular phenotype of patients suffering from rare vascular diseases, and to better evaluate the local and global prognosis of patients with high cardiovascular risk.

Conclusion

The first techniques, developed to evaluate arterial stiffness, use indirect measurements such as pulse wave velocity or the analysis of variations in intra-arterial pressure and volume to estimate arterial stiffness. Techniques based on global pulse wave measurements lack precisions because of the shear modulus measured were traced for systole and diastole for all volunteers. For diastolic pressures, elasticity increases relatively weakly as pressure increases, while for systolic pressures, elasticity increases significantly as pressure goes up, which means that there is strong non-linearity between arterial wall stiffness and an increase in pressure.

Figure 8. Average shear modulus and average pulse wave velocity for each age group. The shear modulus is evaluated in diastole. The pulse wave velocity is evaluated on the peak of the end of systole.

Figure 9. Diastolic (in blue) and systolic (in red) shear modulus according to diastolic and systolic pressure (respectively) on a sub-population of 30 healthy subjects.
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References