New techniques for assessing arterial stiffness

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Abstract

Arterial stiffness is now included in the guidelines of the European Society of Hypertension. In this paper, we review the evidence for the predictive value of arterial stiffness. More than 11 longitudinal trials have proven the predictive value of aortic stiffness measured through carotid to femoral pulse wave velocity, beyond and above classical risk factors. Such evidence is scarcer for central pressure and local arterial stiffness. If we add this evidence to the easiness of performing such measure, carotid to femoral pulse wave velocity is the reference technique for assessing arterial stiffness. Its place in the investigation of patients remains to be precisely determined.

Résumé

Nouvelles techniques de mesure de la rigidité artérielle

La rigidité artérielle est à présent incluse dans les recommandations de l’European Society of Hypertension. Dans cet article, nous passons en revue les preuves de la valeur prédictive de la rigidité artérielle. Plus de 11 études longitudinales ont apporté la preuve de la valeur prédictive de la rigidité aortique par la mesure de la vitesse de l’onde de pouls carotido-fémorale, à côté et au-delà des facteurs de risque cardiovasculaires classiques. De telles preuves sont plus rares pour la pression centrale et la rigidité artérielle locale. Si nous ajoutons à ces preuves la facilité à réaliser une telle mesure, la vitesse de l’onde de pouls carotido-fémorale est la méthode de référence pour mesurer la rigidité artérielle. Sa place dans l’exploration des patients reste à préciser.

Keywords: Artery stiffness; Aorta; Cardiovascular risk; Epidemiology; Mortality; Central pressure

Mots clés : Rigidité artérielle ; Aorte ; Risque cardiovasculaire ; Épidémiologie ; Mortalité ; Pression centrale.

Measurement of arterial stiffness is increasingly popular for assessing target organ damage and cardiovascular risk. In the present paper, we will review the different techniques available and their relative interest.

1. Measurement of aortic pulse wave velocity

We published recently a expert consensus document on arterial stiffness [1]. In this document, over 11 longitudinal studies were listed demonstrating that a simple measure of aortic stiffness through carotid-femoral pulse wave velocity (CF-PWV) (Fig. 1) yielded prognostic values beyond and above traditional risk factors. Other arterial measurements can be used as surrogates for arterial stiffness. Among them, central pulse pressure is interesting since it may be a better estimate of the true pressure acting on target organ damage [2]. The difference between central and peripheral blood pressure is related to arterial stiffness and pressure wave reflection. It may be interesting to substitute...
central blood pressure to peripheral blood pressure, since it has been demonstrated that drugs may have a differential effect on central blood pressure, but not on peripheral [3]. Here again, the level of evidence for the predictive value is lower than for aortic stiffness.

The added value of CF-PWV above and beyond traditional risk factors was demonstrated by two separate studies. The first was performed in 1045 hypertensive patients, with longitudinal follow-up of 5.9 years for CV events (fatal or non-fatal) [4]. The increase in coronary heart disease with tertiles of CF-PWV was steeper for patients belonging to the first and second tertiles of Framingham risk score (FRS). The area under the receiver-operating characteristic curve (AUC) of CF-PWV decreased from the lowest to the highest tertile of FRS (area under the receiver-operating characteristic curve: from 0.65±0.07 to 0.53±0.04; P=0.01). In the group of low to medium risk patients, FRS and CF-PWV had similar predictive value (AUC = 0.65±0.07 and 0.63±0.08, respectively), and when combined, the predictive increased since the area under the receiver operating curve rose to 0.76±0.09 (unpublished data).

More recently, Mattace-Raso et al. published the predictive value of aortic stiffness in the elderly from a general population [5]. In this study, aortic stiffness predicted CV outcome after adjustment on classical risk factors, intima media thickness, wave reflection and pulse pressure. The AUC of the fully adjusted model (including all classical CV risk factors and intima media thickness was 0.70. Including PWIV induced a further significant increase in AUC of 2%, p<0.01. Interestingly enough, for all published studies about the predictive value of aortic stiffness, patients were subsequently treated for their treatable risk factors. This means that the predictive value of arterial stiffness is independent of common CV drug therapy. This may also explain why once detected and treated, classical risk factors cease to be strong risk factors for further events.

Albeit not new, the techniques have now reached a development allowing easy, reproducible measure by either doctors, nurses or technicians. The device in use may offer simultaneous (Complior, Artech medical, Pantin, France) (Fig. 1), or successive measure (Sphygmocor, Atcor, Sydney, Australia) after synchronization on ECG. Both techniques offer the same quality of measure, however, only the Complior can be used if the patient has arrhythmia.

2. Measurement of central pressure

From these results, it can be said that aortic stiffness is a strong independent predictor of CV outcome, providing a level of information equal to classical CV risk factors, and whose value is additive to it. Measurement of central pressure is an important advance in the assessment of large artery properties. Central pressure differs markedly from peripheral blood pressure (i.e. the one measured at the site of brachial artery), mostly because of wave reflection. Indeed, when blood is ejected by the left ventricle, the pressure wave is propagating toward the periphery at a finite speed (the pulse wave velocity), and reflects on reflecting points to return toward the heart. Depending on the place of reflecting points and the pulse wave velocity, the reflected wave occurs at different time during the heart cycle. When BP is measured at the periphery of the vasculature, the reflecting sites are closer to the point of measurement of BP, and thus reflection occurs soon after the rise in BP and adds to it. This is the case for the brachial artery. For sites close to the heart, the pressure wave has to travel to and from the reflecting sites and this takes time. If pulse wave velocity and the heart period are slow, the reflected wave has a chance to reach the heart after the termination of ejection. In this case, the reflected wave does not add with the ejection wave, and blood pressure is not further increased. With aging and high blood pressure, the pulse wave velocity is faster, and the reflected wave comes earlier within the ejection, and adds to the ejection pressure wave, causing amplification (Fig. 2). These phenomenon explain why brachial systolic (and pulse) pressure are larger than central systolic and pulse pressure, and why this amplification of SBP and PP along the arterial tree is decreased with aging and high blood pressure.

Central blood pressure is important in many ways. This is the blood pressure seen by the left ventricle, the kidneys and the brain. To that extent, this is the only blood pressure value which should be considered for target organ damage. Second, reflection patterns directly influence LV work and perfusion. Last, when studying local arterial stiffness, local blood pressure is mandatory to derive correct stiffness values, and for central large arteries such as the aorta and common carotid artery, it has to be measured locally.
3. Methods to measure central blood pressure and wave reflection

3.1. Invasive methods

The most direct way to measure central blood pressure is invasive during left catheterization. Blood pressure could be measured either from fluid filled catheter (albeit with reduced frequency response) or from microtip catheter. The pioneering works of O’Rourke, Kelly, Belthram, Yin etc. were done using this technology [6,7]. This is still applicable for clinical research in cath labs, where a simple additional pressure measurement can yield strong prognostic value. If central BP measurements are to be performed during catheterization, some cautions have to be taken to remove air bubbles from the fluid filled systems, and to avoid excessive motion of the catheter tip, because dynamic overshoot of the pressure (because of blood flow or impact of the catheter on aortic walls) may occur. Because of their cost, microtip catheters are not used in routine. Pulse wave analysis is performed in a identical way as described later in this chapter.

3.2. Non invasive assessment

All techniques are derived from applanation tonometry [8]. Just to set it easy first, applanation tonometry takes advantage of a well established theorem saying that when a segment of a pipe is flattened, the transmural pressure is equal to the endovascular pressure. This technique was first used for ophthalmology, to derive not invasively intraocular pressure. Applied to arteries, it necessitates to apply a pressure sensor through the skin and applanate a superficial artery by applying a downward pressure sufficient to flatten the artery (not too large, because otherwise the blood pressure regimen is too disturbed), and to have a “hard” floor against which to perform applanation. This can be easy for the radial and the femoral artery (the radius and pelvis bones allow applanation). This is more difficult for the brachial artery, because of the interposition of tendons and for the carotid artery because of the interposition of muscles and the presence of body fat behind the artery, but measures are still feasible. Carotid artery pressure is the best direct estimate of central pressure. However, some amplification occurs between carotid and the aorta, which may need further mathematics.

If the pressure sensor is correctly calibrated, the pressure recorded through the applanation tonometry is equal to the pressure inside the vessel, at a constant. Indeed, the mean value of applanation pressure is determined by the pressure applied by the hand of the investigator. This has to be corrected by rescaling the applanation pressure around the mean pressure of the subject, which is constant in the large arteries (Fig. 2).

Although this technique was validated and used by some investigators [9,10], it was criticized because of its operator dependency. It was proposed more recently to rescale central pressure using diastolic blood pressure in addition to mean blood pressure. Pauca showed that the mean to diastolic difference was rather constant throughout the body [11]. Therefore, using a simple correction, this mean-diastolic pressure could be used as scaling factor. For doing so, it is simply needed to have reliable measures of brachial mean and DBP [12]. This brings us to the tricky problem of MBP assessment. Most often, people use oscillatory methods to derive BP values. These validated device directly measure SBP and MBP, and derive DBP from on board, unpublished algorithms. Therefore, these values cannot be taken as granted.

Recently, Van Bortel and coworkers showed that the most correct way to measure central blood pressure is first to measure as accurately as possible SBP and DBP at the brachial artery level, then to perform brachial artery applanation using SBP and DBP as scaling values [13]. Then, MBP is measured from the integration of the brachial pressure wave, and this MBP value will be used to calibrate carotid pressure, together with the DBP after carotid applanation is performed. Although this technique is at evidence the best, this is not always feasible. Therefore, most of the investigators do the same calibration procedure, but using the radial pressure instead of the brachial. In this case, some systematic error occurs, by not taking into account the brachial-radial amplification.

4. Estimation of aortic pressure

As we said before, carotid pressure is the best direct measurement of central pressure, although some amplification occurs between the aorta and the carotid. To overcome this problem, M O’Rourke and coworkers proposed to use a generalized transfer function to synthesize aortic pressure wave [14]. To put it simple, the transfer function is the key for translating a distorted signal into the original signal, by applying the inverse of the cross-correlation function of the
original signal to the distorted one. This is widely used in the industry, transmission, adaptive optics, Hi-Fi etc, when the factors of distortion are predictable. In the present case, O’Rourke et al measured simultaneously in 14 patients and subjects, both the radial pressure wave and the aortic pressure wave. They deduced the transfer function from the cross-correlation of the two waves. They showed that this transfer function was rather constant across a wide range of persons, both in body size, age, sex and BP values. Thus this “generalised transfer function” is proposed to assess aortic pressure from radial pressure. It is to be noted that the scaling from mean and diastolic is performed, also for this technique. The generalization of the transfer function has been challenged, but no reliable alternative exists up to now for non invasive aortic pressure measurements.

4.1. Wave reflection quantification

From carotid and aortic pressure waves, it is possible to measure the amplification index, an estimate of wave reflection. This index is the ratio between the amplitude of the reflected wave (determined between the shoulder and the maximum of the systolic arm of the pressure wave) and pulse pressure (Fig. 2).

5. Available devices

A recent consensus document, [15] makes a good synthesis on the validity of different devices. For the moment, the Sphygmocor device® (Artech medical, Sydney Australia) is the gold standard for central pressure measurement. It represents more than 100 entries in Medline, for 2 publications for its closest competitor. It has been used in very large population samples [16] together with large clinical trials [17]. (The Sphygmocor device takes advantage of the transfer function to calculate central pressure from radial pressure waves. Under certain circumstances, it allows the evaluation of endothelial function (pressure wave response to salbutamol [18]). By successively measuring carotid and femoral pulse waves, synchronized on the EKG R-wave, this device allows the measurement of pulse wave velocity, a measure of aortic stiffness [19].

6. Measurement of local arterial stiffness and intima media thickness

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 pathophysiological and pharmacological studies have used echo-tracking techniques (Fig. 3).
A major advantage 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. 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.

Echotracking devices were developed to measure diameter in end-diastole and stroke change in diameter with a very high precision, 6 to 10 time higher than with video-image systems. Now, the latter development of echotracking device (Artlab system, Esaote, Maastricht, NL) allow the measurement along a segment of artery (4 cm, 128 lines) with high definition measurement of diameter and intima-media thickness (precision 35µm and 17 µm, respectively) in real time, with hand held probe. Moreover, it is possible to measure distension at 14 different sites, with a resolution of 1.7 µm. This device allowed us to discover new behaviour of the arterial wall, with local heterogeneity in stiffness [20], and complex patterns of distension profile (bending stress) at the level of small plaques [21].

Local pressure is usually obtained by applanation tonometry of the vessel in question and calibration of the wave-form to brachial mean and diastolic pressures obtained by integration of the brachial or radial waveform [12], or automatic calculation using transfer function processing (Sphygmocor, AtCor, Sydney Australia) [22,12]. All the superficial arteries are suitable for the geometrical investigation, and particularly the common carotid, common femoral and brachial arteries. Various indices used to describe the elastic properties of blood vessels, non-invasively obtained with ultrasound measurements may be obtained, expressing the complexity of the mechanical behaviour of these organs (Fig. 3).

Carotid stiffness was predictive of CV events in a small number of patients with ESRD [23] or following renal transplantation [24], but had no independent predictive value in a larger number of patients with manifest arterial disease [25,26]. This may be due to methodological reasons: the use of local (carotid) PP in positive studies and brachial PP in negative studies. In addition, upper and lower limb territories, due to their particular pathophysiology may not reflect aortic, cerebral and coronary artery damage[27].

7. Conclusion

Arterial stiffness measurement is now part of assessment of hypertensive patients. It is likely that many other clinical conditions will require such measures to be performed. Given the variety of techniques available, it is mandatory to state which deserve recommendation or not. Now it is clear that carotid to femoral pulse wave velocity is the most validated technique, and should be used in preference to any other. Local stiffness is to be used in specialized labs, for clinical research, because it is too complex to use and interpret. Central pressure is a proxy for arterial stiffness. Although used in a large clinical trial, the CAFÉ study and in several outcome studies, it is difficult to see how central pressure may improve the classification of patients because of the dependence on peripheral blood pressure.

Now what is awaited is evidence of a better prevention of events when arterial stiffness is used in treatment decision. The only available evidence is the paper from Guerin in end stage renal disease patients, showing that arterial stiffness response to graded intervention is predictive of the outcome [28]. Such data need to be established in patients at lesser risk.

No potential conflict of interest revealant to this article was reported.

References

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