

Is arterial stiffness ready for daily clinical practice?

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Arterial stiffness is associated with major cardiovascular risk factors such as age [1], hypertension [2], smoking [3], hypercholesterolemia [4,5], diabetes types I [6] and II [7], insulin resistance [8] and hyperhomocysteinemia [9]. The majority of these data come from observational cross-sectional studies. Although these type of studies can only show an association between arterial stiffness and the cardiovascular risk factor, the cardiovascular risk factor is likely to raise arterial stiffness. However, the likelihood of a causal relation is not always so clear. In this issue of the journal, Mattace-Raso *et al.* [10] describe an association between orthostatic hypotension and arterial stiffness. The question is whether orthostatic hypotension may be due to arterial stiffness or whether the association is a result of a common disease that leads to increased arterial stiffness and to autonomic nervous dysfunction. Although large artery stiffness has been associated with decreased baroreceptor activity [11] and autonomic dysfunction [12], it is not clear whether this is due to the mechanical properties of the vascular wall, mediating the transfer of transmural pressure, or to afferent and/or efferent autonomic dysfunction.

Arterial stiffness is an independent predictor of cardiovascular events. This has been shown for aortic [2] and carotid stiffness [13] in essential hypertension and in end-stage renal disease. In addition, arterial stiffness adds predictive value on top of the Framingham cardiovascular risk score [14] and decreasing elevated arterial stiffness may improve life expectancy [15]. This demonstrates that arterial stiffness can identify those patients with higher cardiovascular risk and that these patients may benefit from treatment. Translation of cardiovascular risk factors into real cardiovascular risk is not easy to predict in a particular patient and can differently apply to different patients. Therefore, it is important to identify, at an early stage, those patients with a higher cardiovascular risk. These are patients with signs of target organ damage [16] such as micro-albuminuria, cardiac hypertrophy, increased carotid artery intima-media thickness and probably also increased arterial stiffness. Arterial stiffness

measurements should therefore be advocated as an intermediate endpoint and should be added to daily practice cardiovascular risk assessment.

Arterial stiffness can be measured as systemic, regional or local stiffness [17]. The predictive value of arterial stiffness has been shown from regional aortic pulse wave velocity [2] and from local carotid artery stiffness [13]. Currently, pulse wave velocity measurements are less time consuming and require less expensive devices than carotid artery stiffness measurements from echo-tracking devices. However, echo-tracking devices provide additional predictive information on intima-media thickness and the presence or absence of plaques [18].

Aortic pulse wave velocity is assessed from carotid-femoral pulse wave velocity using the time difference of pulse wave arrival at the carotid and the femoral artery, respectively. This pulse wave travel time can be measured accurately. To calculate pulse wave velocity, the travel distance has to be divided by the travel time. Assessment of the travel distance is much less accurate. Different methods have been used to assess the length of the aortic tract. The consensus conference on arterial stiffness had a preference for the subtraction of the distance between sternal notch and carotid artery from the distance between sternal notch and the groin [17]. Although no formal validation of the distance has been performed, using this advocated distance assessment, aortic pulse wave velocity appears to reflect very well the in-vitro pulse wave velocity (approximately 6 m/s in a population). A large belly or breast can interfere with these measurements. Another method of distance assessment, as used by Mattace-Raso *et al.* [10], makes use of the direct distance between carotid and femoral sites of measurement. This distance overestimates the real travel distance because the pulse wave travelling to the femoral artery has already passed the aortic arch at the time the same pulse wave arrives at the carotid artery. Using the direct carotid-femoral distance, pulse wave velocity is overestimated by approximately 2 m/s on average. The use of different methods to calculate length of aortic tract makes problematic any pooling of data for meta-analysis and defining reference values for use in daily practice.

Recently, new devices have been proposed to measure arterial stiffness based on pulse wave velocity. Some devices make use of measurements at upper and lower limbs and/or take height or seated height as the travel distance. They result in high pulse wave velocities (up to 20 m/s). It is not clear what these figures reflect because

pulse wave velocity is different in central elastic and peripheral muscular arteries. Because travel time to upper limbs is subtracted from travel time to lower limbs, travel time is tremendously underestimated, whereas travel distance is also very inaccurate. Another method makes use of the time from R-top in the electrocardiogram (ECG) to the arrival of the pulse wave at the brachial artery [19]. This method is confounded by electromechanical dissociation (i.e. the time between R-top in ECG and opening of the aortic valve). This electromechanical dissociation can be influenced by different factors, such as changes in sympathetic tone, and confounds the results of pulse wave velocity. In addition, aortic (carotid–femoral) but not brachial–radial (carotid–radial) pulse wave velocity is of predictive value for cardiovascular events [20].

Furthermore, local carotid artery stiffness is of predictive value for cardiovascular events. Investigators using local stiffness measurements should apply the correct formula and should also use local pulse pressure at the site of the measurement [17]:

$$\begin{aligned} \text{Distensibility coefficient (DC)} &= (\Delta A/A)/\Delta P \\ &= (2\Delta d \cdot d + \Delta d^2)/(\Delta P \cdot d^2) \\ \text{Compliance coefficient (CC)} &= (\Delta A/\Delta P) \\ &= \pi(2d \cdot \Delta d + \Delta d^2)/4\Delta P \end{aligned}$$

where A is the diastolic cross-sectional area of the artery, ΔA is the change in A , d is the diastolic diameter of the artery, Δd is the change in d and ΔP is the change, in pressure.

Other measures of arterial stiffness have been proposed such as pulse pressure and the augmentation index. Although both are influenced by arterial stiffness, they are also determined by cardiac function and timing of wave reflections. This makes them poor surrogates for arterial stiffness [21].

Major confounders of arterial stiffness are age, gender and blood pressure [1]. Arterial stiffness at the operating pressure should be corrected for the level of blood pressure to identify intrinsic arterial stiffness. Some authors correct for systolic blood pressure, others for diastolic blood pressure. For a given heart function, pulse pressure largely reflects large artery stiffness and mean arterial pressure reflects systemic resistance (microcirculation). Therefore, it is obvious that pulse pressure should not be corrected for because this factor is largely the consequence of arterial stiffness. Because systolic (largely) and diastolic blood pressure (to a smaller extent) also partly reflects pulse pressure, a better way to correct arterial stiffness for blood pressure is by correcting for mean arterial pressure.

In conclusion, there is a need for a further standardization of methods and for a closer adherence to the recommen-

dations of the consensus conference on arterial stiffness. This should make clinical studies more suitable for meta-analysis and is expected to help progress in defining recommendations on the use of arterial stiffness in daily clinical practice.

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