



## EDITORIAL COMMENT

# Pulse wave velocity: a marker of arterial stiffness and its applicability in clinical practice

## Velocidade da onda de pulso arterial: um marcador da rigidez arterial e a sua aplicabilidade na prática clínica

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The development of arteriosclerosis is a continuum, a healthy vessel being affected by 'traditional' and other risk factors as well as genetic and environmental determinants, with an intermediate stage of atherosclerosis before the clinical manifestation of cardiovascular disease.

This intermediate stage of subclinical atherosclerosis can be characterized by study of the heart, kidney and arteries using markers of subclinical organ damage<sup>1,2</sup>. This is essential, since such damage is an important determinant of global cardiovascular risk<sup>1,3</sup> and thus helps in deciding whether medical therapy is indicated for primary prevention. Non-invasive techniques for structural and functional assessment of blood vessels include carotid artery angiodynography (Doppler ultrasound) to assess intima-media thickness (IMT) and plaque characteristics<sup>4</sup>, and the ankle-brachial index to detect asymptomatic peripheral arterial disease<sup>5</sup>. Over the years, increasing interest in systolic blood pressure (BP) and pulse pressure as predictors of cardiovascular events<sup>6</sup> has prompted the development of techniques to assess arterial distensibility/stiffness<sup>7,8</sup>. The focus on BP has been broadened to vascular stiffness and aging and then to endothelial dysfunction, which gave rise to the concept of vascular protection. One technique to assess arterial stiffness, the most important determinant of isolated systolic hypertension related to wave reflection and pulse pressure, is measurement of arterial pulse wave velocity (PWV). This is the distance

traveled by blood flow divided by the time it takes to travel that distance (in meters/second). It is measured non-invasively and is the gold standard for assessment of aortic stiffness. The lower the PWV the better, as this means the arteries have maintained their elasticity and are distensible. However, the important question is whether this simple measure of arterial stiffness is of value in risk stratification, compared to risk estimated by traditional risk factors; in other words, is it an independent predictor of cardiovascular events and as such useful in clinical practice? The usefulness of PWV as a possible marker of vascular processes depends on how much more information it can provide on the risk or presence of disease over and above that provided by other markers, and on the extent to which such information influences clinical decisions.

The first consensus on methodological issues and clinical applications of arterial stiffness was arrived at in 2006, and recommended PWV measurement as a simple but valid method for use as a diagnostic procedure in clinical practice that in itself may have prognostic significance<sup>9,10</sup>. Subsequently, other studies strengthened the evidence and increased interest in assessment of arterial stiffness. Data from the Framingham study suggested correlations between markers of neurohumoral activation and vascular stiffness, independently of other risk factors<sup>11</sup>. In the Copenhagen County population study, with a 13-year follow-up, greater PWV (>12 m/s) was associated with a 50% higher risk of

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cardiovascular events<sup>12</sup>. Similarly, PWV was an independent predictor of cardiovascular events in Japanese men followed for 8.2 years<sup>13</sup>. In addition, indirect indices of aortic stiffness and wave reflection (central BP and augmentation index) have also been shown to be independent predictors of cardiovascular events<sup>14,15</sup>. However, after adjustment for other risk factors, including left ventricular mass and carotid IMT, only central systolic BP was a consistent and independent predictor of cardiovascular mortality<sup>15</sup>. As the additional predictive value of central BP over measurement of peripheral (brachial) BP appeared limited in other studies, it is debatable whether central BP should be assessed regularly to determine the clinical profile of hypertensives who may require further investigation<sup>2</sup>.

In the study published in this issue of the *Journal*, Pereira et al.<sup>16</sup> present normal values for carotid-femoral PWV, adjusted for age and gender, in a Portuguese population, based on a subanalysis of the EDIVA project, and assess the relationship between PWV and cardiovascular risk during a two-year follow-up. The reproducibility of these values, estimated by the correlation between inter- and intra-observer measurements, was high (Pearson correlation coefficients of >0.9). Their results are in agreement with other studies that used different but equally valid methodologies in terms of both measurement and statistical analysis<sup>17,18</sup>. While reproducibility is not sufficient to ensure validity, these two characteristics are major statistical attributes of any measure, including diagnostic tests, and if a measure is not reasonably reproducible, it will be of little value. In this study, PWV was assessed with a Complior device in 668 individuals at low cardiovascular risk; the authors opted for a statistical definition of normality based on the 95th percentile, adjusted for age and gender, which was also used to define the clinical significance of age-dependent increases in PWV. Besides proposing an age-related distribution of normal PWV values, the authors, who have a long history of research in the area of arterial stiffness, also present data on risk as analyzed by Cox regression (*in press*), which indicate that the correlation between PWV and cardiovascular risk diminishes with age and in the presence of comorbidities such as hypertension and diabetes. These results are in agreement with a recent meta-analysis<sup>19</sup>, which confirmed that PWV is the best-established measure of arterial stiffness and predictor of cardiovascular events and all-cause mortality, as shown consistently by all 12 studies. In this meta-analysis, after adjustment for the conventional risk factors of age, gender, systolic BP, total and HDL cholesterol, smoking and antihypertensive medication, hazard ratios for one standard deviation (1 SD) of PWV were 1.19 for coronary disease, 1.25 for stroke, 1.27 for cardiovascular events, and 1.18 for all-cause mortality, all of which were statistically significant, implying around a 20% increase in risk for each 1 SD rise in PWV. When the results are stratified by age, the predictive effect of PWV is stronger in individuals aged under 50, although the correlation is still significant for those aged over 50. The next step will be to analyze the same data to determine to what extent PWV measurement adds to conventional screening, independently of other risk factors.

The results of Pereira et al. are important since they demonstrate the value of PWV measurement in estimating

cardiovascular risk and help define reference values of normality, filling a gap that has hindered use of this parameter in routine clinical assessment. However, after several years of investigation, why is it that PWV assessment, as well as other measures of arterial stiffness, are not routinely used in clinical evaluation of individuals at risk of cardiovascular disease, despite being recommended in international guidelines<sup>1-3</sup>? There may be several reasons for this, including the fact that the methodology for carotid-femoral PWV measurement has yet to be standardized, which means there may be differences between absolute values assessed by different methods<sup>20</sup>. Another is that studies have used different cut-offs to indicate increased risk due to the lack of reference values, although these were defined in 2010 based on a large European population<sup>21</sup>. However, while the latter study constitutes a solid base for future research on standardizing PWV values, it has certain methodological limitations. It was a cross-sectional study of a large sample (reference value population [n=11,092], and a subset with optimal/normal BP and no cardiovascular risk factors [n=1455]) from 13 centers in eight European countries, using multiple observers and different methodologies, although algorithms (Sphymocor and Complior systems) were used to harmonize measurements. In addition, no information is given on changes in PWV over time or their effects. For the time being, the question as to whether the reference values should be used as cut-offs to guide treatment remains unanswered. However, the differences in methodology from the study that is the subject of this editorial are not limited to measurement and follow-up. The characteristics of the normal population differed in terms of mean BP and age (both greater in the Portuguese study), which may explain why absolute PWV was higher in the study by Pereira et al., since BP and age are major determinants of arterial stiffness and hence of PWV. In addition, the distribution of PWV by age-group was based on the mean  $\pm$  2 SD, median and 10th and 90th percentile, while the Portuguese study used the mean (SD), range of variation and the 95th percentile. Furthermore, differences in populations and in analysis of covariance, with different cut-offs being used to define increased risk, make it difficult to compare studies analyzing risk and/or prognosis<sup>16,19,21</sup>.

The performance of PWV in clinical practice depends above all on its ability to distinguish a normal state from a pathological process that affects arterial distensibility. Since PWV is a continuous variable, its use as a diagnostic test requires definition of normal values - the main aim of the article published in this issue. Establishing criteria of normality for a variable such as PWV that is dependent on several determinants and associated with a continuous and progressive risk is not easy, nor can an unequivocal definition be expected. The concept of "normal" is defined on the basis of the statistical model used to assess the distribution of the variable under study, and can be because it is common in the population, or is not associated with a treatable disease, or corresponds to values that are desirable in the individual. The most widely used statistical model is based on a Gaussian distribution, with a bell-shaped curve being classified as normal. The most common statistical criteria of normality are a value below the mean  $\pm$  2 SD, or the 95th percentile. The latter classifies

5% of individuals as abnormal, but if multiple tests ( $n$ ) are used in the same individual, the probability of an abnormal result is  $1-(0.95)^n$ . Percentiles are another way of assessing distribution that is increasingly used by researchers, identifying the position of an individual in relation to the population under study and on their likelihood of belonging to the normal or pathological group. However, the term 'normal' is used in clinical practice to distinguish between health and disease and for this purpose the model is often inappropriate, but it is used so frequently that it has become known as "the ghost of Gauss". The Gaussian model is easy to interpret when there are two independent distributions, i.e. two distinct populations, one with disease and the other without, with no overlap, as in the case of certain genetic diseases, but most conditions do not show this pattern of distribution.

In any event, cut-offs need to be defined to distinguish normal from abnormal cases, and positive from negative results, even though these can be arbitrary, as pointed out by Sir George Pickering in the case of the cut-off values used over the years to classify BP. Moreover, as for BP, it is not entirely clear whether normal values for PWV should be defined according to age. In the case of BP, it has been shown that it was incorrect to assume that BP rises physiologically with age<sup>22</sup>, and fixed limits have been defined, independent of age, according to which a large proportion of the elderly are classified as hypertensive. In the same way, based on a fixed PWV value, even adjusted for normal aging, most hypertensives will have high PWV<sup>21</sup>. The recommended PWV cut-off of  $>12$  m/s to define abnormality was determined based on outcomes, but there is no evidence to date on the effect of intervening to improve PWV. So, should this cut-off value be universal or adjusted to take account of other characteristics? This question is relevant in that other studies have established normal values but are limited by small sample size and/or narrow age range, the latter being particularly important since age has a strong influence on PWV. Furthermore, some authors exclude treated hypertensives and those with diabetes or hypercholesterolemia, in whom PWV differs, but this difference is not quantified. It is therefore difficult to determine the influence of other risk factors on PWV, and this requires further investigation. As pointed out by the Reference Values for Arterial Stiffness' Collaboration, the primary requisite for standardization of PWV measurement is undoubtedly to agree a methodology, but this has yet to be achieved. It has yet to be established how to use reference values for patient selection and stratification (adjusted for age and/or BP or not, based on percentiles, etc.). Expert panels will therefore be needed to define a standard method for PWV measurement and to establish cut-offs. Whether values should be adjusted for age is a question that can only be resolved by prospective studies on carotid-femoral PWV; likewise, it remains unclear whether PWV is only a risk or prognostic factor or also an indicator that should prompt therapeutic intervention. Finally, it is not known whether changes in PWV could constitute a surrogate endpoint. Nevertheless, based on PWV distribution by age and BP, it is already possible to identify individuals at increased risk according to age-group and percentile of the reference (normal) population to which they belong. Testing the usefulness of data

independent of the methodology and equipment used will be an important step towards applying PWV measurement to clinical practice.

To summarize, there are issues that need to be investigated further<sup>21</sup>, which is why the American Heart Association<sup>23</sup> does not as yet recommend specific measures of arterial stiffness to estimate cardiovascular risk in asymptomatic adults outside the context of research (class III recommendation; level of evidence C). However, there is now a solid basis from which to proceed towards standardization of PWV measurement. Once this essential prerequisite is met and the European Society of Hypertension issues guidelines on PWV measurement<sup>2</sup>, it is expected that devices for PWV assessment will become more available and be increasingly used in clinical practice, particularly in primary health care.

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