

# Arterial stiffness: reflections on the arterial pulse

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**This editorial refers to 'Expert consensus document on arterial stiffness: methodological issues and clinical applications'<sup>†</sup> by S. Laurent *et al.*, on page 2588**

Arteriosclerosis—arterial stiffening—is the basic cause of isolated systolic hypertension (ISH) and the present epidemic of heart failure in the elderly.<sup>1</sup> Arteriosclerosis is equally important for the development of coronary events, stroke, dementia, and renal failure. The underlying pathology was described by Osler<sup>2</sup> as 'senile arteriosclerosis' to distinguish it from essential hypertension (Osler's 'diffuse arteriosclerosis') and 'nodular arteriosclerosis' that is now described as atherosclerosis. Although we usually identify the precursor as ISH, the measurement of blood pressure by cuff sphygmomanometer is only a surrogate of the underlying disease<sup>3</sup> and an unsatisfactory method for detecting its early presence and progress. Recognizing this, the European Societies of Cardiology and of Hypertension (ESC and ESH, respectively) established guidelines for the management of arterial hypertension, and drew attention to methods for measuring arterial stiffness as pulse wave velocity or analysing the pulse waveform, which may identify the arterial target organ damage at an early stage.<sup>4</sup>

An important step in this field is the publication of a consensus document on arterial stiffness from a European group in good standing with professional associations, and led by Stephane Laurent.<sup>9</sup> Specific statements are given on key issues, based on review and mechanism, practicality of measurement, and evidence of value. The document is a logical development from previous statements and publications including the most recent Handbook of Hypertension<sup>5</sup> to which most authors contributed. It is timely, since the ESC and ESH are reviewing guidelines on management of hypertension in the light of new information that has emerged since the last publication.<sup>4</sup>

Why is this necessary when ISH can be recognized years before development of cardiac failure, and can be (but often is not) treated effectively? The problem is with cuff blood pressure measurement—its accuracy when measured simultaneously by different methods, its accuracy in comparison to intra-arterial pressure, its variability throughout

the day and night, and its distortion and amplification in transmission from aorta to brachial and radial arteries. Sphygmomanometric cuff inaccuracy is sufficient to warrant independent measures of arterial stiffness and its effect on the heart and other blood vessels. This is discussed in the document, and in recent literature.<sup>5</sup> The report by Laurent *et al.* described a hierarchy of methods that can be utilized in clinical trials for gauging arterial stiffness and its effect on the cardiovascular system. The first two of these, favoured by ESC/ESH<sup>4</sup> were applied to this purpose over a century ago, and before introduction of the cuff sphygmomanometer—the pulse wave velocity by Young in the early nineteenth century, and by Bramwell and Hill in the early twentieth century, whereas pulse waveform analysis was applied by Marey, Mahomed, Mackenzie, and Osler, and even implemented into life insurance examinations 100 years ago.<sup>6</sup> As Laurent *et al.*<sup>9</sup> point out, arterial stiffness is an easy concept to understand but immediately becomes complex when one wishes to measure, quantify, and compare.

Laurent *et al.*<sup>9</sup> review all methods used to describe arterial stiffness as biomarkers before focusing on three as being the most practical and relevant for clinical use. Such biomarkers include arterial pressure itself, and must conform with criteria set out by Vasan<sup>3</sup> which include theoretic basis, reproducibility, ease of use, incremental value over other indices known to predict outcome, and ability to monitor and guide treatment. Assessment of all is ongoing, and has to date been positive, with even suggestion of superiority over cuff blood pressure itself in patient management. There may be disagreement from enthusiasts of other techniques, but failure to make the grade to date is based on failure on the Vasan score. Techniques of arterial compliance measurement have generally failed, but are based on an unrealistic model which ignores wave reflection, while for one (HDI) cardiac output is estimated indirectly from age, body size, and pressure values.

The three methods selected by Laurent *et al.*<sup>9</sup> are all basically simple—so are inherently suitable for many clinical applications and multicentre trials. They are also old, with experience collected over decades; hence their shortcomings are reasonably well appreciated.

One might expect that the simplest and most direct measurement of pressure and diameter would be the most useful. Laurent *et al.*<sup>9</sup> recommended this for mechanistic analysis in physiology, pharmacology, and therapeutics rather than for epidemiological studies. The main problem may have been with local pressure measurement—and

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perhaps with reliance on cuff brachial blood pressure determination (rather than on the technique used to convert this to central pressure at the site of diameter measurement). The ultrasonic phase-locked echo tracking method for measuring diameter and diameter-change is very accurate, and is unlikely to be improved with other radiographic or MRI techniques. However, the change in diameter is very small in relation to absolute diameter, and together with manometric problems limits accuracy and reproducibility of measurements.

Laurent *et al.*<sup>9</sup> show preference for the old technique of pulse wave velocity measurement, as described by Young in 1804, and by Bramwell and Hill in 1922. There is general agreement that the 'gold standard' for central arterial stiffness is carotid to femoral PWV. The main problem with this is in making comparisons between trials in which different conventions have been used for determining the distance travelled by the pulse. This is not a problem within any trial where the same technique is used. There are abundant outcome data from different populations on independent value for assessing prognosis, and some limited studies in guiding treatment.

The third method in Laurent's hierarchy is the easiest to apply—the method of pulse wave analysis.<sup>9</sup> The pressure wave is measured with an electronic tonometer at the carotid or radial artery and attention is directed at the waveform, and specifically at the boost or augmentation to pressure in late systole. Augmentation is always greater in the aorta than in the carotid artery, and greater in the carotid than in the radial artery. It is easier to detect in the aorta or carotid artery than in the radial artery. Radial tonometry is easier than carotid tonometry and is usually preferred. With the SphygmoCor system, a generalized transfer function is used to generate the ascending aortic pressure wave from the radial pressure to standards acceptable to the US FDA. With this, augmentation index can be measured at the radial artery and in the ascending aorta. With all methods, carotid or aortic pressure is obtained from calibration against the brachial cuff systolic and diastolic pressures.

In comparison with pulse wave velocity determination, information obtained by pulse wave analysis is more dependent on changes in heart rate, ventricular contraction and drug effects. Although there are a number of different devices that use applanation tonometry in determining central pulse waves non-invasively, to date the SphygmoCor system described by Laurent *et al.*<sup>9</sup> has had the most usage in clinical trials: CAFÉ and REASON have been completed and SEARCH, ACCT, FIELD, and CAERPHILLY are ongoing. The CAFÉ and REASON studies have exposed the differential effects of atenolol and amlodipine/perindopril on the aortic systolic and pulse pressure, and the superiority of the newer agents in effecting aortic and left ventricular systolic pressure reduction. This can also be seen with carotid tonometry, but not so conveniently. Tonometric methods have been successfully introduced in the Framingham study cycles and normal values established. Outcome data will not be known for several years.

Before there is full confidence in the new indices of arterial stiffness, normal values will need to be established. Such work is proceeding at the NIA and Framingham, while

SphygmoCor derived data have been published for normal European cohorts by McEniery *et al.*<sup>7</sup> and Wojciechowska *et al.*<sup>8</sup> The McEniery *et al.* study suggested that Alx may be a more sensitive marker of arterial stiffening and risk in younger persons but aortic PWV is likely to be a better measure in older persons. However, both modalities should be performed on all subjects when practical to obtain maximum diagnostic information.

On the basis of the report of Laurent *et al.*,<sup>9</sup> there appears to be enough information now to warrant use of at least three approved indices in guidelines as surrogates of arterial stiffness, and to chart its course and to plan therapy. Undoubtedly, additional studies will be necessary to confirm the predictive value of these indices over and above the Framingham risk scores and in determining the sensitivity and selectivity of arterial stiffness in comparison to other biomarkers of cardiovascular disease. None of these three recommended indices is perfect; with time more improvements will doubtless be made to each. With time also, shortcomings will become apparent, but should be capable of control. As the scrutiny increases, the value of the cuff method for brachial blood pressure should also be raised, and better cuff methods may emerge. It is entirely possible that one or more of the above methods may prove better than the cuff for estimating severity of underlying arteriosclerosis, and for guiding therapy. Blood pressure is after all just a surrogate of a pathological condition.<sup>3</sup>

**Conflict of interest:** M.F.O'R. is a Founding Director of AtCor Medical, manufacturer of systems for analysing the arterial pulse. S.S.F. reports that he is a Consultant for AtCor Medical, Bristol-Myers Squibb, Merck, and Pfizer; speakers bureau for Boehringer Ingelheim, Bristol-Myers Squibb, and Merck.

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