Towards applicability of measures of arterial stiffness in clinical routine

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This editorial refers to “Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: ‘establishing normal and reference values’,” by The Reference Values for Arterial Stiffness Collaboration on page 2338

Cardiovascular risk is steadily increasing in Western countries. Thus, assessment of risk in individual subjects is becoming more and more important. Already 40 years ago it was recognized that individual risk of cardiovascular events is, in addition to age, dependent on various factors, such as high cholesterol, elevated blood pressure, diabetes, and smoking. These ‘traditional’ risk factors have been studied extensively and therapeutic approaches addressing these factors have shown, largely uniformly, reduction of cardiovascular risk. However, it was also recognized that these factors do not fully explain cardiovascular risk. Many other factors have been claimed to be of importance, but most of them were later found to be of little or no incremental value. On the other hand, it was recognized that consequences of risk factors vary significantly between individual patients, and this individual response may be detectable by measuring signs of organ damage or vascular alterations. In fact, a recent systematic review found that carotid–femoral pulse wave velocity (cfPWV), a measure of large artery stiffness, may even be unrelated to classic risk factors other than hypertension and reflect arterial ageing, although recent data suggest that exposure to risk factors over time, such as smoking, may well play an important additional role. Thus, it is not surprising that organ damage and vascular alterations were found to be of incremental prognostic value independently of ‘traditional’ risk factors. Furthermore, therapies reducing some of these factors such as left ventricular hypertrophy and microalbuminuria were found to be accompanied by a reduction of the risk of subsequent major cardiovascular events. Therefore, these signs of vascular and organ damage are attractive targets for identification of those individuals at highest risk who may profit most from intensive therapeutic interventions.

However, the question remains of whether such signs are commonly used in clinical practice and, if not, why this is not the case. Indeed, some of these markers are well established in the clinical assessment of patients, such as left ventricular hypertrophy and microalbuminuria, and are not only used for prognostic purposes, but may also lead to more aggressive therapy to reduce this risk. Others, however, are not yet used on a regular basis, despite being recommended as useful clinical tools in current guidelines. To the latter belong measures of arterial stiffness.

There are several reasons why arterial stiffness may predict risk independent of other risk factors including hypertension. Thus, central haemodynamics may not directly correspond to peripherally measured blood pressure and this difference may be related to arterial stiffness. Furthermore, data from the Framingham study suggest distinctive patterns of positive associations between markers of neurohumoral activation and vascular stiffness that may be independent of other risk factors. Moreover, reduced C-type natriuretic peptide, which is mainly produced in vascular walls and which is not known to be related to the classical risk factors, may play a role in increasing arterial stiffness.

A recent metanalysis based on 17 longitudinal studies including nearly 16 000 patients found an increased risk in events (Figure 1) by measuring cfPWV, which is the best established measure of stiffness of large arteries. Other measures of arterial stiffness may be subject to considerable variability in agreement and lack sufficient outcome data. Despite some heterogeneity, the findings of the underlying studies were consistent and independent of ‘traditional’ risk factors. It may also predict the risk of stroke in subjects with no overt cardiovascular disease, as well as coronary artery disease, renal failure, and cognitive deficiency, independently of other risk factors including blood pressure and age. Furthermore, increased pulse pressure, though a less precise measure of arterial stiffness, was found to be related to the occurrence of atrial fibrillation. Decreased arterial compliance may lead to premature reflection of the arterial wave, which may increase left ventricular wall stress and result in diastolic dysfunction. Thus, heart failure with
normal left ventricular systolic function was recently suggested to be mainly a vascular problem.

Taken together, there are convincing reasons why cfPWV as a measure of arterial stiffness should be included in routine clinical assessment of patients at risk for cardiovascular diseases. However, this is currently not the case, although it may be measured non-invasively using relatively simple tools. The question is why? Various reasons may account for this, two of which are crucial. Thus, the methodology to measure cfPWV is not yet clearly standardized. Important differences in absolute cfPWV values may exist between different methodologies.\(^1\) Not surprisingly, the studies included in the above-mentioned systematic review used quite different cut-off values to indicate increase risk.\(^2\) This is also due to the lack of reference and normal values, which may allow definition of pathological ranges to identify patients at high risk requiring intensified therapeutic interventions. For those signs of end-organ and vascular damage that are established in clinical assessment such as microalbuminuria and left ventricular hypertrophy, these prerequisites are fulfilled since the necessity was recognized early. For cfPWV, this is not yet the case. The recent article by The Reference Values for Arterial Stiffness’ Collaboration provides normal and reference values for cfPWV, and the authors of this study are to be congratulated on their important work.\(^{15}\) The results presented are based on a very large cohort of subjects (i.e. \(n = 11\,092\)) with a very wide age range, included in different centres and using different methodologies. Other groups have also provided normal values, but these studies have important limitations and are, as a consequence, of limited value for defining normal and reference values. Among others, the number of subjects included was much smaller\(^2\) and the age range very limited.\(^{16,17}\) This is important since age was uniformly found to have a strong influence on cfPWV, and values in the elderly may not be applicable to younger subjects. Despite these differences, the data of these two studies came up with results comparable with the study by the Arterial Stiffness’ Collaboration. Still, this latter study has a much more solid basis, given its size and the multicentre approach, and provides additional information. Thus, the authors confirm other data suggesting that other ‘traditional’ risk factors influence cfPWV less.\(^3\) However, the authors excluded a substantial number of patients because they had diabetes or had treated hypertension or hypercholesterolaemia. Obviously, cfPWV differed significantly in these patients, but the authors do not report by how much. Thus, the influence of other risk factors on cfPWV cannot be fully determined based on the findings of this study and remains a question to be further investigated.

The authors give important weight to standardizing measurements of cfPWV, an important reason for difficulty in interpreting previous studies and direct applicability to clinical practice. Unfortunately, possible differences between centres and the influence of the methodologies used are not reported in sufficient detail. The latter in particular may be of importance. The transit time between two characteristic points on carotid and femoral waveforms is significantly dependent on the algorithm used. The determination of the distance between the two sites of measurements may even have a larger impact. The authors used previously published formulae\(^{18,19}\) for calculative conversion of the values if different methods were used. Without doubt, this is an important step towards standardization, but it may not be sufficient since conversion between the methods is based purely on mathematical formulae and not on current measurements. Confirmation of the correctness of these formulae is required before they can be used as a generally acceptable standard. The database presented would have been sufficiently large to test if the methods used had any impact on the results and if the calculative conversion is sufficient to exclude differences between centres and the methodology used. In the limitation section, the authors provide some information in this regard suggesting that there might indeed be an important influence of the methodology used, but the impact on the results is less clear. Testing the value of data independent of the methodology and equipment used is an important step towards implementation of cfPWV in clinical practice.

Although, as stated by the Arterial Stiffness’ Collaboration, most of the necessity for standardization of cfPWV is purely methodological, this necessity has not yet been achieved. It remains for expert committees to define the standard methodology to be used for measuring cfPWV in the future and to determine threshold values. Whether these should be adjusted for age is an issue to be resolved, but prospective intervention trials based on cfPWV measurement are required to address this sufficiently. Also, whether cfPWV is not only an independent prognosticator but also an indicator on which therapeutic interventions should be based remains to be determined. Recently, it was found that response to antihypertensive therapy was inversely related to cfPWV.\(^{20}\) Finally, changes in cfPWV might well be suitable as a surrogate endpoint, but, again, it remains to be determined if this is true. Thus, the results presented by The Reference Values for Arterial Stiffness’ Collaboration\(^{15}\) do not provide all the answers yet, but may be used as a solid basis for further research and are an important step in the direction of standardization of cfPWV.
Only this will result in a general implementation of this important method in clinical practice.

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References


