Are vascular function measurements ready for the clinic?

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This editorial refers to 'Flow-mediated changes in pulse wave velocity: a new clinical measure of endothelial function'† by K.K. Naka et al., on page 302

The relevance of vascular function assessments to clinical medicine

Changes in vascular function such as endothelial function and arterial stiffness are key early features in the development of human cardiovascular disease, and non-invasive measures of vascular function have been utilized extensively in clinical research. Many non-invasive indices correlate well with more direct and invasive measures and thus can be applied to large cohorts, potentially outside of a laboratory. As some of these techniques are now available for use outside of a research setting, the clinician is increasingly forced to assess their various merits and the relevance of specific findings in individual patients. Although it is logical to suggest that they may, whether such strategies translate into reduced cardiovascular morbidity and mortality in a clinical setting is largely unknown.

Abnormalities can be seen in measures of endothelial function and/or arterial stiffness before overt cardiovascular disease develops and are seen in subjects with or at high risk of developing vascular disease, including subjects with hypercholesterolaemia, hypertension, diabetes, and chronic renal failure. Thus, it is hoped that screening such subjects may direct early targeted intervention. Cross-sectional studies have shown how novel and traditional risk factors interact in determining vascular dysfunction and atherosclerosis. In addition, abnormalities in some vascular assessments provide prognostic data independent of and additive to more well-established risk factors and they are also able to act as surrogate measures in intervention studies because some cardiovascular therapies can lead to early and lasting improvements in measured vascular function. For example, it has been suggested that blood pressure 'independent' effects of therapies such as angiotensin-converting enzyme inhibitors seen in large-scale interventional studies may, in fact, be a manifestation of improvements in arterial stiffness indices.¹

The endothelium plays a key role in vascular homeostasis regulating vascular tone, smooth muscle cell proliferation and migration, and fibrinolysis as well as interactions between the vessel wall, platelets, and leukocytes. Endothelial production of nitric oxide (NO) is central to this function, and abnormalities in NO generation and stability are well described at all stages of atherosclerosis. Endothelial function can be measured non-invasively in the brachial artery (FMD)² using high definition ultrasound that assesses the change in arterial diameter in response to altered flow, an effect which has been shown to be dependent on local NO generation. This measure is used to some extent as a surrogate measure of other endothelial functions. The technique of brachial artery FMD measurement is limited as a tool in direct patient care because it requires a trained operator, a regulated environment, and specialized equipment, ideally including high definition ultrasound, archiving of studies and edge-tracking software. Thus, its role is currently mainly limited to a valuable one in the clinical research setting.³

The peripheral arterial waveform represents a combination of the anterograde systolic wave and reflected waves. Arterial stiffening is associated with increased velocity of the transmitted arterial pulse wave and altered interaction between anterograde and reflected waves with reflected waves interacting earlier (in systole) with the incident wave, contributing to systolic hypertension, decreased diastolic pressure, and thus an increased pulse pressure. Arterial stiffness is determined by a combination of factors including structural characteristics of the vascular wall and dynamic forces impacting on arterial wall tone. Central arterial stiffening is associated with normal ageing but also with a range of disease states, such as hypertension and diabetes. Processes such as vascular calcification and deposition of advanced glycation end-products, such as occur in diabetes and lead to increased collagen cross-linking, are implicated in accelerated arterial stiffening. In peripheral muscular arteries, vascular tone variations, particularly relating to altered flow and...
endothelial NO production, also impact on measured stiffness indices.\(^4\)

The simplest surrogate measure of central arterial stiffness in clinical practice is pulse pressure, although it has been demonstrated that brachial pulse pressure may not fully or accurately represent central pulse pressure. Nevertheless, elevated brachial pulse pressure has been shown to be an important independent predictor of events, particularly in older subjects, such as in the Framingham cohort study.\(^5\) Some other available techniques aim to provide an overall estimate of arterial stiffness and rely on a peripheral non-invasive measurement such as with arterial tonometry.\(^6\) Indices that can be derived include pulse-wave velocity (PWV) and systolic pulse-wave augmentation, largely a manifestation of PWV. More complex techniques rely on modelling the arterial circulation such as with a modified Windkessel model and assess the effect of increased stiffness on the arterial waveform at various points in the arterial circulation.\(^7\) This area is made complex for the clinician by the growth of available techniques, differences in terminology, and lack of available reference values.\(^8\)

Importantly, there is no measure that gives a complete and definitive assessment of vascular health and there is great controversy about the relative validity and utility of some models and techniques. Features such as the heterogeneity of atherosclerosis throughout the arterial tree, the effects of pulse-wave augmentation and of branch points are difficult to account for in a global model of the arterial circulation. There is also a significant degree of theoretical overlap between various measures. For example, as NO appears to regulate arterial stiffness, particularly in small vessels,\(^9\) some of these indices appear at least partly dependent on the function of the endothelium, such as the technique described by Naka et al.\(^10\)

**Measuring endothelial function in clinical practice**

Naka et al.\(^10\) describe a novel technique for assessing ‘endothelial function’ which assesses the effects of altered distal flow on measured PWV in two subject groups, healthy controls, and patients with congestive heart failure, a condition associated with impaired endothelial function. Having established that PWV was reduced by intra-arterial acetylcholine and increased by the NO-inhibitor N-monomethyl-L-arginine, they found that reactive hyperaemia was associated with reduced PWV in controls but not in congestive heart failure patients, suggestive that the capacity to alter PWV with altered flow was lost in those subjects with endothelial dysfunction. Their technique supports the concept that at a practical level, there is overlap between a non-invasive measure of peripheral endothelial function and arterial stiffness, manifested by increased PWV. Unfortunately, there was no direct correlation between this measure and FMD presented. This is important as there have been relatively few studies directly comparing a range of techniques to each other in the same subjects\(^11\) and the extent to which abnormalities in one measure represent those in others is largely unknown. For these techniques to be broadly applied in the clinical setting and aid in guiding therapy, this issue needs to be clarified because there is currently no real ‘gold standard’ measure of vascular function.

**Use of vascular assessments in the clinic**

Much of the data available about vascular function assessment has been collected during clinical research studies in a controlled environment, such as the study by Naka et al. Most studies are performed in steady state conditions at a standardized time (usually morning) after an overnight fast with medications, cigarettes, and caffeine withheld for a defined period prior to testing. Many factors, including the use of vasoactive medications, diurnal variation, fasting state, and exercise prior to testing, appear to cause acute and significant changes in many non-invasive measures of vascular function. Attention to these issues is crucial if these tools are to be employed for serial measurements in an individual over time and/or to assess the effects of therapies. Also, highly relevant is the issue of operator training and experience. It is reasonable to expect a degree of inaccuracy with many techniques when used by inexperienced operators or in a clinic setting where many operators may test the same patient. Thus, available measures should be standardized as much as possible.

**Conclusion**

Non-invasive measurement of vascular function can provide prognostic information and has the potential to guide the care of patients with or at risk of cardiovascular disease. However, for these studies to be become accepted into mainstream clinical practice, evidence needs to be shown that their use in guiding therapy leads to improved outcomes for patients in prospective studies over and above information gained by targeting blood pressure and lipid levels. Until the results of such studies are known, the role of these assessments appears to be primarily a valuable one in clinical research.

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**References**


Clinical vignette

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Emergency endovascular repair of ruptured pseudo-aneurysm at the site of a corrected aortic coarctation

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A 51-year-old patient, previously operated on at the age of 33 for a ruptured aneurysm of the descending aorta at the site of a non-diagnosed coarctation, was referred because of acute haemoptysis. Chest X-ray showed an enlarged left upper mediastinum (Panel A). Chest computer tomography showed the presence of a pseudo-aneurysm at the level of the patch (Panel B), with evidence of an upper left pulmonary lobe haemorrhage (Panel C), compatible with an aorto-bronchial fistula.

A successful urgent endovascular repair was performed with an aorto-aortic talent prosthesis (proximal and distal diameter 38/36 mm: Medtronic, MN, USA) excluding the pseudo-aneurysm, stabilizing the patient and improving his symptoms.

No further complication occurred and recovery was rapid without functional sequelae. The 3-year follow-up thoracic spiral CT scan shows correct positioned endoprotheses and exclusion of the endoleak (Panel D). This case illustrates that urgent endovascular repair of aortic aneurysm is feasible in selected cases avoiding major thoracic surgery.

Panel A. Chest X-ray shows an enlarged left upper mediastinum.
Panel B. Thorax CT-scan showing a pseudo-aneurysm in the descending part of the thoracic aorta at the side of the previously implanted patch with evidence of extraluminal contrast medium (arrow).
Panel C. Thorax CT scan showing an upper left pulmonary lobe high-density opacification (arrows) caused by blood, probably due to an aorto-bronchial fistula.
Panel D. Thorax CT scan at 3-year follow-up showing complete exclusion of the aneurysm.