Arterial stiffness: intermediate or surrogate endpoint for cardiovascular events?

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Identification of cardiovascular (CV) risk is mandatory to determine the intensity of interventions. Despite the recognized advantages of classical algorithms for global risk assessment, important limitations have been noticed, and current research is focusing on subclinical markers of arterial disease accessible to non-invasive investigation, including arterial stiffness, carotid intima-media thickness, and endothelial dysfunction. The current growing interest in arterial stiffness originates from the repeated demonstration of its predictive value for CV events, including CV mortality, myocardial infarction, and stroke.

An indirect argument for the influence of arterial stiffness on the occurrence of CV events comes from cross-sectional studies showing that arterial stiffness and CV risk factors for atherosclerotic lesions are correlated. A major limitation of these studies is their cross-sectional feature. This is a crucial point. These studies showed that aortic stiffness was associated with other markers of CV risk or with the extent of atherosclerosis, but could not conclude that arterial stiffness was predictive of CV events as patients were not followed-up. In other words, these studies showed that arterial stiffness was a marker of CV risk, but did not demonstrate its predictive value as an intermediate endpoint.

Only recently have longitudinal studies directly demonstrated that arterial stiffness, measured through carotid–femoral pulse wave velocity (PWV) ratio, was an independent predictor of all-cause and CV mortality, coronary events, and stroke, in patients with uncomplicated essential hypertension. Additional evidences were provided in patients with endstage renal disease (ESRD), with diabetes, and in elderly subjects. Thus, arterial stiffness is now well accepted as an intermediate endpoint for CV events. In some studies, arterial stiffness was measured at the site of the thoracic and descending aorta through carotid–femoral PWV. Indeed, PWV, measured along the aortic and aorto–iliac pathway, is the most clinically relevant measure since the aorta and its first branches, which are elastic arteries in young healthy subjects, are responsible for most of the pathophysiological effects of arterial stiffness.

Besides aortic stiffness, it is important to determine the predictive value of carotid stiffness because carotid artery is a site prone to atherosclerosis and a reference for the measurement of intima–media thickness. Also, any carotid damage may closely reflect arterial damage in the cerebrovascular and coronary territories. Two studies performed in a small number of patients at very high CV risk (i.e. ESRD and after renal transplantation) previously showed that carotid stiffness was a strong independent predictor for CV mortality.

In their study, Dijk et al. measured various indices of carotid stiffness in the 2183 patients of the SMART study cohort, having a mean follow-up of 2.8 years. These authors observed that none of the carotid stiffness parameters were independently related to the occurrence of vascular events. Decreased vascular stiffness was related to decreased vascular risk only in subjects with low baseline systolic blood pressure.

One strength of the study by Dijk et al. is that gold standard parameters were measured (internal diameter, pulsatile change in diameter, and intima–media...
thickness) and various indices of arterial mechanics were calculated, all exploring different aspects of arterial mechanical properties: beta stiffness index, which is supposed to be independent of distending pressure; cross-sectional distensibility, which informs on the mechanical behaviour of the artery as a whole; cross-sectional compliance, which takes into account the volume of the artery, and mainly the age-induced enlargement; Peterson elastic modulus, which is inversely related to cross-sectional distensibility; and Young’s elastic modulus ($E_{inc}$), which gives insights on the mechanical behaviour of the wall material. All these parameters are well accepted as indices of arterial stiffness. The use of brachial pulse pressure for these calculations (instead of carotid pulse pressure) may limit the precision by which arterial stiffness parameters are determined. However, this is an improvement over the measurement of the relative change in diameter (systolic minus diastolic/diastolic) used by Dijk et al. and others in various studies as a surrogate of arterial stiffness, which it is not. Indeed, the relative change in diameter cannot be retained as an index of arterial stiffness, since the pressure (i.e. pulse pressure) which participates in the mechanical force distending the artery is not taken into account.

Another strength of the paper by Dijk et al. is that carotid stiffness was measured in patients at high CV risk. Indeed, overt arterial disease, which is a powerful risk for further complications, was present at baseline. The fact that carotid stiffness has no independent predictive value in such a population while it has a powerful predictive value in ESRD and post-transplantation patients is indicative of a different pathogenesis of cardio-vascular events in these different populations. Indeed, treatments aiming at correcting classical risk factors are virtually the same in all high-risk populations (statins, angiotensin-converting enzyme-inhibitors, or angiotensin receptor blockers, aspirin, etc.), and are therefore unlikely to confound the analysis. Thus, one may speculate that the observed differences lie in the mechanisms of ischaemic events. In patients with prominent atherosclerosis, thrombosis at the site of vulnerable plaques is a major mechanism leading to ischaemic events. The present paper shows that acute plaque complication at any arterial site is marginally influenced by carotid stiffness. As suggested by the authors, the high arterial stiffness level of these patients may have reached a plateau, at which the range of stiffness and its predictive value are reduced.

In their paper, Dijk et al. discussed some additional reasons why no independent relationship was observed between at least one of these stiffness indices and CV events: no measurement of carotid pulse pressure; low-risk vs. high-risk patient; carotid vs. aorta. This last point raised by the authors deserves to be further investigated. Indeed, the predictive value of carotid stiffness may be restricted to some events, for instance, ischaemic cerebrovascular disease. The pathophysiological mechanisms relating carotid stiffness to stroke have been already reviewed. Local pulse pressure, which is increased in stiff conducting arteries, may influence arterial remodelling both at the site of the extracranial and intracranial arteries, increasing the carotid wall thickness and the development of stenosis and plaques, the likelihood of plaque rupture, and the prevalence and severity of cerebral white matter lesions. In addition, the measurement of aortic stiffness, which integrates the alterations of the arterial wall, may also reflect parallel lesions present at the site of cerebral vasculature. As discussed earlier, another explanation may be that in patients with patent cardiovascular diseases, mechanisms other than arterial stiffness, including thrombosis and inflammation, are involved in the pathogenesis of ischaemic complications. In contrast, aortic stiffness may be more closely related to the risk of coronary events than is carotid stiffness. A generally accepted mechanistic view is that aortic stiffness causes a premature return of reflected waves in late systole, increasing central pulse pressure and thus systolic blood pressure and load on the ventricle, reducing ejection fraction and increasing myocardial oxygen demand. Unfortunately, carotid–femoral PWV, which could have provided interesting information on the predictive value of aortic stiffness, when compared with carotid stiffness, has not been measured in the work by Dijk et al.

Further analyses of the SMART cohort with a longer follow-up may unmask a higher number of recurrent CV events, thus raising the statistical power of the study to detect a relationship between carotid stiffness parameters and specific CV events such as cerebrovascular events. The present results urge the need to measure both aortic and carotid stiffness in large cohorts of patients at low to moderate CV risk, in whom the prediction of primary events is the most important, to determine whether carotid stiffness may have additive value to aortic stiffness, measured with PWV.

Finally, although aortic stiffness is now well accepted as an independent endpoint for CV events (i.e. a significant longitudinal relationship between aortic stiffness and the occurrence of CV events has been demonstrated, independently of classical CV risk factors), its value as a surrogate endpoint has not been demonstrated in the general population. Data from Guerin et al. showed the first clear evidence in 150 patients with ESRD monitored for an average duration of 51 months. The absence of PWV decrease in response to blood pressure decrease was a significant predictor of all-cause and CV mortality. This suggests that aortic stiffness is a good surrogate endpoint, i.e. its attenuation is predictive of the reduction in all-cause and CV mortality. This is an important issue: whether drug treatment is able to prevent CV events through a reduction in arterial stiffness, independently of the correction of CV risk factors, including the lowering of BP.
References


