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REVIEW

Arterial stiffness: From surrogate marker to therapeutic target☆

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Abstract Carotid-femoral (aortic) pulse wave velocity (PWV) is the modern benchmark for the assessment of arterial stiffness. Current European hypertension guidelines acknowledge the good cardiovascular (CV) predictive value, reproducibility and cost-effectiveness of PWV. Aortic PWV is an asset to classical cardiovascular risk scores and can reclassify patients. Reference values for carotid-femoral PWV have been established. Together with standardisation of user procedures and patient conditions, these reference values are needed for an appropriate use of aortic stiffness in daily clinical practice. Finally, the existing evidence for a decrease in CV risk by decreasing aortic stiffness is discussed.

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The aim of this article is to review how arterial stiffness has become an important asset in cardiovascular risk (CV) stratification and a therapeutic target in patients with elevated CV risk. It also deals with current views on standardisation of methods to make arterial stiffness suitable for use in daily clinical practice.

Aortic stiffness and CV risk

In the nineties of the previous era arterial stiffness was found associated with many cardiovascular risk factors such as age, hypertension, diabetes, insulin resistance, hypercholesterolemia, hyperhomocysteinemia and acute effects of smoking.[1] These findings were followed by numerous studies showing that carotid-femoral (aortic) pulse wave velocity (PWV) was an independent risk factor for CV disease and events.[1] A meta-analysis of 17 longitudinal studies showed that an increase in aortic PWV of 1 m/s independently of other risk factors increases the relative risk of both all-cause and CV mortality by 15% ($p < 0.001$).[2]

In the Framingham Heart Study, a large population study, aortic stiffness was a clear predictor of incident hypertension and major cardiovascular events, while augmentation index, pulse pressure amplification and central pulse pressure did not show any predictive value.[3,4]

Aortic stiffness is the gold standard

The predictive value of arterial stiffness differs between vascular territories. Carotid-radial PWV, including muscular arteries of the upper limb, did not predict CV events,[4] while carotid-ankle and heart-ankle PWV, including the aorta and muscular arteries of the lower limbs were predictive.[5,6] But head-to-head comparison of the latter 2 with carotid-femoral PWV is lacking.

Like the aorta, the common carotid artery (CCA) is an elastic artery. However, early studies on the predictive value of CCA stiffness are not unequivocal. In patients with end-stage renal disease and after kidney transplantation[7,8] CCA stiffness was an independent predictor of CV disease, but not in population-based studies like SMART[9] and the Rotterdam Study.[10] On the contrary, the more recent Hoorn Study, also a population study but with excess of diabetes patients, showed predictive value of carotid and femoral artery stiffness. But these predictive values differed from aortic stiffness.[11] A recent systematic review and meta-analyses of aggregate and individual patient data confirmed the results of the Hoorn Study on carotid artery stiffness being predictive of CV events and CV and all-cause mortality.[12]

Aortic PWV also helps reclassify patients to higher or lower risk groups. This was first shown by Boutouyrie et al.[13] In hypertensive patients the risk for a primary coronary heart disease within 6 years increased with increasing Framingham risk score (FRS) and with aortic stiffness. But in patients within the highest tertile of aortic stiffness and the lowest tertile of FRS, this risk was similar to those with the lowest aortic stiffness and highest FRS, showing that arterial stiffness can correct risk over-as well as underestimation by FRS. Other studies confirmed that aortic stiffness can reclassify patients not only to higher and lower risk measured by FRS but also by SCORE.[14,15] Carotid stiffness also improved stroke risk prediction beyond Framingham and aortic stiffness, but not of coronary heart events.[12]

In addition, Paini et al. found the effect of ageing being similar on CCA and aorta stiffening when no CV risk factors were present. But in the presence of CV risk factors like hypertension and diabetes, the aorta showed an accelerated stiffening with ageing compared to the CCA, suggesting a better than CCA predictive value of aortic stiffening.[16]

Based on all these results aortic stiffness measured as carotid-femoral PWV is considered the gold standard and entered the 2007 joint guidelines of the European Societies of Cardiology (ESC) and Hypertension (ESH) as target organ damage.[17]

Standardisation of carotid-femoral PWV is urgently needed

Pulse wave velocity is calculated from the distance and time travelled by a pulse wave. Whereas the travel time of carotid-femoral PWV can be measured accurately, the non-invasive estimation of the travel distance was not standardized. Numerous methods exist to estimate the travel distance: the direct distance between the measurement sites at the carotid and femoral arteries, promoted by the Complior®, overestimates the travelled path length by 25%, while the subtracted distance using the sternal notch underestimates the path length by 29% (Table 1).[18,19] The subtracted distance using the suprasternal notch, advocated by the Sphygmocor® and also used in the Framingham Heart Study, underestimates the distance with 10%.

The distance from carotid artery to the femoral artery × 0.8 was found to give the best real-life approximation of real aortic path length and became the standard distance.[18,19] Since the cut-off value of 12 m/s published in the 2007 joint ESH/ESC guidelines[17] was based on the full carotid-femoral distance, recalculation of the PWV cut-off

Table 1 Comparison of reference distance of aortic path length (APL) with estimated distance of APL.

Tape-estimated APL	Tape-MRI (cm; mean ± SD)	Tape/MRI (%)	Cutoff (m/s)
(CA-FA) − (SSN-CA)	2.3 ± 3.8	+4%	9.98
(CA-FA) − (SN-CA)	−2.4 ± 3.8	−5%	9.12
(SSN-FA) − (SSN-CA)	−5.1 ± 3.5	−10%	8.64
(CA-FA)	13.0 ± 4.2	+25%	12.00
(SN-FA) − (SN-CA)	−14.8 ± 3.9	−29%	6.82
(CA-FA) × 0.8	0.3 ± 3.8	+0.4%	9.64
(Body height ÷ 4) + 7.28	−0.5 ± 3.9	−1%	9.50
Body height × 0.29	−0.9 ± 4.0	−1.8%	9.43

Adapted from: Van Bortel et al. J Hypertens. 2012; 30:445–8.[18,19] Reference distance used for comparison was (AA-FA) − (AA-CA) measured with MRI, Abbreviations: AA, ascending aorta; CA, carotid artery; FA, femoral artery; MRI, magnetic resonance imaging; SD, standard deviation; SN, sternal notch; SSN, suprasternal notch.