Surrogate Measures of Arterial Stiffness
Do They Have Additive Predictive Value or Are They Only Surrogates of a Surrogate?

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Recent epidemiological studies have shown that arterial stiffness, measured through carotid-femoral pulse wave velocity (PWV), has an independent predictive value for cardiovascular (CV) events in several populations, including patients with uncomplicated essential hypertension\(^1,2\) and type 2 diabetes.\(^3\) Arterial stiffness is thus an intermediate end point for CV events, predicting CV events independently of and beyond peripheral pulse pressure (PP).

Peripheral PP, central PP, and augmentation index, which provide additional information on wave reflection, are considered “surrogates” of arterial stiffness, because their pathophysiological meaning is clearly different.\(^4–6\) Central PP and augmentation index are dependent on the speed of wave travel, the amplitude of reflected wave, the reflectance point, and the duration and pattern of ventricular ejection, especially with respect to change in heart rate and ventricular contractility. Aortic PWV, which is the speed of wave travel, represents intrinsically arterial stiffness, according to the Bramwell-Hill formula.\(^4–6\)

Two articles\(^7,8\) in the present issue of *Hypertension* raise the issue of the predictive value of “surrogates of arterial stiffness” for CV events. Li et al\(^7\) studied the dynamic relationship between diastolic blood pressure (DBP0 and systolic blood pressure (SBP) in ambulatory blood pressure monitoring (ABPM) data throughout the day and calculated a novel index as \(1 - \) the regression slope of DBP on SBP. This index was named ambulatory arterial stiffness index (AASI) on the basis that “average distending BP varies during the day, and that the relation between DBP and SBP with this changing distending BP largely depends on the structural and functional characteristics of the large arteries.”\(^8\) The authors\(^7\) stated that it was a “novel measure of arterial stiffness” from the demonstration that AASI closely correlated with aortic PWV and the central and peripheral augmentation indexes. In a companion article, Dolan et al\(^8\) determined AASI in 11 291 participants to the Dublin Outcome Study and showed its independent predictive value for stroke mortality but not cardiac mortality, in contrast to 24-hour PP, which had an independent predictive value for cardiac mortality but not stroke mortality. These findings and statements call for several comments.

First, AASI should not be confused with arterial stiffness. A close univariate association between 2 parameters (AASI and aortic PWV) does not imply a single mechanistic link. For instance, although brachial PP and aortic PWV are strongly linked, they represent 2 aspects of hemodynamics. Pulse pressure increases when aortic stiffness increases because the pressure wave, which travels from the heart to the periphery (during each cardiac cycle), is reflected at some point, and returns to the heart. The stiffer the aorta, the faster the return of the reflected wave, which superimposes on the forward wave in late systole, thus increasing the amplitude of PP and SBP in the ascending aorta, and to a lesser extent in peripheral arteries. In addition, factors other than arterial stiffness can influence the value of brachial PP, such as heart rate, cardiac contractility, venous pressure, and amplification phenomenon.\(^4–6\) Particularly, Li et al\(^7\) provided no demonstration that AASI remained significantly correlated to aortic PWV after full adjustment for confounding factors.

Second, the hemodynamic significance of AASI, which is inversely related to the slope of brachial DBP versus SBP, is closer to brachial PP than arterial stiffness. Indeed, by contrast to what was discussed above, AASI remained significantly correlated to peripheral and central systolic augmentation after adjustment on confounding factors.\(^7\) Pathophysiological conditions and drugs can change PP and augmentation index without changing aortic PWV, suggesting a predominant effect on reflectance points, heart rate, or ventricular ejection, and no change in aortic stiffness.\(^9\)

Third, because arterial stiffness, directly measured by aortic PWV, is the final common pathway on which BP and other CV risk factors operate, it may have a higher predictive value than “surrogate” indexes. This may explain why the predictive value of AASI for CV mortality and fatal stroke, reported in the article by Dolan et al\(^8\) was lower than that reported with aortic PWV by others.\(^1–3\) For instance, AASI had no independent predictive value for CV mortality in the population of the Irish Outcome Study, whereas aortic PWV was an independent predictor of CV mortality in English diabetic patients\(^8\) and French hypertensive patients.\(^1\) For fatal stroke, the multiple adjusted relative hazard ratio for 1 SD increase in AASI (1.21 [1.01 to 1.45], \(P<0.05\)), reported in the article by Dolan et al,\(^8\) was lower than that observed with aortic PWV in a French hypertensive population (1.39 [1.08 to 1.72], \(P<0.05\); calculated from data of Reference 2) and no longer significant when restricted to the hypertensive population of the Irish Outcome Study. To increase the sensitivity of AASI, the author used a dichotomized value, comparing...
the 5% highest value to the 95% lowest. Even under these conditions, the independent predictive value of AASI for CV mortality (1.59 [1.23 to 2.04], \( P < 0.05 \)) was much lower than that of aortic PWV in a French hypertensive population (6.02 [3.05 to 11.85], \( P < 0.0001 \); calculated from data of Reference 1). Fourth, the authors state that the determination of AASI is easier than that of aortic stiffness, since “ABPM is implemented in most hospitals and a growing number of family practices,” whereas measurement of arterial stiffness “requires special equipment and trained observers.” Although it is unfortunate that arterial stiffness is underused in clinical practice for risk stratification, this is because of the absence of guidelines rather than the difficulty of measurements. Various apparatuses are currently available to easily determine aortic PWV in outpatient clinic facilities in less time than an EKG, with no more training than for performing a more disturbing 24-hour ABPM.

Finally, AASI is considered by the authors as a novel index of arterial stiffness, thus adding one more parameter to the already long list of surrogate indexes for arterial stiffness, including augmentation index, augmentation pressure, central PP, and brachial PP. This may reduce the understanding of an already complex area of research and hamper the implementation of simple guidelines into clinical practice. Arterial stiffness has demonstrated its surrogate value for CV events in patients with end-stage renal disease (ie, that a reduction in PWV could predict a reduction in CV events, independently of the normalization of classical CV risk factors). The impact of aortic stiffness reduction on CV mortality, coronary events, and stroke remains to be established in other populations, particularly those at lower but still high CV risk. Thus, instead of measuring the surrogate of a surrogate end point, why not use the direct measurement of arterial stiffness through aortic PWV, which has the largest amount of epidemiological evidence for its predictive value for CV events, requires little technical expertise, and is considered as the “gold standard” for arterial stiffness by most experts?

References
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