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COMMENTARY

More than a REASON to use arterial stiffness as risk marker and therapeutic target in hypertension

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Prevention of cardiovascular (CV) disease is largely based on a strict control of traditional risk factors, such as hypertension, smoking, dyslipidemia and diabetes. These factors are detrimental to arterial integrity by way of altering its structure, properties and function.[1] In particular, changes in the stiffness of the large arteries may largely account for the changes in systolic blood pressure (BP), diastolic BP and pulse pressure (PP) that occur from 50 years of age onward. Hence, there is a strong rationale for understanding the mechanisms of arterial stiffness to improve CV risk stratification and to better treat hypertension.

During the past few years, arterial stiffness has been widely investigated. Several non-invasive methods to assess arterial stiffness have become available.[2] Although office and ambulatory PP are the simplest surrogate measures of arterial stiffness, other quantitative methods and indices have been developed, namely: pulse transit time and pressure pulse waveform (aortic pulse wave velocity (PWV), central BP and augmentation index), local mechanical properties (arterial compliance and distensibility) and the correlation between ambulatory diastolic and systolic BP (ambulatory arterial stiffness index (AASI)).[2] Most of them showed a significant association with poor CV outcome over and above classical CV risk factors.[2–6] However, consistent data support the measurement of PWV as the most simple, non-invasive, robust and reproducible method to determine arterial stiffness.[2,7] A recent systematic review and meta-analysis[7] of 17 longitudinal studies evaluated the predictive value of aortic PWV for future CV events and all-cause mortality. The pooled relative risk of clinical events increased in a stepwise, linear-like fashion from the first to the third tertile of aortic PWV. The pooled relative risk of total CV events, CV mortality and all-cause mortality were 2.26 (95% confidence interval (CI): 1.89–2.70), 2.02 (95% CI: 1.68–2.42) and 1.90 (95% CI: 1.61–2.24), respectively, for high *vs.* low aortic PWV subjects. In particular, each increase in aortic PWV by $1\,m\,s^{-1}$ corresponded to an age-, sex- and risk factor-adjusted risk increase of 14, 15 and 15% in total CV events, CV mortality and all-cause mortality, respectively.

In this exciting and challenging area, the ancillary analysis of the REASON (*Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study*) trial reported in the current issue of this journal[8] focused on two key aspects regarding estimate and treatment of arterial stiffness. In particular, this study compared the influence of a pharmacological intervention on PP, aortic PWV and AASI.

This new analysis included patients enrolled in 32 of the 52 REASON (*Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study*) centers, which opted to perform ambulatory blood pressure monitoring. Arterial stiffness was estimated using ambulatory PP, AASI and aortic PWV in 201 out of 471 patients originally enrolled. Interestingly, baseline aortic PWV was more closely associated with 24-h ambulatory PP ($r=0.58$, $P<0.001$) than was AASI ($r=0.44$, $P<0.001$). These different indices of arterial stiffness remained significantly associated after adjustment for sex, age, body height, 24-h mean BP and 24-h heart rate.

The strict concordance observed between ambulatory PP and aortic PWV might lend support to ambulatory PP as a better surrogate of aortic PWV than AASI. However, both ambulatory PP and AASI have some limitations when compared with aortic PWV for the estimation of arterial stiffness (Figure 1). Peripheral PP is directly related to the mean arterial pressure and lowering BP may therefore lead to a reduction in PP without necessarily exerting a direct effect on the arterial wall. On the other hand, AASI describes, in a single number or coefficient, the dynamic relationship between diastolic and systolic ambulatory BP over 24 h by reflecting the mechanical properties of small arteries. Moreover, the predictive value of AASI seems to be not comparable to the predictive value of PWV, and measurement of aortic PWV appears to be less time-consuming and distressing for patients.[2]

The effect of different antihypertensive agents on arterial stiffness is an additive aspect of this study, which deserves some comment.

After a 4-week placebo-washout period, the patients were randomly assigned to treatment for 1 year with perindopril plus indapamide (107 patients) or atenolol (94 patients).

Office systolic BP decreased significantly more in the perindopril plus indapamide group than in the patients randomized to atenolol (adjusted mean difference 4.49 mm Hg, $P=0.002$); similar results were obtained considering 24-h ambulatory PP (adjusted mean difference 5.51 mm Hg, $P<0.001$). In contrast, the perindopril plus indapamide group failed to show a favorable effect on arterial stiffness rather than atenolol: for both aortic PWV and AASI, the between-group differences in the treatment-induced changes were not statistically significant.[8]

Despite the low power of this analysis (to detect a significant two-tailed difference

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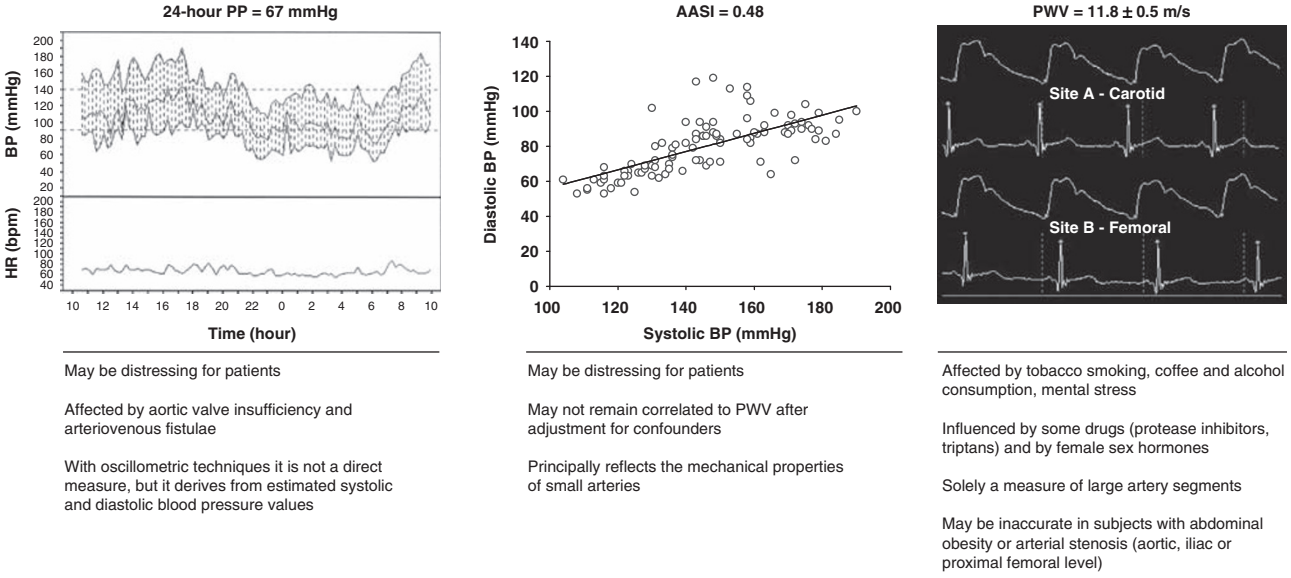

Figure 1 Main limitations of different techniques used in the ancillary analysis of the REASON trial for the estimation of arterial stiffness in a 39-year-old hypertensive male patient.

of $0.5 \pm 1.2\,m\,s^{-1}$ in aortic PWV with 95% power, the required number of subjects was estimated to be 300), the results are in keeping with those obtained in the entire trial cohort, where the two agents lowered PWV equally.[9]

Although it is conceivable that reduction of arterial stiffness may become a major primary goal of treatment, only few other clinical trials specifically investigated the effects of different BP-lowering drugs on arterial wall. One of the main intervention trials demonstrating the prognostic role of arterial stiffness and its treatment was conducted in hemodialysis patients.[3] The primary aim of this study was to lower CV morbidity and mortality through a complex therapeutic plan involving an initial salt and water depletion by dialysis, followed by, according to a multiarm randomization, an angiotensin-converting enzyme inhibitor or a calcium channel blocker (CCB) or the combination of the two agents and/or their association with a beta-blocker. Over a long-term follow-up (51 months), mean brachial BP, brachial PP and aortic PWV in survivors were lowered in parallel. In contrast, for patients who died from CV events, mean brachial BP had been reduced to the same extent as in survivors, but neither PWV nor brachial PP had been significantly modified by drug treatment. Thus, survival of end-stage renal disease patients seemed to be significantly better when aortic PWV declined in response to BP lowering. The adjusted relative risk in those with unchanged PWV in response to BP changes was 2.59 (95% CI, 1.51–4.43, $P<0.01$) for all-cause mortality and 2.35 (95% CI, 1.23–4.51, $P<0.01$) for CV mortality. The prognostic value for survival of PWV sensitivity to BP reduction was independent of age, BP changes and blood chemistries. Finally, prolonged survival was favorably associated with the use of an angiotensin-converting enzyme inhibitor, whereas the use of beta-blockers and/or CCBs had no direct impact on outcomes.[3]

More recently, in the Conduit Artery Function Evaluation (CAFE) study,[4] a subanalysis of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), 2073 participants underwent radial artery applanation tonometry and measurement of PWV. In keeping with the REASON study,[9] the results indicate that atenolol had lesser effect on central aortic BP and PP, despite similar brachial artery BP reduction, than a CCB regimen. Central aortic PP was also associated with clinical outcomes independently of age, other traditional CV risk factors and even peripheral PP.

A recent study examined the effects of a CCB (azelnidipine) *vs.* a diuretic (hydrochlorothiazide) in combination with the same angiotensin receptor blocker.[10] After adjustment for baseline covariates, central systolic BP decreased more in the angiotensin receptor blocker/CCB group (between-group difference of 5.2 mm Hg, $P=0.039$), whereas brachial and ambulatory systolic BP decreased similarly in the two groups (2.6 mm Hg, $P=0.29$). Moreover, aortic PWV showed a significantly greater reduction for the angiotensin receptor blocker/CCB combination than for the angiotensin receptor blocker/diuretic combination ($0.8\,m\,s^{-1}$; $P<0.001$) after adjustment for potential confounders.

Taken together, these studies not only demonstrated that brachial PP does not always reflect the impact of different pressure-lowering treatments on central aortic pressures and PWV, but also indicate that it is possible to obtain selective reduction of arterial stiffness and wave reflections through complex interactions between small-artery and large-artery effects.

Despite the fact that arterial stiffness can be quantitatively assessed by several methods, they are all far from perfection and none can thoroughly explore wall properties (Figure 1).[2] PWV is presently considered the 'gold standard' for the assessment of arterial stiffness and subclinical target organ damage and it seems to predict CV risk better than traditional measures. Conversely, insufficient data are available to conceivably introduce other markers of arterial integrity into routine clinical practice. In particular, further studies are required before AASI can be relied upon for a robust assessment of arterial stiffness.

Finally, arterial stiffness may be used to distinguish the beneficial effects of an intervention rather than simply measuring its effect on BP. However, sparse data are available to identify antihypertensive agents that specifically target the arterial wall. Whether or not different treatments can affect the long-term prognosis of patients with stiff arteries remains to be established. These REASON findings open the way for the development of

long-term CV treatment strategies involving both small and large arteries.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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