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COMMENTARY

Is ambulatory arterial stiffness index a marker of large-artery stiffness? Evidence from intervention studies

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When blood pressure (BP) is measured several times in a given individual, as it typically happens during ambulatory or home BP monitoring, the linear relationship between systolic and diastolic BP can be taken as the basis for a number of clinical markers, which may give information on the large-artery functional properties without the need for dedicated equipment and personnel.[1] The most widely used parameter based on the linear relationship between systolic and diastolic BP is the so-called 'ambulatory arterial stiffness index' (AASI).[2] It can be assumed that, for any given increase in distending arterial pressure, systolic and diastolic pressures tend to increase in a parallel manner in a compliant artery, while in a stiff artery the increase in systolic pressure is accompanied by a lesser increase, or even by a decrease, in diastolic pressure. The regression slope of diastolic-on-systolic BP measurements obtained through 24-h ambulatory BP monitoring has been considered as a global measure of arterial compliance, and its reciprocal (1 minus the slope), named AASI, as a measure of arterial stiffness.[2]

CLINICAL VALUE OF AASI

The popularity of AASI among researchers and clinicians derives from its widely established prognostic value.[3] AASI has been correlated with target organ damage in cross-sectional studies,[4] but more importantly prospective studies have found that an elevated AASI is an independent predictor of cardiovascular mortality[5–7] and stroke.[8] In a recent meta-analysis, Aznaouridis *et al.*[9] found that each 1 s.d. AASI increase conferred a 26% excess risk for stroke (95% confidence interval, 8–45%) after adjustment for age, sex, body mass index, cardiovascular risk factors and 24-h pulse pressure, and a 9% multivariate-adjusted excess risk for cardiovascular morbidity and/or mortality (95% confidence interval, 1–18%).

Despite its established prognostic value, the true physiological meaning of AASI remains elusive. It has been clearly demonstrated that AASI is related to surrogate measures of arterial stiffness, such as age and office or 24-h pulse pressure.[2,6,10,11] However, a number of studies have shown that AASI may not be a measure of arterial stiffness. Carotid-femoral pulse wave velocity, which is considered a direct measure of aortic stiffness, was found to have a relatively weak correlation with AASI in two large, independent cross-sectional studies carried out in hypertensive subjects.[10,12] In both studies, the above correlations became non-significant following adjustment for age.[10,12] Overall, AASI was found to be a poor predictor of aortic pulse wave velocity, with 95% prediction limits for the AASI to predict pulse wave velocity as wide as $\pm 4\,m \times s^{-1}$.[10] These findings were substantially confirmed in a meta-analysis of nine studies ($n = 4123$) in which the pooled correlation coefficient of AASI with carotid-femoral pulse wave velocity was 0.30 (95% confidence interval, 0.19–0.42).[9] In a meta-analysis of 20 studies ($n = 29\,186$) examined, the pooled correlation coefficient of AASI with 24-h pulse pressure as an indirect index of arterial stiffness was 0.47 (95% confidence interval, 0.40–0.54).[9] The weak correlation between AASI and arterial stiffness has been recently confirmed in a computer model of the human circulation.[13] Overall, available data suggest that AASI is a valuable tool for cardiovascular risk stratification in hypertension and in other clinical settings, despite being a relatively poor index of arterial stiffness.

THE PRESENT STUDY

A further insight into the actual physiological meaning of AASI and of its questionable link with arterial stiffness may come from studies addressing the issue of how the above measures change in response to BP-lowering treatment. In the previous issue of *Hypertension Research*, Kollias *et al.*[14] report on an intervention study, in which 104 hypertensive subjects underwent 24-h ambulatory BP monitoring twice, before treatment and after 1 year of BP-lowering treatment based on renin–angiotensin–aldosterone system blocking agents. The authors should also be commended for putting their study in the context of the current literature, by performing a systematic review and a meta-analysis of the studies investigating how AASI changes with antihypertensive treatment. The main findings of the study can be summarized as follows.

(1) AASI did not change significantly after treatment, despite substantial reductions in 24-h systolic, diastolic and pulse pressures, and in carotid-femoral PWV. AASI was 0.38 ± 0.14 at baseline, and increased non-significantly by 0.012 (95% confidence interval, -0.020 to $+0.044$).

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(2) Treatment-induced changes in AASI were found to have two independent correlates, that is, baseline AASI and treatment-induced changes in nocturnal BP dipping. AASI changes had significant bivariate associations with both baseline 24-h pulse pressure and treatment-induced pulse pressure changes, although the above relationships did not hold in a multivariate analysis. No significant relation was found between AASI change and treatment-induced change in carotid-femoral pulse wave velocity.
(3) In a meta-analysis of 8 studies with a total of 990 participants, in which AASI was measured both before and after antihypertensive treatment (study duration, 3–54 weeks), the authors found that antihypertensive drug treatment induced a marginal and barely significant reduction of AASI (−0.018; 95% confidence interval, −0.033 to −0.003). The results were not materially different if the analysis was restricted to the studies in which treatment was based on the use of renin–angiotensin–aldosterone system blockers.

The lack of a significant effect of BP-lowering drug treatment on AASI is at partial variance with the findings of three small observational or intervention studies, in which paced slow breathing and the summer season, but not reduced salt intake, were associated with a reduction in the 24-h systolic-on-diastolic BP regression slope.[15] These data suggest that environmental stimuli and lifestyle changes might have an impact on AASI, although the small study population (with approximately one dozen patients enrolled in each of the three studies) and the lack of a control group limit the interpretation and applicability of the results.

The observation by Kollias *et al.*[14] that AASI changes and pulse wave velocity changes over a 1-year BP-lowering treatment are not related to each other lends further support to the view that AASI is only weakly determined by arterial stiffness,[10,12] and may be related to different pathophysiologic mechanisms.[16]

WHAT IS AASI?

AASI is a complex physiologic parameter, which depends on a number of factors other than arterial stiffness, which are summarized in the Table 1.

First of all, AASI is affected by a number of spurious correlations, which derive from its mathematical definition. AASI is defined as 1 minus the diastolic-on-systolic BP regression slope, the latter obtained using a standard or asymmetric regression of diastolic-on-systolic BP readings during a 24-h ambulatory BP monitoring session. As such, AASI is intrinsically dependent on the correlation coefficient between systolic and diastolic BP.[17] Systolic-on-diastolic BP slope and diastolic-on-systolic BP slope calculated using standard asymmetric regression are reciprocal to each other only when the correlation coefficient between systolic and diastolic BP is 1. In all the other cases, use of an asymmetric regression leads to artifactual dependence of AASI on the correlation coefficient between systolic and diastolic BP.[17] One important consequence of the artifactual dependence of AASI on the correlation between systolic and diastolic BP is its strong dependence on the degree of nocturnal BP reduction.[10] By definition, subjects with a low nocturnal BP fall (non-dippers) have a narrower range of 24-h diastolic BP (which is the dependent variable in the regression equation that generates AASI). As a consequence, the coefficient of regression B of diastolic-on-systolic BP decreases, and its complement (AASI or 1 minus B) increases. The artifactual dependence of AASI on the correlation between systolic and diastolic BP may be eliminated if AASI is calculated using a symmetric regression model.[17] Due to the above relationship between AASI and day-night BP reduction, AASI also depends on the ratio of night-time over daytime BP readings number, which is determined by the time intervals between consecutive measurements during the day and the night.[18,19]

Table 1 Factors influencing ambulatory arterial stiffness index in a positive or negative way

	Reference
Positive	
Arterial stiffness	Li *et al.*[2]
Day/night ratio of BP readings	Gavish *et al.*[17]
Strength of the systolic-diastolic BP correlation (r_{SD})	Schillaci and Pucci[16]
Diastolic-to-systolic arterial stiffening	Schillaci and Pucci[16]
Negative	
Nocturnal diastolic BP reduction ('dipping')	Hansen *et al.*[8,13]
Heart rate	Craiem *et al.*[22]
Total peripheral resistance	Craiem *et al.*[22]

Abbreviation: BP, blood pressure.

In the study by Kollias *et al.*,[14] treatment-induced change in nocturnal diastolic BP dipping was a strong univariate correlate of AASI change, and the only independent determinant of AASI changes apart from baseline AASI. This observation is in line with the studies showing the spurious association of AASI with nocturnal diastolic BP dipping.[10] Interestingly, when symmetrical AASI changes were considered instead of asymmetric or traditional AASI, a weak *albeit* significant relationship with treatment-induced changes in 24-h pulse pressure emerged. However, neither symmetric nor asymmetric AASI changes had a significant relationship with changes in carotid-femoral pulse velocity.

Westerhof *et al.*[20] suggested that AASI may be more an expression of ventriculo-arterial coupling than of arterial stiffness. Gavish[21] proposed that the systolic-on-diastolic BP slope could be related more to the increase in arterial stiffness from diastolic-to-systolic values ('diastolic-to-systolic stiffening') than to diastolic stiffness, the latter being typically measured by pulse wave velocity. Similarly, Craiem *et al.*[22] showed that AASI can be accurately predicted by a model, which takes into account the non-linear behavior of the arterial wall. Interestingly, other surrogate measures of arterial systolic stiffening, such as the cardio-ankle vascular index, also have a predictive value for cardiovascular complications.[23,24]

Heart rate and total peripheral resistance are further determinants of AASI. In a previously validated computer model of the arterial circulation, Kips *et al.*[13] showed that an increase in heart rate or peripheral resistance from 80% to 120% of its default value caused the AASI to decrease by 37% or 9%, respectively. While there was no overlap in the arterial distensibility ranges for the three theoretical subjects considered by the model, the amount of overlap between the AASI distributions was substantial.

Overall, the prospective study and the meta-analysis by Kollias *et al.*[14] provide compelling evidence that AASI may not be a measure of large-artery stiffness measured at the level of diastolic BP, as in its most widely used and direct estimate, that is, carotid-femoral pulse wave velocity. The relationship between systolic and diastolic BP describes a physiological process that is different and only partially related to diastolic arterial stiffness as typically measured by pulse wave velocity. Despite the evidence that AASI may

not be a good surrogate of arterial stiffness, the analysis of the dynamic relation between systolic and diastolic BP over a wide range of values may potentially broaden our understanding of the mechanical properties of human arteries and improve current cardiovascular risk stratification.[16]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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