

## Correspondence

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### Putting a spin on the ambulatory arterial stiffness index

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We defined the ambulatory arterial stiffness index (AASI) as unity minus the slope of diastolic on systolic blood pressure [1,2]. When determined from 24-h ambulatory blood pressure recordings, AASI reflects the dynamic relation between diastolic and systolic blood pressure throughout the day [1]. According to physiological concepts already proposed in 1914 [3], the stiffer the arterial tree, the closer the regression slope and AASI are to zero and one, respectively.

Since our original publications [1,2], several investigators have published on AASI. In the February issue of the *Journal of Hypertension* two articles [4,5] and one editorial comment [6] addressed the merits and limitations of AASI as a simple surrogate measure of arterial stiffness. Gavish and colleagues [4] proposed the use of the so-called symmetrical regression instead of ordinary regression to compute AASI. Baumann and colleagues [5] misread our publications [1,2] and computed AASI from the regression slope of systolic on diastolic blood pressure.

The study by Gavish *et al.* [4] included a selected group of 140 referred hypertensive patients, of whom 76 (54.3%) were on antihypertensive drug treatment. The study by Baumann *et al.* [5] included 106 potential kidney donors, of whom 31 were hypertensive (29.2%), and 22 (20.8%) were treated. The small sample size, selection, and the use of antihypertensive drugs make a reasonable interpretation of the results impossible. Our original publications derived conclusions from a considerably larger sample size and included a randomly selected Chinese population ( $n=348$  [1]) and untreated hypertensive patients ( $n=11291$  [2]).

Both publications [4,5] also built part of their argument on the correlation of AASI with pulse pressure. These associations are spurious because the dependent and independent variables are both calculated from the same systolic and diastolic blood pressure readings. Nevertheless, while keeping this potential flaw in mind, in our Belgian cohort ( $n=552$  [7]), the correlation with pulse pressure was stronger for AASI than for symmetrical AASI (0.50 vs 0.17;  $P<0.001$ ). Moreover, the correlation between AASI and pulse pressure was almost identical in 428 diastolic dippers and 124 diastolic nondippers (0.44 vs. 0.44;  $P=0.98$ ). Baumann and co-workers [5] only had about 19 nondippers to investigate these associations.

The studies by Gavish *et al.* [4] and Baumann *et al.* [5] spin an issue first raised by Schillaci and co-workers [8], and subsequently confirmed by us [9], that AASI is inversely correlated with night-time dipping. According to the experts [10], aortic pulse wave velocity (PWV) is the gold standard for measuring arterial stiffness. In 166 Chinese volunteers [1], in whom we measured AASI and PWV within 24 h, the correlation coefficients with the percentage fall in nocturnal blood pressure were similar for PWV and AASI [MTEST statement in the PROC REG procedure of the SAS package, version 9.1.3 (SAS Institute Inc., Cary, North Carolina, USA);  $P>0.54$ ], amounting to  $-0.54$  and  $-0.49$  for systolic dipping and to  $-0.56$  and  $-0.57$  for diastolic dipping. Moreover, AASI was consistently and significantly related to PWV in 99 diastolic dippers ( $r=0.27$ ;  $P=0.007$ ) as well as in 67 diastolic nondippers ( $r=0.41$ ;  $P=0.0005$ ).

We concur with our colleagues [6,10] that AASI is an indirect measure of arterial stiffness and must be under the influence of other haemodynamic factors such as heart rate and the velocity of left ventricular ejection. However, we strongly believe that with regard to AASI, researchers should now leave the circular argumentation and the mathematical hair-splitting. What clinically counts at the end of the line is that AASI improves the risk stratification based on ambulatory blood pressure monitoring. To date, several cross-sectional studies [11,12] and at least three prospective cohort studies [2,13,14] have demonstrated the association of AASI with either the signs of target organ damage in never-treated hypertensive patients [11] or the incidence of cardiovascular mortality and morbidity [2,13,14]. When adjusted for pulse pressure [2,13,14] or PWV [15], AASI remained predictive, in particular of stroke.

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## Reply

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The authors point in their comment to the fact that we computed ambulatory arterial stiffness index (AASI) based on the regression slope of systolic–diastolic blood pressure. If we computed our data according to the original work of Li *et al.* [1] and Dolan *et al.* [2], the correlation between diastolic dipping and AASI remained significant ( $r = -0.28$ ;  $P = 0.006$ ). Moreover, the difference between nondipper and dipper with respect to AASI remained significant (mean  $\pm$  SD; nondipper,  $0.36 \pm 0.14$ ; dipper,  $0.29 \pm 0.11$ ;  $P = 0.01$ ).

Another point made by the authors was the heterogeneity of our group including normotensive and hypertensive

subjects. Therefore, we computed our data according to the original work of Li *et al.* [1] and Dolan *et al.* [2], excluding our 31 hypertensive individuals. Again, the correlation between diastolic dipping and AASI remained significant; however, to a lesser extent ( $r = -0.23$ ;  $P = 0.03$ ). Moreover, the difference between nondipper and dipper with respect to AASI remained significant for the normotensive cohort (mean  $\pm$  SD; nondipper,  $0.35 \pm 0.15$ ; dipper,  $0.29 \pm 0.11$ ;  $P = 0.04$ ). Therefore, our data are in line with the work of several groups including the authors [3].

Schillaci *et al.* [4] pointed out hemodynamic factors potentially influencing AASI. Similarly, our discussion focused on the potential role of autonomic nerve function as a cause of dipping [5] and thus as factor influencing AASI. We believe that understanding factors influencing AASI, such as the autonomic nerve function, may be useful for the further interpretation of AASI, as we fully agree with the authors that AASI improves the risk stratification based on ambulatory blood pressure monitoring.

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## Reply

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We concur with Adiyaman *et al.* [1] that the ultimate testing ground for ambulatory arterial stiffness index (AASI), as for any newly proposed index of target organ damage, is represented by its ability to predict cardiovascular complications over and above the prognostic

power of established risk factors and markers of organ damage. In this regard, several of the authors of the study by Adiyaman *et al.* should be commended for their tremendous amount of work aimed at elucidating the prognostic contribution of AASI as well as its limitations [2–5]. Overall, in different clinical settings, AASI was found to be an independent predictor of stroke [2–4] and cardiovascular mortality [2,3] but not of cardiovascular events [5] and coronary heart disease [3,5].

On the contrary, we are certain that Adiyaman *et al.* will agree with our view that the actual physiological significance of AASI is far from being clarified [6]. Recently published data [7] confirm our finding [8] that, at least in hypertensive individuals, AASI may not be considered as a surrogate marker of arterial stiffness. In 515 volunteers examined by us [8,9] and in 824 individuals observed by Jerrard-Dunne *et al.* [7], the positive correlation between AASI and carotid-femoral pulse-wave velocity, which is considered as a direct measure of aortic stiffness, was considerably weaker than that reported earlier in a smaller cohort of 166 predominantly normotensive Chinese individuals [10] and was lost following adjustment for age [7–9]. 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  $\pm 4.18$  m/s [7].

We had previously shown that this lack of association between AASI and established, though indirect, measures of arterial stiffness might be in part related to the strong, spurious inverse association between AASI and day–night diastolic, and consequently systolic, blood pressure (BP) reduction [8]. It has been suggested that such a strong relation may be due to the fact that nocturnal BP fall might be in itself a correlate of arterial stiffness [1]. However, the absence of a significant relationship between nocturnal BP fall and aortic pulse-wave velocity in two large, independent studies on hypertensive individuals [7,8] makes this hypothesis unlikely. The paper by Gavish *et al.* [11] is a first attempt to eliminate the limitations characterizing such artefactual relationship by using a symmetrical regression model.

In conclusion, the development of AASI [2,10] unquestionably represents a theoretically attractive means of easily exploring arterial stiffness without the use of dedicated, operator-dependent equipment. However, given the present uncertainties regarding the meaning and the clinical importance of AASI, we believe that any contribution toward a better understanding of AASI should not be considered as a pedant hair-splitting exercise but as an attempt to more deeply appreciate the mechanisms and the clinical significance of the dynamic features characterizing the relation between systolic and diastolic BPs.

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## Reply

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The possibility that the observed linear relationship between repeatedly measured systolic and diastolic blood pressures can provide parameters that express mechanical properties of arteries and have clinical significance is exciting. Schillaci and Parati [1] expressed the increasing interest in this phenomenon by devoting an editorial to two articles on this topic [2,3]. This correspondence is a response to the letter by Staessen and colleagues, who addressed these publications [1–3]. We raise basic questions related to definition, determination and physiological origins of selected parameters in an attempt to widen the interest in this newly emerging topic, beyond arterial stiffness index (AASI) and arterial stiffness.

## Parameter definition and determination

The linear relationship between variations in systolic and diastolic pressures over time is known for office measurements with follow-up over years in the Framingham study [4]; 24-h ambulatory measurements [5–7] and can be clearly demonstrated in home measurements over months and in beat-by-beat measurements within few minutes. Therefore, this phenomenon is not limited to

ambulatory blood pressure measurements, suggesting that the dipping status may be important mainly as a generator of variability range, as already pointed out by Schillaci *et al.* [8]. The relevant parameter is the slope of the regression line associated with either systolic versus diastolic plot ('S–D slope') or with diastolic versus systolic plot ('D–S slope'), where AASI is defined by  $1 - [D-S \text{ slope}]$ . The S–D and D–S slopes are reciprocal to each other when calculated by symmetric regression (but not with standard regression) [2] and can be referred collectively as 'slope'. The importance of using appropriate regression procedure for 'slope' determination cannot be underestimated when correlations with clinical and demographic variables are found to depend strongly on the regression method applied. 'Slope' determination by standard regression, as commonly used, leads to flattening of a strong dependence on age and generates a negative correlation between AASI and systolic dipping, as observed by Schillaci *et al.* [8] and Bauman *et al.* [3]. This correlation turns weak and positive upon using symmetric regression [2]. The underlying intriguing phenomenon is the observed relationship between systolic–diastolic correlation coefficient  $r$  and systolic or diastolic dipping [2]. In fact, neither AASI nor S–D slope were found to depend on  $r$  when determined by symmetric regression [2].

### Underlying physiological principles

Real arteries cannot be described as simple elastic tubes characterized by a single value of arterial stiffness. Instead, arterial stiffness increases for greater pressure. This 'arterial-stiffening' property that sharply increases after age 50–60 years reflects the nonlinear pressure–diameter (or volume) relationship [9]. As a result, arterial stiffness, as well as pulse-wave velocity, may undergo large variations between systolic and diastolic pressures during the cardiac cycle [10,11] and both are expected to decrease with nocturnal blood pressure fall. In contrast, 'slope' is by definition a parameter that is independent of pressure over the entire pressure range. The fact that 'slope' measured by 24-h ambulatory blood pressure monitoring displayed independence of mean arterial pressure in a tested population of 140 patients [2] casts further doubts about the justification of associating AASI with arterial stiffness, in spite of its observed correlation with pulse-wave velocity [6,8].

The possibility that the 'slope' expresses the arterial stiffening during the cardiac cycle and not arterial stiffness is challenging. Support for this view comes from a theoretical derivation by Gavish [12] showing that S–D slope expresses quantitatively the relative increase of arterial stiffness during the systole that appears independent of pressure [2], as well as from important work by Conway and Smith [13] and Abboud and Huston [14] that attempted to characterize arterial stiffening by a parameter called 'arterial rigidity index'. These

researchers measured beat-to-beat intra-arterial pressure in response to inhalation of amyl nitrite. This parameter increased with age and showed good potential as an index for arterial aging and degenerative vascular disease. Arterial stiffening was found to reflect increased loading of the collagen tissue in the vascular wall [15]. Increased collagen/elastin ratio that characterizes vascular aging and pathology may lead to increase in both stiffness and stiffening. This pressure-independent structural aspect may explain why AASI positively correlates with pulse-wave velocity and expresses arterial stiffening but not stiffness. The present view is consistent with the finding of Dolan *et al.* [7] that AASI is a predictor of cardiovascular mortality in hypertensive patients.

In conclusion, in searching for the clinical significance and the physiological origin of the linear relationship between systolic and diastolic pressures, it is necessary to expand the view beyond ambulatory blood pressure measurements and arterial stiffness. The possibility of characterizing the nonlinear mechanical properties of arteries using pressure-independent parameters derived from blood pressure measurements is stimulating.

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