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COMMENTARY

The relationship between systolic and diastolic blood pressure: a clinically meaningful slope?

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The traditional paradigm of hypertension as a product of increased stroke volume and peripheral resistance[1] has been progressively replaced over the last few decades by a more complex interpretative model, in which the left ventricle and peripheral arteries are functionally coupled with large arteries. The growing scientific interest in the functional properties of the large arteries has been driven primarily by an improved understanding of waveforms and of their modifications in physiological and pathological conditions.[2] Additional factors include the availability of non-invasive devices that are able to accurately estimate large-artery and muscular-artery stiffness,[3] and the publication of several clinical studies that have shown the role of arterial stiffness as a predictor of cardiovascular damage and complications.[4,5] Aortic pulse-wave velocity, an index of large-artery stiffness and an independent predictor of cardiovascular complications in different clinical settings,[4,5] has thus been added to the list of factors influencing prognosis in hypertensive subjects,[6] although the need for dedicated equipment and trained personnel has hindered its application in daily clinical practice. A technique to estimate arterial stiffness without the use of special equipment or qualified observers would thus be welcome.

By measuring blood pressure (BP) several times in a given individual, possibly under different circumstances, systolic BP (SBP) values can be plotted against diastolic BP (DBP) values. The slope of the relationship between SBP and DBP has been proposed as a theoretically attractive means of investigating large-artery functional properties.[7] In principle, the link between SBP-on-DBP slope and arterial functional properties is rather straightforward.[8] A change in DBP in a given subject is generally accompanied by a change in SBP that goes in the same direction. However, for a given increase in DBP, SBP might be expected to increase more in a stiffer artery than in a more pliable one. Thus, the increase in SBP for a given increase in DBP (SBP-on-DBP slope) could be related to arterial stiffness. The opposite holds for the increase in DBP for a given increase in SBP (DBP-on-SBP slope), which could be considered as a measure of arterial compliance. A slope-derived parameter obtained from 24-h ambulatory BP monitoring, namely the ambulatory arterial stiffness index (AASI),[7] has received great attention from the scientific community, despite the need for caution inherent to the use of a surrogate for more direct measures of arterial rigidity.[9,10]

In the present issue of *Hypertension Research*, Gavish *et al.*[11] report the findings of a *post-hoc* analysis of three small studies that examined the effects of season, salt intake and paced breathing on 24-h BP and the related SBP-on-DBP slope. In one study, 13 hypertensive subjects were examined before and after 8 weeks of 15-min daily sessions of slow breathing guided by a device used to lower the high BP. In another study, 17 elderly subjects living in a nursing home underwent 24-h BP measurement before and 6 months after replacing dietary salt with low-sodium, high-potassium salt. In a third study, BP was measured in 12 subjects during the winter and the summer. Notably, slope-related measures were calculated using two different regression procedures (symmetric *vs.* asymmetric, see below) and three different BP-averaging methods (average of individual raw BP data over 24 h, mean of individual hourly average values and hourly averaged BP further averaged over the patient population).

The study shows that paced breathing and the summer season are both associated with a reduction in 24-h SBP and DBP as compared with baseline and winter values, respectively. More importantly, the 24-h SBP-on-DBP regression slope was significantly lower during summer and after paced breathing. Moreover, the authors found that changes in slope-related measures were sensitive to the methods used for analysis. Indexes based on symmetric regression (symmetric AASI, symmetric SBP-on-DBP slope or its equivalent, and the BP variability ratio[12]) showed a larger and more significant response to intervention or a change in condition than those based on asymmetric regression ('traditional' AASI). Also, a comparison of 24-h BP profiles based on hourly averaged BP, further averaged over the general population, yielded larger and more significant differences than the average of individual raw BP data.

The effect of treatment on SBP-on-DBP slope has received little attention thus far. In 188 hypertensive subjects, treatment with an angiotensin-receptor blocker was associated with a reduction in AASI, whereas patients treated with calcium-channel blockers showed no significant changes, despite a similar reduction in BP.[13] In a randomized study, the impact of 1-year treatment with perindopril/indapamide on AASI and aortic pulse-wave velocity was not significantly different from that of atenolol.[14] In a small study carried out in treated hypertensive patients, both asymmetric and symmetric AASI were lower in the subjects with high adherence to treatment.[15] Overall, the present study suggests for the first time that non-drug interventions and changes in conditions known to affect BP have the potential to

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Table 1 Parameters based on the slope of the relation between systolic and diastolic blood pressure

Parameter	*Technique*	*Definition*	*Advantages*	*Disadvantages*
Ambulatory arterial stiffness index (AASI)	24-h ambulatory BP monitoring	1−(DBP-on-SBP slope), using standard asymmetric regression	• Predicts cardiovascular outcomes • Association with target organ damage	• Depends on nocturnal BP dipping • Depends on the strength of SBP–DBP correlation • Depends on day/night ratio of BP readings • Weak correlation with arterial stiffness
Home arterial stiffness index	Home BP monitoring	1−(DBP-on-SBP slope), using standard asymmetric regression	• Cheap, widely available	• Fewer measurements • Limited BP range • Weaker correlation than AASI with age and pulse pressure • No prognostic data
Symmetric ambulatory arterial stiffness index AASI	24-h ambulatory BP monitoring	1−(DBP-on-SBP slope), using symmetric regression	• Independent from nocturnal BP fall • Independent from SBP/DBP correlation	• Limited prognostic data
SBP-on-DBP slope	24-h ambulatory BP monitoring	SBP-on-DBP slope, using symmetric regression SBP-on-DBP slope=1/(1−symmetric AASI)	Same as SBP-on-DBP slope	
BP variability ratio	24-h ambulatory BP monitoring	24-h SBP-s.d./DBP-s.d. BP variability ratio=SBP-on-DBP slope	Same as SBP-on-DBP slope	

Abbreviations: AASI, ambulatory arterial stiffness index; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

favorably modify the SBP–DBP slope over a period of 24 h.

HOW TO MEASURE SBP-ON-DBP REGRESSION SLOPE?

Several different indexes have been proposed to assess the slope of the relationship between SBP and DBP (Table 1). AASI is defined as 1 minus the DBP-on-SBP regression slope, the latter obtained using a standard asymmetric regression of DBP-on-SBP readings during a 24-h ambulatory BP monitoring session.[7] The clinical relevance of AASI is suggested by its cross-sectional correlation with pre-clinical target-organ damage[16–18] and its predictive value for future cardiovascular morbidity and mortality,[19–22] although the superiority of AASI over more widely accepted surrogate measures of arterial stiffness such as 24-h pulse pressure[23] has not been established.[24,25] Some methodological drawbacks of AASI need to be considered, however.[10] First, AASI is strongly dependent on the degree of nocturnal BP drop.[26–28] By definition, subjects with a low nocturnal BP fall (non-dippers) tended to have a narrower range of DBP values over the 24-h period (that is, the dependent variable in the regression equation that generates AASI). As a mathematical consequence, the coefficient of regression B of DBP on SBP tends to decrease over the 24 h, and its complement (AASI, or $1-B$) increases.[26] Notably, adjustment for nocturnal BP reduction eliminates the relationship of AASI with measures of target-organ damage, such as left ventricular hypertrophy[26] and microalbuminuria.[29] Second, the ratio of nocturnal over diurnal BP readings, determined by the nighttime and daytime between-measurement time intervals, has an effect on AASI—the lower the number of nocturnal readings as compared with daytime readings, the higher the AASI.[30] This confounding effect is due to the above relationship between day–night BP reduction and AASI.[31] Third, AASI is intrinsically dependent on the correlation coefficient between SBP and DBP.[12] SBP-on-DBP slope and DBP-on-SBP slope calculated using standard asymmetric regression are reciprocal to each other only when the correlation coefficient between SBP and DBP is 1. In all the other cases, using asymmetric regression leads to artifactual dependence of AASI on the SBP–DBP correlation coefficient.[12]

A modified AASI, calculated with symmetric regression, may reduce its dependence on day–night BP changes and on the correlation between SBP and DBP, and has been associated with all-cause mortality.[32,33] The method, however, has not been compared with direct measures of arterial stiffness, and its clinical and prognostic relevance awaits further confirmation. Notably, symmetric AASI is mathematically connected to the ratio between the standard deviation of 24-h SBP and 24-h DBP (BP variability ratio)[12] (Table 1).

A cheaper and more universally available alternative way to obtain a large number of BP readings may be represented by home BP monitoring. Home arterial stiffness index, an index of the dynamic behavior of the relationship between SBP and DBP in a given individual obtained from home BP monitoring, has shown a direct correlation with age and pulse pressure, although such associations were invariably weaker than those observed with AASI.[34] Possible reasons for the inferiority of home arterial stiffness index as compared with AASI are a lower number of BP readings and the fact that home arterial stiffness index is based on BP measurements taken at rest and in a standardized position, whereas AASI includes measurements taken during the execution of typical daily activities.

SBP-ON-DBP SLOPE: A MEASURE OF VASCULAR STIFFNESS?

AASI, the most widely investigated measure of DBP-on-SBP slope, has been related to carotid-to-femoral pulse-wave velocity, a direct measure of aortic stiffness,[7] although most studies did not confirm this finding in larger cohorts.[26,35–37] In these studies, the relation between AASI and aortic pulse-wave velocity was weak, and, importantly, was affected or entirely negated after adjustment for age and other factors.[26,35–37] Additionally, 24-h pulse pressure showed a stronger relationship with aortic pulse-wave velocity than AASI.[36,37]

The physiological significance of slope-related parameters is currently debated.

Based on a computer model, Craiem *et al.*[38] concluded that AASI is higher in stiffer arteries due to the nonlinearity of arterial elasticity. Westerhof[39] suggested that AASI expresses ventriculo-arterial coupling rather than arterial stiffness. Gavish[40] suggested that the SBP-on-DBP slope could reflect the increase in arterial stiffness from diastolic to systolic values ('systolic stiffening') rather than diastolic stiffness, the latter typically measured by pulse-wave velocity. It was demonstrated over half a century ago that the slope of the change in pulse pressure over the change in diastolic pressure after inhalation of amyl nitrite (the so-called 'arterial rigidity index') increases with age and with clinical evidence of atherosclerosis.[41,42] Thus, the relationship between SBP and DBP might describe a physiological process that is different and only partially related to diastolic arterial stiffness as measured by pulse-wave velocity. The study by Gavish *et al.*[11] suggests that paced breathing and the summer season might have a positive effect on arterial functional properties as expressed by the slope of SBP-on-DBP over the 24-h period.

STUDY LIMITATIONS AND PERSPECTIVES

The findings of the article by Gavish *et al.*[11] should be interpreted within the context of its limitations. Data from the salt restriction study were quite unexpected. Replacing common salt with low-sodium, potassium-enriched salt had no effect on slope-related measures and, most importantly, was followed by a paradoxical increase in SBP and pulse pressure. These data are in sharp contrast with the current literature, which shows a beneficial effect of salt restriction on arterial stiffness.[43,44] The authors provide no explanation for this puzzling finding. The examined population was very small, with approximately one dozen patients enrolled in each of the three studies. The small study sample limits the strength of the conclusions and prevented more refined data analyses. Also, the absence of a control group should be noted.

Given the methodological limitations of this study, these results would need to be confirmed in a larger group of patients and with a more robust methodological approach. Nevertheless, its conclusions may stimulate further investigations on the impact of lifestyle and drug treatment of hypertension on the relation between SBP and DBP.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Beevers G, Lip GY, O'Brien E. ABC of hypertension: the pathophysiology of hypertension. *BMJ* 2001; **322**: 912–916.
2 Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*, 5th edn. Hodder Arnold Publication: London, UK, 2005.
3 Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness: current understanding and future directions. *J Am Coll Cardiol* 2011; **57**: 1511–1522.
4 Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**: 1236–1241.
5 Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; **55**: 1318–1327.
6 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**: 1105–1187.
7 Li Y, Wang J-G, Dolan E, Gao P-J, Guo H-F, Nawrot T, Stanton AV, Zhu D-L, O'Brien E, Staessen JA. Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring. *Hypertension* 2006; **47**: 359–364.
8 Schillaci G, Pucci G. The dynamic relationship between systolic and diastolic blood pressure: yet another marker of vascular aging? *Hypertens Res* 2010; **33**: 659–661.
9 Laurent S. Surrogate measures of arterial stiffness: do they have additive predictive value or are they only surrogates of a surrogate? *Hypertension* 2006; **47**: 325–326.
10 Schillaci G, Parati G. Ambulatory arterial stiffness index: merits and limitations of a simple surrogate measure of arterial compliance. *J Hypertens* 2008; **26**: 182–185.
11 Gavish B, Alter A, Barkai Y, Rachima-Maoz C, Peleg E, Rosenthal T. Effect of non-drug interventions on arterial properties determined from 24-h ambulatory blood pressure measurements. *Hypertens Res* 2011; **34**: 1233–1238.
12 Gavish B, Ben-Dov IZ, Bursztyn M. The linear relationship between systolic and diastolic blood pressure monitored over 24 h: assessment and correlates. *J Hypertens* 2008; **26**: 199–209.
13 Andreadis EA, Sfakianakis ME, Tsourous GI, Georgiopoulos DX, Fragouli EG, Katsanou PM, Tavoularis EI, Skarlatou MG, Marakomichelakis GE, Ifanti GK, Diamantopoulos EJ. Differential impact of angiotensin receptor blockers and calcium channel blockers on arterial stiffness. *Int Angiol* 2010; **29**: 266–272.
14 Jin Y, Thijs L, Richart T, Li Y, Dolan E, Wang JG, Protogerou A, O'Brien E, Staessen JA, Safar ME. Responses of the ambulatory arterial stiffness index and other measures of arterial function to antihypertensive drugs. *Hypertens Res* 2011; **34**: 489–495.
15 Berni A, Ciani E, Cecioni I, Poggesi L, Abbate R, Boddi M. Adherence to antihypertensive therapy affects Ambulatory Arterial Stiffness Index. *Eur J Intern Med* 2011; **22**: 93–98.
16 Leoncini G, Ratto E, Viazzi F, Vaccaro V, Parodi A, Falqui V, Conti N, Tomolillo C, Deferrari G, Pontremoli R. Increased ambulatory arterial stiffness index is associated with target organ damage in primary hypertension. *Hypertension* 2006; **48**: 397–403.
17 Mulè G, Cottone S, Cusimano P, Incalcaterra F, Giandalia M, Costanzo M, Nardi E, Palermo A, Geraci C, Costa R, Cerasola G. Inverse relationship between ambulatory arterial stiffness index and glomerular filtration rate in arterial hypertension. *Am J Hypertens* 2008; **21**: 35–40.
18 García-García A, Gómez-Marcos MA, Recio-Rodriguez JI, González-Elena LJ, Parra-Sanchez J, Fe Muñoz-Moreno M, Alonso CP, Gude F, García-Ortiz L. Relationship between ambulatory arterial stiffness index and subclinical target organ damage in hypertensive patients. *Hypertens Res* 2011; **34**: 180–186.
19 Dolan E, Thijs L, Li Y, Atkins N, McCormack P, McClory S, O'Brien E, Staessen JA, Stanton AV. Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the Dublin Outcome Study. *Hypertension* 2006; **47**: 365–370.
20 Hansen TW, Staessen JA, Torp-Pedersen C, Rasmussen C, Li Y, Dolan E, Thijs L, Wang J-G, O'Brien E, Ibsen H, Jeppesen J. Ambulatory arterial stiffness index predicts stroke in a general population. *J Hypertens* 2006; **24**: 2247–2253.
21 Kikuya M, Staessen JA, Ohkubo T, Thijs L, Metoki H, Asayama K, Obara T, Inoue R, Li Y, Dolan E, Hoshi H, Hashimoto J, Totsune K, Satoh H, Wang JG, O'Brien E, Imai Y. Ambulatory arterial stiffness index and 24-hour ambulatory pulse pressure as predictors of mortality: results from the Ohasama study. *Stroke* 2007; **38**: 1161–1166.
22 Muxfeldt ES, Cardoso CR, Dias VB, Nascimento AC, Salles GF. Prognostic impact of the ambulatory arterial stiffness index in resistant hypertension. *J Hypertens* 2010; **28**: 1547–1553.
23 Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Pede S, Porcellati C. Ambulatory pulse pressure: a potent predictor of total cardiovascular risk in hypertension. *Hypertension* 1998; **32**: 983–988.
24 Laugesen E, Rossen NB, Poulsen PL, Hansen KW, Ebbehøj E, Knudsen ST. Pulse pressure and systolic night–day ratio interact in prediction of macrovascular disease in patients with type 2 diabetes mellitus. *J Hum Hypertens* 2011; **34**: 655–661.
25 Palmas W, Pickering TG, Teresi J, Schwartz JE, Moran A, Weinstock RS, Shea S. Ambulatory blood pressure monitoring and all-cause mortality in elderly people with diabetes mellitus. *Hypertension* 2009; **53**: 120–127.
26 Schillaci G, Parati G, Pirro M, Pucci G, Mannarino MR, Sperandini L, Mannarino E. Ambulatory arterial stiffness index is not a specific marker of reduced arterial compliance. *Hypertension* 2007; **49**: 986–991.
27 Baumann M, Dan L, Nürnberger J, Heemann U, Witzke O. Association of ambulatory arterial stiffness index and brachial pulse pressure is restricted to dippers. *J Hypertens* 2008; **26**: 210–214.
28 Liu Z, Hesse C, Curry TB, Pike TL, Issa A, Bernal M, Charkoudian N, Joyner MJ, Eisenach JH. Ambulatory arterial stiffness index is not correlated with the pressor response to laboratory stressors in normotensive humans. *J Hypertens* 2009; **27**: 763–768.
29 Laugesen E, Hansen KW, Knudsen ST, Erlandsen M, Ebbehøj E, Mogensen CE, Poulsen PL. Increased ambulatory arterial stiffness index and pulse pressure in microalbuminuric patients with type 1 diabetes. *Am J Hypertens* 2009; **22**: 513–519.
30 Dechering DG, Adiyaman A, van der Steen M, Thien T. Interstudy variability in the ambulatory arterial stiffness index. *Hypertension* 2007; **50**: e65.
31 Schillaci G, Pucci G, Pirro M, Parati G. Response to: interstudy variability in the ambulatory arterial stiffness index. *Hypertension* 2007; **50**: e66.
32 Ben-Dov IZ, Gavish B, Kark JD, Mekler J, Bursztyn M. A modified ambulatory arterial stiffness index is independently associated with all-cause mortality. *J Hum Hypertens* 2008; **22**: 761–766.
33 Gavish B, Ben-Dov IZ, Kark JD, Mekler J, Bursztyn M. The association of a simple blood pressure-independent parameter derived from ambulatory blood pressure variability with short-term mortality. *Hypertens Res* 2009; **32**: 488–495.

34 Stergiou GS, Kollias A, Rarra VC, Nasothymiou EG, Roussias LG. Arterial stiffness index based on home (HASI) versus ambulatory (AASI) blood pressure measurements. *Hypertens Res* 2010; **33**: 731–736.
35 Jerrard-Dunne P, Mahmud A, Feely J. Ambulatory arterial stiffness index, pulse wave velocity and augmentation index—interchangeable or mutually exclusive measures? *J Hypertens* 2008; **26**: 529–534.
36 Muxfeldt ES, Fiszman R, Castelpoggi CH, Salles GF. Ambulatory arterial stiffness index or pulse pressure: which correlates better with arterial stiffness in resistant hypertension? *Hypertens Res* 2008; **31**: 607–613.
37 Stergiou GS, Kollias A, Giovas PP, Papagiannis J, Roussias LG. Ambulatory arterial stiffness index, pulse pressure and pulse wave velocity in children and adolescents. *Hypertens Res* 2010; **33**: 1272–1277.
38 Craiem D, Graf S, Salvucci F, Chironi G, Megnien JL, Simon A, Armentano RL. The physiological impact of the nonlinearity of arterial elasticity in the ambulatory arterial stiffness index. *Physiol Meas* 2010; **31**: 1037–1046.
39 Westerhof N, Lankhaar JW, Westerhof BE. Ambulatory arterial stiffness index is not a stiffness parameter but a ventriculo-arterial coupling factor. *Hypertension* 2007; **49**: e7.
40 Gavish B. The relationship between systolic and diastolic pressures: a possible link between risk-related clinical measures and arterial properties. *Hypertens Res* 2010; **33**: 657–658.
41 Conway J, Smith KS. Aging of arteries in relation to hypertension. *Circulation* 1957; **15**: 827–835.
42 Abboud FM, Huston JH. Measurement of arterial aging in hypertensive patients. *J Clin Invest* 1961; **40**: 933–939.
43 He FJ, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, MacGregor GA. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. *Hypertension* 2009; **54**: 482–488.
44 Hu J, Jiang X, Li N, Yu X, Perkovic V, Chen B, Zhao L, Neal B, Wu Y. Effects of salt substitute on pulse wave analysis among individuals at high cardiovascular risk in rural China: a randomized controlled trial. *Hypertens Res* 2009; **32**: 282–288.