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ORIGINAL ARTICLE

Relationships between 24-h blood pressure variability and 24-h central arterial pressure, pulse wave velocity and augmentation index in hypertensive patients

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Twenty-four-h blood pressure variability (BPV) predicts cardiovascular complications in hypertension, but its association with pulse wave indices (central arterial pressure, pulse wave velocity (PWV) and augmentation index (AIx)) is poorly understood. In the present study, we assessed the degree of the effect of 24-h BPV on 24-h pulse wave indices. Brachial blood pressure was measured non-invasively over the 24 h with an electronic, oscillometric, automated device (BPLab) in 661 uncomplicated treated or untreated hypertensive patients. Digitalized oscillometric waveforms were analyzed with a validated algorithm to obtain pulse wave indices. Twenty-four-h BPV was calculated as the unweighted (SDu) or weighted s.d. (SDw) of the mean blood pressure or as the average real variability (ARV). Twenty-four-h systolic BPV showed a direct and significant relationship with the central arterial systolic pressure ($r = 0.28$ SDu, $r = 0.40$ SDw, $r = 0.34$ ARV), PWV ($r = 0.10$ SDu, $r = 0.21$ SDw, $r = 0.19$ ARV) and AIx ($r = 0.17$ SDu, $r = 0.27$ SDw, $r = 0.23$ ARV). After adjustment for age, sex, body mass index, antihypertensive treatment and 24-h systolic blood pressure, the relationship lost some power but was still significant for all measures, except for the AIx. Pulse wave indices were higher in patients with high BPV than in those with low BPV: after adjustment, these differences were abolished for the AIx. The diastolic BPV showed a weak association with the pulse wave indices. In conclusion, in hypertensive patients, 24-h systolic BPV is moderately and independently associated with 24-h central arterial pressure and stiffness.
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Keywords: ambulatory blood pressure monitoring; arterial hypertension; arterial stiffness; blood pressure variability; central arterial pressure

INTRODUCTION

Twenty-four-h blood pressure variability (BPV) has been recognized in several longitudinal studies as a predictor of hypertension-related cardiovascular (CV) complications,[1–4] as well as a marker of target organ damage, specifically of carotid artery alteration and left ventricular hypertrophy.[5–8] Recently, an increased BPV has been independently associated with increased left atrium dimension in drug-naive hypertensive patients, whereas an increased heart rate (HR) variability during the night has been indicated as a predictor of the progression of cerebral small-vessel disease in community-dwelling elderly people.[9,10] The easiest and most widely used approach to assessing 24-h BPV is the calculation of the s.d. of 24-h average BP values, obtained non-invasively by automated, oscillometric, intermittent ambulatory BP monitoring (ABPM).[11] More recently, new parameters such as the weighted s.d (SDw; the average of the daytime and nighttime s.d. weighted for the duration of the daytime and nighttime interval) and the average real variability (ARV, the average of the absolute differences between consecutive BP readings) have been proposed to capture 24-h BPV because of their stronger association with the increased CV risk than unweighted s.d. (SDu).[3,12–15]

Arterial stiffness measured by carotid-to-femoral pulse wave velocity (PWV), as well as estimates of central hemodynamics and wave reflections, such as central arterial pressure and augmentation index (AIx),[16,17] are also independent predictors of future CV events and all-cause mortality in both general and hypertensive populations.[18–20] Arterial stiffness, central hemodynamics and wave reflections may also be assessed in daily life conditions with oscillometric ABPM devices using specific algorithms for pulse wave analysis (PWA).[21–24]

Recent studies have suggested that an increased 24-h BPV may be associated with arterial stiffness, as determined at rest by measurement of PWV in young healthy subjects[25,26] as well as in cases of hypertension.[27–29] Such a relation appears to be stronger with measures of BPV focusing on short-term changes, such as ARV and SDw.[28]

At present, there is no information on the association between different measures of 24-h BPV and estimates of 24-h vascular

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function and structure, such as central arterial pressure, PWV and AIx. However, such information could be of practical value, complementing current knowledge of arterial physiology and offering new perspectives for the diagnosis and management of arterial hypertension. For this reason, we performed a BPV analysis on previously published data obtained on hypertensive patients through a non-invasive, clinically validated PWA technology embedded in an oscillometric BP measuring device.[30]

METHODS

Study population and design

Details on the study design and methods have been described elsewhere.[30] Briefly, the present non-randomized cross-sectional study included treated or untreated uncomplicated hypertensive adults recruited from among consecutive patients with a known history of high BP presenting at the outpatient clinic of the Cardiology Research Complex in Moscow between September 2008 and December 2012. Patients with previous or current CV disease or any other concomitant significant systemic condition were excluded. All individuals were subjected to a 24-h ABPM preceded by office automatic BP determination with the same device used for ambulatory monitoring. Three sequential (2-min interval) office BP measurements were obtained in sitting position after 5 min of rest, and the average of the three measurements was taken as a reference.

The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the study center. Written informed consent was obtained from all eligible patients before their inclusion into the study.

Measurement of ambulatory brachial and central arterial pressure, AIx and PWV

Twenty-four-h ABPM was performed with an electronic, oscillometric, automated BPLab device (BPLab GmbH, Schwalbach am Taunus, Germany), which has been found to be accurate for estimation of BP in properly conducted validation studies.[31–33] Ambulatory BP was measured automatically every 15–30 min during waking hours (from 0600 to 2200 hours) and every 30–60 min during nighttime sleep (from 2200 to 0600 hours) through a cuff wrapped around each subject's non-dominant arm. Each recording started in the morning. After the device was fitted, patients were sent home, asked to resume normal activities and to return 24 h later for removal of the device.

The oscillometric BP monitor also allowed ambulatory central BP, AIx and PWV determination. As detailed in previous publications,[21,30,34,35] these measurements were possible through recording of the pulsatile pressure changes at the brachial artery level during a step-by-step cuff deflation and by analysis of the digitalized pressure signal with proprietary mathematical algorithms. The PWA technology is based on a specially developed hemodynamic model to obtain the PWV and a transfer function that utilizes a modification in a certain frequency range within the acquired pulse signal to derive the central arterial pressure wave and thus assess central BP and AIx. Because measures of arterial stiffness depend on BP and HR values,[16] the PWV was normalized to a systolic BP (SBP) of 100 mm Hg and an HR of 60 b.p.m. by a regression analysis of 24-h PWV to 24-h SBP and 24-h HR in each individual, whereas the AIx was corrected for an HR of 75 b.p.m. The accuracy of the BPLab device for the assessment of vascular indices has been documented in validation studies in which it was compared with a non-invasive gold standard.[35,36]

Statistical analysis

As has been described elsewhere,[30] in valid ABPM recordings, all the BPs and PWA indices estimated in each single BP measurement were averaged for each patient to obtain the 24-h mean value. For the purpose of the present study, BPV was obtained for both the SBP and diastolic BP (DBP) by calculating (i) the SDu, defined as the s.d. of the 24-h mean value of brachial SBP and DBP;[11] (ii) the SDw, defined as the s.d. of the average of all brachial SBP and DBP values during daytime and nighttime, with weights corresponding to the duration of daytime and nighttime;[12] and (iii) the ARV, defined as the mean of the successive absolute differences between adjacent brachial SBP and DBP values over the 24 h.[13] Mean values obtained for each individual patient were averaged over the whole study population. Pearson's correlation coefficients (r) between the BPV (estimated by the three methods) and 24-h PWA indices (central BP, PWV and AIx) were determined before adjustment and after accounting for age, sex, body mass index, antihypertensive drug treatment and the 24-h mean BP (partial correlation coefficient). Adjustment for the 24-h mean BP was not applied to PWV because this measure was already normalized to an SBP of 100 mm Hg and to central arterial pressure.

The study cohort was also subdivided according to BPV values (separately for SDw and ARV) into two groups of patients with BPV either above or below the median value of the whole study population. Then a comparison of the central arterial pressure, AIx and PWV was made between the two subgroups through analysis of variance. The level of statistical significance was kept at 0.05 throughout the whole study. Data are shown as the mean ± s.d. or 95% confidence intervals for continuous variables and as absolute (n) and relative (%) frequencies for discrete variables.

Table 1 Demographic and clinical characteristics of the study population

	n = *661*
Age (years)	58.1 ± 14.9
Gender	
Males	292 (44.2)
Females	369 (55.8)
Height (cm)	170.8 ± 10.2
Weight (kg)	78.6 ± 11.6
BMI (kg m^{-2})	26.9 ± 2.9
Antihypertensive treatment	159 (24.1)
Office SBP (mm Hg)	135.2 ± 11.9
Office DBP (mm Hg)	78.5 ± 8.0
24-h brachial SBP (mm Hg)	129.3 ± 11.6
24-h brachial DBP (mm Hg)	74.3 ± 6.6
24-h central arterial SBP (mm Hg)	119.3 ± 10.7
24-h central arterial DBP (mm Hg)	75.6 ± 6.7
24-h PWV (m s^{-1})	10.3 ± 1.2
24-h AIx (%)	24.7 ± 16.0
24-h unweighted s.d. SBP (mm Hg)	14.4 ± 3.7
24-h unweighted s.d. DBP (mm Hg)	10.1 ± 2.2
24-h weighted s.d. SBP (mm Hg)	12.3 ± 3.3
24-h weighted s.d. DBP (mm Hg)	8.6 ± 1.9
24-h ARV SBP (mm Hg)	11.5 ± 3.1
24-h ARV DBP (mm Hg)	8.4 ± 2.1

Abbreviations: AIx, Augmentation Index; ARV, average real variability; BMI, body mass index; DBP, diastolic blood pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.
Data are reported as means ± s.d. or as absolute (n) and relative (%) frequencies.

RESULTS

Demographic and clinical characteristics of the study population

As summarized in Table 1, the mean age of the patients was 58.1 ± 14.9 years, and there was a larger prevalence of females (55.8%). Most of the studied patients (75.9%) were untreated. As expected, the brachial SBP was higher than the central arterial SBP. The SDw and ARV were smaller than the SDu for both SBP and DBP. The SBPV was always greater than the DBPV for all BPV measures.

SBPV, central arterial SBP, PWV and AIx

As shown in Figure 1, the SBPV was directly related to the central arterial SBP, PWV and AIx (correlation coefficient ranging between 0.10 and 0.40). The strongest relationship was observed for the SDw

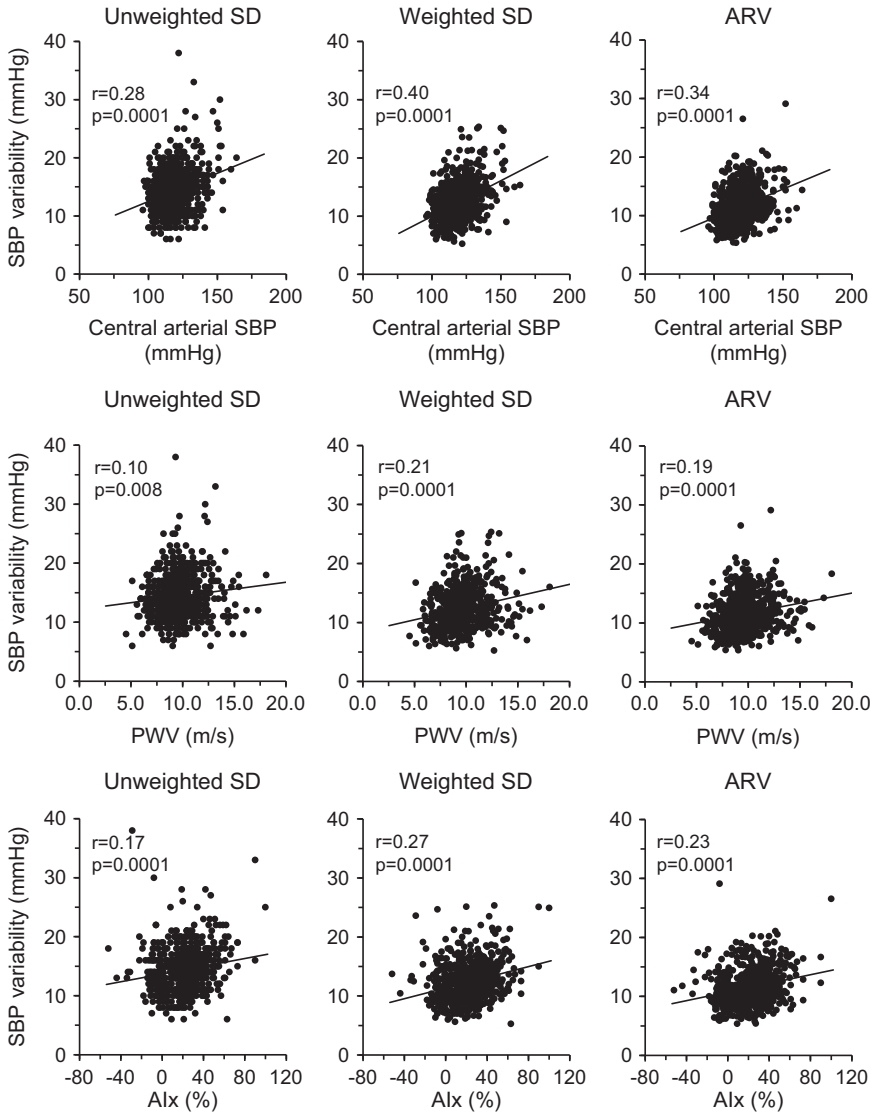

Figure 1 Scatterplots of unweighted s.d., weighted s.d. and ARV vs central arterial SBP, PWV and AIx. Unadjusted Pearson's correlation coefficients (*r*) and the corresponding *P*-values are reported in each panel together with the regression line. AIx: Augmentation Index; ARV: average real variability; PWV: pulse wave velocity; SBP: systolic blood pressure.

Table 2 Unadjusted and adjusted (partial) correlation coefficients of unweighted and weighted s.d. and of average real variability (ARV) of 24-h systolic (SBP) and diastolic blood pressure (DBP) vs central arterial SBP and DBP, pulse wave velocity (PWV) and augmentation index (AIx) in 661 hypertensive patients

		SBP						*DBP*			
		Unadjusted		*Adjusted*				*Unadjusted*		*Adjusted*	
		r	P-*value*	*Partial* r	P-*value*			*r*	P-*value*	*Partial* r	P-*value*
Central arterial SBP (mm Hg)[a]	Unweighted s.d.	0.28	0.0001	0.25	0.0001	Central arterial DBP (mm Hg)[a]	Unweighted s.d.	0.13	0.001	0.12	0.003
	Weighted s.d.	0.40	0.0001	0.33	0.0001		Weighted s.d.	0.19	0.001	0.19	0.0001
	ARV	0.34	0.0001	0.26	0.0001		ARV	0.07	0.076	0.07	0.066
PWV (m s^{-1})[a]	Unweighted s.d.	0.10	0.008	0.11	0.004	PWV (m s^{-1})[a]	Unweighted s.d.	−0.12	0.001	−0.04	0.299
	Weighted s.d.	0.21	0.0001	0.18	0.0001		Weighted s.d.	0.02	0.542	0.06	0.154
	ARV	0.19	0.0001	0.16	0.0001		ARV	−0.001	0.977	0.02	0.628
AIx (%)[b]	Unweighted s.d.	0.17	0.0001	0.07	0.067	AIx (%)[b]	Unweighted s.d.	−0.11	0.006	−0.06	0.140
	Weighted s.d.	0.27	0.0001	0.10	0.013		Weighted s.d.	−0.01	0.746	−0.02	0.617
	ARV	0.23	0.0001	0.05	0.214		ARV	−0.02	0.707	−0.04	0.352

P-values indicate the level of the statistical significance of the correlation coefficients.
[a]Adjusted by age, gender, body mass index and antihypertensive drug treatment.
[b]Adjusted by age, gender, body mass index, antihypertensive drug treatment and 24-h SBP.

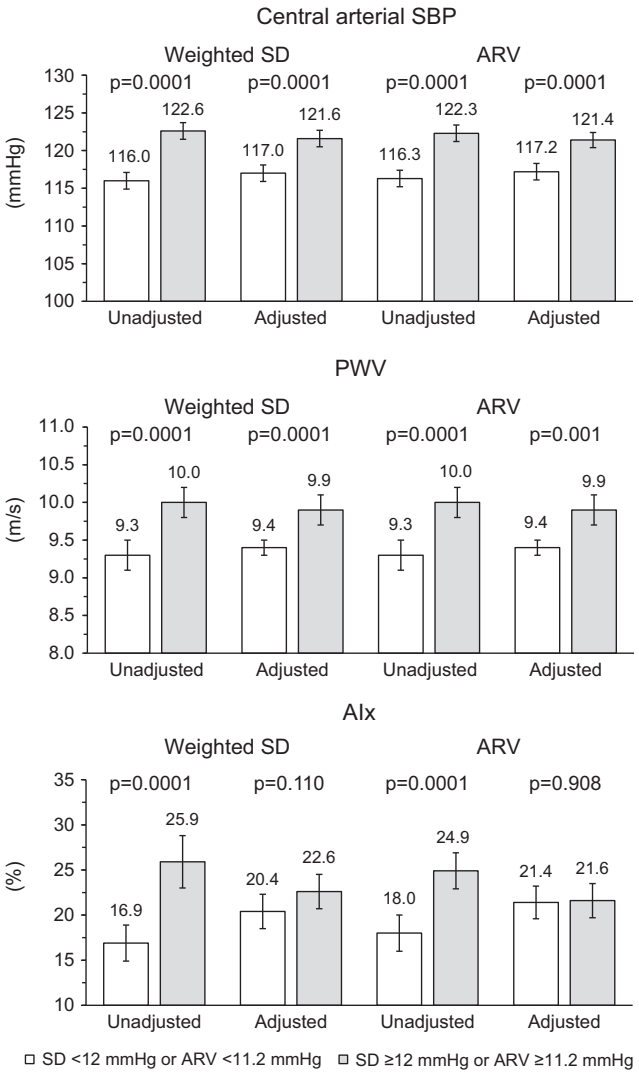

Figure 2 Unadjusted and adjusted estimates of the central arterial SBP, PWV and AIx in the study patients grouped according to the median value of the weighted 24-h s.d. of the SBP (s.d.< or ⩾12.0 mm Hg) or the median value of the ARV of the SBP (ARV < or ⩾11.2 mm Hg). *P*-values indicate the level of statistical significance of the comparisons. Symbols and abbreviations are as described in the preceding figure.

(range 0.21–0.40) followed by the ARV (range 0.19–0.34), whereas it was the weakest for the SDu (range 0.10–0.28).

As shown in Table 2, after adjustment for confounding variables, the strength of the relationship was attenuated (partial correlation coefficient ranging from 0.05 to 0.33) and was no more statistically significant for AIx vs SDu ($r=0.07$, $P=0.067$) and ARV ($r=0.05$, $P=0.214$).

The central arterial SBP, PWV and AIx were significantly higher in patients with high SBPV than in those with low SBPV (Figure 2). However, after adjustment for age, sex, body mass index, antihypertensive treatment and 24-h SBP, the difference between the high and low SBPV groups was still statistically significant for the central arterial SBP and PWV but not for the AIx.

DBPV, central arterial DBP, PWV and AIx

The relationships among the peripheral DBPV and central arterial DBP and stiffness were weaker than that observed for the SBPV. The average 24-h DBPV showed a weak direct relationship with central arterial DBP (range 0.07–0.19), which was statistically significant for only the SDu and SDw. An inverse or scarcely positive correlation was observed between the DBPV and PWV and AIx (r ranging from −0.12 to 0.02) (Table 2). The degree and direction of the correlation was unchanged after adjustment for confounding factors.

The average 24-h central arterial DBP was significantly higher in patients with a high 24-h DBPV in the case of SDw but not for ARV. No significant trends according to the DBPV level were observed for the PWV and AIx, with the exception of significantly ($P=0.011$) larger adjusted PWV values at high SDw and significantly ($P=0.023$) larger adjusted AIx at low ARV (Table 3).

DISCUSSION

In the present study, we documented a statistically significant, although moderate, relation between the 24-h SBPV and vascular indices such as the central arterial SBP, PWV and AIx obtained in ambulatory conditions. The relationship was only occasionally statistically significant and was weaker for the 24-h DBPV. Furthermore, the association was independent of age, sex, body mass index, use of antihypertensive medication and 24-h absolute BP level for all measures, except for AIx. These findings suggest that the link between short-term BP fluctuations and central arterial pressure and stiffness is independent of, and additive to, the relationship between arterial indices and 24-h BP, which we have reported in a recent paper based

Table 3 Unadjusted and adjusted estimates of central arterial diastolic blood pressure (DBP), pulse wave velocity (PWV) and augmentation index (AIx) in 661 hypertensive patients grouped according to the median value of the weighted 24-h DBP variability (s.d. < or ⩾ 8.4 mm Hg) and the median value of the average real variability for DBP (ARV < or ⩾ 8.2 mm Hg)

	S.d. <8.4 mm Hg (n = *331*)	*S.d. ⩾ 8.4 mm Hg* (n = *330*)	P-*value*	*ARV <8.2 mm Hg* (n = *330*)	*ARV ⩾ 8.2 mm Hg* (n = *331*)	P-*value*
Central arterial DBP (mm Hg)						
Unadjusted	74.5 (73.8, 75.3)	76.6 (75.9, 77.3)	0.0001	75.2 (74.5, 75.9)	75.9 (75.2, 76.7)	0.159
Adjusted[a]	74.6 (73.8, 75.3)	76.6 (75.9, 77.3)	0.0001	75.2 (74.5, 75.9)	75.9 (75.2, 76.7)	0.152
PWV ($m\,s^{-1}$)						
Unadjusted	9.6 (9.4, 9.8)	9.8 (9.6, 10.0)	0.150	9.7 (9.5, 9.9)	9.6 (9.5, 9.8)	0.886
Adjusted[a]	9.5 (9.3, 9,7)	9.8 (9.6, 10.0)	0.011	9.6 (9.4, 9.8)	9.7 (9.5, 9.9)	0.403
AIx (%)						
Unadjusted	22.1 (20.1, 24.3)	20.8 (18.7, 22.9)	0.961	22.6 (20.5, 24.7)	20.4 (18.3, 22.5)	0.139
Adjusted[b]	22.3 (20.5, 24.1)	20.6 (18.9, 22.4)	0.195	22.9 (21.2, 24.7)	20.0 (18.2, 21.8)	0.023

Data are shown as mean and 95% confidence interval. *P*-values indicate the level of the statistical significance of the comparisons.
[a]Adjusted by age, gender, body mass index and antihypertensive drug treatment.
[b]Adjusted by age, gender, body mass index, antihypertensive drug treatment and 24-h SBP.

on the same population of the present study.[30] However, the contribution of BPV to increased aortic stiffness and BP, although statistically significant, was limited, thus emphasizing the possible importance of other factors.

BPV evaluated by non-invasive intermittent ABPM has been found to be associated with CV morbidity and mortality in hypertensive patients as well as in the general population.[1–4,15] Previous studies have also reported a significant relation between large-artery stiffness, as assessed by carotid–femoral PWV and 24-h BPV in hypertensive patients[27–29] as well as in young healthy subjects.[25,26] However, unlike our study, in these previous studies, PWV was evaluated non-invasively, at rest, in a recumbent or seated position, in controlled laboratory conditions, by pletismography, applanation tonometry or through a mechano-transducer, and no evaluation of central arterial pressure and AIx was provided. Thus, to our knowledge, this is the first study evaluating the relationship between BPV and vascular indices in daily life conditions over 24 h.

Interestingly, the magnitude of the correlation coefficient between SBPV or DBPV and PWV in our study was very similar to that found in previous studies, with respect to not only hypertensive populations[27–29] but also healthy young adults, adolescents and children.[25,26] We also showed that when patients were subdivided into two groups with BPV above and BPV below the median value of the whole study population, those with a higher BPV had higher central arterial SBP, PWV and AIx values. Finally, we confirmed that DBPV is weakly related to PWV, as has been suggested in previous studies, extending this evidence to central DBP and AIx.[25–29] The observation that SBPV and not DBPV is associated with aortic stiffness is not surprising. In fact, arterial stiffness is strongly associated with pulse pressure, and a change in the SBP but not the DBP is the major determinant of pulse pressure increase in different aortic stiffening models.[37,38]

Unfortunately, given the observational design of our study, we were unable to investigate the nature of the mechanisms underlying the relationship between BPV and PWA indices. We did not collect all the relevant clinical information nor did we evaluate organ damage or metabolic abnormalities. In particular, we were not able to retrospectively obtain information on smoking habits, dyslipidemia or diabetes mellitus, which are common risk factors for hypertension and increased arterial stiffness. However, because the close relationship between increased BPV and alteration of vascular indices was maintained after adjustment for their main determinants, including age, sex, body mass index, antihypertensive treatment and the mean 24-h BP level, we hypothesize that an increased BPV may precede the increase of arterial stiffness and the decrease in the compliance of large elastic arteries in patients with high BP, as has been suggested by animal data.[39–41] Such studies, performed in rats, have shown that the increase in BPV induced by arterial baroreceptor denervation or by discontinuous treatment with a BP-lowering drug is associated with aortic atherosclerosis, decreased arterial distensibility and increased collagen content and density in the arterial wall. Because this is a fairly new research field, mechanistic studies must be performed to elucidate whether BPV has a causative role or is a result of arterial stiffening.

The strength of the relationship between the BPV and the central arterial pressure, PWV and AIx was different with the different measures of BPV; this relationship was closest for the SDw, followed by the ARV, and the weakest with the SDu. These findings confirm previous observations by Schillaci *et al.*[28] that the strength of the association between BPV and aortic stiffness may be sensitive to how BPV is defined. In our study, we added to the current evidence by extending the finding to central arterial pressure and AIx.

This study has a number of limitations. First, its cross-sectional design did not allow us to separate cause from effect; thus we cannot definitively conclude whether BPV causes vascular stiffness or instead whether high BP causes vascular alterations that are responsible for the increased BPV. However, we will be able to properly address this question in an ongoing longitudinal prospective study, the VASOTENS (Vascular health ASsessment Of The hypertENSive patients) Registry, which will also collect long-term survival data and information on organ damage status.[42] Second, most of the studied patients were untreated, and all of them were free from CV diseases or major comorbidities and thus represented a relatively low-risk subset of the hypertensive population. For this reason, we cannot generalize the findings of the study to the entire hypertensive population. Third, antihypertensive treatment may affect BPV as well as vascular indices. Although our sample comprised a small proportion of treated patients, we deliberately chose to pool subjects together irrespective of treatment because our main hypothesis was to assess the relationship between BPV and vascular indices rather than to investigate the origin and nature of this relationship. However, the results obtained after adjustment for antihypertensive treatment did not differ from unadjusted ones. Fourth, we determined central BP, PWV and AIx non-invasively over the 24 h through PWA of reconstructed waveforms from oscillometric readings rather than via a direct intra-arterial method. BP and vascular markers were also assessed with the same device and technique, which might potentially have made these estimates not completely independent from one another. However, this technique allowed us to obtain, in an easy, convenient and affordable way, information on large artery stiffness and hemodynamics in daily life conditions while causing minimal discomfort to the patients. Because proper validation studies of the technique vs established radial tonometry methods have demonstrated its accuracy and reliability, we can reasonably rely on its validity.[35,36] Fifth, we evaluated short-term BPV on the basis of BP measurements taken discontinuously every 15–30 min during waking hours and every 30–60 min during sleeping hours. Thus our estimation of the BPV may not accurately reflect the extent and features of BP fluctuations occurring during daily life conditions, as recorded during beat-to-beat measurement over the 24 h.[11] However, oscillometric intermittent ABPM is currently the most affordable and widely adopted technique for assessing absolute BP and its variations in dynamic conditions. Sixth, owing to the different daily activities (for example, working and relaxation periods, including nap and night sleep), the BPV and arterial hemodynamics and stiffness dynamically changed during a full 24-h cycle and varied among subjects. For this reason, we performed our analysis by disregarding the classical separation of the 24 h in daytime and nighttime subperiods. Finally, although statistically significant, the correlation between the SBPV and indices obtained through the PWA was not particularly strong, and its magnitude was in line with that observed in previous studies in which vascular indices were measured at rest and not in ambulatory conditions.[27–29]

In conclusion, the findings of the present study indicate that an increased 24-h BPV is significantly associated with increased 24-h arterial stiffness and pressure in hypertensive patients. Because both BPV and PWA indices are independent predictors of CV morbidity and mortality in hypertensive patients, increased BPV and central BP and arterial wall stiffness can adversely affect one another and thereby contribute to the adverse CV prognosis of the hypertensive patients. Further larger longitudinal studies are needed to assess the long-term effects of BPV on the progression of arterial stiffness in hypertension and to determine the causative effects of the mechanism underlying the relationships between BPV and indices of vascular health.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Kikuya M, Hozawa A, Ohokubo T, Tsuji I, Michimata M, Matsubara M, Ota M, Nagai K, Araki T, Satoh H, Ito S, Hisamichi S, Imai Y. Prognostic significance of blood pressure and heart rate variabilities: the Ohasama study. *Hypertension* 2000; **36**: 901–906.
2 Mancia G, Bombelli M, Facchetti R, Madotto F, Corrao G, Trevano FQ, Grassi G, Sega R. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 2007; **49**: 1265–1270.
3 Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, Richart T, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Imai Y, Wang J, Ibsen H, O'Brien E, Staessen JA. International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension* 2010; **55**: 1049–1057.
4 Stolarz-Skrzypek K, Thijs L, Li Y, Hansen TW, Boggia J, Kuznetsova T, Kikuya M, Maestre G, Mena L, Kawecka-Jaszcz K, Staessen JA. Short-term blood pressure variability in relation to outcome in the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO). *Acta Cardiol* 2011; **66**: 701–706.
5 Mancia G, Parati G, Hennig M, Flatau B, Omboni S, Glavina F, Costa B, Scherz R, Bond G, Zanchetti A. ELSA Investigators. Relation between blood pressure variability and carotid artery damage in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis (ELSA). *J Hypertens* 2001; **19**: 1981–1989.
6 Sega R, Corrao G, Bombelli M, Beltrame L, Facchetti R, Grassi G, Ferrario M, Mancia G. Blood pressure variability and organ damage in a general population: results from the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni). *Hypertension* 2002; **39**: 710–714.
7 Shintani Y, Kikuya M, Hara A, Ohkubo T, Metoki H, Asayama K, Inoue R, Obara T, Aono Y, Hashimoto T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: the Ohasama study. *J Hypertens* 2007; **25**: 1704–1710.
8 Madden JM, O'Flynn AM, Fitzgerald AP, Kearney PM. Correlation between short-term blood pressure variability and left-ventricular mass index: a meta-analysis. *Hypertens Res* 2016; **39**: 171–177.
9 Cipollini F, Arcangeli E, Seghieri G. Left atrial dimension is related to blood pressure variability in newly diagnosed untreated hypertensive patients. *Hypertens Res* 2016; **39**: 583–587.
10 Yamaguchi Y, Wada M, Sato H, Nagasawa H, Koyama S, Takahashi Y, Kawanami T, Kato T. Impact of nocturnal heart rate variability on cerebral small-vessel disease progression: a longitudinal study in community-dwelling elderly Japanese. *Hypertens Res* 2015; **38**: 564–569.
11 Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Bertinieri G, Grassi G, di Rienzo M, Pedotti A, Zanchetti A. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ Res* 1983; **53**: 96–104.
12 Bilo G, Giglio A, Styczkiewicz K, Caldara G, Maronati A, Kawecka-Jaszcz K, Mancia G, Parati G. A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. *J Hypertens* 2007; **25**: 2058–2066.
13 Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T. A reliable index for the prognostic significance of blood pressure variability. *J Hypertens* 2005; **23**: 505–511.
14 Mena LJ, Maestre GE, Hansen TW, Thijs L, Liu Y, Boggia J, Li Y, Kikuya M, Björklund-Bodegård K, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Filipovsky J, Lmai Y, Wang J, O'Brien E, Staessen JA. International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators. How many measurements are needed to estimate blood pressure variability without loss of prognostic information? *Am J Hypertens* 2014; **27**: 46–55.
15 Stolarz-Skrzypek K, Thijs L, Richart T, Li Y, Hansen TW, Boggia J, Kuznetsova T, Kikuya M, Kawecka-Jaszcz K, Staessen JA. Blood pressure variability in relation to outcome in the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome. *Hypertens Res* 2010; **33**: 757–766.
16 Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; **27**: 2588–2605.
17 Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cífková R, Cosentino F, De Carlo M, Gallino A, Landmesser U, Laurent S, Lekakis J, Mikhailidis DP, Naka KK, Protogerou AD, Rizzoni D, Schmidt-Trucksäss A, Van Bortel L, Weber T, Yamashina A, Zimlichman R, Boutouyrie P, Cockcroft J, O'Rourke M, Park JB, Schillaci G, Sillesen H, Townsend RR. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 2015; **241**: 507–532.
18 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 College Cardiol* 2010; **55**: 1318–1327.
19 Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J* 2010; **31**: 1865–1871.
20 Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Willum Hansen T, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014; **63**: 636–646.
21 Posokhov IN. Pulse wave velocity 24-hour monitoring with one-site measurements by oscillometry. *Med Devices (Auckl)* 2013; **6**: 11–15.
22 Protogerou AD, Argyris A, Nasothimiou E, Vrachatis D, Papaioannou TG, Tzamouranis D, Blacher J, Safar ME, Sfikakis P, Stergiou GS. Feasibility and reproducibility of noninvasive 24-h ambulatory aortic blood pressure monitoring with a brachial cuff-based oscillometric device. *Am J Hypertens* 2012; **25**: 876–882.
23 Luzardo L, Lujambio I, Sottolano M, da Rosa A, Thijs L, Noboa O, Staessen JA, Boggia J. 24-h ambulatory recording of aortic pulse wave velocity and central systolic augmentation: a feasibility study. *Hypertens Res* 2012; **35**: 980–987.
24 Williams B, Lacy PS, Baschiera F, Brunel P, Düsing R. Novel description of the 24-hour circadian rhythms of brachial versus central aortic blood pressure and the impact of blood pressure treatment in a randomized controlled clinical trial: the Ambulatory Central Aortic Pressure (AmCAP) Study. *Hypertension* 2013; **61**: 1168–1176.
25 Kotsis V, Stabouli S, Karafillis I, Papakatsika S, Rizos Z, Miyakis S, Goulopoulou S, Parati G, Nilsson P. Arterial stiffness and 24 h ambulatory blood pressure monitoring in young healthy volunteers: the Early Vascular Ageing Aristotle University Thessaloniki Study (EVA-ARIS Study). *Atherosclerosis* 2011; **219**: 194–199.
26 Stabouli S, Papakatsika S, Kotronis G, Papadopoulou-Legbelou K, Rizos Z, Kotsis V. Arterial stiffness and SBP variability in children and adolescents. *J Hypertens* 2015; **33**: 88–95.
27 Ichihara A, Kaneshiro Y, Takemitsu T, Sakoda M, Hayashi M. Ambulatory blood pressure variability and brachial-ankle pulse wave velocity in untreated hypertensive patients. *J Hum Hypertens* 2006; **20**: 529–536.
28 Schillaci G, Bilo G, Pucci G, Laurent S, Macquin-Mavier I, Boutouyrie P, Battista F, Settimi L, Desamericq G, Dolbeau G, Faini A, Salvi P, Mannarino E, Parati G. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension* 2012; **60**: 369–377.
29 García-García Á, García-Ortiz L, Recio-Rodríguez JI, Patino-Alonso MC, Agudo-Conde C, Rodriguez-Sanchez E, Gómez-Marcos MA. Relationship of 24-h blood pressure variability with vascular structure and function in hypertensive patients. *Blood Press Monit* 2013; **18**: 101–106.
30 Omboni S, Posokhov IN, Rogoza AN. Evaluation of 24-hour arterial stiffness indices and central hemodynamics in healthy normotensive subjects versus treated or untreated hypertensive patients: a feasibility study. *Int J Hypertens* 2015; **2015**: 601812.
31 Koudryavtcev SA, Lazarev VM. Validation of the BPLab(®) 24-hour blood pressure monitoring system according to the European standard BS EN 1060-4:2004 and British Hypertension Society protocol. *Med Devices (Auckl)* 2011; **4**: 193–196.
32 Dorogova IV, Panina ES. Comparison of the BPLab® sphygmomanometer for ambulatory blood pressure monitoring with mercury sphygmomanometry in pregnant women: validation study according to the British Hypertension Society protocol. *Vasc Health Risk Manag* 2015; **11**: 245–249.
33 Ledyaev MY, Stepanova OV, Ledyaeva AM. Validation of the BPLab(®) 24-hour blood pressure monitoring system in a pediatric population according to the 1993 British Hypertension Society protocol. *Med Devices (Auckl)* 2015; **8**: 115–118.
34 Ageenkova OA, Purygina MA. Central aortic blood pressure, augmentation index, and reflected wave transit time: reproducibility and repeatability of data obtained by oscillometry. *Vasc Health Risk Manag* 2011; **7**: 649–656.
35 Rogoza AN, Kuznetsova AA. Central aortic blood pressure and augmentation index: comparison between Vasotens and SphygmoCor technology. *Res Rep Clin Cardiol* 2012; **3**: 27–33.
36 Kotovskaya YV, Kobalava ZD, Orlov AV. Validation of the integration of technology that measures additional "vascular" indices into an ambulatory blood pressure monitoring system. *Med Devices (Auckl)* 2014; **7**: 91–97.
37 Guo X, Lu X, Yang J, Kassab GS. Increased aortic stiffness elevates pulse and mean pressure and compromises endothelial function in Wistar rats. *Am J Physiol Heart Circ Physiol* 2014; **307**: H880–H887.
38 Avolio AP, Xu K, Butlin M. Effect of large arteries on blood pressure variability. *Conf Proc IEEE Eng Med Biol Soc* 2013; **2013**: 4078–4081.
39 Sasaki S, Yoneda Y, Fujita H, Uchida A, Takenaka K, Takesako T, Itoh H, Nakata T, Takeda K, Nakagawa M. Association of blood pressure variability with induction of atherosclerosis in cholesterol-fed rats. *Am J Hypertens* 1994; **7**: 453–459.

40 Lacolley P, Bezie Y, Girerd X, Challande P, Benetos A, Boutouyrie P, Ghodsi N, Lucet B, Azoui R, Laurent S. Aortic distensibility and structural changes in sinoaortic-denervated rats. *Hypertension* 1995; **26**: 337–340.
41 Bouissou-Schurtz C, Lindesay G, Regnault V, Renet S, Safar ME, Molinie V, Dabire H, Bezie Y. Development of an experimental model to study the relationship between day-to-day variability in blood pressure and aortic stiffness. *Front Physiol* 2015; **6**: 368.
42 Omboni S, Posokhov IN, Parati G, Avolio A, Rogoza AN, Kotovskaya YV, Mulè G, Muiesan ML, Orlova IA, Grigoricheva EA, Cardona Muñoz E, Zelveian PH, Pereira T, Peixoto Maldonado JM. Vascular Health Assessment of The Hypertensive Patients (VASOTENS) Registry: study protocol of an international, web-based telemonitoring registry for ambulatory blood pressure and arterial stiffness. *JMIR Res Protoc* 2016; **52**: e137.