Journal of Human Hypertension (2017) **31,** 633–639

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ORIGINAL ARTICLE

Association of left ventricular structural and functional abnormalities with aortic and brachial blood pressure variability in hypertensive patients: the SAFAR study

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Both brachial blood pressure (BP) level and its variability (BPV) significantly associate with left ventricular (LV) structure and function. Recent studies indicate that aortic BP is superior to brachial BP in the association with LV abnormalities. However, it remains unknown whether aortic BPV better associate with LV structural and functional abnormalities. We therefore aimed to investigate and compare aortic versus brachial BPV, in terms of the identification of LV abnormalities. Two hundred and three participants who underwent echocardiography were included in this study. Twenty-four-hour aortic and brachial ambulatory BP was measured simultaneously by a validated BP monitor (Mobil-O-Graph, Stolberg, Germany) and BPV was calculated with validated formulae. LV mass and LV diastolic dysfunction (LVDD) were evaluated by echocardiography. The prevalence of LV hypertrophy (LVH) and LVDD increased significantly with BPV indices ($P \leqslant 0.04$) in trend tests. After adjustment to potential confounders, only aortic average real variability (ARV), but not brachial ARV or weighted s.d. (wSD, neither aortic nor brachial) significantly associated with LV mass index ($P = 0.02$). Similar results were observed in logistic regression. After adjustment, only aortic ARV significantly associated with LVH (odds ratio (OR) and 95% confidence interval (CI): 2.28 (1.08, 4.82)). As for LVDD, neither the brachial nor the aortic 24-hour wSD, but the aortic and brachial ARV, associated with LVDD significantly, with OR = 2.28 (95% CI: (1.03, 5.02)) and OR = 2.36 (95% CI: (1.10, 5.05)), respectively. In summary, aortic BPV, especially aortic ARV, seems to be superior to brachial BPV in the association of LV structural and functional abnormalities.

Journal of Human Hypertension (2017) **31,** 633–639; doi:10.1038/jhh.2017.37; published online 1 June 2017

INTRODUCTION

Growing evidence has shown that blood pressure variability (BPV), independent of blood pressure (BP) level, has a close relationship with cardiovascular (CV) risk, with higher occurrences of CV events in patients with higher BPV.[1] High BPV was proved to be an independent predictor of CV events.[2–4] Moreover, it was reported that high BPV significantly associated with hypertensive target organ damage (TOD),[5] for which BPV carries more prognostic value. More recently, data from meta-analysis showed that, different anti-hypertensive agents varied in their effects on BPV, but with similar BP reduction. Among all the first-line anti-hypertensive agents, calcium channel blockers were proved to be more efficient in reducing the variation in systolic BP (SBP), leading to the greatest protective effects on stroke.[6]

The causal relationship between high BP and TOD or CV events has not been clarified yet, but it might be either attributed to the long-term exposure of target organs to higher pressure load (for the same usual BP level) or to other coexisting risk factors.[7] Theoretically, aortic BP can better reflect the hemodynamic stress that the heart directly confronts than brachial BP does. Therefore, it has been proposed that TOD and CV events are more closely related to aortic than brachial BP. Although the superiority of office aortic BP over office brachial BP had been established in multiple clinical trials and meta-analyses,[8] such as the REASON study[9] and the substudy of ASCOT trial,[10] the final verdict is still open.[11] In our previous publications, with the use of a novel 24hr aortic ambulatory BP monitoring device, we extended previous findings and reported that both left ventricular (LV) hypertrophy (LVH)[12] and LV diastolic dysfunction (DD)[13] were better associated with aortic than brachial systolic 24 h BP.

Current guidelines recommend that, LV structure and function should be assessed by echocardiography in hypertensive patients, since LVH and LVDD are significantly associated with CV outcomes.[14] In previous studies, independent of BP level, brachial BPV significantly associated with LVH and LVDD.[9,15] However, it remains unclear that if aortic BPV, as compared to brachial BPV, better associated with TOD, such as LVH and LVDD. Therefore, we aimed to investigate the independent association of LV abnormalities with aortic BPV as well as its superiority over brachial BPV on the association with cardiac structure and function in hypertensive patients.

MATERIALS AND METHODS

Study design and population

The 'noninvaSive Aortic ambulatory BP monitoring For the detection of tARrget organ damage' (SAFAR) study is an ongoing prospective

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Received 31 August 2016; revised 13 March 2017; accepted 27 March 2017; published online 1 June 2017

observational study recruiting patients over 18 years old with established or suspected hypertension (with or without anti-hypertensive agents) for BP and global CV-risk assessment. Patients without sinus rhythm or with any modification in CV disease medication during the past month were excluded. Until May 2015, 203 Caucasian participants who underwent cardiac ultrasound examination were investigated in the present cross-sectional analysis. Structured standard questionnaire was applied to obtain some information about participants such as age, gender, medical history, family history and so on. The blood and urine samples were gathered and tested in the 'Laiko' hospital. This study was approved by the Ethical/Scientific Committee of the 'Laiko' Hospital and all participants provided informed consent.

Office BP assessment

After at least 10 min of rest, office BP was assessed in the morning (0830 to 1230 h) in a temperature-controlled (22–25 °C) room. The brachial BP was measured three times (with 1-min interval between readings) in the supine position with a validated automated device (Microlife WatchBP Office; Microlife AG, Widnau, Switzerland) in the right arm. The average of the three readings was calculated and used in subsequent statistical analysis if necessary, as well as in calibration of the radial pressure waveform recorded by the Sphymocor apparatus (AtCor, Sydney, NSW, Australia) to assess office aortic BP.

Ambulatory (brachial and aortic) blood pressure monitoring

The ambulatory brachial and aortic BP monitoring were assessed noninvasively with validated devices (Mobil-O-Graph NG apparatus, I.E.M., Stolberg, Germany). The right arm was used to measure the ambulatory BP recordings. The device was set to record brachial BP (four times per hour from 0800 to 2359 h and two times per hour from 0000 to 0759 h) together with brachial pressure waveform simultaneously. If there is a missing reading, the closest reading will be the surrogate for the missing value. Aortic BP was assessed by software analysis (with the application of pulse wave analysis and of a generalized transfer function) when the data were downloaded to the manufacturer's software (HMS version 4.6, I.E.M.). Two parameters were calculated to assess the BPV, namely weighted s.d. (wSD) and average real variability (ARV) (brachial and aortic, respectively). The formulas that we applied to calculate the wSD and ARV were listed below:[16,17]

$$\mathrm{ARV} = \frac{1}{\sum} w \sum_{k=1}^{n} w \times \left| BP_k - BP_{k-1} \right|$$

$$\mathrm{SD} = \sqrt{\sum_{k=1}^{n} [w_k \times (BP_k - \overline{BP})^2] / (n-1) / \sum_{k=1}^{n} w_k}$$

$$\mathrm{wSD} = (\mathrm{DaytimeSD} \times \mathrm{AT} + \mathrm{NighttimeSD} \times \mathrm{ST}) / (\mathrm{AT} + \mathrm{ST})$$

where k ranges from 1 to n, w represents corresponding time interval, BP_k is one BP measurement and n represents the number of BP readings in 24 h (in ARV) or the number of BP readings in corresponding daytime or nighttime (in wSD). AT: awake time hours, from 0800 to 2359 h in this study. ST, sleep time hours, from 0000 to 0759 h in this study.

Measurements of echocardiography

One experienced operator, blinded to the characteristics of each participant, performed the transthoracic echocardiography in all participants with an ultrasound system (Vivid 7 Pro; General Electric, Fairfield, CT, USA) according to the American Society of Echocardiography recomimendations.[18]

LVM was evaluated with the formula recommended by the American Society of Echocardiography from two-dimensional echo views. The LVM was standardized to body surface area as LVM index (LVMI). LVH was defined as LVMI greater than 110 g m^{-2} in women or 125g m^{-2} in men. Similarly, the left atrial volume (LAV) was calculated according to the American Society of Echocardiography recommendations and standardized to body surface area as LAV index (LAVI), which was described in detail previously.[13]

Transmitral early diastolic peak flow (E), atrial peek flow (A) and deceleration time of E wave (DTE) were measured by Pulse-wave Doppler. Early diastolic movement (Ea) in the septum and lateral side was measured by Tissue Doppler. Ratio of E and Ea wave (E/Ea) was calculated for the evaluation of LV diastolic function. According to the recommendations from American Society of Echocardiography,[18] LVDD was identified if E/Ea $\geqslant 15$, or if E/Ea was between 8 and 15 and with any of the following evidences: (1) age > 50years and E/A < 0.5 and DTE > 280 ms; (2) LAVI > 40 ml m^{-2}; and (3) LVMI > 149 g m^{-2} (male) or LVMI > 122 g m^{-2} (female).

Sample size estimation

To estimate the sample size, an interim pilot analysis of the first 20 consecutively recruited patients was performed. The correlation coefficient between LVMI and brachial wSD was 0.32, and the correlation coefficient between LVMI and aortic wSD was 0.16. A sample size of at least 173 participants was estimated to provide 80% power to detect a significant difference in correlation coefficients at a significance level of 0.05 within a single sample.

Statistical analysis

Statistical analysis was performed using SAS software, version 9.2 (SAS Institute, Cary, NC, USA). Statistical significance was defined as P less than 0.05. Continuous values were expressed as mean ± s.d. and the discontinuous as absolute numbers and percentage. Pearson's correlation coefficient was applied to test the linear association of LVMI and E/Ea with BPV indices. Participants were divided into three groups by tertiles of BPV indices and the percentages of the participants with LV structural and functional abnormalities were calculated. Cochran–Armitage test for trend was applied to assess the tendency. Then, multiple linear regression models were constructed to evaluate the changes in LVMI or E/Ea in relation to 1 s.d. increment in BPV indices, with (model 2) or without (model 1) adjustment to age, gender, body mass index, hypertension, the use of antihypertensive agents, smoking and mean 24-h SBP (brachial and aortic, respectively). Binary logistic models with similar adjustment were applied to assess the association between LVH or LVDD and BPV indices.

Results

Out of 203 participants (mean age: 54.1 ± 15.1 years), there were 112 (55%) men, 126 (62%) smokers, 145 (71%) hypertensive patients and 13 (6.4%) diabetic patients (see Table 1). Patients' BP components, including brachial and aortic BP level and BP variations, are presented in Table 2. On the average, 79.3 ± 8.1 BP measurements were performed by the Mobil-O-Graph device on each patient. The mean valid brachial BP readings were 72.0 ± 10.1 (90.8%) and the mean valid aortic BP readings were 62.3 ± 11.2 (78.6%). Office brachial SBP was significantly higher than aortic SBP (136.2 ± 17.9 mm Hg vs 132.1 ± 16.7 mm Hg, $P < 0.001$). Similarly, brachial 24-h mean SBP was higher than 24- h mean aortic SBP (127.0 ± 13.0 mm Hg vs 117.6 ± 12.4 mm Hg, $P < 0.001$), as well as the BP variability, expressed either as 24hr wSD model (12.9 ± 3.3 vs 11.8 ± 3.1, $P < 0.001$), or ARV model (10.7 ± 2.7 vs 10.5 ± 2.8, $P = 0.01$). Echocardiographic parameters are also listed in Table 2. There were 16

Table 1. Clinical characteristics of participants ($n = 203$)

Basic demographics	
Male	112 (55%)
Age	54.1 ± 15.1
BMI	27.2 ± 4.2
Smoker	126 (62%)
Hypertensive patients	145 (71%)
Diabetic patients	13 (6.4%)
Anti-hypertensive agents	
Total anti-HTN patients	124 (61%)
ACE inhibitor	16 (7.9%)
ARB	45 (22%)
CCB	35 (17%)
Diuretics	28 (14%)
Beta blocker	27 (13%)
ALD receptor antagonist	3 (1.5%)

Abbreviations: ACE, angiotensin converting enzyme; ALD, aldosterone; Anti-HTN, anti-hypertensive; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker.

Table 2. Blood pressure and echocardiography parameters

Office blood pressure	
Brachial systolic BP	136.2 ± 17.9
Brachial diastolic BP	81.9 ± 11.0
Aortic systolic BP	132.1 ± 16.7
Aortic diastolic BP	80.0 ± 10.8
Mean systolic blood pressure	
Brachial mean 24 h SBP	127.0 ± 13.0
Aortic mean 24h SBP	117.6 ± 12.4
Systolic blood pressure variablity	
Brachial 24 hwSD	12.9 ± 3.3
Aortic 24 hwSD	11.8 ± 3.1
Brachial ARV	10.7 ± 2.7
Aortic ARV	10.5 ± 2.8
Cardiac structure and function	
LV mass index	97.3 ± 25.3
LV hypertrophy	16 (7.9%)
mean E/Ea ratio	8.9 ± 3.2
Diastolic dysfunction	11 (5.5%)

Abbreviations: ARV, average real variability; BP, blood pressure; LV, left ventricular; SBP, systolic blood pressure; wSD, weighted s.d.

participants (7.9%) with LVH, and 11 participants (5.5%) with LVDD in the present study.

Cochran–Armitage test for trend

The participants were divided into three groups by the tertiles of 24 h wSD and ARV, namely low BPV group (group 1), middle BPV group (group 2) and high BPV group (group 3). The percentages of participants with LVH or LVDD were shown in Figure 1. Cochran–Armitage test for trend was performed. The prevalence of LVH significantly increased with BPV indices, with $P = 0.01$ (grouped by brachial wSD), $P = 0.04$ (grouped by aortic wSD), $P = 0.001$ (grouped by brachial ARV) and $P = 0.01$ (grouped by aortic ARV), respectively. Similarly, the prevalence of LVDD significantly increased with BPV indices too, with $P = 0.001$ (grouped by brachial wSD), $P = 0.01$ (grouped by aortic wSD), $P < 0.001$ (grouped by brachial ARV) and $P = 0.001$ (grouped by aortic ARV), respectively.

Univariate correlation between LVMI or E/Ea and BPV

In Table 3, Pearson's correlation analyses were applied to investigate the association of LVMI and E/Ea with brachial and aortic BP and BPV. LVMI was significantly correlated with age, BMI and all brachial and aortic BP and BPV indices ($P \leqslant 0.045$), and E/Ea was also significantly correlated with those parameters ($P \leqslant 0.01$), except the association between E/Ea and BMI ($P = 0.62$).

Multiple linear regression of LVMI and E/Ea with BPV parameters

In multivariate linear analyses (Table 4), all four BPV parameters significantly associated with LVMI and E/Ea without adjustment, with all *P*-values $\leqslant 0.003$. After adjustment to age, gender, body mass index, the presence of hypertension, use of antihypertensive agents, smoking and the mean 24 h brachial or aortic SBP, 1 s.d. increment in ARV significantly associated with 4.35 ± 1.80 g m^{-2} increment in LVMI ($P = 0.02$), whereas the association of LVMI with brachial ARV did not reach statistical significance ($P \geqslant 0.07$, Figure 2). Neither aortic nor brachial wSD significantly associated with LVMI. No significant association of E/Ea with aortic or brachial BPV, neither for ARV nor for wSD model, was found ($P \geqslant 0.30$).

Multivariate logistic regression of LVH and LVDD with BPV parameters

In Table 5, multivariate logistic regression analyses were performed to evaluate the independent association of LVH and LVDD with brachial and aortic BPV. Similar as the results in linear regression, all four BPV parameters significantly associated with LVH and LVDD without adjustment to potential confounders, with $P \leqslant 0.046$. After adjustment to age, gender, body mass index, the presence of hypertension, use of antihypertensive agents, smoking and the mean 24-h brachial or aortic SBP, it was showed that 1 s.d. increment in aortic ARV significantly associated with LVH (odds ratio (OR) (95% confidence interval (CI)): 2.28 (1.08, 4.82), $P = 0.04$), but no significant association of LVH with brachial ARV was detected ($P \geqslant 0.09$). No significant association of aortic or brachial wSD with LVH was found. As for cardiac diastolic dysfunction, both aortic and brachial ARV significantly associated with LVDD, with OR (95% CI) of 2.36 (1.10, 5.05) ($P = 0.03$) and 2.28 (1.03, 5.02) ($P = 0.04$), respectively. Of note, there was no significant association of cardiac structure and function with BPV in wSD model ($P \geqslant 0.14$), as shown in Figure 3.

DISCUSSION

The present study indicates that, after adjustment to potential confounders, aortic BPV, especially aortic ARV, seems to be better associated with LV abnormalities, including mainly LVH and secondarily LVDD, than brachial BPV, independent of BP level. To our knowledge, this is the first study presenting the superiority of the association between TOD and aortic over brachial BPV.

Because of the development of ambulatory BP monitoring devices, it is possible now to make an accurate assessment of short-term BPV within a 24 h period continuously and noninvasively. Previous studies indicated that, though sometimes still in debate, the increase of short-term BPV within 24 h might be an important cause for the development of multiple TOD and the increasing incurrences of CV events in hypertensive patients.[19] Several mathematical models for BPV calculation were developed. After simply calculating the SD of all BP recordings, time-weighted SD was proposed later to weight the duration of day-time and night-time BP s.d., respectively, in order to avoid the effect of physiological night-time BP dipping.[17] Meanwhile, the ARV model, which is not affected by the 'dipping' phenomenon, were raised,[16] and soon showed its superiority over simple s.d. in the association of TOD and CV risks.[20] Thus, we chose wSD and ARV as the markers of patients' BPV, and investigated their associations with LV structure and function.

SBP varies between the aortic to the brachial artery up to 40 mm Hg and the relationship between aortic and brachial BP is not linear.[21] From the physiological point of view, the aortic BP waveform is composed of a forward and a backward travelling wave, and the backward travelling wave is largely dependent on peripheral arterial stiffness. On the other hand, from the pathophysiological point of view, target organs, including heart, kidney and brain, directly confront the aortic BP rather than the brachial BP. Indeed, brachial BP is the surrogate of aortic BP when aortic BP is not available. Thus, aortic BP and its variability may be better related to TOD and future CV events than the brachial, since it reflects both the aortic stiffness and the 'real' pressure burden on those organs. Emerging evidences now are supporting the superiority of aortic BP over brachial BP, in either the resting or the ambulatory settings. Recently, McEniery *et al.* summarized evidences on the importance of aortic BP and more than 10 observational and longitudinal studies were included in his analysis.[22] However, the superiority of aortic BPV over brachial BPV has not yet been definitely proven. Our observational data for the first time indicates the superiority of aortic BPV over peripheral BPV.

Many clinical issues need to be considered in relation to the present results. First, more clinical evidences, especially from the prospective studies, need to be obtained to prove the prognostic value. Particularly, the increment of prognostic significance of aortic BP variability over the usual BP level needs to be verified. This SAFAR study is still ongoing and in the near future the SAFAR-China study will start. We may have more interesting findings when SAFAR-China study is completed. Second, we need to be very cautious to recommend the BPV-driven antihypertensive therapy as an important supplement of the current BP-driven antihypertensive therapy, let alone the aortic BPV-driven antihypertensive therapy. As early as 2010, Hansen TW *et al.* reviewed the data from 11 populations and found that, though higher systolic ARV did predict CV events, it only increased $< 1\%$

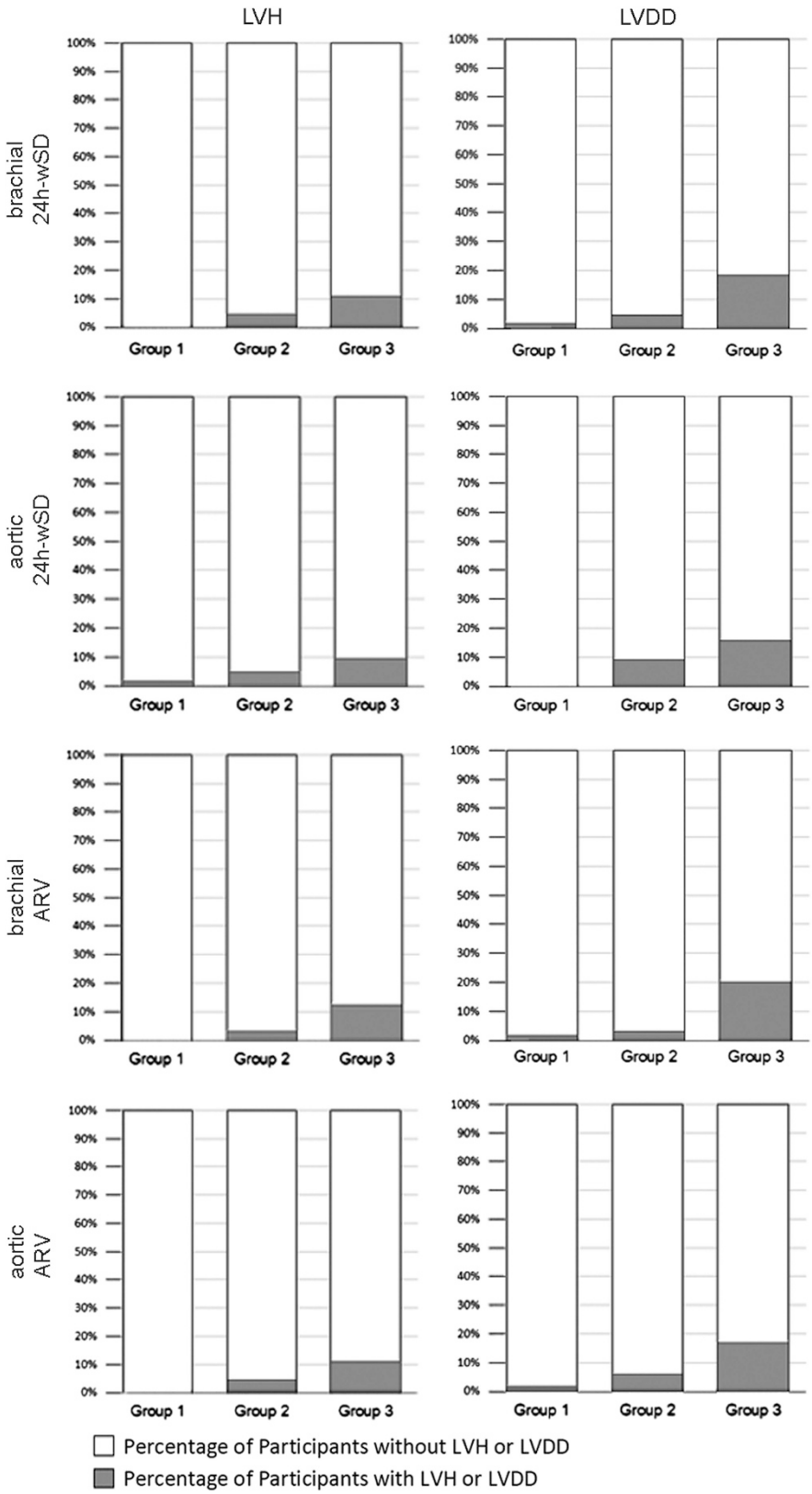

Figure 1. Prevalence of LVH and LVDD in participants with different BPV levels. The participants were divided into three groups by the tertiles of BPV, namely low BPV group (group 1), middle BPV group (group 2) and high BPV group (group 3). Though the participant were grouped by four different BPV indices (brachial wSD and ARV, aortic wSD and ARV, respectively), the prevalence of LVH and LVDD increased significantly with all BPV indices. ARV, average real variability; BPV, blood pressure variability; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; wSD, 24-h weighted s.d.

additional prognostic significance over the BP level.[23] Recently, Zhang YQ *et al.* reported that, in 9711 hypertensive patients from the Felodipine Event Reduction (FEVER) study, BPV significantly predicted the subsequent stroke, but was less important than level of systolic BP, age and level of diastolic BP in this cohort.[24] As suggested in this paper, whether aortic BPV carries more prognostic value than brachial BPV needs to be further addressed,

Table 3. Univariate correlations between cardiac structure and function indexes and cardiac risk factors

	LVMI		*E/Ea ratio*	
	R	*P*	*R*	*P*
Age	0.14	**0.045**	0.57	< **0.001**
BMI	0.21	**0.003**	0.04	0.624
Brachial mean 24h SBP	0.42	< **0.001**	0.22	**0.002**
Aortic mean 24h SBP	0.36	< **0.001**	0.18	**0.012**
Brachial systolic 24hwSD	0.26	< **0.001**	0.32	< **0.001**
Aortic systolic 24hwSD	0.22	**0.002**	0.36	< **0.001**
Brachial systolic ARV	0.23	**0.001**	0.31	< **0.001**
Aortic systolic ARV	0.23	**0.001**	0.32	< **0.001**

Abbreviations: ARV, average real variability; BP, blood pressure; BMI, body mass index; LVMI, left ventricular mass index; wSD, weighted s.d. All values in bold indicate that these *P*-values are less than 0.05 with statistical significance.

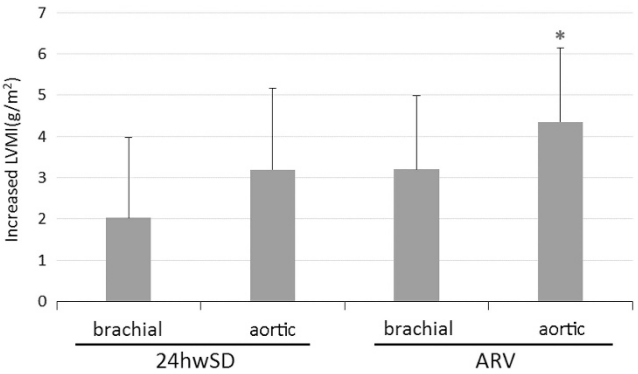

Figure 2. Associations of LVMI with systolic BPV parameters. Multiple linear regressions were performed to investigate the association of LVMI with 1 s.d. increment of four blood pressure variability parameters (brachial and aortic systolic 24hwSD, and brachial and aortic systolic ARV), respectively. The adjustment models included: age, gender, body mass index, the use of antihypertensive agents, smoking and the mean 24-h brachial or aortic systolic blood pressure. * indicates the association is significant after adjustment. 24 hwSD, 24-h weighted s.d.; ARV, average real variability; BP, blood pressure; BPV, blood pressure variability; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy. * indicates LVMI significantly increased when aortic systolic ARV increased 1 s.d. A full colour version of this figure is available at the *Journal of Human Hypertension* journal online.

Table 4. Associations of LVMI and E/Ea ratio with BPV parameters (β-coefficient and *P*-value)

	LVMI ($\beta \pm$ *s.e.*)	*P*-value	*E/Ea* ($\beta \pm$ *s.e.*)	*P*-value
Model 1: without adjustment				
Brachial systolic 24 hwSD	6.75 ± 1.68	< 0.001	1.02 ± 0.22	< 0.001
Aortic systolic 24 hwSD	5.32 ± 1.69	0.002	1.01 ± 0.22	< 0.001
Brachial systolic ARV	5.77 ± 1.70	< 0.001	1.17 ± 0.22	< 0.001
Aortic systolic ARV	5.12 ± 1.70	0.003	1.01 ± 0.22	< 0.001
Model 2: with adjustment				
Brachial systolic 24 hwSD	2.02 ± 1.96	0.3	0.14 ± 0.24	0.56
Aortic systolic 24 hwSD	3.19 ± 1.97	0.11	0.21 ± 0.24	0.39
Brachial systolic ARV	3.21 ± 1.77	0.07	0.22 ± 0.22	0.3
Aortic systolic ARV	4.35 ± 1.80	**0.02**	0.16 ± 0.22	0.53

Abbreviations: ARV, average real variability; BPV, blood pressure variability; LVMI, left ventricular mass index; wSD, weighted s.d. Multiple linear regressions were performed to investigate the association of LVMI and E/Ea ratio with 1 s.d. increment of four blood pressure variability parameters (brachial and aortic systolic 24 hwSD, and brachial and aortic systolic ARV), respectively. The adjustment models included: age, gender, body mass index, the use of antihypertensive agents, smoking and the mean 24 h brachial or aortic systolic blood pressure. All values in bold indicate that these *P*-values are less than 0.05 with statistical significance.

Table 5. Associations of LVH and LVDD with systolic BPV parameters

	LVH (95% CI), n = *202*	*P*-value	*LVDD (95% CI),* n = *199*	*P*-value
Model 1: without adjustment				
Brachial systolic 24 hwSD	2.06 (1.13, 3.74)	0.02	2.41 (1.44, 4.02)	< 0.001
Aortic systolic 24 hwSD	3.10 (1.59, 6.03)	< 0.001	3.00 (1.74, 5.16)	< 0.001
Brachial systolic ARV	1.82 (1.01, 3.28)	0.046	2.39 (1.44, 3.97)	< 0.001
Aortic systolic ARV	2.52 (1.43, 4.45)	0.002	2.62 (1.59, 4.33)	< 0.001
Model 2: with adjustment				
Brachial systolic 24 hwSD	1.40 (0.84, 2.33)	0.23	1.53 (0.66, 3.51)	0.32
Aortic systolic 24 hwSD	1.59 (0.75, 3.39)	0.23	1.91 (0.82, 4.45)	0.14
Brachial systolic ARV	1.86 (0.92, 3.79)	0.09	2.28 (1.03, 5.02)	**0.04**
Aortic systolic ARV	2.28 (1.08, 4.82)	**0.04**	2.36 (1.10, 5.05)	**0.03**

Abbreviations: ARV, average real variability; BP, blood pressure; BPV, blood pressure variability; CI, confidence interval; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; wSD, weighted s.d. Logistic regressions were performed to investigate the association of: (i) LVH and (ii) LVDD (1 = presence and 0 = absence), with 1 s.d. increment of four blood pressure variability parameters (brachial and aortic systolic 24 hwSD, and brachial and aortic systolic ARV), respectively. The adjustment models included: age, gender, body mass index, the use of antihypertensive agents, smoking and the mean 24-h brachial or aortic systolic BP. All values in bold indicate that these *P*-values are less than 0.05 with statistical significance.

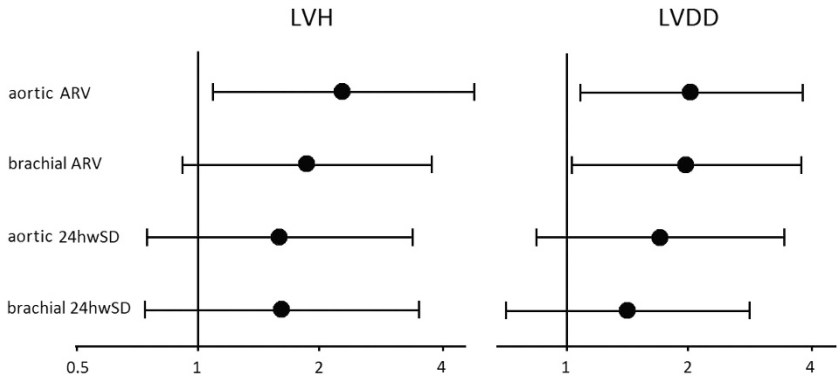

Figure 3. Associations of LVH and LVDD with systolic BPV parameters. Logistic regressions were performed to investigate the association of: (i) LVH and (ii) LVDD (1 = presence and 0 = absence), with 1 s.d. increment of four blood pressure variability parameters (brachial and aortic systolic 24 hwSD, and brachial and aortic systolic ARV), respectively. The adjustment models included: age, gender, body mass index, the use of antihypertensive agents, smoking and the mean 24-h brachial or aortic systolic blood pressure. 24 hwSD, 24-h weighted s.d.; ARV, average real variability; BP, blood pressure; BPV, blood pressure variability; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy.

and more clinical data are warranted to verify the application of BPV. We hold the opinion that, with the increasing clinical evidences, BPV would be considered as a necessary supplement of BP measurement, and it would be valuable in the therapeutic strategy for patients after considering their BP level. In this case, aortic BPV together with aortic BP level could be routinely examined and prevailed as a novel and valuable biomarker.

Our study needs to be interpreted with its limitations. As a cross-sectional study with a small sample size, the causal relationship of BPV and TOD needs to be further discussed and the results should be verified by large prospective studies. For the same reason and the shortage of current knowledge about the mechanisms of short-term BPV, our study, though proving the association between aortic BPV and TOD independently of BP level, could not give further explanations on the mechanisms of this association. Experimental studies are warranted to solve the question. Second, our study did not involve the pulse wave velocity as an important confounding factor. We have no idea how the aortic stiffness accounted for in the calculations. Third, the population of this study is composed of the outpatients in 'Laiko' Hospital with suspected or diagnosed hypertension. It should be very cautious to extend our results to other populations.

CONCLUSION

Twenty-four hour aortic BPV, especially aortic ARV, significantly associated with LVH and LVDD independently of BP level, and seemed to be superior to brachial BPV in this association. This finding, together with our previous publications, favors the application of 24h ambulatory aortic BP measurement in clinical practice. However, clinical prospective studies are warranted to further elucidate its value.

What is known about topic?

- Both brachial and central blood pressure are associated with target organ damages.
- Central blood pressure is better associated with target organ damages than brachial blood pressure.
- Brachial systolic blood pressure variability is associated with target organ damages.

What this study adds?

- Central blood pressure variability is associated with left ventricular hypertrophy and diastolic dysfunction.
- Central blood pressure variability, especially central average real variability, may be better associated with cardiac structural and functional abnormalities than brachial blood pressure variability.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G. Relationship of 24-h blood pressure mean and variability to severity of target-organ damage in hypertension. *J Hypertens* 1987; **5**: 93–98.
2 Eguchi K, Ishikawa J, Hoshide S, Pickering TG, Schwartz JE, Shimada K *et al.* Night time blood pressure variability is a strong predictor for cardiovascular events in patients with type 2 diabetes. *Am J Hypertens* 2009; **22**(1): 46–51.
3 Vishram JK, Dahlöf B, Devereux RB, Ibsen H, Kjeldsen SE, Lindholm LH *et al.* Blood pressure variability predicts cardiovascular events independently of traditional cardiovascular risk factors and target organ damage: a LIFE substudy. *J Hypertens* 2015; **33**(12): 2422–2430.
4 Sander D, Kukla C, Klingelhofer J, Winbeck K, Conrad B. Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis: A 3-year follow-up study. *Circulation* 2000; **102**: 1536–1541.
5 Sega R, Corrao G, Bombelli M, Beltrame L, Facchetti R, Grassi G *et al.* Blood pressure variability and organ damage in a general population: results from the PAMELA study. *Hypertension* 2002; **39**: 710–714.
6 Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet* 2010; **375**: 906–915.
7 Devereux RB, Alderman MH. Role of preclinical cardiovascular disease in the evolution from risk factor exposure to development of morbid events. *Circulation* 1993; **88**: 1444–1455.
8 Kollias A, Lagou S, Zeniodi ME, Boubouchairopoulou N, Stergiou GS. Association of central versus brachial blood pressure with target-organ damage: systematic review and meta-analysis. *Hypertension* 2016; **67**; 183–190.
9 de Luca N, Asmar RG, LondonGM, O'Rourke MF, Safar ME. Selective reduction of cardiac mass and aortic blood pressure on low-dose combination perindopril/indapamide in hypertensive subjects. *J Hypertens* 2004; **22**: 1623–1630.
10 Manisty CH, Zambanini A, Parker KH, Davies JE, Francis DP, Mayet J *et al.* Differences in the magnitude ofwave reflection account for differential effects of amlodipine- versus atenolol-based regimens on aortic blood pressure: an Anglo-Scandinavian Cardiac Outcome Trial substudy. *Hypertension* 2009; **54**: 724–730.
11 Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C *et al.* Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J* 2010; **31**(15): 1865–1871.
12 Protogerou AD, Argyris AA, Papaioannou TG, Kollias GE, Konstantonis GD, Nasothimiou E *et al.* Left-ventricular hypertrophy is associated better with 24-h aortic pressure than 24-h brachial pressure in hypertensive patients: the SAFAR study. *J Hypertens* 2014; **32**(9): 1805–1814.
13 Zhang Y, Kollias G, Argyris AA, Papaioannou TG, Tountas C, Konstantonis GD *et al.* Association of left ventricular diastolic dysfunction with 24-h aortic ambulatory blood pressure: the SAFAR study. *J Hum Hypertens* 2015; **29**: 442–448.
14 Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M *et al.* 2013 ESH/ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European ociety of

Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; **31**: 1281–1357.
15 Tatasciore A, Zimarino M, Renda G, Zurro M, Soccio M, Prontera C *et al.* Awake blood pressure variability, inflammatory markers and target organ damage in newly diagnosed hypertension. *Hypertens Res* 2008; **31**(12): 2137–2146.
16 Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T *et al.* A reliable index for the prognostic significance of blood pressure variability. *J Hypertens* 2005; **23**(3): 505–511.
17 Bilo G, Giglio A, Styczkiewicz K, Caldara G, Maronati A, Kawecka-Jaszcz K *et al.* A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. *J Hypertens* 2007; **25**(10): 2058–2066.
18 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA *et al.* Recommendations for chamber quantification. *Eur J Echocardiogr* 2006; **7**: 79–108.
19 Mancia G. Short-and long-term blood pressure variability: present and future. *Hypertension* 2012; **60**: 512–517.
20 Stolarz-Skrzypek K, Thijs L, Li Y, Hansen TW, Boggia J, Kuznetsova T *et al.* 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.
21 Ohte N, Saeki T, Miyabe H, Sakata S, Mukai S, Hayano J *et al.* Relationship between blood pressure obtained from the upper arm with a cuff-type sphygmomanometer and central blood pressure measured with a catheter-tipped micromanometer. *Heart Vessels* 2007; **22**: 410–415.
22 McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. *Eur Heart J* 2014; **35**: 1719–1725.
23 Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K *et al.* Prognostic value of reading-to-reading blood pressure variability over 24 h in 8938 subjects from 11 populations. *Hypertension* 2010; **55**(4): 1049–1057.
24 Zhang Y, Zhang X, Liu L, Zanchetti A. Visit-to-visit blood pressure variability and cardiovascular outcomes in felodipine event reduction study. *J Hypertens* 2015; **33**: e46.