Original Article

Relationship of 24-h ambulatory blood pressure variability with micro and macrovascular parameters and hypertension status

Stella-Lida Papadopoulou[a], Eugenia Gkaliagkousi[a], Konstantina Dipla[b], Nikolaos Koletsos[a], Andreas Zafeiridis[b], Xenophon Zabulis[c], Antonios Lazaridis[a], George Stergiou[d], Stella Douma[a], and Areti Triantafyllou[a]

Objectives: Increased blood pressure variability (BPV) has been associated with an increased risk of subclinical organ damage and cardiovascular events, independently of elevated average BP values. We aimed to investigate the association of BPV indices with micro- and macrovascular parameters, some of them not previously studied.

Methods: We evaluated 344 individuals (233 never-treated/newly diagnosed hypertensive and 111 normotensive individuals). BPV was assessed using average real variability (ARV) during 24-h, daytime and night-time ambulatory blood pressure monitoring, and systolic weighted standard deviation (wSD). Retinal microvascular diameter was assessed by nonmydriatic retinal photography. Arterial stiffness was assessed by pulse wave velocity (PWV) and aortic augmentation index (AIx); subendocardial variability ratio (SEVR) was used as an index of myocardial perfusion. Carotid intima-media thickness (cIMT) was measured by ultrasound. Data were analyzed using multiple regression analysis.

Results: After adjusting for potential confounders, PWV and cIMT were independently associated with ARV components in the total sample ($P < 0.023$ and $P < 0.014$, respectively). Within hypertensives only PWV and cIMT were independently associated with ARV components ($P < 0.002$ for PWV and $P < 0.003$ for cIMT). In contrast, within normotensives, only retinal parameters and AIx were associated with ARV components ($P < 0.017$ and $P = 0.013$, respectively). None of the univariate correlations between vascular parameters and wSD remained significant after adjustment for potential confounders.

Conclusion: Short-term BPV as assessed by ARV is independently associated with macrovascular parameters in untreated hypertensive patients, and with microvascular parameters in normotensive individuals.

Keywords: average real variability, blood pressure variability, macrocirculation, microcirculation, target organ damage

Abbreviations: ABPM, ambulatory blood pressure monitoring; AIx, aortic augmentation index; ARV, average real variability; AVR, arteriovenous ratio; BP, blood pressure; BPV, blood pressure variability; cIMT, carotid intima-media thickness; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; CV, coefficient of variance; DBP, diastolic blood pressure; PWV, pulse wave velocity; SBP, systolic blood pressure; SD, standard deviation; SEVR, subendocardial variability ratio; TOD, target organ damage; wSD, weighted standard deviation

INTRODUCTION

Elevated blood pressure (BP) is a leading modifiable risk factor for cardiovascular morbidity and mortality worldwide [1,2]. Structural and functional alterations in both macro- and microvasculature are associated with hypertension [3–5]. However, it has been established that BP is not a fixed variable and it shows profound fluctuations over short-term and long-term periods [6]. Thus, wider use of out-of-office BP measurement with home or ambulatory blood pressure monitoring (ABPM) has been suggested by the guidelines [7,8] as an option to confirm the diagnosis of hypertension, detect white-coat and masked hypertension, and monitor BP. The use of ABPM has been documented of a greater value over office BP for the prediction of cardiovascular events [9]. In addition, existing data suggest that out-of-office BP measurements are superior to office measurements in regard to their association with preclinical target organ damage (TOD) [10]. The presence of subclinical TOD has significant prognostic and therapeutic implications in the

Journal of Hypertension 2023, 41:74–82

[a]3rd Department of Internal Medicine, Papageorgiou Hospital and, [b]Exercise Physiology and Biochemistry Laboratory, Department of Physical Education and Sports Science at Serres, Aristotle University of Thessaloniki, Thessaloniki, [c]Institute of Computer Science (ICS), Foundation for Research and Technology – Hellas (FORTH) and [d]Hypertension Center STRIDE-7, National and Kapodistrian University of Athens, School of Medicine, Third Department of Medicine, Sotiria Hospital, Athens, Greece

Correspondence to Areti Triantafyllou, MD, MSc, PhD, Assistant Professor of Internal Medicine, 3rd Department of Internal Medicine, Papageorgiou Hospital, Aristotle University of Thessaloniki, Nea Efkarpia, Ring Road, 56429, Thessaloniki, Greece. E-mail: artriant@auth.gr

Received 8 December 2021 **Revised** 22 August 2022 **Accepted** 1 September 2022

DOI:10.1097/HJH.0000000000003300

management of patients with arterial hypertension, as acknowledged by international guidelines [7].

Besides the elevated BP values, indices of augmented blood pressure variability (BPV) have been independently associated with a greater risk of cardiovascular events [11,12] and severity of preclinical TOD [13–15]. BP values show substantial variation within 24 h (short-term BPV), between measurements of different days (mid-term BPV) or between follow-up office visits performed over weeks, months, or years (long-term BPV) [16]. Long-term BPV can be estimated by recurrent office BP measurements; however, these measurements are subject to limitations such as the white-coat and masked hypertension effect. Short-term BPV over 24 h can be measured using ABPM and the classic distribution indices used for BPV quantification are standard deviation (SD), and coefficient of variance (CV) of average BP. However, the short-term BPV derived by 24-h ABPM can be influenced by several factors, such as insufficient number of BP readings, which may result in an inaccurate estimation of the true BPV [17].

The average real variability (ARV) has been introduced as one of the most recent measures of BPV [18]. ARV is calculated as the average of the absolute differences between every two consecutive BP readings; it is affected by the sequence of individual BP measures and is less sensitive to low sampling frequency. According to previous studies, ARV performed better than the SD and the other BPV indices regarding both the prognostic value [18,19] and reproducibility [20]. As reported in a recent meta-analysis by Mena *et al.* [21], early studies showed that increased ARV in hypertensive patients is associated with more severe TOD and increased risk of cardiovascular events. Previous studies investigating the relation of ARV with subclinical TOD included predominantly patients with hypertension [22–26] or patients with comorbidities such as chronic kidney disease [27,28] and diabetes [29]. To the best of our knowledge, there is no prior investigation on the relationship of ARV with retinal microvascular lesions and myocardial microvascular perfusion. The retinal vascular calibers are vascular parameters which are easy to assess and are well correlated with cardiovascular events [30]. Furthermore, SEVR was used as an index of the function of the cardiac microvasculature, another TOD in hypertension that is difficult to directly assess. A recent meta-analysis [31] demonstrated that retinal vascular calibers were independently associated with an increased risk of hypertension and the associations persist in those with optimal BP at baseline. Similarly, we hypothesized that individuals with increased ARV might, even being normotensives, have increased TOD.

The aim of the present study was to investigate the association of BPV indices with micro-and macrovascular parameters in a population of normotensive and untreated hypertensive individuals without cardiovascular comorbidities.

METHODS

Patient population

The study population consisted of individuals who attended the Outpatient Unit of Hypertension, because of increased BP, for participating in vascular assessment studies, or for routine follow-up. Inclusion criteria were: Caucasians aged older than 18 years; absence of current use of antihypertensive or any type of long-term medication known to affect BP; absence of any other known disease, such as clinically overt cardiac disease, arrhythmias, diabetes mellitus and renal disease, verified through medical history, physical examination and routine laboratory tests; absence of diagnosed or suspected secondary causes of hypertension assessed by history and clinical and routine laboratory tests. Blood samples were collected from all patients after an overnight fast, and serum total cholesterol, high- and low-density lipoprotein cholesterol, and triglyceride levels were estimated. The study protocol was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Hospital Scientific/Ethics Committee. Signed informed consent was obtained by all participants.

Office and ambulatory BP measurement

Office BP was measured with the patient after a 5-min rest, using a validated automatic upper-arm cuff oscillometric device (Microlife Exact BP; Microlife AG, Widnau, Switzerland) according to standard recommendations for office BP measurement [16], using appropriate cuff size according to each participant's arm size. After a 5-min seated rest, three consecutive measurements were taken on the arm with the higher BP (with a 1-min interval in between) and the mean of the last two BP readings was considered as the patient's office BP.

Twenty-four-hour ABPM was performed within 1 week from the micro or macrovascular parameters assessment. The validated Spacelabs 90217A device (Spacelabs Medical, Issequah, Washington, USA) was used to monitor ambulatory blood pressure. Appropriate cuffs were placed according to the arm size of each patient, and the device was programmed to perform measurements every 20 min during daytime (0600–2200 h) and every 30 min during the night (2200–0600 h). Daytime and night-time intervals were customized to each participant's reported actual sleeping hours (from the time the patient went to bed until awaking). Participants were advised to maintain their usual activities. At least 70% of recorded readings and >20 awake or >7 asleep BP measurements during 24 h had to be valid, in order to be used for the analysis. Average 24-h, day (awake) and night-time (asleep) systolic and diastolic BP (SBP/DBP) were calculated.

Based on office BP and ABPM levels participants were classified into two groups: hypertensives of any phenotype (office BP $\geq$ 140/90 mmHg or daytime ABPM $\geq$ 135/85 mmHg), or both; and normotensives (office BP $<$ 140/90 mmHg and daytime ABPM $<$ 135/85 mmHg).

Short-term blood pressure variability measurement

According to a recent meta-analysis [12], indices unaffected by day-to-night changes, such as ARV or weighted 24-h SD, should be preferred for 24-h BPV. Short-term BPV of SBP and DBP over 24-h, daytime and night-time periods was evaluated by the read-to-read ARV [18]. ARV was calculated as:

$$\mathrm{ARV} = \frac{1}{N-1}\sum_{k=1}^{N-1}\left|\mathrm{BP}_{k+1} - \mathrm{BP}_{k}\right|$$

where N denotes the number of valid BP measurements, and k is the order of measurements. In-house software was developed in collaboration with the Institute of Computer Science, Foundation for Research and Technology – Hellas, for the automated computation of ARV using raw ABPM data. The weighted standard deviation (wSD) of 24-h systolic BP was also calculated as a classic BPV measure (i.e. the average of daytime and night-time SD corrected for the respective duration of day and night) using the same software.

Assessment of micro and macrovascular parameters

Retinal vascular calibers

All patients underwent bilateral, nonmydriatic digital fundus photography using a NIDEK AFC-230/210 camera (NIDEK, Fremont, California, USA). Two images were obtained from each eye, centered in the mid-fundus between the optic disc and the macula, and the best one was examined by a trained grader blinded to the participant's identity and clinical characteristics. To achieve retinal vessel measurement and analysis, semiautomated computer software was developed by our Hypertension Unit in collaboration with the Institute of Computer Science, Foundation for Research and Technology – Hellas [32]. Retinal photographs were assessed according to a standard protocol, which has been described in detail elsewhere [33]. In brief, the software consisted of a measurement module that estimates vessel diameter in the input images and a graphical user interface module that facilitates user intervention at points of interest. The measurement area of the images was defined as the area from one half to one disc diameter from the optic disc margin. Parr and Hubbard formula, as modified in the Atherosclerosis Risk in Communities protocol [34], was calculated automatically to summarize indices of the average retinal arteriolar and venular diameters, referred to as the central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE), respectively [34,35], as well as their ratio (arteriovenous ratio (AVR) = CRAE/CRVE).

Arterial stiffness parameters

Carotid–femoral pulse wave velocity (PWV) and augmentation index (AIx) were assessed with applanation tonometry as indices of arterial stiffness. The Sphygmocor device (AtCor Medical, Sydney, Australia) was used for their assessment according to a standard protocol after overnight fasting. Participants were instructed to abstain from caffeine, smoking, and alcohol for at least 2 h before assessment of arterial properties and intense physical activity for 24 h. Regarding PWV, waveforms at the right common carotid and right femoral site were recorded sequentially after a 15-min supine rest position. Surface distance between the two recording sites was measured (sternal notch to carotid site and sternal notch to femoral site). Wave transit time was calculated using a simultaneously recorded electrocardiogram as a reference. Two successive measurements were recorded and their average was used.

The radial pressure waveform was detected in the radial artery with a micromanometer-tipped probe using applanation tonometry with the Sphygmocor device (AtCor Medical), and was subsequently analyzed to estimate the aortic pressure waveform. AIx is assessed as the ratio of the late systolic component, which consists mainly of the pressure wave reflected back from the peripheral arteries to the early systolic component in the pulse and is thought to detect a degree of functional arterial stiffening in the distal muscular conduit arteries. Aortic augmentation pressure was calculated as the difference between the first and second systolic peaks of the ascending aortic waveform, obtained from applanation tonometry. For our analysis, we used AIx corrected for the mean heart rate of 75 bpm.

Microvascular coronary perfusion

The subendocardial viability ratio (SEVR), proposed by Buckberg *et al.* [36] as the 'supply:demand' ratio, was used as a functional index of microvascular coronary perfusion. SEVR was noninvasively estimated by applanation tonometry in the radial artery with the SphygmoCor device (AtCor Medical). The software calculates the SEVR as the ratio of the area under the diastolic segment of the derived aortic pressure waveform (diastolic pressure-time index – DPTI), to the area under the systolic segment of the waveform (tension-time index – TTI), which represent the myocardial supply and demand, respectively. Three successive, high-quality measurements were taken in the supine position after a 15-min rest, and the average value was used for the analysis. Lower values of SEVR correspond to poorer perfusion of the myocardium [36–38].

Carotid intima-media thickness

An Aloka ProSound A7 Ultrasound System with a high resolution, linear array probe was used for the assessment of carotid intima-media thickness (cIMT). Images were obtained in the longitudinal plane in the supine position. Measurements were performed in the far wall of the distal 1 cm of the common carotid artery. cIMT was calculated as the mean value of three consecutive sets of readings between the inner echogenic line representing the intima blood interface and the outer echogenic line representing the adventitia-media junction, and the average cIMT of the left and right carotid artery was used for the analysis [39].

Statistical analysis

All data are expressed for continuous variables as mean ± standard deviation or as median (interquartile range) for non-normally distributed variables, and for categorical variables as frequencies. Continuous variables were tested for normality of distribution by examining the standard scores (z-values) for skewness and kurtosis and the respective histograms, normal Q–Q plots, and boxplots. Statistical analyses were performed using Student's t-test or the nonparametric Mann–Whitney test to compare differences between two groups. Relationships between the continuous variables were assessed by calculation of Pearson's or Spearman's rank correlation coefficient depending on the data distribution, whereas the chi-square test was used for comparing categorical variables. Logarithmic transformation was performed for non-normally distributed variables. The data are presented in the original form for ease of interpretation.

We performed interaction analyses for 'hypertension status' to precede the rest of the investigation. Initially, we visualized the moderation interaction by creating scatter plots of the association between ARV and the micro-macrovascular parameters and by adding the respective fit lines for the subgroups using 'hypertension status' as a dichotomized grouped moderator. In order to examine if the lines are significantly nonparallel at different levels of the categorical predictor (hypertension) we tested for differences between the two groups ('Hypertensive' and 'Normotensive' groups) in their relationship between ARV and vascular damage parameters; a test for the differences between the simple slopes was estimated, using the method described by Robinson *et al*. [40] for testing moderation effects in regression models. The respective *P*-values were calculated using the *t*-statistic.

Multiple linear regression models were constructed using the enter method in order to adjust for potential confounders and assess the independent relationship of BPV with the microvascular and macrovascular parameters (dependent variables). The models included all variables with important relations with the microvascular and macrovascular parameters derived from the univariate correlation analyses, using *P*-value >0.10 as a threshold to enter the model. In the regression models, age, sex, smoking habits (current vs. past/never smokers), body mass index, fasting plasma glucose, dyslipidemia, and 24-h mean SBP or DBP (the one with the highest correlation coefficient) were considered as possible confounding factors. For each BPV component (24-h, daytime, and night-time) a separate regression model was constructed with the microvascular and macrovascular parameters as dependent variables. Graphical inspection of scatter plots between predicted values of the dependent variable and regression standardized residuals excluded any heteroscedasticity of distribution. The final models were evaluated for other linear relationships among variables in the model (collinearity), by examining the variance inflation factor values, which all were < 2, indicating no collinearity among the covariates in the models.

An additional analysis was performed by categorizing the participants into groups of low and high BP variability (below and above the 50th percentile of the BPV distribution, respectively) for the 24-h systolic and diastolic ARV to determine their relationship to the microvascular and macrovascular parameters.

A *P*-value <0.05 was considered as statistically significant. All analyses were carried out with SPSS software (version 22.0; SPSS Inc., Chicago, Illinois, USA).

RESULTS

In total 364 individuals fulfilled the inclusion criteria and in 344 (95%) of them the technical quality of the ABPM recording was deemed adequate for analysis. The clinical characteristics and all the vascular parameters of the participants are presented in Table 1. Hypertensive individuals were more frequently male, and their office BP, 24-h BP, and BPV were higher than the normotensive group. The ABPM parameters of the study population are reported in Table 2.

The results of the interaction analyses for the association between ARV and vascular parameters based on hypertension status are presented in Figure 1, Supplemental Digital Content, http://links.lww.com/HJH/C77, Table 1, Supplemental Digital Content, http://links.lww.com/HJH/C78 and Table 2, Supplemental Digital Content, http://links.lww.com/HJH/C79. For the majority of the micro-macrovascular

TABLE 1. Baseline characteristics of the study population

Clinical characteristics	All patients ($n=344$)	Normotensives ($n=111$)	Hypertensives ($n=233$)	*P*-value*
Age (years)	44.5 ± 12.1	45.4 ± 12.3	44.0 ± 12.0	NS
Male (%) *n*	58.4 (201)	42.3 (47)	66.1 (154)	<0.001
Body mass index (kg/m^2)	27.0 (24.3–29.8)	27.1 (24.0–29.5)	26.9 (24.4–29.9)	NS
Current smoking (%) *n*	38.4 (132)	42.3 (47)	36.5 (85)	NS
Office SBP (mmHg)	135.7 ± 18.2	119.1 ± 10.0	143.6 ± 15.7	<0.001
Office DBP (mmHg)	86.9 ± 12.2	76.6 ± 6.9	91.8 ± 11.1	<0.001
Office pulse rate (beats/min)	71.3 ± 10.9	68.6 ± 9.8	72.6 ± 11.2	0.001
eGFR (ml/min per 1.73 m^2)	116.5 ± 33.0	112.7 ± 32.5	118.3 ± 33.2	NS
Serum glucose (mg/dl)	88.0 (81.5–94.0)	86.0 (81.0–93.0)	88.0 (82.0–94.0)	NS
Total cholesterol (mg/dl)	206.4 ± 39.4	210.6 ± 39.0	204.2 ± 39.5	NS
Triglycerides (mg/dl)	97.0 (69.0–139.0)	93.0 (64.0–130.0)	98.0 (72.0–143.8)	NS
LDL-cholesterol (mg/dl)	135.1 ± 33.5	137.7 ± 35.6	133.8 ± 32.4	NS
Vascular parameters				
CRAE (μm)	87.5 (80.6–95.6)	93.48 (85.9–101.5)	85.7 (79.8–92.6)	<0.001
CRVE (μm)	118.0 (106.3–128.0)	121.7 (109.1–130.7)	117.5 (106.3–127.0)	NS
AVR	0.75 (0.69–0.82)	0.80 (0.71–0.84)	0.74 (0.68–0.81)	0.006
SEVR (%)	149.7 (135.4–167.0)	156.8 (140.5–172.3)	145.0 (132.3–164.8)	0.006
PWV (m/s)	7.4 (6.5–8.5)	6.6 (6.0–7.5)	7.8 (7.0–8.8)	<0.001
AIx (%)	21.2 ± 13.4	19.2 ± 13.9	22.2 ± 13.0	0.053
cIMT (mm)	0.57 (0.52–0.66)	0.56 (0.51–0.64)	0.58 (0.52–0.67)	NS

*Comparison between normotensive and hypertensive patients. Continuous variables are presented as mean ± SD or as median (interquartile range) according to the shape of their distribution.
AIx, augmentation index; AVR, arteriovenous ratio; cIMT, carotid intima-media thickness; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; PWV, pulse wave velocity; SBP, systolic blood pressure; SEVR, sub-endocardial viability ratio.

TABLE 2. Ambulatory blood pressure monitoring and variability parameters of the study patients

Parameters	All patients ($n = 344$)	Normotensives ($n = 111$)	Hypertensives ($n = 233$)	*P*-value*
24-h SBP	129.3 ± 15.4	114.5 ± 8.5	136.4 ± 12.7	<0.001
24-h DBP	81.6 ± 11.0	71.9 ± 6.1	81.6 ± 11.0	<0.001
Day-SBP	134.5 ± 15.7	118.7 ± 8.8	141.9 ± 12.5	<0.001
Day-DBP	85.7 ± 11.1	75.6 ± 6.1	90.4 ± 9.6	<0.001
Night-SBP	117.5 ± 15.4	105.0 ± 8.5	123.4 ± 14.3	<0.001
Night-DBP	72.3 ± 11.1	64.1 ± 6.9	76.1 ± 10.6	<0.001
24-h ARV systolic	9.2 ± 1.8	8.5 ± 1.5	9.5 ± 1.8	<0.001
24-h ARV diastolic	7.5 ± 1.6	7.1 ± 1.4	7.6 ± 1.6	0.003
Day ARV systolic	9.4 ± 2.0	8.8 ± 1.9	9.7 ± 2.0	<0.001
Day ARV diastolic	7.7 ± 1.9	7.4 ± 1.8	7.8 ± 1.9	NS
Night ARV systolic	8.7 ± 3.1	8.0 ± 2.9	9.1 ± 3.2	0.002
Night ARV diastolic	7.2 ± 2.5	6.5 ± 2.6	7.5 ± 2.4	0.001
Weighted SD	11.1 ± 2.7	10.0 ± 2.3	11.6 ± 2.7	<0.001

*Comparison between normotensive and hypertensive patients.
ARV, average real variability; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

parameters, the slopes of the association with ARV components were significantly different between hypertensives and normotensives.

The bivariate correlation analyses between BPV indices and the vascular parameters are presented in detail in Table 3 for all patients and for the two subgroups (of hypertensive and normotensive individuals). After controlling for potential confounders with the multiple regression models, PWV and cIMT were independently associated with ARV components in the total population (Table 4). Specifically, PWV was associated with 24-h systolic, daytime systolic, night-time systolic and night-time diastolic ARV; and cIMT was associated with 24-h systolic and daytime systolic ARV. However, in the multiple regression models, none of the univariate correlations between the vascular parameters and wSD remained significant after adjustment for potential confounders. Within the hypertensive group of patients, PWV was independently correlated with night-time systolic and night-time diastolic ARV; and cIMT was associated with 24-h systolic and daytime systolic ARV (Table 4). Within the group of normotensive individuals, CRVE was significantly correlated with 24-h systolic, 24-h diastolic and daytime systolic ARV. The AVR was associated with daytime systolic ARV; and AIx was associated with daytime diastolic ARV (Table 4). However, in the multiple regression models, none of the univariate correlations between the vascular

TABLE 3. Correlation coefficients between blood pressure variability and vascular parameters in the total study population and the two groups of normotensive and hypertensive individuals

BPV measure	CRAE	CRVE	AVR	PWV	AIx	SEVR	cIMT
All patients ($n = 344$)							
24-h ARV systolic	−0.058	0.030	−0.087	0.240*	0.148**	−0.106#	0.239*
24-h ARV diastolic	−0.036	0.087	−0.126#	0.043	−0.007	−0.016	−0.012
Day ARV systolic	−0.006	0.043	−0.065	0.195*	0.201*	−0.082	0.239*
Day ARV diastolic	−0.051	0.033	−0.087	0.012	0.038	0.017	0.034
Night ARV systolic	−0.030	0.046	−0.066	0.199*	−0.092	−0.069	0.085
Night ARV diastolic	−0.017	0.125#	−0.110	0.153**	−0.054	−0.040	−0.024
Weighted SD	−0.077	−0.013	−0.075	0.232*	0.084	−0.064	0.287*
Normotensives ($n = 111$)							
24-h ARV systolic	−0.088	0.323**	−0.323**	0.215**	0.205**	0.023	0.135
24-h ARV diastolic	−0.077	0.374*	−0.407*	−0.151	0.128	−0.032	−0.163
Day ARV systolic	−0.024	0.480*	−0.428*	0.196**	0.280*	−0.015	0.119
Day ARV diastolic	−0.052	0.261**	−0.304**	−0.093	0.193**	−0.079	−0.116
Night ARV systolic	−0.086	−0.013	0.048	0.068	−0.084	0.085	0.145
Night ARV diastolic	0.009	0.252#	−0.212	−0.037	−0.012	0.114	−0.014
Weighted SD	−0.081	0.245#	−0.264**	0.140	0.185	−0.037	0.259**
Hypertensives ($n = 233$)							
24-h ARV systolic	0.022	−0.056	0.055	0.150**	0.099	−0.051	0.262*
24-h ARV diastolic	0.008	0.004	−0.001	0.049	−0.071	0.052	0.056
Day ARV systolic	0.040	−0.094	0.096	0.125#	0.144**	−0.020	0.286*
Day ARV diastolic	−0.033	−0.063	0.015	0.020	−0.034	0.080	0.097
Night ARV systolic	0.041	0.084	−0.061	0.162**	−0.110	−0.109	0.037
Night ARV diastolic	0.051	0.134#	−0.063	0.144**	−0.094	−0.064	−0.049
Weighted SD	−0.050	−0.070	0.016	0.157**	0.005	−0.021	0.279*

Pearson's *r* or Spearman's rho correlation coefficients were used according to the normality of the variables distribution.
AIx, augmentation index; ARV, average real variability; AVR, arteriovenous ratio; cIMT, carotid intima-media thickness; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; PWV, pulse wave velocity; SD, standard deviation; SEVR, sub-endocardial viability ratio.
* $P < 0.01$, ** $P < 0.05$, # $P < 0.1$.

TABLE 4. Multiple linear regression models with the significant associations between average real variability indices and vascular parameters (dependent variables)

All patients					
Vascular parameter	**ARV index included in the model**	**Model R^2**	**Unstandardized *B* (95% CI)**	**Standardized β**	***P*-value**
PWV (1)	24-h systolic ARV	0.475	0.015 (0.006, 0.024)	0.137	0.002
	Daytime systolic ARV	0.467	0.010 (0.001, 0.018)	0.099	0.023
	Night-time systolic ARV	0.472	0.008 (0.003, 0.013)	0.129	0.003
	Night-time diastolic ARV	0.468	0.009 (0.002, 0.015)	0.111	0.012
cIMT (2)	24-h systolic ARV	0.451	0.015 (0.003, 0.027)	0.137	0.014
	Daytime systolic ARV	0.451	0.013 (0.003, 0.023)	0.134	0.014
Normotensives					
Vascular parameter	**ARV index included in the model**	**Model R^2**	**Unstandardized *B* (95% CI)**	**Standardized β**	***P*-value**
CRVE (3)	24-h systolic ARV	0.254	3.997 (1.262, 6.732)	0.378	0.005
	24-h diastolic ARV	0.220	3.464 (0.646, 6.281)	0.321	0.017
	Daytime systolic ARV	0.285	3.866 (1.546, 6.185)	0.448	0.002
AVR (4)	Daytime systolic ARV	0.193	−0.020 (−0.036, −0.005)	−0.363	0.011
AIx (5)	Daytime diastolic ARV	0.568	1.337 (0.285, 2.389)	0.177	0.013
Hypertensives					
Vascular parameter	**ARV index included in the model**	**Model R^2**	**Unstandardized *B* (95% CI)**	**Standardized β**	***P*-value**
PWV (6)	Night-time systolic ARV	0.407	0.011 (0.005, 0.018)	0.190	0.001
	Night-time diastolic ARV	0.402	0.014 (0.005, 0.023)	0.178	0.002
cIMT (7)	24-h systolic ARV	0.471	0.022 (0.008, 0.036)	0.196	0.003
	Daytime systolic ARV	0.471	0.020 (0.007, 0.032)	0.198	0.003

(1) Model adjusted for age, sex, BMI, fasting plasma glucose, smoking, dyslipidemia, and 24-h DBP.
(2) Model adjusted for age, BMI, fasting plasma glucose, dyslipidemia, and 24-h SBP.
(3) Model adjusted for age, BMI, and 24-h DBP.
(4) Model adjusted for age, fasting plasma glucose, and 24-h DBP.
(5) Model adjusted for age, sex, dyslipidemia, and 24-h DBP.
(6) Model adjusted for age, BMI, fasting plasma glucose, dyslipidemia, and 24-h DBP.
(7) Model adjusted for age, BMI, fasting plasma glucose, dyslipidemia, and 24-h SBP.
AIx, augmentation index; ARV, average real variability; AVR, arteriovenous ratio; BMI, body mass index; CI, confidence interval; cIMT, carotid intima-media thickness; CRVE, central retinal venular equivalent; PWV, pulse wave velocity.

parameters and wSD remained significant after adjustment for potential confounders.

In a complementary analysis, when all the patients were divided in low/high BPV groups (Fig. 1), there were significant differences between the low vs. high systolic ARV groups for PWV [7.20 (6.40–8.10) vs. 7.67 (6.60–8.80), respectively, $P=0.008$], for cIMT [0.557 (0.510–0.617) vs. 0.603 (0.523–0.678), respectively, $P=0.008$] and a trend for SEVR (155.0 ± 26.9 vs. 149.9 ± 21.0, respectively, $P=0.065$).

DISCUSSION

Our study showed that in people without established cardiovascular disease, several ARV indices were significantly associated with microvascular and macrovascular parameters. In contrast, after adjustment for potential confounders, none of univariate correlations between wSD and the vascular parameters remained significant. Moreover, an interesting finding was revealed in the subgroup analyses showing that ARV indices correlate with macrocirculation parameters (PWV and cIMT) in hypertensives, whereas in normotensives they reflect mostly microcirculation damage (correlation with retinal calibers and AIx).

This is a comprehensive investigation examining simultaneously the relationship between ARV and several micro- and macrovascular parameters, in a meticulously selected treatment-naïve population. Notably, the results of our investigation revealed a different pattern for the two groups of hypertension phenotype regarding the associations between ARV indices and micro and macrovascular parameters. In normotensives, only the microvascular parameters were associated with ARV, whereas in untreated hypertensives only the macrovascular parameters were related to ARV. A plausible mechanism for this difference based on hypertension status could be speculated. Microcirculation is the site where the earliest manifestations of cardiovascular disease – in particular, inflammatory processes – occur. An important function of the microcirculation is to avoid large fluctuations in hydrostatic pressure at the level of the capillaries causing disturbances in capillary exchange [41]. We may hypothesize that the microcirculation is more sensitive to high blood pressure variability and may be damaged earlier that the macrocirculation, even before the onset of hypertension. This could potentially explain the independent association of ARV with microcirculation but not macrocirculation in the normotensive group. On the other hand, there is evidence to suggest that microvascular abnormality might initiate the pathogenic sequence in primary hypertension. If, as seems likely, microvascular abnormalities can both result from and contribute to hypertension, a 'vicious cycle' may exist in which the microcirculation maintains or even amplifies an initial increase in blood pressure. In the group of patients with established hypertension, we might hypothesize that the fluctuations in BP levels as reflected by the ARV are not affecting any longer the microcirculation as strongly as the actual BP elevation itself.

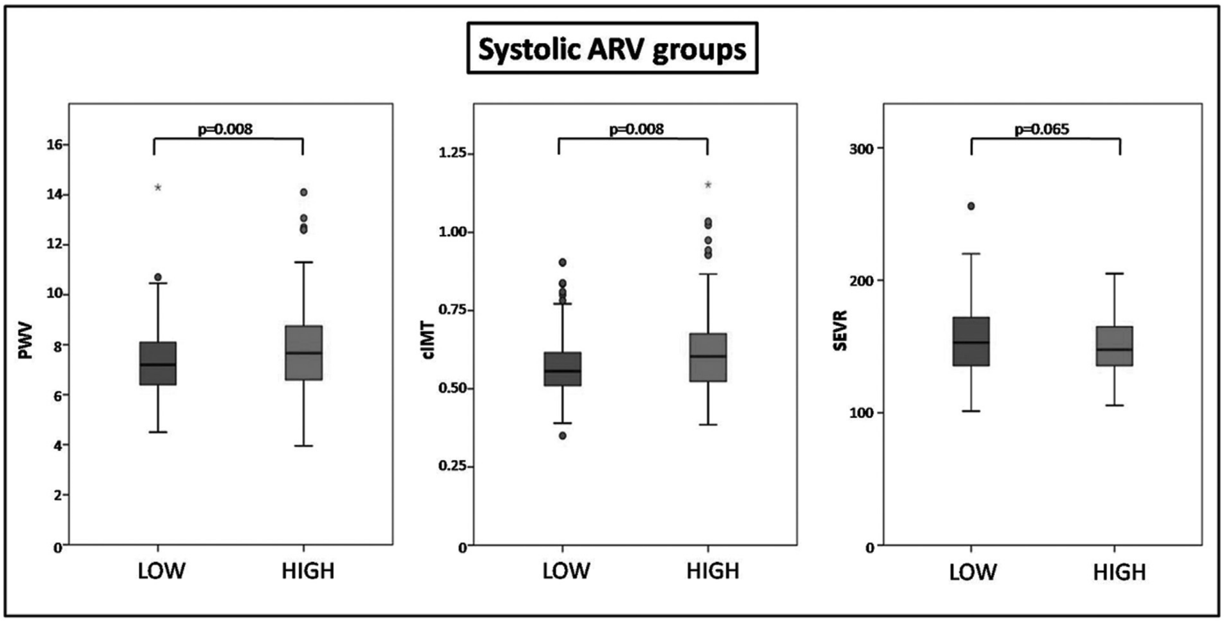

FIGURE 1 Target organ damage parameters (PWV, cIMT and SEVR) according to low vs. high systolic ARV groups (only significantly different groups are displayed). ARV, average real variability; cIMT, carotid intima-media thickness; PWV, pulse wave velocity; SEVR, sub-endocardial viability ratio.

Based on these findings, short-term BPV assessed by ARV could potentially serve as a surrogate marker to identify individuals that are at higher risk of subclinical TOD or development of hypertension, even among a normotensive population, using an affordable and widely available method such as the 24-h ABPM. A strength of this study is that normotensive participants were true normotensives (low office and ambulatory BP), whereas the hypertensive group included individuals with white-coat and masked hypertensives. If in the hypertensive group only people with sustained hypertension (elevated office and ambulatory BP) were included, the differences vs. normotensives would be expected to be larger.

Relation of blood pressure variability with microvascular parameters

Our results showed that in the normotensive individuals the retinal vascular calibers were independently associated with several ARV components, both systolic and diastolic. In our study the ARVs were independently associated with CRVE and AVR, but not CRAE. A previous study found that CRAE was more strongly influenced by BP than CRVE [42], however it is necessary to keep in mind that BPV is a different parameter that BP and previous research findings on BP association with retinal parameters may not apply automatically when BPV is investigated. Importantly, retinal venular widening has been shown to be related to systemic inflammation, measures of atherosclerosis, and metabolic abnormalities [43]. Moreover, retinal venular widening has been hypothesized to be a general marker of retinal ischemia and hypoperfusion secondary to microvascular rarefaction [44] and may reflect endothelial dysfunction which is involved in microvascular remodeling [45]. A recent meta-analysis [31] showed that retinal vascular calibers are independently associated with an increased risk of hypertension and the associations persist in those with optimal BP at baseline. The authors' findings suggested that generalized microvascular dysfunction, seen in the retinal vasculature, precedes the onset and development of hypertension.

In addition, we observed that in normotensive individuals the correlation between ARV and AIx remained significant after adjustment for potential confounders. Noteworthy, in a longitudinal community-based cohort study [46], the investigators demonstrated prospectively that AIx is related to future systolic blood pressure, pulse pressure, and incident hypertension and that initial measures of endothelial function and microcirculation are associated prospectively with incident hypertension, even after considering the potential confounding effect of initial blood pressure. Although AIx depends upon the elastic properties of the entire arterial tree, it seems to reflect more the circulation in the peripheral arteries than in the aorta, since the principal determinant of AIx is the reflection coefficient, which is strongly influenced by peripheral vasomotor tone [47]. These findings highlight the potential value of 24-h ARV and its components to identify individuals at higher risk to develop hypertension, using an accessible method such as the 24-h ABPM.

Notably, in our population SEVR was not associated with any of the BPV indices. It has been hypothesized that higher BPV may predispose to a greater variation in tissue perfusion, which may be harmful to some sensitive tissues. We could speculate that since the microvasculature of the myocardium is experiencing some physiological variations of blood flow due to its contraction during the cardiac cycle, it may be less sensitive to blood pressure variability.

Relation of blood pressure variability with macrovascular parameters

Our results also corroborate previous clinical studies in hypertensive patients [24,48,49], which described a significant association between ARV and large-artery stiffness, as assessed by PWV. In agreement with these reports, we found that this association mainly present for the systolic components of the ARV (24-h, daytime, and night-time). Furthermore, previous data suggest that BPV expressed by ARV is positively related to the cIMT in treated and untreated hypertensive patients [22,23,25,26,29], which is also confirmed by our results. In the normotensive individuals the association of ARV with macrovascular parameters was not significant after adjusting for confounding factors. As previously mentioned, we might hypothesize that in the group of untreated hypertensive patients the fluctuations in BP levels as reflected by the ARV are not affecting any longer the microcirculation as strongly as the actual BP elevation itself.

Possible mechanisms involved in blood pressure variability and target organ damage

The underlying mechanisms of the association between short-term BPV and target organ damage have been investigated by several researchers. Evidence based on animal data [50,51] showed that elevated BPV induced by arterial baroreceptor denervation in rats, without an accompanying increase in average BP levels, was associated with reduced arterial distensibility and increased collagen content and density in arterial walls. A possible mechanism for the structural and functional changes in the carotid artery wall is based on the hypothesis that high BPV increases oscillatory shear stress in the walls of large arteries [52,53], which ultimately leads to vascular wall remodeling and, in some arterial beds, to atherosclerosis [54].

Furthermore, there is a potential role for hemodynamic effects. Higher BPV may predispose to a greater variation in tissue perfusion, which may be harmful to some sensitive tissues. Cellular metabolism may be disturbed by such a variation. Using a chronic SAD rat model, Miao *et al.* [55] hypothesized that a large variation of BP may produce a direct effect on endothelial cells of arteries through mechanical effects, which leads to unbalance of endothelium-derived vasodilators and vasoconstrictors and/or direct lesion of endothelium, resulting in arterial remodeling. It is possible that the activation of neurohumoral systems may be associated with sinoaortic denervation-induced vascular remodeling. In addition, the investigators found that aortic angiotensin II concentration was significantly increased, whereas plasma angiotensin II concentration was unchanged, after 10-week sinoaortic denervation. These data suggest that activation of tissue RAS, rather than circulating RAS, might have been related to arterial wall thickening.

Limitations

These data should be evaluated by considering several limitations. Our population was selected to have relatively low cardiovascular risk; the exclusion of patients with diabetes and previous cardiac or renal disease makes our findings not directly applicable to the entire general hypertensive population. Moreover, we did not adjust for possible magnification effects in the calculation of CRAE and CRVE. In addition, the cross-sectional design of our work does not allow investigating a causal link of BPV with micro and macrovascular parameters. It should be noted that ARV also has technical limitations. First, no existing ABPM devices incorporate automatic quantification of ARV or other novel BPV indices. To partly overcome this difficulty, we used in-house developed software to automatically calculate ARV directly from the ABPM raw data. Another issue is that the minimum number of valid BP readings needed to provide accurate evaluation of BPV is uncertain and may not be feasible to obtain in real-world patients.

In conclusion, our study showed that short-term BPV represented by ARV indices is independently associated with macrovascular parameters in untreated hypertensive patients and with microvascular parameters in normotensives. Further studies are warranted to investigate which BPV cut-off values may determine a subgroup of individuals at high risk of TOD and future development of hypertension regardless of the average BP measures.

ACKNOWLEDGEMENTS

Funding: S.-L.P. was supported by a scholarship from the Hellenic Society of Cardiology.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, *et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study. *Lancet* 2010; 380:2224–2260.
2. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, *et al.* Global burden of hypertension and systolic blood pressure of at least 110 to 115 mmHg, 1990–2015. *JAMA* 2017; 317:165–182.
3. Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S. Association between local pulse pressure, mean blood pressure, and large-artery remodeling. *Circulation* 1999; 100:1387–1393.
4. Heagerty AM, Izzard AS. Small-artery changes in hypertension. *J Hypertens* 1995; 13:1560–1565.
5. 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* 2015; 67:183–190.
6. Grassi G, Bombelli M, Brambilla G, Trevano FQ, Dell'oro R, Mancia G. Total cardiovascular risk, blood pressure variability and adrenergic overdrive in hypertension: evidence, mechanisms and clinical implications. *Curr Hypertens Rep;* 2012; 14:333–338.
7. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39:3021–3104.
8. Parati G, Stergiou GS, Bilo G, Kollias A, Pengo M, Ochoa JE, *et al.* Home blood pressure monitoring: methodology, clinical relevance and practical application: a 2021 position paper by the Working Group on Blood Pressure Monitoring and Cardiovascular Variability of the European Society of Hypertension. *J Hypertens;* 2021; 39:1742–1767.
9. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, *et al.* Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension* 2005; 46:156–161.
10. Bliziotis IA, Destounis A, Stergiou GS. Home versus ambulatory and office blood pressure in predicting target organ damage in hypertension: a systematic review and meta-analysis. *J Hypertens* 2012; 30:1289–1299.
11. Poortvliet RK, Ford I, Lloyd SM, Sattar N, Mooijaart SP, de Craen AJ, *et al.* Blood pressure variability and cardiovascular risk in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *PLoS One* 2012; 7:e52438.
12. Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, *et al.* Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2016; 354:i4098.

13. 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.
14. Irigoyen MC, De Angelis K, Dos Santos F, Dartora DR, Rodrigues B, Consolim-Colombo FM. Hypertension, blood pressure variability, and target organ lesion. *Curr Hypertens Rep* 2016; 18:31.
15. Garcia-Garcia A, Garcia-Ortiz L, Recio-Rodriguez JI, Patino-Alonso MC, Agudo-Conde C, Rodriguez-Sanchez E, *et al.* Relationship of 24-h blood pressure variability with vascular structure and function in hypertensive patients. *Blood Press Monit* 2013; 18:101–106.
16. Stergiou GS, Parati G, Vlachopoulos C, Achimastos A, Andreadis E, Asmar R, *et al.* Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: current status and future directions – position statement of the European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability. *J Hypertens* 2016; 34:1665–1677.
17. Palatini P, Mormino P, Canali C, Santonastaso M, De Venuto G, Zanata G, *et al.* Factors affecting ambulatory blood pressure reproducibility. Results of the HARVEST Trial. Hypertension and Ambulatory Recording Venetia Study. *Hypertension* 1994; 23:211–216.
18. Mena L, Pintos S, Queipo NV, Aizpurua JA, Maestre G, Sulbaran T. A reliable index for the prognostic significance of blood pressure variability. *J Hypertens* 2005; 23:505–511.
19. Pierdomenico SD, Di Nicola M, Esposito AL, Di Mascio R, Ballone E, Lapenna D, *et al.* Prognostic value of different indices of blood pressure variability in hypertensive patients. *Am J Hypertens* 2009; 22:842–847.
20. Eguchi K, Hoshide S, Hoshide Y, Ishikawa S, Shimada K, Kario K. Reproducibility of ambulatory blood pressure in treated and untreated hypertensive patients. *J Hypertens* 2010; 28:918–924.
21. Mena LJ, Felix VG, Melgarejo JD, Maestre GE. 24-Hour blood pressure variability assessed by average real variability: a systematic review and meta-analysis. *J Am Heart Assoc* 2017; 6:; doi: 10.1161/jaha.117.006895.
22. El Mokadem M, Boshra H, Abd El Hady Y, Kasla A, Gouda A. Correlation between blood pressure variability and subclinical target organ damage in patients with essential hypertension. *J Hum Hypertens;* 2019; 34:641–647.
23. Leoncini G, Viazzi F, Storace G, Deferrari G, Pontremoli R. Blood pressure variability and multiple organ damage in primary hypertension. *J Hum Hypertens* 2013; 27:663–670.
24. Schillaci G, Bilo G, Pucci G, Laurent S, Macquin-Mavier I, Boutouyrie P, *et al.* Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension* 2012; 60:369–377.
25. Xiong H, Wu D, Tian X, Lin WH, Li C, Zhang H, *et al.* The relationship between the 24 h blood pressure variability and carotid intima-media thickness: a compared study. *Comput Math Methods Med* 2014; 2014:303159.
26. Chen Y, Xiong H, Wu D, Pirbhulal S, Tian X, Zhang R, *et al.* Relationship of short-term blood pressure variability with carotid intima-media thickness in hypertensive patients. *Biomed Eng Online;* 2015; 14:71.
27. Ozkayar N, Altun B, Yildirim T, Yilmaz R, Dede F, Arik G, *et al.* Blood pressure measurements, blood pressure variability and endothelial function in renal transplant recipients. *Clin Exp Hypertens* 2013; 36:392–397.
28. Ryu J, Cha RH, Kim DK, Lee JH, Yoon SA, Ryu DR, *et al.* The clinical association of the blood pressure variability with the target organ damage in hypertensive patients with chronic kidney disease. *J Korean Med Sci;* 2014; 29:957–964.
29. Wu D, Li C, Chen Y, Xiong H, Tian X, Wu W, *et al.* Influence of blood pressure variability on early carotid atherosclerosis in hypertension with and without diabetes. *Medicine (Baltimore);* 2016; 95:e3864.
30. McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Sharrett AR, *et al.* Risk prediction of coronary heart disease based on retinal vascular caliber (from the Atherosclerosis Risk In Communities [ARIC] Study). *Am J Cardiol* 2008; 102:58–63.
31. Ding J, Wai KL, McGeechan K, Ikram MK, Kawasaki R, Xie J, *et al.* Retinal vascular caliber and the development of hypertension: a meta-analysis of individual participant data. *J Hypertens;* 2014; 32:207–215.
32. Manikis G, Sakkalis C, Zabulis X, Karamaounas P, Triantafyllou A, Douma S, *et al.* An image analysis framework for the early assessment of hypertensive retinopathy signs. In International Conference on e-Health and Bioengineering. 2011. Iasi, Romania.
33. Triantafyllou A, Doumas M, Anyfanti P, Gkaliagkousi E, Zabulis X, Petidis K, *et al.* Divergent retinal vascular abnormalities in normotensive persons and patients with never-treated, masked, white coat hypertension. *Am J Hypertens* 2013; 26:318–325.
34. Hubbard LD, Brothers RJ, King WN, Clegg LX, Klein R, Cooper LS, *et al.* Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology* 1999; 106:2269–2280.
35. Parr JC, Spears GF. General caliber of the retinal arteries expressed as the equivalent width of the central retinal artery. *Am J Ophthalmol* 1974; 77:472–477.
36. Buckberg GD, Fixler DE, Archie JP, Hoffman JI. Experimental subendocardial ischemia in dogs with normal coronary arteries. *Circ Res* 1972; 30:67–81.
37. Hoffman JI, Buckberg GD. The myocardial oxygen supply:demand index revisited. *J Am Heart Assoc;* 2014; 3:e000285.
38. Tsiachris D, Tsioufis C, Syrseloudis D, Roussos D, Tatsis I, Dimitriadis K, *et al.* Subendocardial viability ratio as an index of impaired coronary flow reserve in hypertensives without significant coronary artery stenoses. *J Hum Hypertens* ; 26:64–70.
39. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, *et al.* Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008; 21:93–111; quiz 189–190.
40. Robinson C. Tests of moderation effects: difference in simple slopes versus the interaction term. *Multiple Linear Regression Viewpoints* 2013; 39:16–24.
41. Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HA. Microcirculation in hypertension: a new target for treatment? *Circulation* 2001; 104:735–740.
42. Kumagai K, Tabara Y, Yamashiro K, Miyake M, Akagi-Kurashige Y, Oishi M, *et al.* Central blood pressure relates more strongly to retinal arteriolar narrowing than brachial blood pressure: the Nagahama Study. *J Hypertens* 2015; 33:323–329.
43. Sun C, Wang JJ, Mackey DA, Wong TY. Retinal vascular caliber: systemic, environmental, and genetic associations. *Surv Ophthalmol* 2009; 54:74–95.
44. Saldivar E, Cabrales P, Tsai AG, Intaglietta M. Microcirculatory changes during chronic adaptation to hypoxia. *Am J Physiol Heart Circ Physiol* 2003; 285:H2064–H2071.
45. Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, *et al.* Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. *Circulation* 2008; 118:968–976.
46. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, *et al.* Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA* 2012; 308:875–881.
47. Izzo JL. Hemodynamics of hypertension. In: Lip GYH, John E, editors. Comprehensive hypertension. Mosby; 2007, pp. 123–133.
48. Wei FF, Li Y, Zhang L, Xu TY, Ding FH, Wang JG, *et al.* Beat-to-beat, reading-to-reading, and day-to-day blood pressure variability in relation to organ damage in untreated Chinese. *Hypertension* 2014; 63:790–796.
49. Omboni S, Posokhov IN, Rogoza AN. Relationships between 24-h blood pressure variability and 24-h central arterial pressure, pulse wave velocity and augmentation index in hypertensive patients. *Hypertens Res* 2016; 40:385–391.
50. Lacolley P, Bezie Y, Girerd X, Challande P, Benetos A, Boutouyrie P, *et al.* Aortic distensibility and structural changes in sinoaortic-denervated rats. *Hypertension* 1995; 26:337–340.
51. Sasaki S, Yoneda Y, Fujita H, Uchida A, Takenaka K, Takesako T, *et al.* Association of blood pressure variability with induction of atherosclerosis in cholesterol-fed rats. *Am J Hypertens* 1994; 7:453–459.
52. 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.
53. Shintani Y, Kikuya M, Hara A, Ohkubo T, Metoki H, Asayama K, *et al.* Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: the Ohasama study. *J Hypertens* 2007; 25:1704–1710.
54. Shaaban AM, Duerinckx AJ. Wall shear stress and early atherosclerosis: a review. *AJR Am J Roentgenol* 2000; 174:1657–1665.
55. Miao CY, Tao X, Gong K, Zhang SH, Chu ZX, Su DF. Arterial remodeling in chronic sinoaortic-denervated rats. *J Cardiovasc Pharmacol* 2001; 37:6–15.