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The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

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ABSTRACT

Objectives Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) has not been investigated. Thus, our study aimed to investigate whether ABPV is associated with EPVS by 24-hour ambulatory blood pressure monitoring (ABPM).

Design We conducted this study as a cross-sectional study.

Settings The study was based on patients who presented for physical examinations in our hospital from May 2013 to June 2016.

Participants Patients with both brain MRI scans and 24-hour ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese patients were prospectively enrolled in this study.

Primary and secondary outcome measures EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by the Fazekas scale. Coefficient of variation (CV) and SD were considered as metrics of ABPV. Spearman correlation analysis and ordinal logistic regression analysis were used to assess the relationship between ABPV and EPVS.

Results There were statistical differences among the subgroups stratified by the severity of EPVS in BG in the following ABPV metrics: SD and CV of systolic blood pressure (SBP), CV of diastolic blood pressure (DBP) in 24 hours, daytime and nighttime and SD of DBP in nighttime. The above ABPV metrics were positively associated with the degree of EPVS. The association was unchanged after adjusting for confounders. Spearman correlation analysis showed ABPV was not related to the degree of EPVS in the WM.

Conclusion ABPV was independently associated with EPVS in BG after controlling for blood pressure, but not in the WM. Pathogenesis of EPVS in BG and WM might be different.

Strengths and limitations of this study

- ► Assessments of enlarged perivascular spaces (EPVS) and white matter hyperintensities were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- ► Detailed information on some confounders crucial to the interpretation of EPVS was collected and ordinal logistic regression analysis was performed to determine the independency of association.
- ► The study was based on a population who presented to the hospital for physical examination in a single centre and the cohort may not represent the general population.
- ► This was a cross-sectional study, and the causal relationship between ambulatory blood pressure variability and EPVS could not be established.

INTRODUCTION

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluids and solute in the brain.[1] They can dilate with accumulation of the interstitial fluids.[2 3] Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluids (CSF) on all MRI sequences in the white matter (WM), basal ganglia (BG), hippocampus and brainstem.[4 5] Recent studies indicated that EPVS were a MRI marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes.[6 7] Some studies found that EPVS were associated with impaired cognitive function,[5] incident dementia[8] and sleep disorders.[9] Therefore, it is of clinical importance to understand the risk factors for EPVS and search for treatable options in the future.

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single office blood pressure measurement.[10 11]

Ambulatory blood pressure variability (ABPV) could be well documented by 24-hour ABPM. Previous studies demonstrated that higher ABPV increased the risk of cardiovascular events,[12 13] WMH, lacunar infarction and cognitive decline.[14 15] WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension.[16] However, the relationship between ABPV and EPVS has never been investigated. Thus, in the present study, we aimed to investigate whether ABPV, which was reflected by 24 hours ABPM, was independently associated with EPVS.

METHODS

Study subjects

We conducted this study as a cross-sectional study. The inpatients for physical examinations in Medicine Department and Neurology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University were prospectively identified from May 2013 to June 2016. Some of them had a history of hypertension, diabetes mellitus, lacunar stroke or other risk factors for vascular diseases. They worried about the cerebrovascular diseases and wanted a well check-up. They were screened according to our inclusion and exclusion criteria. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients underwent both brain MRI scans and 24-hour ABPM within 1 month; and (2) patients agreed to participate in our study and signed an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumour; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumour; (3) patients with a history of severe ischaemic (the largest diameter of infarct size >20 mm on diffusion-weighted imaging and fluid-attenuated inversion recovery) or haemorrhagic stroke because of difficulty assessments on EPVS; and (4) patients with invalid 24-hour ABPM data (24-hour ABPM data were considered invalid if measurement times was <70%, or less than 1 measurement per hour during daytime, or less than six in total during nighttime).

Assessments of EPVS and WMH

The neurological image examinations were performed in Radiology Department of our hospital. MR images were acquired on a 3.0 T MR scanner (Siemens, Erlangen, Germany).

EPVS were defined as CSF-like signal intensity lesions of round, ovoid or linear shape of <3 mm and located in areas supplied by perforating arteries.[6 17] We distinguished lacune from EPVS by their larger size (>3 mm), spheroid shape and surrounding hyperintensities on fluid-attenuated inversion recovery. WMH were defined as hyperintense signals on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR imaging.

EPVS in BG and WM were separately assessed according to the scales which were used in other studies.[18] In BG, EPVS were rated according to the number in the slice containing the maximum amount of EPVS. The grades of EPVS were rated as follows: grade 1: <5 EPVS, grade 2: 5–10 EPVS, grade 3: 10–20 EPVS and grade 4: >20 EPVS. In the WM, EPVS were scored as follows: grade 1: <10 EPVS in total WM, grade 2: >10 in total WM and <10 in the slice containing the maximum number of EPVS, grade 3: 10–20 EPVS in the slice containing the maximum number of EPVS and grade 4: >20 in the slice containing the maximum number of EPVS. We classified EPVS into three categories: degree 1=grade 1; degree 2=grade 2; degree 3=grades 3 and 4.

WMH were scored by the Fazekas scale. The detailed description of assessments has been previously published.[19] Periventricular and deep WMH were evaluated separately and then added together as Fazekas scores.

The intrarater agreement for the rating of EPVS and WMH was assessed on a random sample of 100 individuals with a month interval between the first and second readings. Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information to avoid bias. Random scans of 100 individuals were independently examined by the two experienced neurologists blinded to each other's readings. The *k* statistics of intrarater and inter-rater agreement was ≥0.80, indicating good reliability. Disagreement was resolved by discussing with other coauthors.

24-hour ABPM

Twenty-four-hour ABPM was performed using an automated system (FB-250; Fukuda Denshi, Tokyo, Japan). BP was measured every 30 min during the daytime (8:00 AM to 11:00 PM) and every 60 min during the nighttime (11:00 PM to 8:00 AM). We excluded a 2-hour transition period around the reported rising and retiring times. The mean systolic blood pressure (SBP), diastolic blood pressure (DBP), coefficient of variation (CV) and SD of SBP and DBP during 24 hours, daytime and nighttime were collected. The CV value was defined as the ratio between the SD and the mean SBP or DBP at the same periods. SD and CV were considered as metrics of blood pressure variability (BPV) in this study. Patients continued taking their previous medications, and we registered the use of antihypertension drugs.

Statistical analysis

Continuous variables were summarised as mean values±SD or median (IQR) according to whether its distribution conformed to a normal distribution. Analysis of variance (ANOVA) was used for comparison of continuous variables with both normal distribution and homogeneity of variance, while Kruskal-Wallis test was used for continuous variables with non-nornal distribution or heterogeneity of variance. Categorical variables were presented as

absolute numbers and percentages. The X^2 test was used for the comparison of categorical variables. Spearman correlation analysis was used to calculate the association between ABPV and the severity of EPVS. The proportional odds assumption was met, thus ordinal logistic regression analysis was performed to determine whether the ABPV was independently associated with EPVS after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3). The results were based on valid data; missing data were excluded. Analyses were performed with Statistical Package for Social Sciences (SPSS V.21.0), and statistical significance was accepted at p<0.05.

RESULTS

Baseline characteristics of the study participants

A total of 742 patients underwent both brain MRI scans and 24 hours ABPM within 1 month in the Medicine Department or Neurology Department of our hospital from May 2013 to June 2016. Of them, 40 patients were excluded because of acute stroke, 21 were excluded because of a history of severe or haemorrhagic stroke, 15 were excluded because of a history of tumour and 93 were excluded because of invalid ABPM data, leaving 573 patients enrolled in the present study. None of them had missing data. There were no statistical differences (p>0.05) in age, body mass index, proportion of male, current smoking, current alcohol, diabetes, hypertension, coronary artery disease (CAD) and using of antihypertensive drugs between the excluded subjects and the final group (online supplementary file 1). Table 1 shows the characteristics of all enrolled subjects and subgroups stratified by the degree of EPVS in different brain regions. Age, Fazekas scale, proportion of hypertension and stroke/transient ischaemic attack (TIA), levels of blood urea nitrogen and creatinine increased with the degree of EPVS in BG increasing. There were statistical differences in age, Fazekas scale and proportion of CAD among subgroups based on the degree of EPVS in the WM.

Ambulatory blood pressure (ABP) levels for each EPVS category are presented in table 2. There were statistical differences in the mean SBP during 24 hours, daytime and nighttime among the categories stratified by the degree of EPVS in BG. The results of Spearman correlation analysis showed SBP was positively related to higher degree of EPVS in BG during all periods (SBP of 24 hours: r=0.23, p<0.01; SBP of daytime: r=0.25, p<0.01; SBP of nighttime: r=0.30, p<0.01). The mean DBP of daytime and nighttime increased with the degree of EPVS in WMH increasing. However, the results of Spearman correlation analysis showed that DBP levels were not associated with higher numbers of EPVS in the WM (p>0.05).

Association between ABPV and EPVS in BG

SD and CV of ABP in different categories stratified by the degree of EPVS in BG are presented in table 3. There were statistical differences (p<0.05) among the three subgroups stratified by the severity of EPVS in all of the following BPV metrics: SD and CV of SBP, CV of DBP during 24 hours, daytime and nighttime and SD of DBP during nighttime. Theses metrics gradually increased with the degree of EPVS increasing (figures 1–3). The results of Spearman correlation analysis demonstrated theses metrics were positively associated with the degree of EPVS in BG (r>0, p<0.05). The association between ABPV and EPVS were unchanged even after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3), which indicated that the ABPV were independently associated with EPVS in BG. The results of ordinal logistic regression analysis are presented in table 4.

Association between ABPV and EPVS in the WM

SD and CV of ABP in different categories stratified by degree of EPVS in WM are also presented in table 3. There were statistical differences (p<0.05) in SD of SBP, CV of SBP, SD of DBP and CV of DBP during 24 hours and daytime among the three categories. However, there were not linear trend among the three subgroups. The results of Spearman correlation analysis showed that there were no linear correlation between theses metrics and the degree of EPVS in the WM (p>0.05).

DISCUSSION

In this study, we explored the relationship between ABPV and EPVS based on the population that presented for physical examinations. Our data suggested that all of the following metrics: SD of SBP, CV of SBP and CV of DBP during 24 hours, daytime and nighttime and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association between the above ABPV metrics and EPVS in BG were unchanged after adjusting for demographic confounders, Fazekas scale and the mean SBP or DBP during the same period. Although there were statistical differences in ABPV metrics during 24 hours and daytime among the three subgroups stratified by EPVS severity in the WM, there were no linear correlation between ABPV and the degree of EPVS in the WM. In addition, we found that age, Fazekas scale, hypertension, stroke/TIA, levels of blood urea nitrogen and creatinine were positively associated with the degree of EPVS in BG.

There were methodological strengths of our study. We recruited participants strictly according to inclusion and exclusion criteria to avoid selection bias. The patients with acute cerebrovascular and cardiovascular disorders were excluded to avoid the impact of the acute stroke, recent myocardial infarction or angina pectoris on blood pressure. The patients with a history of severe ischaemic (the largest diameter of infarct size >20 mm on diffusion-weighted imaging and fluid-attenuated inversion recovery) or haemorrhagic stroke were excluded because of difficulty and inaccurate assessment on EPVS. In addition, the assessments of EPVS and WMH were performed by two experienced

Table 1 General characteristics of all enrolled subjects and each EPVS category stratified by the severity of EPVS

Characteristics	All patients	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
n (%)	573	244 (42.6%)	179 (31.2%)	150 (26.2%)	200 (34.9%)	207 (36.1%)	166 (29.0%)
Age† (years)	69(55–81)	58(51–74)**	68(57–80)**	80(73–85)**	75(57–83)**	66(55–78)**	66(54–80)**
Sex, man (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61 (34.1)*	18 (12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)
CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5)*	45 (21.7)*	34 (20.5)*
Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI‡ (kg/m^2)	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL† (mmol/L)	1.16 (1.00–1.38)	1.15 (0.99–1.37)	1.17 (0.98–1.41)	1.17 (1.00–1.32)	1.17 (1.00–1.38)	1.15 (0.98–1.37)	1.15 (0.99–1.34)
LDL† (mmol/L)	2.40 (1.90–2.94)	2.42 (1.96–3.00)	2.47 (1.88–2.93)	2.20 (1.79–2.91)	2.32 (1.88–2.94)	2.29 (1.81–2.90)	2.51 (2.00–3.00)
HbA1c† (%)	6.0 (5.7–6.7)	6.0 (5.7–6.7)	6.0 (5.7–6.7)	6.1 (5.7–6.7)	6.1 (5.7–6.8)	6.0 (5.7–6.6)	6.0 (5.7–6.8)
BUN† (mmol/L)	5.46 (4.46–6.70)	5.18 (4.34–6.34)**	5.36 (4.32–6.59)**	5.97 (4.82–7.42)**	5.50 (4.55–7.02)	5.39 (4.36–6.39)	5.42 (4.50–6.81)
Creatinine† (μmol/L)	74.2 (62.8–89.2)	70.2 (59.7–84.6)**	74.5 (63.7–89.6)**	81.9 (66.4–94.1)**	77.0 (62.8–92.1)	72.5 (61.5–87.0)	74.0 (62.9–89.1)
Fazekas scale†	3 (2–5)	2 (1–3)**	3 (2–4)**	5 (4–6)**	3 (2–6)**	2 (2–4)**	3 (2–4)**
Using of antihypertensive drugs (%)	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)
Class of antihypertensive drugs							
Dihydropyridinic CCB (%)	226 (39.4)	74 (30.3)	67 (37.4)	63 (42.0)	69 (34.5)	79 (38.2)	55 (33.1)
ACEI (%)	26 (4.5)	11 (4.5)	6 (3.4)	9 (6.0)	8 (4.0)	9 (4.3)	9 (5.7)
ARB (%)	160 (27.9)	70 (28.7)	46 (25.7)	44 (29.3)	69 (34.5)*	52 (25.1)*	39 (23.5)*
β-Blockers (%)	96 (16.8)	34 (13.9)	28 (15.6)	34 (22.7)	40 (20.0)	31 (15.0)	25 (15.1)
Non-loop diuretics (%)	39 (6.8)	20 (8.2)	12 (6.7)	7 (4.7)	16 (8.0)	13 (6.3)	10 (6.0)

†Continuous variables with non-normally distribution were expressed as median (IQR) and compared with the Kruskal-Wallis test.
‡Continuous variables with normal distribution were expressed as mean values±SD, but with heterogeneity of variance, thus were compared with the Kruskal-Wallis test.
*p<0.05, **p<0.01.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BG, basal ganglia; BMI, body mass index; BUN, blood urea nitrogen; CCB, calcium-channel blocker; CAD, coronary artery disease; EPVS, enlarged perivascular spaces; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TIA, transient ischaemic attack; WM, white matter.

Table 2 ABP levels of all enrolled subjects and each EPVS category stratified by the severity of EPVS

Characteristics	All patients	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
24 hours							
SBP†,‡(mm Hg)	132(121–143)	127(117–138)**	133(124–143)**	136(127–148)**	133±16.5	132±17.1	132.9±15.4
DBP‡(mm Hg)	76±9.6	77±9.5	76±10.0	75±9.1	75±9.5*	76±9.6*	77±9.6*
Daytime							
SBP†,‡(mm Hg)	134(123–145)	129(118–141)**	135(126–144)**	140(130–150)**	135±16.6	134±17.6	135±15.3
DBP‡(mm Hg)	77±10.0	77±10.0*	77±10.3*	75±9.5*	75±9.9*	77±10.1*	78±9.9*
Nighttime							
SBP†(mm Hg)	126(116–142)	120(110–134)**	131(118–142)**	135(123–149)**	127(115–144)	124(113–140)	128(117–142)
DBP† (mm Hg)	73(66–80)	74(66–81)	73(66–81)	73(67–80)	71(65–79)	73(66–80)	75(68–82)

†Continuous variables with non-normally distribution were expressed as median (IQR) and compared with the Kruskal-Wallis test.
‡Continuous variables with normal distribution were expressed as mean values±SD, but with heterogeneity of variance, thus were compared with the Kruskal-Wallis test.
*p<0.05, **p<0.01.
ABP, ambulatory blood pressure; BG, basal ganglia; DBP, diastolic blood pressure; EPVS, enlarged perivascular spaces; SBP, systolic blood pressure; WM, white matter.

neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments. We collected detailed information on vascular confounders, WMH, levels of blood urea nitrogen and creatinine, which are crucial to the interpretation of EPVS.[6 20] So we think that the reliability of the data is high. There were some limitations in our study. First, our study was based on a population that visited the hospital for physical examination in a single centre and the cohort may not represent the general population. According to our observation, these people had a higher economic status than that of the general population in China, and some of them showed more symptoms of anxiety. But it is regrettable that we did not assess the anxiety symptoms by the Hamilton Anxiety Rating Scale or assess the patients' education level. Second, this was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established. Third, all participants underwent 24-hour ABPM which could only show short-term ABPV. It has been demonstrated that the prognostic significance of BPV on vascular diseases is weaker for short-term than for long-term BPV.[21] Forth, the variables were compared among three categories and the type I error was probably elevated.

This is the first study to investigate the relationship between ABPV and EPVS. Previously, several studies investigated the relationship between EPVS and hypertension. In a prospective, multicentre, hospital-based study, Zhang *et al*[22] found that hypertension was associated with the severity of EPVS in the WM, not in BG. Klarenbeek *et al*[23] investigated the association between ABP levels and EPVS in first-ever lacunar stroke patients. They found higher day SBP, day DBP and 24-hour DBP levels were independently associated EPVS in BG, and no relationship between ABP levels and EPVS in the WM. We also analysed the correlation between ABP levels and EPVS. We found that ABP levels were associated with EPVS in BG, but not in WMH, which is consistent with Klarenbeek *et al*'s study. However, we found that only SBP was positively related to higher degree of EPVS in BG in all periods, and there was no relationship between DBP and EPVS, which are different from previous results. The different study population and different scoring methods of assessing EPVS may partly lead to the different results. Our data suggested that SD of SBP, CV of SBP and CV of DBP in all periods were positively associated with the degree of EPVS in BG, but not in the WM. The present study could not explain the phenomenon. This may be caused by different pathogenesis of EPVS at the different locations.[22 24 25] Previous studies have found that the anatomical structures of EPVS located in BG and WM were different.[26] The arteries in the BG are surrounded by two distinct coats of leptomeninges separated by a perivascular space which is continuous with the perivascular space around arteries in the subarachnoid space. Whereas there is only a single periarterial layer of leptomeninges surrounding the arteries in the cerebral cortex and it penetrates into the WM. Drainage of interstitial fluid from the brain to cervical lymph nodes may mainly go along perivascular spaces in the WM rather than in BG.[3 27] In addition,

Table 3 Results of ABPV in all subjects and subgroups stratified by the severity of EPVS

	EPVS in BG				EPVS in WM			
	Degree 1	Degree 2	Degree 3	P	Degree 1	Degree 2	Degree 3	P
24 hours								
SD of SBP* (mm Hg)	16.6 (13.8–20.2)	18.1 (15.1–21.5)	18.8 (15.5–23.9)	<0.001	18.2 (14.7–22.8)	16.9 (13.7–20.2)	17.7 (15.0–21.7)	0.004
SD of DBP* (mm Hg)	11.8 (9.8–14.3)	12.2 (10.1–15.2)	12.5 (10.1–15.3)	0.149	12.7 (10.1–14.5)	11.4 (9.4–14.1)	12.7 (10.7–15.5)	0.001
CV of SBP* (%)	12.9 (10.4–15.3)	13.6 (11.4–16.2)	14.4 (11.2–17.4)	0.004	13.6 (11.3–16.5)	13.2 (10.3–15.5)	13.5 (11.5–16.5)	0.028
CV of DBP* (%)	15.4 (12.9–19.0)	16.1 (13.5–19.9)	17.3 (13.8–20.2)	0.013	17.1 (13.9–19.8)	15.0 (12.4–18.4)	16.6 (13.8–19.9)	0.001
Daytime								
SD of SBP* (mm Hg)	16.2 (13.2–19.8)	17.1 (14.2–21.5)	18.7 (14.8–25.0)	<0.001	18.2 (14.1–22.6)	16.3 (13.2–19.7)	17.2 (14.3–22.6)	0.004
SD of DBP* (mm Hg)	11.7 (9.6–14.8)	11.8 (9.5–15.0)	12.7 (9.8–15.7)	0.241	12.2 (9.7–15.3)	11.3 (8.8–13.6)	12.6 (10.2–16.0)	0.001
CV of SBP* (%)	12.2 (10.1–15.1)	12.9 (10.8–16.1)	13.9 (10.8–17.5)	0.005	13.3 (10.6–16.7)	12.3 (9.8–15.1)	13.1 (10.5–16.6)	0.016
CV of DBP* (%)	15.3 (12.2–19.4)	15.1 (12.7–20.5)	17.1 (13.5–20.4)	0.024	16.4 (13.3–20.3)	14.8 (11.7–19.1)	16.3 (13.2–20.4)	0.002
Nighttime								
SD of SBP* (mm Hg)	12.5 (9.5–16.4)	14.8 (11.0–19.0)	16.5 (11.3–22.6)	<0.001	13.5 (10.9–18.6)	13.4 (9.8–18.9)	15.2 (10.6–19.8)	0.180
SD of DBP* (mm Hg)	9.4 (6.9–12.0)	10.1 (7.6–13.4)	10.7 (7.6–13.5)	0.010	9.9 (7.3–12.6)	9.7 (6.9–12.1)	10.5 (7.6–13.5)	0.247
CV of SBP* (%)	10.5 (7.9–13.3)	11.1 (8.4–14.4)	12.0 (8.5–16.7)	0.005	10.9 (8.5–14.2)	10.5 (7.5–14.4)	11.6 (8.4–14.6)	0.411
CV of DBP* (%)	12.8 (10.0–16.1)	13.9 (11.1–17.8)	14.7 (10.7–18.5)	0.003	14.3 (10.7–16.9)	13.1 (10.2–16.9)	13.9 (10.9–18.1)	0.426

*Continuous variables with non-normally distribution were expressed as median (IQR) and compared with the Kruskal-Wallis test.
ABPV, ambulatory blood pressure variability; BG, basal ganglia; CV, coefficient of variation; DBP, diastolic blood pressure; EPVS, enlarged perivascular spaces; SBP, systolic blood pressure; WM, white matter.

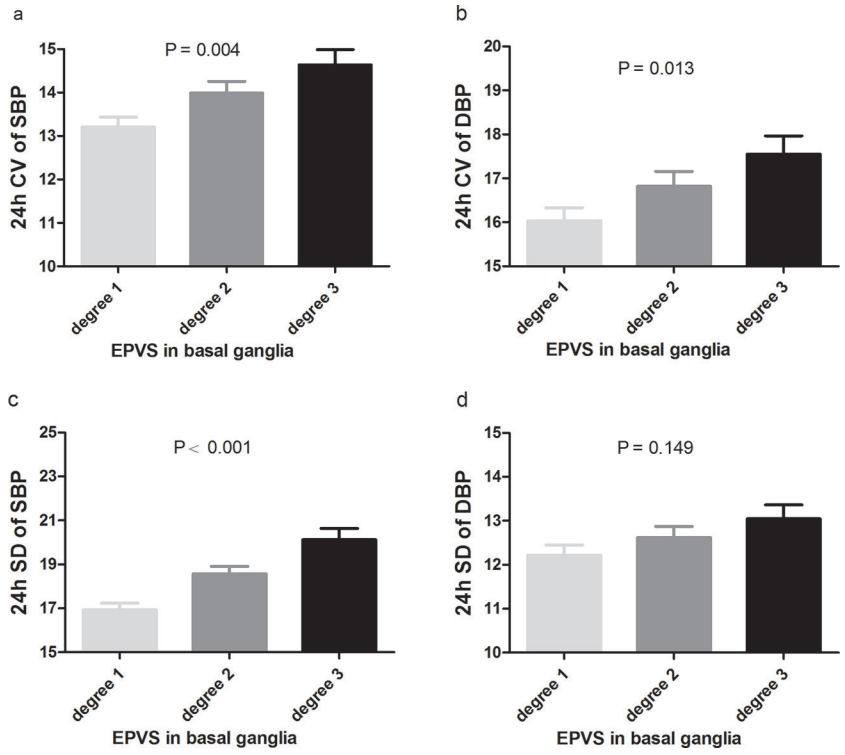

Figure 1 The ABPV metrics of subgroups stratified by EPVS severity in BG during 24 hours. (a) CV of systolic blood pressure. (b) CV of DBP. (c) SD of SBP. (d) SD of DBP. ABPV, ambulatory blood pressure variability; BG, basal ganglia; CV, coefficient of variation; DBP, diastolic blood pressure; EPVS, enlarged perivascular spaces; SBP, systolic blood pressure.

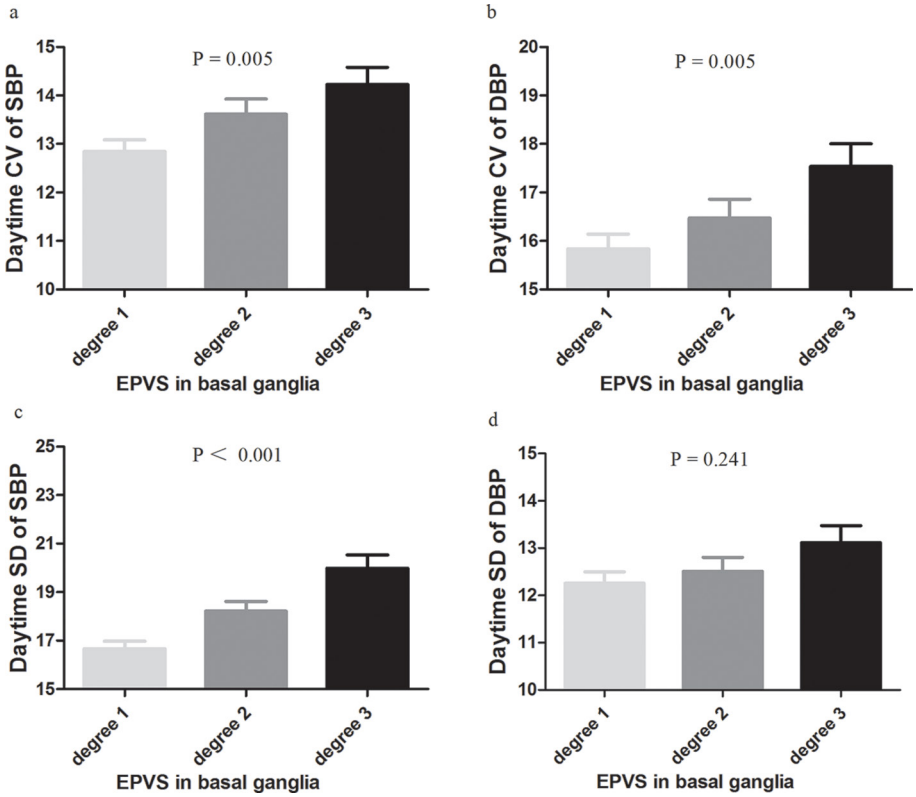

Figure 2 The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of DBP. (c) SD of SBP. (d) SD of DBP. ABPV, ambulatory blood pressure variability; BG, basal ganglia; CV, coefficient of variation; DBP, diastolic blood pressure; EPVS, enlarged perivascular spaces; SBP, systolic blood pressure.

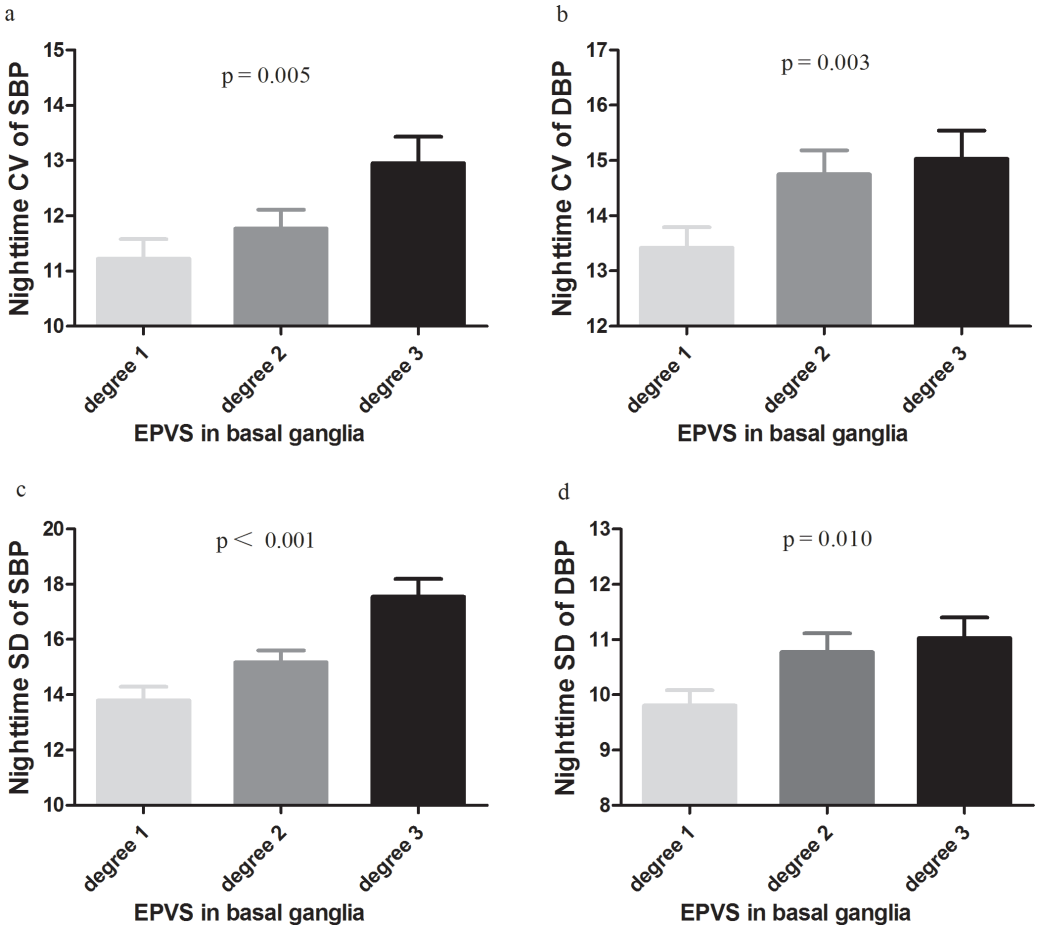

Figure 3 The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of DBP. (c) SD of SBP. (d) SD of DBP. ABPV, ambulatory blood pressure variability; BG, basal ganglia; CV, coefficient of variation; DBP, diastolic blood pressure; EPVS, enlarged perivascular spaces; SBP, systolic blood pressure.

the impact of age and hypertension on EPVS seem to be stronger for EPVS located in BG than for those located in the WM.[24] Similarly, the association between EPVS and the load of WMH, taken as a marker of CSVD, also appears to be stronger in BG than in the WM. Thus, their dilations may present differences in terms of risk factors as well as in mechanisms in BG and WM. However, the reason SBP is related differently in these two locations remains unclear because there are a very limited number of studies on mechanisms underlying dilation of perivascular spaces in BG and WM. Several studies have demonstrated that higher ABPV increased the risk of neuroimaging features of CSVD, such as WMH and lacunar infarction.[14 15] Our results found that higher ABPV was independently associated with higher degree of EPVS in BG, which support the finding that EPVS in BG are a separate marker of CSVD.

An increased permeability of the small vessel walls and blood–brain barrier are considered to contribute to the development of EPVS, which has been reported to be associated with damage of microvascular endothelial cells and their tight junctions.[1 16 28] Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial injury[29] and arterial stiffness.[30] Therefore, it is reasonable that high ABPV contribute to the development of EPVS by damaging endothelial cells. Our results may remind clinicians that they should pay attention to patients' ABPV and reduce it in their clinical practices. In the future, a prospective cohort study will help better establish the relationship between ABPV and EPVS.

CONCLUSION

SD of SBP, CV of SBP and CV of DBP during all periods and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association was unchanged after adjusting for confounders. No relationship was found between ABPV and EPVS in the WM. It is important for clinicians to reduce both patients' high blood pressure levels and ABPV.

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Patient consent Obtained.

Table 4 Results of ordinal logistic regression analysis between ABPV and EPVS in BG

	Model 1		Model 2		Model 3	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
24 hours						
SD of SBP	1.55 (1.32 to 1.83)	<0.001	1.48 (1.25 to 1.75)	<0.001	1.41 (1.19 to 1.68)	<0.001
CV of SBP	1.47 (1.19 to 1.83)	<0.001	1.48 (1.18 to 1.85)	0.001	1.60 (1.27 to 2.02)	<0.001
CV of DBP	1.59 (1.13 to 2.24)	0.008	1.69 (1.18 to 2.42)	0.004	1.81 (1.25 to 2.60)	0.001
Daytime						
SD of SBP	1.44 (1.25 to 1.67)	<0.001	1.39 (1.19 to 1.61)	<0.001	1.31 (1.12 to 1.54)	0.001
CV of SBP	1.32 (1.08 to 1.61)	0.006	1.32 (1.08 to 1.62)	0.008	1.43 (1.16 to 1.77)	0.001
CV of DBP	1.49 (1.10 to 2.04)	0.011	1.59 (1.15 to 2.19)	0.005	1.67 (1.21 to 2.31)	0.002
Nighttime						
SD of SBP	1.29 (1.15 to 1.46)	<0.001	1.25 (1.11 to 1.40)	<0.001	1.21 (1.07 to 1.37)	0.002
SD of DBP	1.39 (1.15 to 1.67)	<0.001	1.33 (1.11 to 1.61)	0.003	1.31 (1.12 to 1.54)	0.001
CV of SBP	1.27 (1.09 to 1.48)	0.002	1.26 (1.08 to 1.47)	0.003	1.31 (1.08 to 1.58)	0.006
CV of DBP	1.19 (1.04 to 1.36)	0.013	1.20 (1.04 to 1.37)	0.012	1.21 (1.05 to 1.39)	0.008

Model 1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN, creatinine and using of antihypertensive drugs.
Model 2: model 1+Fazekas scale.
Model 3: model 2+the mean SBP or DBP during the same period.
ABPV, ambulatory blood pressure variability; BG, basal ganglia; CV, coefficient of variation; DBP, diastolic blood pressure; EPVS, enlarged perivascular spaces; SBP, systolic blood pressure.

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