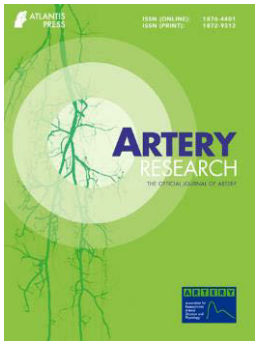

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Relationships between blood pressure variability and silent cerebral infarction in patients with primary hypertension

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KEYWORDS
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Abstract *Aims:* This study aimed to investigate the relationship between blood pressure variability and the incidence of silent cerebral infarction (SCI) in patients with primary hypertension.
Methods: The 346 hospitalized patients with primary hypertension were divided into primary hypertension group (160 cases) and primary hypertension combined with SCI group (186 cases). The 24-h ambulatory blood pressure was measured. Clinical data were collected. Univariate and multivariate logistic regression analysis was performed.
Results: There were significant differences between patients with primary hypertension combined with SCI and patients with primary hypertension only in age, stroke history, diabetes history, smoking, alcohol consumption, FBG, Hcy, and Lp-PLA2. The 24-h ambulatory blood pressure monitoring results suggested that dSBP, dSSD, 24hSBP, nSSD, dDBP, dDSD, nDSD, 24hDSD, ddnSBP, and ddnDBP in patients with hypertension and SCI were higher than those in patients with primary hypertension only. Non-dipper blood pressure was more common. Multivariate logistic regression analysis showed dSSD (OR: 1.374, 95%CI [1.173–1.609]), 24 h DSD (OR: 1.194, 95%CI [1.017,1.402]), dSBP (OR: 1.062, 95%CI [1.022, 1.103]), age (OR: 1.042, 95%CI [1.005, 1.080]), smoking (OR: 2.610, 95%CI [1.495, 4.556]), fasting plasma glucose (OR: 1.183, 95%CI [1.040, 1.345]), and Lp-PLA2 (OR: 1.004, 95%CI [1.003, 1.006]) were positively correlated with SCI in hypertension patients.

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Conclusions: Blood pressure variability (dSSD and24hDSD) is independently associated with SCI in patients with primary hypertension. In addition, traditional risk factors, blood pressure level (dSBP), age, smoking, fasting plasma glucose, and Lp-PLA2 were also independently associated with SCI in patients with primary hypertension.

Introduction

Many studies[1–3] reports that hypertension patients have higher incidences of blood pressure variability (BPV) than healthy people. The increase in BPV may be more predictive of target organ damage than blood pressure elevation.[1,3] Improvement of BPV has become an important part of blood pressure management in patients with hypertension and arteriosclerosis,[1,3] and improving BPV may also be more important than lowering blood pressure levels.[1,3,4]

BPV can be divided into several types, such as beat-to-beat BPV, short-term BPV (between minutes and within 24 h), mid-term BPV (between days), and long-term BPV (between follow-ups and seasons).[5–7] There are many metrics of BPV, such as standard deviations of systolic blood pressure (SSD), standard deviations of diastolic pressure (DSD), coefficient of variation (CV), variation independent of mean (VIM), and maximum—minimum difference (MMD).[6,7] Each indicator has its own advantages and disadvantages. There are no universally recognized and uniform standards.

Silent cerebral infarction (SCI) is a type of subclinical stroke that has attracted wide attention in recent years, especially with the widespread use of cranial CT and cranial MRI. It has been reported[8] that the prevalence of SCI in the whole age group was approximately 5%—62% and most of the SCI prevalence was between 10% and 20%. The prevalence of SCI in Chinese population is approximately 32.5%.[9] With the increased aging, the prevalence of SCI can reach 30%—40% in older adults over 70 years of age.[10] In addition to age, the major risk factor for SCI is hypertension.[8,10] Therefore, exploring the relationship between BPV and the risk of SCI is needed.

Based on our previous study,[11] the factors of SSD, MDD, the difference between daytime BP and nighttime BP (ddnBP), and morning blood pressure surge (MBPS) from 24 h ambulatory blood pressure measurement were chosen as evaluation indicators. In combination with other risk factors for stroke, the relationship between BPV and SCI in hypertension patients was discussed. Assuming that BPV is risk factor affecting SCI independent of blood pressure, then we have reason to find BPV indicators that are independently related to SCI, which is the purpose of this study. The findings may help to understand the role of BPV in the development of SCI in hypertension patients and contribute to the foundation for reducing the incidence of SCI from the perspective of improving BPV.

Methods and materials

Patients

Totally 346 patients with primary hypertension hospitalized in the Department of Neurology and Cardiology of Weihai Central Hospital Affiliated to Medical College of Qingdao University from February 2015 to December 2017 were enrolled in this study. There were 190 males and 156 females. Their age ranged from 45 to 92 years old, with mean of 67.49 $\pm$ 8.24 years. Patients were grouped into control group (patients with primary hypertension only, n = 160 cases) and SCI group (patients with primary hypertension combined with SCI, n = 186 cases). The clinical characteristics of patients were listed in Table 1. All patients completed 24 h ambulatory blood pressure measurement, laboratory and auxiliary examinations (blood fat, blood glucose, high-sensitivity C-reactive protein, homocysteine, cervical vascular ultrasound, head CT/MRI, etc.). Informed consent was obtained from each patient and this study was approved by the Ethical Committee of Weihai Central Hospital Affiliated to Medical College of Qingdao University.

Inclusion criteria

All the hypertensive patients were included according to the following diagnostic criteria for hypertension: 1) The blood pressure was measured for 3 times on different days, in quiet state and without intake of antihypertensive drugs; 2) The diagnostic criteria for primary hypertension was systolic blood pressure (SBP) $\geq$140 mmHg, and/or diastolic blood pressure (DBP) $\geq$90 mmHg (1 mmHg = 0.133 KPa)[12]; and 3) the hypertension was also diagnosed when patients had history of hypertension, with intake of antihypertensive drugs and had blood pressure of $<$140/90 mmHg. Diagnostic criteria for SCI included: cerebral infarcts were defined as any injury $\geq$3 mm and $\leq$15 mm in diameter, high signal intensity on the T2-weighted scan, low signal intensity on the T1-weighted sequence, and located in the periventricular white matter, basal ganglia, or internal capsule.[13]

Exclusion criteria

The exclusion criteria were as follows. 1) Patients with blood pressure exceeding 220/110 mmHg after admission and needed oral antihypertensive drugs; 2) Patients with

Table 1 Baseline characteristics of patients.

Parameters	Control group	SCI group	P value
Patients number	160	186	—
Age (years)	65.41 ± 8.28	69.27 ± 7.79	0.000
Gender (number of male/ratio)	86 (54%)	104 (56%)	0.687
BMI (kg/m^{-2})	25.72 ± 3.17	25.37 ± 2.85	0.280
Coronary heart disease	37 (23%)	55 (30%)	0.177
Stroke	24 (15%)	51 (27%)	0.005
Diabetes	31 (19%)	60 (32%)	0.007
Hypertension	127 (79%)	133 (72%)	0.092
Smoking	47 (29%)	82 (44%)	0.005
Drinking	35 (22%)	59 (32%)	0.040
Intake of antihypertensive drugs	125 (78%)	128 (69%)	0.052
TG (mmol/l)	1.78 (1.07—2.60)	1.57 (1.02—2.23)	0.132
TC (mmol/l)	5.02 (4.30—5.62)	5.00 (4.22—5.57)	0.618
LDL-C (mmol/l)	3.25 (2.69—3.75)	3.14 (2.44—3.75)	0.316
HDL-C (mmol/l)	1.27 (1.10—1.47)	1.25 (1.05—1.43)	0.307
FBG (mmol/l)	6.56 ± 1.80	7.24 ± 1.84	0.001
Uric acid (umol/L)	334.70 ± 90.02	322.46 ± 89.22	0.206
Hs-CRP (mg/L)	2.47 (1.10—4.03)	2.66 (1.20—4.33)	0.181
Hcy (mmol/l)	13.55 (10.80—19.55)	19.35 (12.78—22.53)	0.000
Lp-PLA2 (U/L)	252.38 ± 119.48	443.82 ± 254.00	0.000
GFR (ml/min)	82.15 ± 15.57	79.98 ± 13.15	0.162
Fibrinogen (g/L)	2.72 ± 0.63	2.68 ± 0.55	0.523
Urine protein	28 (17.5%)	36 (19%)	0.658
IMT (mm)	0.96 ± 0.22	1.01 ± 0.18	0.025

Note: SCI: silent cerebral infarction; BMI: body mass index; TG: triacylglycerol; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; FBG: fasting blood glucose; Hs-CRP: hypersensitivity C-reactive protein; Hcy: homocysteine; Lp-PLA2: lipoprotein-associated phospholipase A2; GFR: glomerular filtration rate; IMT: carotid intima-media thickness.

severe heart in sufficiency (including acute and severe chronic heart failure, severe valvar heart disease, recent myocardial infarction, and severe arrhythmia), liver insufficiency, and renal insufficiency; 3) Patients with severe pulmonary disease, hemorrhagic stroke, ischemic stroke with signs and symptoms of focal neurological deficits confirmed by imaging; 4) Patients with other definite diseases of the central nervous system, such as infections and demyelinating diseases; 5) Patients with severe cognitive dysfunctions (We used Mini-mental State Examination (MMSE) to evaluate cognitive function in clinical work. MMSE $\leq$9 was classified as severe cognitive dysfunction); 6) Patients with acute or chronic infectious diseases; 7) Patients with immune diseases; 8) Patients with hyperthyroidism, pregnancy, and cancer; 9) Patients with severe hematological diseases; 10) Patients with recent trauma and surgery.

Clinical data collection

The factors of age, gender, height, weight, smoking status, history of drinking, coronary heart diseases, hypertension and diabetes were recorded and analyzed. Smoking was defined as at least one cigarette a day on average in the past year. Drinking was defined as average daily liquor consumption of 100 ml (alcohol content >50%) in the past year. Fasting blood was collected on the second day of admission. The triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), uric acid (UA), and high sensitivity C-reactive protein (hs-CRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and homocysteine (Hcy) were detected by automatic biochemical analyzer.

Carotid intima-media thickness (IMT) and atherosclerotic lesions

Using the Toshiba Aplio 80 color Doppler ultrasound system, probe frequency 10 MHz, by the ultrasound room professionals for all selected patients carotid cranial Outer segment color ultrasound Doppler detection. That is, the bilateral common carotid arteries (1—2 cm below the horizontal junction of the internal and external carotid bifurcations), the common bifurcation of the common carotid artery, and the initial segment of the internal carotid artery (1—2 cm above the level of the bifurcation) were detected. The inner diameter of the blood vessel and the IMT of the vessel wall were measured, and the presence or absence of plaque formation, and the echo intensity, location, shape, size, number of the atherosclerotic plaque were confirmed, and whether the lumen is narrow and its extent. If the IMT is inconsistent on both sides, the most severe side of the lesion will prevail.

The 24 h ambulatory blood pressure measurement

All patients stopped taking all antihypertensive drugs immediately after admission. Ambulatory blood pressure

measurement was performed within 24 h on the first 3–5 days without antihypertensive drugs. The Mindray MC-6700 ABPM (Shenzhen, Guangzhou, China) was used to measure blood pressure. Necessary measures were taken to avoid false results. For example, the upper arm was kept still during the pressure measurement. The measurement interval was 30 min at daytime (6:00–22:00) and 1 h at night (22:00–6:00). The number of effective blood pressure measurements was greater than 70% of the times that should be obtained, or the number of successful readings during the day $\geq$10 and during the night $\geq$5. The measurement interval should not exceed 2 h, and the invalid blood pressure measurements were measured on alternate days. The following data were collected: daytime SBP (dSBP), daytime DBP (dDBP), night SBP (nSBP), night DBP (nDBP), 24hSBP, 24hDBP, 24 h SSD, 24 h DSD, daytime SSD (dSSD), daytime DSD (dDSD), night SSD (nSSD), night DSD (nDSD). The differences between daytime SBP and nighttime SBP (ddnSBP) and the differences between daytime DBP and nighttime DBP (ddnDBP) were calculated. The MMD was defined as difference between the maximum SBP and the minimum SBP.

Blood pressure rhythm

The rhythm of blood pressure was measured according to the percentage decrease of nighttime blood pressure. Nighttime blood pressure decrease percentage = (average daytime blood pressure-night average blood pressure)/ average daytime blood pressure. The nighttime blood pressure decrease percentage of 10%–20% suggested the blood pressure circadian rhythm and was defined as dipper pressure; that less than 10% was defined as non-dipper blood pressure; that >20% was defined as over-dipper blood pressure. The nighttime blood pressure increase was defined as anti-dipper blood pressure. The latter three were collectively referred to as non-dipper blood pressure. When the SBP and DBP were inconsistent, the SBP was used.

Morning blood pressure surge (MBPS)

There is no uniform standard for the calculation of MBPS. MBPS was often calculated based on ambulatory blood pressure and by the formula of (the average blood pressure within 2 h after awakening - the lowest blood pressure during nighttime sleep). MBPS $\geq$35 mm Hg was defined as the increase of MBPS.

Statistical analysis

SPSS19.0 statistical software was used for analysis. Measurement data with normal distribution was expressed as mean $\pm$ standard deviation. Independent sample t test was used for comparison between two samples. The quantitative data with non-normal distribution was presented as median (interquartile range) and analyzed with the Mann–Whitney rank sum test. The quantitative data was expressed as percentages (%) and analyzed using the X^2 test or the Fisher's exact probability method. The multivariate logistic regression model was used to analyze the independent variables with $P < 0.1$ obtained by univariate analysis. $P < 0.05$ was considered statistically significant.

Results

Comparison of basic characteristics of patients

As shown in Table 1, there were no significant differences between the control and SCI groups in gender, body mass index (BMI), coronary heart disease, history of hypertension, intake of antihypertensive drugs, TG, TC, HDL-C, LDL-C, UA, Hs-CRP, glomerular filtration rate, fibrinogen, and urine protein ($P > 0.05$). There were significant differences in age, stroking history, diabetes history, smoking, alcohol consumption, carotid intima-media thickness (IMT), FBG, Hcy, and Lp-PLA2 ($P < 0.05$).

Comparison of 24-h ambulatory blood pressure and BPV parameters

There was no significant difference in nSBP, 24hSSD, nDBP, 24hDBP, ddnDBP, MMD and MBPS between the two groups ($P > 0.05$). There were significant differences between the two groups in the factors ofdSBP, dSSD, nSSD, nDSD, 24hSBP, dDBP, dDSD, 24 h DSD, ddnSBP, and rhythm of blood pressure ($P < 0.05$), as shown in Table 2.

Multivariate logistic regression analysis

The comorbidity of SCI was considered as the dependent variable. Variables with $P < 0.1$ in the univariate analysis were included in the logistic regression model. Independent variable assignment was as follows. The independent variables, including age, BMI, TC, TG, LDL-C, HDL-C, FBG, Hs-CRP, Lp-PLA2, Hcy, nSBP, 24hSBP, dSSD, dDSD, 24hSSD, 24hDSD, and MMD were all continuous variables. Alcohol consumption, history of smoking, history of diabetes, history of hypertension, intake of antihypertensive drugs, history of stroke, MBPS, and blood pressure circadian rhythm were binary variable and were assigned as Yes = 0 and No = 1. As shown in Table 3, the factors of dSSD, 24hDSD, dSBP, age, smoking, FBG, and Lp-PLA2 were positively related to SCI ($P < 0.05$).

Discussion

BPV is a controversial but promising research areas in the field of hypertension. Many studies have reported the relationship between BPV and cerebral infarction.[11,14] However, there are few reports on the relationship between BPV and SCI.

SCI, also known as asymptomatic cerebral infarction or subclinical cerebral infarction, refers to cerebral infarction without obvious neurological symptoms and local signs (or infarcts in areas unrelated to the symptoms), however, ischemic cerebrovascular changes can be revealed by radiology or autopsy.[15,16] So far, whether SCI can be called a stroke is still in controversy.[15] The clinical manifestations of cerebral infarction and the infarct volume are generally positively correlated. Therefore, most SCIs are lacunar

Table 2 Comparison of blood pressure levels and BPV parameters between the control group and the SCI group.

	Control group	SCI group	P value
SBP			
dSBP, mmHg	153.10 ± 9.19	157.48 ± 9.14	0.000
nSBP, mmHg	135.44 ± 10.88	137.74 ± 11.89	0.064
24hSBP, mmHg	144.52 ± 8.60	147.61 ± 8.90	0.001
dSSD, mmHg	13.16 ± 2.66	14.60 ± 3.14	0.000
nSSD, mmHg	9.64 ± 1.90	10.17 ± 2.44	0.028
24hSSD, mmHg	13.92 ± 2.83	14.46 ± 3.14	0.092
ddnSBP	17 (14–29)	15 (13–25)	0.015
DBP			
dDBP, mmHg	87.82 ± 5.49	89.66 ± 8.12	0.016
nDBP, mmHg	79.38 ± 6.11	79.93 ± 8.52	0.498
24hDBP, mmHg	83.52 ± 5.33	84.80 ± 7.74	0.078
dDSD, mmHg	9.44 ± 2.16	10.60 ± 2.78	0.000
nDSD, mmHg	6.85 ± 2.06	7.39 ± 2.58	0.032
24hDSD, mmHg	10.39 ± 2.38	11.27 ± 2.51	0.001
ddnDBP, in 24 h, mmHg	8 (7–10)	9 (7–13)	0.055
MMD	37 (31–43)	36.5 (29.75–43.25)	0.947
Blood pressure rhythm	56 (35%)	45 (24%)	0.028
MBPS	47 (29%)	60 (32%)	0.563

Note: SCI: silent cerebral infarction; SBP: systolic blood pressure; SSD: standard deviation of systolic blood pressure; DBP: diastolic blood pressure; DSD: standard deviation of diastolic pressure; ddnSBP: differences between daytime SBP and nighttime SBP; ddnDBP: differences between daytime DBP and nighttime DBP; MMD: maximum–minimum difference; MBPS: morning blood pressure surge. dSBP: daytime SBP; dDBP: daytime DBP (dDBP); nSBP: night SBP; nDBP: night DBP.

infarcts and belong to the category of cerebral vascular disease.[16] The SCI patients selected in this study all met these criteria. The lesions were located in the subcortex or cortex, and the lesion size was generally between 3 mm and 20 mm. This is also related to the pathophysiological characteristics of hypertension. Hypertension mainly affects small resistance blood vessels in the early stages, leading to remodeling of small blood vessels.[17,18] As long-lasting elevated blood pressure, vascular changes occur predominantly in conduit arteries which become stiffer.[18] Therefore, many hypertensive patients do not have obvious clinical manifestations at early stage, and may present with non-specific symptoms such as headache, dizziness, and fatigue.[18] If cranial imaging examinations are performed at this stage, many patients already have SCI.[19] In 2008, Das et al.[19] have found that relevant SCI is associated with stage I hypertension. If not actively intervened, the risk of atherosclerotic symptomatic cerebral infarction may be greatly increased.[20]

The prevalence of SCI is not consistent. In most reports, the prevalence of SCI is between 5.8% and 20.8%.[15,16] It is reported that the prevalence of SCI was related to age,[17] with the SCI detection rate of 3% for patients with the age below 40,9% for patients between 40 and 50 years old, 27% for 51–60 years old, and 67% for older than 61 years old. For every 10 years of age increase, the risk of SCI increased by 1.5–2 times. However, there is study based on large sample sizes. It has been shown that SCI is an important risk factor for symptomatic cerebral infarction. For example, a study from China[18] suggested that the risk of SCI developing into symptomatic cerebral infarction was 34.4%. Another report[19] found that the risk of cerebral infarction in patients with SCI could increase 2–10 times within the next 2–4 years, and SCI could easily develop into vascular dementia.[20]

The pathophysiology and risk factors of SCI are similar with symptomatic cerebral infarction. The main risk factors included age, hypertension, diabetes, carotid atherosclerosis and atrial fibrillation.[15,16,19,20] In this study, there were 186 patients with SCI, and some of them did not have obvious history of hypertension, but we still considered them as having hypertension-related SCI. The reasons are as follows: 1) among the included 186 patients, 78.89% had hypertension. In other words, these patients had different levels of increased blood pressure and most of them had intake history of antihypertensive drugs; 2) they met the diagnostic criteria for hypertension; and 3) currently, it is estimated that almost 50% of stroke cases may be attributable to hypertension.[21] However, if we consider the relationships between BPV and cardiovascular/cerebrovascular diseases, more than 90% of strokes may be related to hypertension.[11]

Assuming that BPV is risk factor affecting SCI independent of blood pressure, then we have reason to find BPV indicators that are independently related to SCI, which is the purpose of this study. According to our previous study,[11]

Table 3 Multivariate logistic regression analysis.

Independent variable	Regression coefficients	Standard error	Wald value	P value	OR value	95%*CI*
dSSD	0.318	0.081	15.505	0.000	1.374	1.173–1.609
24hDSD	0.177	0.082	4.677	0.031	1.194	1.017–1.402
dSBP	0.060	0.019	9.475	0.002	1.062	1.022–1.103
Age	0.041	0.018	5.055	0.025	1.042	1.005–1.080
Smoking	0.959	0.284	11.384	0.001	2.610	1.495–4.556
FBG	0.168	0.066	6.517	0.011	1.183	1.040–1.345
Lp-PLA2	0.004	0.001	33.136	0.000	1.004	1.003–1.006

Note: dSSD: standard deviation of systolic pressure during the day; 24hSSD: standard deviation diastolic blood pressure of 24 h; dSBP: daytime systolic blood pressure; FBG: fasting plasma glucose; Lp-PLA2: lipoprotein-associated phospholipase A2; OR: odds ratio; CI: confidence interval.

BPV (mainly dSSD) was independently associated with the degree of carotid atherosclerosis in primary hypertension patients. In this study, we found that dSSD and 24 h DSD were positively correlated with SCI. The dSBP was also independently associated with SCI in hypertension patients, which is consistent with previous research.[22] In addition, the traditional risk factors, such as age, smoking, and FBG were also related to the incidence of SCI, which is also consistent with previous reports.[23,24] In this study, univariate analysis found that there were statistically significant differences in age, stroke history, diabetes history, smoking, alcohol consumption, FBG, Hcy, Lp-PLA2, and IMT between hypertension patients and hypertension patients with SCI. However, in logistic regression analysis, there was no significant difference in history of stroke alcohol consumption, IMT, and Hcy. This may be caused by the small sample size and possible selection bias. Further studies are warranted.

Lp-PLA2 is closely related to atherosclerosis and can be used as a predictor of ischemic cardiovascular and cerebrovascular disease.[25] In both the univariate and logistic regression analyses of this study, there was a statistically significant difference in Lp-PLA2 levels between hypertension patients and hypertension patients with SCI, which is consistent with the reports by Riba-Llena et al.[26] But so far, the conclusive evidence of clinical evidence-based medicine is still lacking, and it is expected that large-scale related clinical research will provide more evidence in the future.

The univariate analysis of this study found that there was a statistically significant difference between the two groups in ddnSBP, suggesting that ddnSBP may be a protective factor for SCI and could be used as an alternative indicator for BPV hypo-responsiveness. However, this relationship was not found in Logistic regression analysis. This may still be related to the small sample size and the anti-dipper blood pressure increase in the SCI group at night. Further research is needed to confirm this in the future.

A study from China[27] found that non-dipper hypertension may have a certain relationship with the occurrence of SCI, and abnormal blood pressure circadian rhythm may be a parameter for assessing cerebrovascular damage and SCI. Zhang Li et al.[28] found that the 24-h mean systolic blood pressure coefficient of variation (24 hSBPV), the mean daytime systolic blood pressure coefficient of variation (dSBPV), and the mean nighttime systolic blood pressure coefficient of variation (nSBPV), average 24 h DBPV, 24 d DBPV, dDBPV, and nDBPV were higher in hypertension patients combined with lacunar infarction than those with simple hypertension. In addition, the morning BPV levels were also higher in patients with hypertension and lacunar infarction. These results suggest that BPV increase is one of the important risk factors for SCI. This study found that BPV (mainly dSSD and 24hDSD) is positively correlated with the onset of SCI in hypertension patients. However, we did not investigate the relationship between BPV and secondary cerebral infarction in patients with SCI.

The current difficulties are as follows: 1) there are multiple indicators of BPV, and new indicators are also being discovered one after another; 2) there are different degrees of correlation between BPV indicators; 3) BPV is susceptible to many factors. BPV has obvious variability, dynamism and poor repeatability, which makes it difficult to reach an agreement with valid reference ranges for various BPV indicators. Therefore, the research on BPV is still in its infancy, and its in-depth research has a long way to go.

In conclusion, for the first time, our results showed that, blood pressure variability (dSSD and 24hDSD) was independently associated with SCI in patients with essential hypertension. These findings may provide new evidence for the investigation of SCI risk in hypertensive patients, from the perspective of BPV. Further in-depth studies are still needed to find BPV indicators with satisfactory stability and sensitivity, and to explore its relationship with the SCI risk in patients with hypertension.

Disclosures

All authors declare no financial and non-financial competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.artres.2018.11.001.

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