

Correlation Between Blood Pressure Variability and Serum Vascular Endothelial Growth Factor Concentration in Patients with Type I Cerebral Small Vessel Disease

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Objective: To investigate the relationship between blood pressure variability (BPV) and serum vascular endothelial growth factor (VEGF) levels in patients with type I cerebral small vessel disease (CSVD).

Methods: 144 Patients admitted to the Neurology Department of our Hospital between December 2021 and December 2022 were included and categorized into 5 groups according to CSVD burden, which was evaluated based on MRI findings. Group 0–2 were categorized as mild patients, group 3 as moderate patients, group 4 as severe patients. All patients underwent 24-hour ambulatory blood pressure monitoring. Serum samples were collected to measure the concentration of VEGF. The differences of general information, BPV and serum VEGF levels in five groups were compared. Spearman correlation analysis was used to analyze the correlation between total CSVD burden and BPV, as well as total CSVD burden and serum VEGF concentration. Additionally, Pearson correlation analysis was used to explore the correlation between serum VEGF level and BPV.

Results: 83 males and 61 females with mean age of (67.5±9.9) years were enrolled. Significant differences were observed in age and hypertension history among the five groups ($p<0.001$). In both mild and severe groups, 24hSBP, 24hSBP-SD, 24hSBP-CV, 24hSBP-ARV, DSBP, DSBP-SD, DSBP-ARV, 24hDBP, 24hDBP-SD, DDBP, NDBP showed a significant positive correlation with the total CSVD burden scores. The differences in serum VEGF concentration among the five groups were statistically significant ($P<0.05$), with the lowest in group 4 and the highest in group 3. Serum VEGF concentration showed a significant positive correlation with the total CSVD burden scores in patients with mild to moderate CSVD. Pearson's correlation analysis revealed that serum VEGF concentration was significantly and positively correlated with 24hSBP-SD, 24hSBP-ARV, DSBP-SD, DSBP-ARV, and SBP-wSD.

Conclusion: VEGF may be associated with the impact of BPV on CSVD patients, and potentially correlated to delaying disease progression.

Keywords: cerebral small vessel disease, blood pressure variability, vascular endothelial growth factor, total CSVD burden score

Introduction

Cerebral small vessel disease (CSVD) encompasses a range of syndromes characterized by the involvement of small cerebral vessels, including small cerebral arteries and their distal branches, micro-arteries, capillaries, micro-venules, and small veins. Clinical manifestations are diverse, featuring both acute ischemic presentations and chronic, insidious onset syndromes. Chronic CSVD often presents non-specifically and may lack overt symptoms, with diagnosis relying mainly on neuroimaging. Some patients may experience cognitive decline, depression, gait abnormalities, dysphagia, and urinary

problems. Magnetic Resonance Imaging (MRI) plays a crucial role in the assessment of CSVD, with key features including recent small subcortical infarcts, cerebral atrophy, lacunar infarcts (LIs), white matter hyperintensity (WMH), cerebral microbleeds (CMBs), and enlarged perivascular spaces (EPVS). Among these, the latter four are frequently utilized as primary indicators for quantifying the MRI burden scores associated with CSVD, which offer a comprehensive evaluation of the overall burden of CSVD in patients. Notably, the total burden score, which integrates these imaging markers, is particularly effective in measuring the severity of CSVD.¹

Depending on the etiology, CSVD can be divided into six types, the most common of which is atherosclerosis-related type I CSVD.² Hypertension is the most clear and important intervenable risk factor for type I CSVD.³ However, recent studies have found that merely controlling blood pressure within the normal range has limited efficacy in slowing the progression of CSVD. Blood pressure variability (BPV) has gradually garnered increasing attention, with studies indicating that elevated BPV is closely associated with all-cause and cardiovascular mortality, as well as stroke incidence.⁴ Furthermore, existing research has highlighted the critical role of BPV in the progression of CSVD.⁵ Most studies on the relationship between BPV and CSVD show that BPV level is associated with CSVD burden scores as well as the severity of WMH. Furthermore, increased BPV has been identified as an independent risk factor for cerebral microhemorrhage.⁵

BPV can be used to reflect the degree of blood pressure fluctuations over a while. Several studies have demonstrated a correlation between elevated 24-hour BPV and an increased incidence of cerebrovascular disease.⁶ Ambulatory blood pressure monitoring (ABPM) is the most common test used to detect BPV. ABPM enables the assessment of blood pressure fluctuations throughout the day, which is of great importance for the treatment of CSVD patients. There are several indicators for the assessment of BPV, among which the commonly used ones include standard deviation (SD), coefficient of variation (CV), weighted standard deviation (wSD), and average true variability (ARV). wSD avoids the effect of physiological regulation of the nocturnal BP drop on BPV, and ARV is the mean of the absolute differences between successive BP measurements, reflecting the temporal order and variability of BP measurements, focusing on the order of BP readings, and is more reliable in expressing temporal variability.⁷

Small vessel lesions in the brain lead to insufficient blood flow and oxygen supply to the brain,⁸ which can promote the angiogenesis process and increase the release of signaling proteins related to angiogenesis. Among these proteins, vascular endothelial growth factor (VEGF), also known as vascular permeability factor (VPF) or angiogenic factor, plays a crucial role in promoting the proliferation of vascular endothelial cells as well as angiogenesis.⁹ Previous studies have shown that VEGF not only promotes angiogenesis during neural tissue development but also significantly enhances vascular generation under ischemic or hypoxic conditions in the brain.¹⁰ Its primary physiological functions include regulating endothelial cell proliferation and differentiation, increasing vascular permeability, and promoting vessel wall proliferation.¹¹ Recent research has also identified a direct neuroprotective role for VEGF. Following brain injury, VEGF facilitates the remodeling of the neurovascular unit, mitigates ischemic brain injury, reduces the volume of infarcts, and decreases neuronal cell death.¹² Overall, VEGF plays a crucial role in neurogenesis, neuronal nourishment, and axonal development.

The correlation between VEGF and CSVD is mainly reflected in the key role of VEGF in vascular and lymphatic repair and regeneration. Existing studies indicated a close relationship between VEGF levels and the severity of CSVD, highlighting VEGF's significant role in repairing endothelial damage in small cerebral vessels, promoting the formation of new microvessels, and increasing blood-brain barrier permeability. Previous research also demonstrated a significant association between increased BPV and CSVD, elevated BPV may damage endothelial cells and exacerbate cerebral ischemia, thereby contributing to CSVD progression.^{13,14} Further investigation is needed to determine whether the affecting of brain perfusion and small vessel integrity by increased BPV will influences VEGF production. Although existing literature has elucidated the pivotal role of VEGF in angiogenesis and neuroprotection, the specific role of VEGF in CSVD remains poorly understood. Most studies have focused on the function of VEGF in the repair of small cerebral vessel damage, the promotion of new microvascular formation, and the enhancement of blood-brain barrier permeability. However, the precise role of VEGF in the pathogenesis of CSVD, whether beneficial or detrimental, is still a matter of debate. Different from previous studies, this research aims to investigate the relationship between BPV and serum VEGF levels, particularly through an in-depth analysis of type I CSVD patients with varying disease severity. This study tries to

fill a significant gap in the current literature by addressing the potential interplay between BPV and VEGF, and revealing how BPV may modulate VEGF regulation, thereby influencing the progression of CSVD. Furthermore, this research wants to clarify the controversial role of VEGF in the pathogenesis of CSVD, providing new insights for clinical treatment strategies.

Through this study, we aim to provide theoretical support for the early diagnosis and precision treatment of CSVD, particularly by exploring how regulating BPV can impact VEGF expression to preserve vascular endothelial cell function, thus slowing the progression of CSVD. Additionally, this research offers novel perspectives and potential therapeutic targets for the clinical management of CSVD.

Materials and Methods

Participants

A total of 188 patients were initially included with symptoms of dizziness, cognitive decline, depression, gait disturbance, and abnormal swallowing and urinary function. The patients with previous infectious and toxic brain injury, severe ischemic or hemorrhagic stroke (massive cerebral infarction or large vessel lesion), acute myocardial infarction or other severe heart diseases, nephritic or hepatic insufficiency, tumor, and who cannot fulfill the MRI scanning or with invalid 24-h ABPM recording for the assessment were excluded. 6 patients were excluded due to non-type I CSVD, 21 patients were excluded due to a history of massive cerebral infarction or acute severe ischemic or hemorrhagic stroke, and 17 patients were excluded due to invalid ABPM data. Therefore, 144 patients aged 45 years or older with type I CSVD admitted to the Department of Neurology of our Hospital from December 2021 to December 2022, including 83 males and 61 females (Figure 1) were enrolled. All patients with hypertension were consistently administered antihypertensive medications prior to admission, and their medication regimens remained unchanged throughout the study period.

The study was approved by the Ethics Committee of our Hospital (Approval Number: HZKY-PJ-2020-44). Informed consent was obtained from all patients upon admission, and they were informed that their data might be utilized in a clinical study.

Data Collection

Clinical information, including age, sex, body mass index (BMI), and medical history related to hypertension, diabetes mellitus, cigarette use, alcohol consumption, hypercholesterolemia, and previous stroke, were collected from all

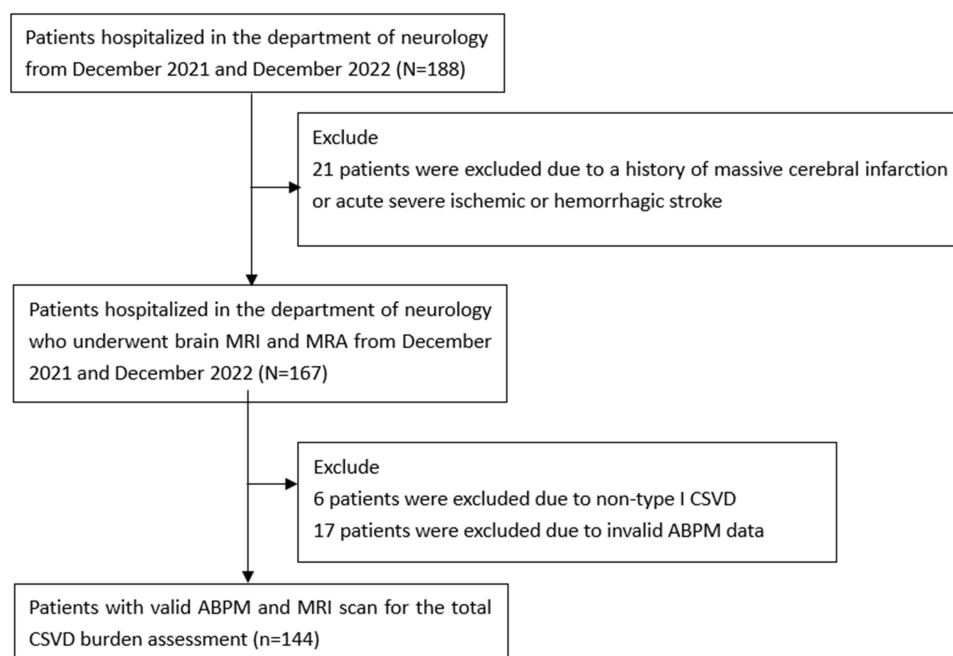


Figure 1 Flow chart of enrollment in the current study.

participants. Fasting venous blood samples were obtained from all subjects early in the morning on the day of the 24-hour ABPM, following a fasting period of at least 8 hours. Laboratory assessments were conducted to measure total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), homocysteine, etc.

Brain MRI scans were conducted within 7 days of admission using a 3.0T MR scanner (GE 750, USA). The MRI sequences included T1WI, T2WI, FLAIR, DWI, and SWI. The total burden score of CSVD was evaluated based on the presence of four MRI markers: lacunes, WMH, CMBs, and EPVS within the basal ganglia, following previously established methodologies.¹ Lacunes were defined as ovoid or rounded lesions exhibiting cerebrospinal fluid-like signal intensity, with diameters ranging from 3 to 15 mm. One point was awarded if there were one or more lacunes. WMH was identified as iso- or hypointense signals on T1WI and hyperintense signals on T2WI and FLAIR. A score of one point was given if the periventricular WMH Fazekas score reached 3, or if the deep WMH Fazekas score was 2 or 3. On the SWI image, CMBs were defined as small, rounded, or circular well-defined hypointense lesions within the brain parenchyma. One point was added to the total score only if one or more microbleeds were identified in the deep areas. On all sequences, EPVS were defined as fluid-filled spaces exhibiting signal intensities similar to cerebrospinal fluid, with ovoid, round, or linear shapes and diameters of less than 3 mm. The number of EPVS at the basal ganglia level was quantified, with the higher count between the two hemispheres being considered. If the count exceeded 10, one point was assigned.¹ Two radiologists independently assessed the images without knowledge of clinical information or each other's readings. To assess inter-rater reliability, we calculated the Cohen's Kappa coefficient. The values for the LI were 0.899 (95% CI: 0.826, 0.972), for EPVS were 0.844 (95% CI: 0.750, 0.937), for WMH were 0.911 (95% CI: 0.842, 0.981), and for CMB were 0.884 (95% CI: 0.806, 0.962), indicating near-perfect agreement between the two radiologists' assessments for these four imaging features. Finally, for patients with discrepancies, the two radiologists reached a consensus decision through discussion.

24h ABPM

All admitted patients underwent 24-h ABPM using an automated ambulatory blood pressure recorder (ABP-021, Beneware, China) within 7 days of admission. The recorder was set to record blood pressure every 30 min in the daytime (6:00–22:00) and every 1 h in the nighttime (22:00–next 6:00). The mean systolic blood pressure (SBP) and the mean diastolic blood pressure (DBP) during daytime, nighttime, and 24h were collected. If the measurement frequency was below 70%, with less than one measurement per hour during the day and less than six measurements in total at night, a 24-h ABPM recording was considered invalid.¹⁵

Measurements of 24-hour mean systolic blood pressure (24hSBP), 24-hour mean diastolic blood pressure (24hDBP), daytime mean systolic blood pressure (DSBP), daytime mean diastolic blood pressure (DDBP), nighttime mean systolic blood pressure (NSBP), and nighttime mean diastolic blood pressure (NDBP) were analyzed for each subject. All SD, CV, ARV of 24hSBP, 24hDBP, DSBP, DDBP, NSBP, NDBP and wSD of SBP and DBP were calculated.

Determination of Serum VEGF Concentration

All enrolled patients had fasting venous blood drawn on the morning of the 24-hABPM. After to clot at room temperature for 30 minutes, samples were centrifuged at $1000 \times g$ for 15 minutes. The supernatant was carefully collected, aliquoted, and stored at -80°C for test. Serum VEGF levels were measured using a double-antibody sandwich ELISA kit (Proteintech Group). Standard or test samples were added to a microplate pre-coated with purified human VEGF monoclonal antibodies, allowing VEGF to bind. Next, biotinylated anti-human VEGF antibodies were added, followed by HRP-conjugated streptavidin for specific binding to biotin. TMB substrate was added, resulting in a color change from colorless to blue, which turned yellow upon adding the stop solution. Optical density (OD) was measured at 450 nm using a Thermo Fisher Scientific plate reader, and the actual sample concentrations were calculated using ELISACalc software.

Statistical Analysis

SPSS 23.0 (IBM Corp, Armonk, NY) was used for statistical analysis and the difference was considered statistically significant if $P < 0.05$. Data of continuous variables were presented as mean \pm SD if normally distributed and median (interquartile range, IQR) otherwise. Analysis of variance was used for the comparison among groups for the normally distributed continuous variables, while the Kruskal–Wallis test was used if the variables were abnormally distributed. The date of categorical variables was presented as n (%), and the χ^2 test was used for determining the difference between groups. Pearson correlation analysis was used to examine the correlation between BPV-related indicators and serum VEGF levels. Spearman correlation analysis was used to examine the correlation between each BPV index as well as VEGF level and CSVD burden score.

Results

Participants Characteristics

The mean age of 144 patients was 67.5 ± 9.9 years, and 57.6% (83/144) of them were male. In total, 21 patients (14.6%) presented no concerning imaging markers, 35 patients (24.3%) had one imaging marker, 30 patients (20.8%) had two markers, and 34 patients (23.6%) had three imaging markers, whereas 24 patients (16.7%) had all the four imaging markers. We finally divided all the patients into five groups based on a CSVD score of 0 to 4. Of these, group 0–2 were categorized as mild patients, group 3 as moderate patients, and group 4 as severe patients.

Among the five groups, age differed significantly, with higher ages in groups with higher CSVD burden score ($P < 0.001$). The history of hypertension was significantly different between the five groups ($P = 0.004$). The higher the total CSVD burden, the higher the proportion of patients with a history of hypertension. Sex, diabetes, hyperlipidemia, cigarette use and alcohol consumption did not differ significantly among 5 groups. No significant difference was observed in the level of BMI, homocysteine, total cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein cholesterol (Table 1).

BPV-Related Indicators

There were statistically significant differences in 24hSBP ($P < 0.001$), 24hSBP-SD ($P = 0.001$), 24hSBP-CV ($P = 0.009$), 24hSBP-ARV ($P = 0.009$), 24hDBP ($P = 0.002$), 24hDBP-SD ($P = 0.030$), DSBP ($P < 0.001$), DSBP-SD ($P = 0.033$), DSBP-

Table 1 Demographic and Clinical Characteristics of Patients in Different CSVD Burden Groups

Item	Total Case n=144	Total CSVD Burden Score					F/Z/ χ^2	P
		0	1	2	3	4		
		n=21	n=35	n=30	n=34	n=24		
Age, mean (SD), Y	67.5 \pm 9.9	59.6 \pm 11.3	64.9 \pm 8.8	69.7 \pm 8.4	70.9 \pm 10.0	70.9 \pm 6.7	7.193	<0.001
Sex (male), n (%)	83 (57.6)	9 (42.9)	20 (57.1)	15 (50.0)	23 (67.6)	16 (66.7)	4.796	0.309
Hypertension, n (%)	103 (71.5)	5 (23.8)	26 (74.3)	23 (76.7)	31 (91.2)	18 (75.0)	30.587	<0.001
Diabetes, n (%)	46 (31.9)	6 (28.6)	19 (42.9)	6 (20.0)	13 (38.2)	8 (33.3)	8.634	0.071
Cigarette use, n (%)	39 (27.1)	3 (14.3)	10 (28.6)	6 (20.0)	10 (29.4)	8 (33.3)	3.072	0.546
Alcohol consumption, n (%)	46 (31.9)	4 (19.0)	12 (34.3)	8 (26.7)	12 (35.3)	10 (41.7)	3.298	0.509
Body mass index, mean (SD)	24.8 \pm 3.5	24.5 \pm 3.2	24.8 \pm 3.7	24.5 \pm 3.9	25.4 \pm 2.3	24.6 \pm 4.3	0.358	0.838
Total cholesterol, mmol/L	4.3 \pm 1.0	4.4 \pm 0.8	4.3 \pm 1.3	4.4 \pm 0.9	4.1 \pm 1.0	4.3 \pm 1.2	0.295	0.881
Triglycerides, mmol/L	1.4 \pm 0.7	1.3 \pm 0.9	1.5 \pm 0.9	1.2 \pm 0.6	1.4 \pm 0.6	1.4 \pm 0.7	7.610	0.107
High-density lipoprotein, mmol/L	1.1 \pm 0.3	1.1 \pm 0.3	1.0 \pm 0.2	1.1 \pm 0.3	1.1 \pm 0.2	1.0 \pm 0.2	1.167	0.328
Low-density lipoprotein, mmol/L	2.3 \pm 0.8	2.3 \pm 0.6	2.3 \pm 1.0	2.4 \pm 0.6	2.2 \pm 0.7	2.2 \pm 0.8	0.288	0.885
Homocysteine, μ mol/L	13.2 \pm 6.1	12.9 \pm 5.5	13.2 \pm 8.2	12.4 \pm 3.8	13.8 \pm 6.4	13.8 \pm 5.2	0.286	0.887
VEGF, pg/mL	389.9 \pm 169.3	361.5 \pm 196.0	368.7 \pm 170.6	387.9 \pm 145.3	466.8 \pm 155.3	339.2 \pm 166.4	2.701	<0.033

Table 2 Blood Pressure Levels and Variability in Different CSVD Burden Groups

BPV indicator	Total Case (n=144)	Total CSVD Burden Score					F	P
		0 (n=21)	1 (n=35)	2 (n=30)	3 (n=34)	4 (n=24)		
24hSBP	136.68±14.59	125±11	135.11±13.71	137±14.83	141.24±11.7	142.33±16.68	5.911	<0.001*
24hSBP-SD	12.57±3.64	10.79±2.83	11.99±3.25	12.72±4.69	12.32±2.59	15.12±3.46	4.977	0.001*
24hSBP-CV	9.19±2.39	8.63±2.06	8.89±2.26	9.20±2.67	8.74±1.77	10.75±2.74	3.505	0.009*
24hSBP-ARV	9.89±2.89	8.77±2.24	9.57±3.04	9.59±3.50	9.94±1.75	11.67±3.04	3.491	0.009*
24hDBP	78.59±10.20	74.00±7.12	76.09±8.78	78.27±9.75	79.76±10.93	85.00±11.12	4.477	0.002*
24hDBP-SD	10.09±3.09	9.14±2.86	9.87±3.03	10.13±3.19	9.63±2.68	11.83±3.34	2.755	0.030*
24hDBP-CV	12.84±3.61	12.37±3.72	12.99±3.73	12.88±3.50	12.08±2.94	14.09±4.20	1.189	0.319
24hDBP-ARV	8.99±5.35	7.97±2.39	8.42±2.86	10.35±10.37	8.11±2.14	10.25±3.51	1.347	0.256
DSBP	137.48±14.61	125.95±11.21	135.54±13.74	138.00±14.87	141.26±12.09	144.38±15.89	6.100	<0.001*
DSBP-SD	12.27±3.95	10.81±3.38	11.88±3.57	12.44±5.06	11.93±3.01	14.37±3.98	2.696	0.033*
DSBP-CV	8.94±2.71	8.58±2.47	8.77±2.52	8.96±3.09	8.48±2.19	10.10±3.19	1.483	0.211
DSBP-ARV	7.66±2.50	6.51±1.46	7.49±2.61	7.79±3.27	7.47±1.73	9.02±2.43	3.175	0.016*
DDBP	79.60±10.40	75.00±7.16	76.74±8.86	79.63±9.92	80.38±11.25	86.67±11.00	5.017	0.001*
DDBP-SD	9.86±3.59	9.06±3.51	9.58±3.40	9.87±3.94	9.63±3.06	11.31±4.03	1.343	0.257
DDBP-CV	12.40±4.23	12.11±4.60	12.48±4.20	12.32±4.36	12.00±3.42	13.21±5.00	0.320	0.864
DDBP-ARV	6.61±2.46	6.10±2.28	6.36±2.41	6.54±2.28	6.31±1.94	7.93±3.21	2.248	0.067
NSBP	134.27±17.18	122.14±12.03	133.11±15.51	134.40±18.38	141.62±12.64	136.00±20.90	4.715	0.001*
NSBP-SD	9.45±3.67	8.31±3.17	8.94±3.40	8.62±3.42	10.98±3.71	10.09±4.14	2.856	0.026*
NSBP-CV	7.12±2.74	6.81±2.51	6.81±2.60	6.59±2.98	7.74±2.44	7.60±3.17	1.092	0.363
NSBP-ARV	2.03±0.92	2.08±1.30	1.90±0.92	1.79±0.66	2.26±0.76	2.16±1.00	1.354	0.253
NDBP	76.24±12.36	72.00±9.47	73.57±10.23	74.73±11.12	79.59±14.10	80.96±14.37	2.763	0.030*
NDBP-SD	7.90±2.98	6.93±2.42	7.89±2.89	7.71±2.82	7.91±2.85	8.99±3.75	1.410	0.234
NDBP-CV	10.48±3.87	9.64±3.24	10.84±3.66	10.49±4.37	9.98±3.33	11.36±4.72	0.777	0.542
NDBP-ARV	1.78±0.84	1.66±0.83	1.75±0.84	1.63±0.64	1.74±0.67	2.16±1.17	1.667	0.161
SBP-wSD	11.30±3.12	9.88±2.64	10.87±2.98	11.10±3.63	11.63±2.42	12.98±3.35	3.302	0.013*
DBP-wSD	9.19±2.82	8.25±2.34	9.02±2.91	9.17±2.71	8.95±2.36	10.61±3.44	2.287	0.063

ARV (P=0.016), DDBP (P=0.001), NSBP (P=0.001), NSBP-SD (P=0.026), NDBP (P=0.03), SBP-wSD (P=0.013) among the 5 groups (Table 2).

Correlation Between BPV-Related Indicators and CSVD Burden

In the mild and severe groups, Spearman correlation analysis indicated that higher CSVD burden were positively correlated with 24hSBP ($r=0.331$, $P<0.001$), 24hSBP-SD ($r=0.337$, $P<0.001$), 24hSBP-CV ($r=0.214$, $P=0.010$), 24hSBP-ARV ($r=0.330$, $P<0.001$), DSBP ($r=0.346$, $P<0.001$), DSBP-SD ($r=0.241$, $P=0.004$), DSBP-ARV ($r=0.279$, $P=0.001$), 24hDBP ($r=0.309$, $P<0.001$), 24hDBP-SD ($r=0.221$, $P=0.008$), DDBP ($r=0.313$, $P<0.001$), NDBP ($r=0.235$, $P=0.005$). However, in the moderate group, all BPV-related indicators decreased, and Spearman correlation analysis indicated that higher CSVD burden were positively correlated with SBP-wSD ($r=0.312$, $P<0.001$) (Table 3).

Correlation Between Serum VEGF Concentration and CSVD Burden

Serum VEGF concentrations in the five groups were 361.50±196.0pg/mL, 368.7±170.6 pg/mL, 387.9±145.3 pg/mL, 466.8±155.3 pg/mL, and 339.2±166.4 pg/mL, respectively, and there was a statistically difference between the five groups ($P<0.05$). The highest VEGF concentrations were found in patients with total CSVD burden scores of 3 and the lowest in patients with total CSVD burden scores of 4 (Table 1 and Figure 2).

Spearman correlation analysis showed a significant positive correlation between serum VEGF levels and total CSVD burden in the group of patients with mild to moderate CSVD (total CSVD burden score 0–3) ($r=0.386$, $P<0.001$) (Figure 3).

Table 3 Spearman Correlation Analysis of BPV-Related Indicators and Total CSVD Burden Score

ITEM	r	P
24hSBP	0.331	<0.001
24hSBP-SD	0.337	<0.001
24hSBP-CV	0.214	0.010
24hSBP-ARV	0.330	<0.001
24hDBP	0.309	<0.001
24hDBP-SD	0.221	0.008
DSBP	0.346	<0.001
DSBP-SD	0.241	0.004
DSBP-ARV	0.279	0.001
DDBP	0.313	<0.001
NSBP	0.241	0.004
NSBP-SD	0.200	0.016
NDBP	0.235	0.005
SBP-wSD	0.312	<0.001

Correlation Between BPV and Serum VEGF Concentration

Pearson's correlation analysis showed that serum VEGF concentration was significantly and positively correlated with 24hSBP-SD ($r=0.207$, $P=0.024$), 24hSBP - ARV ($r=0.216$, $P=0.023$), DSBP-SD ($r=0.211$, $P=0.021$), DSBP-ARV ($r=0.224$, $P=0.014$), and SBP-wSD ($r=0.208$, $P=0.023$), which are indicators of systolic BPV (Table 4). There was no significant linear relationship between the aforementioned indicators and VEGF concentration. In the mild groups, as VEGF increased, BPV showed a slight increase. In the moderate group, VEGF levels significantly increased while BPV decreased. In severe group, VEGF levels significantly decreased while BPV increased (Figure 4).

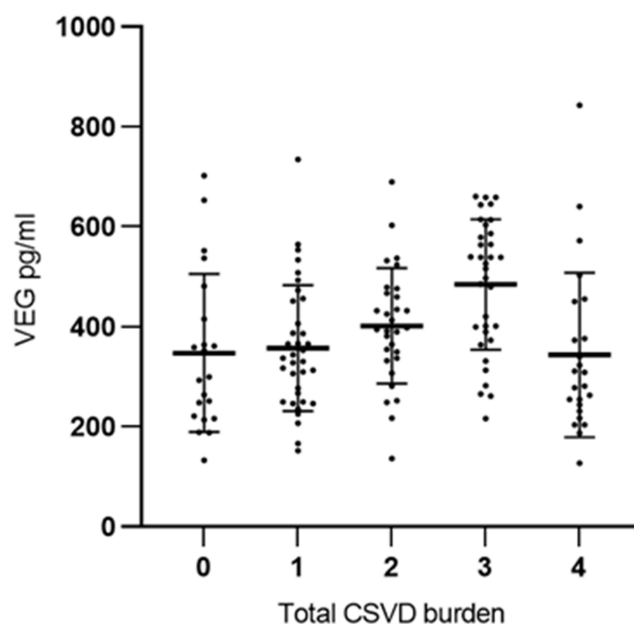


Figure 2 Comparison of serum VEGF concentrations among different CSVD burden groups.

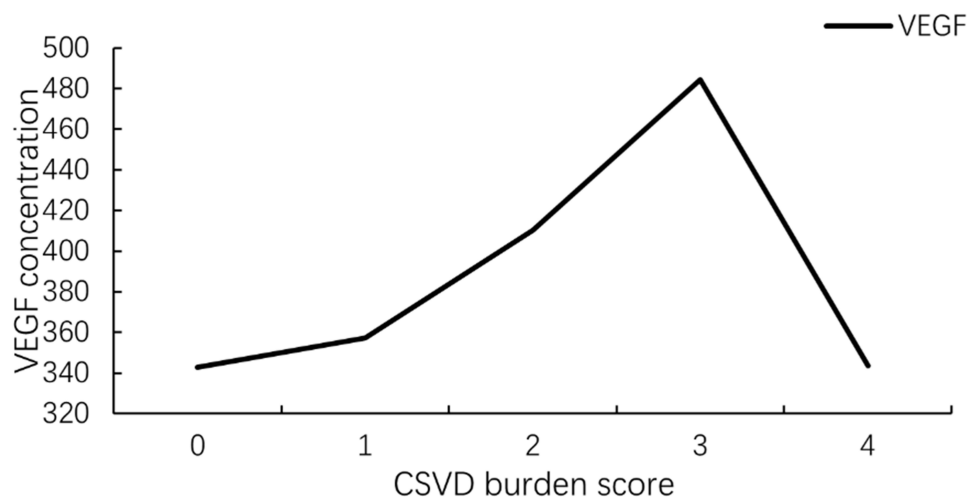


Figure 3 Variation in VEGF concentrations among different CSVD burden groups.

Discussion

Abnormal blood pressure fluctuation increases the risk of target organ damage and cerebrovascular mortality.¹⁶ BPV is an important indicator to evaluate blood pressure fluctuation, and a number of studies have consistently shown that the increased BPV is closely related to cerebrovascular events, especially type I CSVD, which will lead to different degrees of target organ damage.¹⁷ Recent guidelines for the diagnosis and treatment of CSVD have established dynamic blood pressure monitoring as a necessary examination for these patients.^{18,19} However, the mechanisms underlying increased BPV in CSVD are still under exploration.

Several studies have reported an association between increased BPV and markers of CSVD. Filomena et al found that patients with WMH and LI had significantly higher levels of 24-h, daytime, and nighttime ARV compared to non-CSVD patients, and ARV was identified as an independent risk factor for CSVD.²⁰ Similarly, Kim et al conducted a six-month follow-up study on hypertensive patients with acute ischemic stroke and found that the greater the SBP-SD, the more obvious WMH progression, and multivariate analysis showed that SBP-SD was an independent risk factor for WMH progression.²¹ In a prospective cohort study, SBP and DBP were found to be significantly associated with WMH, LI, and CMB.²² A prospective cohort study showed that systolic CV, instead of diastolic CV, was strongly correlated with WMH progression.²³ Liu et al discovered that patients with CMB had higher SD and CV of SBP and DBP, with SBP-SD and SBP-CV identified as independent risk factors for CMB.²⁴ Shuna et al found that 24hSBP-SD, DSBP-SD, NSBP-SD, SBP-wSD, and SBP-CV were statistically different among patients with different CSVD burden and served as independent risk factors for CSVD, while diastolic variability did not show statistical differences between groups.²⁵ A study based on home blood pressure testing also found significant differences in systolic CV among patients with different

Table 4 Pearson Correlation Analysis of VEGF and BPV

ITEM	r	P
24hSBP-SD	0.207	0.024*
24hSBP-CV	0.151	0.100
24hSBP-ARV	0.206	0.023*
24hDBP-SD	0.033	0.721
DSBP-SD	0.211	0.021*
DSBP-ARV	0.224	0.014*
NSBP-SD	0.070	0.445
SBP-wSD	0.208	0.023*

Note: *P<0.05.

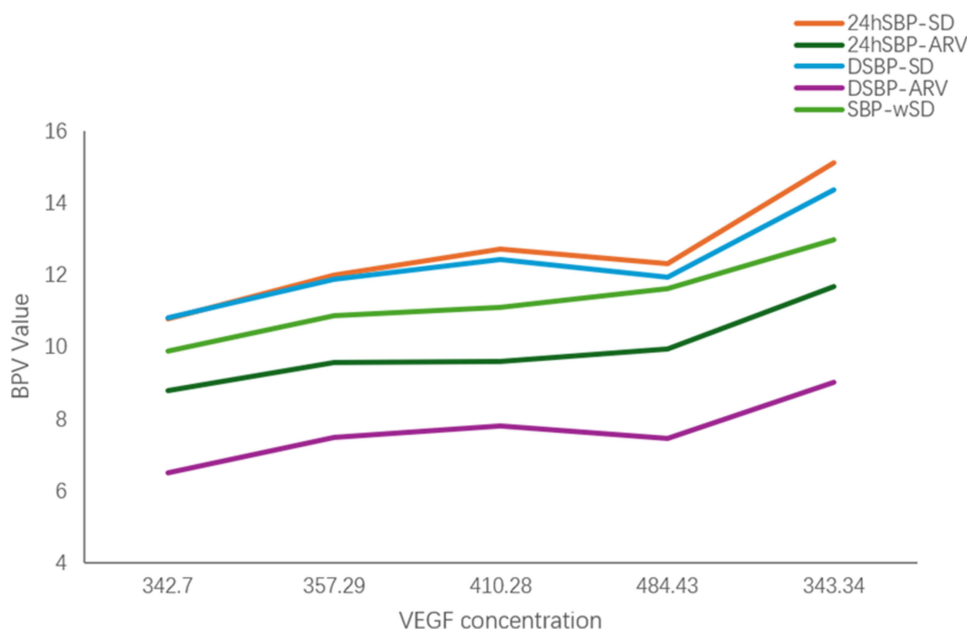


Figure 4 Relationship between VEGF Concentration and BPV in different CSVD burden groups.

CSVD burden scores, and identified SBP as an independent risk factor for CSVD burden scores.²⁶ Our study aligns with these findings as we observed statistically significant differences in various blood pressure indicators, including 24hSBP, 24hSBP-SD, 24hSBP-CV, 24hSBP-ARV, 24hDBP, 24hDBP-SD, DSBP, DSBP-SD, DSBP-ARV, DDBP, NSBP, NSBP-SD, NDBP, and SBP-wSD, among all five groups. Furthermore, these indicators showed positive correlations with total CSVD burden scores.

Animal studies indicate that elevated BPV disrupts the smoothness of cerebral blood flow, reduces nitric oxide production, and impairs endothelial function, leading to damage in the neurovascular unit and abnormalities in the blood-brain barrier, ultimately resulting in small vessel lesions.^{27–29} Increased BPV in patients with CSVD may have the following effects. Elevated BPV enhances the pulsatility of blood flow, hinders the patency of small arteries, and damages cerebral microvasculature.³⁰ Chronic elevation of BPV can damage the vascular endothelium, resulting in lipid hyaline degeneration and lumen occlusion within small arteries, which can contribute to LI.³¹ In individuals with atherosclerosis, the harmful effects of increased BPV on blood vessels are exacerbated, further promoting the development of WMH.^{32–34}

VEGF stabilizes cerebral blood flow, promotes the formation of small cerebral vessels, maintains endothelial cell function, and reduces blood pressure variability, thereby delaying the progression of CSVD. Additionally, elevated VEGF levels may enhance the excitability of sympathetic nerve cells, which in turn affects blood pressure.³⁵ Francesco Arba found no correlation between total CSVD burden scores and plasma VEGF concentration during the acute phase of ischemic stroke, however, a positive correlation was observed 90 days post-stroke onset.³⁶ Kapoor et al found a positive correlation between plasma VEGF-D levels and CSVD burden in an elderly population without a history of dementia or stroke.³⁷ Hannah Tayler et al reported significantly higher VEGF levels in the parietal white matter of brains with severe CSVD compared to those with mild or no CSVD.³⁸ Interestingly, our results are very consistent with those found by Dobrynina et al, that serum VEGF-A levels were significantly higher in patients with milder imaging features and clinical symptoms than in patients with extensive WMH, EPV, CMB, and atrophy.³⁹

It's found in our study that serum VEGF was significantly and positively correlated with 24hSBP-SD, 24hSBP-ARV, DSBP-SD, DSBP-ARV, and SBP-wSD. In mild groups, serum VEGF levels were moderately elevated, with the exception of decreased NSBP-ARV and NDBP-ARV, the remaining BPV-related indicators showed slightly increased. Serum VEGF were significantly higher but 24hSBP-SD, DSBP-SD, 24hDBP-SD, DDBP-SD, 24hSBP-CV, 24hDBP-CV, DSBP-ARV, DDBP-ARV, and DBP-wSD were significantly lower in patients with moderate CSVD compared to mild

CSVD. Serum VEGF concentrations were significantly lower in patients with severe CSVD compared to moderate CSVD, and all BPV indices were significantly higher except NSBP-SD and NSBP-CV.

We found that the relationship between BPV-related indicators and VEGF concentration is not linear, but still holds significant importance. In patients with mild CSVD, cerebral ischemia and hypoxia are relatively mild and of shorter duration, leading to a slight overexpression of VEGF induced by hypoxia. The mildly elevated VEGF has a limited effect on BPV, with only minor increases in multiple BPV-related indicators. In patients with moderate CSVD, cerebral ischemia and hypoxia are significantly more severe, resulting in a marked increase in VEGF production. Higher VEGF concentrations can effectively regulate BPV and significantly reduce several BPV-related indicators, thereby mitigating the impact of BPV elevation on CSVD. However, in severe CSVD patients, cerebral ischemia and hypoxia are so pronounced that endothelial cells are extensively damaged. The homeostasis of adult vessels requires autocrine VEGF, and paracrine VEGF cannot compensate for the loss of endothelial VEGF,⁴⁰ further impairing the secretion of endothelial VEGF in ischemic-hypoxic regions. Furthermore, in the early stages of the disease, endothelial progenitor cells in circulation are largely depleted, preventing sufficient replenishment of endothelial cells, which leads to insufficient VEGF production.⁴¹ Patients with mild CSVD have a lower degree of cerebral ischemia and hypoxia, resulting in a mild elevation of VEGF. This mild elevation in VEGF has a limited impact on BPV. Cerebral ischemia and hypoxia were notable in patients with moderate CSVD, which significantly promoted the production of VEGF, resulting in a significant increase in VEGF. Higher VEGF concentration can effectively regulate BPV and significantly reduce multiple indexes of BPV, thus reducing the influence of BPV increase on CSVD. In patients with severe CSVD, cerebral ischemia and hypoxia are already so severe that endothelial progenitor cells are severely depleted early in the disease, leading to insufficient VEGF production. This is why the VEGF levels found in this group were lower than those in the mild to moderate patient group. The relatively low VEGF concentrations seem to exert minimal influence on BPV, which remains significantly elevated. During this process, moderate upregulation of VEGF may regulate BPV in two ways: First, by activating the PI3K/Akt-eNOS signaling pathway, VEGF accelerates the regeneration and repair of damaged vascular endothelium, significantly improving endothelial-dependent vasodilation and restoring endothelial cell homeostasis. The recovery of endothelial function not only helps maintain physiological vascular tone but also reduces the levels of vasoconstrictive factors such as endothelin-1 (ET-1) and thromboxane A2 (TXA2) in circulation, thereby reducing endothelial-originated blood pressure oscillations. Second, VEGF may reduce sympathetic reflex excitation induced by ischemia by improving vascular function and local blood flow, ultimately achieving a reduction in short-term blood pressure fluctuations. Although VEGF plays a critical role in promoting angiogenesis, and our study has found a certain correlation between VEGF levels and blood pressure variability (BPV) in patients with type I cerebral small vessel disease (CSVD), VEGF holds promise as a potential therapeutic target for slowing the progression of CSVD. Despite extensive research into VEGF's role in angiogenesis, its clinical application remains in the experimental stage. Clinical trials involving coronary VEGF infusion in patients with myocardial ischemia have failed to demonstrate significant efficacy over placebo,⁴² a result that has notably impacted the clinical prospects of VEGF in regenerative medicine. Our findings may provide a new perspective to explain this phenomenon and further propel the clinical application of VEGF.

In this study, we observed that serum VEGF levels were significantly elevated in patients with mild and moderate CSVD. Additional VEGF supplementation did not appear to yield substantial improvements in disease progression. Therefore, future research may need to focus on patients with severe CSVD, exploring exogenous VEGF supplementation as a new therapeutic strategy. By reducing BPV and delaying the progression of CSVD, this strategy holds promise for further validating the role of VEGF in CSVD and its potential impact on BPV.

Limitation

There are several limitations to be addressed. Firstly, the assessment of CSVD disease severity was based only on the total CSVD burden scores, without quantifying individual imaging features such as the number of LI, the volume and location of WMH, the location and number of CMB. Because these characteristics may not have the same effect on overall severity, patients with the same total CSVD burden score may exhibit different true severity. Secondly, the sample size of this study is relatively small. Thirdly, this study did not conduct longitudinal follow-up of VEGF levels and BPV in the enrolled patients, preventing us from determining the temporal relationship between changes in BPV and serum VEGF concentrations.

Conclusion

In patients with type I CSVD, average blood pressure levels and BPV are significantly positively correlated with overall imaging burden, with a stronger correlation observed for systolic BPV. In patients with mild to moderate type I CSVD, serum VEGF levels are also significantly positively correlated with overall imaging burden. VEGF concentration was significantly and positively correlated with indicators of systolic BPV. VEGF may be associated with the impact of BPV on patients with CSVD and thus potentially related to somewhat delay of the progression of disease.

Data Sharing Statement

Data are available on reasonable request. Study data are available on reasonable request to the corresponding author.

Ethics Approval and Consent to Participate

This study was conducted per the Declaration of Helsinki and was approved by the Ethics Committee of PLA General Hospital (Approval Number: HZKY-PJ-2020-44). Informed consent was obtained from all patients upon admission.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*. 2014;83(14):1228–1234. doi:10.1212/WNL.0000000000000837
2. Litak J, Mazurek M, Kulesza B, et al. Cerebral small vessel disease. *Int J Mol Sci*. 2020;21(24).
3. Hilal S, Mok V, Youn YC, Wong A, Ikram MK, Chen CL. Prevalence, risk factors and consequences of cerebral small vessel diseases: data from three Asian countries. *J Neurol Neurosurg*. 2017;88(8):669–674. doi:10.1136/jnnp-2016-315324
4. Parati G, Bilo G, Kollias A, et al. Blood pressure variability: methodological aspects, clinical relevance and practical indications for management - a European society of hypertension position paper ? *J Hypertens*. 2023;41(4):527–544. doi:10.1097/HJH.0000000000003363
5. Ma Y, Song A, Viswanathan A, et al. Blood pressure variability and cerebral small vessel disease: a systematic review and meta-analysis of population-based cohorts. *Stroke*. 2020;51(1):82–89. doi:10.1161/STROKEAHA.119.026739
6. Cuspidi C, Carugo S, Tadic M. Blood pressure variability and target organ damage regression in hypertension. *J Clin Hypertension*. 2021;23(6):1159–1161. doi:10.1111/jch.14208
7. 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(10). doi:10.1161/JAHA.117.006895
8. Quick S, Moss J, Rajani RM, Williams A. A vessel for change: endothelial dysfunction in cerebral small vessel disease. *Trends Neurosci*. 2021;44(4):289–305. doi:10.1016/j.tins.2020.11.003
9. Shahriar S, Biswas S, Zhao K, et al. VEGF-A-mediated venous endothelial cell proliferation results in neoangiogenesis during neuroinflammation. *Nat Neurosci*. 2024;27(10):1904–1917. doi:10.1038/s41593-024-01746-9
10. Pérez-Gutiérrez L, Ferrara N. Biology and therapeutic targeting of vascular endothelial growth factor A. *Nat Rev Mol Cell Biol*. 2023;24(11):816–834. doi:10.1038/s41580-023-00631-w
11. Simons M, Gordon E, Claesson-Welsh L. Mechanisms and regulation of endothelial VEGF receptor signalling. (1471-0080 (Electronic)).
12. Liu YP, Sekin H, Izci Y, Du Z, Yan Y, Bakaya MK. Neuroprotective effects of mesenchymal stem cells derived from human embryonic stem cells in transient focal cerebral ischemia in rats. (1559-7016 (Electronic)).

13. Diaz KM, Veerabhadrapa P, Kashem MA, et al. Visit-to-visit and 24-h blood pressure variability: association with endothelial and smooth muscle function in African Americans. *J Hum Hypertens.* 2013;27(11):671–677. doi:10.1038/jhh.2013.33
14. Schillaci G, Bilo G, Pucci G, et al. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension.* 2012;60(2):369–377. doi:10.1161/HYPERTENSIONAHA.112.197491
15. Kario K, Shin J, Chen C-H, et al. Expert panel consensus recommendations for ambulatory blood pressure monitoring in Asia: the HOPE Asia Network. *J Clin Hypertens.* 2019;21(9):1250–1283. doi:10.1111/jch.13652
16. Boggia J, Li Y, Thijs L, et al. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet.* 2007;370(9594):1219–1229. doi:10.1016/S0140-6736(07)61538-4
17. Hansen TW, Thijs L, Li Y, et al. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension.* 2010;55(4):1049–1057. doi:10.1161/HYPERTENSIONAHA.109.140798
18. Shim YA-O, Shin HE. Impact of the ambulatory blood pressure monitoring profile on cognitive and imaging findings of cerebral small-vessel disease in older adults with cognitive complaints. (1476-5527 (Electronic)).
19. Xu Y, Gong C, Liao J, et al. Absence of fluctuation and inverted circadian rhythm of blood pressure increase the risk of cognitive dysfunction in cerebral small vessel disease patients. Impact of the ambulatory blood pressure monitoring profile on cognitive and imaging findings of cerebral small-vessel disease in older adults with cognitive complaints. (1471-2377 (Electronic)).
20. Filomena J, Riba-Llena I, Vinyoles E, et al. Short-term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension. *Hypertension.* 2015;66(3):634–640. [discussion 445]. doi:10.1161/HYPERTENSIONAHA.115.05440
21. Kim BJ, Kwon SU, Park JM, et al. Blood pressure variability is associated with white matter lesion growth in intracranial atherosclerosis. *Am J Hypertens.* 2019;32(9):918–924. doi:10.1093/ajh/hpz068
22. Ma Y, Yilmaz P, Bos D, et al. Blood pressure variation and subclinical brain disease. *J Am College Cardiol.* 2020;75(19):2387–2399. doi:10.1016/j.jacc.2020.03.043
23. van Middelaar T, Richard E, Moll van Charante EP, van Gool WA, van Dalen JW. Visit-to-visit blood pressure variability and progression of white matter hyperintensities among older people with hypertension. *J Am Med Directors Assoc.* 2019;20(9):1175–1177.e1171. doi:10.1016/j.jamda.2019.04.003
24. Liu W, Liu R, Sun W, et al. Different impacts of blood pressure variability on the progression of cerebral microbleeds and white matter lesions. *Stroke.* 2012;43(11):2916–2922. doi:10.1161/STROKEAHA.112.658369
25. Fan Y, Hou C, Peng L, Gao X, Xu Y. Twenty-four-hour ambulatory blood pressure variability associated with cerebral small vessel disease MRI burden and its progression in inpatients with cerebrovascular disease. *Front Neurol.* 2020;11:513067. doi:10.3389/fneur.2020.513067
26. de Heus RAA, Reumers SFI, van der Have A, Tumelaire M, Tully PJ, Claassen J. Day-to-Day home blood pressure variability is associated with cerebral small vessel disease burden in a memory clinic population. *J Alzheimer's Dis.* 2020;74(2):463–472. doi:10.3233/JAD-191134
27. Eto M, Toba K, Akishita M, et al. Reduced endothelial vasomotor function and enhanced neointimal formation after vascular injury in a rat model of blood pressure lability. *Hypertension Res.* 2003;26(12):991–998. doi:10.1291/hypres.26.991
28. Abbott NJ, Rønnbeck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci.* 2006;7(1):41–53. doi:10.1038/nrn1824
29. Wardlaw JM. Blood-brain barrier and cerebral small vessel disease. *J Neurol Sci.* 2010;299(1–2):66–71. doi:10.1016/j.jns.2010.08.042
30. Mitchell GF, van Buchem MA, Sigurdsson S, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the age, gene/environment susceptibility-Reykjavik study. *Brain.* 2011;134(Pt 11):3398–3407. doi:10.1093/brain/awr253
31. Yan T, Yu JR, Zhang YP, Li T. Analysis on correlation of white matter lesion and lacunar infarction with vascular cognitive impairment. *Int J Clin Exp Med.* 2015;8(8):14119–14122.
32. van Sloten TT, Protogerou AD, Henry RM, Schram MT, Launer LJ, Stehouwer CD. Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2015;53:121–130. doi:10.1016/j.neubiorev.2015.03.011
33. Poels MM, Zaccal K, Verwoert GC, et al. Arterial stiffness and cerebral small vessel disease: the Rotterdam Scan Study. *Stroke.* 2012;43(10):2637–2642. doi:10.1161/STROKEAHA.111.642264
34. Tsao CW, Seshadri S, Beiser AS, et al. Relations of arterial stiffness and endothelial function to brain aging in the community. *Neurology.* 2013;81(11):984–991. doi:10.1212/WNL.0b013e3182a43e1c
35. Gruber T, Pan C, Contreras RE, et al. Obesity-associated hyperleptinemia alters the gliovascular interface of the hypothalamus to promote hypertension. *Cell Metab.* 2021;33(6):1155–1170.e10. doi:10.1016/j.cmet.2021.04.007
36. Arba F, Giannini A, Piccardi B, et al. Small vessel disease and biomarkers of endothelial dysfunction after ischaemic stroke. *Eur Stroke J.* 2019;4(2):119–126. doi:10.1177/2396987318805905
37. Kapoor A, Gaubert A, Marshall A, et al. Increased levels of circulating angiogenic cells and signaling proteins in older adults with cerebral small vessel disease. *Front Aging Neurosci.* 2021;13:711784. doi:10.3389/fnagi.2021.711784
38. Tayler H, Miners JS, Güzel O, MacLachlan R, Love S. Mediators of cerebral hypoperfusion and blood-brain barrier leakiness in Alzheimer's disease, vascular dementia and mixed dementia. *Brain Pathol.* 2021;31(4):e12935. doi:10.1111/bpa.12935
39. Dobrynina LA, Zabitova MR, Shabalina AA, et al. MRI types of cerebral small vessel disease and circulating markers of vascular wall damage. *Diagnostics.* 2020;10(6).
40. Lee S, Chen TT, Barber CL, et al. Autocrine VEGF signaling is required for vascular homeostasis. *Cell.* 2007;130(4):691–703. doi:10.1016/j.cell.2007.06.054
41. Iadecola C. The pathobiology of vascular dementia. *Neuron.* 2013;80(4):844–866. doi:10.1016/j.neuron.2013.10.008
42. Kabrun N, Bühring HJ, Choi K, Ullrich A, Risau W, Keller G. Flk-1 expression defines a population of early embryonic hematopoietic precursors. *Development.* 1997;124(10):2039–2048. doi:10.1242/dev.124.10.2039

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