The Relationship Between Heart Rate Variability and the Cerebral Distribution of Enlarged Perivascular Spaces (Postprint)

Authors: Zhou Dongyang, Chen Jing, Lu Chang, Bai Hongying

Date: 2022-09-13T00:00:00+00:00

Abstract

Background Enlarged perivascular spaces (EPVS) are closely associated with cognitive dysfunction, affective disorders, stroke, and poor post-stroke outcomes. Early detection and management are of utmost importance.

Objective To investigate the relationship between heart rate variability (HRV) and the cerebral distribution of EPVS.

Methods Patients hospitalized in the Department of Neurology at the Second Affiliated Hospital of Zhengzhou University between 2020 and 2022 who completed 24-hour ambulatory electrocardiogram monitoring and brain magnetic resonance imaging (MRI) were enrolled as study subjects for analysis. EPVS burden was assessed in patients. Based on EPVS scores, the severity of basal ganglia EPVS (BG-EPVS) and centrum semiovale EPVS (CS-EPVS) were categorized into groups. BG-EPVS was divided into 3 groups: mild group (Potter score 1, 126 cases), moderate group (Potter score 2, 46 cases), and severe group (Potter score 3-4, 27 cases). CS-EPVS was divided into 3 groups: mild group (Potter score 1, 131 cases), moderate group (Potter score 2, 45 cases), and severe group (Potter score 3-4, 23 cases). EPVS dominance patterns were classified based on the relative quantities of BG-EPVS and CS-EPVS: Pattern 1 = BG > CS (119 cases), Pattern 2 = BG = CS (20 cases), Pattern 3 = BG < CS (60 cases). General clinical characteristics and HRV parameters were compared among groups.

Results The age of the mild BG-EPVS group was lower than that of the severe BG-EPVS group ($P < 0.05$). The root mean square of successive differences between normal intervals in the target range (rMSSD) and total power (TP) in the severe BG-EPVS group were lower than those in the mild BG-EPVS group ($P < 0.05$). Multivariate logistic regression analysis after adjusting for

confounding factors showed that rMMSD was an independent influencing factor for BG-EPVS (P = 0.002), and rMMSD was an independent influencing factor for EPVS dominance patterns (P = 0.003). Spearman correlation analysis showed that rMMSD, TP, and the percentage of adjacent normal intervals >50ms (pNN50) among HRV parameters were negatively correlated with BG-EPVS severity (P < 0.05). The average standard deviation of normal intervals per 5 minutes in the target range (SDNN index) and rMMSD were positively correlated with EPVS dominance patterns (P < 0.05).

Conclusion Decreased rMMSD indicates autonomic nervous system imbalance, which may cause blood-brain barrier disruption or reduced clearance of metabolic waste in the brain, thereby participating in the pathophysiological mechanisms of BG-EPVS formation.

Full Text

Relationship Between Heart Rate Variability and Brain Distribution of Enlarged Perivascular Spaces

Authors: Zhou Dongyang, Chen Jing, Lu Chang, Bai Hongying*
Affiliation: Department of Neurology, the Second Affiliated Hospital of Zhengzhou University, Zhengzhou 450000, Henan Province, China
Corresponding Author: Bai Hongying, Professor, Chief Physician; E-mail: hybai@126.com

Abstract

Background: Enlarged perivascular spaces (EPVS) are closely associated with cognitive dysfunction, affective disorders, stroke, and adverse post-stroke outcomes, making early detection and management critically important. **Objective:** To investigate the relationship between heart rate variability (HRV) and the cerebral distribution of EPVS. **Methods:** We retrospectively analyzed patients hospitalized in the Department of Neurology at the Second Affiliated Hospital of Zhengzhou University between 2020 and 2022 who completed 24-hour ambulatory electrocardiogram monitoring and brain magnetic resonance imaging (MRI). EPVS burden was assessed, and the severity of basal ganglia EPVS (BG-EPVS) and centrum semiovale EPVS (CS-EPVS) was categorized based on EPVS scores. BG-EPVS was divided into three groups: mild (Potter score 1, n=126), moderate (Potter score 2, n=46), and severe (Potter score 3-4, n=27). CS-EPVS was similarly divided: mild (Potter score 1, n=131), moderate (Potter score 2, n=45), and severe (Potter score 3-4, n=23). EPVS dominance models were established based on the relative numbers of BG-EPVS and CS-EPVS: Model 1 = BG > CS (n=119), Model 2 = BG = CS (n=20), and Model 3 = BG < CS (n=60). General clinical data and HRV parameters were compared across groups. **Results:** The mild BG-EPVS group was younger than the severe BG-EPVS group (P < 0.05). The severe BG-EPVS group exhibited lower root mean square of successive differences of Normal-Normal intervals

(rMSSD) and total power (TP) compared to the mild BG-EPVS group ($P < 0.05$). After adjusting for confounders, multivariate logistic regression analysis revealed that rMSSD was an independent influencing factor for BG-EPVS ($P = 0.002$) and for the EPVS dominance model ($P = 0.003$). Spearman correlation analysis showed that rMSSD, TP, and percentage of adjacent NN intervals larger than 50 ms (PNN50) were negatively correlated with BG-EPVS severity ($P < 0.05$). SDNN index and rMSSD were positively correlated with the EPVS dominance model ($P < 0.05$). **Conclusion:** Decreased rMSSD indicates autonomic nervous system imbalance, which may lead to blood-brain barrier disruption or reduced clearance of metabolic waste in the brain, participating in the pathophysiological mechanisms underlying BG-EPVS formation.

Keywords: Enlarged perivascular space; Basal ganglia area; Heart rate variability; Cerebral small vessel disease; Autonomic nervous system

Introduction

With the acceleration of population aging and advances in magnetic resonance imaging (MRI) technology, enlarged perivascular spaces (EPVS) are being observed with increasing frequency [1]. Perivascular spaces are fluid-filled cavities surrounding penetrating arterioles and venules that serve as important drainage pathways for interstitial fluid and solutes in the brain. EPVS form when these spaces become enlarged due to various physiological and/or pathological factors [2]. Recent research has identified EPVS as an early imaging manifestation of cerebral small vessel disease (CSVD) [3], commonly appearing in the basal ganglia and centrum semiovale, though they can also be observed in the hippocampus and midbrain [4]. Studies have demonstrated that EPVS are closely associated with cognitive dysfunction [5-6], affective disorders [7-8], stroke [9], and adverse post-stroke outcomes [10]. However, the risk factors and pathogenesis of EPVS remain incompletely understood.

Recent investigations have revealed that heart rate variability (HRV) correlates with the risk of cerebrovascular events and their prognosis [11-12]. HRV, a non-invasive monitoring indicator, has become an important and widely recognized tool for assessing autonomic function. While studies have explored the relationship between HRV and CSVD markers such as lacunar infarcts and white matter hyperintensities (WMH) [13-14], the association between HRV and EPVS—a primary marker of CSVD—remains unclear. Previous research indicates that BG-EPVS is closely associated with other CSVD imaging features (e.g., WMH, lacunar infarcts) and is considered a marker of hypertension-related arteriopathy [15-16], whereas CS-EPVS is more prevalent in patients with cerebral amyloid angiopathy and correlates with lobar microbleeds and iron deposition [16-18]. These findings suggest that EPVS in different brain regions may have distinct origins. Since autonomic dysfunction can induce hemodynamic and blood pressure changes [19], we hypothesized that autonomic dysfunction would be more

strongly associated with BG-EPVS than CS-EPVS and would play a role in the dominance model where BG-EPVS burden exceeds CS-EPVS burden [16,20]. This study tests this hypothesis to further elucidate the pathogenesis of EPVS in different brain regions and provide a basis for prevention and treatment.

Methods

Study Participants

We conducted a retrospective analysis of patients hospitalized in the Department of Neurology at the Second Affiliated Hospital of Zhengzhou University between 2020 and 2022 who completed 24-hour ambulatory electrocardiogram monitoring. A total of 199 patients were ultimately included. All participants or their authorized representatives provided informed consent. The cohort comprised 105 males (52.8%) and 94 females (47.2%), with a mean age of 63.2 $\pm$ 11.6 years.

Inclusion criteria: (1) Age $\geq$ 35 years; (2) Underwent 3.0-T brain MRI; (3) Completed intracranial and extracranial vascular examinations (e.g., carotid ultrasound or transcranial Doppler).

Exclusion criteria: (1) Difficult EPVS assessment; (2) Vascular examination indicating >50% stenosis of intracranial and/or extracranial large vessels; (3) MRI evidence of previous or acute cerebrovascular disease (e.g., ischemic infarction >20 mm in diameter, intracerebral hemorrhage, or subarachnoid hemorrhage); (4) Diagnosed neurodegenerative diseases such as Parkinson' s disease or multiple system atrophy; (5) Pacemaker implantation and/or severe cardiac conditions (e.g., cardiomyopathy, heart failure, myocardial infarction, arrhythmia) that could affect HRV; (6) Abnormal body temperature or infection; (7) Use of medications affecting autonomic function prior to HRV monitoring, such as β-blockers, calcium channel blockers, statins, or atropine.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (approval number: 2022193).

Data Collection

General Clinical Data This retrospective clinical analysis collected baseline data including sex, age, smoking history, alcohol consumption history, and medical history of hypertension and diabetes. Laboratory examination indicators were also collected: homocysteine, small dense low-density lipoprotein, triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein.

HRV Parameter Analysis All participants underwent long-term HRV monitoring (>18 hours) using a 12-lead ambulatory electrocardiograph recorder (DMS300-4A, DMS). HRV data were collected and reviewed by a cardiologist

who was blinded to MRI data and clinical information. During monitoring, patients were advised to avoid activities that could interfere with HRV, such as smoking, alcohol consumption, and strong emotional fluctuations. HRV parameters included:

Frequency domain: Low frequency power (LF), high frequency power (HF), total power (TP), and LF/HF ratio.
Time domain: Standard deviation of Normal-Normal intervals (SDNN), root mean square of successive differences of NN intervals for period of interest (rMSSD), standard deviation of the mean of NN intervals every 5 minutes for period of interest (SDANN), percentage of adjacent NN intervals larger than 50 ms (PNN50), and average of NN intervals standard deviation every 5 minutes for period of interest (SDNN index).

Brain Imaging Evaluation and Grouping Brain MRI was performed on a 3.0-T scanner (Siemens Skyra, Germany). The severity of EPVS in different brain regions was assessed independently by two radiologists, with consensus reached through discussion in cases of disagreement.

EPVS identification: EPVS were identified primarily using axial T1-weighted, T2-weighted, and FLAIR sequences. Characteristic features include: alignment with vascular course; linear, round, or oval shape; signal intensity matching cerebrospinal fluid; hyperintensity on T2-weighted imaging without surrounding hyperintensity on FLAIR; hypointensity on T1-weighted and FLAIR sequences; no contrast enhancement or mass effect; clear and smooth boundaries; diameter <3 mm.

EPVS quantification: The validated Potter visual semi-quantitative assessment method [9] was applied to each hemisphere, with the higher score used for analysis. For both BG-EPVS and CS-EPVS, the scoring system was: 1 point = 1-10 EPVS, 2 points = 11-20 EPVS, 3 points = 21-40 EPVS, and 4 points = >40 EPVS. Based on these scores, BG-EPVS was categorized into three groups: mild (score 1, n=126), moderate (score 2, n=46), and severe (scores 3-4, n=27). CS-EPVS was similarly categorized: mild (score 1, n=131), moderate (score 2, n=45), and severe (scores 3-4, n=23). EPVS dominance models were established based on the relative quantities of BG-EPVS and CS-EPVS [16,20]: Model 1 = BG > CS (n=119), Model 2 = BG = CS (n=20), and Model 3 = BG < CS (n=60).

Statistical Analysis Categorical variables are expressed as percentages and compared between groups using the ^{2} test. Continuous, normally distributed data are presented as mean ± standard deviation (± s), while non-parametric data are described as median (interquartile range) [M(QR)]. For continuous variables, one-way ANOVA or Kruskal-Wallis H test was used for multi-group comparisons, with SNK-q test for pairwise comparisons. HRV indicators showing statistical significance in univariate analysis were subjected to multivariate logistic regression analysis to identify independent influencing factors of EPVS

severity and dominance models, adjusting for confounders such as age, sex, hypertension history, diabetes history, smoking history, and alcohol consumption history. Spearman correlation analysis was used to explore the relationship between HRV parameters and EPVS. Statistical analysis was performed using SPSS software version 26.0, with statistical significance set at $P < 0.05$.

Results

Comparison of General Data and HRV Parameters Across EPVS Severity Groups

BG-EPVS: Age differed significantly among the three groups, with the mild BG-EPVS group being younger than the severe BG-EPVS group ($P < 0.05$). Significant differences were observed in rMSSD and TP among the three BG-EPVS groups ($P < 0.05$), with the severe BG-EPVS group showing lower rMSSD and TP compared to the mild group ($P < 0.05$). No significant differences were found in SDNN, SDANN index, SDNN index, PNN50, LF, HF, or LF/HF ratio among the three BG-EPVS groups ($P > 0.05$).

CS-EPVS: Low-density lipoprotein levels differed among the three CS-EPVS groups, with the mild CS-EPVS group showing lower levels than the moderate CS-EPVS group ($P < 0.05$). Smoking history also differed significantly among the three CS-EPVS groups ($P < 0.05$). No significant differences were observed in SDNN, SDANN index, SDNN index, rMSSD, PNN50, TP, LF, HF, or LF/HF ratio among the three CS-EPVS groups ($P > 0.05$). No significant differences were found between BG-EPVS and CS-EPVS groups in terms of sex, hypertension history, diabetes history, alcohol consumption history, or laboratory indicators except low-density lipoprotein ($P > 0.05$). Detailed results are presented in Table 1 .

Relationship Between HRV and EPVS

Multivariate logistic regression analysis was performed on HRV indicators showing statistical significance in univariate analysis (Table 1). Independent variables (rMSSD and TP) were entered as continuous values, while the dependent variable (BG-EPVS severity) was coded as: mild BG-EPVS = 1, moderate BG-EPVS = 2, severe BG-EPVS = 3, with the mild BG-EPVS group serving as the reference. After adjusting for confounders including age, sex, hypertension history, diabetes history, smoking history, and alcohol consumption history, the results indicated that rMSSD was an independent influencing factor for BG-EPVS severity ($P = 0.002$) (Table 2).

Spearman correlation analysis revealed that rMSSD, PNN50, and TP were negatively correlated with BG-EPVS severity ($P < 0.05$) (Table 3).

Comparison of General Data, HRV Parameters, and EPVS Severity Across Dominance Models

No significant differences were observed among the three EPVS dominance models in terms of sex, age, hypertension history, diabetes history, smoking history, alcohol consumption history, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, small dense low-density lipoprotein, homocysteine, SDNN, SDANN index, PNN50, TP, LF, or HF ($P > 0.05$). However, significant differences were found in SDNN index, rMSSD, LF/HF ratio, BG-EPVS severity, and CS-EPVS severity among the three models ($P < 0.05$). Specifically, Model 1 (BG > CS) showed a trend toward lower rMSSD compared to Model 2 (BG = CS) and Model 3 (BG < CS) ($P < 0.05$). Detailed results are presented in Table 4 .

Relationship Between HRV and EPVS Dominance Models

Multivariate logistic regression analysis was conducted on HRV indicators showing statistical significance in univariate analysis (Table 4). Independent variables (SDNN index, rMSSD, and LF/HF) were entered as continuous values, while the dependent variable (EPVS dominance model) was coded as: Model 1 = 1, Model 2 = 2, Model 3 = 3, with Model 1 serving as the reference. After adjusting for confounders including age, sex, hypertension history, diabetes history, smoking history, and alcohol consumption history, the results showed that rMSSD was an independent influencing factor for the three dominance models ($P = 0.003$) (Table 5).

Spearman correlation analysis demonstrated that SDNN index and rMSSD were positively correlated with the EPVS dominance model ($P < 0.05$) (Table 6).

Discussion

EPVS represents an early imaging marker of CSVD and is considered a potential indicator of brain aging [3,21]. The underlying mechanisms remain largely unknown, though recent research has begun to explore the relationship between autonomic function and CSVD. HRV data obtained from ambulatory electrocardiogram monitoring, which reflects autonomic function, has shown that reduced HRV is associated with WMH and total CSVD burden [13,22]. Cross-sectional studies suggest that EPVS in different brain regions may have distinct risk factors: age, lacunar infarcts, and WMH show significant correlations with BG-EPVS, while CS-EPVS formation may be related to tau protein deposition [16-17,23]. Investigating the relationship between HRV and EPVS severity/distribution in different brain regions is therefore meaningful for elucidating EPVS pathogenesis and providing a theoretical basis for early detection and prevention.

Using long-term ambulatory electrocardiography, we analyzed the relationship

between HRV and BG-EPVS/CS-EPVS severity as well as EPVS distribution dominance models. Multivariate logistic regression analysis revealed that after adjusting for confounders, rMSSD was an independent influencing factor for both BG-EPVS severity and the EPVS dominance model. Spearman correlation analysis showed that rMSSD, PNN50, and TP were negatively correlated with BG-EPVS severity, while SDNN index and rMSSD were positively correlated with the EPVS dominance model—meaning that lower SDNN index and rMSSD levels were associated with relatively greater BG-EPVS burden compared to CS-EPVS burden. SDNN index and TP reflect overall autonomic activity, while PNN50 and rMSSD reflect parasympathetic activity [24]. These findings suggest that BG-EPVS severity is associated with decreased parasympathetic activity and a higher likelihood of BG-EPVS burden exceeding CS-EPVS burden.

Our results align with Moon et al.' s study, which examined the relationship between HRV and CSVD in patients with obstructive sleep apnea and found a significant correlation between reduced HRV and CSVD occurrence and progression [25]. Another study analyzing HRV and total CSVD burden scores in patients over 60 with obstructive sleep apnea reported a significant negative correlation between nocturnal HRV and CSVD burden [13]. Additionally, a two-sample Mendelian randomization analysis reported that reduced HRV was associated with increased CSVD risk [14], providing further theoretical support for our findings. However, these results contrast with Yamaguchi et al.' s community-based study using ambulatory blood pressure monitoring, which found that elevated HRV was a risk factor for CSVD progression in elderly individuals [26], and another longitudinal community study that failed to find an association between HRV and WMH [27]. These discrepancies may be attributable to differences in HRV measurement methods or monitoring periods.

The mechanisms linking autonomic dysfunction, particularly reduced parasympathetic activity, to EPVS development remain unclear but may involve several pathways:

1. **Hemodynamic alterations:** Reduced parasympathetic activity leads to sympathetic-parasympathetic imbalance, causing cardiac dysfunction and abnormalities in blood pressure, heart rate, and hemodynamics [19]. Clearance of metabolic waste from perivascular spaces depends on microvascular pulsation; changes in blood pressure or hemodynamics can alter microvascular amplitude, reducing net flow in perivascular spaces and decreasing metabolic waste clearance, potentially leading to EPVS formation [28-29].
2. **Cerebrovascular dysregulation:** The autonomic nervous system regulates cardiac output and cerebral capillary diameter to maintain stable cerebral blood flow [30-31]. When autonomic function is impaired, cerebrovascular autoregulation may be compromised, potentially causing global cerebral hypoperfusion. The basal ganglia region lacks collateral vascular anastomoses, making it particularly vulnerable to local ischemia and hypoxia, which can trigger oxidative stress, activate inflammatory cascades, and disrupt blood-brain barrier integrity, leading to glial and

neuronal damage [32]. Additionally, increased sympathetic activity or decreased parasympathetic activity is associated with increased vascular wall pulsation, which may exert mechanical stress on endothelial cells and cause endothelial dysfunction [33], potentially loosening the blood-brain barrier and allowing metabolic waste and small proteins to leak into perivascular spaces. If not cleared promptly, this may promote EPVS formation—a key pathogenic process in CSVD [34]. Recent research showing that BG-EPVS, but not CS-EPVS, is associated with impaired blood-brain barrier integrity [23] may explain why reduced HRV correlates with BG-EPVS severity but not CS-EPVS.

3. **Neuroinflammatory mechanisms:** Reduced vagal activity decreases the activity of the central cholinergic anti-inflammatory system [37-38], leading to increased inflammatory cytokines, vascular endothelial damage, and neurovascular unit injury with blood-brain barrier abnormalities [39-40]. This creates a vicious cycle of endothelial injury, blood-brain barrier impairment, and intravascular substance leakage/accumulation, promoting EPVS progression. Given the complex interactions among autonomic dysfunction, inflammation, and vascular endothelial system impairment, multiple mechanisms likely contribute synergistically to EPVS development.

The relationship between reduced HRV and cerebrovascular disease is not yet fully elucidated. Some observational studies suggest that cerebrovascular lesions may directly cause autonomic dysfunction [41-42].

This study has several limitations. Our cohort was limited to hospitalized patients, which may introduce selection bias and requires caution when generalizing findings to community populations. The cross-sectional design precludes determination of causality, necessitating future large-scale longitudinal studies to explore the causal relationship between HRV and EPVS. Additionally, HRV monitoring was conducted during hospitalization, which may not reflect HRV in daily life.

In conclusion, decreased rMSSD is an independent influencing factor for increased BG-EPVS burden and the BG > CS-EPVS dominance model, suggesting that autonomic dysfunction may participate in the pathophysiological mechanisms of BG-EPVS development. These findings provide theoretical support for exploring early biomarkers of EPVS. Patients with altered HRV but without overt autonomic dysfunction symptoms may benefit from early intervention to slow EPVS emergence or progression.

Author Contributions

Zhou Dongyang designed the study, collected and organized case data, performed statistical analysis, and drafted the manuscript. Chen Jing participated

in study design and provided financial support. Lu Chang assisted with data collection and organization. Bai Hongying supervised and led the overall planning and execution of the research activities.

References

[1] Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration[J]. Lancet Neurol, 2013, 12(8):822-838. DOI: 10.1016/S1474-4422(13)70124-8.

[2] Caunca MR, De Leon-Benedetti A, Latour L, et al. Neuroimaging of Cerebral Small Vessel Disease and Age-Related Cognitive Changes[J]. Front Aging Neurosci, 2019, 11:145. DOI: 10.3389/fnagi.2019.00145.

[3] Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging[J]. Lancet Neurol, 2013, 12(5):483-497. DOI: 10.1016/S1474-4422(13)70060-7.

[4] Chen X, Wang J, Shan Y, et al. Cerebral small vessel disease: neuroimaging markers and clinical implication[J]. J Neurol, 2019, 266(10):2347-2362. DOI: 10.1007/s00415-018-9077-3.

[5] Jie W, Lin G, Liu Z, et al. The Relationship Between Enlarged Perivascular Spaces and Cognitive Function: A Meta-Analysis of Observational Studies[J]. Front Pharmacol, 2020, 11:715. DOI: 10.3389/fphar.2020.00715.

[6] Paradise M, Crawford JD, Lam B, et al. Association of Dilated Perivascular Spaces With Cognitive Decline and Incident Dementia[J]. Neurology, 2021, 96(11):e1501-e1511. DOI:10.1212/WNL.0000000000011537.

[7] Shi Y, Xiang Y, Yang Y, et al. Depression after minor stroke: Prevalence and predictors[J]. J Psychosom Res, 2015, 79(2):143-147. DOI: 10.1016/j.jpsychores.2015.03.012.

[8] Zhang Y, Wang C, Sun C, et al. Neural complexity in patients with poststroke depression: A resting EEG study[J]. J Affect Disord, 2015, 188:310-318. DOI: 10.1016/j.jad.2015.09.017.

[9] Potter GM, Doubal FN, Jackson CA, et al. Enlarged perivascular spaces and cerebral small vessel disease[J]. Int J Stroke, 2015, 10(3):376-381. DOI: 10.1111/ijs.12054.

[10] Boulouis G, Charidimou A, Pasi M, et al. Hemorrhage recurrence risk factors in cerebral amyloid angiopathy: Comparative analysis of the overall small vessel disease severity score versus individual neuroimaging markers[J]. J Neurol Sci, 2017, 380:64-67. DOI: 10.1016/j.jns.2017.07.015.

[11] Sluyter JD, Camargo CA Jr, Lowe A, et al. Pulse rate variability predicts atrial fibrillation and cerebrovascular events in a large, population-based cohort[J]. Int J Cardiol, 2019, 275:83-88. DOI: 10.1016/j.ijcard.2018.10.026.

[12] Tang S, Xiong L, Fan Y, et al. Stroke Outcome Prediction by Blood Pressure Variability, Heart Rate Variability, and Baroreflex Sensitivity[J]. Stroke, 2020, 51(4):1317-1320. DOI: 10.1161/STROKEAHA.119.027981.

[13] Del Brutto OH, Mera RM, Costa AF, et al. Effect of Heart Rate Variability on the Association Between the Apnea-Hypopnea Index and Cerebral Small Vessel Disease[J]. Stroke, 2019, 50(9):2486-2491. DOI: 10.1161/STROKEAHA.119.026095.

[14] Tian D, Zhang L, Zhuang Z, et al. A two-sample Mendelian randomization analysis of heart rate variability and cerebral small vessel disease[J]. J Clin Hypertens (Greenwich), 2021, 23(8):1608-1614. DOI: 10.1111/jch.14316.

[15] Yakusiji Y, Charidimou A, Hara M, et al. Topography and associations of perivascular spaces in healthy adults: the Kashima scan study[J]. Neurology, 2014, 83(23):2116-2123. DOI: 10.1212/WNL.0000000000001054.

[16] Charidimou A, Boulouis G, Pasi M, et al. MRI-visible perivascular spaces in cerebral amyloid angiopathy and hypertensive arteriopathy[J]. Neurology, 2017, 88(12):1157-1164. DOI: 10.1212/WNL.0000000000003746.

[17] Lau KK, Li L, Lovelock CE, et al. Clinical Correlates, Ethnic Differences, and Prognostic Implications of Perivascular Spaces in Transient Ischemic Attack and Ischemic Stroke[J]. Stroke, 2017, 48(6):1470-1477. DOI: 10.1161/STROKEAHA.117.016694.

[18] Charidimou A, Jaunmuktane Z, Baron JC, et al. White matter perivascular spaces: an MRI marker in pathology-proven cerebral amyloid angiopathy?[J]. Neurology, 2014, 82(1):57-62. DOI: 10.1212/01.wnl.0000438225.02729.04.

[19] Bai M, Yuan ZM, Zhang P. Relationship between increased heart rate and autonomic function in hypertensive patients[J]. Journal of Clinical Electrocardiology, 2021, 30(5):356-358. DOI: 10.3969/j.issn.1005-0272.2021.05.011.

[20] Huo Y, Huang S, Li R, et al. Elevated hemoglobin is independently associated with enlarged perivascular spaces in the central semiovale[J]. Sci Rep, 2021, 11(1):2820. DOI: 10.1038/s41598-021-82327-9.

[21] Groeschel S, Chong WK, Surtees R, et al. Virchow-Robin spaces on magnetic resonance images: normative data, their dilatation, and a review of the literature[J]. Neuroradiology, 2006, 48(10):745-754. DOI: 10.1007/s00234-006-0112-1.

[22] Del Brutto OH, Mera RM, Peñaherrera E. The role of nighttime heart rate variability to detect white matter hyperintensities of presumed vascular origin in community-dwelling older adults[J]. Int J Stroke, 2018, 13(9):NP22-NP23. DOI: 10.1177/1747493018806172.

[23] Wang ML, Yu MM, Wei XE, et al. Association of enlarged perivascular spaces with Aβ and tau deposition in cognitively normal older population[J]. Neurobiol Aging, 2021, 100:32-38. DOI: 10.1016/j.neurobiolaging.2020.12.014.

[24] Tarvainen MP, Niskanen JP, Lipponen JA, et al. Kubios HRV–heart rate variability analysis software[J]. Comput Methods Programs Biomed, 2014, 113(1):210-220. DOI: 10.1016/j.cmpb.2013.07.024.

[25] Moon J, Choi KH, Park JH, et al. Sympathetic Overactivity Based on Heart-Rate Variability in Patients with Obstructive Sleep Apnea and Cerebral Small-Vessel Disease[J]. J Clin Neurol, 2018, 14(3):310-319. DOI: 10.3988/jcn.2018.14.3.310.

[26] Yamaguchi Y, Wada M, Sato H, et al. Impact of nocturnal heart rate variability on cerebral small-vessel disease progression: a longitudinal study in community-dwelling elderly Japanese[J]. Hypertens Res, 2015, 38(8):564-569. DOI: 10.1038/hr.2015.38.

[27] Nakanishi K, Jin Z, Homma S, et al. Association Between Heart Rate and Subclinical Cerebrovascular Disease in the Elderly[J]. Stroke, 2018, 49(2):319-324. DOI: 10.1161/STROKEAHA.117.019355.

[28] Kwee RM, Kwee TC. Virchow-Robin spaces at MR imaging[J]. Radiographics, 2007, 27(4):1071-1086. DOI: 10.1148/rg.274065722.

[29] Mestre H, Tithof J, Du T, et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension[J]. Nat Commun, 2018, 9(1):4878. DOI: 10.1038/s41467-018-07318-3.

[30] Peppiatt CM, Howarth C, Mobbs P, et al. Bidirectional control of CNS capillary diameter by pericytes[J]. Nature, 2006, 443(7112):700-704. DOI: 10.1038/nature05193.

[31] Krueger M, Bechmann I. CNS pericytes: concepts, misconceptions, and a way out[J]. Glia, 2010, 58(1):1-10. DOI: 10.1002/glia.20898.

[32] Chen HL, Lu CH, Lin HC, et al. White matter damage and systemic inflammation in obstructive sleep apnea[J]. Sleep, 2015, 38(3):361-370. DOI: 10.5665/sleep.4490.

[33] Tessier A, Sibon I, Poli M, et al. Resting Heart Rate Predicts Depression and Cognition Early after Ischemic Stroke: A Pilot Study[J]. J Stroke Cerebrovasc Dis, 2017, 26(10):2435-2441. DOI: 10.1016/j.jstrokecerebrovasdis.2017.05.040.

[34] Li Y, Li M, Zhang X, et al. Higher blood-brain barrier permeability is associated with higher white matter hyperintensities burden[J]. J Neurol, 2017, 264(7):1474-1481. DOI: 10.1007/s00415-017-8550-8.

[35] Zhang X, Ding L, Yang L, et al. Brain Atrophy Correlates with Severe Enlarged Perivascular Spaces in Basal Ganglia among Lacunar Stroke Patients[J]. PLoS One, 2016, 11(2):e0149593. DOI: 10.1371/journal.pone.0149593.

[36] Ma Y, Yilmaz P, Bos D, et al. Blood Pressure Variation and Subclinical Brain Disease[J]. J Am Coll Cardiol, 2020, 75(19):2387-2399. DOI: 10.1016/j.jacc.2020.03.043.

[37] Parada E, Egea J, Buendia I, et al. The microglial $ $7-acetylcholine nicotinic receptor is a key element in promoting neuroprotection by inducing heme oxygenase-1 via nuclear factor erythroid-2-related factor 2[J]. Antioxid Redox Signal, 2013, 19(11):1135-1148. DOI: 10.1089/ars.2012.4671.

[38] Revathikumar P, Bergqvist F, Gopalakrishnan S, et al. Immunomodulatory effects of nicotine on interleukin 1β activated human astrocytes and the role of cyclooxygenase 2 in the underlying mechanism[J]. J Neuroinflammation, 2016, 13(1):256. DOI: 10.1186/s12974-016-0725-2.

[39] Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier[J]. Nat Rev Neurosci, 2006, 7(1):41-53. DOI: 10.1038/nrn1824.

[40] Li Q, Yang Y, Reis C, et al. Cerebral Small Vessel Disease[J]. Cell Transplant, 2018, 27(12):1711-1722. DOI: 10.1177/0963689718795148.

[41] Dorrance AM, Fink G. Effects of Stroke on the Autonomic Nervous System[J]. Compr Physiol, 2015, 5(3):1241-1263. DOI: 10.1002/cphy.c140016.

[42] Constantinescu V, Arsenescu-Georgescu C, Matei D, et al. Heart rate variability analysis and cardiac dysautonomia in ischemic stroke patients[J]. Clin Neurol Neurosurg, 2019, 186:105528. DOI: 10.1016/j.clineuro.2019.105528.

Note: Figure translations are in progress. See original paper for figures.