Neuropsychiatric Disease and Treatment

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

The Roles of Heart Rate Variability in Cerebral Stroke

Huijun Wang[1,*], Jiayao Jiang[2,*], Guochao Zhou[3,*], Yelei Zhang[1]

[1]Department of Neurosurgery, Xishan People's Hospital of Wuxi City, Wuxi Branch of Zhongda Hospital Southeast University, Wuxi, People's Republic of China; [2]Department of Orthopedics, The 904th Hospital of the Joint Logistics Support Force of the PLA, Wuxi, Jiangsu Province, People's Republic of China; [3]Department of Orthopedics, The Army 947th Hospital, Kashgar, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yelei Zhang, Department of Neurosurgery, Xishan People's Hospital of Wuxi City, Wuxi Branch of Zhongda Hospital Southeast University, Wuxi, People's Republic of China, Email zhangyelei2019@163.com

Abstract: Heart rate variability (HRV), as a safe and noninvasive marker of autonomic activity, is becoming a prescreening tool for the prediction of cardiovascular complications such as myocardial infarction and heart failure after cerebral stroke. With good reproducibility and quantitative assessment of autonomic nervous system function, the association of some HRV parameters with neurological functional prognosis and stroke recurrence has been widely reported. However, current studies on the relationship between HRV and the clinical outcomes of stroke remain controversial. Previous studies on HRV have mainly focused on stroke prognosis or its role as a clinical biomarker, whereas other roles have rarely been explored. In this article, we review recent advances in the role of HRV in cerebral stroke according to current progress. Specifically, we summarized the role of HRV in the outcomes, complications, treatments, and mechanisms of stroke, based on the latest research. Further, in-depth implications of HRV in stroke are discussed.

Keywords: heart rate variability, cerebral stroke, acute ischemic stroke, autonomic nervous system, outcome

Introduction

Recently, crosstalk between the brain and the heart has received much attention.[1] A complex neural network, including certain higher cortical and subcortical forebrain areas regulates the activity and function of the heart.[2] Hypothalamic function is affected by acute brain injury due to cerebral ischemia, hypoxia, and increased intracranial pressure, leading to dysfunction of the autonomic nervous system (ANS) of the heart, and subsequently affecting the cardiac conduction system, resulting in arrhythmia. Sudden cardiac death can occur in severe cases. ANS function has been proven to be a predictive factor of death in patients with myocardial infarction and heart failure.[3] In critically ill patients, it may be caused by adverse reactions in the body, leading to prolonged activation of the sympathetic nervous system and an imbalance in the sympathetic and parasympathetic nerve outputs. Studies of patients with brain injuries have reported similar findings regarding ANS dysfunction.[4,5] Given that various neural anatomical regions controlled by the ANS are susceptible to damage from trauma, stroke, bleeding, and inflammatory processes, autonomic dysfunction as a potential marker of disease severity or predictor of neurological deterioration is particularly important in the treatment of critical neurological illnesses. Therefore, quantitative physiological modeling of ANS function may be a promising and under-utilized tool in critical neurological care.

Heart rate variability (HRV) refers to the time variation between successive cardiac cycles during sinus rhythm and offers insight into the functioning of ANS.[6] It is considered a noninvasive electrocardiographic detection technique with good reproducibility and quantitative assessment of ANS function. HRV derived from ECG waveforms has been used to evaluate cardiac autonomic function related to neurological disorders.[7] Autonomic dysfunction is a potential complication after acute brain injury, such as stroke, in which HRV may undergo quantitative changes. Research has shown that

Received: 2 January 2025
Accepted: 12 May 2025
Published: 16 May 2025

HRV is the preferred method for evaluating autonomic dysfunction in critically ill patients owing to its simplicity, noninvasiveness, and speed.[8] However, there is currently a lack of large-scale clinical evidence to confirm the diagnostic and prognostic value of HRV in stroke patients. This review summarizes the latest progress in HRV measurements in patients with cerebral stroke. We emphasize the clinical value of measuring HRV and discuss future application scenarios.

HRV Measurements

Commonly used HRV analysis methods in clinical practice include linear and non-linear analyses. Linear methods mainly include time- and frequency-domain analyses. Non-linear analysis methods include scatter plots, non-linear predictions, and parameter estimation. In the routine clinical evaluation of HRV, time-domain analysis and frequency-domain analysis are the most widely used methods, where certain indicators have become independent risk factors for cardiovascular events.[9] Time-domain analysis is a statistical analysis of the 24-hour RR interval. The indicators of time-domain analysis mainly include the standard deviation of beat-to-beat intervals (SDNN), standard deviation of the average sinus RR interval every 5 min (SDANN), mean of the standard deviations of successive 5-min RR intervals over 24 h(SDNN index), root mean square of the difference (rMSSD) between all adjacent sinus RR intervals within 24 h, number of heartbeats with a difference of more than 50 ms between all adjacent RR intervals within 24 h (NN50), and percentage of NN50 to all sinus heartbeats (pNN50).[10] SDNN mainly reflects the overall HRV of the body. SDANN reflects changes in sympathetic nervous system function, and its value is negatively correlated with the sympathetic nervous system activity. A decrease in the SDANN value indicates an increase in the sympathetic nervous system activity. The rMSSD and pNN50 reflect changes in vagus nerve function, and their values are positively correlated with vagus nerve activity. A decrease in rMSSD and pNN50 values indicated a decrease in vagus nerve activity. The frequency-domain analysis method is another analysis method converts the interval between heartbeats into a spectrum, and calculates the power spectral density. The parameters involved in the frequency-domain analysis method mainly include the low-frequency power (LF), high-frequency power (HF), and LF/HF values. In the range of 0.15–0.50 hz (HF), the parasympathetic nervous system has a more significant regulation of heart rate. In the range of 0.04–0.15 hz (LF), HRV is jointly regulated by the sympathetic nervous system and the parasympathetic nervous system. HF mainly reflects the activity of the vagus nerve, whereas LF is regulated by both the vagus and sympathetic nerves but mainly reflects the activity of the sympathetic nervous system. The LF/HF ratio reflects the balance between the sympathetic and parasympathetic in the body.[11] Initially, linear methods such as time-domain analysis and frequency-domain analysis were heavily employed for its calculation, but the last decade has seen a steady rise in non-linear approaches using methods from chaos theory and fractal analysis,[12] especially with the progress of machine learning and data processing algorithms. It is important to note that these methodologies for HRV have some limitations, particularly regarding their complexity and the potential for misinterpretation in clinical settings, such as first pass effect for endovascular treatment in large vessel occlusion stroke,[13] presence of early ischemic changes involving cortical areas,[14] clot features along with patients' clinical features.[15]

The Role of HRV in the Outcomes of Ischemic Stroke

The relationship between HRV and neurological function in patients with ischemic stroke was also explored (Table 1). Aftyka et al[16] retrospectively investigated whether HRV could predict favorable or unfavorable stroke outcomes. Prolonged hospitalization was also considered. The study included 59 patients with acute ischemic stroke (AIS), with unfavorable outcomes in 22 patients. Night HRV was analyzed using nocturnal ECG recordings from 10 p.m. to 6 a.m. data from 24 h Holter ECG during hospitalization. They employed an original and innovative non-linear measure to analyze HRV, which was based on symbolic dynamics consisting of comparing the "length of the longest words". The modified Rankin scale (mRS) score was assessed at 3 months follow-up. The results showed that the non-linear, symbolic method for HRV analysis could be a predictor of prolonged hospitalization and an increased risk of clinical progression in AIS. Recently, Wu et al[17] performed frequency-domain analysis of HRV, including TP, LF, HF, LF/HF ratio, and LF%. A time-domain HRV parameter, mean RR, was also used. A comparison of HRV parameters and 3-month behavioral functional outcomes in 58 patients showed that RR was significantly correlated with other variables. A decreased mean RR may result in unfavorable outcomes in patients with ischemic stroke. Further, using univariate and multivariable

Table 1 Recent Studies on the Relationship of HRV and Cerebral Stroke

Author, (Year)	Population	Study Design	HRV Measurement	Outcomes Evaluation	Results
Wang et al[18] (2024)	191 patients with mechanical thrombectomy treated after acute ischemic stroke • 58.6% male • Mean age 65.5 years • 51 (26.7%) died at 3-month follow-up	Retrospective cohort study	The initial 72 h of hourly heart rate information after MT therapy was acquired. HRV using 2 statistical methodologies, ie SD and CV were calculated.	All-cause mortality at 3-month. Change in mRS score at 14-day and 3-month	Increased mean heart rate per 10-bpm, heart rate SD and CV per 5-unit were all associated with the increased risk of mortality
Wu MJ et al[17] (2024)	58 patients with ischemic stroke • 56.9% male • Mean age 70 years	Prospective cohort study	The frequency-domain HRV parameters included TP, LF, HF, LF/HF ratio, and LF%. A time-domain HRV parameter, the RR mean was also examined.	The behavioral functional outcome was represented by a mRS score at 3-month.	The median of RR mean, alongside specific clinical factors and neurological function at admission, may serve as potential prognostic indicators for 3-month outcome in ischemic stroke.
Dimova V et al[19] (2024)	42 acute stroke patients. • 16 women • Mean age 66 years 20 matched controls. • 10 women • Mean age 60.7 years	Prospective study	HRV was assessed at rest, in a supine position and individual breathing rhythmus for 5 min. The VC, RMSSD, LF, and HF, frequency bands were used.	Acute stroke lesions were marked on diffusion-weighted images employing MRIcroN and co-registered to a T1-weighted structural volume-dataset.	The results suggest that HRV alteration after acute stroke might be due to affecting resting-state brain networks.
Nelde A et al[20] (2024)	1755 stroke patients with 96 SAP. • 960 males • Mean age 73.8 years	Retrospective cohort study	HRV parameters were SDNN, RMSSD, LF, HF, LF/HF.	Based on HRV and other large-scale clinical data warehouses to predict SAP using automated machine learning.	HRV along with HR and blood pressure metrics during the first 48 h after admission exhibited distinct differences between patients with SAP diagnosis and those without.
Filchenko I et al[21] (2023)	359 acute ischemic stroke patients with 20% developed a future CCVE. • 129 females • Mean age 67.1 years	Prospective longitudinal observational cohort study	HRV-parameters were represented in 3 main domains: the time domain was represented by rrHRV, SDNN, SDSD, TI, RMSSD, and pNN50. The frequency domain was represented by nuLf power, nuHF power, nuLF/nuHf ratio, LF power, HF power and VLF power. Lastly, non-linear measurements were represented by SD1 and SD2 from Poincaré plots, SD1/SD2 ratio, DFA1, DFA2 and ApEn.	The main outcome of the study was a composite of fatal and non-fatal future CCVE that included ischemic or hemorrhagic stroke, transient ischemic attack, myocardial infarction, unplanned hospitalization for unstable angina or heart failure and urgent revascularization.	High blood pressure variability, high nocturnal HRV and endothelial function contribute to the risk for future CCVE after stroke.
Qu Y et al[22] (2023)	466 patients with acute stroke, of which 224 underwent IVT (48.1%), and 242 did not (51.9%) • IVT group:182 male, mean age 57.95 years • Non-IVT group: 210 male, mean age 57.41 years.	Prospectively study.	In the time domain, the RMSSD was analyzed. In the frequency domain, LF, HF, TP were analyzed.	A modified Rankin scale score ≥2 at 90 days was defined as an unfavorable outcome.	Lower HRV values at 1 to 3 and 7 to 10 days after stroke were independently associated with unfavorable outcomes in patients with acute ischemic stroke after IVT, and addition of heart rate variability parameters to conventional risk factors significantly improved the predictive ability of 3-month unfavorable outcomes.
Qu Y et al[23] (2023)	122 patients with ICH and 122 age- and sex-matched volunteers were included. • 90 male • Mean age 54.7 years	Prospective study	Time domain (SDNN, CV) and frequency domain (TP, VLF, LF, HF, LF%, HF%, LF/HF) indices were calculated.	A modified Rankin Scale score ≥ 3 at 3 months was defined as a poor outcome.	The time domain and absolute frequency domain HRV parameters (total power, LF, and HF) in the ICH group were significantly decreased within 7 days and 10–14 days. And LF% and HF% measured at 10–14 days were independently associated with 3-month outcomes.

(*Continued*)

Table 1 (Continued).

Author, (Year)	Population	Study Design	HRV Measurement	Outcomes Evaluation	Results
Tian Y et al[24] (2023)	4676 acute ischemic stroke patients.	A multicenter prospective observational clinical cohort study.	HRVs were generated from ECG recordings in participants who received 24-h Holter monitoring within 7 days of hospitalization. Two most commonly time-domain HRV indicators were used including SDNN and RMSSD.	All neuroimaging markers of CSVD, including WMH, EPVS, lacunes, CMBs, and BA, were analyzed according to a 3.0 Tesla MRI.	Decreased HRV parameters, including RMSSD and SDNN, were partly associated with the presence, severity, and imaging markers of CSVD.
Tian Y et al[25] (2023)	A total of 5743 participants • 3316 males • Mean age 62.0 years	A prospective multiple - centers study.	HRV parameters were SDNN, a time-domain HRV parameter, calculated by the standard deviation of all normal N–N intervals (R-R intervals) over 24 h in milliseconds (ms).	The primary outcome was recurrent stroke (including recurrent ischemic stroke and recurrent hemorrhagic stroke) at 1-year follow-up.	The combination of HRV and ABCD2 score might efficiently stratify the risk of 1-year recurrent stroke After MS/TIA. Moreover, lower SDNN was independently related to recurrent stroke in patients with MS/TIA, Especially for those with low-to-moderate traditional vascular risk factors.
Aftyka J et al[16] (2023)	59 patients with AIS • 58% were females • Mean age 65.6 ± 13.2 years	Retrospective study	Night HRV was analyzed from the nocturnal ECG recordings from 10 p.m. to 6 a.m data from 24 h Holter ECG during hospitalization. They employed an original and innovative non-linear measure was to analyze HRV, which was based on symbolic dynamics consisting of comparing the "length of the longest words".	The mRS score was assessed for 3 months follow-up.	Results showed the non-linear, symbolic method for HRV analysis could be as a predictor of prolonged hospitalization and increased risk of clinical progression in AIS.
Nelde A et al[12] (2023)	287 stroke patients • 45.6% female • Mean age 74.5 years	Retrospectively observational cohort study	HR was calculated as the number of beats per minute. Five HRV measures were considered in this study: SDNN, RMSSD, LF, HF, and LF/HF.	The short-term unfavorable functional outcome after stroke indicated through mRS score of > 2 at discharge.	The examined HRV parameters were not associated with the outcomes after stroke at discharge.
Von Rennenberg R et al[26] (2021)	308 patients with AIS • 37% female • Median age 69 years	Prospective study	HRV parameters were assessed during the in-hospital stay using a 10-min section of each patient's ECG recording at day and nighttime, calculating time and frequency domain HRV parameters.	Endpoint of recurrent stroke, myocardial infarction or death of any cause and the respective individual events were assessed 12 months after the index stroke. Patients' functional outcome was measured by mRS at 12 months.	HRV did not predict recurrent vascular events or functional outcome in patients with AIS.

Abbreviations: AIS, acute ischemic stroke; CCVE, cerebro-cardiovascular events; CV, coefficient of variation; CSVD, cerebral small vessel disease; HF, high frequency; ICH, intracerebral hemorrhage; IVT (intravenous thrombolysis); LF, low frequency; mRS, modified Rankin Scale; RMSSD (root mean square of successive differences); SAP, stroke-associated pneumonia; SD, standard deviation; TP, total power.

logistic regression analyses, they concluded that the median RR mean, alongside hemoglobin concentration and neurological function at admission, may serve as potential indicators for functional outcome in ischemic stroke. The study was limited by a short follow-up of 3-month. The sensitivity and specificity of potential predictive factors should be investigated to determine their clinical value.

In contrast, some researchers have reported that the HRV parameters examined were not associated with outcomes after stroke at discharge.[12] This observational cohort study included 287 stroke patients. Five HRV measures were considered: SDNN, RMSSD, LF, HF, and LF/HF ratio. The results showed no significant differences between the groups. Another study has reported similar results. In a study of 308 patients with AIS,[26] HRV parameters were assessed during the in-hospital stay using a 10-min section of ECG recordings at day and night, including time and frequency domain

 https://doi.org/10.2147/NDT.S515306

parameters. The endpoints of recurrent stroke, death, and mRS scores were assessed at 12 months after the index stroke. These results suggest that HRV does not predict recurrent vascular events or functional outcomes in patients with AIS. This could be because of its unstable nature, which is easily influenced by many immutable factors in acute clinical settings, such as cardioactive drugs, circadian rhythm, and physical activity levels.

The Role of HRV in the Treatments of Ischemic Stroke

According to these guidelines,[27] mechanical thrombectomy (MT) is usually recommended for patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO). However, changes in the heat rate after MT may not have drawn attention. Wang et al[27] explored the effect of heart rate on poor outcomes in patients with stroke treated with intra-arterial thrombectomy. In a 191 population with 51 (26.7%) deaths at the 3-month follow-up, they found that increased mean heart rate per 10-bpm, heart rate standard deviation (SD), and coefficient of variation (CV) per 5-unit were all associated with an increased risk of mortality. However, HRV was calculated using two statistical methodologies, SD and CV, from the initial 72h electrocardiograph monitor. Moreover, R-R interval analysis of heart rate was not conducted, which included fewer parameters than most HRV analysis. Recently. A retrospective multicenter study suggested that patients with minor stroke due to M2 occlusion and atrial fibrillation should be closely monitored for possible worsening during BMM and, in this case, promptly considered for rMT.[28] Therefore, HRV monitoring may serve as a simple and convenient monitoring method. Intravenous thrombolysis (IVT) is an essential treatment modality for AIS. However, the relationship between HRV and the clinical outcomes in patients undergoing IVT remains unclear. Qu et al[22] prospectively recruited 466 patients, of which 224 underwent IVT (48.1%) and 242 did not (51.9%). HRV values were measured 1–3 and 7–10 days after stroke using time-domain and frequency-domain analyses. An mRS score ≥2 at 90 days was considered an unfavorable outcome. All HRV parameters, including RMSSD, TP, LF, and HF power, were found to decrease significantly 7–10 days after stroke compared with those measured 1–3 days after stroke in the IVT and non-IVT groups. Lower HRV parameters after stroke were independently associated with unfavorable outcomes in patients with AIS after IVT. This study showed that IVT positively affected HRV at different time points in patients with AIS. However, the longer duration (>10 days after stroke) of HRV alterations after discharge remains unknown.

The Role of HRV in the Complications of Ischemic Stroke

In addition to neurological function assessment using the mRS score, cerebral small vessel disease (CSVD) on MRI could also be explored for its relationship with HRV in stroke patients. Tian et al[24] have investigated the effects of HRV on cerebral small vessel disease. Based on 4676 participants from the Third China National Stroke Registry (CNSR-III) study, the results showed that decreased HRV parameters, including RMSSD and SDNN, were partly associated with the presence, severity, and imaging markers of CSVD. These findings suggest that ANS intervention may be a novel therapeutic target for CSVD in stroke patients. Tian et al[25] also explored the role of HRV in the risk of recurrent strokes. Combined with the traditional ABCD2 score, they found that the HRV parameter (SDNN) might efficiently stratify the risk of 1-year recurrent stroke after an acute minor stroke (MS) or transient ischemic attack (TIA). Moreover, a lower SDNN was independently associated with recurrent stroke in patients with MS/TIA, particularly in those with low-to-moderate traditional vascular risk factors. These two studies demonstrated the value of HRV in predicting the prognosis of stroke and its potential to become a target for intervention.

The incidence of cerebrovascular events (CCVE) is high in patients with ischemic stroke, with 6.2% being affected by recurrent CCVE within one year.[29] Therefore, identifying predictive factors is important for guiding these populations. Filchenko et al[21] analyzed 359 patients diagnosed with AIS or transient ischemic attack. In this analysis, 20% of the patients developed future CCVE. Cardiovascular parameters such as blood pressure, nocturnal heart rate, diurnal heart rate, endothelial function, and arterial stiffness were assessed. Using multivariate Cox regression analysis, they concluded that high blood pressure variability, high nocturnal HRV, and endothelial function prognosis could be associated with CCVE risk. According to previous research, patients with stroke should be carefully monitored using HRV analysis to avoid CCVE.

Stroke-associated pneumonia (SAP) is a common complication in patients with stroke that can lead to poor outcomes. HRV, as a processed data indicator of heart rate and a component of vital signs, can also be evaluated for the occurrence

https://doi.org/10.2147/NDT.S515306

of SAP. Nelde et al[20] used multimodal and ANS parameters (HRV) with machine learning to predict clinically apparent stroke-associated pneumonia in A development and testing study. In 1755 stroke patients with 96 SAP, HRV along with HR and blood pressure metrics during the first 48 h after admission exhibited distinct differences between patients with and without SAP. Whether altered HRV biomarkers could serve as potential targets for preventive measures is worth considering. Modulation of HRV to mitigate the risk of SAP would be of interest in future research.

The Role of HRV in Hemorrhagic Stroke

ANS dysfunction after spontaneous intracerebral hemorrhage (ICH) is closely associated with patient prognosis. Paroxysmal sympathetic hyperactivity is a serious ANS dysfunction characterized by a cluster of symptoms and abnormal vital signs, and has been demonstrated to lead to poor outcomes in ICH.[30] The relationship between HRV and the clinical outcomes of ICH has also been reported.[23] This prospective study included 122 patients with ICH and 122 age- and sex-matched volunteers. The analysis showed that the time domain and absolute frequency domain HRV parameters (TP, LF, and HF) in the ICH group significantly decreased within 7 and 10–14 days. LF% and HF% measured at 10–14 days were independently associated with 3-month outcomes. The hematomas of patients with ICH included in this study were distributed in different locations, such as the basal ganglia, thalamus, lobar, brainstem, and cerebellum, which could affect ANS function to varying degrees. Therefore, more reasonable screening criteria could lead to more valuable results.

The Role of HRV in the Mechanisms of Stroke

HRV is affected by AIS; however, its underlying mechanisms are poorly understood. Dimova et al[19] explored the underlying mechanisms by which AIS influences resting HRV from the perspective of brain connectivity. They investigated 42 patients with acute stroke and recruited 20 healthy volunteers as the matched controls. Resting HRV was recorded for 5 min using ECG electrodes (FAN, Schwarzer, Germany) attached to the extremities. VC and RMSSD were calculated as the time-domain parameters. The low-frequency (LF) and high-frequency (HF) frequency bands of the R-R intervals (RRI) were analyzed. Structural MRI and resting-state functional MRI (rs-fMRI) were performed. LF and VC levels are frequently reduced in patients with stroke. Altered HRV parameters, such as HF power, reflect increased vagal modulation and have been verified to be correlated with higher gain values of cerebral autoregulation in AIS patients.[31] A higher vagal modulation was also associated with a later large infarct volume. Thus, understanding the mechanisms of ANS interface with cerebrovascular control and larger infarcts can be useful as novel therapeutic targets.

Using independent component analysis (ICA), they revealed one covarying lesion pattern for the LF and a similar pattern for the VC, predominantly affecting the right hemisphere. Activity in brain areas corresponding to these lesions mainly affects limbic and salience ventral attention networks in the group with reduced LF power, but affects control and default mode networks in the group with physiological LF power. These results suggest that HRV alterations after acute stroke may affect resting-state brain networks. This study provides brain connectivity networks as an important tool for elucidating the mechanisms by which AIS influences resting HRV, which would be instructive. However, additional samples and standard statistical analyses are required to verify their relevance.

The cortical dynamic cerebral autoregulation impairment (dCA) after stroke could be a dysfunction of ANS regulation of cerebral perfusion. Patients with vertebrobasilar artery ischemia (VBI) usually suffer from CBF (cortical cerebral blood flow) disturbances and are frequently accompanied by ANS disturbance.[32] However, it is uncertain whether the ANS contributes to cortical CBF disturbances following stroke. Lakatos et al[33] assessed whether vertebro-basilar artery ischemia (VBI) affects CBF regulation by using blood pressure and HRV analysis. HRV spectral analysis revealed distinct HRV spectral peaks in patients with VBI compared with controls. The control group exhibited a strong peak around 0.11 hz that was absent in the VBI. This implies that the mechanism responsible for the 0.11 hz peak of the Mayer wave in controls (possibly sympathetic and/or myogenic) is suppressed in patients with VBI. The HRV spectra of the patients exhibit a strong peak around 0.36 hz, implying that the mechanism responsible for this peak in the VBI patients may be due to a dysregulated vagal tone caused by the ischemic stroke. Thus, patients with VBI and dCA impairments exhibit signs of both sympathetic and parasympathetic dysregulation. The contribution of ANS failure induced by infarction can be speculated.

In general, the mechanisms underlying the relationship between HRV and stroke outcomes may due to heart–brain interactions,[34] which are governed by the central autonomic network (CAN). This neural regulatory system integrates prefrontal cortical regions (anterior cingulate, insular, orbitofrontal, and ventromedial cortices), limbic structures (central amygdala, hypothalamus), and brainstem nuclei (periaqueductal gray, nucleus tractus solitarius, nucleus ambiguus, ventrolateral/ventromedial medulla) to coordinate emotional, cognitive, and autonomic responses. Operating as an integrative control hub, the CAN enables adaptive cardiovascular regulation through three primary mechanisms: visceromotor pathways modulating parasympathetic (PNS) and sympathetic (SNS) outflow, neuroendocrine signaling, and behavioral adaptations.

Central to this regulatory process is the prefrontal cortex, which exerts top-down control over the PNS via its executive and emotional processing functions. Enhanced prefrontal activity promotes PNS dominance, evidenced by increased HRV, while diminished cortical engagement heightens SNS activity.[35,36] This bidirectional relationship underpins the established association between elevated HRV and improved health outcomes, reflecting the cardiovascular system's sensitivity to integrated neural regulation of stress adaptation and homeostasis maintenance.

Future Prospects

Studies on the relationship between HRV and clinical outcomes of stroke remain controversial. However, some issues must be addressed for practical applications. First, the optimal method of HRV measurement is still a topic of debate, and which HRV indices are most appropriate in various stroke patient populations needs to be confirmed. In future research, it will be necessary to control for variables such as age and sex to avoid selective bias. Secondly, HRV has been validated as an effective biomarker for assessing ANS function and stroke prognosis. Therefore, the development of precise wearable portable equipment for HRV analysis can guide clinical management and self-monitoring. Third, more animal experiments and clinical trials, including neuroimaging, neuropathology, and molecular testing, are required to elucidate the relationship between HRV and neurological function. Finally, large-scale randomized controlled clinical studies are needed to clarify the clinical value of HRV in stroke patients.

The role of HRV in stroke patients cannot be limited to clinical prognosis assessments. For example, in stroke patients undergoing motor imagery, action observation, and action execution interventions, RMSSD as an HRV parameter has been demonstrated to be significantly different[37], given that motor imagery, action observation, and action execution represent major paradigms of brain-computer interfaces (BCIs) to control the movement of objects for stroke recovery,[38,39] ANS function evaluated by HRV could help determine whether patients actually engage in imagery during the task. Therefore, HRV may contribute to the successful execution of novel experimental paradigms for BCIs. Vagus nerve stimulation is an emerging, safe, and effective treatment for improving long-term moderate-to-severe arm impairment after ischemic stroke.[40] However, the underlying mechanism remains unclear. Some believe that this could be related to ANS rebalancing. However, Meng et al[41] found that there was no significant difference in HRV analysis between patients with stroke who underwent transcutaneous auricular vagus nerve stimulation and those who did not. Despite the controversial results of limited studies, the noninvasive characteristic of HRV could be used for the implication of vagus nerve stimulation in stroke rehabilitation.

Conclusions

HRV as an excellent non-invasive electrocardiographic method with superior reproducibility, enables quantitative assessment of ANS function. Notably, alterations in HRV parameters have demonstrated significant predictive value for functional recovery outcomes in post-stroke patients. Although the underlying mechanisms require further investigation, HRV monitoring has emerged as a valuable clinical tool for evaluating disease progression, informing diagnostic strategies, and guiding therapeutic interventions in stroke management.

Funding

This work was supported by grants from the Scientific Research Program of the Wuxi Health Commission (no. Q202209) to Yelei Zhang.

Disclosure

The authors declare that they have no conflicts of interest.

References

1. Jammal Salameh L, Bitzenhofer SH, Hanganu-Opatz IL, Dutschmann M, Egger V. Blood pressure pulsations modulate central neuronal activity via mechanosensitive ion channels. *Science*. 2024;383(6682):eadk8511. In eng. doi:10.1126/science.adk8511
2. Bo W, Cai M, Ma Y, et al. Manipulation of glutamatergic neuronal activity in the primary motor cortex regulates cardiac function in normal and myocardial infarction mice. *Adv Sci*. 2024;11(20):e2305581. In eng. doi:10.1002/advs.202305581
3. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation*. 1998;98(15):1510–1516. In eng. doi:10.1161/01.cir.98.15.1510
4. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol*. 2017;16(12):987–1048. In eng. doi:10.1016/s1474-4422(17)30371-x
5. Valenza G, Toschi N, Barbieri R. Uncovering brain-heart information through advanced signal and image processing. *Philos Trans a Math Phys Eng Sci*. 2016;374(2067). In eng. doi:10.1098/rsta.2016.0020
6. Ouahiba E-M, Darya M, Alexander B, et al. The effect of stress-reducing interventions on heart rate variability in cardiovascular disease: a systematic review and meta-analysis. *Life*. 2024;14(6). doi:10.3390/life14060749
7. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. *Med Biol Eng Comput*. 2006;44 (12):1031–1051. In eng. doi:10.1007/s11517-006-0119-0
8. Toweill D, Sonnenthal K, Kimberly B, Lai S, Goldstein B. Linear and nonlinear analysis of hemodynamic signals during sepsis and septic shock. *Crit Care Med*. 2000;28(6):2051–2057. In eng. doi:10.1097/00003246-200006000-00063
9. Guan L, Wang Y, Claydon VE, et al. Autonomic parameter and stress profile predict secondary ischemic events after transient ischemic attack or minor stroke. *Stroke*. 2019;50(8):2007–2015. In eng. doi:10.1161/strokeaha.118.022844
10. C H, M MA, K Z. Power spectral analysis of heart rate variability in psychiatry. *Psychother Psychosom*. 1999;68(2). doi:10.1159/000012314
11. McCraty R, Shaffer F. Heart rate variability: new perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. *Glob Adv Health Med*. 2015;4(1):46–61. In eng. doi:10.7453/gahmj.2014.073
12. Nelde A, Klammer MG, Nolte CH, et al. Data lake-driven analytics identify nocturnal non-dipping of heart rate as predictor of unfavorable stroke outcome at discharge. *J Neurol*. 2023;270(8):3810–3820. In eng. doi:10.1007/s00415-023-11718-x
13. Radu RA, Costalat V, Fahed R, et al. First pass effect as an independent predictor of functional outcomes in medium vessel occlusions: an analysis of an international multicenter study. *Eur Stroke J*. 2024;9(1):114–123. In eng. doi:10.1177/23969873231208276
14. Alexandre AM, Monforte M, Brunetti V, et al. Baseline clinical and neuroradiological predictors of outcome in patients with large ischemic core undergoing mechanical thrombectomy: a retrospective multicenter study. *Int J Stroke*. 2024;19(7):779–788. In eng. doi:10.1177/17474930241245828
15. Pilato F, Valente I, Calandrelli R, et al. Clot evaluation and distal embolization risk during mechanical thrombectomy in anterior circulation stroke. *J Neurol Sci*. 2022;432:120087. In eng. doi:10.1016/j.jns.2021.120087
16. Aftyka J, Staszewski J, Dębiec A, Pogoda-Wesołowska A, Żebrowski J. Can HRV predict prolonged hospitalization and favorable or unfavorable short-term outcome in patients with acute ischemic stroke? *Life*. 2023;13(4):856. In eng. doi:10.3390/life13040856
17. Wu MJ, Dewi SRK, Hsu WT, et al. Exploring relationships of heart rate variability, neurological function, and clinical factors with mortality and behavioral functional outcome in patients with ischemic stroke. *Diagnostics*. 2024;14(12):1304. In eng. doi:10.3390/diagnostics14121304
18. Wang H, Xu L, Dong L, Li Y, Liu H, Xiao G. Effect of heart rate on poor outcome in stroke patients treated with intra-arterial thrombectomy. *BMC Neurol*. 2024;24(1):164. In eng. doi:10.1186/s12883-024-03662-8
19. Dimova V, Welte-Jzyk C, Kronfeld A, et al. Brain connectivity networks underlying resting heart rate variability in acute ischemic stroke. *Neuroimage Clin*. 2024;41:103558. In eng. doi:10.1016/j.nicl.2023.103558
20. Nelde A, Krumm L, Arafat S, et al. Machine learning using multimodal and autonomic nervous system parameters predicts clinically apparent stroke-associated pneumonia in a development and testing study. *J Neurol*. 2024;271(2):899–908. In eng. doi:10.1007/s00415-023-12031-3
21. Filchenko I, Mürner N, Dekkers MPJ, et al. Blood pressure variability, nocturnal heart rate variability and endothelial function predict recurrent cerebro-cardiovascular events following ischemic stroke. *Front Cardiovasc Med*. 2023;10:1288109. In eng. doi:10.3389/fcvm.2023.1288109
22. Qu Y, Sun YY, Abuduxukuer R, et al. Heart rate variability parameter changes in patients with acute ischemic stroke undergoing intravenous thrombolysis. *J Am Heart Assoc*. 2023;12(11):e028778. In eng. doi:10.1161/jaha.122.028778
23. Qu Y, Yang Y, Sun X, et al. Heart rate variability in patients with spontaneous intracerebral hemorrhage and its relationship with clinical outcomes. *Neurocrit Care*. 2024;40(1):282–291. In eng. doi:10.1007/s12028-023-01704-6
24. Tian Y, Yao D, Pan Y, et al. Implication of heart rate variability on cerebral small vessel disease: a potential therapeutic target. *CNS Neurosci Ther*. 2023;29(5):1379–1391. In eng. doi:10.1111/cns.14111
25. Tian Y, Pan Y, Wang M, et al. The combination of heart rate variability and ABCD(2) score portends adverse outcomes after minor stroke or transient ischemic attack. *J Neurol Sci*. 2023;445:120522. In eng. doi:10.1016/j.jns.2022.120522
26. von Rennenberg R, Krause T, Herm J, et al. Heart rate variability and recurrent stroke and myocardial infarction in patients with acute mild to moderate stroke. *Front Neurol*. 2021;12:772674. In eng. doi:10.3389/fneur.2021.772674
27. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart association/ American stroke association. *Stroke*. 2019;50(12):e344–e418. In eng. doi:10.1161/str.0000000000000211
28. Broccolini A, Brunetti V, Colò F, et al. Early neurological deterioration in patients with minor stroke due to isolated M2 occlusion undergoing medical management: a retrospective multicenter study. *J Neurointerv Surg*. 2023;16(1):38–44. In eng. doi:10.1136/jnis-2023-020118
29. Amarenco P, Lavallée PC, Labreuche J, et al. One-year risk of stroke after transient ischemic attack or minor stroke. *N Engl J Med*. 2016;374 (16):1533–1542. In eng. doi:10.1056/NEJMoa1412981

30. Li Z, Chen W, Zhu Y, et al. Risk factors and clinical features of paroxysmal sympathetic hyperactivity after spontaneous intracerebral hemorrhage. *Auton Neurosci*. 2020;225:102643. In eng. doi:10.1016/j.autneu.2020.102643
31. Castro P, Serrador J, Sorond F, Azevedo E, Rocha I. Sympathovagal imbalance in early ischemic stroke is linked to impaired cerebral autoregulation and increased infarct volumes. *Auton Neurosci*. 2022;241:102986. In eng. doi:10.1016/j.autneu.2022.102986
32. Wang R, Köhrmann M, Kollmar R, et al. Posterior circulation ischemic stroke not involving the brainstem is associated with cardiovascular autonomic dysfunction. *Eur J Neurol*. 2022;29(9):2690–2700. In eng. doi:10.1111/ene.15427
33. Lakatos LB, Shin DC, Müller M, Österreich M, Marmarelis V, Bolognese M. Impaired dynamic cerebral autoregulation measured in the middle cerebral artery in patients with vertebrobasilar ischemia is associated with autonomic failure. *J Stroke Cerebrovasc Dis*. 2024;33(1):107454. In eng. doi:10.1016/j.jstrokecerebrovasdis.2023.107454
34. Lee Y, Walsh RJ, Fong MWM, Sykora M, Doering MM, Wong AWK. Heart rate variability as a biomarker of functional outcomes in persons with acquired brain injury: systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2021;131:737–754. In eng. doi:10.1016/j.neubiorev.2021.10.004
35. Ernst G. Heart-rate variability-more than heart beats? *Front Public Health*. 2017;5:240. In eng. doi:10.3389/fpubh.2017.00240
36. Kemp AH, Quintana DS. The relationship between mental and physical health: insights from the study of heart rate variability. *Int J Psychophysiol*. 2013;89(3):288–296. In eng. doi:10.1016/j.ijpsycho.2013.06.018
37. Kiloatar H, Aydogdu Delibay A, Gokpinar HH. The effect of motor imagery and action observation on autonomic functions in patients with chronic stroke. *Top Stroke Rehabil*. 2024:1–10. In eng. doi:10.1080/10749357.2024.2322884
38. Rossi F, Savi F, Prestia A, Mongardi A, Demarchi D, Buccino G. Combining action observation treatment with a brain-computer interface system: perspectives on neurorehabilitation. *Sensors*. 2021;21(24). In eng. doi:10.3390/s21248504
39. Habashy AG, Azab AM, Eldawlatly S, Aly GM. Toward calibration-free motor imagery brain-computer interfaces: a VGG-based convolutional neural network and WGAN approach. *J Neural Eng*. 2024;21:046032. In eng. doi:10.1088/1741-2552/ad6598
40. Jesse D, Charles YL, Gerard EF, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet*. 2021;397(10284):1545–53.
41. Meng-Huan W, Yi-Xiu W, Min X, et al. Transcutaneous auricular vagus nerve stimulation with task-oriented training improves upper extremity function in patients with subacute stroke: a randomized clinical trial. *Front Neurosci*. 2024;18. doi:10.3389/fnins.2024.1346634