Heart Rate Variability in Patients with Acute Ischemic Stroke at Different Stages of Renal Dysfunction: A Cross-sectional Observational Study

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Abstract

Background: Renal function is associated with mortality and functional disabilities in stroke patients, and impaired autonomic function is common in stroke, but little is known regarding its effects on stroke patients with renal dysfunction. This study sought to evaluate the association between autonomic function and stroke in patients with renal dysfunction.

Methods: This study comprised 232 patients with acute ischemic stroke consecutively enrolled from February 2013 to November 2014 at Guangdong Provincial Hospital of Chinese Medicine in China. All patients recruited underwent laboratory evaluation and 24 h Holter electrocardiography (ECG). Autonomic function was measured based on the heart rate variability (HRV) using 24 h Holter ECG. Renal damage was assessed through the estimated glomerular filtration rate (eGFR), and stroke severity was rated according to the National Institutes of Health Stroke Scale (NIHSS). The Barthel index and modified Rankin score were also determined following admission. All the clinical covariates that could potentially affect autonomic outcome variables were adjusted with linear regression.

Results: In the patients with a mild or moderate decreased eGFR, the values for the standard deviation of the averaged normal-to-normal RR interval (SDANN) index ($P = 0.022$), very low frequency (VLF) ($P = 0.043$), low frequency (LF) ($P = 0.023$), and ratio of low-to-high frequency power (LF/HF) ($P = 0.001$) were significantly lower than those in the patients with a normal eGFR. A multinomial linear regression indicated that eGFR ($t = 2.47$, $P = 0.014$), gender ($t = -3.60$, $P < 0.001$), and a history of hypertension ($t = -2.65$, $P = 0.008$) were the risk factors of LF/HF; the NIHSS score (SDANN index: $t = -3.83$, $P < 0.001$; VLF: $t = -3.07$, $P = 0.002$; LF: $t = -2.79$, $P = 0.006$) and a history of diabetes (SDANN index: $t = -3.58$, $P < 0.001$; VLF: $t = -2.54$, $P = 0.012$; LF: $t = -2.87$, $P = 0.004$) were independent factors for the SDANN index, VLF, and LF; the Oxfordshire Community Stroke Project ($t = -2.38$, $P = 0.018$) was related to the SDANN index.

Conclusions: Autonomic dysfunction is aggravated with the progression of eGFR stage in patients with acute ischemic stroke; the eGFR is an independent factor of LF/HF in the adjusted models. Stroke severity and a history of diabetes are more significantly associated with HRV in patients with acute ischemic stroke at different stages of renal dysfunction.

Key words: Autonomic Function; Heart Rate Variability; Renal Dysfunction; Stroke

Introduction

Impaired autonomic function is a common complication strongly associated with the risk of an unfavorable outcome in patients with ischemic stroke.[1-3] A large of researches demonstrated that autonomic dysfunction differs according to the stroke stage,[4-6] ischemic location,[7,8] and ischemic subtype.[6,9] It occurs in the acute phase of ischemic stroke

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and even persists to 6 months afterward.[10] In patients with severe ischemic stroke, autonomic dysfunction particularly depresses the parasympathetic tone.[6,9-11] Researchers have found that autonomic function is also associated with other organ damage in stroke patients, such as carotid atherosclerosis and cardiovascular diseases.[12,13] Renal function is closely linked to all-cause mortality and functional disabilities in patients with stroke.[14-16] A severely decreased estimated glomerular filtration rate (eGFR) is a prognostic indicator of a poor outcome in stroke.[17] Heart rate variability (HRV) is a predictor of mortality in chronic kidney disease (CKD).[18] Therefore, the objective of this study was to investigate the independent relationships between renal dysfunction and HRV parameters reflecting autonomic imbalance in a large group of high-risk patients with acute stroke.

Methods

Patients and ethics

This cross-sectional study comprised 232 patients with acute ischemic stroke consecutively enrolled from February 2013 to November 2014 at Guangdong Province Hospital of Chinese Medicine, Guangzhou University of Chinese Medicine in China.

The study inclusion criteria were as follows: (1) age from 18 to 85 years and (2) computed tomography or magnetic resonance imaging findings indicating cerebral ischemic stroke. Ischemic stroke was diagnosed according to the established criteria.[19] The exclusion criteria were as follows: (1) myocardial infarction, coronary revascularization, and/or carotid stenting, (2) a history of cancer, liver failure, and (3) atrial fibrillation or frequent ectopic beats assessed by Holter monitor.

All patients recruited underwent a complete clinical examination, laboratory evaluation, and 24 h Holter electrocardiography (ECG) on the 1st day of hospitalization. The stroke severity of the patients was assessed according to the National Institutes of Health Stroke Scale (NIHSS)[20] and was categorized as mild (0–3), moderate (4–11), or severe (12–29).[21] Stroke subtype based on etiology was classified according to the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST):[22] (1) large-artery atherosclerosis, (2) cardioembolic stroke, (3) small-artery occlusion (lacunes), (4) stroke of other determined causes, and (5) stroke of undetermined cause. We districted the location of stroke into four classifications: (1) total anterior circulation infarcts, (2) partial anterior circulation infarcts, (3) lacunar infarcts, and (4) posterior circulation infarcts, using the Oxfordshire Community Stroke Project (OCSP) classification system.[23] The eGFR was determined using the CKD-Epidemiology Collaboration formula,[24] and CKD was assessed through the eGFR. Kidney involvement was quantified as follows:

1. Normal eGFR (eGFR $\geq$90 ml·min^{-1}·1.73 m^{-2})
2. Mildly decreased eGFR (60 $\leq$ eGFR <90 ml·min^{-1}·1.73 m^{-2})
3. Moderately decreased eGFR (eGFR <60 ml·min^{-1}·1.73 m^{-2}).

The autonomic function detected by HRV, which is defined as variations in the RR interval over time, assesses patients conveniently using a 24-h ambulatory ECG monitoring, which is a well-established tool for the establishment of autonomic function.

This study was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (No. B201515601). All participants signed the informed consent before enrollment.

Measurement of heart rate variability

ECG was recorded over 24 h using a 12-channel digital Holter recorder (DMS, DM Software Inc., Stateline, NV, USA). All patients underwent a 24-h ECG Holter recording 2–7 days after admission. The recorders were taking from 9 to 11 a.m., and the patients were asked to refrain from caffeine ingestion and perform usual daily activities during the investigations. The long-term HRV measurements that rely on nominal 24-h recordings were performed according to the international guidelines.[25] Time-domain HRV measures and frequency-domain HRV components were analyzed using specialized software (DM Software Inc.), based on the series of normal-to-normal RR intervals.

Five time-domain indices were measured: the standard deviation of all normal-to-normal RR intervals in the entire recording (SDNN); the mean of the standard deviations of the normal RR intervals in all 5-min segments in the entire 24-h recording (SDNN index); and the mean of the standard deviation of the averaged normal-to-normal RR intervals in all 5-min segments of the 24-h recording (SDANN index) represent the autonomic function; the root mean square of successive differences normal RR intervals and the percent of the differences between the adjacent normal-to-normal intervals >50 ms (pNN50), both of them are considered as a maker of parasympathetic tone.

The frequency-domain HRV analysis is based on the estimation of the power spectral density. The frequency power bands are the following: the total spectral power (<0.4 Hz) represents the autonomic function; the very low frequency ([VLF] <0.04 Hz), its physiological correlate is still unclear; the low frequency ([LF] 0.04–0.15 Hz), which is influenced simultaneously by parasympathetic and sympathetic tones; the high frequency ([HF] 0.16–0.40 Hz), which is considered as measures of parasympathetic tone, and the ratio of LF/HF power, which represents the sympathovagal balance.

Statistical analysis

For observational study, the sample content is equal to 5–10 times the independent variable. The research observed 22 independent variables; the minimum sample size should be in 110 cases.

Demographic differences between patients with stroke were ascertained using the descriptive analysis. All the continuous variables were nonnormally distributed in this research tested by Kolmogorov-Smirnov test and were expressed as medians and interquartile ranges. Categorical variables were shown as percentage of patients per each group. To compare the characteristics of patients by eGFR, all the nonnormally distributed continuous variables were analyzed with the rank test (Kruskal-Wallist test), and categorical variables with the Chi-squared test. Regression was performed for each HRV measure to check whether it significantly differed among the groups. All the clinical covariates that could potentially affect autonomic outcome variables were adjusted in linear regression, such as age, gender, and a history of diabetes or hypertension. Data were analyzed using SPSS statistical package version 17 (IBM-SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was regarded statistically significant.

Results

A total of 256 patients with ischemic stroke met the inclusion criteria and took the 24-h Holter ECG; 24 patients were excluded from the analyses because atrial fibrillation was detected by the 24-h Holter ECG. Finally, 232 patients who did not have atrial fibrillation, premature atrial contractions, or premature ventricular contractions were included in the analyses.

The baseline characteristics of the participants are shown in Table 1: 57.8% were males and 42.2% were females. The age range was 35–85 years (69.0 [IQR 19.0] years). The mean NIHSS score at admission was 3.0 (range 0–18), and the median eGFR was 85.5 (IQR 31.8) ml·min^{-1}·1.73 m^{-2}.

The study sample characteristics are categorized by the eGFR as shown in Table 2. The moderately decreased eGFR group was significantly older than the other groups ($P < 0.001$) and had significantly higher proportions of patients with hypertension and β-blockers ($\chi^2 = 14.67$, $P < 0.001$). The proportion of smokers in the moderately decreased eGFR group was lower than the other groups. There were no statistically significant differences among the three groups with regard to a history of alcohol consumption, body mass index (BMI), diabetes, initial NIHSS, MRS or Barthel index (BI) scores, or the utilization of angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, or calcium channel blocker drugs.

Descriptive statistics of the HRV measures in the groups stratified by eGFR are summarized in Table 3. The three groups significantly differed with regard to the SDANN index ($P = 0.022$), VLF ($P = 0.043$), LF ($P = 0.023$), and LF/HF ($P = 0.001$). A multinomial linear regression was used to evaluate these measures as influential factors. As a result of this study and other research, the multinomial linear regression selected age, gender, BMI, NIHSS, TOAST, OCSP, eGFR, modified Rankin score, BI, histories of hypertension and diabetes, and the use of β-blockers. The results were shown in Table 4: the SDANN index was associated with the NIHSS score ($t = -3.83$, $P < 0.001$), a history of diabetes ($t = -3.58$, $P < 0.001$), age ($t = -2.09$, $P = 0.038$), and OCSP ($t = -2.38$, $P = 0.018$); the VLF and LF were related to the NIHSS score ($t = -3.07$, $P = 0.002$; $t = -2.79$, $P = 0.006$), a history of diabetes ($t = -2.54$,

Table 1: Baseline characteristics of the patients with acute ischemic stroke enrolled in this study ($n = 232$)

Characteristics	Values
Age (years), median (IQR)	69.0 (19.0)
Sex (male/female), %	57.8/42.2
Smokers (yes/no), %	31.9/68.1
Drinkers (yes/no), %	15.9/84.1
Diabetes (yes/no), %	40.9/59.1
Hypertension (yes/no), %	70.7/29.3
BMI (kg/m^2), median (IQR)	24.0 (2.7)
NIHSS score, median (IQR)	3.0 (3.0)
TOAST (1/2/3/4/5), %	23.3/6.9/47.8/1.3/20.7
OCSP (1/2/3/4), %	5.6/33.6/47.0/13.8
Modified Rankin score, median (IQR)	2.0 (2.0)
Barthel index, median (IQR)	75.0 (20.0)
eGFR (ml·min^{-1}·1.73 m^{-2}), median (IQR)	85.5 (31.8)
β-blockers (yes/no), %	14.7/85.3
ARB (yes/no), %	15.5/84.5
ACEI (yes/no), %	5.6/94.4
CCB (yes/no), %	36.6/63.4
Antiplatelets (yes/no), %	78.4/21.6
Fasting blood glucose (mmol/L), median (IQR)	5.7 (2.5)
Total cholesterol (mmol/L), median (IQR)	4.4 (1.5)
Triglyceride (mmol/L), median (IQR)	1.1 (0.8)
High-density lipoprotein (mmol/L), median (IQR)	1.1 (0.4)
Low-density lipoprotein (mmol/L), median (IQR)	2.9 (1.4)
SDNN, median (IQR)	117.5 (70.0)
SDANN index, median (IQR)	96.0 (50.0)
SDNN index, median (IQR)	53.5 (37.0)
rMSSD, median (IQR)	49.5 (46.0)
pNN50, median (IQR)	6.0 (12.0)
TOTPWR, median (IQR)	1707.3 (1700.7)
ULF, median (IQR)	1233.8 (1187.1)
LF, median (IQR)	247.2 (298.6)
HF, median (IQR)	103.4 (144.6)
LF/HF, median (IQR)	2.3 (2.1)

TOAST: 1 - Large-artery atherosclerosis, 2 - Cardioembolic stroke, 3 - Small-artery occlusion (lacunes), 4 - Stroke of other determined causes, 5 - Stroke of undetermined cause; OCSP: 1 - TACIs, 2 - PACIs, 3 - LACIs, 4 - POCIs; NIHSS: National Institutes of Health Stroke Scale; ARB: Angiotensin receptor blocker; ACEI: Angiotensin-converting enzyme inhibitor; CCB: Calcium channel blocker; TACI: Total anterior circulation infarct; PACIs: Partial anterior circulation infarcts; LACIs: lacunar infarcts; POCIs: Posterior circulation infarcts; SDANN: Standard deviation of the averaged normal-to-normal RR intervals; SDNN: Standard deviation of all normal-to-normal RR intervals; rMSSD: Root mean square of successive differences normal RR intervals; TOTPWR: Total spectral power; VLF: Very low frequency; LF: Low frequency; HF: High frequency; IQRs: Interquartile ranges; pNN50: Percent of the differences between the adjacent normal-to-normal intervals >50 ms; ULF: Ultra-low frequency; TOAST: Trial of ORG 10172 in the Acute Stroke Treatment; OCSP: Oxfordshire Community Stroke Project; eGFR: Estimated glomerular filtration rate; BMI: Body mass index.

Table 2: Characteristics of patients with acute ischemic stroke stratified according to the eGFR

Variables	Normal eGFR (n = 90)	Mildly decreased eGFR (n = 100)	Moderately decreased eGFR (n = 42)	χ^2	P
Age (years), median (IQR)	59.5 (16.0)	71.0 (16.0)	77.5 (14.0)	–	<0.001
Gender (male/female), %	64.4/35.6	55.0/45.0	50.0/50.0	2.99	0.232
Smokers (yes/no), %	60.0/40.0	70.0/30.0	81.0/19.0	6.17	0.048
Drinkers (yes/no), %	81.1/18.9	85.0/15.0	88.1/11.9	1.16	0.560
Diabetes (yes/no), %	55.6/44.4	67.0/33.0	47.6/52.4	5.33	0.069
Hypertension (yes/no), %	33.3/66.7	33.0/67.0	11.9/88.1	7.50	0.024
BMI (kg/m^2), median (IQR)	24.2 (2.9)	23.6 (2.7)	24.1 (2.9)	–	0.414
NIHSS score, median (IQR)	3.0 (4.0)	2.0 (2.0)	4.0 (3.0)	–	0.158
Modified Rankin score, median (IQR)	2.0 (2.0)	2.0 (2.0)	2.0 (2.0)	–	0.506
Barthel index, median (IQR)	75.0 (15.0)	75.0 (20.0)	70.0 (21.0)	–	0.384
TOAST (1/2/3/4/5), %	28.9/8.9/47.8/0/14.4	21/8/46/2/23	16.7/0/52.4/2.4/28.6	11.22	0.189
OCSP (1/2/3/4/5), %	7.8/28.9/48.9/14.4	0/44/44/12	14.3/19/50/16.7	19.32	0.004
eGFR (ml·min^{-1}·1.73 m^{-2}), median (IQR)	98.5 (11.2)	79.3 (17.3)	48.5 (19.7)	–	<0.001
β-blocker (yes/no), %	91.1/8.9	88.0/12.0	66.7/33.3	14.67	0.001
ARB (yes/no), %	91.1/8.9	79.0/21.0	83.3/16.7	5.35	0.069
ACEI (yes/no), %	95.6/4.4	96.0/4.0	88.1/11.9	3.86	0.145
CCB (yes/no), %	66.7/33.3	66.0/34.0	50.0/50.0	3.95	0.139

–: No statistic values for Kruskal-Wallist test. eGFR: Estimated glomerular filtration; IQR: Interquartile range; TOAST: 1 - Large-artery atherosclerosis, 2 - Cardioembolic stroke, 3 - Small-artery occlusion (lacunes), 4 - Stroke of other determined cause, 5 - Stroke of undetermined cause; OCSP: 1 - TACIs, 2 - PACIs, 3 - LACIs, 4 - POCIs; NIHSS: National Institutes of Health Stroke Scale; ARB: Angiotensin receptor blocker; ACEI: Angiotensin-converting enzyme inhibitor; CCB: Calcium channel blocker; TACI: Total anterior circulation infarct; PACIs: Partial anterior circulation infarcts; LACIs: Lacunar infarcts; POCIs: Posterior circulation infarcts; SDANN: Standard deviation of the averaged normal-to-normal RR intervals; SDNN: Standard deviation of all normal-to-normal RR intervals; rMSSD: Root mean square of successive differences normal RR intervals; TOTPWR: Total spectral power; VLF: Very low frequency; LF: Low frequency; HF: High frequency; IQRs: Interquartile ranges; pNN50: Percent of the differences between the adjacent normal-to-normal intervals >50 ms; ULF: Ultra low frequency; TOAST: Trial of ORG 10172 in the Acute Stroke Treatment; OCSP: Oxfordshire Community Stroke Project; BMI: Body mass index.

Table 3: Comparisons of HRV measures in patients with acute ischemic stroke stratified by eGFR

eGFR	Quartiles (%)	SDNN	SDANN index	SDNN index	rMSSD	pNN50	TOTPWR	VLF	HF	LF	LF/HF
Normal eGFR	25	87.0	76.0	39.0	31.0	2.0	1188.5	880.8	53.0	142.3	1.7
	50	117.5	97.5	54.0	47.0	5.0	1900.4	1429.9	105.3	331.9	2.6
	75	154.0	125.0	75.0	67.0	14.0	2833.9	2015.5	232.1	463.7	3.6
	Mean rank	113.3	117.6	116.6	109.2	113.9	128.7	127.7	122.8	129.9	127.1
Mildly decreased eGFR	25	99.0	79.5	41.5	34.0	3.0	995.2	764.4	51.3	139.6	1.5
	50	119.0	100.0	51.0	51.5	6.0	1511.7	1146.6	99.3	234.8	2.5
	75	165.5	129.5	74.0	80.0	13.0	2379.4	1699.6	170.6	343.8	3.6
	Mean rank	124.9	125.8	119.7	123.6	118.6	112.5	114.8	112.1	112.7	121.6
Moderately decreased eGFR	25	81.0	62.0	34.0	32.0	1.0	690.5	488.6	38.7	56.5	1.0
	50	114.0	84.0	53.0	53.5	6.0	1216.7	828.35	92.25	147.9	1.5
	75	151.0	103.0	80.0	81.0	19.0	2860.7	1730.5	213.5	447.5	2.6
	Mean rank	103.1	91.8	108.4	114.9	116.9	99.9	96.5	113.3	96.8	81.5
P		0.178	0.022	0.660	0.330	0.893	0.053	0.043	0.517	0.023	0.001

P values refer to Kruskal-Wallis test. SDANN: Standard deviation of the averaged normal-to-normal RR intervals; SDNN: Standard deviation of all normal-to-normal RR intervals; rMSSD: Root mean square of successive differences normal RR intervals; TOTPWR: Total spectral power; VLF: Very low frequency; LF: Low frequency; HF: High frequency; eGFR: Estimated glomerular filtration rate; HRV: Heart rate variability; pNN50: Percent of the differences between the adjacent normal-to-normal intervals >50 ms.

P = 0.012; t = −2.87, P = 0.004), VLF was also related to gender (t = −2.50, P = 0.013); and the LF/HF was associated with eGFR (t = 2.47, P = 0.014), gender (t = −3.60, P < 0.001), and a history of hypertension (t = −2.65, P = 0.008).

Discussion

This study investigated the standard linear HRV measures in stroke patients and categorized the patients through the severity of renal dysfunction according to different eGFR levels. In acute stroke patients, autonomic dysfunction was decreased with the eGFR stage progression. The NIHSS score, age, gender, a history of diabetes or hypertension, and the OCSP subtype of stroke were associated with the imbalance of sympathovagal in stroke patients with renal dysfunction.

The current findings indicated that some HRV measures were significantly lower in the moderately decreased

Table 4: Multinomial linear regression models

Variables	Unstandardized coefficients		Standardized coefficients		P
	B	SE	β	t statistics	
SDANN index					
NIHSS score	−2.75	0.72	−2.59	−3.83	<0.001
Diabetes	−15.28	4.27	−0.22	−3.58	<0.001
Age	−0.38	0.18	−0.13	−2.09	0.038
β-blockers	−11.08	5.89	−0.11	−1.88	0.061
OCSP	−6.98	2.93	−0.16	−2.38	0.018
Constant	163.88	16.16	–	10.13	<0.001
VLF					
NIHSS score	−72.58	23.63	−0.19	−3.07	0.002
Diabetes	−389.00	153.06	−0.16	−2.54	0.012
Gender	−377.44	150.87	−0.16	−2.50	0.013
Constant	2492.22	253.94	–	9.81	<0.001
LF					
NIHSS score	−24.08	8.63	−1.79	−2.79	0.006
Diabetes	−160.67	55.91	−1.85	−2.87	0.004
Constant	525.62	47.91	–	10.97	<0.001
LF/HF					
eGFR	0.01	0.004	0.15	2.47	0.014
Gender	−0.66	0.18	−0.22	−3.60	<0.001
Hypertension	−0.53	0.20	−1.66	−2.65	0.008
Constant	3.08	0.50	–	6.08	<0.001

SE: Standard error; LF: Low frequency; HF: High frequency; NIHSS: National Institutes of Health Stroke Scale; VLF: Very low frequency; OCSP: Oxfordshire Community Stroke Project; SDANN: Standard deviation of the averaged normal-to-normal RR intervals; –: Not applicable.

eGFR group of acute ischemic stroke patients, such as SDANN index, VLF, LF, and LF/HF. These findings were relatively consistent with previous studies with regard to the relationship between HRV and renal function.[26-28] The LF/HF, which reflects the sympathovagal balance, decreased in the patients with a moderately decreased eGFR (15≤ eGFR <60 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), indicates unbalanced autonomic function. In the multivariable regression for LF/HF, the eGFR also remains with a significant association with LF/HF, confirming the involvement of autonomic imbalance in patients with acute stroke. This result is similar to that of Melillo *et al*.,[29] they found that LF/HF was decreased in the mild and moderated decreased eGFR groups in patients with hypertension. The SDANN index, VLF, and LF were also depressed in the patients with a moderately decreased eGFR; this finding is consistent with recent studies[30-32] which indicated that a lower HRV was related to an increased risk of progression to end-stage kidney disease, and the autonomic dysfunction might lead to renal damage. The potential reasons might be renal ischemia, reduced nitric oxide, and uremic toxins.[27] Hemodialysis or renal transplantation may improve HRV in these patients.[33,34] Gujjar *et al*.[35] also determined that the LF and VLF correlated with mortality in patients with stroke. HF reflects parasympathetic modulation; it is lower in patients with a mildly or moderately decreased eGFR compared with a normal eGFR; however, this difference was not significant in the current study. Interestingly, in the Chronic Renal Insufficiency Cohort study,[18] there was a lack of an association between HRV and ESRD in patients with CKD, and the explanation is that the underlying risk of ESRD is sufficiently high in that HRV has no additive predictive value. It is difficult to detect an effect of HRV on these outcomes because of several major confounders.

For these significant measures of HRV compared in different eGFR groups, a multivariable linear regression model was used, after adjustment for age, gender, BMI, history of hypertension and diabetes, the NIHSS score, TOAST, OCSP, modified Rankin score, BI score, eGFR, and β-blockers; the NIHSS score and a history of diabetes were significant predictors for the SDANN index, VLF, and LF. In patients with stroke, the NIHSS is a well-accepted and widely used scoring scheme that captures neurological deficits.[36] A large number of previous studies[2,5,9,11,37] indicated that the severity of stroke was significantly associated with HRV, which particularly depresses the parasympathetic tone.[6,9-11] Sympathetic hyperactivity and parasympathetic dysfunction may cause tachy- or brady-arrhythmias, increased troponin T, myocardial infarction, myocyte vacuolization, and reduced cerebral vasodilatation in animal stroke studies, as well as subsequent further cerebral vasoconstriction.[38-40] A reduced HRV has been made in association with increased mortality in patients with type 2 diabetic with high cardiovascular risk.[41,42] In insulin-treated type 2 diabetic patients, Klimontov *et al*.[43] reported that the postprandial glucose excursions were associated with a reduction in the sympathetic and parasympathetic activities. Gender is an influential factor of VLF and LF/HF, which is consistent with studies in healthy controls[44] and patients with hypertension.[45] In many studies, β-blocker drugs have been demonstrated to enhance cardiac parasympathetic control;[46,47] in this study, β-blocker drugs have also been associated with the SDANN index. The OCSP classification was significantly associated with SDANN index, possibly related to the location of stroke. Many evidence exist regarding the location of stroke which influences the autonomic function in patients with stroke, especially in insular stroke.[48] Ay *et al*.[49] found that the first-ever acute ischemic stroke patients with right-sided insular involvement have more pronounced decrease in HRV measurements. However, Chen *et al*.[50] showed that brainstem infarction may cause a much greater increase in sympathetic modulation and reduced vagal activity compared to the right hemispheric or left hemispheric infarction. It is necessary to take further investigations to explore the relationship of ischemic location and autonomic dysfunction in patients with stroke.

Several limitations of this study should be noted. First, the study population included patients with a normal eGFR, mildly decreased eGFR, and moderately decreased eGFR; the sample of severely decreased eGFR (eGFR ≤30 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) was too small (four patients) to divide independently, so it was included in moderately decreased eGFR group. This approach might affect the further analysis of the data, and further research is necessary. Second, considering the sample, we did not exclude patients with diabetes. Third, the present study did not analyze the extent of the cause of renal damage and the degree of proteinuria. In addition, larger and prospective studies are necessary to investigate these issues, which might help improve strategic management and outcomes for patients with ischemic stroke.

In conclusion, the study demonstrated three major findings in patients with acute stroke. (1) autonomic dysfunction was aggravated with the eGFR stage progression in patients with acute stroke. (2) renal function was significantly associated with LF/HF in patients with acute stroke. (3) NIHSS score and a history of diabetes more significantly affected the parasympathetic nerve changes in acute ischemic stroke patients with renal dysfunction. However, the causal relationship between autonomic dysfunction and abnormal renal function is not very clear, further studies are needed to confirm it.

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Conflicts of interest

There are no conflicts of interest.

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