Assessing Autonomic Nervous Function by Heart Rate Variability and Heart Rate Turbulence in Patients with Acute Ischemic Stroke

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Abstract

Background: Acute ischemic stroke (AIS) induces adverse effects on the cardiovascular system by affecting the autonomic nervous system (ANS). **Objectives:** This study aimed to determine whether the parameters of heart rate variability (HRV) and heart rate turbulence (HRT) differed in patients with AIS as compared to that in the control group. Furthermore, we aimed to determine the differences in the involvement of the ANS between right and left hemisphere (LH) strokes. **Methods:** A total of 148 [74 right hemispheres (RH) and 74 left hemispheres] patients with AIS and 80 control subjects were included in the study. The Holter device was used to obtain elcctrocardiogram readings for over 20 h from all patients. Results of HRV and HRT parameters [Tonset (TO) and Tslope (TS)] were acquired through an automatic analysis of the program. **Results:** All HRV parameters were found to be low in patients with AIS ($P < 0.05$, for all parameters). TO and TS were disrupted in 99 patients with AIS (66.8%) and in 15 control subjects (18.7%) (HRT–1 and HRT–2 groups, $P = <0.001$). HRV parameters were detected to be similar in patients, irrespective of the left or right infarct. TO and TS were normal in 31 patients (41.9%) with left hemisphere localization and in only 18 patients (24.3%) with right hemisphere localization. **Conclusions:** Combined evaluation of HRV and HRT parameters may provide important information regarding the alterations in the ANS in patients with AIS. The utility of HRT in the determination of ANS alterations in patients with AIS should be investigated in larger future prospective studies.

Keywords: Acute ischemic stroke, cardiac autonomic dysfunction, heart rate turbulence, heart rate variability

INTRODUCTION

Ischemic stroke is one of the most common causes of death worldwide.[1] The autonomic nervous system (ANS) has been shown to be affected after a stroke. Classically, this effect is hypothesized to be due to an increase in the sympathetic tone and a decrease in the parasympathetic tonus due to catecholamine discharge.[2] However, another hypothesize that has been deliberated is that ANS dysfunction occurs due to the disruption of the physiological asymmetry between the right and left cerebral hemispheres in the modulation of ANS activity of the central nervous system.[3] Remarkably, Brunetti *et al*. investigated the changes of heart rate variability (HRV) during wakefulness in their recent study and suggested that ANS dysfunction observed in acute ischemic stroke (AIS) may be the result of the loss of circadian modification of sympatho-vagal balance.[4] Overall, although the exact mechanism is not fully understood, several studies remark that the autonomic dysfunction thus created, especially the one occurring in the acute phase of the stroke, increases cardiac mortality and morbidity.[5-8]

HRV and heart rate turbulence (HRT) are reliable Holter parameters that indicate cardiac autonomic function. HRV (a measure of the variations of the interval between consecutive heartbeats) enables an independent measurement of parasympathetic and sympathetic components of the ANS. HRT is defined in two parts: i) decrease in blood pressure due to decreased cardiac filling after ventricular premature beats (VPBs) and increase in heart rate by means of baroreflex mechanism (turbulence onset-TO) and ii) initiation of baroreflex response by restoring blood pressure to a normal level and restoring normal heart rate through parasympathetic signals from the brain (turbulence slope-TS).[9,10]

HRV and HRT may provide information regarding tendencies of cardiac arrhythmias and increased mortality risk.[10-13] To the best of our knowledge, HRT parameters of patients with previous AIS have never been evaluated. Combined evaluation of HRV and HRT in Holter elcctrocardiogram (ECG), which is an easily accessible and a noninvasive examination, may provide strong data on the cardiac prognosis of these patients. This study, therefore, aimed to determine whether the HRV and

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HRT parameters differed in patients with AIS as compared to that in the control group. The study also intended to investigate if the hemisphere with ischemia has any impact on these parameters.

MATERIALS AND METHODS

This prospective and cross-sectional study included 148 patients (85 men and 63 women, mean age 66.72 ± 13.07) admitted to the neurology clinic between September 2018 and April 2019 with the diagnosis of AIS. The diagnosis was made by neurologists through clinical evaluation and findings of magnetic resonance imaging. In addition, 80 (40 men and 40 women, mean age 65.30 ± 10.71) control participants having similar demographic features as the stroke group were also included in the study. The control group consisted of patients who admitted to cardiology polyclinic due to complaints of palpitation.

Patients with a previous cerebrovascular event history, kidney failure, or renal malignancy, those diagnosed with atrial fibrillation (AF) or AF detected in Holter monitor, having coronary artery disease, ejection fraction <%50, severe heart valve disease, complete or incomplete branch block, resistant or uncontrolled hypertension, acute infections, and hypo- and hyperthyroidism were excluded from the study. Besides, none of the patients were using beta-blockers, Ca-channel blockers, or antiarrhythmic medications that may have affected the ANS.

Echocardiography was performed 2–5 days after the AIS patients were admitted to the hospital and the ECG records were evaluated together with laboratory and Holter results. The Holter monitors were performed within the first week of the event in all patients with AIS. A total of 89 participants were excluded from the study as they had less than five VPBs [Figure 1]. All results were obtained from hospital records. Standard echocardiographic evaluations in the parasternal and apical positions were also performed. The ejection fraction was calculated by using the modified Simpson method.
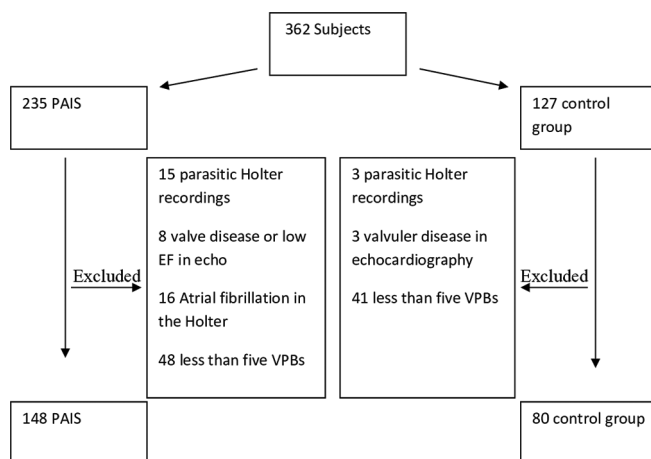

Figure 1: Patient selection

The local ethical committee reviewed and approved the study (approval no: 030.04.01) according to the ethical principles for human investigations, and a written consent form was obtained from all participants, as indicated in the Declaration of Helsinki.

Heart rate variability and heart rate turbulence analysis

All subjects underwent Holter ECG monitoring (GE medical systems information technologies, Inc., software version 8.0.3, Milwaukee, USA). Recordings lasting more than 20 h and of sufficient quality for evaluation were analyzed. None of the patients were on sedation or ventilation during the time of Holter monitoring. A physician completely blind to the study assessed the Holter ECG records. All recordings were transferred to the computer. They were firstly analysed by the Holter program and, thereafter, manually screened. The VPBs were evaluated one by one and the artifacts diagnosed as VPBs were deleted.

HRT and HRV parameters were measured by an automatic computer program. HRV parameters *time-domain measures* included the standard deviation of the normal-to-normal (NN) interval (SDNN), the standard deviation of the average NN interval (SDANN) calculated over 5 min periods, average standard deviation of the averages of all NN RR intervals in all 5-min segments of the entire recording (ASDNN), the square root of the mean squared differences of successive NN intervals (rMSSD), and the division of the number of interval differences of successive NN intervals of more than 50 ms by the total number of NN intervals (pNN50); and *frequency-domain measures* included very low frequency (VLF) at frequency between 0.0033 and 0.04 Hz, low frequency (LF) at frequency between 0.04 and 0.15 Hz, high frequency (HF) at frequency between 0.15 and 0.4 Hz, and low frequency/high-frequency ratio (LF/HF). Time-domain indices of HRV quantify the amount of variability in measurements of the interbeat interval, which is the time period between successive heartbeats. Frequency-domain measurements estimate the distribution of absolute or relative power into different frequency bands.

Two phases of HRT were quantified numerically as TO and TS. The patients were in sinus rhythm at least 70% of Holter recording and ectopic beats were <10%. TO defined as the percentage change RR intervals after VPBs compare to pre-VPB period. To represents the initial acceleration of heart rate (HR) following VPB. TS was defined as the maximum positive regression slope obtained over any five consecutive sinus RR intervals within the first 15 sinus RR intervals following the VPB. TS represents the late deceleration of HR after the VPB. TO <% 0 (negative TO) and TS >2.5 ms/RR (positive TS) were accepted as normal values.[12] The patients were divided into three groups as follows: i) patients with normal HRT (HRT-0), ii) patients with abnormal TO or TS (HRT-1), and iii) patients with abnormal TO and TS (HRT-2).

All analyses were made according to the standards determined by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[9]

Statistical analyses

Data were analyzed by using SPSS 21.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA). The variables were examined using analytical methods (the Kolmogorov–Simirnov test) to determine whether or not they were normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables (parametric) and medians (interquartile range) for the nonnormally (nonparametric) distributed variables. Categorical variables were presented using percentages. The independent *t*-test was used for comparisons between groups regarding the means of the numerical variables, whereas the Mann–Whitney U test was used for the comparison of medians. Pearson's Chi-square analysis was used to compare categorical data. Pearson's correlation test was used for the normally distributed data, and the Spearman's correlation test was used for data not showing a normal distribution. All tests of significance were two-tailed. Statistical significance was defined as $P < 0.05$.

RESULTS

The basal characteristics of the participants are depicted in Table 1. Infarction area was observed to be on the left hemisphere in 50% (74) of the patients with AIS and there was no significant difference between basal characteristics of both the groups. In addition, the maximum, minimum, mean heartbeats, and VPBs counts were found to be similar in both groups [Table 2].

According to the Trial of Org 10172 in Acute Stroke Treatment classification, 57 (38.5%) of them were evaluated as large-vessel atherosclerosis, 26 (17.5) cardioembolic,

48 (32.4%) small vessel occlusion, and 17 (11.5%) stroke of undetermined etiology.

The patients with acute ischemic infarction were found to have higher urea and sedimentation values ($P = 0.002$, $P = 0.03$, respectively). All HRV parameters (VLF, LF, HF, SDNN, SDANN, ASDNN, rMSSD, pNN50) were significantly lower in the stroke group ($P < 0.05$, for all parameters). LF/HF ratio was higher in the stroke group ($P = 0.002$). TO and TS values differed significantly in the control group and the stroke group ($<p = 0.001$, $P = 0.005$, respectively) [Table 2]. At least one of the two HRT parameters (TO or TS) extended outside the normal values in 66.8% of the AIS group and 18.8% of the control group patients (HRT–1 and HRT–2 group, $P = <0.001$) [Table 3].

There were no differences in clinical and laboratory findingns between left hemisphere and right hemisphere strokes [Table 4]. HRV parameters were similar in all patients, irrespective of the hemisphere infarction [Table 5]. Both the HRT parameters (TO and TS) were normal in 41.9% (31/74) of the patients with left cerebral infarct and in only 24.3% (18/74) of the patients with right cerebral infarct; a significant difference was observed between the HRT parameters of the two groups (HRT–0 group, $P = 0.023$). In addition, either of the two HRT parameters (TO or TS) was disrupted in 33.8% (25) of the patients with left cerebral infarct and in 52.7% (39) of the patients with right cerebral infarct (HRT–1 group, $P = 0.020$) [Table 6]. Besides, no statistical difference was found in any of the HRV and HRT parameters between patient groups with anterior circulation strokes and posterior circulation strokes [Table 7]. Of note, correlation analyses between all HRV parameters and age were performed which showed significant negative correlations with age for all the HRV parameters [Figure 2].

Table 1: Baseline characteristics and laboratory findings of the study participants

	Total (*n*=228)	PAIS (*n*=148) (65%)	Control (*n*=80) (35%)	*P*
Age	66.22±12.29	66.72±13.07	65.30±10.71	0.40
Sex (male), *n* (%)	125 (54.8)	85 (57.4)	40 (50)	0.28
Hypertension, *n* (%)	132 (57.9)	92 (62.2)	40 (50)	0.08
Diabetes mellitus, *n* (%)	72 (31.6)	48 (32.4)	24 (30)	0.71
Smoker, *n* (%)	53 (23.2)	31 (20.9)	22 (27.5)	0.26
Hyperlipidemia	44 (19.3)	27 (18.2)	17 (21.3)	0.58
EF %	60.00 (56.00-63.00)	60.00 (55.00-63.00)	61.00 (58.00-63.00)	0.13
Urea	37.00 (29.00-44.75)	38.00 (31.25-46.00)	34.00 (28.00-40.00)	0.002
Creatine	0.81 (0.70-1.00)	0.80 (0.70-0.96)	0.87 (0.72-1.00)	0.12
Sodium	138.00 (137.00-140.00)	138.00 (137.00-140.00)	138.00 (137.00-140.00)	0.83
Potassium	4.16±0.42	4.18±0.40	4.20±0.45	0.82
WBC (×10³/ml)	7.85 (6.52-9.20)	7.80 (6.52-9.00)	8.20 (6.55-10.17)	0.25
Hemoglobin	13.45±1.87	13.44±1.81	13.47±2.00	0.91
PLT	225.35±75.50	201.50±79.46	241.00±66.77	0.12
Neutrophil	5.00 (3.80-6.40)	4.95 (3.52-6.40)	5.10 (4.40-6.30)	0.16
Lymphocyte	1.90 (1.50-2.50)	1.90 (1.50-2.50)	2.04 (1.42-2.60)	0.51
TSH	1.37±0.89	1.37±0.90	1.37±0.87	0.98
Sedimentation rate	14.00 (8.00-22.00)	16.00 (7.25-24.00)	12.50 (9.00-18.00)	0.03
C-reactive protein	0.70 (0.40-1.20)	0.70 (0.31-1.38)	0.73 (0.40-1.08)	0.80

PAIS: Patients with acute ischemic stroke, EF: Ejection fraction, WBC: white blood cell, PLT: platelets, TSH: throid-stimulating hormone

Table 2: Holter parameters of the study population

	Total (*n*=228)	PAIS (*n*=148) (%65)	Control (*n*=80) (%35)	*P*
Minimum HR	46.28±9.23	45.83±9.74	47.11±8.20	0.32
Average HR	74.94±10.70	74.73±11.06	75.32±10.07	0.69
Maximum HR	130.32±23.14	129.46±22.44	131.91±24.46	0.45
Total QRS	101550.22±17625.03	100429.24±19178.07	103624.03±14195.42	0.16
VLF	24.87 (20.05-33.30)	23.19 (18.89-31.16)	29.03 (22.82)	<0.001
LF	18.87 (13.86-27.24)	16.62 (11.12-22.95)	23.20 (18.22-31.97)	<0.001
HF	13.94 (10.17-19.43)	11.57 (8.28-15.16)	18.67 (15.06-23.79)	<0.001
LF/HF ratio	1.44±0.51	1.50±0.58	1.32±0.32	0.002
SDNN	114.32±42.62	96.29±33.15	147.68±37.92	<0.001
SDANN	98.95±43.79	80.68±37.18	132.76±34.00	<0.001
ASDNN	51.00 (39.25-62.75)	46.00 (33.25-58.75)	58.00 (47.00-72.50)	<0.001
rMSSD	33.00 (27.00-42.00)	33.00 (24.00-41.75)	33.50 (30.00-43.75)	0.03
pNN50	11.70 (6.90-20.47)	11.30 (5.00-20.60)	12.70 (9.50-20.47)	0.02
Tonset	-0.40 (-1.55 to 0.61)	0.03 (-0.84-1.00)	-1.22 (-2.58-0.67)	<0.001
Tslope	3.76 (2.25-6.60)	3.55 (1.60-6.46)	4.10 (2.98-6.76)	0.005
PVBs	15.00 (9.00-77.25)	14.00 (8.00-102.50)	17.00 (10.00-50.25)	0.83

PAIS: Patients with acute ischemic stroke, HR: heart rate, VLF: very low frequency, LF: low frequency power, HF: high frequency power, LF/HF ratio: ratio of power in low/high frequency, Mean NN: the mean of all normal RR intervals, SDNN: standard deviation of normal-to-normal R wave in the entire recording, SDANN: standard deviation of the averages of all normal-to-normal RR intervals in all 5 min segments of the entire recording, ASDNN: average standard deviation of the averages of all normal-to-normal RR intervals in all 5 min segments of the entire recording, RMSSD: root mean square of the mean of the squared difference of two consecutive R-R intervals, pNN50: Percent of the differences between the adjacent normal-to-normal intervals >50 ms, BB50: Total number of instances per hour in which two consecutive RR intervals differ by more than 50 msec, PVBs: Premature ventricular beats

Table 3: Grouping the patient population according to HRT analysis

Parameters	PAIS (*n*=148)	Control (*n*=80)	*P*
HRT-0, *n* (%)	49 (33.1)	65 (81.3)	<0.001
HRT-1, *n* (%)	64 (43.2)	13 (16.3)	<0.001
HRT-2, *n* (%)	35 (23.6)	2 (2.5)	<0.001

PAIS: Patients with acute ischemic stroke

DISCUSSION

In this study, we have evaluated the characteristics of the Holter parameters (HRV and HRT), which are easily accessible, quantitative, noninvasive, and believed to be effective on the sympathetic and parasympathetic systems of the heart, in patients with AIS. All HRV parameters were found to be low in patients with AIS and disruption was observed in the HRT parameters (TO and TS). LF/HF ratio, which gives information about the dominance of the sympathetic system, was found to be increased.

Dysfunction in the ANS occurs during acute or chronic stages in patients with ischemic stroke. This disruption induces arrhythmias in the cardiac system.[5,14] Some studies have shown that this disruption causes changes in HRV parameters as well. Such disruptions in Holter parameters may predict cardiac arrhythmia according to some reports.[14,15] HRV parameters provide information about the ANS balance. SDNN is associated with the parasympathetic system; SDNN decrease in 24 h Holter recordings is considered as a gold standard for the evaluation of cardiovascular autonomous system.[9] Furthermore, a decrease in SDNN was found to be predictive of cardiac mortality and morbidity.[16] PNN50 and rMSSD were

reported to be associated with the parasympathetic activity[17,18] and low rMSSD values were established to be correlated with unexplained sudden death risk in epilepsy patients.[19] VLF is accepted as a measure of the sympathetic nervous system.[20] VLF is found to be more closely related to all-cause mortality as compared to LF and HF.[21,22] In addition, low VLF values are associated with fatal arrhythmias.[11] Of note, we used a recording of 5 min while assessing VLF which is remarked as a non-reliable technique according to the guidelines of HRV analysis that may constitute another limitation of our study.[9] LF exhibits both vagal and sympathetic tone,[23] whereas HF is primarily controlled by vagal tone.[24] It was seen that the total vagal blockage and HF oscillation disappeared almost completely and LF decreased significantly. The importance of the LF/HF ratio was determined in the 24 h Holter records. This ratio is thought to enable sympathovagal balance in the heart.[20] The high LF/HF ratio indicates a dominant sympathetic system.[16] We have found that all of these HRV parameters were significantly distinctive between the patient group and control group which were strictly encouraging conclusions. In a previous study conducted by Korpelainen *et al.*, all HRV parameters were also found to be low during the acute period and after 1 and 6th months in the patients with ischemic stroke (independent of ischemia size). This also suggests that HRV parameters may be important in terms of prognosis during the acute period of stroke. In addition, decreased HRV parameters have been shown to be independent predictive factors for 1-year mortality after the first ischemic attack.[5] Similarly, in another study, 24 h Holter records of patients with acute ischemia (in infarction of both hemispheres and the brain stem) showed that SDNN, VLF, and LF parameters

Table 4: Baseline characteristics and laboratory findings of patients with acute ischemic stroke

	Left hemisphere stroke (n=74)	Right hemisphere stroke (n=74)	P
Age	67.62±12.96	65.83±13.21	0.41
Sex (male), n (%)	44 (59.5)	41 (55.4)	0.62
Hypertension, n (%)	45 (60.8)	47 (63.5)	0.74
Diabetes mellitus, n (%)	24 (32.4)	24 (32.4)	1.00
Smoker, n (%)	12 (16.2)	19 (25.7)	0.16
Hyperlipidemia	12 (16.2)	15 (20.3)	0.52
EF %	60.00 (56.75-63.25)	60.00 (55.00-63.00)	0.28
Urea	41.48±14.47	40.22±14.06	0.59
Creatine	0.84±0.26	0.83±0.25	0.93
Sodium	138.00 (137.00-140.00)	138.00 (137.00-140.00)	0.62
Potassium	4.17±0.38	4.20±0.42	0.5
WBC (×10³/ml)	8.17±2.83	8.05±2.39	0.77
Hemoglobin	13.30±1.84	13.57±1.78	0.37
PLT	217.40±80.12	221.93±79.29	0.73
Neutrophil	5.44±2.73	5.27±2.28	0.69
Lymphocyte	1.90 (1.45-2.40)	1.90 (1.50-2.62)	0.51
TSH	1.41±0.83	1.34±0.97	0.67
Sedimentation rate	16.91±2.36	18.79±13.82	0.37
C-reactive protein	0.75 (0.37-1.25)	0.70 (0.30-1.40)	0.61

PAIS: Patients with acute ischemic stroke, EF: Ejection fraction, WBC: white blood cells, PLT: platelets, TSH: throid-stimulating hormone

Table 5: Holter parameters of patients with acute ischemic stroke

	Left hemisphere stroke (n=74)	Right hemisphere stroke (n=74)	P
Minimum heart rate	46.51±9.44	45.16±10.05	0.40
Average heart rate	75.68±19.74	73.78±10.93	0.30
Maximum heart rate	129.63±19.74	129.29±24.98	0.93
Total QRS	100901.12±19736.52	99957.36±18725.74	0.77
VLF	23.29 (18.64-32.46)	22.96 (18.99-29.95)	0.84
LF	16.62 (10.58-21.64)	16.31 (11.17-24.18)	0.64
HF	12.40 (8.45-15.70)	11.25 (8.13-14.65)	0.53
LF/HF ratio	1.42±0.55	1.57±0.60	0.12
SDNN	97.10±33.75	95.47±32.75	0.77
SDANN	81.18±31.85	80.17±42.05	0.87
ASDNN	49.37±23.42	48.93±20.04	0.90
rMSSD	34.08±13.34	32.48±12.96	0.46
pNN50	13.05 (5.22-22.10)	8.80 (4.60-19.50)	0.14
Tonset	0.01 (-1.41-1.01)	0.08 (-0.50-1.00)	0.43
Tslope	3.84 (1.89-5.79)	2.97 (1.25-6.66)	0.15
PVBs	17.00 (9.00-82.25)	12.00 (7.00-113.00)	0.50

PAIS: Patients with acute ischemic stroke, HR: heart rate, VLF: very low frequency, LF: low frequency power, HF: high frequency power, LF/HF ratio: ratio of power in low/high frequency, Mean NN: the mean of all normal RR intervals, SDNN: standard deviation of normal-to-normal R wave in the entire recording, SDANN: standard deviation of the averages of all normal-to-normal RR intervals in all 5 min segments of the entire recording, ASDNN: average standard deviation of the averages of all normal-to-normal RR intervals in all 5 min segments of the entire recording, rMSSD: root mean square of the mean of the squared difference of two consecutive R-R intervals, pNN50: Percent of the differences between the adjacent normal-to-normal intervals >50 ms, BB50: Total number of instances per hour in which two consecutive RR intervals differ by more than 50 msec, PVBs: Premature ventricular beats

were particularly decreased in the acute period and in the measurements recorded six months later.[25] In another study, the 24 h Holter recordings of HRV parameters (especially VLF, LF, and HF components) were shown to be decreased in AIS independent of the location or hemisphere of the lesion.[26] Although the exact mechanisms remain to be elucidated, the decrease in the HRV parameters of stroke patients was suggested to be caused by the compression in the parasympathetic system and thus the creation of a dominant sympathetic system.[27,28] This disrupted vagal inhibition on the heart is associated with cardiac morbidity.[29] The results of HRV analyses in our study were in accordance with the findings of these previous studies and strongly convincing. However, no difference was observed between the HRV parameters among patients with different hemisphere involvement. On the contrary, the findings of the HRT analyses were also found to

Table 6: Grouping the patients with acute ischemic stroke according to HRT analysis

Parameters	Left hemisphere stroke (n=74)	Right hemisphere stroke (n=74)	P
HRT-0, n (%)	31 (41.9)	18 (24.3)	0.023
HRT-1, n (%)	25 (33.8)	39 (52.7)	0.020
HRT-2, n (%)	18 (24.3)	17 (23.0)	0.847

PAIS: Patients with acute ischemic stroke

Table 7: Comparison of the HRV and HRT parameters between anterior circulation strokes and posterior circulation strokes

	Anterior (n=103)	Posterior (n=45)	P
Minimum heart rate	46.1±9.2	45.1±10.8	0.563
Average heart rate	74.6±10.5	74.8±12.3	0.951
Maximum heart rate	130.0±22.8	128.2±21.5	0.663
Total QRS	99791.4±19116.9	101889.1±19453.8	0.542
LF	18.8±10.9	19.2±14.3	0.614
HF	13.3±7.7	12.6±7.4	0.704
LF/HF ratio	1.5±0.6	1.4±0.4	0.953
SDNN	95.3±31.0	98.4±37.9	0.596
SDANN	79.4±37.7	83.4±36.1	0.555
ASDNN	49.1±20.3	49.2±24.8	0.980
rMSSD	33.8±13.6	31.8±11.9	0.395
pNN50	14.2±12.2	12.4±9.2	0.708
Tonset	0.11±2.4	-0.28±1.4	0.293
Tslope	4.7±4.7	4.1±3.2	0.963
PVBs	86.9±191.9	193.6±335.7	0.059

PAIS: Patients with acute ischemic stroke, HR: heart rate, VLF: very low frequency, LF: low frequency power, HF: high frequency power, LF/HF ratio: ratio of power in low/high frequency, Mean NN: the mean of all normal RR intervals, SDNN: standard deviation of normal-to-normal R wave in the entire recording, SDANN: standard deviation of the averages of all normal-to-normal RR intervals in all 5 min segments of the entire recording, ASDNN: average standard deviation of the averages of all normal-to-normal RR intervals in all 5-min segments of the entire recording, rMSSD: root mean square of the mean of the squared difference of two consecutive R-R intervals, pNN50: Percent of the differences between the adjacent normal-to-normal intervals >50 ms, BB50: Total number of instances per hour in which two consecutive RR intervals differ by more than 50 msec, PVBs: Premature ventricular beats

be discriminative in terms of stroke lateralization (significantly higher disruption was found in one of their HRT parameters in right-sided infarction).

HRT has been demonstrated to be significantly related to HRV parameters in both, time and frequency domains.[30] However, its sensitivity and specificity have been found to be higher than that of HRV.[31] Besides, HRT analysis is thought to be more effective than conventional methods in predicting the prognosis of cardiovascular diseases.[10] The two parameters of HRT (TO and TS) are vagal-dependent and provide information about the parasympathetic system.[32] HRT has been shown to be considerably affected after disorders like myocardial infarction and cardiac insufficiency.[33,34] Disrupted HRT parameters [lack of sudden acceleration or disrupted sinus rhythm deceleration (positive values of TO) and blunt rate of subsequent deceleration with lower TS values] have been considered as high cardiac risk factors.[35] Such that, Perkiomaki et al. conducted an 8-year follow-up of 569 patients with cardiac insufficiency and reported that decreased HRV and abnormal HRT values were significantly associated with hospitalization.[36] In another study, HRT was found to be an important parameter that may predict postmyocardial infarction mortality.[12] In another study on patients with acute myocardial infarctions, a method similar to our study was performed in terms of classification of HRT groups; and HRT–2 group was found to have four times higher cardiac arrhythmic death risk than the HRT–0 group in postinfarction (myocardial infarction) patients who had been on follow-up for 20.3 months on an average.[37] In patients with nonischemic cardiomyopathy, where primary endpoint is considered as cardiac mortality or continuous ventricular tachycardia, patients with abnormal HRT values were found to have a 4.5 times higher risk of mortality.[38] Ergo, all these, above mentioned, studies consistently show the value of HRT in terms of cardiac prognosis of patients and diagnostic sensitivity and specificity of ANS dysfunction. However, up to date, no previous study has been conducted to investigate its diagnostic utility in patients with AIS making the results of our study highly remarkable. Previously, the disruption of the parasympathetic system in patients with stroke has been demonstrated by many researchers.[5,14,27,28,39,40] However, the methods used in these studies were heterogeneous including measurement of 24-h urinary norepinephrine and its metabolites, measuring plasma norepinephrine, microneurography, and assessment of organ-specific norepinephrine, analysis of spontaneous HRV, and there is no a consensus in this regard. In the present study, we have found that the HRT parameters were significantly distinct in AIS patients according to control group, and the HRT parameters were also discriminative in terms of stroke lateralization. Therefore, our results thus obtained are strongly convincing and in accordance with the aforementioned studies.

Independent of the hemisphere of ischemia, the cardiac parasympathetic system undergoes various disruptions in patients with AIS. In addition, a sympathetic cardiovascular system emerged to be more dominant in patients with right-sided stroke.[28] However, there are still debated at that point. Although some previous studies have reported disrupted HRV parameters in patients with right-sided strokes,[14,41] other studies have found no difference.[26,28,42] In our study, no difference in HRV parameters was detected irrespective of the side of the hemisphere involved. However, disruption of HRT parameters was more significant in patients with right-sided infarction. HRT–0 was more in patients with left hemisphere infarction, whereas HRT–1 was higher in patients with right hemisphere infarction, possibly suggesting that HRT may be more sensitive than HRV.

Besides, in the present study, erythrocyte sedimentation rate was higher in stroke patients than that in the control group, in accordance with the literature data.[43] The reason for higher
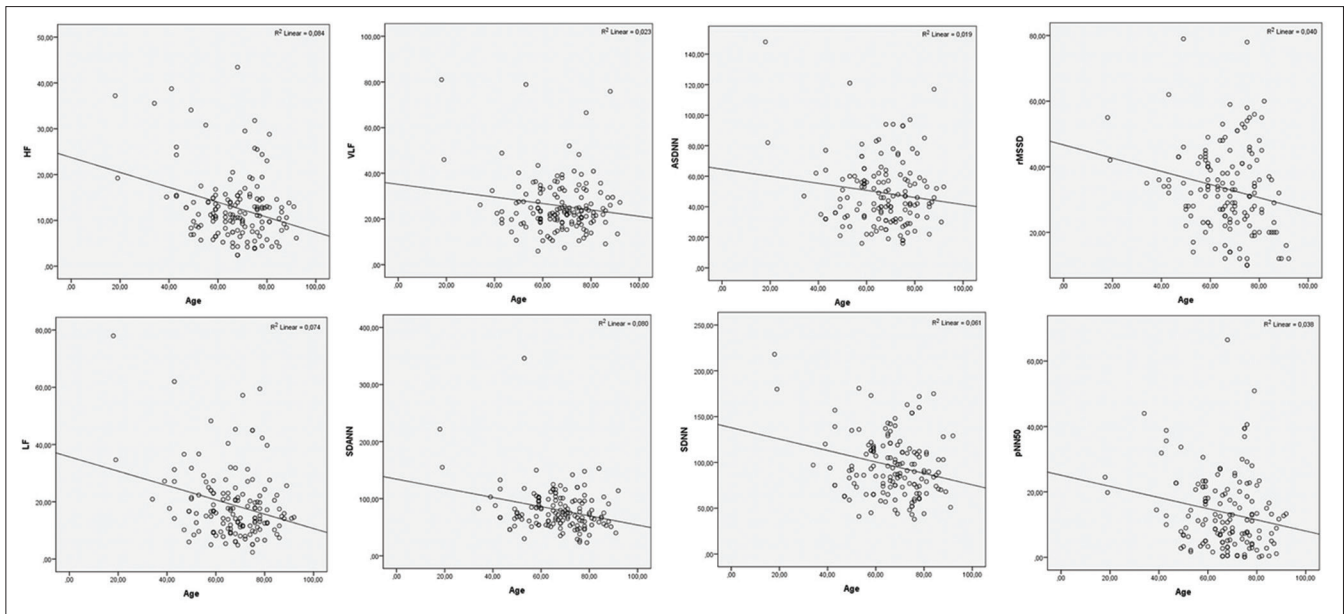
Figure 2: The scatter plots showing negative correlations between age and all the parameters of HRV in the patient group

urea values in stroke patients, as seen in this study, may probably be associated with the decreased oral intake and mild dehydration encountered after stroke. Of note, we also performed correlation analyses between all HRV parameters and age in the patient group which showed significant negative correlations with age for all the HRV parameters. This was also in accordance with the literature knowledge.[44,45]

One of the limitations of this study may be that we have not evaluated the infarction size and the affected lobe specifically. Second, we have excluded patients with hypertension (considering its potential effect in ANS and cardiac status) which might constitute a bias effect. However, since there were no differences between the patient group and control group in terms of the existence of hypertension, we think that this method has not constituted a confounding factor. In addition, we have not performed a method of excluding diabetes mellitus and sleep apnea syndrome which may also lead to ANS dysfunction and constitute potential confounding factors in the study results. However, the prevalence of diabetes mellitus in the patient group and the control group was similar and no difference was found ($P = 0.71$). Finally, we conducted a method of a single time data point that avoids evaluating the temporal course of the ANS dysfunction in the subacute and chronic phase of the stroke. Investigation of these findings with follow-up measurements may add crucial contributions regarding the unknown aspects of the pathophysiology of ANS dysfunctions in stroke.

CONCLUSION

The combined evaluation of HRV, which is the response of the ANS to external stimuli, and HRT, which reflects the intrinsic baroreceptor reflex, may provide valuable information in patients with AIS. We think that the results of our study also

provide encouraging conclusions supporting the use of HRT in future prospective studies. Confirmation of our results, particularly the discriminative value of HRT in lateralization of infarction, in these studies may give critical conclusions to be kept in mind in the clinical practice during the investigation of ischemic stroke patients.

Conflicts of interest

There are no conflicts of interest.

Author contributions

Conception and design of the study or analysis and interpretation of data, or both (MC, HO);

Manuscript drafting or critical revision for important intellectual content (MC);

Final approval of the manuscript submitted (MC).

REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-28.
2. Colivicchi F, Bassi A, Santini M, Caltagirone C. Prognostic implications of right-sided insular damage, cardiac autonomic derangement, and arrhythmias after acute ischemic stroke. Stroke 2005;36:1710-5.
3. Al-Qudah ZA, Yacoub HA, Souayah N. Disorders of the autonomic nervous system after hemispheric cerebrovascular disorders: An update. J Vasc Interv Neurol 2015;8:43-52.
4. Brunetti V, Vollono C, Testani E, Pilato F, Della Marca G. Autonomic nervous system modifications during wakefulness and sleep in a cohort of patients with acute ischemic stroke. J Stroke Cerebrovasc Dis

2019;28:1455-62.

5. Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllya VV. Abnormal heart rate variability as a manifestation of autonomic dysfunction in hemispheric brain infarction. Stroke 1996;27:2059-63.

6. De Raedt S, De Vos A, De Keyser J. Autonomic dysfunction in acute ischemic stroke: An underexplored therapeutic area? J Neurol Sci 2015;348:24-34.

7. Soros P, Hachinski V. Cardiovascular and neurological causes of sudden death after ischaemic stroke. Lancet Neurol 2012;11:179-88.

8. McLaren A, Kerr S, Allan L, Steen IN, Ballard C, Allen J, *et al.* Autonomic function is impaired in elderly stroke survivors. Stroke 2005;36:1026-30.

9. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93:1043-65.

10. Bauer A, Malik M, Schmidt G, Barthel P, Bonnemeier H, Cygankiewicz I, *et al.* Heart rate turbulence: Standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus. J Am Coll Cardiol 2008;52:1353-65.

11. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992;85:164-71.

12. Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, *et al.* Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999;353:1390-6.

13. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, *et al.* Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 1996;94:2850-5.

14. Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac autonomic derangement and arrhythmias in right-sided stroke with insular involvement. Stroke 2004;35:2094-8.

15. Disertori M, Mase M, Rigoni M, Nollo G, Ravelli F. Heart rate turbulence is a powerful predictor of cardiac death and ventricular arrhythmias in postmyocardial infarction and heart failure patients: A systematic review and meta-analysis. Circ Arrhythm Electrophysiol 2016;9.pii: e004610.

16. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health 2017;5:258.

17. Pumprla J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: Physiological basis and practical applications. Int J Cardiol 2002;84:1-14.

18. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. J Am Coll Cardiol 1998;31:593-601.

19. DeGiorgio CM, Miller P, Meymandi S, Chin A, Epps J, Gordon S, *et al.* RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: The SUDEP-7 Inventory. Epilepsy Behav 2010;19:78-81.

20. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. Front Psychol 2014;5:1040.

21. Hadase M, Azuma A, Zen K, Asada S, Kawasaki T, Kamitani T, *et al.* Very low frequency power of heart rate variability is a powerful predictor of clinical prognosis in patients with congestive heart failure. Circ J 2004;68:343-7.

22. Tsuji H, Venditti FJ Jr, Manders ES, Evans JC, Larson MG, Feldman CL, *et al.* Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation 1994;90:878-83.

23. Lehrer PM, Vaschillo E, Vaschillo B. Resonant frequency biofeedback training to increase cardiac variability: Rationale and manual for training. Appl Psychophysiol Biofeedback 2000;25:177-91.

24. Fouad FM, Tarazi RC, Ferrario CM, Fighaly S, Alicandri C. Assessment of parasympathetic control of heart rate by a noninvasive method. Am J Physiol 1984;246:H838-42.

25. Korpelainen JT, Sotaniemi KA, Makikallio A, Huikuri HV, Myllyla VV. Dynamic behavior of heart rate in ischemic stroke. Stroke 1999;30:1008-13.

26. Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllyla VV. Circadian rhythm of heart rate variability is reversibly abolished in ischemic stroke. Stroke 1997;28:2150-4.

27. Xiong L, Leung HW, Chen XY, Leung WH, Soo OY, Wong KS. Autonomic dysfunction in different subtypes of post-acute ischemic stroke. J Neurol Sci 2014;337:141-6.

28. Dutsch M, Burger M, Dorfler C, Schwab S, Hilz MJ. Cardiovascular autonomic function in poststroke patients. Neurology 2007;69:2249-55.

29. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol 2010;141:122-31.

30. Cygankiewicz I, Wranicz JK, Bolinska H, Zaslonka J, Zareba W. Relationship between heart rate turbulence and heart rate, heart rate variability, and number of ventricular premature beats in coronary patients. J Cardiovasc Electrophysiol 2004;15:731-7.

31. Lin K, Wei L, Huang Z, Zeng Q. Combination of Ewing test, heart rate variability, and heart rate turbulence analysis for early diagnosis of diabetic cardiac autonomic neuropathy. Medicine (Baltimore) 2017;96:e8296.

32. Lin LY, Lai LP, Lin JL, Du CC, Shau WY, Chan HL, *et al.* Tight mechanism correlation between heart rate turbulence and baroreflex sensitivity: Sequential autonomic blockade analysis. J Cardiovasc Electrophysiol 2002;13:427-31.

33. Sestito A, Valsecchi S, Infusino F, Sgueglia GA, Bellocci F, Zecchi P, *et al.* Differences in heart rate turbulence between patients with coronary artery disease and patients with ventricular arrhythmias but structurally normal hearts. Am J Cardiol 2004;93:1114-8.

34. Cygankiewicz I, Zareba W, Vazquez R, Vallverdu M, Cino J, Cinca J, *et al.* Relation of heart rate turbulence to severity of heart failure. Am J Cardiol 2006;98:1635-40.

35. Cygankiewicz I. Heart rate turbulence. Prog Cardiovasc Dis 2013;56:160-71.

36. Perkiomaki JS, Hamekoski S, Junttila MJ, Jokinen V, Tapanainen J, Huikuri HV. Predictors of long-term risk for heart failure hospitalization after acute myocardial infarction. Ann Noninvasive Electrocardiol 2010;15:250-8.

37. Ghuran A, Reid F, La Rovere MT, Schmidt G, Bigger JT Jr, Camm AJ, *et al.* Heart rate turbulence-based predictors of fatal and nonfatal cardiac arrest (The Autonomic Tone and Reflexes After Myocardial Infarction substudy). Am J Cardiol 2002;89:184-90.

38. Ikeda T, Miwa Y, Abe A, Nakazawa K. Usefulness of heart rate turbulence for predicting cardiac events in patients with nonischemic dilated cardiomyopathy. J Electrocardiol 2011;44:669-72.

39. Esler M, Jennings G, Korner P, Willett I, Dudley F, Hasking G, *et al.* Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. Hypertension 1988;11:3-20.

40. Yucha CB. Use of microneurography to evaluate sympathetic activity in hypertension: A brief review. Appl Psychophysiol Biofeedback 2000;25:55-63.

41. Naver HK, Blomstrand C, Wallin BG. Reduced heart rate variability after right-sided stroke. Stroke 1996;27:247-51.

42. Korpelainen JT, Sotaniemi KA, Myllyla VV. Autonomic nervous system disorders in stroke. Clin Auton Res 1999;9:325-33.

43. Singh AS, Atam V, Yathish BE, Das L, Koonwar S. Role of erythrocyte sedimentation rate in ischemic stroke as an inflammatory marker of carotid atherosclerosis. J Neurosci Rural Pract 2014;5:40-5.

44. Hotta H, Uchida S. Aging of the autonomic nervous system and possible improvements in autonomic activity using somatic afferent stimulation. Geriatr Gerontol Int 2010;10(Suppl 1):S127-36.

45. Parashar R, Amir M, Pakhare A, Rathi P, Chaudhary L. Age related changes in autonomic functions. J Clin Diagn Res 2016;10:CC11-5.