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ORIGINAL ARTICLE

The relationship between lesion lateralization and heart rate variability, functional recovery status, and mortality rate in patients with ischemic stroke

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ABSTRACT

Objectives: This study aimed to investigate autonomic dysfunction in acute ischemic stroke and its relationship with hemispheric lateralization, localization, and prognosis.

Patients and methods: The study was conducted with 60 patients (32 males, 28 females; mean age: 70.5±14.0 years; range, 36 to 89 years) with acute ischemic stroke and 30 healthy controls (14 males, 16 females; mean age: 69.6±11.3 years; range, 30 to 70 years) between December 1, 2018 and December 31, 2019. The location of the infarct was evaluated by computed tomography or cranial magnetic resonance imaging. Heart rate variability (HRV) was evaluated using the frequency-based spectral analysis method. The National Institute of Health (NIH) stroke scale was used for neurological deficit evaluation, and the modified Rankin scale was used for the prognosis.

Results: There were no differences between the hemispheres in baseline NIH values. High-frequency power value, one of the HRV parameters, increased in all patients (p=0.036). When evaluated according to insular involvement regardless of the side, all HRV parameters increased in insular strokes; low-frequency power value (p=0.053) increased particularly in right insular strokes, and very low-frequency power value increased in left insular strokes (p=0.039). The mortality rate increased in strokes affecting the insular region without any difference between hemispheres (p=0.015).

Conclusion: As reported in previous studies, the insula disrupted cardiac autonomic balance more than other hemispheric areas, and the right insula increased cardiac sympathetic activity. In addition, insular stroke increased mortality rates.

Keywords: Arrhythmia, heart rate variability, insula, stroke, sudden cardiac death.

Most of the risk factors for stroke are due to cardiovascular problems; however, stroke leads to some cardiac changes.[1] These abnormalities may depend on the location and size of the lesion. Areas such as insula, limbic cortex, and hypothalamus are connected with the autonomic system. Regardless of primary heart disease, if these regions are damaged, catecholamine levels rise, resulting cardiac arrhythmias. It is believed arrhythmias and cardiac involvement affect the prognosis of stroke.[2]

The connection between the brain and heart was first demonstrated by Levy's sympathetic denervation, which eliminated premature ventricular beats. Two possible mechanisms considered by stroke affect the cardiac system. These are centrally-mediated catecholamine release and neuronal effects of nerve endings that originate from the central nervous system and end in the heart.[3] Catecholamines cause impairment in permeability by altering membrane potential in calcium-dependent myocardial cells,

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and arrhythmias are prevented by cutting fibers originating from the hypothalamus.[3,4] Clinical studies found insular cortex damage consequences such as arrhythmia, myocardial damage, and changes in catecholamine and glucose levels.[5] Oppenheimer et al.[5,6] reported that the stimulation of the left insula resulted in bradycardia and that the stimulation of the right insula resulted in tachycardia in human studies. Eckardt et al.[7] reported that the QT duration was prolonged in insular strokes. Kaya et al.[8] reported that the QRS duration was prolonged in cerebellar infarct. Christensen et al.[9] observed that atrial fibrillation (AF), atrioventricular block, premature beats, and mortality were more common in right insular cortex lesions. The rate of sudden death due to arrhythmias in patients with acute stroke was reported to be 6%.[10] Factors affecting the mortality rate after stroke include initial severity and type of stroke, location of the lesion, and presence of impaired consciousness.[11] Thus, we aimed to investigate the relationship between autonomic dysfunction and mortality rate with the location of lesions in patients with stroke. We used Heart rate variability (HRV) parameters, which is a noninvasive test based on cardiovascular reflexes, to evaluate autonomic dysfunction.[12]

Heart rate variability analysis is used to evaluate sinoatrial response to autonomic stimuli and to predict mortality risk in selected patient populations. Factors that lead to periodic fluctuations in heart rate are respiration, thermoregulation, baroreflex mechanisms.[12] The distribution of spectral power density in frequency areas is examined in frequency-based spectral analyses used to determine HRV. It consists of the following five frequency bands: total power (TP), low-frequency power (LFP), high-frequency power (HFP), very-low-frequency power (VLFP), and ultra-low-frequency power (ULFP). Frequency measurements are made by separating periodic heart rate oscillations into four primary frequency bands with spectral power density analysis.[13] The clinical significance of ULFP and VLFP, which constitute the majority of TP, is unknown. Efferent vagal activity is associated with HFP component. Low-frequency power is accepted as an indicator of sympathetic activity. Additionally, characterizing baroreflex sensitivity is important. Rarely vagal activity is associated with LFP.[13,14] The ratio of LFP to HFP (LFP/HFP) is regarded as a measure of sympathovagal balance. In a study evaluating patients with acute ischemic stroke, Giubilei et al.[15] found a significant increase in VLF and a decrease in LFP and HFP in patients. Barron et al.[16] found that the decrease in parasympathetic innervation was more pronounced in right hemisphere lesions. Tokgözoglu et al.[17] found a significant reduction in HRV parameters in patients with the stroke which was more commonly associated with right insular lesions. Dütsch et al.[18] reported a significant increase in LFP, LFP/HFP, and a significant decrease in HFP in right hemisphere lesions.

PATIENTS AND METHODS

The noninvasive clinical study was conducted at the Cumhuriyet University Faculty of Medicine, Department of Neurology between December 1, 2018 and December 31, 2019. A total of 60 patients (32 males, 28 females; mean age: 70.5±14.0 years; range, 36 to 89 years) and with acute ischemic stroke in the first three days of the disease were included in the study. Areas of the lesion were detected by computed tomography or magnetic resonance imaging, and 30 healthy controls (14 males, 16 females; mean age: 69.6±11.3 years; range, 30 to 70 years) were included. All patients and/or their relatives (for noncooperative patients). Patients with no lesions on brain imaging, multiple infarcts in different cerebral hemispheres, or infarcts in the brainstem or cerebellum were excluded from the study. Patients with accompanying diseases that could affect the autonomic nervous system (dilated and hypertrophic cardiomyopathy, acute coronary syndrome, acute renal disease, respiratory failure, Stage 3 or 4 congestive heart failure, diabetes mellitus, alcoholism, AF, and ventricular arrhythmia), those using drugs that could affect the autonomic nervous system (beta-blockers, anticholinergic, cholinergic, or beta-agonist drugs, and angiotensin-converting enzyme inhibitors), and those receiving mechanical ventilation support were excluded. In the control group, exclusion criteria were determined as having a diagnosis that could affect the central nervous system (e.g., cerebrovascular disease, brain tumor, epilepsy, and meningitis-encephalitis), accompanying diseases that could affect the autonomic nervous system (cardiomyopathy, acute coronary syndrome, acute renal disease, respiratory failure, Stage 3 or 4 congestive heart failure, diabetes mellitus, alcoholism, AF, and ventricular arrhythmia), and drugs that could affect the autonomic system. Written informed consent was obtained from all participants. The

TABLE 1
Frequency domain measures of HRV

Variables	Frequency range	Effect
HFP	0.15-0.4 Hz (2.5-7 sec)	Parasympathetic activity and vagal tone
LFP	0.04-0.15 Hz (7-25 sec)	Sympathetic activity
VLFP	0.0033-0.4 Hz (25-300 sec)	Efferent sympathetic activity
ULFP	0.0033 Hz (<300 sec)	Circadian oscillations in heart rate

HRV: Heart rate variability; HFP: High-frequency power; LFP: Low-frequency power; VLFP: Very low-frequency power: ULFP: Ultra low-frequency power.

study protocol was approved by Cumhuriyet University Clinical Research Ethics Committee (Date 14.01.2020, No: 2020-01/94). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The National Institute of Health (NIH) stroke scale was used to determine initial stroke severity, and disability was evaluated the modified Rankin scale (mRS) initially and at the end of the third month following stroke. In addition to the clinical cardiac evaluation and daily electrocardiogram recordings, patients had their HRV measured within the first three days of the stroke. Patients were monitored with a bedside monitor for 24 h on admission. Cardiac necrosis was ruled out by creatine kinase myocardial isoenzyme measurements. Sudden death was considered if symptoms of a patient, whose clinical condition was stable during the hospitalization period, started to deteriorate 1 h before death or death occurred during sleep.[17]

Electrophysiological recording was performed in the neurobiophysiological recording system in the autonomic laboratory of the Department of Neurology, Cumhuriyet University, Faculty of Medicine. Heart rate variability was determined using frequency-based spectral analysis software NeXus-4 physiological data acquisition device (Human Karigar, Pune, India) and Biotrace+ software (Human Karigar, Pune, India) were used for measurements. The device measured heartbeat signals via a blood volume pulse sensor attached to a finger. Data were collected and analyzed using the HRV protocol of software. Total power, LFP, VLFP, HFP, and LFP/HFP values obtained from frequency domain analyses of data were recorded (Table 1).

Activities, such as exercise, and consumption of substances that could cause sympathetic activation were prevented within 1 h of HRV measurement in all individuals. Measurements were taken when vital signs were stable in the first three days of the stroke. Measurements of individuals with fever, decreased oxygen saturation, blood pressure exceeding 180/110 mmHg was postponed. Pulse sensor of the device was placed on the patient's thumb. Measurements were performed in the supine position for at least 10 min. Artificial intelligence-assisted technologies were not used in this study.

Statistical analysis

Data were analyzed using Biotrace+ software (Human Karigar, Pune, India). The Kolmogorov-Smirnov test was used when parametric test assumptions were fulfilled. The Mann-Whitney U test was used to compare the measurements obtained from independent paired groups when parametric test assumptions for the significance of the difference between means were not fulfilled. The Kruskal-Wallis test was used to compare data obtained from more than two groups in terms of a variable obtained by measurement. The chi-square test and Fisher's exact test were used to evaluate data obtained by calculation. A p-value <0.05 was considered statistically significant.

RESULTS

The patient and control groups were similar in terms of age (p=0.761) and sex (p=0.551). In the patient group, 30 (33.3%) individuals had lesions on the right side, and 30 (33.3%) individuals had lesions on the left side. Of the patients, 45 (75%) had middle cerebral artery (MCA), 13 (21.7%) had posterior cerebral artery, and two (3.3%) had anterior cerebral artery infarcts. Nineteen (31.7%) patients had insular involvement, and 41 (68.3%) had no insular involvement. There was insular involvement in 19 patients, and the insula was preserved in 21. Insular involvement was similar based on lateralization (p=0.781). The degree of

TABLE 2
Comparison of HRV values of patient and control groups

	n	Mean±SD	Median	*p*
TP				
Patients	60	6854.55±15719.16	1442.00	0.077
Controls	30	7402.43±21856.93	764.00	
VLFP				
Patient	60	1370.41±2329.80	346.50	0.162
Control	30	3053.10±11657.78	228.00	
LFP				
Patient	60	2335.06±5555.48	395.50	0.140
Control	30	1943.56±6019.47	287.00	
HFP				
Patient	60	3149.16±9453.57	471.50	0.036*
Control	30	2405.96±7682.75	187.50	
LFP/HFP				
Patient	60	1.39±1.05	1.00	0.423
Control	30	1.63±1.26	1.50	

HRV: Heart rate variability; SD: Standard deviation; TP: Total power; VLFP: Very low-frequency power; LFP: Low-frequency power; HFP: High-frequency power; * p<0.05.

TABLE 3
Comparison of HRV values based on hemispheric lateralization

	n	Mean±SD	Median	*p*
TP				
Right	30	7578.43±16169.92	1973.00	0.225
Left	30	6130.66±15496.89	1196.50	
VLFP				
Right	30	1378.10±2282.81	342.00	0.451
Left	30	1362.73±2414.92	360.50	
LFP				
Right	30	3065.46±7304.60	571.50	0.311
Left	30	1604.66±2886.17	277.50	
HFP				
Right	30	3134.96±6862.56	776.00	0.110
Left	30	3163.36±11607.18	417.00	
LFP/HFP				
Right	30	1.15±0.82	0.90	0.149
Left	30	1.63±1.22	1.25	

HRV: Heart rate variability; SD: Standard deviation; TP: Total power; VLFP: Very low-frequency power; LFP: Low-frequency power; HFP: High-frequency power.

neurological deficit was compared in right and left hemisphere strokes. The ratio between the hemispheres was similar to the baseline NIH score. For the evaluation of neurological deficits in the third month, three patients could not be reached. When mRS scores were compared, a difference was not found between the hemispheres (p=0.228). When HRV values of the two groups were compared, HFP was higher in the patient group, whereas the other parameters (TP, LFP, VLFP, and LFP/HFP) were similar between the groups (Table 2).

TABLE 4
Comparison of HRV values based on insular involvement

	n	Mean±SD	Median	*p*
TP				
Insula (+)	19	13464.78±21147.48	3211.00	0.004*
Insula (–)	41	3791.26±11525.61	877.00	
VLFP				
Insula (+)	19	2382.78±2780.13	749.00	0.004*
Insula (–)	41	901.26±1953.40	236.00	
LFP				
Insula (+)	19	4153.94±6192.35	1004.00	0.004*
Insula (–)	41	1492.17±5095.92	274.00	
HFP				
Insula (+)	19	6928.36±14895.94	933.00	0.012*
Insula (–)	41	1397.82±4694.97	359.00	
LFP/HFP				
Insula (+)	19	1.50±1.21	0.90	0.842
Insula (–)	41	1.34±0.99	1.11	

HRV: Heart rate variability; SD: Standard deviation; TP: Total power; VLFP: Very low-frequency power; LFP: Low-frequency power; HFP: High-frequency power; * p<0.05.

TABLE 5
Heart rate variability values based on lateralization and insular involvement

	LFP	*p*	VLFP	*p*
Left insular stroke	3335.44	0.090	2791.44	0.039*
Left hemisphere stroke	862.90		750.42	
Right insular stroke	4890.60	0.033*	2015.00	0.053
Right hemisphere stroke	2152.90		1059.65	

HRV: Heart rate variability; LFP: Low-frequency power; VLFP: Very low-frequency power; * p<0.05.

TABLE 6
Mortality rates based on insular involvement

Insular involvement	Ex	Alive	Total	*p*
Yes				
Number	4	15	19	
%	21.1	78.9	100.0	
No				0.015*
Number	1	40	41	
%	2.4	97.6	100.0	
Total number	5	55	60	
%	8.3	91.7	100.0	

Ex: Exanimate; * p<0.05.

No difference was found between HRV values in right and left hemisphere strokes (Table 3). The HRV values were similar in right and left MCA involvement. When HRV values were compared according to insular involvement without side differentiation in subgroup analyses, LFP, HFP, VLFP, and TP increased in patients with insular involvement (Table 4).

When HRV values were compared according to lateralization and insular involvement, LFP increased in those with right insular involvement compared to those with preserved right insula, and VLFP increased in those with left insular involvement compared to those with preserved left insula (Table 5). The rates were similar in comparison to HRV values concerning the right and left sides in insular strokes.

There was no difference between the mortality rates of patients with right- and left-sided stroke (p=0.353). Mortality rates increased in insular strokes compared to those with a spared insula, regardless of side (Table 6). Of the patients who died, one had right MCA, three had left MCA, and one had left posterior cerebral artery strokes. And all patients with MCA strokes who died had insular involvement. One patient who died on admission was considered sudden death. Blood laboratory tests and infective markers of this patient were normal. There was no sudden deterioration without any initial deterioration in the neurological status. The initial NIH score of this patient was 17, and the patient had a subtotal MCA stroke involving the right insula. Other patients died during the three-month follow-up period after discharge.

DISCUSSION

Some cardiac complications may occur as a result of systemic effects caused by stroke. In several studies, the rate of development of cardiac complications ranges between 40% and 96%.[7,9,19] Using the HRV parameter, we demonstrated the cardiac involvement that may occur after stroke. When HRV parameters were compared between groups, we found an increase in HFP in the patient group, unlike most of the previous studies. In one of the rare studies contradicting these results, Lubjuhn et al.[20] experimentally induced brain ischemia in mice, and contrary to human studies, they found increased HRV parameters and increased parasympathetic tone. Ottani et al.[21] found a parasympathomimetic increase in an experimental study in animals and showed that the reason for this was the stimulation of the vagal pathway by increased endogenous melanopeptides with neuroprotective effects after brain ischemia. The vagus-mediated anti-inflammatory pathway can also be stimulated with transcutaneous messages and some drugs, which are known to increase HRV.[22] Patients with known use of drugs that could affect the autonomic system were not included; however, drugs that affect the sympathovagal balance, particularly statins, may have been initiated during hospitalization. The increase in vagal tone found in the patient group may be associated with these factors.

Many studies reported that the parasympathetic tone decreased and the balance was disrupted in favor of sympathetic activity in right hemisphere strokes.[16,17,23] Dütsch et al.[18] found a significant increase in LFP and LFP/HFP and a significant decrease in HFP in right hemisphere lesions. A similar difference was not found in the present study according to hemisphere lateralization. We believe this is due to the small number of patients included in the study. In our study, TP, VLFP, LFP, and HFP increased in insular strokes compared to the group with a spared insula. When the right and left strokes were examined in subgroups based on insular involvement, increased LFP in right insular strokes and increased VLFP in left insular strokes were observed. No statistical difference was observed when right and left insular strokes were compared within themselves. These findings highlight the regulatory role of the insula in autonomic function, with the right insula serving as an important center for the sympathetic system. The insular cortex has an inhibitory effect on the activation of the sympathoadrenal system, and the involvement of this cortex results in decreased inhibitory insular activity. Insular hemispheric lesions cause an increase in blood pressure and pulse rate.[24] Sposato et al.[25] followed stroke patients to evaluate prognosis and found the relationship with poor prognosis and mortality more pronounced in patients with right insular stroke. Christensen et al.[9] found that electrocardiogram changes were more common in right insular cortex lesions, and mortality was higher in those with right insular cortex lesions. Tokgözoglu et al.[17] reported that all seven cases that resulted in sudden death had insular lesions. Similarly, we found an increase in LFP, particularly on the right side, in all insular strokes

and increased rate of mortality in insular strokes. Of five patients who died in our study, four had an MCA stroke, and four had insular involvement. There was right insular involvement in a patient with sudden death. Furthermore, we could not obtain a significant finding that could lateralize the mRS scores in terms of the baseline NIH value and functional recovery status at the third month.

There were some limitations to this study, the most important of which were the low number of patients with insular lesions and the short follow-up period. In addition, autonomic functions were evaluated only with the HRV method, which could not be correlated with any molecular parameter. Additionally, patients underwent echocardiography and rhythm Holter monitoring during the hospitalization but not in the acute phase (the first three days of stroke). Lastly, we did not perform echocardiography and rhythm Holter monitoring in the control group. Therefore, we could not present a statistical comparison.

In conclusion, the findings of our study suggest that the insula disturbed the cardiac autonomic balance more than other hemispheric areas, the right insula increased sympathetic activity, and the resulting autonomic dysfunction increased the risk of mortality in patients with ischemic stroke. Being more attentive while following patients with insular stroke may contribute to better prognosis and may protect from sudden death.

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Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Medical practice, literature review, data collection or processing, writing: A.G.S.; Analysis or interpretation, design: A.G.S., B.C.; Consept, idea, funding: A.S.T.

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