DYSAUTONOMIA FOLLOWING ACUTE ISCHEMIC STROKES: A SINGLE INSTITUTIONAL EXPERIENCE

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Submitted: 15/1/2021; Accepted: 10/10/2021; Published: 21/3/2022

ABSTRACT

Background

Many studies have found that patients with ischemic stroke can develop autonomic system disturbances, affecting the heart, causing different types of arrhythmias and even sudden death.

Objectives

To analyze the occurrence of cardiovascular autonomic dysfunction and cardiac arrhythmias after acute ischemic stroke.

Patients and Methods

This case-controlled study was conducted at the Rizgary Teaching Hospital from July 1st, 2018, to September 30th, 2019. Fifty patients with acute ischemic stroke were enrolled consecutively and were age-matched and gender-matched with a group of 50 individuals (control group). Four bedside autonomic function tests (deep breathing, heart rate response to standing, isometric handgrip test, and blood pressure response to standing) were used to assess autonomic dysfunction during the acute post-stroke phase. In addition, all patients and controls underwent 24-hour Holter cardiac monitoring.

Results

Although abnormal autonomic function testing was more frequent in post-stroke cases than in healthy controls, there was no statistically significant difference in these results among stroke sub-groups. There were more arrhythmias in patients with stroke in comparison with the control group; premature ventricular and atrial contractions were more frequent in stroke patients than in the control group (P-value <0.001 and P-value<0.001, respectively).

Conclusion

Cardiac dysautonomia is common in patients with acute ischemic stroke, and cardiac dysrhythmias are commonly encountered in patients with insular infarctions. Whether these dysrhythmias are life-threatening or not, further analytic studies are required to uncover their clinical significance.

Keywords: *Ischemic stroke, Arrhythmia, Autonomic function tests, Dysautonomia.*

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https://doi.org/10.17656/jsmc.10342

INTRODUCTION

Stroke has been defined as a rapidly developing focal or global clinical sign of brain dysfunction; the resulting features should last at least 24 hours or end with death. There should be no clear aetiology other than vascular [1] .Stroke is responsible for about10% of all deaths at a global level [2]. In addition, in developing countries, it is considered a significant public health problem; morbidity and mortality rates have been escalating and have reached an epidemic level while representing a burden a challenge for the healthcare systems. Approximately 65% of stroke deaths occur in low resources countries [3]. The development of cardiac events has accounted for a more significant percentage of mortality after stroke itself; the risk of fatal cardiac events was about2 times the risk of fatal stroke after five years [4].

Over a long period of 3 decades, some evidence has been documented to demonstrate that, in a subgroup of patients, acute ischemic stroke is linked to cardiac insult, even in the absence of acute cardiac ischemia [5]. Proofs of neurogencardiac insultult have arrived from animal models of middle cerebral artery occlusions [6]. The diffuse cardiac cell insult and injury is characterized by micro-islands of cell necrosis and monocytic cell infiltrations subendocardial haemorrhage; the co-called myocytolysis. High levels of the hormone/ neurotransmitter epinephrine were found in patients with acute ischemic stroke who demonstrated elevated serum levels of troponin I when compared to those who have normal ones [7].

The myocardial cell alterations detected after stroke are similar to those found in Takotsubo cardiomyopathy (which resembles acute coronary syndrome); these have been receiving more and more attention since Takotsubo cardiomyopathy was initially described in the year 1990. Takotsubo cardiomyopathy patients demonstrate hypokinesis or akinesis of the left ventricle's apex, elevated ST-segment, and elevated plasma levels of troponin. A stressful event commonly precedes SinceTakotsubo cardiomyopathy and dysautonomia develops with a catecholamines output surge, this is supposed to be the underlying pathophysiology. Typically, Takotsubo cardiomyopathy is a reversible condition, but, in addition, it may incite the development of life-threatening dysrhythmia, which can end up with sudden death. Brain insular electrical stimulation, in addition to stimulation of the anterior cingular cortex as well as the medial temporal lobe, have all resulted in alterations in both cardiac rate and systemic blood pressure levels [8,9].

PATIENTS AND METHODS

This case-controlled study was conducted at the Rizgary Teaching Hospital from July 1st, 2018, to September 30th, 2019. Fifty patients with acute ischemic stroke were enrolled consecutively and were age-matched and gender-matched with a group of fifty individuals attending our outpatients' clinic.

Inclusion criteria and initial workup

Patients with a clinical and imaging diagnosis of acute ischemic stroke were enrolled consecutively. Patients were excluded from the study if they had a fever, structural heart disease (e.g., cardiomyopathy), chronic pulmonary disease (e.g., chronic persistent asthma), cardiac dysrhythmia (e.g., permanent atrial fibrillation), taking a medication which could affect the heart rate (e.g., beta-blockers), electrolyte and acid-base disturbances (e.g., hypokalemia, uremia).

All patients underwent a battery of investigations within three days of hospital admission: complete blood counts, ESR, urea and electrolytes, liver function tests, blood sugar, blood lipids, TSH, chest X-ray, 12-lead resting electrocardiography, trans-thoracic echocardiography, and 24-hour Holter monitoring. In addition, all participants(n=100) underwent brain CT scans; only the patients' group (n=50) underwent brain MRI examination with diffusion-weighted sequences.

Patients and individuals in both groups were assessed and managed by different neurologists and neurology residents. Hypertension was ascertained if the patient had a history of hypertension or systolic blood pressure >140 mmHg or diastolic blood pressure >90 mm Hg. The patient was considered diabetic if he had a history of diabetes or had a random blood glucose level of more than 200 mg/dl or a recent fasting blood glucose level of more than 126 mg/dl on two occasions. Dyslipidemia was defined if one or more of the following had been detected: serum total cholesterol >240 mg/dL, serum triglycerides (TG) >200 mg/dl, low-density lipoprotein (LDL) >160 mg/dl, and/or high-density lipoprotein (HDL) <40 mg/dl (10-12).

Four bedside autonomic function tests (deep breathing, heart rate response to standing, isometric handgrip test, and blood pressure response to standing) were

used to assess autonomic dysfunction during the acute post-stroke phase and the control group. First, the parasympathetic nervous system function was assessed by the heart rate variability with deep breathing and the response to standing (30:15 ratio). Next, the sympathetic nervous system function was assessed using the isometric handgrip test and blood pressure response upon standing.

Cardiac rate variability with deep breathing

The patients' heart rate variability was measured using a bedside test of one minute while patients did force deep respiration. It was carried out using a 12-lead electrocardiography machine. The patients were lying supine on a bed, and lead II of the ECG machines was used for recording the heart rate. After getting a stable heart rate, patients were told to breathe in and out profoundly at 6-8 cycles per minute (each respiratory cycle took 10 seconds; 5 seconds for the inspiration and the other 5 seconds for the expiration). The shortest and the most prolonged R-R intervals were determined, the heart rates were calculated, and the difference between these two rates was considered the heart rate variability. The R-R intervals around ventricular ectopic beats were excluded from the measurement. The heart rate variability factor should not be less than 11-15 beats/ minute in normal individuals.

Heart rate response to standing (30:15 ratio)

Patients were asked to stand up while the ECG machine's leads were still connected to them. Another one minute was recorded, and the ratio between the R-R interval of the 30th and 15th beats was calculated. The ratio of ≤1is considered abnormal.

Blood pressure response to standing

Fluctuations of blood pressure were assessed by calculating the difference between the baseline supine blood pressure and the blood pressure after standing up for at least 3 minutes. A fall in the systolic blood pressure of greater than 20 mmHg and by greater than ten mmHg (diastolic) is considered an abnormal reading.

Isometric handgrip test

An incremental value in the diastolic blood pressure was detected during isometric pressing of a handgrip dynamometer; this is done at approximately 1/3rdof the maximum contraction force and should last for 3-5 minutes. In addition, multiple blood pressure measurements were documented at the contralateral limb at a one-minute interval. The test value was expressed as the difference between the highest diastolic pressure during the test and the average value of the diastolic pressure measurement while at rest. Typically, the result should be more significant than 15 mmHg.

24-hour Holter monitoring

A 24-hour Holter monitoring (HM) was carried out in all patients; this was done within3 days of their hospital admission; the control group of individuals did HM during their ordinary daily activities. This type of ECG recording was carried out using a 3-channel bipolar device, and it was scrutinized after digitization. As a result, the following data were obtained in each patient:

1. The total number of ventricular ectopic beats (premature ventricular complexes; VPCs).

2. The occurrence of ventricular couplets (VC), ventricular bigeminy, ventricular trigeminy, and ventricular ectopic run length (VERL).

3. The development and number of episodes of non-sustained ventricular tachycardia (NSVT; defined as three or more consecutive PVCs).

4. The total number of premature supraventricular contractions (PSVC).

5. Presence of supraventricular couplets (SVC), supraventricular bigeminy, supraventricular trigeminy, and supraventricular ectopic run length (SVERL).

6. Presence of supraventricular tachyarrhythmias (SVT) episodes, including atrial tachycardia and atrial fibrillation.

Statistical analysis

Our data were analyzed by an independent statistician using the statistical package for social sciences (SPSS), version 19.0. First, the Chi-square test of association was used to compare proportions. Fisher's exact test was used when the chi-square was not applicable. Next, the Mann-Whitney test (non-parametric test) was used to compare the mean ranks of the two groups. Finally, the Kruskal-Wallis test was used to compare the mean ranks of four groups. A P-value of≤0.05 was considered statistically significant.

RESULTS

In each group, 34 (68%) out of 50 individuals were above 59 years; the rest (32%) were between the ages of 40-59 years (P-value=1.0). Males outnumbered females; 68% of the stroke group and 60% of the control group. Hypertension was the most familiar vascular risk factor. A history of hypertension was present72% of the stroke group and 64% of the control group (P-value <0.061). Hypertension at the time of hospital admission was detected in 80% of the stroke group, while it was present in 60% of the control group during their outpatient's clinic visit (P-value <0.029). Concerning dyslipidemia (hypercholesterolemia and hypertriglyceridemia), there was no statistically significant difference between the two groups (P-value <0.18 and P-value <0.16, respectively).

Table 1 shows no statistically significant difference between the two groups concerning their baseline electrocardiography and echocardiographic findings.

Autonomic function tests

All the autonomic tests demonstrated statistically significant differences between the stroke and control groups (Table 2).

Stroke patients were divided into subgroups according to the side and site of the infarcted area of the brain and the presence or absence of insular involvement. Twenty-nine (58%) out of the 50stroke patients developed a right-sidedhemispheric infarction, while 21 (42%) out of those 50 cases had developed a left-sided hemispheric infarction. In addition, the right insular area was infarcted 13 (44.8%) out of the 29 patients with right-sided hemispheric infarction. In comparison, the insula was damaged in 8 (38%) out of the 21 patients with left-sided lesions (Tables 3 and 4).

Cardiac dysrhythmia

All tests demonstrated statistically significant differences between the stroke and control groups (table 5). In addition, the mean ranks of cardiac dysrhythmias in the stroke sub-groups showed statistically significant differences among those subgroups (table 6; Figures 1 and 2).

Table 1.Baseline electrocardiographic and echocardiographic findings in the patients' (stroke) group (n=50) and control group (n=50).

	Patients n (%)	Control n (%)	P-value*
ECG			
Normal	33 (66)	36 (66)	
Sinus Tachycardia	3 (6)	1(2)	
Ectopic beats	2(4)	4(8)	0.586
T-inversion	10(20)	6(12)	
Bradycardia	2(4)	3(6)	
Echocardiography			
Normal	43 (86)	44 (88)	
LV dysfunction	6(12)	4(8)	0.8
LA dilatation	1(2)	2(4)	

***Fisher's exact test. P-value ≤0.05 is statistically significant.**

Table 2. Comparison of autonomic function tests between the patients' group (n=50) and control group (n=50).

Autonomic function tests	Patients n (%)	Control n (%)	P-value*
A. Parasympathetic			
Deep breathing test			
Normal	8 (16)	44 (88)	
Borderline	4(8)	5(10)	**<0.001**
Abnormal	38(76)	1(2)	
Heart rate response to standing (30:15 ratio)			
Normal	10 (20)	43 (86)	
Borderline	12(24)	4(8)	**<0.001**
Abnormal	28(56)	3(6)	
B. Sympathetic			
Handgrip test			
Normal	2 (4)	42 (84)	
Borderline	18(36)	7(14)	**<0.001**
Abnormal	30(60)	1(2)	
Blood pressure response to standing			
Normal	42 (84)	48 (96)	
Abnormal	8(16)	2(4)	**0.046**

***Fisher's exact test. P-value ≤0.05 is statistically significant.**
- For normal values and ranges, please refer to the Methods section above.

Table 3. Parasympathetic autonomic tests according to the site and side of the infarcted area of the brain (n=50).

Parasympathetic tests	Rt infarction with insular involvement n(%)	Rt infarction without insular involvement n(%)	Lt infarction with insular involvement n(%)	Lt infarction without insular involvement n(%)	P-value*
Deep breathing test					
Normal	8(15.4)	0	13(25)	15(30.8)	
Borderline	0	13(25)	0	0	0.035
Abnormal	42(84.6)	37(75)	37(75)	35(69.2)	
Heart rate response to standing (30:15 ratio)					
Normal	0	25	12.5	38.5	
Borderline	12(23.1)	18.8	37.5	23.1	0.23
Abnormal	38(76.9)	56.3	50	38.5	

***Fisher's exact test. P-value ≤0.05 is statistically significant.**
- Rt, right; Lt left.
- For normal values and ranges, please refer to the Methods section above.

Table 4.Sympathetic autonomic tests according to the site and side of the infarcted area of the brain (n=50).

Sympathetic tests	Rt infarction with insular involvement (%)	Rt infarction without insular involvement (%)	Lt infarction with insular involvement (%)	Lt infarction without insular involvement (%)	P-value*
Handgrip test					
Normal	0	6.3	0	7.7	
Borderline	46.2	31.3	50	23.1	**0.8**
Abnormal	53.8	62.5	50	69.2	
Blood pressure response to standing					
Normal	76.9	75	87.5	100	**0.23**
Abnormal	23.1	25	12.5	0	

***Fisher's exact test. P-value ≤0.05 is statistically significant.**
- Rt, right; Lt left.
- For normal values and ranges, please refer to the Methods section above.

Table 5.Cardiac arrhythmia comparison between the stroke patients (n=50) and control group (n=50).

Variable	Patients (mean ranks)	Control (mean ranks)	P-value*
PVC	72.41	28.59	**<0.001**
VC	72.22	28.78	**<0.001**
Ventricular bigeminy	69.41	31.59	**<0.001**
Ventricular trigeminy	64.9	36.1	**<0.001**
VERL	72.2	28.8	**<0.001**
NSVT	54.5	46.5	**<0.001**
PSVC	70.9	30.1	**<0.001**
SVC	69.42	31.58	**<0.001**
Supraventricular bigeminy	59.54	41.46	**0.001**
Supraventricular trigeminy	60.42	40.58	**<0.001**
SVERL	69.89	31.11	**<0.001**

***P-value ≤0.05 is statistically significant.**
- PVC, ventricular premature contractions; VC, ventricular couplets; VERL, ventricular ectopic run length; NSVT, episodes of non-sustained ventricular tachycardia; PSVT, premature supraventricular contractions; SVC, supraventricular couplets; SVERL, supraventricular ectopic run length.

Table 6. Comparison of cardiac arrhythmias among the stroke patients' sub-groups (n=50).

Variable	Rt infarction with insular involvement(mean ranks)	Rt infarction without insular involvement (Mean ranks)	Lt infarction with insular involvement (mean ranks)	Lt infarction without insular involvement (mean ranks)	P-value
PVC	42.65	10.41	31.31	23.35	**< 0.001**
VC	42.88	11.38	33.06	20.85	**< 0.001**
Ventricular bigeminy	43.38	13.91	21.69	24.23	**< 0.001**
Ventricular trigeminy	40.88	19.75	25.06	17.46	**< 0.001**
VERL	40.58	9.31	31.13	26.88	**< 0.001**
NSVT	29.81	21.50	33.00	21.50	**0.004**
PSVC	33.27	12.56	40.50	24.42	**< 0.001**
SVC	31.58	14.53	40.25	23.85	**< 0.001**
Supraventricular bigeminy	31.04	16.75	43.06	19.92	**0.001**
Supraventricular trigeminy	30.00	18.31	39.88	21.00	**0.002**
SVERL	37.35	12.22	39.00	21.69	**< 0.001**

P-value ≤0.05 is statistically significant.

- Rt, right; Lt, left; PVC, ventricular premature contractions; VC, ventricular couplets; VERL, ventricular ectopic run length; NSVT, episodes of non-sustained ventricular tachycardia; PSVT, premature supraventricular contractions; SVC, supraventricular couplets; SVERL, supraventricular ectopic run length.

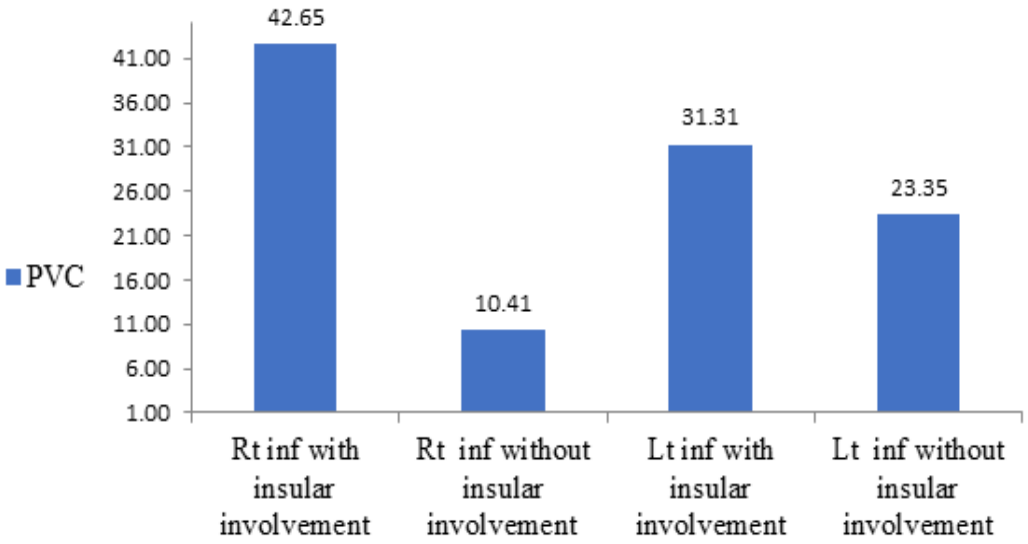

Figure 1. Premature ventricular contractions (PVC). Comparison of the "mean ranks" among stroke patients' subgroups (P-value <0.001).-Rt, right; Lt, left; inf, infarction.

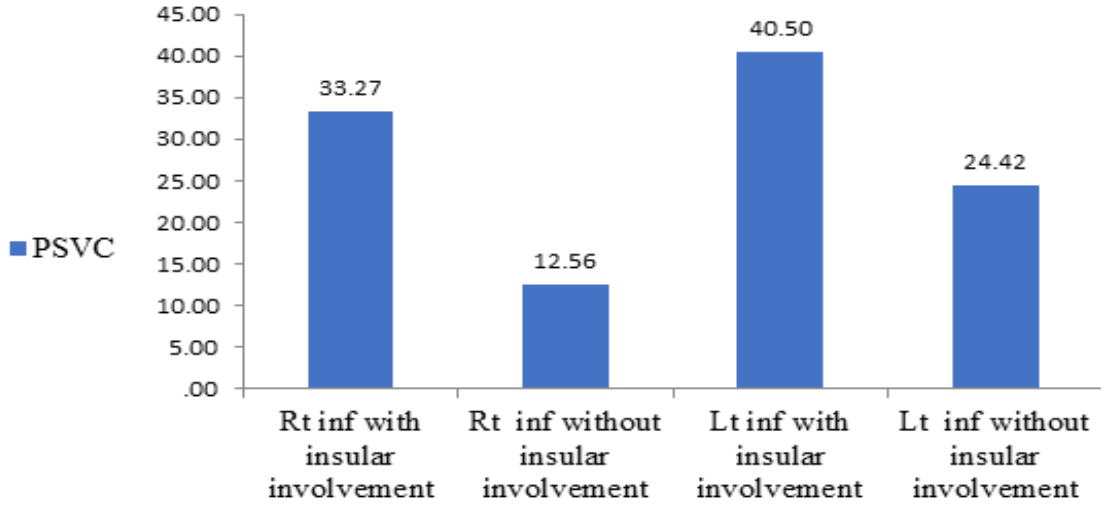

Figure 2. Premature supraventricular contractions (PSVC). Comparison of the "mean ranks" among stroke subgroups (P-value <0.001).-Rt, right; Lt, left; inf, infarction.

DISCUSSION

The findings reflect the gradual recovery of disorganized cardiac autonomic balance in those individuals who have developed ischemic stroke within a few months after the acute insult. The resulting heart rate variability still is significantly much lower, even after six months of the acute phase, when compared to healthy individuals. Research on a group of 122 patients who have had an ischemic and hemorrhagic stroke,84 patients (69%) demonstrated specific ECG abnormalities; ST-segment changes (34%), QT interval prolongation (31%), and atrial fibrillation (27%). The involvement of the insular cortex and previous attack of stroke independently predicted QT interval prolongation in patients who have developed small infarctions [13,14].

Many dysrhythmias (e.g., supraventricular tachycardia, ventricular tachycardia, bradycardia, atrial and ventricular ectopic, and atrial fibrillation) are commonly observed in patients in the acute stroke setting. One highly effective method for detecting severe dysrhythmia is telemetric monitoring in acute stroke patients. Most cardiac events were observed within the first 24 hours of the stroke event and admission to the stroke unit, but some may be observed later. In addition to older patients age, stroke severities were independent predictors of cardiac dysrhythmia. They may be applied for risk stratification and allocation of long-term cardiac monitoring after developing stroke. The current published guidelines do not mention clear-cut practical advice regarding who should undergo cardiac monitoring and how long it should be performed in patients with acute stroke. Because data on some factors and temporal profile of dysrhythmia onset in the acute setting are few [15,16-19].

Many studies have shown that patients with ischemic stroke can develop autonomic nervous system disturbances, affecting the heart and causing different arrhythmias and sudden death. Such anomalies form the nor reflect the existence of complex disorganization of autonomic system balance, probably affecting both sympathetic and parasympathetic nervous systems [20].

In this study, the mean age of ischemic stroke was (64±SD of 2 years). the results of a study conducted in the USA in which the mean age of ischemic stroke was (73±SD 12.9years) [21] However; a national study had found that the mean age of ischemic stroke is 59.88 ±SD of 15.09years [22] .

Hypertension was the most significant risk factor for ischemic stroke. The consistent with a study conducted by Ohira et al., which found that hypertension was the most prominent risk factor for ischemic stroke [23] Serum cholesterol and triglyceride showed elevated levels in more than half of cases (52% and 56%, respectively). Mahmood et al. had concluded that serum cholesterol elevation (42%) was more common than the elevation of serum triglyceride (4%) in Pakistani patients [24] .

There was a significant difference between stroke patients and the control group concerning the results

of the autonomic function tests. In post-stroke cases, most of the results were abnormal apart from the blood pressure response to standing (which was normal in 84%), in contrast to the control group, in whom most of the results were normal. In this study, parasympathetic autonomic function tests were abnormal in the majority of patients, while the blood pressure response to standing (which measures the sympathetic nervous system response) was normal in most cases; this may be due to sympathetic overactivity during the acute phase of the stroke to maintain a high cerebral blood flow. However, the handgrip test (which also assesses the sympathetic system activity) was abnormal in most stroke patients. The comparison of autonomic function tests between the patients and the control group showed statistically significant results. These results are consistent with a previous study. The major finding was suppressing heart rate response to parasympathetic stimuli in patients with brainstem infarction and those with hemispheric infarction. This under-functioning of parasympathetic output was mainly observed in the acute stroke setting and is clearly not just a temporary factor but a long-lasting event. Nevertheless, the difference between that study targets and their control individuals was statistically insignificant [(25)].

The site and side of the infarction and involvement of the insular lobe had not resulted in any change of the results of the autonomic function tests in our study. This contradicts another study carried out by Meyer et al., which showed that right insular cortex strokes are associated with an excessive and sustained increase in cardio-sympathetic tone [(26)]. This study also does not match the results of a study performed by Colivicchi et al., which showed that the decrease of all heart rate variability measures is more pronounced in patients with right-sided insular involvement [(27)] The explanation for this mismatch may be that the tests were performed manually in this study because of the absence of an autonomic function test laboratory in our hospital. The insular brain area is relatively a small one but is considered a complex structure that is located in the Sylvian fissure's depth. At the same time, the frontoparietal-temporal operculum covers it.

Several findings revealed that in terms of functionality, the insular cortex is disarrayed through the anterior-posterior pathway of the cortical hemispheric sensory domain; a head-to-head comparison of painful temperature and trivial touch stimulate using brain functional MRI studies has shown that pain perception was associated with stimulation of the anterior insular part.

In contrast, tactile stimuli perception was associated with overaction of the dorsal insular. As well as pain perception, the anterior insula has been connected to the processing of mild yet unpleasant external stimuli (e.g., teeth vibratory stimuli) in addition to gustatory and visceral afferent input [(15,28)]

Positron emission tomography (PET) studies in normal subjects confirm that noxious thermal stimuli activate the thalamus, insula, and secondary somatosensory cortex regions. Lesions of the insular cortex or the sub-insular white matter are associated with alterations in autonomic tone, resulting in impaired control of blood pressure and heart rate and ultimately life-threatening cardiac arrhythmias. Ischemic strokes limited to the insula are rare and have not been well studied. Research on insular lesions' consequences is complicated because most insular lesions are part of a larger infarct in the distribution of the middle cerebral artery [(15,29,30)].

Right hemispheric inactivation induced a significant decrease of blood pressure and an increase of high-frequency power of heart rate and blood pressure. Left inactivation increased both signals' heart rate, blood pressure, and low-frequency power and decreased baroreflex sensitivity by nearly 30%. Plasma noradrenaline was significantly elevated in a group of stroke patients compared with non-stroke controls. The cardiac rate physiological changes and fluctuation reflects the heart's ability to adapt itself to specific circulatory abnormalities and act as a critical factor for the determination of autonomic functions. Many researchers have found reduced heart rate variability in stroke patients, not only in the acute setting but also at one month and at six months of the original stroke event [(15, 30-32)].

There were more arrhythmias in patients with stroke in comparison with the control group, with premature ventricular contractions (PVC) showing mean ranks of 72.41in the patients versus 28.78 in the control subjects (P-value<0.001) and premature supraventricular contractions (PSVC) showing mean ranks of 70.9 in the patients versus30.1 in the control subjects (P-value<0.001). The results of this study agree with those of Colivicchiet al study, in which both ventricular and supraventricular arrhythmias were found to be more frequent and complex in all subgroups of ischemic stroke patients than in the control group [(27)].

In Colivicchi et al.'s study, right-sided brain infarctions were associated with more frequent arrhythmias than left-sided lesions. Furthermore, right insular damage was associated with more complex arrhythmias, namely ventricular couplets, non-sustained ventricular tachycardia, and sustained ventricular tachycardia than any other localization. In contrast, this study showed that right insular damage is associated with more premature ventricular contractions, while left insular damage is associated with more premature supraventricular contractions. In general, involvement of the insula, whether right-sided or left-sided, had resulted in more arrhythmias [27]

In conclusion, there were more abnormal autonomic function tests in ischemic stroke patients than in the control group. However, there was no statistically significant difference in autonomic function tests among stroke patients' sub-groups. Arrhythmias were more frequent in stroke patients than in the control subjects, and they were more familiar with the insular lobe infarctions. Premature ventricular contractions were encountered more frequently in right-sided insular lobe involvement, whereas premature supraventricular contractions were more frequent in left-side infarctions of the insula.

Declaration
Funding: None
Conflict of interest: None
Ethical approval: Obtained

REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. heart disease and Stroke Statistics-2019 Update: A Report from the American Heart Association. Circulation. 2019;139(10): e56-e528.

2. Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. Lancet Neurology. 2009;8(4):345-54.

3. Bender M, Jusufovic E, Railic V, Kelava S, Tinjak S, Dzevdetbegovic D, et al. High Burden of Stroke Risk Factors in Developing Country: The Case Study of Bosnia-Herzegovina. Mater Sociomed. 2017;29(4):277-9.

4. Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. Neurology. 2006;66(5):641-6.

5. Jespersen CM, Hansen JF. Myocardial stress in patients with acute cerebrovascular events. Cardiology. 2008;110(2):123-8.

6. Min J, Farooq MU, Greenberg E, Aloka F, Bhatt A. Cardiac dysfunction after left permanent cerebral focal ischemia: the brain and heart connection. Stroke. 2009;40(7):2560-3.

7. Barber M, Morton JJ, Macfarlane PW, Barlow N, Roditi G, Stott DJ. Elevated troponin levels are associated with sympathoadrenal activation in acute ischaemic stroke. Cerebrovasc Dis. 2006;23(4):260-6.

8. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J. 2088;155(3):408-17.

9. Kimmerly DS, O'Leary DD, Menon RS, Gati JS, Shoemaker JK. Cortical regions are associated with autonomic cardiovascular regulation during lower body negative pressure in humans. J Physiol. 2005;569(Pt 1):331-45.

10. Amin OS, Shwani S. Hypocholesterolemia and hypertensive intracerebral haemorrhage: Any association? Gulhane Med J. 2018;60(4):125-9.

11. Amin OSM. Bilateral internal carotid artery occlusion and recurrent ischemic stroke. BMJ Case Rep. 2015 June 8th;2015. PII: bcr2014207341.

12. Amin OSM. Lacunar strokes: a single institutional experience. Cukurova Med J. 2013;38(4):659-66.

13. Lakusic N, Mahovic D, Babic T. Gradual recovery of impaired cardiac autonomic balance within first six months after ischemic cerebral stroke. Acta Neurol Belg. 2005;105(1):39-42.

14. Tatschl C, Stöllberger C, Matz K, Yilmaz N, Eckhardt R, Nowotny M, et al. Insular involvement is associated with QT prolongation: ECG abnormalities in patients with acute stroke. Cerebrovasc Dis. 2006;21(1-2):47-53.

15. Lemieux F, Lanthier S,Chevrier MC, Gioia L,Rouleau I, Cereda C, et al. Insular Ischemic Stroke: Clinical Presentation and Outcome. Cerebrovasc Dis Extra. 2012;2(1):80-7.

16. Kallmünzer B, Breuer L, Kahl N, Bobinger T, Raaz-Schrauder D, Huttner HB, et al. Serious Cardiac Arrhythmias After Stroke: Incidence, Time Course, and Predictors--A Systematic, Prospective Analysis. Stroke. 2012;43(11):2892-7.

17. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for the management of ischaemic stroke and transient

ischaemic attack 2008. Cerebrovasc Dis. 2008;25(5):457-507.

18. Adams HP , Alberts MJ, Grubb RL, Bhatt DL, Brass L, Jauch EC, et al. Guidelines for the early management of adults with ischemic stroke. Circulation. 2007;115(20):e478–e534.

19. Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S. Predictors of early cardiac morbidity and mortality after ischemic stroke. Stroke. 2007;38(8):2295-302.

20. Malik M. Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and Clinical Use. Circulation. 1996;93(5):1043-65.

21. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of Ischemic Stroke Subtypes According to TOAST Criteria: Incidence, Recurrence, and Long-Term Survival in Ischemic Stroke Subtypes: A Population-Based Study. Stroke. 2001;32(12):2735-40.

22. Mawlood FJ.Prevalence of stroke in Hawler city; a household survey [dissertation]. Hawler: Hawler Medical College;2009.

23. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH, Folsom AR. Risk Factors for Ischemic Stroke Subtypes. Stroke. 2006;37(10):2493-8.

24. Mahmood A, Sharif MA, Khan MN, Ali UZ. Comparison of Serum Lipid Profile in Ischaemic and Haemorrhagic Stroke. J Coll Physicians Surg Pak. 2010;20(5):317-20.

25. Korpelainen JT, Sotaniemi KA, Suominen K, Tolonen U, Myllylä V. Cardiovascular autonomic reflexes in brain infarction. Stroke. 1994;25(4):787-92.

26. Meyer S,Strittmatter M, Fischer C, Georg T, Schmitz B. Lateralization in autonomic dysfunction in ischemic. NeuroReport. 2004;15(2):357-61.

27. Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac Autonomic Derangement and Arrhythmias in Right-Sided Stroke With Insular Involvement. Stroke. 2004;35(9):2094-8.

28. Sörös P, Marmurek J, Tam F, Baker N, Staines WR, Graham SJ. Functional MRI of working memory and selective attention in vibrotactile frequency discrimination. BMC Neurosci. 2007;8:48.

29. Davis KD, Kwan CL, Crawley AP, Mikulis DJ. Functional MRI Study of Thalamic and Cortical Activations Evoked by Cutaneous Heat, Cold, and Tactile Stimuli. J Neurophysiol. 1998;80(3):1533-46.

30. Sörös P, Hachinski V. Cardiovascular and neurological causes of sudden death after ischaemic stroke. Lancet Neurology. 2012;11(2):179-88.

31. Hilz MJ, Dütsch M, Perrine K, Nelson PK, Rauhut U, Devinsky O. Hemispheric influence on autonomic modulation and baroreflex sensitivity. Ann Neurol. 2001;49(5):575-84.

32. Myers MG, Norris JW, Hachinski VC, Weingert ME, Sole MJ.Cardiac sequelae of acute stroke. stroke. 1982;13(6):838-42.