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Heart rate variability of acute ischemic stroke patients according to troponin levels

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ABSTRACT

Objective: Neurogenic myocardial stunning is a type of stress-induced cardiomyopathy thought to be a result of dysregulation of the autonomic nervous system. Heart rate variability (HRV) analysis is a potential method for understanding the underlying mechanisms of autonomic dysfunction in ischemic stroke. The aim of the study was to investigate HRV in stroke patients in accordance with troponin levels.

Patients and Methods: Sixty-six patients (mean age 65 ± 13 years; 39 male) presenting with acute ischemic stroke were consecutively included. High-sensitive cardiac troponin I (hs-cTnI) levels were accepted as elevated when> 0.04 ng/mL. All patients underwent ambulatory electrocardiographic (ECG) monitoring within the first seven days to obtain time-domain and frequency-domain measures of HRV.

Results: Twenty patients (30.3 %) had elevated hs-cTnI. Patients with high troponin levels had significantly lower left ventricular ejection fraction (LVEF), higher ST-segment-T wave changes, and higher N terminal pro-brain natriuretic peptide (NT-proBNP) levels. Low-frequency/high-frequency (LF/HF) value was significantly higher in the troponin-positive group, but other ambulatory ECG monitoring parameters such as SDNN, SDANN, RMSSD, and pNN50 were similar among patients.

Conclusion: Neurogenic myocardial damage presenting with high troponin levels can be seen in ischemic stroke patients and may be associated with sympathetic overactivity.

Keywords: Myocardial stunning, Neurogenic cardiac injury, Troponin

1. INTRODUCTION

Neurogenic stunned myocardium (NSM) is a spectrum of cardiac changes seen after various neurologic events [1]. Cardiac abnormalities seen in NSM include electrocardiographic changes, an increase of cardiac biomarkers such as B-type natriuretic peptide and troponin, arrhythmias, and echocardiographic changes such as wall motion abnormalities with decreased ventricular ejection fraction (LVEF) and diastolic dysfunction [2,3]. Sympathetic overactivity and catecholamine surges that occur after neurological events or dysfunction of the autonomic nerve system after brain injury are the leading underlying mechanisms [4,5]. NSM, a reversible myocardial dysfunction, is mainly caused by dysfunction of the autonomic nervous system [6]. Heart rate variability (HRV) can be used as a biomarker of autonomic dysregulation in patients with ischemic stroke [7].

Heart rate variability refers to beat-to-beat variations in the duration of the RR intervals [8]. It is a non-invasive method used to understand the autonomic regulation of the heart [9]. With HRV it is possible to analyze parasympathetic or sympathetic activity and their response to different conditions. Reduced HRV has been reported in acute ischemic stroke patients compared to healthy controls [10]. Also, autonomic dysfunction has been linked to poor prognoses in ischemic stroke patients [11]. Changes in the autonomic nervous system after ischemic stroke may be associated with stroke recurrence and recovery [7]. Therefore, HRV has an important role in the detection of autonomic dysfunction after stroke.

The aim of our study was to investigate HRV parameters with ambulatory electrocardiographic (ECG) monitoring in patients with neurogenic stunned myocardium.

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2. PATIENTS and METHODS

The investigation conformed to the principles outlined in the Declaration of Helsinki. All participants gave written informed consent. The study was approved by the ethics committee of the Marmara University School of Medicine.

Seventy-eight consecutive patients admitted to the neurology clinics with the diagnosis of acute ischemic stroke were invited to participate in the study. After the exclusion of the 5 patients with artifacts in ambulatory ECG recordings and 7 patients with poor image quality for transthoracic echocardiography the remaining 66 patients were included. The Baseline National Institutes of Health Stroke Scale (NIHSS) of patients were noted at admission. Transient ischemic attacks (TIA) were not included in our study population because the diagnosis was based on subjective neurological evaluation.

A detailed medical history, physical examination, and 12-lead electrocardiography were obtained from all patients. Serum troponin I levels were analyzed by the Siemens ADVIA Centaur hs-cTnI assay (Siemens Healthcare Diagnostics, Deerfield, IL, USA), and a hs-cTnI > 0.04 ng/mL was accepted as elevated in our laboratory. A detailed transthoracic examination was performed using a commercially available system (Epiq 7, Philips Healthcare, Andover, MA, USA) by an experienced cardiologist within the first three days following acute ischemic stroke. Conventional left ventricular echocardiographic parameters were measured according to the standard recommendations and LVEF was calculated using the biplane Simpson method [12].

Heart Rate Variability Assessment

The ECG raw data was recorded in three channels using a miniature ambulatory ECG monitoring device, 'DMS 9800' for 24 hours and were digitalized with a 128-Hz sampling rate. HRV indices were measured with commercially available HRV software (Cardioscan 12.0, DMS, USA). Time domain and frequency domain analyses were performed using this software. For time domain analysis, the standard deviation of all normal-to-normal RR intervals (SDNN) and standard deviation of the mean of all 5-minute segments of normal RR intervals (SDANN) indicate sympathetic activity. As well as the root mean square of the sum of the differences of adjacent normal to normal R-R intervals (RMSSD) and the percentage of interval differences of adjacent normal-to-normal R-R intervals greater than 50 msec (pNN50) indicate the vagal influence on HRV. For frequency domain analysis, total power represents variations between normal-to-normal RR intervals, and low-frequency power (LF: 0.04–0.15 Hz) represents a combination of sympathetic and parasympathetic activity with a slight predominance of the first one. High-frequency power (HF: 0.15–0.40 Hz) indicates vagal activity, while LF/HF represents sympathovagal balance in favor of sympathetic activity [13].

During the recording period, participants were encouraged to continue their daily activities. Five of the ambulatory ECG monitoring revealed more than 2% artifact beats per total beats and the recordings were excluded from the analysis.

Table I. *The characteristics and laboratory parameters of the ischemic stroke patients according to troponin levels*

	Stroke patients with elevated troponin (n= 20)	Stroke patients with normal troponin (n= 46)	P
Age (years)	67.9 ± 15	64.3 ± 13	0.326
Male sex (n – %)	12 (60%)	27 (58.7%)	0.921
BMI (kg/m^2)	26.4 ± 3.9	27 ± 4.5	0.578
NIHSS	5.05 ± 3.3	5.1 ± 2.5	0.889
Hypertension (n – %)	15 (75%)	32 (69.6%)	0.654
Diabetes (n – %)	9 (45%)	20 (43.5%)	0.909
Hyperlipidemia (n – %)	4 (20%)	13 (28.3%)	0.481
Coronary artery disease (n – %)	9 (45%)	10 (21.7%)	0.055
Chronic kidney failure (n – %)	2 (10%)	3 (6.5%)	0.635
Glucose (mg/dL)	136.6 ± 65.3	118.5 ± 49.4	0.283
Creatinine (mg/dL)	1.01 ± 0.35	0.9 ± 0.40	0.061
Total cholesterol (mg/dL)	185 ± 55.4	199.2 ± 44.8	0.277
LDL cholesterol (mg/dL)	114 ± 50.9	127 ± 35.9	0.239
HDL cholesterol (mg/dL)	38.7 ± 10.5	42.4 ± 11.6	0.221
hs-CRP (mg/L)	21.6 ± 30.8	16.2 ± 24.6	0.353
hs-cTnI (ng/mL)	0.45 ± 0.77	0.01 ± 0.007	**<0.001**
NT-proBNP (pg/mL)	3119 ± 6955	1581 ± 3341	**0.036**
ST segment/T wave changes (n – %)	17 (85.2%)	17 (37.8%)	**<0.001**
Beta-blocker usage (n – %)	8 (40%)	10 (21.7%)	0.126

BMI: Body mass index, NIHSS: National Institutes of Health Stroke Scale, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, hs-CRP: High sensitive C reactive protein, hs-cTnI: High sensitive cardiac troponin I, NT-proBNP: N terminal pro-brain natriuretic peptide

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Statistical Analysis

Statistical analyses were performed by statistical software (SPSS 21.0 for Windows, Chicago, IL, USA). Continuous variables were checked for normal distribution by the Kolmogorov-Smirnov test and were expressed as mean ± standard deviation. Where appropriate, differences between continuous variables were tested using the independent sample Student's t-test or Mann–Whitney U test. Categorical data were presented as numbers or percentages and the Chi-square test was used for the comparison of categorical variables. A value of $P<0.05$ was considered statistically significant.

3. RESULTS

Sixty-six acute ischemic stroke patients (mean age: 65 ± 13 years; 39 male) were consecutively included in the study. Twenty patients (30.3%) had elevated hs-cTnI. The general characteristics and laboratory parameters of the patients according to troponin levels are shown in Table I. Although, there were not any significant differences in the general characteristics of the patients, the stroke patients with elevated hs-cTnI had significantly higher NT-proBNP and higher frequency of ST segment/T wave changes compared to those with normal hs-cTnI. There were no significant differences in the NIHSS scores and beta-blocker usage among patients with different troponin levels. Although, the frequency of coronary artery disease was numerically higher in the troponin-positive group, this difference could not reach statistical significance.

Table II. *The conventional transthoracic echocardiographic measures and ambulatory ECG monitoring parameters of the ischemic stroke patients according to troponin levels*

	Stroke patients with elevated troponin (n= 20)	Stroke patients with normal troponin (n= 46)	P
Left atrium (mm)	47.5 ± 10.6	40.6 ± 7.3	**0.020**
LAVI (mL/m²)	31.3 ± 10.9	23.6 ± 10.1	**0.013**
LVEDD (mm)	50.4 ± 9.5	46.8 ± 6.2	0.217
LVESD (mm)	34.2 ± 10.7	31.2 ± 7.5	0.499
IVS (mm)	13.6 ± 2.4	12.5 ± 2.1	0.255
PW (mm)	10.8 ± 1.3	10.3 ± 1.4	0.178
LVEF (%)	50.3 ± 13.5	58.4 ± 8.9	**0.028**
E/e'	10.9 ± 5.4	9 ± 3.1	0.422
AES (n)	952 ± 1298	1780 ± 3225	0.409
SDNN	102.4 ± 48.9	95.5 ± 34.5	0.515
SDANN	122.2 ± 90.2	87.4 ± 45.4	0.163
RMSSD	45.9 ± 71.6	34.5 ± 29	0.989
pNN50	11.03 ± 18.3	11.8 ± 19	0.784
LF/HF	2.5 ± 1.1	1.7 ± 1.04	**0.011**

LAVI: Left atrial volume index, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, IVS: Interventricular septum thickness, PW: Posterior wall thickness, LVEF: left ventricular ejection fraction, E/e': the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity, AES: Atrial extrasystole, SDNN: standard deviation of all normal-to-normal RR intervals, SDANN: standard deviation of the average NN intervals for each 5 min segments, RMSSD: root mean square of differences of adjacent normal-to-normal RR intervals, pNN50: percentage of successive RR intervals that differ by more than 50 msec, LF/HF: Low frequency/high frequency

The conventional transthoracic echocardiographic parameters and ambulatory ECG monitoring parameters of the patients are listed in Table II. The troponin-positive group had significantly larger left atriums and lower LVEF values compared to patients with normal troponin levels. LF/HF value was significantly higher in the troponin-positive group, but other ambulatory ECG monitoring parameters such as SDNN, SDANN, RMSSD, and pNN50 were similar among patients.

4. DISCUSSION

In our study, we evaluated the HRV in neurogenic stunned myocardium. We found sympathetic overactivity in patients with high troponin levels, which is an important result in terms of demonstrating the presence of autonomic dysregulation in these patients.

Heart rate variability, the beat-to-beat change in heart rate, provides information about the autonomic nervous system function [9]. HRV parameters are altered in different stages of ischemic stroke and have a prognostic value [7]. Autonomic dysregulation seen after acute ischemic stroke, is associated with non-neurological deaths [7]. Changes in autonomic functions due to cardiac reasons or infection in the acute phase of stroke reduce HRV [7,14]. In these patients, time domain measures of HRV such as SDNN, SDANN, and RMSSD are lower, and frequency domain measures exhibit low-frequency predominance [7]. The HF part of the HRV shows parasympathetic activity and the LF part shows sympathetic activity. In our study, we could not find the difference between the groups in terms of time domain measures, but we found an increased LF/HF ratio indicating sympathetic overactivity. Approximately 60% of stroke cases have an increased LF/HF ratio indicating higher sympathetic activity [15]. There are conflicting findings as to which of the right and left hemisphere involvement has more sympathetic overactivity [16,17]. Due to the small number of patients in our study, we could not show the relationship between stroke localization and sympathetic overactivity.

Neurogenic stunned myocardium is diagnosed with elevated troponin levels, ECG changes, and decreased LVEF values. In our study, we found that while the frequency of coronary artery disease was similar between the groups, the LVEF values were significantly lower and the frequency of ST segment-T wave changes was higher in the troponin-positive group. One of the important features of NSM is reversible left ventricular dysfunction, but we could not demonstrate the reversibility in LVEF value since our study was not a follow-up study.

Neurogenic stunned myocardium is defined as one of the stress-related cardiomyopathies, and the underlying mechanism is not clearly known [18]. The mechanisms that may be the cause of myocardial dysfunction in acute stroke are sympathetic overactivity, local catecholamine release from nerve endings in the myocardium, neurohormonal activation, and autonomic nervous system dysregulation [1,19,20]. Depending on the acute trigger, the dominant sympathetic response can be of two types, neural and adrenal [21]. The neural type is catecholamine

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release from local nerve endings in the myocardium, while the adrenal type is increased catecholamine release in blood circulation [21]. Unopposed sympathetic overactivity is thought to cause dysfunction as a result of uncontrolled inflammation in the myocardium [3,6]. On the other hand, sympathetic overstimulation and hypercatecholamine can also cause reversible myocardial damage through coronary spasm, endothelial dysfunction, and microcirculation involvement [22].

A high NIHSS score was found to be correlated with autonomic dysfunction characterized by decreased parasympathetic tone and it was suggested that it can be used in risk stratification of cardiovascular events [23]. Also, in another study reduced HRV is associated with stroke severity [24]. Although, we found increased sympathetic activity in patients with high troponin levels in our study, we could not show any difference between the groups in terms of NIHSS.

Heart rate variability parameters change after an ischemic stroke and decreased parasympathetic activity and unopposed sympathetic activation may persist until the chronic phase of the stroke [25]. HRV analysis in patients with ischemic stroke can be used as a prognostic tool to understand the pathophysiological mechanisms of autonomic disorders common after stroke [7]. With future research on HRV, we can better understand the heart and brain interactions and obtain better prognostic value.

Study Limitations

The first limitation of our study was the lack of a consensus definition of NSM. In our study, we used elevated troponin levels as a sign of NSM as most studies defined NSM based on data from troponin, ECG, and transthoracic echocardiogram. The second limitation was a small sample size, and the study was a single-center study. Another limitation of the study was that we did not repeat transthoracic echocardiography to evaluate the reversibility of LV dysfunction.

Conclusion

In acute ischemic stroke, troponin levels may be elevated, which may be accompanied by a decrease in LVEF and ST segment-T wave changes and these may be a sign of NSM. Although, the pathophysiology of NSM is not fully understood, autonomic dysfunction characterized by sympathetic overactivation may play an important role. Therefore, HRV analysis in ischemic stroke patients is a valuable approach to understand the underlying pathophysiological mechanisms of NSM.

Compliance with Ethical Standards

Ethical Approval: The study was approved by the ethics committee of the Marmara University School of Medicine on 11.02.2022 (approval number: 09.2022.282). The investigation conformed to the principles outlined in the Declaration of Helsinki. All participants gave written informed consent.

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Conflict of Interest: None declared.

Authors Contributions: CI: Concept and design, IM: Supervision, CI and ZD: Data collection and/or processing, analysis and/or interpretation, CI: Literature search and writing, CI, ZD and IM:Critical review. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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