

Heart Rate Variability Analysis

A Useful Tool to Assess Poststroke Cardiac Dysautonomia

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Background: Neurogenic heart syndrome represents a phenomenon often encountered in clinical practice after ischemic stroke. Further poststroke cardiovascular complications are possibly related to cardiac autonomic dysregulation. Multiple Trigonometric Regressive Spectral (MTRS) analysis of the heart rate variability (HRV) allows a precise evaluation of cardiovascular modulation under different conditions.

Objectives: This research aims to evaluate the impact of the middle cerebral artery (MCA) ischemic stroke on cardiac autonomic function, using the MTRS analysis of HRV, during sympathetic and parasympathetic activation tests.

Methods: The authors analyzed HRV parameters in 20 patients who had a right and 20 who had a left MCA ischemic stroke, under rest condition and during autonomic activation tests (deep breathing and standing tests). Data were compared with 20 age-matched and sex-matched healthy controls.

Results: Patients who had a right MCA ischemic stroke presented a decreased vagal modulation of the heart rate compared with healthy controls and patients who had a left MCA ischemic stroke, in resting state and during autonomic activation tests. Decreased root mean square of the successive differences, pNN50, high frequency, and high-frequency normalized units values ($P < 0.05$) and increased low frequency/high frequency ratio ($P < 0.05$) in resting state and during autonomic activation tests in patients who had a right MCA stroke indicate a sympathetic predominance in the control of the heart rate. The parasympathetic activation test did not change the sympathovagal balance in this group of patients.

Conclusions: The autonomic nervous system represents an attractive target for the therapeutic approach. As MCA ischemic stroke, especially in the right hemisphere, seems to cause significant long-lasting autonomic dysregulation, implementing early pharmacological or non-pharmacological intervention for autonomic restoration may improve the outcome of patients who had an ischemic stroke.

Key Words: ischemic stroke, autonomic dysfunction, heart rate variability, sympathetic and parasympathetic activation tests, multiple trigonometric regressive spectral analysis

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Cardiac disease is a risk factor for ischemic stroke¹ and cardiovascular complications represent the second leading cause of poststroke death.² The bidirectional relationship, however, has been less explored. Recent evidence shows that brain ischemia can conversely alter cardiovascular and autonomic function.^{3–5}

Although investigations and treatment possibilities in the acute phase of ischemic stroke have evolved during the last decades, primary and secondary prevention strategies play an essential role in reducing long-term stroke-related mortality. Monitoring cardiovascular parameters in patients with acute ischemic stroke is important because of the increased risk of secondary vascular events, such as cardiac arrhythmias, myocardial infarction, uncontrolled arterial hypertension, and cardiogenic shock.⁶ Less obvious are the delayed consequences of ischemic stroke on cardiovascular function. The aforementioned cardiovascular complications are related to disturbances of the autonomic nervous system, arisen secondary to the cerebral lesion. In this context, understanding the underlying mechanisms responsible for autonomic dysregulation together with a quantification of autonomic cardiac dysfunction represents a necessary step in managing patients who had a stroke, bringing new perspectives on the therapeutic approach of these patients.

There is considerable evidence regarding the role of forebrain lateralization in cardiovascular autonomic regulation in patients with ischemic stroke.⁷ Certain specialized cerebral structures, such as the insular cortex, are actively involved in this bidirectional brain-heart axis mediation with an immediate impact on the cardiocirculatory parameters, thus influencing the patients' clinical outcome. Damage to the insular cortex, a complex structure supplied by the middle cerebral artery (MCA), is associated with a more pronounced autonomic imbalance leading to life-threatening arrhythmias and sudden death.⁷

Complex systems present a temporal variation of biological processes, characterizing the biological rhythms.⁸ The analysis of biological rhythms may serve as an important tool for unraveling the pathophysiology of different diseases, including cerebrovascular pathology. Heart rate variability (HRV) illustrates the ability of the heart to adapt to different hemodynamic and external environmental changes, or in response to certain pathologic conditions, outlining the autonomic cardiac control. There is a close relationship between sympathetic hyperactivation and reduced cardiac vagal modulation associated with low HRV, involving a higher risk of cardiac arrhythmia and sudden death.⁹ Some studies reported a decrease in HRV in patients who had a stroke, not only in the acute phase but also present up to 6 months after the acute cerebrovascular event.^{10–12}

Rüdiger and colleagues proposed an algorithm to detect physiological oscillations of the heart rate on the basis of R wave to R wave (RR) intervals measurements from the ECG

recordings—the trigonometric regressive spectral analysis.¹³ The HRV parameters are often analyzed by Fourier Transform. The mathematical approach using trigonometric regressions excluded the RR intervals equidistance issue, arising with the method of Fourier Transform, whereas the heart rate is irregular with a high degree of beat to beat variability.

The dynamic assessment of HRV by Multiple Trigonometric Regressive Spectral (MTRS) analysis allows a precise evaluation of cardiovascular modulation under different conditions, as the local data segments required for MTRS analysis can be as short as 20 seconds.¹⁴

OBJECTIVES

This research aims to evaluate the impact of the MCA ischemic stroke on cardiac autonomic function, during sympathetic and parasympathetic activation tests, using MTRS analysis of HRV. The hypothesis is that right MCA ischemic stroke leads to sympathetic hyperactivation, less present in left MCA ischemic stroke and absent in controls, underlined by MTRS analysis of HRV.

METHODS

We evaluated a group of 40 patients who had an ischemic stroke, which was divided into 2 subgroups: the first subgroup of 20 patients (12 men and 8 women, mean age 62.5 ± 9.6 years) with ischemic stroke in the right MCA territory and the second subgroup of 20 patients (10 men and 10 women, mean age 63.5 ± 7.5 years) with ischemic stroke located in the left MCA territory. The features of this group of patients were compared with a control group consisting of 20 healthy volunteers (8 men and 12 women, mean age 56.2 ± 2.7 years), without cardiovascular or cerebrovascular disorders. The patients were recruited from the Neurology Department and were evaluated 3 months after the acute ischemic stroke. The study protocol was approved by the local ethics committee and all subjects provided written informed consent before inclusion. The study was carried out in accordance with the Helsinki Declaration.

Patients were included in the study according to the following criteria: right-handed subjects, older than 18 years, clinical examination evocative for stroke, evidence of left or right MCA

ischemic stroke on imagistic investigations, single ischemic lesion, cardiologic assessment before being included in the study.

Patients presenting the following comorbidities were excluded: moderate or severe valvular dysfunction, heart failure, cardiac arrhythmia present upon the current admission, history of myocardial infarction, febrile status, hypoxic status, impaired consciousness or hemodynamic decompensation during admission, dementia, severe renal insufficiency, diabetes mellitus, or other already diagnosed metabolic pathology with present polyneuropathy.

Some of the patients enrolled in our study were taking specific medication for their associated pathologies, such as statins or fenofibrate for dyslipidemia, antiplatelet agents, antihypertensive treatment. Patients under beta-blockers, anticholinergic drugs, or amiodarone were excluded. The control group was not under medical treatment. The autonomic control over heart rate in patients who had a stroke and healthy volunteers was evaluated under standardized conditions. The ECG recordings were performed according to the following criteria: in the afternoon (4 to 6 PM), after 30 minutes of the supine position, in a quiet room, at a constant temperature of 22°C , in the absence of prior physical effort or ingestion of caffeinated or alcoholic beverages 24 hours before the test. The evaluation sequence was similar for all the patients and the healthy subjects, consisting of a 5-minute ECG recording in the each of the following conditions: resting state (supine position), “deep breathing” test (6 complete cycles of deep inhale and exhale over 60 s with timing, 10 s for each cycle), and “standing” test (orthostatic position).

BIOPAC acquisition system was used for collecting and processing biological signals, converting biologic parameters to numeric data. AcqKnowledge software, version 3.9.1.6, permitted to refine the data, detecting, measuring, and analyzing the recorded signal.

The data gathered were subsequently processed using MTRS software version 7.3.2.0 (UniversitätsKlinikum, Zentrum für Klinische Neurowissenschaften, Dresden, Germany). This software assesses the HRV time domain and frequency domain parameters, on the basis of the trigonometric regressive analysis.

TABLE 1. HRV Parameters for the 3 Groups

Parameter	Right MCA Ischemic Stroke			Left MCA Ischemic Stroke			Control Group		
	RS	DB	ST	RS	DB	ST	RS	DB	ST
RMSSD (ms)									
Mean	15.26	17.97	11.98	26.40	31.77	23.79	32.26	38.99	27.82
SD	6.06	9.75	4.49	17.95	19.29	16.61	16.65	22.09	17.31
HF (rel. values)									
Mean	23.83	21.59	16.48	32.13	37.35	22.85	32.28	31.54	25.71
SD	10.97	10.04	7.37	14.00	13.49	13.74	12.86	10.42	8.74
LF (rel. values)									
Mean	51.94	52.59	58.12	41.92	38.25	50.39	48.13	50.66	56.81
SD	12.91	10.79	8.98	13.82	14.40	14.36	12.71	11.39	10.95
VLF									
Mean	14.37	17.57	18.54	12.93	11.23	15.47	9.73	9.15	11.22
SD	6.87	7.96	6.94	7.63	4.88	8.71	3.57	3.54	4.31
LF/HF									
Mean	4.47	4.63	7.62	2.72	2.41	4.44	2.41	2.44	3.83
SD	3.20	4.02	6.08	2.29	2.27	2.71	1.35	1.38	2.28
HFnu									
Mean	27.38	25.28	19.73	36.23	41.41	26.28	35.55	34.84	28.54
SD	11.90	10.83	8.67	14.14	14.36	14.44	13.89	11.51	8.84

DB indicates deep breathing test; HF, high frequency; HFnu, high frequency normalized unit; LF, low frequency; MCA, middle cerebral artery; RMSSD, root mean square of the successive differences; RS, resting state; ST, standing test; VLF, very low frequency.

All oscillations of the biosignals are analyzed using the following condition: $\sum (RRI(t(i)) - \text{Reg}(t(i)))^2 = > \text{minimum}$, with $RRI(t(i))$ being the original RR intervals and $\text{Reg}(t(i)) = A * \sin(\omega t(i) + \phi(i))$ being a trigonometric function of the parameters A (amplitude), ω (frequency), and ϕ (phase shift).¹⁴ We used the same local data segment settings of 30 seconds for each recording, with a minimum variance reduction of 1%, a shift of the local data segment of 1 and delta frequency 0.006 Hz.

Time and frequency domain HRV parameters were analyzed from the ECG recordings in the 3 conditions mentioned above (resting state and the 2 autonomic activation tests).

Time-domain RMSSD parameter (root mean square of the successive differences) describes the vagal influence on the heart rate.⁹ pNN50 represents another time domain parameter, reflecting the ratio between NN50 (number of RR intervals considered normal-successive “NN” with differences > 50 ms between them) and the total number of RR intervals, being expressed in percentages. It characterizes the vagal control on the heart rate.⁹

Heart rhythm oscillations may be categorized into 4 primary frequency bands: ultra-low frequency, very low frequency, low frequency (LF), and high frequency (HF). Respiration modulates the vagal activity and contributes to the HF component of the spectra, ranging from 0.15 to 0.4 Hz.¹⁵ LF component (0.04 to 0.15 Hz) is thought to be the combined sympathetic and vagal response to arterial baroreceptors.¹⁶ The LF and HF values may also be calculated in normalized units (LFnu, HFnu), defining the relative values of each frequency spectrum reported to the total spectral power, from which the very low frequency component was excluded from the calculation as it is considered to be influenced by thermoregulation mechanisms and renin-angiotensin system activity. LF/HF ratio describes the sympathovagal balance.⁹

Data were analyzed using GraphPad Prism version 8.0.2 (GraphPad Software Inc.). The results of descriptive statistics

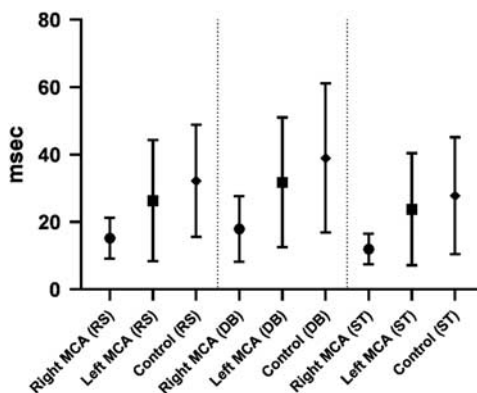


FIGURE 1. RMSSD values for stroke patients and controls during tests. Values are depicted as mean with standard deviation. DB indicates deep breathing test; RMSSD, root mean square of the successive differences; RS, resting state; ST, standing test.

were reported as mean ± standard deviation. Taking into consideration the small sample size, series normalization is very difficult. When the assumption of normal distribution was not met, we applied a nonparametric test. Analysis of the 3 groups of patients was performed using the Kruskal-Wallis test. When comparing the patient’s group with the control group and between stroke groups, the Mann-Whitney test was applied. Analysis between different autonomic tests in the same group was performed applying the Wilcoxon matched-pairs signed-rank test. The significance was met when $P < 0.05$.

RESULTS

Patients who had a right MCA ischemic stroke displayed a decreased parasympathetic control of the heart rate in resting state, illustrated by lower values of RMSSD, pNN50, HF, and HFnu parameters, compared with left MCA ischemic stroke group and the healthy control group (Tables 1, 2). After autonomic activation tests, patients who had a right MCA ischemic stroke maintained lower values of the parasympathetic specific parameters mentioned above, compared with the left MCA ischemic stroke group and the control group (Figs. 1, 2). The same characteristics of the sympathovagal balance were observed after the activation tests when analyzing the LF/HF ratio, indicating increased sympathetic activity in the patients

TABLE 2. Differences in HRV Parameters Between the 3 Groups

HRV Parameter	Mann-Whitney Test (P-value)			All Groups Kruskal-Wallis Test
	Right vs. Left MCA Ischemic Stroke	Right MCA Ischemic Stroke vs. Controls	Left MCA Ischemic Stroke vs. Controls	
RMSSD (RS)	0.021	<0.001	0.182	0.002
RMSSD (DB)	0.004	<0.001	0.301	0.001
RMSSD (ST)	<0.001	<0.001	0.461	<0.001
pNN50 (RS)	0.037	<0.001	0.062	0.001
pNN50 (DB)	0.002	<0.001	0.139	<0.001
pNN50 (ST)	<0.001	<0.001	0.380	<0.001
HF (RS)	0.059	0.040	0.883	0.072
HF (DB)	<0.001	0.006	0.211	0.001
HF (ST)	0.157	0.001	0.129	0.008
HFnu (RS)	0.040	0.040	0.738	0.056
HFnu (DB)	0.001	0.019	0.157	0.002
HFnu (ST)	0.201	0.005	0.141	0.020
LF (RS)	0.013	0.383	0.108	0.041
LF (DB)	0.001	0.511	0.006	0.003
LF (ST)	0.081	0.583	0.288	0.214
LF/HF (RS)	0.043	0.015	0.722	0.037
LF/HF (DB)	0.015	0.026	0.383	0.022
LF/HF (ST)	0.046	0.002	0.596	0.013

DB indicates deep breathing test; HF, high frequency; HFnu, high-frequency normalized unit; LF, low frequency; MCA, middle cerebral artery; RMSSD, root mean square of the successive differences; RS, resting state; ST, standing test.

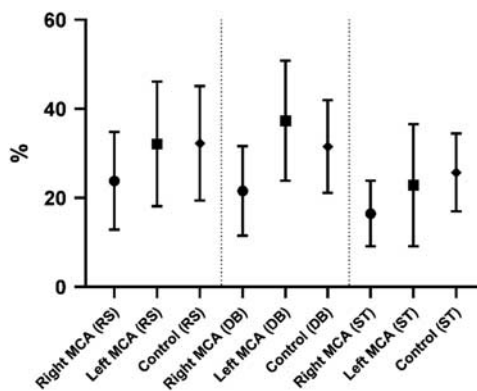


FIGURE 2. HF values for stroke patients and controls during tests. Values are depicted as mean with standard deviation. DB indicates deep breathing test; HF, high frequency; RS, resting state; ST, standing test.

TABLE 3. Differences in HRV Parameters Between Tests for Stroke Patients

HRV Parameter	Wilcoxon Matched-Pairs Signed-Rank Test (P-value)		
	Autonomic Activation Tests	Right MCA Ischemic Stroke	Left MCA Ischemic Stroke
RMSSD	RS vs. DB	0.189	0.013*
	RS vs. ST	0.005*	0.132
	DB vs. ST	< 0.001*	< 0.001*
pNN50	RS vs. DB	0.552	0.015*
	RS vs. ST	0.151	0.611
	DB vs. ST	0.052	0.014*
HF	RS vs. DB	0.756	0.202
	RS vs. ST	0.006*	0.001*
	DB vs. ST	0.010*	< 0.001*
HFnu	RS vs. DB	0.927	0.330
	RS vs. ST	0.004*	< 0.001*
	DB vs. ST	0.017*	< 0.001*
LF	RS vs. DB	0.956	0.756
	RS vs. ST	0.069	0.002*
	DB vs. ST	0.053	0.003*
LF/HF	RS vs. DB	0.589	0.819
	RS vs. ST	0.005*	0.002*
	DB vs. ST	< 0.001*	< 0.001*

DB indicates deep breathing test; HF, high frequency; HFnu, high-frequency normalized unit; LF, low frequency; MCA, middle cerebral artery; RMSSD, root mean square of the successive differences; RS, resting state; ST, standing test. *P < 0.05.

who had a right MCA ischemic stroke. There was no significant difference between the left MCA ischemic stroke group and the control group (Table 2).

Comparing the values of the time and frequency domain parameters RMSSD, pNN50, HF, HFnu, LF, LF/HF for the right MCA ischemic stroke group, between resting state and the 2 autonomic activation tests, we observed a consistent sympathetic activation response after standing test (Table 3). The parasympathetic activation test did not induce a significant change in the sympathovagal balance in this group of patients (Fig. 3).

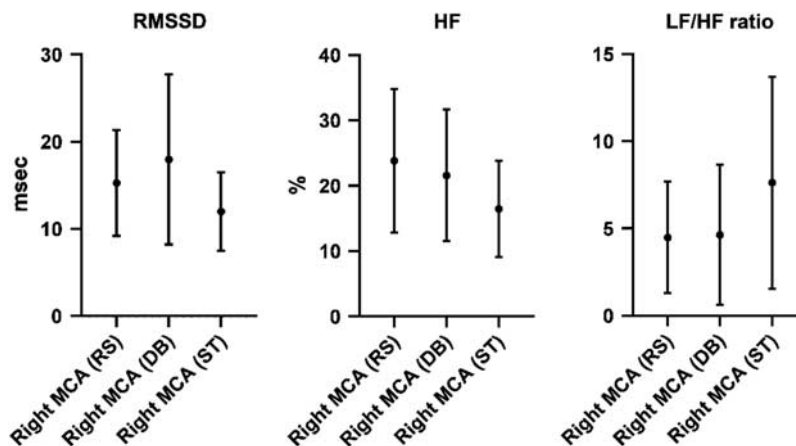


FIGURE 3. RMSSD, HF, and LF/HF values during tests for patients who had a right MCA stroke. Values are depicted as mean with standard deviation. DB indicates deep breathing test; HF, high frequency; LF, low frequency; MCA, middle cerebral artery; RMSSD, root mean square of the successive differences; RS, resting state; ST, standing test.

Patients who had a left MCA ischemic stroke presented a decrease of the parasympathetic specific parameters RMSSD, pNN50, HF, HFnu after the standing test and an increase of the LF/HF ratio (Fig. 4), indicating a sympathetic activation in accordance to the autonomic test (Table 3). Higher values of RMSSD and pNN50 compared with resting state indicate a regular vagal activation response after deep breathing test.

DISCUSSION

Our results indicated a decreased vagal modulation of the heart rate in patients who had a right MCA ischemic stroke compared with healthy controls. The standing test determined sympathetic activation in both groups of patients and in healthy controls. During the deep breathing test, we observed an attenuated parasympathetic activation response in patients who had a right MCA ischemic stroke. Reductions in time and frequency domain HRV parameter values, as observed in our study for patients who had a right MCA ischemic stroke, are consistently associated with increased risk of stroke.¹⁷ These data strongly indicate that ischemic stroke has an important influence on cardiac function and this is likely mediated through alterations of sympathovagal balance.

Cerebral lesions involving the central network of the autonomic control may induce downstream effects on spinal cord preganglionic autonomic nerves, determining HRV changes.¹⁸ Previous research has already shown a neural source of HRV changes in patients who had a ischemic stroke.¹⁹

The total spectral power of RR intervals from the HRV analysis is reduced in patients who had a stroke compared with age-/sex-matched controls.²⁰ Cardiac parasympathetic neural activity is particularly affected after stroke, determining a shift in the sympathovagal balance. In patients with sympathetic hyperactivity, the risk for cardiac complications is higher in the period immediately after cerebral infarction.²¹ Some studies reported that cardiac sympathetic control on the heart rate was enhanced within 5 days of stroke symptoms onset, but similar findings were described by other authors for longer periods.^{22–24} Decreased vagal modulation and sympathetic hyperactivity can be underlined both during the resting condition and after exercises specific to the motor recovery, including sympathetic and parasympathetic activation activities, as a potential source of cardiovascular complications.

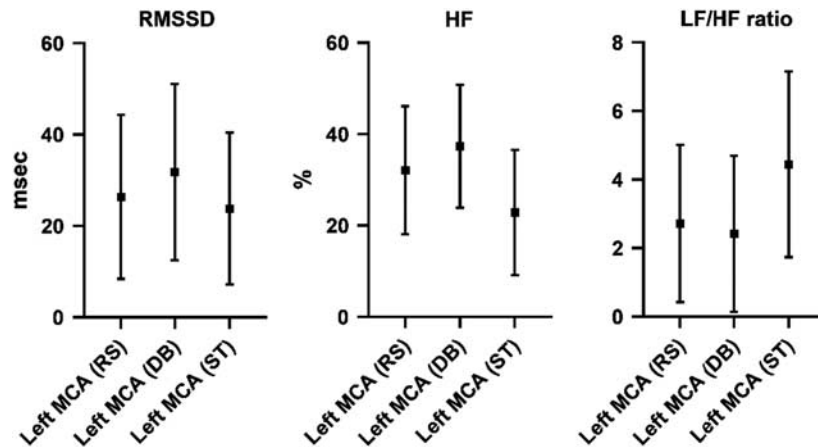


FIGURE 4. RMSSD, HF and LF/HF values during tests for patients who had a left MCA stroke. Values are depicted as mean with standard deviation. DB indicates deep breathing test; HF, high frequency; LF, low frequency; MCA, middle cerebral artery; RMSSD, root mean square of the successive differences; RS, resting state; ST, standing test.

The originality of our study consists mainly of applying the MTRS analysis of the HRV in patients who had an ischemic stroke, whereas, most commonly, a power spectral analysis of HRV was performed in previous studies through the Fast Fourier Transform. Unlike the Fast Fourier Transform, MTRS analysis does not need interpolation on nonequidistant RR intervals^{13,14} and can be successfully applied to analyze shorter local data segments.

The influence of cerebral structures on the autonomic nervous system activity relies on several factors: the topography of the brain lesion, the hemispheric lateralization, and the functional remodeling of the cerebral structures, described as brain plasticity, depending on the type of aggression.

There is still controversy about hemispheric lateralization and involvement of specific cortical structures in central autonomic control, mainly attributed to the interhemispheric functional and anatomic asymmetries of the central nervous system.^{25,26}

In right MCA infarction with insular cortex involvement, a reduction of poststroke total spectral power of the HRV has been noticed.^{27,28} Moreover, increased levels of serum noradrenaline, reduced circadian variability in blood pressure, prolongation of QTc, and recurrent cardiac arrhythmias were identified following right MCA ischemic stroke.²⁹ Other studies revealed a higher risk of cardiac complications and increased long-term mortality in left hemisphere brain infarction, particularly in the left insular ischemic stroke.^{30,31} The sympathetic hyperactivity was described as an independent risk factor of long-term unfavorable cardio and cerebrovascular outcome.^{29,32} In our study, we found a decreased vagal modulation of the heart rate and enhanced sympathetic tone in patients who had a right MCA ischemic stroke compared with left MCA ischemic stroke. These findings were in line with previous results from our studies when HRV was analyzed using the Fourier Transform.^{33,34}

Our study is limited by the low number of participants which may decrease the statistical power. Further studies on larger groups are needed to confirm and strengthen these results.

The autonomic nervous system is becoming an attractive target for the therapeutic approach. Current options that may amplify the vagal component of the nervous system have already been exploited in patients with heart failure or epilepsy.^{35,36} The widening of the spectrum of indications of cerebrovascular diseases can be analyzed.

Evaluating autonomic modulation may improve the outcome of patients who had an ischemic stroke by implementing

early personalized pharmacological or nonpharmacological interventions for autonomic restoration in these patients.

Less used in the general neurological practice, HRV analysis may be added to current investigations in patients who had an ischemic stroke to identify possible dysfunction of the central modulation of the autonomic cardiovascular activity.

Autonomic dysfunction can predict poor outcome in patients who had an ischemic stroke. HRV analysis together with clinical evaluation (eg, NIHSS score and blood pressure measurements), other cardiovascular biomarkers such as troponin, proBNP, QT interval, hormonal markers (catecholamines, other steroids), and imagistic data depicting the right insular involvement, can contribute, through interdisciplinary consensus, to the development of a prognostic score relevant in current practice. Such a score would help identify patients who had a stroke at risk of cardiac complications.

CONCLUSIONS

Our research brings new perspectives on personalized therapeutic approaches and integrated management of patients who had a stroke presenting an alteration of the sympathovagal balance.

We propose MTRS analysis of the HRV as a useful tool to assess the autonomic control on the heart rate using short local data segments to prevent fatal cardiac events in patients who had an ischemic stroke.

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