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Heart rate variability analysis and cardiac dysautonomia in ischemic stroke patients

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ABSTRACT

Objectives: Autonomic nervous system dysfunction after ischemic stroke predisposes to cardiovascular complications. We aimed to investigate cardiac autonomic activity in ischemic stroke patients using heart rate variability analysis, illustrating the sympathovagal balance at different sympathetic and parasympathetic activation tests.

Patients and methods: We studied the dynamics of the linear and non-linear heart rate variability parameters in 31 left and 40 right middle cerebral artery ischemic stroke patients in rest condition and during autonomic activation tests (handgrip, standing, deep breathing and Valsalva maneuver). Data were compared with 30 age- and sex-matched healthy controls.

Results: We found different responses after autonomic activation tests in stroke patients depending on the cortical lateralization of the ischemic lesion. In resting state, left hemisphere stroke patients presented enhanced parasympathetic modulation of the heart rate (higher values for RMSSD, pNN50, HF and SD1, $p < 0.05$), comparing to right hemisphere stroke patients. This second group displayed a reduced cardiac parasympathetic control in resting state and during autonomic activation tests (handgrip and standing tests) compared to the left hemisphere stroke group and controls. Non-linear parameters SD1 and DFA α1 showed a decrease of variability and complexity of the heart rate in right hemisphere stroke patients, ameliorated during vagal activation tests.

Conclusion: To prevent possible complications with vital risk, assessment of cardiovascular autonomic activity becomes a necessary stage in stroke patient management, facilitating immediate implementation of preventive and therapeutic strategies. Heart rate variability analysis in resting state and during autonomic activation tests allows identifying patients prone to sympathetic hyperactivity. New therapeutic perspectives for stroke management may emerge founded on the modulation of the autonomic nervous system.

1. Introduction

Autonomic nervous system dysfunction, caused by an acute cerebral lesion, predisposes to cardiovascular complications, such as uncontrolled arterial hypertension, cardiac arrhythmias, myocardial infarction, or cardiogenic shock [1]. The assessment of cardiovascular autonomic activity is a pivotal step to prevent these vital risk complications.

Quantification of heart rate variability (HRV) represents a non-invasive method of sympathovagal balance evaluation [2]. It reflects the cardiac ability to comply with hemodynamic fluctuations and external environment variations, a relevant parameter for the appraisal of the autonomic modulation on the cardiovascular activity [3].

HRV evaluation may be completed by conventional time and frequency-domain analysis methods, by analyzing the spectral power, or using non-linear analysis that may indicate sensitive adjustments in the dynamics of post-stroke heart rate [3–8], highlighting qualitative properties of the heart rate fluctuation [2,9].

The increase of sympathetic and the decrease of parasympathetic activity are closely interrelated, raising the risk of cardiac arrhythmia. A low HRV is associated with an increased risk of cardiac arrhythmias and sudden death [3,10], being a mortality predictor [11]. The

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decrease in HRV was observed not only in the acute phase but also up to six months after the acute cerebrovascular event [12–14].

Specific cerebral structures, such as the insula, are involved in the bi-directional heart-brain mediation, having an immediate impact on the cardio-circulatory parameters [15]. Insular involvement in the ischemic stroke generates autonomic imbalance [15].

There is still controversy about hemispheric lateralization and the involvement of specific cortical structures in central autonomic nervous system control that determine post-stroke prognosis [16,17].

After an ischemic stroke in the right middle cerebral artery (MCA) territory, particularly with right insular cortex involvement, the total spectral power of the variability of the heart rate is reduced [18,19]. Right hemisphere stroke, compared to left hemisphere stroke, may reduce the circadian variability of blood pressure, increasing nocturnal blood pressure levels. Several other alterations have been described in right hemispheric strokes such as an increase of plasma noradrenaline, prolongation of QTc and recurrent cardiac arrhythmias [20,21].

The sympathetic hyperactivity represents an independent risk factor for long-term cardio and cerebrovascular events [20,22]. Other studies revealed a higher risk for fatal and non-fatal cardiac events such as myocardial infarction in patients with left insular ischemic stroke versus non-insular stroke, especially for those without other comorbidities, like coronary artery disease [23].

This study aims to evaluate the sympathovagal balance using HRV analysis in MCA ischemic stroke patients applying different autonomic activation tests in the first six months after the acute event.

2. Material and methods

We evaluated 71 ischemic stroke patients from the Neurology Unit with right and left MCA ischemic stroke and a control group of 30 healthy volunteers, without cardiovascular or cerebrovascular disorders. All patients included in our study presented the acute ischemic stroke four to six months prior to the HRV evaluation. Forty-eight patients had subcortical stroke (NIHSS 5.56 ± 1.70) while twenty-three patients had corticosubcortical stroke (NIHSS 8.43 ± 2.21). All patients and healthy volunteers were duly informed according to the study protocol and consented to the assessment in agreement with ethical principles. The study was carried out in accordance with the Helsinki Declaration.

The following inclusion criteria were considered: age ranging from 39 to 79 years, right-handed subjects, clinical assessment suggesting stroke, imagistic confirmation by cerebral CT scan or cerebral MRI, single ischemic lesion, first stroke in the medical history and cardiologic assessment before inclusion.

The following exclusion criteria were considered: cardiac arrhythmia present upon the current admission (including atrial fibrillation), heart failure, moderate or severe valvular dysfunction, history of myocardial infarction or left ventricular hypertrophy, febrile status, oxygen desaturation, impaired consciousness or hemodynamic decompensation upon admission, renal insufficiency, oncologic pathology, dementia, diagnosed diabetes mellitus with polyneuropathy, current beta-blocker medication. A study population diagram is presented in Fig. 1.

Other specific medications for associated pathologies were allowed: statins or fenofibrate, antiplatelet agents, antihypertensive medication in various combinations, including diuretics, Angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers or Angiotensin Receptor Blocker (ARB). The control group was not under medication.

The autonomic control over heart rate was assessed in resting state and during four autonomic activation tests (Ewing tests), each test entailing a 5 min ECG recording. BIOPAC® acquisition system was used for data collection and analysis. AcqKnowledge software version 3.9.1.6 was used for refining the recorded data. Data processing was done using Kubios HRV software version 2.2 (Biosignal Analysis and Medical Imaging Group, University of Eastern Finland). A standardized protocol was applied for each HRV analysis. A manual data correction of ECG artifacts was carried out before each analysis. A second correction was performed automatically using BIOPAC®, indicating and selecting the NN-intervals (Normal-to-Normal intervals), supplementary artifacts on the ECG recordings being removed from the final processing. A minimum of 256 RR intervals was analyzed for each evaluation.

HRV time-domain parameters RMSSD ("Root Mean Square of the Successive Differences") and pNN50 describe the vagal influence on the heart rate. pNN50 represents the ratio of successive "NN" with differences higher than 50 ms between them (NN50) and the total number of NN intervals.

The frequency-domain analysis concerned the following parameters: HF ("High Frequency"), LF ("Low Frequency"), VLF ("Very Low Frequency") and the LF/HF ratio. The HF parameter (expressed in ms^2) illustrates the vagal control on the heart rate. 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 VLF ("Very Low Frequency") component was excluded from the calculation.

These parameters were analyzed from the ECG recordings together with non-linear parameters SD1 and DFAα1, that reflect the variability of the heart rate.

We applied a standardized protocol for the ECG recording: assessment at the same time range (4–6 PM), after 20 min of clinostatism rest, in a quiet room, constant temperature ($22^{O}C$), in the absence of prior physical effort or ingestion of caffeinated or alcoholic beverages 24 h before the test.

Two sympathetic activation tests were performed: a 5 min standing test and the "handgrip" test corresponding to the maximal voluntary isometric contraction of the fist, using a dynamometer, and two parasympathetic activation tests: "deep breathing" test, consisting of 6 complete cycles of deep inhale and exhale over 60 s, with timing, 10 s for each cycle, and Valsalva maneuver.

The test sequence was standardized: resting state, deep breathing test, handgrip test, standing test and Valsalva maneuver for all the patients and the healthy subjects.

The data were analyzed using the SPSS software V.24. (IBM Statistical Package for the Social Sciences, Chicago, Ilinois). If the analyzed data showed a normal distribution, we used the parametric inferential method – respectively One Way Anova and for data without a normal distribution nonparametric inferential methods, respectively Kruskal – Wallis test were applied. The One Way Anova test (95% CI) was applied for the comparative analysis. The "t Student", Pearson-$\chi 2$, Fisher, ANOVA, linear regression, logistic regression, and multivariate analysis test were also applied, using generalized linear models. The descriptive statistics indicators (mean, standard deviation, standard error, minimum, maximum and quartile intervals) were calculated for the continuous variables. In the case of the categorical or ordinal variables, the nonparametric analysis based on comparative tests founded on a "Chi-squared" distribution was tracked. Pearson's Chi-square test was the most used $\chi 2$ significance test. To identify differences in the three studied groups' parameters, we used post hoc multiple comparison analysis tests (Dunnett's test). Receiver Operating Characteristic Curves (ROC curve) were performed to evaluate the discriminative power of the HRV parameters.

3. Results

Corticosubcortical ischemic strokes were associated with an increased clinical severity score (NIHSS) compared to subcortical strokes ($p < 0.001$). Comparing ipsilesional ischemic strokes, NIHSS values were higher in the right MCA corticosubcortical compared to subcortical strokes ($p < 0.05$), while for the left MCA infarctions there was no significant difference.

Regarding the corticosubcortical localization, there was no difference concerning stroke severity (reflected by NIHSS) between the left

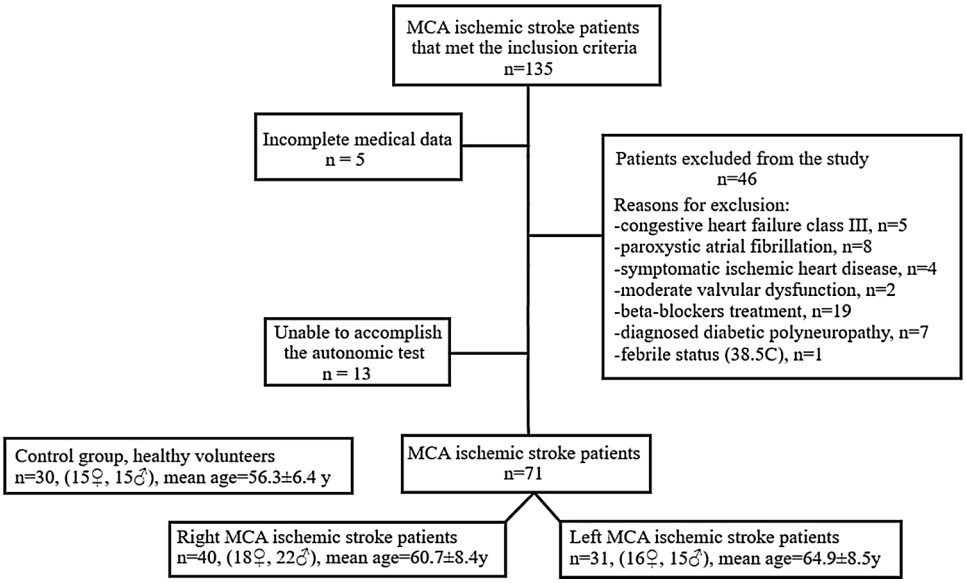

Fig. 1. Study population diagram.

(n = 11) and right (n = 12) hemisphere infarcts (p = 0.182).

For the subcortical ischemic stroke group, there were no significant differences between right (n = 28) and left (n = 20) subgroups (p = 0.332).

Patients with right MCA infarctions presented a decreased vagal modulation, reflected by lower values of RMSSD, HFnu, SD1 (Fig. 2) during the autonomic activation tests in both corticosubcortical and subcortical stroke groups.

Right MCA ischemic stroke patients presented diminished vagal tonus in resting state, expressed by lower values of the RMSSD, pNN50 and HF compared to the other two studied groups (Table 1). This has also been noticed during parasympathetic and sympathetic activation tests (Table 1). We observed normal cardiac autonomic responses during vagal activation tests in both groups of patients and controls, suggested by increased RMSSD, pNN50, HF values (Fig. 3) and decreased LF/HF. After the vagal activation maneuvers, we noticed a tendency towards re-balancing the sympathovagal activity (Fig. 3).

The sympathetic activation tests led to a more pronounced sympathetic response in the right MCA ischemic stroke group ($p < 0.001$ for the handgrip and standing tests), therefore pointing towards a predisposition for rapid sympathetic activation in these patients (Fig. 3).

HFnu (expressed in normalized units) is unanimously considered a marker of the parasympathetic activity. This parameter showed the same differentiation in the two groups of stroke patients according to the involved cerebral hemisphere, as shown by other parameters also (vagal predominance in patients with left MCA ischemic stroke and

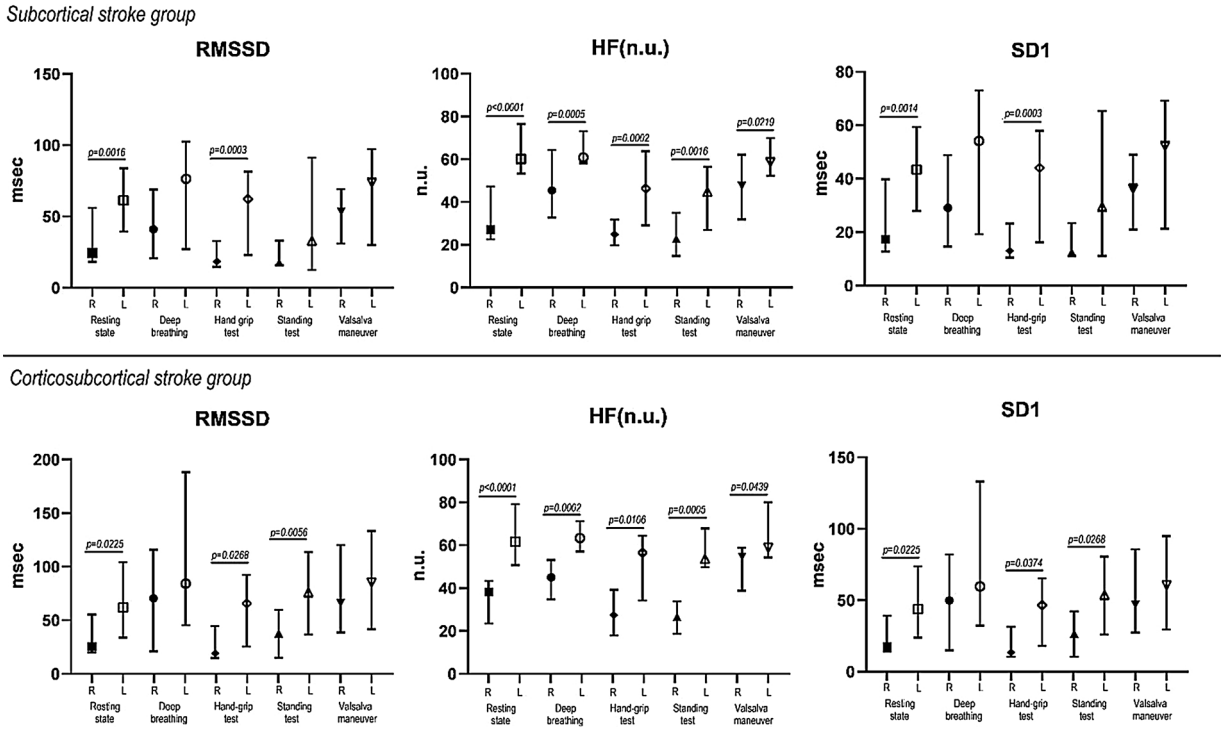

Fig. 2. Comparison between stroke localization: subcortical vs. corticosubcortical.

Table 1
Groups differences reflected in HRV parameters during autonomic tests.

HRV Parameter		Right vs. Left MCA stroke	Right MCA stroke vs. Control	Left MCA stroke vs. Control
	RS	36.68/71.63 **	36.68/57.32 *	71.63/57.32
	DB	57.26/87.29 *	57.26/44.35	87.29/44.35 **
RMSSD	HG	30.75/65.17 **	30.75/31.96 **	65.17/31.96 **
(msec)	ST	31.31/62.55 **	31.31/40.81	62.55/40.81 *
	VA	65.61/82.61	65.61/89.77	82.61/89.77
	RS	3.06/10.21 *	3.06/14.50 **	10.21/14.50
	DB	6.33/9.77 *	6.33/14.84 *	9.77/14.84
pNN50	HG	3.25/8.40 *	3.25/6.07	8.40/6.07
(%)	ST	3.38/7.44 *	3.38/9.52 **	7.44/9.52
	VA	5.55/9.55 *	5.55/11.35 *	9.55//11.35
	RS	430.60/884 *	430.60/758.10	884/758.10
	DB	1405.4/1761.2*	1405.4/1656.11 *	1761.20/1656.11
HF	HG	425.27/1072.8*	425.27/409.13	1072.80/409.13 *
(ms^2)	ST	467.23/1116.7*	467.23/284.97	1116.70/284.97 *
	VA	1383.30/1644	1383.3/933.53	1644/933.53 *
	RS	668.40/424.71	668.40/897.33	424.71/897.33 *
	DB	562.01/399.30	562.01/557.80	399.30/557.80
LF	HG	600.35/920.48	600.35/882.27	920.48/882.27
(ms^2)	ST	801.70 /864.77	801.70/700.60	864.77/700.60
	VA	1290.9/1059.3	1290.9/675.07 *	1059.3/675.07
	RS	2.56/0.62 **	2.56/1.24 **	0.62/1.24 *
	DB	1.55/0.57 **	1.55/0.62 *	0.57/0.62
LF/HF	HG	3.32/1.46 **	3.32/2.89	1.46/2.89 **
	ST	3.91/1.45 **	3.91/2.57 *	1.45/2.57 *
	VA	1.59/0.66 **	1.59/0.64 *	0.66/0.64
	RS	33.35/64.52 **	33.35/45.24 **	64.52/45.24 **
	DB	45.84/64.85 **	45.84/60.54 **	64.85/60.54
HF	HG	28.15/47.75 **	28.15/27.92	47.75/27.92 **
(n.u.)	ST	26.67/47.68 **	26.67/35.03 *	47.68/35.03 *
	VA	48.61/61.86 **	48.61/61.26 **	61.86/61.26
	RS	66.50/35.09 **	66.50/54.20 **	35.09/54.20 **
	DB	53.97/34.77 **	53.97/37.79 **	34.77/37.79
LF	HG	71.72/51.53 **	71.72/71.97	51.53/71.97 **
(n.u.)	ST	73.18/52.04 **	73.18/64.84 *	52.04/64.84 *
	VA	51.72/37.86 **	51.72/38.35 **	37.86/38.35
	RS	25.99/50.81 **	25.99/39.18 *	*50.81/39.18*
	DB	40.57/61.91 *	40.57/34.44	61.91/34.44 *
SD1	HG	21.79/46.21 **	21.79/22.67	46.21/22.67 **
(msec)	ST	22.18/45.88 **	22.18/30.51	45.88/30.51 *
	VA	45.52/58.55	45.52/63.64 *	58.55/63.64
	RS	1.14/0.70 **	1.14/0.91 *	0.70/0.91 *
	DB	1.02/0.73 **	1.02/0.73	0.73/0.97 *
DFAα1	HG	1.24/0.86 **	1.24/1.25	0.86/1.25 **
	ST	1.30/0.89 **	1.30/1.14	0.89/1.14 *
	VA	0.98/0.78 *	0.98/0.67 **	0.78/0.67

RS = resting state, DB = deep breathing, HG = handgrip test.
ST = standing test, VA = Valsalva maneuver.
(*) = $p < 0.05$; (**) = $p < 0.001$.
• HRV values are expressed as mean.

sympathetic predominance in patients with right MCA ischemic stroke). The reference value of the control group (45.24 nu) confirms the tendency of polarisation of the sympathovagal balance depending on the hemispheric lateralization of the stroke again (Fig. 4).

We evaluated HRV non-linear parameters (SD1, DFAα1) in resting state and during the Ewing tests, correspondingly to the linear parameters ahead discussed (Fig. 4). Our results showed differential values for SD1 between the two groups of patients: vagal predominance in patients with left MCA ischemic stroke, intermediate values, within normal range for the control group and lower values indicating a diminished vagal influence on the heart rate and a decreased variability of the heart rate in patients with right MCA ischemic stroke. For this last group, the non-linear HRV parameter DFA α1 reflects a decreased complexity and loss of the fractal properties when the values of the exponent α are higher than 1, and, in this case, is correlated with a reduced vagal influence and an augmented sympathetic control over the heart rate.

We estimated reference values (cut-offs), depending on the hemispheric lateralization (Table 2). We determined the optimal cut-offs for each of the parameters, successively comparing the three groups, having into consideration the values of the area under the ROC curve (AUC) (Table 2).

To analyze the treatment effect on HRV parameters in ischemic stroke patients, we used multivariate linear regression analysis. This regression model was chosen taking into account that the dependent variable is a continuous one (HRV parameters). The patients enrolled were under treatment for secondary stroke prevention, having different vascular risk factors. Fifty-five patients were diagnosed with arterial hypertension, being treated with following drugs: Angiotensin-converting enzyme inhibitors - ACEI (31 patients), diuretics (21 patients), ARBs (10 patients), Calcium channel blockers (20 patients). The beta-blocker medication was excluded. Fifty patients were under treatment with statins. Data analysis regarding medication is detailed in Table 3.

In resting state, ACEI did not alter the sympathovagal balance after analyzing the following parameters: RMSSD, HF, SD1, LF/HF ratio. No consistent changes in sympathovagal balance were noticed in patients under the other antihypertensive drugs, as shown by the analyzed HRV parameters (Table 3).

4. Discussion

The central autonomic control of the heart rate is reflected by the values of the linear and non-linear parameters of the HRV analysis. Changes in the sympathovagal balance associated with HRV reduction were described up to six months after stroke [12,19,24,25].

Our results showed different values of the HRV parameters during resting state and the four autonomic activation tests, depending on the cortical lateralization of the ischemic stroke. A vagal predominance in the control of the heart rate in left MCA ischemic stroke patients was observed, while right MCA ischemic stroke patients presented a predominant sympathetic control on the heart rate.

Currently, there is no normative data for the HRV assessment over short periods for patients with neurological pathology [26]. Establishing specific cut-off values for the most frequently used parameters in the ECG analysis can be useful in the rapid analysis of the sympathovagal balance in stroke patients, in resting state or during autonomic activation tests. The identification of a sympathetic hyperactivity (low RMSSD or pNN50 values for time-domain parameters and low HF or HFnu, elevated LF/HF values for frequency-domain parameters), associated to a decrease of variability of the heart rate (high DFA α1 values, low SD1 values) may announce a potential risk of cardiac arrhythmia, having also therapeutic impact.

Specific functional lateralization concerning the sympathetic and parasympathetic central control involving the right, respectively, the left insular lobe was described [27–29]. Our results support this hypothesis of an inter-hemispheric functional differentiation of the central autonomic control, in accordance with other clinical trials [30]. Moreover, we performed four autonomic activation tests. The results maintained differentiated characteristics between the two groups, depending on the hemispheric laterality. Patients with a right hemisphere infarction showed, after the vagal activation tests, both a significant increase in the total variability of the heart rate, as well as an increase of certain linear parameters specific to vagal activity (e.g., RMSSD, HF), highlighting the potentiation of the parasympathetic influence on the heart rate. This appears to be cardioprotective in elderly patients [31]. Depending on the particularities of the autonomic nervous system activity, new therapeutic perspectives may emerge.

Furthermore, in order to clarify the contradictory results on the specific role and attributions of the central nervous system structures, functional cerebral imaging studies are needed. This would allow a thorough understanding of the cortical functional lateralization and a more accurate description of the brain structures involved in cardiac dysautonomic phenomena in cerebrovascular pathology.

Regarding the involvement of medication on autonomic control, the

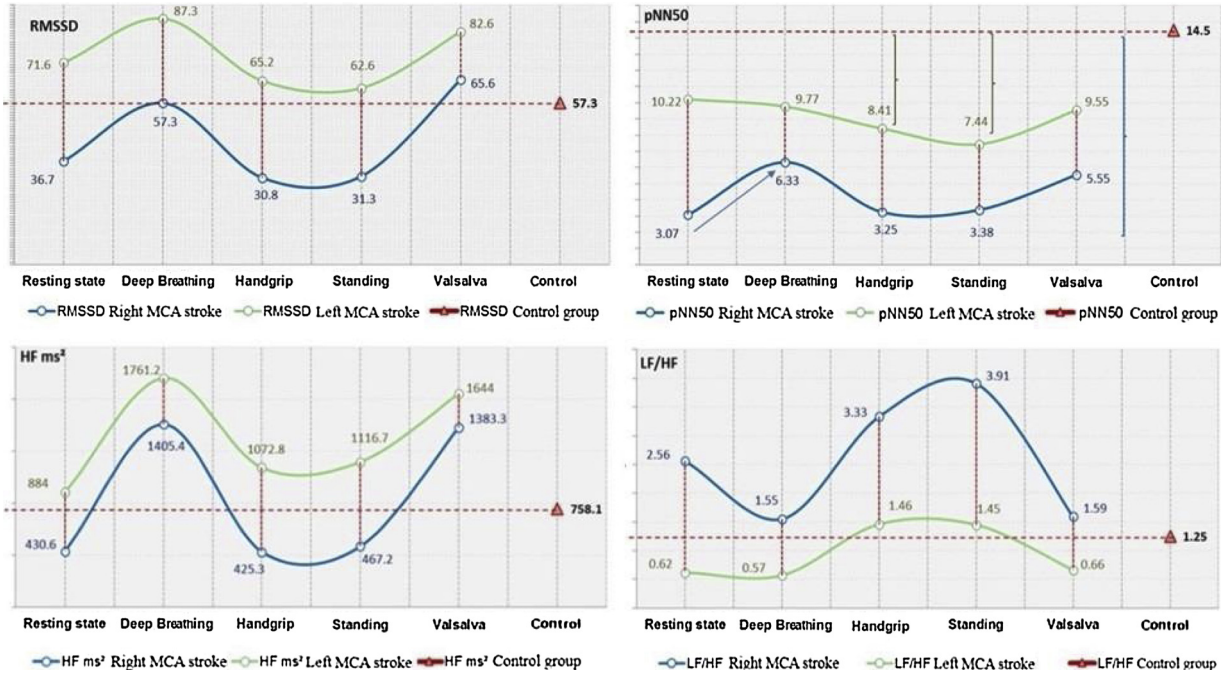

Fig. 3. Comparative assessment of RMSSD, pNN50, HF(ms^2) and LF/HF values in dynamics.

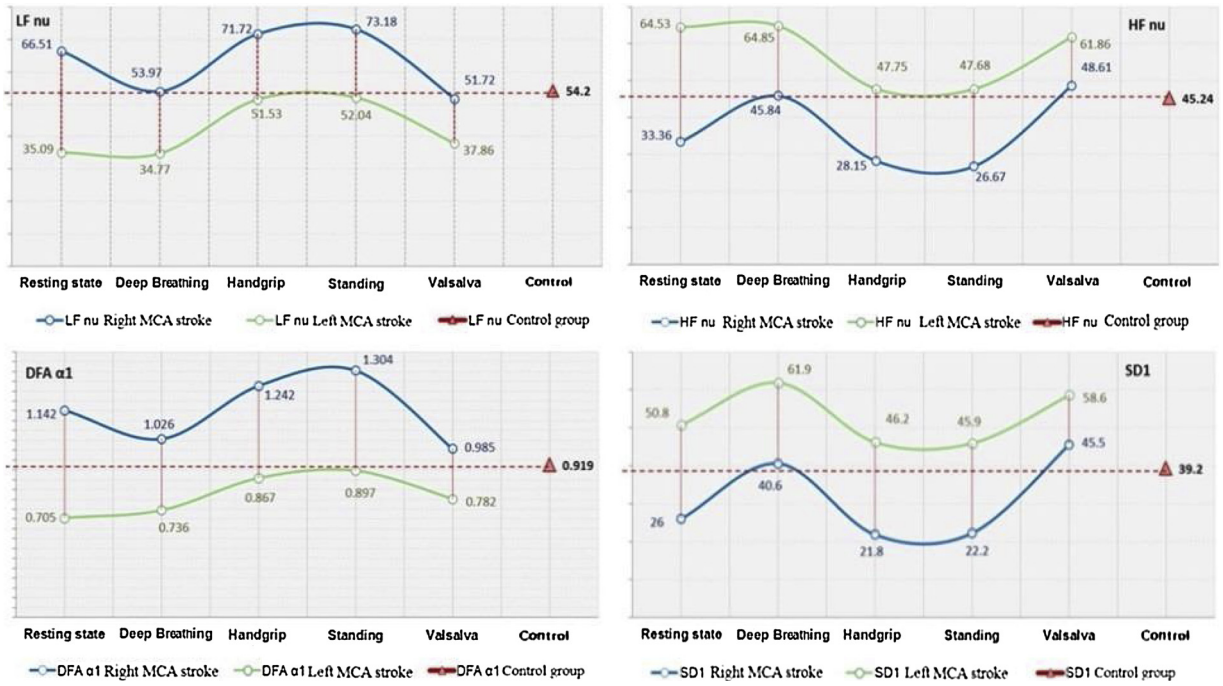

Fig. 4. Comparative assessment of LF(nu), HF(nu), DFA α1 and SD1 values in dynamics.

effects of several antihypertensive drugs are still debated. While some studies support the benefits of ACEI in patients with cardiac disease, data on cerebrovascular disease is scarce [32]. In patients receiving ACEI treatment within the first 30 days after myocardial infarction, an improvement in vagal tonus expressed by time-domain parameters has been shown, while others did not report any significant changes in sympathovagal balance [32,33]. Studies performed in patients with heart failure sustain the recovery of parasympathetic tonus under ACEI treatment [34,35]. Our results support this observation. During sympathetic activation tests (handgrip and standing) we observed a decrease of RMSSD, HF and SD1 in patients with ACEI treatment. The influence of ACEI on autonomic function may be related not to sympathetic suppression, but to other mechanisms, as described in heart failure patients [36].

Other classes of antihypertensive medication did not influence HRV parameters at rest and did not provide conclusive results on sympathovagal balance changes during autonomic activation tests. Further studies on larger groups are needed to understand the impact of medication on sympathovagal balance better.

Statin-treated patients had higher values of parasympathetic specific parameters during autonomic activation tests. Studies are demonstrating the beneficial role of statins in modulating the autonomic nervous system activity in patients with heart failure [37,38], but there is scarce data related to cerebrovascular pathology.

Table 2
Cut-off values and Area Under the ROC Curve (AUC) estimated for several HRV parameters in ischemic stroke patients.

Cut-off values / AUC for different linear and non-linear parameters in ischemic stroke patients					
Parameter	Resting state	Deep breathing	Handgrip	Standing	Valsalva
RMSSD (ms)	60.15 / 0.771	73 / 0.651	63.40 / 0.783	63.40 / 0.677	–
pNN50 (%)	2 / 0.691	11.65 / 0.650	–	1.50 / 0.798	7.80 / 0.596
LF/HF	1.20 / 0.937	0.94 / 0.834	1.66 / 0.829	2.18 / 0.838	1.06 / 0.753
LFnu (n.u.)	54.50 / 0.936	48.57 / 0.833	56.30 / 0.834	55.70 / 0.814	51.45 / 0.731
HFnu (n.u.)	48.80 / 0.939	51.29 / 0.835	28.45 / 0.831	44.25 / 0.812	48.25 / 0.717
SD1 (ms)	40.45 / 0.773	51.70 / 0.687	39.95 / 0.783	44.95 / 0.708	–
DFA α1	0.96 / 0.844	0.93 / 0.747	0.86 / 0.810	1.01 / 0.808	1.10 / 0.760

Table 3
Multiple linear regression HRV parameters vs. treatment.

Autonomic tests		RMSSD		HF		LF/HF		SD1	
Deep breathing	(Constant)	4.607	.000	2.826	.006	5.191	.000	4.609	.000
	Diuretic	.024	.981	−.913	.364	.465	.643	.023	.982
	ARB	−.240	.811	.674	.503	−.978	.332	−.244	.808
	Ca-blocker	−.424	.673	−.278	.782	.509	.612	−.428	.670
	ACEI	.053	.958	−.255	.799	−1.895	.033*	.051	.960
	Statin	1.054	.296	1.080	.284	−.221	.826	1.055	.295
Handgrip	(Constant)	4.129	.000	1.527	.131	6.453	.000	4.132	.000
	Diuretic	.684	.496	.808	.422	−1.755	.044*	.681	.498
	ARB	−1.130	.262	−.777	.440	.380	.705	−1.130	.263
	Ca-blocker	−.200	.842	−.652	.517	−.251	.802	−.203	.839
	ACEI	−2.174	.033*	−2.339	.022*	.500	.619	−2.173	.023*
	Statin	2.825	.043*	2.266	.027*	−1.183	.241	1.825	.033*
Resting state	(Constant)	4.724	.000	2.392	.020	4.667	.000	4.729	.000
	Diuretic	.936	.353	−.159	.875	−.179	.858	.933	.354
	ARB	−.522	.603	.203	.839	−.568	.572	−.526	.601
	Ca-blocker	−1.267	.210	−1.058	.294	.864	.391	−1.269	.209
	ACEI	−.282	.779	−.621	.537	−.865	.390	−.288	.774
	Statin	.252	.802	1.265	.210	−.088	.930	.258	.797
Standing	(Constant)	4.080	.000	1.851	.069	6.436	.000	4.013	.000
	Diuretic	.779	.439	1.782	.039*	.085	.932	1.085	.282
	ARB	−1.552	.126	−1.505	.137	−.087	.931	−1.575	.120
	Ca-blocker	−.508	.613	−.722	.473	1.235	.221	−.686	.495
	ACEI	−2.084	.031*	−1.777	.030*	−.040	.968	−1.948	.036*
	Statin	1.849	.039*	1.516	.134	−2.786	.007*	1.978	.032*
Valsalva	(Constant)	4.399	.000	3.343	.001	4.258	.000	4.119	.000
	Diuretic	.412	.681	−.910	.366	−.578	.565	.466	.643
	ARB	1.272	.208	2.373	.021*	−.823	.413	1.278	.206
	Ca-blocker	−.927	.357	−1.972	.043*	1.299	.199	−.880	.382
	ACEI	−.737	.464	.771	.443	.763	.448	−.667	.507
	Statin	1.414	.012*	.855	.396	−1.806	.035*	1.569	.121

Statistical test - 95%CI (Confidence Interval) – (*) Marked effects are significant at $p < 0.05$: *Predictors (Constant): treatment type; displayed T and p-values for each HRV parameter.*

This research attempts to establish a practical utility for the use of linear and non-linear analysis of HRV in neurological patients, offering a practical contribution to the current clinical activity in the neurovascular units. This supports the inclusion of HRV parameters reflecting independent cardiovascular activity in the assessment of ischemic stroke patients.

Recognizing the "neurogenic cardiac syndrome" [39] as well as establishing a personalized therapeutic strategy in ischemic stroke patients with altered sympathovagal balance represents an important management point because of the elevated risk of cardiac arrhythmias, especially in patients with sympathetic hyperactivity [40].

Our study reported a tendency to normalize the values of the linear parameters following vagal activation tests in patients with sympathetic hyperactivity. This opens new therapeutic perspectives, such as the vagal nerve stimulation (VNS).

Based on the results obtained in this study, prognostic scores could be developed for stroke patients at risk of neurogenic cardiac syndrome. This could complete the current treatment guidelines for patients with acute stroke in preventing fatal cardiac events in the short and long term.

Data statement

The data used to support the findings of this study are available from the corresponding author upon request.

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Declaration of Competing Interest

None.

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