NEUROLOGIA I NEUROCHIRURGIA POLSKA 52 (2018) 194–206

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Original research article

Linear and nonlinear parameters of heart rate variability in ischemic stroke patients

V. Constantinescu [a], D. Matei [b,*], V. Costache [c], D. Cuciureanu [a], C. Arsenescu-Georgescu [d]

[a] Neurology Department, Faculty of Medicine, University of Medicine and Pharmacy, No 16, University Street, Iasi 700115, Romania[1]

[b] Department of Biomedical Sciences, Faculty of Medical Bioengineering, University of Medicine and Pharmacy, No 16, University Street, Iasi 700115, Romania

[c] Cardiovascular Surgery Department, University "L. Blaga", Faculty of Medicine, No 2A, Lucian Blaga Street, Sibiu 550169, Romania

[d] Cardiology Department, Faculty of Medicine, University of Medicine and Pharmacy, No 16, University Street, Iasi 700115, Romania

ARTICLE INFO

Article history:
Received 16 May 2017
Accepted 3 October 2017
Available online 11 October 2017

Keywords:
Cardiac autonomic dysfunction
Ischemic stroke
Heart rate variability
Sympatho-vagal balance

ABSTRACT

Introduction: Cardiovascular system presents cortical modulation. Post-stroke outcome can be highly influenced by autonomic nervous system disruption. Heart rate variability (HRV) analysis is a simple non-invasive method to assess sympatho-vagal balance.

Objectives: The purpose of this study was to investigate cardiac autonomic activity in ischemic stroke patients and to asses HRV nonlinear parameters beside linear ones.

Methods: We analyzed HRV parameters in 15 right and 15 left middle cerebral artery ischemic stroke patients, in rest condition and during challenge (standing and deep breathing). Data were compared with 15 age- and sex-matched healthy controls.

Results: There was an asymmetric response after autonomic stimulation tests depending on the cortical lateralization in ischemic stroke patients. In resting state, left hemisphere stroke patients presented enhanced parasympathetic control of the heart rate (higher values for RMSSD, pNN50 and HF in normalized units). Right hemisphere ischemic stroke patients displayed a reduced cardiac parasympathetic modulation during deep breathing test. Beside time and frequency domain, using short-term ECG monitoring, cardiac parasympathetic modulation can also be assessed by nonlinear parameter SD1, that presented strong positive correlation with time and frequency domain parameters RMSSD, pNN50, HFnu, while DFA $\alpha 1$ index presented negative correlation with the same indices and positive correlation with the LFnu and LF/HF ratio, indicating a positive association with the sympatho-vagal balance.

Conclusions: Cardiac monitoring in clinical routine using HRV analysis in order to identify autonomic imbalance may highlight cardiac dysfunctions, thus helping preventing

* *Corresponding author at*: Department of Biomedical Sciences, Faculty of Medical Bioengineering, University of Medicine and Pharmacy, No 9-13, Kogalniceanu Street, 700454 Iasi, Romania.
E-mail address: daniela.matei@umfiasi.ro (D. Matei).

[1] Department and institution to which the work is to be attributed.

https://doi.org/10.1016/j.pjnns.2017.10.002

potential cardiovascular complications, especially in right hemisphere ischemic stroke patients with sympathetic hyperactivation.

1. Introduction

Cardiac dysautonomia is a common complication of stroke [1–3]. Post stroke autonomic nervous system dysregulation has attracted significant interest in the last couple of decades. Many facts involved in short term evolution and prognostic still need to be clarified.

Cardiovascular system presents cortical modulation. Both human studies and experimental data revealed that insular cortex, anterior cingulate gyrus, hypothalamus and amygdala may be involved in central autonomic nervous system regulation [4–6]. Lesions at these levels might be held responsible of cardiac arrhythmias. After acute cerebrovascular events arrhythmias and electrocardiographic abnormalities are common, even in the absence of structural heart disease, with a high incidence of dysautonomia [7].

Studies about heart–brain connections proposed the concept of neurogenic cardiac disease, clinically and pathogenically different from the actual cardiac disease [8–11].

Identifying high risk patients prone to develop neurogenic cardiac complications, by better understanding dysautonomia pathophysiology, and further implementation of adequate prophylactic and therapeutic measures, may significantly reduce mortality rate in stroke patients. The influence of stroke's hemispheric lateralization in cardiovascular autonomic dysregulation [12] has been illustrated using modern neuroimaging data, including positron emission tomography and functional magnetic resonance imaging data [13].

An acute ischemic lesion involving the cortical network controlling the activity of the autonomic nervous system may imbalance autonomic responses at cardiac level and lead to an increased risk of arrhythmia [14]. Insular cortex, a complex structure supplied by the middle cerebral artery (MCA), was often used as a model to illustrate the possible lateralization impact on sympatho-vagal balance, depending on the hemispheric localization of the stroke. It has been reported that cardiosympathetic centers are located in the anterior, medial and superior parts of the insula, while posterior insula and inferior parietal lobe are responsible for inhibiting and modulating the cardiosympathetic outflow of the other parts of the insula [15]. Autonomic imbalance associating increased sympathetic activity may be reflected in cardiovascular impairment post insular stroke [1].

Among different variables assessing the autonomic response, heart rate variability (HRV) quantifies sympatho-vagal modulation at sino-atrial level. It has been shown that a reduction of HRV may be an indicator of general illness, including acute stroke, and it correlates with enhanced sympathetic or reduced vagal tone, which may predispose to higher risk of arrhythmia [16,17] and increased risk of sudden cardiac death. HRV might provide prognostic information in ischemic stroke. Graff and collaborators [18] underlined the contribution of HRV in-depth analysis to stroke prognosis and stated that while HRV assessed by linear methods may provide long-term prognostic value, complex, non-linear measures of HRV may rather assess the impact of the neurological state on temporary patterns of heart rate post stroke [18]. In the same line of evidence, it has been recently shown that acute ischemic stroke patients had a significant reduced complexity of HRV. Early assessment of HRV by non-linear methods can be a potential predictor of stroke-in-evolution in newly admitted non- atrial fibrillation ischemic stroke patients [19].

In addition to linear parameters, nonlinear parameters of HRV might be useful to identify patients prone to cardiac arrhythmia, thus a prognostic marker of cardiac function.

The Poincaré plot is a visual representation of the dependence between successive RR intervals, first used as a qualitative tool [20] by fitting an ellipse to the shape of the Poincaré plot in order to calculate HRV indices [21]. This geometrical technique can be used to assess the dynamics of HRV by a representation of the values of each pair of R–R intervals into a simplified phase space, describing the dynamics of a phenomenon that can recognize the hidden correlation patterns of a time series signal [22,23]. Each pair of successive elements in a time series (tachogram) is pictured into a simplified Cartesian plane [24,25]. Series of these points at successive times outline a trajectory. This describes the system's evolution and therefore is commonly applied to assess the dynamics of HRV. Using this technique, SD1 and SD2 are the semi-axis of this ellipse. SD1 is related to the fast beat-to-beat variability, while SD2 describes the longer-term variability, SD1/SD2 showing the ratio of short-term to long-term interval variation. This quantitative method of analysis is based on the notion of different temporal effects of changes in the vagal and sympathetic modulation of the HR on the subsequent R–R intervals without a requirement for a stationary quality of the data [22,24,26,27].

SD1 is considered a parasympathetic index of sinus node control being a measure of rapid changes in R–R intervals, because vagal effects on the sinus node are known to develop faster than sympathetically mediated effects [28,29] and SD2 is influenced by both parasympathetic and sympathetic tonus [30].

Other useful parameter is approximate entropy (ApEn), a measure of the disorder in the HR signal which quantifies the regularity and complexity of time series. Sample entropy (SampEn) is a less biased measure derived from approximate entropy [23,31], which quantifies signal complexity robustly within short time segments [32]. The name refers to the applicability to time series data sampled from a continuous process and the algorithm suggests ways to employ sample statistics to evaluate the results [33]. It measures system complexity and unpredictability [34] and is the negative natural logarithm of the conditional probability that two

sequences similar for m points remain similar at the next point, where self-matches are not included in calculating the probability. Thus a lower value of SampEn also indicates more self-similarity in the time series [33].

Detrended fluctuation analysis (DFA) is used to quantify the fractal scaling properties of R–R interval [35] and has been validated for time series data [36]. DFA calculates the root-mean-square fluctuation of integrated and detrended time series, permits the detection of intrinsic self-similarity embedded in a non-stationary time series, and also avoids the spurious detection of apparent self-similarity [36]. The scaling exponent, the self-similarity α parameter represents the autocorrelation properties of the signal: <0.5 anti-correlated signal, large and small values of the time series are more likely to alternate; $\alpha = 0.5$ corresponds to white noise, an α greater than 0.5 and less than 1.0 indicates positive autocorrelation in the signal such that a large inter-beat interval is more likely to be followed by large interval and vice versa. $\alpha = 1$ represents $1/f$ noise; for $\alpha \geq 1$, correlations exist but cease to be of a power-law form and $\alpha = 1.5$ indicates Brownian noise or random walk [37–40]. DFA plot is not strictly linear but rather consisted of two distinct regions of different slopes, there is a short range scaling exponent ($\alpha 1$) over periods of 4–11 beats (or 4–13), and a long-range exponent ($\alpha 2$), over longer periods (larger than 11 beats) [36,37].

2. Aim

The aim of this research is to illustrate autonomic nervous system dysregulation in ischemic MCA stroke patients.

3. Materials and methods

The study included 30 ischemic stroke patients, within 6 months post stroke and 15 age- and sex-matched healthy controls, volunteers from community dwelling people, with no previous history of cerebrovascular pathology. All the subjects were divided into three groups. In the first group there were 15 patients with right MCA ischemic stroke (8 men and 7 women), 59.7 ± 10.3 years old, in the second group there were 15 patients with left MCA ischemic stroke (7 men and 8 women), 59.4 ± 8.43 years old, and the control group was based on healthy volunteers (8 men and 7 women), 59.33 ± 7.28 years old. Patients were recruited from neurological department and all patients gave consent in accordance with ethical principles. The study was carried out in accordance with the Helsinki Declaration.

Inclusion criteria were as follows: age between 40 and 75 years old, right handed patients, clinical assessment suggestive of stroke, evaluation in the first 6 months after the acute event, computed tomography (CT) or magnetic resonance imaging (MRI) showing a single ischemic lesion within left or right hemisphere (superficial and/or profound MCA territory) and cardiologic evaluation prior to stroke.

Exclusion criteria were: congestive heart failure, moderate-to-severe valvular dysfunction, any cardiomyopathy, previous acute myocardial infarction and left ventricular hypertrophy, arrhythmia on current admission (including atrial fibrillation), dementia, any major concurrent illness (including renal failure and malignancies), diabetes mellitus or other metabolic pathologies generating polyneuropathy, any medication interfering with HR (beta-blockers), fever, hypoxia, alterations in consciousness or any relevant hemodynamic compromise on admission.

For the stroke group, the patients were under specific medication for their associated cardiovascular co-morbidities, including statins (in case of hypercholesterolemia), platelet antiaggregants and antihypertensive drugs (in case of arterial hypertension) in different associations, including angiotensin-converting-enzyme inhibitors, thiazide-like diuretics, calcium channel blockers or angiotensin receptor blockers, but not beta-blockers which could influence the presented data. Even though, a pharmacological implication of these drugs in the immediate outcome of stroke patients is an interesting subject per se, this was not the topic of the present work. The control group was not using any medication.

Sympathetic and parasympathetic modulation of the HR was assessed in MCA ischemic stroke patients by analyzing HRV parameters in resting condition and during challenge, using BIOPAC® Acquisition System. This is an integrated hardware and software system used for collecting and processing biologic signals. BIOPAC System converts biologic parameters in numeric data. Interpretation was based on AcqKnowledge software, version 3.9.1.6, that allows detecting, measuring and automatic assays the registered signal. The data was afterwards analyzed using Kubios HRV program, version 2.2 (Biosignal Analysis and Medical Imaging Group, University of Eastern Finland). This program assesses HRV in time and frequency domain, calculating linear and non-linear parameters, as exemplified in Figs. 1 and 2.

HRV comprises numerous parameters. Standard deviation of the HR, known as standard deviation of N–N interval (normal-to-normal) – SDNN, meaning the square root of its variance, reflects the influence of the parasympathetic and sympathetic system on HR modulation [16,41]. pNN50 is a parameter evaluating parasympathetic activity [16,41]. It illustrates the proportion of differences in consecutive, so-called normal-to-normal RR intervals on ECG that are longer than 50 ms and reflects the percentage of such intervals in comparison to the total number of analyzed intervals. Similarly, the root of the mean squared differences of successive NN intervals (RMSSD) reflects parasympathetic activity. The coefficient of variation and the RMSSD are the most valuable time-domain parameters for routine evaluation in resting state as they provide highly reproducible results and are not influenced by mean resting HR.

We calculated frequency domain parameters that assign bands of frequency and then count the number of NN intervals that match each band: high frequency (HF) from 0.15 to 0.4 Hz, low frequency (LF) from 0.04 to 0.15 Hz and the very low frequency (VLF) from 0.0033 to 0.04 Hz. Despite controversy on the concept [42–44], it is generally agreed that the high-frequency (HF) component reflects parasympathetic outflow to the heart [45–47]. However, the origin of the low-frequency (LF) component is less certain. It has been hypothesized that LF spectral power is a marker of cardiac sympathetic modulation in humans [48] and assumed that LF has a dominant sympathetic component [16,49,50]. A more complex mechanism beyond this

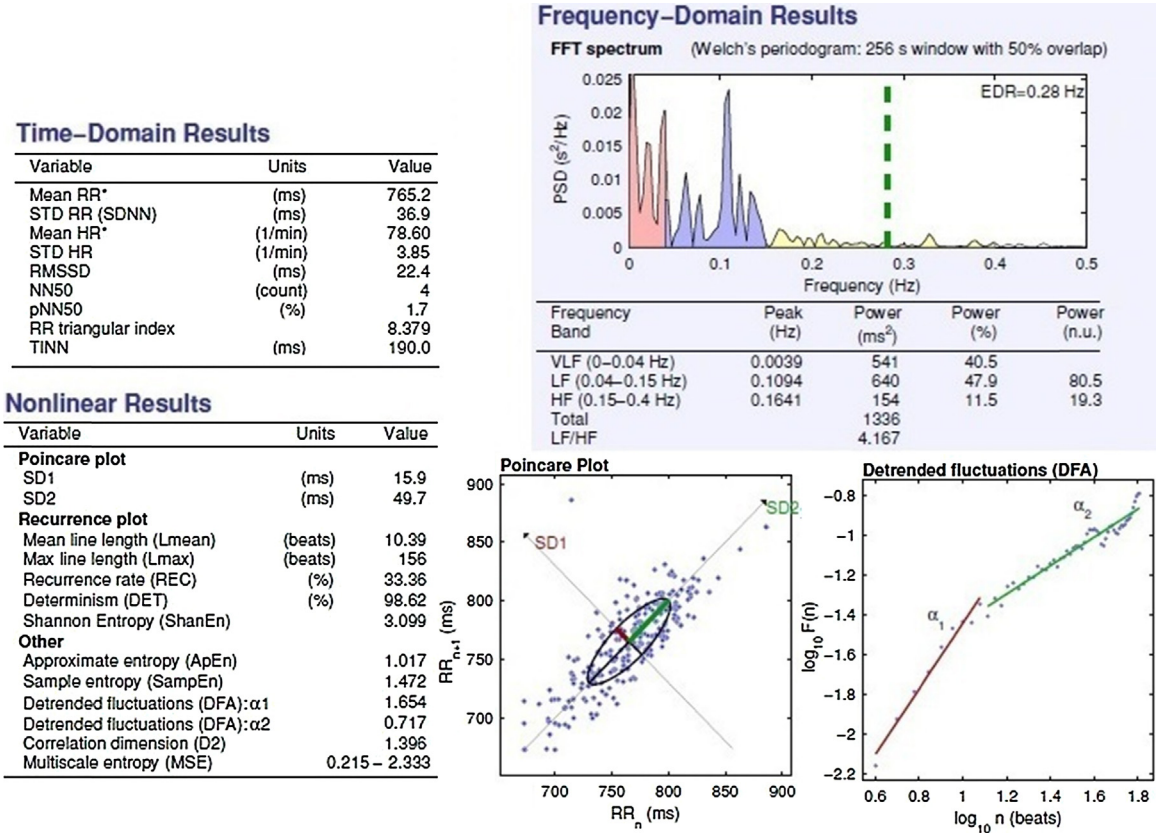

Fig. 1 – Linear and nonlinear parameters of the heart rate variability using Kubios HRV® 2.2 analysis. Enhanced sympathetic control of the heart rate in resting state recording in a right hemisphere ischemic stroke patient.

simplified association between sympathetic component and LF is still under debate. Also, despite serious limitations, the LF/HF ratio was presumed as a tool to assess cardiovascular autonomic regulation, while increases in LF/HF were assumed to reflect a shift to sympathetic enhanced tonus while decreases in this index correspond to a parasympathetic enhanced tonus. With or without adjustment for HF spectral power, total power or respiration, LF spectral power seems to provide an index not of cardiac sympathetic tone, but of baroreflex function [51,52]. Manipulations and drugs that change LF power or LF/HF ratio may do so, not by affecting cardiac autonomic outflows directly, but by affecting modulation of those outflows by baroreflexes [53].

Recent clinical and animal studies concluded that although sympathetic nerve activity was not directly recorded, the LF component of the HR power spectrum probably results from an interaction of sympathetic and parasympathetic nervous systems and, as such, does not accurately reflect changes in the sympathetic activity [54–57].

The VLF spectral power depends on more complex mechanisms, influenced by the thermoregulatory and renin-angiotensin system, in this respect, we preferred to use the normalized units for the LF and HF (LFnu, HFnu), that remove the VLF from the estimation.

All stroke patients and control subjects were evaluated using BIOPAC system. ECG recordings were performed at least 5 min in each subject in a 22 °C atmosphere, in resting state, after 20 min of supine position, in the absence of any anterior physical effort. A minimum of 264 RR intervals for each recording were analyzed. It was recommended for all subjects to refrain from drinking alcohol and caffeine one day prior to the recordings and to be quiet and calm during ECG registration.

Autonomic function was also evaluated by ''deep breathing test'', which assesses parasympathetic response, measures HR changes after 6 deep breaths during 1minute and ''standing test'' that measure HR changes during passive movement from supine position to orthostatic position, evaluating sympathetic response. Orthostatic hypotension was defined as a decrease in systolic blood pressure of 20 mmHg or a decrease in diastolic blood pressure of 10 mmHg within three minutes of standing when compared with blood pressure in the supine position.

Beside time and frequency domain parameters, some authors considered the following algorithm in order to analyze R–R variation: $(RR_{max} - RR_{min}) \times 100/RR_{mean}$, which is the difference between the shortest and longest RR interval registered during short-term ECG recordings, given as a percentage of the mean of all maximal and minimal peaks. RR interval variation responses at rest were considered abnormal when less than 10% [15,58].

The linear indexes obtained from time and frequency domain analysis (mean RR, mean HR, SDNN, RMSSD, pNN50, LFnu, HFnu, LF/HF ratio) and the nonlinear parameters (SD1,

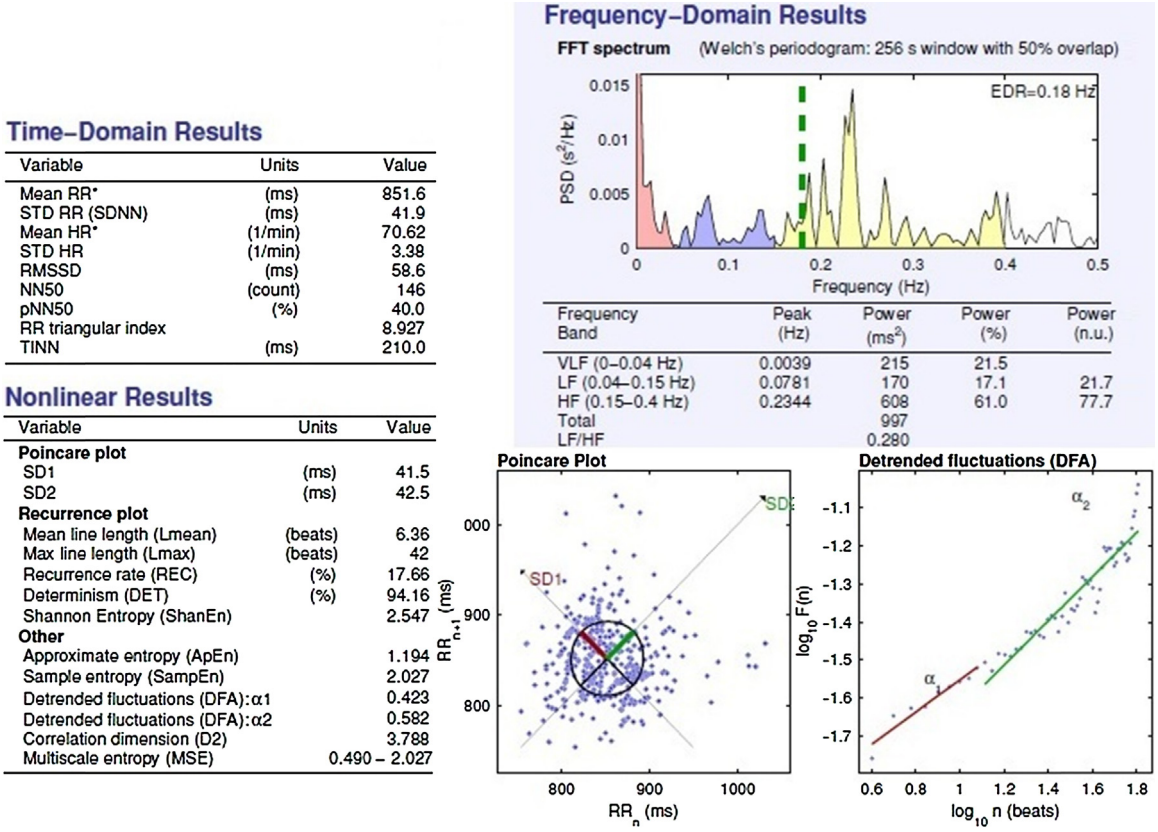

Fig. 2 – Linear and nonlinear parameters of the heart rate variability using Kubios HRV® 2.2 analysis. Enhanced parasympathetic control of the heart rate in resting state recording in a left hemisphere ischemic stroke patient.

ApEn, SampEn, DFA $\alpha 1$ and $\alpha 2$) were obtained with the aid of Kubios HRV analysis software.

SD2 may represent a reliable tool on 24 h ECG recordings. Since the ECG tracks in our study were not obtained on 24 h recordings, we preferred to not include these results in our conclusions. Relationships between linear and nonlinear indexes were tested using specific correlation tests.

Data were analyzed using the SPSS version 22.0 (IBM Corporation, Chicago, IL, USA). The results of the univariate analysis were reported as mean ± standard deviation for continuous variables.

Having into consideration the small sample size, series normalization is very difficult. This was evaluated using Kolmogorov–Smirnov test. Applied comparative tests were specific to the characteristics of the analyzed series. In the case of pretest analysis, the homogeneity of variance for the studied parameters was analyzed using Levene test, this being the mandatory condition for applying the ANOVA analysis. In the case of nonhomogeneous series, the groups were compared using Kruskal–Wallis. In order to identify differences in the three studied groups' parameters, we used post hoc multiple comparison analysis tests. In the case of homogenous series we applied Duncan Test because, when compared to Newman–Keuls or Tukey, there are the lowest chances of type I error results. When in the three groups there were statistically significant differences between the variance of analyzed parameters, we used Dunnett's test.

Total count and percent were reported for categorical variables. Chi-square test (Maximum-Likelihood and Yates) was performed for categorical variables. Correlations between variables were determined using univariate analysis based on the nonparametric test Spearman Rank test. The significance level (p-value), which represents the maximum error probability, was considered to be 0.05 (5%); a confidence interval of 95% shows that the decision is correct.

4. Results

80% of right MCA ischemic stroke patients were hypertensive and 86.6% of left MCA ischemic stroke patients had hypertension as a vascular risk factor. We found orthostatic hypotension in 40% of patients with left hemisphere stroke, significantly elevated percentage when compared with right hemisphere stroke patients ($p < 0.05$).

Left hemisphere stroke patients presented enhanced parasympathetic control of the HR, evidenced by higher RMSSD and pNN50 values in resting state when compared to right hemisphere stroke patients ($p < 0.05$) (Table 1). Also, in resting state, pNN50 values were lower in right hemisphere stroke patients compared to controls ($p < 0.05$) (Table 1). Moreover, frequency domain parameters (HFnu) also showed enhanced parasympathetic control of the HR in left MCA infarction compared to right MCA infarction ($p < 0.05$) and to

Table 1 – Heart rate variability parameters in resting state.

HRV parameters in resting state	Group 1 – right hemisphere stroke ($n = 15$)	Group 2 – left hemisphere stroke ($n = 15$)	Control group ($n = 15$)	Levene test df = 2	Group 1 vs. Group 2	Group 1 vs. control	Group 2 vs. control
				p-Value			
RR (ms)	874.4 ± 108.4	782 ± 92.3	797.9 ± 85.7	0.546	0.0135	0.031	0.645
SDNN	47.1 ± 19.8	66.7 ± 46.8	65.5 ± 34.1	0.290	0.152	0.154	0.926
Heart rate	74.8 ± 9.7	74.3 ± 7.5	69.8 ± 6.9	0.422	0.884	0.112	0.124
RMSSD	37.7 ± 22.4	81.7 ± 64.1	65.3 ± 34.3	0.100	0.010	0.087	0.304
pNN50	3.2 ± 3.8	12.2 ± 13.7	17.2 ± 16.8	0.0003*	0.052	0.004	0.282
LFnu	67.1 ± 12.5	32.4 ± 15.7	57 ± 8.7	0.010*	0.0001	0.032	0.0001
HFnu	32.7 ± 12.4	66.1 ± 15.3	42.6 ± 8.4	0.016*	0.0001	0.040	0.0001
LF/HF	2.6 ± 1.6	0.5 ± 0.3	1.3 ± 0.3	0.000*	0.0001	0.001	0.049
SD1	26.7 ± 15.8	58.1 ± 45.4	43.4 ± 20.8	0.020*	0.005	0.013	0.018
SD2	58.7 ± 24.2	70.1 ± 51.9	71.2 ± 41.3	0.253	0.442	0.426	0.936
ApEn	0.8 ± 0.2	0.6 ± 0.2	0.8 ± 0.1	0.331	0.097	0.770	0.066
SampEn	1.1 ± 0.3	0.8 ± 0.5	0.9 ± 0.4	0.280	0.224	0.704	0.359
DFA $\alpha 1$	1.1 ± 0.3	0.5 ± 0.2	0.9 ± 0.2*	0.329	0.00006	0.023	0.003
DFA $\alpha 2$	0.9 ± 0.2	0.8 ± 0.3	0.5 ± 0.2*	0.206	0.314	0.0004	0.005

Values are expressed as a mean ± standard deviation.
p-value < 0.05 was considered to be statistically significant; df – degrees of freedom.
* p-value < 0.05 for Levene test → the Dunnett's test was used for comparison.

control group ($p < 0.05$) and lower LF/HF ratio values ($p < 0.05$). The increased vagal influence on the HR in left hemisphere stroke patients is also confirmed by high SD1 levels in resting state when compared to controls ($p < 0.05$).

On the other hand, in patients with right MCA stroke we found a higher sympathetic control of the HR, when compared to left MCA strokes ($p < 0.05$) and to controls ($p < 0.05$), according to time and frequency domain parameters, associating higher values for the nonlinear parameter DFA $\alpha 1$.

During deep breathing test, left hemisphere stroke patients described more pronounced vagal influence on the HR expressed by RMSSD and HFnu parameters compared to right hemisphere stroke patients ($p < 0.05$) and to control group ($p < 0.05$), as shown in Table 2. LF/HF was lower in left hemisphere stroke patients, according to the same results. Nonlinear parameters SD1 also show higher values in left hemisphere stroke patients compared to controls ($p < 0.05$) (Table 2).

During standing test we noticed a decreased parasympathetic control of the HR in right MCA ischemic stroke patients (lower pNN50, SDNN values) compared to controls ($p < 0.05$). The frequency-domain parameters (LFnu, HFnu) underline the same results toward a more decreased parasympathetic control of the HR in right MCA ischemic stroke patients vs. controls. Nonlinear parameters showed difference between right and left hemisphere stroke patients, as shown in Table 3.

Table 2 – Heart rate variability parameters in deep breathing test.

HRV parameters in deep breathing test	Group 1 – right hemisphere stroke ($n = 15$)	Group 2 – left hemisphere stroke ($n = 15$)	Control group ($n = 15$)	Levene test df = 2	Group 1 vs. Group 2	Group 1 vs. control	Group 2 vs. control
				p-Value			
RR (ms)	862.3 ± 111.3	788.5 ± 98.1	733.2 ± 70.7	0.141	0.036	0.0007	0.112
SDNN	69.3 ± 24.9	93.8 ± 62.6	34.9 ± 22.3	0.002*	0.104	0.024	0.0004
Heart rate	73.1 ± 7.9	69.8 ± 4.2	68.7 ± 6.8	0.011*	0.054	0.021	0.905
RMSSD	38.3 ± 23.8	117.6 ± 85.2	74.8 ± 46.2	0.001*	0.001	0.086	0.045
pNN50	6.1 ± 5.4	13.9 ± 16.9	5.8 ± 3.8	0.00002*	0.103	0.998	0.106
LFnu	47.4 ± 1	29.9 ± 11.7	47.0 ± 11.1	0.291	0.001	0.996	0.002
HFnu	52.3 ± 15.8	69.6 ± 11.6	52.9 ± 11.2	0.317	0.001	0.992	0.002
LF/HF	1.1 ± 0.7	0.5 ± 0.2	1.1 ± 0.5	0.005*	0.01	0.954	0.027
SD1	53.1 ± 32.8	83.4 ± 60.4	28.6 ± 15.5	0.0004*	0.102	0.246	0.002
SD2	79.3 ± 24.6	100.8 ± 68.2	46.8 ± 24.1	0.0009*	0.183	0.047	0.002
ApEn	0.6 ± 0.1	0.5 ± 0.1	0.7 ± 0.2	0.457	0.179	0.336	0.061
SampEn	0.8 ± 0.4	0.7 ± 0.4	1.0 ± 0.5	0.664	0.489	0.279	0.184
DFA $\alpha 1$	0.9 ± 0.3	0.7 ± 0.2	0.9 ± 0.2	0.163	0.071	0.693	0.128
DFA $\alpha 2$	0.9 ± 0.2	0.9 ± 0.3	0.7 ± 0.4*	0.466	0.611	0.053	0.121

Values are expressed as a mean ± standard deviation.
p-value < 0.05 was considered to be statistically significant; df – degrees of freedom.
* p-value < 0.05 for Levene test → the Dunnett's test was used for comparison.

Table 3 – Heart rate variability parameters in standing test.

HRV parameters in standing test	Group 1 – right hemisphere stroke ($n = 15$)	Group 2 – left hemisphere stroke ($n = 15$)	Control group ($n = 15$)	Levene test df = 2	Group 1 vs. Group 2	Group 1 vs. control	Group 2 vs. control
				p-Value			
RR (ms)	823.0 ± 99.2	767.7 ± 106.0	759.3 ± 80.1	0.259	0.114	0.085	0.808
SDNN	43.6 ± 29.4	56.4 ± 33.3	68.5 ± 22.1	0.245	0.240	0.024	0.217
Heart rate	83.6 ± 8.1	81.0 ± 10.9	74.4 ± 8.6	0.763	0.056	0.012	0.450
RMSSD	32.4 ± 19.6	49.2 ± 46.7	35.2 ± 22.2	0.0002*	0.320	0.814	0.228
pNN50	3.4 ± 3.6	5.7 ± 9.9	10.1 ± 8.1	0.211	0.402	0.024	0.119
LFnu	73.60 ± 11.8	67.3 ± 18.9	58.2 ± 6.1	0.007*	0.201	0.003	0.067
HFnu	26.3 ± 11.7	32.4 ± 18.7	41.5 ± 6.1	0.007*	0.403	0.007	0.153
LF/HF	4.0 ± 3.4	2.7 ± 1.9	2.3 ± 0.7	0.015*	0.139	0.069	0.649
SD1	23.3 ± 13.9	37.9 ± 32.4	31.4 ± 19.8	0.002*	0.099	0.323	0.442
SD2	93.0 ± 30.1	67.2 ± 39.3	57.9 ± 34.2	0.584	0.044	0.009	0.457
ApEn	0.6 ± 0.1	0.6 ± 0.2	0.6 ± 0.2	0.753	0.710	0.821	0.576
SampEn	0.6 ± 0.2	0.7 ± 0.4	0.8 ± 0.5	0.016*	0.735	0.239	0.359
DFA $\alpha 1$	1.2 ± 0.2	1.0 ± 0.4	1.1 ± 0.3	0.328	0.087	0.298	0.802
DFA $\alpha 2$	1.2 ± 0.2	1.1 ± 0.3	0.9 ± 0.4	0.021*	0.892	0.063	0.159

Values are expressed as a mean ± standard deviation.
p-value < 0.05 was considered to be statistically significant; df – degrees of freedom.
* *p*-value < 0.05 for Levene test → the Dunnett's test was used for comparison.

In *right hemisphere stroke patients*, in resting state, we found a very strong correlation between SD1 and SDNN ($r = 0.9$, $p < 0.05$) and between SD1 and RMSSD ($r = 0.9$, $p < 0.05$) (Table 4). We found a negative correlation between SD1 and DFA $\alpha 1$ ($r = -0.7$, $p < 0.05$) (Table 4). SDNN presented a negative correlation with DFA $\alpha 1$ ($r = -0.6$, $p < 0.05$) and with RMSSD ($r = 0.9$, $p < 0.05$) (Table 4). DFA $\alpha 1$ presented a negative correlation with HFnu ($r = -0.5$, $p < 0.05$) and a positive correlation with LFnu ($r = 0.6$, $p < 0.05$) and LF/HF ratio ($r = 0.5$, $p < 0.05$) (Table 4).

During deep breathing test we found interesting connections between SD1 and other nonlinear parameters, as it follows: SampEn ($r = -0.7$, $p < 0.05$), DFA$\alpha 1$ ($r = -0.4$, $p > 0.05$) and DFA $\alpha 2$ ($r = -0.7$, $p < 0.05$) (Table 5). Same as during resting state, we deduced a very strong correlation between SD1 and time domain parameters SDNN ($r = 0.8$, $p < 0.05$) and RMSSD

Table 4 – Relationships between linear (SDNN, RMSSD, LFnu, HFnu and LF/HF) and nonlinear indexes (SD1, SD2, SampEn, ApEn, DFA $\alpha 1$ and DFA $\alpha 2$) in resting state.

	Correlation coefficients calculated based on the Spearman Rank Order test									
	RMSSD	LF/HF	LF nu	HF nu	SD1	SD2	ApEn	SampEn	DFA $\alpha 1$	DFA $\alpha 2$
Include condition: Group 1 – right hemisphere stroke										
SDNN	0.908*	−0.169	−0.169	0.177	0.908*	0.914*	−0.238	−0.371	−0.611*	−0.315
RMSSD		−0.344	−0.341	0.352	0.995*	0.779*	−0.247	−0.484	−0.769*	−0.353
LF/HF			0.997*	−0.999*	−0.344	0.006	−0.024	0.341	0.596*	−0.091
LF nu				−0.995*	−0.341	0.003	−0.035	0.330	0.601*	−0.115
HF nu					0.352	0.009	0.012	−0.349	−0.590*	0.075
SD1						0.779*	−0.247	−0.484	−0.769*	−0.353
SD2							−0.188	−0.328	−0.406	−0.300
ApEn								0.524*	0.278	0.159
SampEn									0.428	−0.206
DFA $\alpha 1$										0.082
Include condition: Group 2 – left hemisphere stroke										
SDNN	0.667*	0.153	0.165	−0.132	0.644*	0.918*	−0.571*	−0.571*	−0.003	−0.179
RMSSD		−0.408	−0.398	0.411	0.996*	0.561*	−0.493	−0.375	−0.595*	−0.515*
LF/HF			0.999*	−0.997*	−0.432	0.253	−0.218	−0.326	0.726*	0.332
LF nu				−0.995*	−0.424	0.271	−0.233	−0.343	0.731*	0.336
HF nu					0.435	−0.221	0.221	0.321	−0.712*	−0.315
SD1						0.526*	−0.468	−0.329	−0.597*	−0.524*
SD2							−0.662*	−0.706*	0.135	0.026
ApEn								0.924*	−0.044	0.100
SampEn									−0.053	0.059
DFA $\alpha 1$										0.562*

* *p*-Value < 0.05 was considered to be statistically significant.

Table 5 – Relationships between linear (SDNN, RMSSD, LFnu, HFnu and LF/HF) and nonlinear indexes (SD1, SD2, SampEn, ApEn, DFA α1 and DFA α2) in deep breathing test.

	Correlation coefficients calculated based on the Spearman Rank Order test									
	RMSSD	LF/HF	LF nu	HF nu	SD1	SD2	ApEn	SampEn	DFA α1	DFA α2
Include condition: Group 1 – right hemisphere stroke										
SDNN	0.891*	−0.300	−0.300	0.300	0.891*	0.909*	−0.171	−0.726*	−0.318	−0.579*
RMSSD		−0.432	−0.432	0.432	0.996*	0.732*	−0.403	−0.759*	−0.459	−0.703*
LF/HF			0.993*	−0.998*	−0.432	−0.009	0.162	0.462	0.679*	0.338
LF nu				−0.997*	−0.432	−0.009	0.162	0.462	0.679*	0.338
HF nu					0.432	0.009	−0.162	−0.462	−0.679*	−0.338
SD1						0.732*	−0.403	−0.759*	−0.459	−0.703*
SD2							−0.026	−0.574*	−0.132	−0.385
ApEn								0.541*	0.379	0.362
SampEn									0.691*	0.535*
DFA α1										0.471
Include condition: Group 2 – left hemisphere stroke										
SDNN	0.891*	0.059	0.084	−0.091	0.891*	0.971*	0.019	−0.318	0.037	−0.318
RMSSD		0.138	−0.021	0.028	0.994*	0.821*	−0.031	−0.256	−0.271	−0.388
LF/HF			0.646*	−0.646*	0.138	−0.024	−0.144	−0.341	−0.074	−0.568*
LF nu				−0.999*	−0.021	0.140	−0.158	−0.499*	0.259	−0.313
HF nu					0.028	−0.149	0.158	0.497*	−0.295	0.318
SD1						0.821*	−0.031	−0.256	−0.271	−0.388
SD2							−0.016	−0.353	0.141	−0.241
ApEn								0.542*	−0.125	0.228
SampEn									0.135	0.153
DFA α1										0.001

* p-Value < 0.05 was considered to be statistically significant.

($r = 0.9$, $p < 0.05$) (Table 5). SampEn presented negative correlation with SDNN ($r = -0.7$, $p < 0.05$). DFA α1 presented negative correlation with frequency domain parameter HFnu ($r = -0.6$, $p < 0.05$) and positive strong correlation with LFnu ($r = 0.6$, $p < 0.05$) and with LF/HF ratio ($r = 0.6$, $p < 0.05$) (Table 5). During standing test, a sympathetic activation test, we found a very strong correlation between SD1 and RMSSD ($r = 0.9$, $p < 0.05$) and positive correlation between SD1 and SDNN ($r = 0.5$, $p < 0.05$) (Table 6). DFA α1 presented negative correlation with RMSSD ($r = -0.6$, $p < 0.05$) and with SD1 ($r = -0.6$, $p < 0.05$) (Table 6).

In *left hemisphere stroke patients*, in resting state, we observed very strong correlations between nonlinear parameters SD1 and SDNN ($r = 0.6$, $p < 0.05$), RMSSD ($r = 0.9$, $p < 0.05$) (Table 4). Another nonlinear parameter, ApEn, presented negative correlation with SDNN ($r = -0.5$, $p < 0.05$) and SampEn a negative correlation with SDNN ($r = -0.5$, $p < 0.05$). DFA α1 presented negative correlation with RMSSD ($r = -0.5$, $p < 0.05$), with frequency domain parameter HFnu ($r = -0.7$, $p < 0.05$) and negative correlation with SD1 ($r = -0.5$, $p < 0.05$) (Table 4). During deep breathing test, we found a very strong correlation between SD1 and SDNN ($r = 0.8$, $p < 0.05$) and RMSSD ($r = 0.9$, $p < 0.05$) (Table 5). During standing test, we found a strong negative correlation between SD1 and DFA α1 ($r = -0.7$, $p < 0.05$). SD1 correlate with time domain parameters SDNN ($r = 0.8$, $p < 0.05$), RMSSD ($r = 0.8$, $p < 0.05$) (Table 6). Also SampEn correlates negatively with SDNN ($r = -0.5$, $p < 0.05$) and DFA α1 correlates negatively, as in the other tests, with a parasympathetic marker RMSSD ($r = -0.6$, $p < 0.05$) (Table 6).

Using the algorithm described in Methods, we found in right hemisphere stroke patients attenuated responses to Ewing tests indicated by low HRV based on RR interval variation (resting state 5.4 ± 2.2%, standing test 8.4 ± 2.9% and deep breathing test 8.1 ± 3.1%, $p < 0.05$), thus suggesting a predominant sympathetic control of the heart rate. In left hemisphere stroke patients we observed a tendency for intensified HRV responses after applied activation tests (resting state 8.7 ± 6.2%, standing test 7.3 ± 4.1% and deep breathing test 11.9 ± 8.4%, $p = 0.06$). This data is in line with our previous results using time and frequency domain parameters, characterizing the asymmetrical involvement of the autonomic nervous system in the central control of the HR. This data needs further confirmation on larger study groups.

5. Discussion

HRV represents a simple, non-invasive method to assess and monitor the sympathovagal balance in dynamics in healthy and pathological condition. In 1987, Kleiger [59] demonstrated a possible role of HRV in predicting mortality after acute myocardial infarction. Since then, HRV has been investigated as a risk marker in cardiology, intensive care, neurology and many other fields [60,61]. It was established that reduced HRV is a predictor for general mortality [62] and anticipated the development of a number of risk factors, such as hypertension or obesity, and that lowering risk profiles is associated with increased HRV [63]. The purpose of our research was to underline the differentiated central control influence on the autonomic HR modulation in right and left MCA ischemic stroke patients. We considered in our analysis time domain parameters attributed to the parasympathetic activity as RMSSD and pNN50 and frequency domain parameters as HF (a large accepted parasympathetic parameter) or LF, which has

Table 6 – Relationships between linear (SDNN, RMSSD, LFnu, HFnu and LF/HF) and nonlinear indexes (SD1, SD2, SampEn, ApEn, DFA α1 and DFA α2) in standing test.

	Correlation coefficients calculated based on the Spearman Rank Order test									
	RMSSD	LF/HF	LF nu	HF nu	SD1	SD2	ApEn	SampEn	DFA α1	DFA α2
Include condition: Group 1 – right hemisphere stroke										
SDNN	0.539*	−0.325	−0.325	0.325	0.539*	0.973*	−0.303	−0.371	−0.299	−0.102
RMSSD		−0.400	−0.400	0.400	0.995*	0.415	0.116	0.075	−0.606*	−0.418
LF/HF			0.991*	−0.995*	−0.400	−0.321	−0.024	−0.034	0.403	0.153
LF nu				−0.994*	−0.400	−0.321	−0.024	−0.034	0.403	0.153
HF nu					0.400	0.321	0.024	0.034	−0.403	−0.153
SD1						0.415	0.116	0.075	−0.606*	−0.418
SD2							−0.290	−0.389	−0.209	−0.079
ApEn								0.923*	0.046	−0.062
SampEn									0.044	−0.159
DFA α1										0.265
Include condition: Group 2 – left hemisphere stroke										
SDNN	0.729*	−0.211	−0.082	0.077	0.862*	0.968*	−0.296	−0.537*	−0.469	−0.555*
RMSSD		−0.247	−0.365	0.364	0.867*	0.624*	0.026	−0.132	−0.695*	−0.539*
LF/HF			0.867*	−0.867*	−0.330	−0.197	0.440	0.403	0.406	−0.029
LF nu				−0.999*	−0.188	−0.068	0.191	0.162	0.288	−0.206
HF nu					0.187	0.065	−0.196	−0.156	−0.286	0.215
SD1						0.759*	−0.177	−0.330	−0.771*	−0.730*
SD2							−0.309	−0.562*	−0.276	−0.421
ApEn								0.759*	0.126	−0.159
SampEn									0.185	0.162
DFA α1										0.691*

* p-Value < 0.05 was considered to be statistically significant.

a more complex, still debated origin, but we did not built our conclusion on the LF and LF/HF ratio values. The involvement of nonlinear parameters is still debated, as they are not routinely used to define sympatho-vagal balance. We searched for a correlation between linear parameters and the non-linear parameters of the HRV (e.g. SD1 that reflects the short-term variability, DFA α1) in stroke patients in order to underline the sympathetic overactivation associated to reduced variability of the heart rate in a group of patients more prone to develop cardiac complications. It is known that healthy physiological systems have several parallel regulatory mechanisms that increase stability, and that stability is associated with complex patterns in time series like heart beats [64]. These systems are organized in such a way that they display scale invariance [65] and long-range order [66]. Pathologic states are defined by a breakdown of these two related fractal attributes. A consequence of such reorganization is often a loss of fractal, multiscale complexity and the emergence of highly periodic (single-scale) behavior. This approach may serve important implications for new approaches to early disease detection and prognostic assessment [64–68].

There are currently no normative data universally assumed for short-term measures of HRV [69]. Several recent studies on HRV data [70,71] proposed such normative for short-term recordings of HRV obtained in normally healthy individuals, but discrepant values were identified. Age, ethnicity, habitual physical activity and cardio-metabolic condition contributed importantly to the variability of the results, even in large cohorts [69]. Given the spectrum of physiopathological conditions that generate approximate values for the HRV, its role may principally serve to signal a general pattern of the autonomic nervous system response in a given, temporary physiopathological context. As comprehensive investigations of HRV indices in large diseased populations are still lacking, it is difficult to formulate pertinent clinical measures based on HRV evaluation in neurovascular patients, and further research needs to establish precise sets of values reflecting autonomic response, pragmatically applicable in clinical setups.

Stroke can induce cardiac autonomic imbalance, therefore causing secondary cardiovascular complications. As suggested by Ozdemir and Hachinski [12], awareness of a ''neurogenic heart syndrome'' and recognition of right hemispheric involvement, especially the insular cortex, is important [72]. The risk of developing cardiac arrhythmia (atrial fibrillation, ventricular tachyarrhythmia) or other ECG modifications (prolonged QT, AV block, inversed T wave) in post stroke patients is higher when associated to raised sympathetic activity and low HRV. Several investigators have reported decreased HRV in stroke patients, not only in the acute phase, but also within the next six months [73–76]. Amplified by catecholaminergic storm, it may induce cardiac ventricular arrhythmias or myocardial detriment, which is often associated with sudden death [77,78]. Early cardiac monitoring may change long-term prognosis, since sympathetic overactivity predisposes to secondary cerebro- and cardiovascular events. Therefore, it is highly important to manage dysautonomic imbalance, cardiac causes being held responsible for 2 up to 6% of total mortality three months after acute ischemic stroke [79].

In our research, patients from the studied groups presented cortical lateralization reflected by linear parameters (RMSSD, pNN50, SDNN, HFnu, LFnu, LF/HF ratio): sympathetic activation reflected on the control of the HR in right hemisphere

stroke patients and parasympathetic predominance on the control of the HR in left MCA in ischemic stroke patients. SD1 could be considered as a reliable parameter for the parasympathetic modulation in short-term (5 min) ECG recordings, as it presented very strong correlations with parasympathetic time domain parameters, both in resting state and during activation tests.

We also observed a negative correlation of DFA $\alpha 1$ nonlinear parameter with SD1 and HFnu, and a positive correlation with LFnu and LF/HF ratio, indicating a positive association with the sympatho-vagal balance. We did not find consistent results regarding ApEn and SampEn nonlinear parameters during resting state and activation tests.

These data are in line with other clinical studies, where intraoperative electrical stimulation of the insula determined cardiovascular activity changes in right handed patients, which appear to be lateralized: left insular cortex stimulation was correlated with bradycardia and arterial hypotension (parasympathetic activation), while right insular cortex generated tachycardia and hypertension [80]. In epileptic patients with drug refractory seizures who underwent intracarotid amobarbital injections (wada test), it was noticed a sympathetic tonus predominance in the right hemisphere and a parasympathetic predominance and up regulation of baroreceptor sensitivity in the left hemisphere [81].

In rodents, when right posterior insular cortex ablation determined increased heart rate and blood pressure [82] and the occlusion of right MCA determined myocytolysis, increased blood pressure and circulating norepinephrine levels, especially when the insular cortex was involved [83].

Therefore, the left insular cortex appears to modulate the vagal activity, reflected on the cardiac autonomic control by bradycardia and increasing HRV [9], which is mediated by the parasympathetic nervous system through the vagus nerve.

There are important results [84] that showed significant increases in total HRV and increased parasympathetic drive (as revealed by time domain measures of HRV, i.e., an increase in RMSSD) in subjects with bradycardia. Clinically, bradycardia is likely to be cardioprotective in aging populations based upon these HRV findings [84].

Using for the first time continuous ECG monitoring in acute ischemic stroke patients, Colivicchi et al. [72] noticed that right insular cortex involvement associated significantly lower values of SDNN, of RMSSD and higher LF/HF ratio. This data supports our findings that in right ischemic stroke patients there is higher sympathetic tonus predominance on the HR control. Cardiac dysfunction appears secondary to impaired cerebral structures involved in central control, particularly the insular cortex which is located in the vascular territory of the MCA. Insular cortex was often used as a model to illustrate the possible lateralization impact on sympatho-vagal balance, depending on the hemispheric localization of the stroke.

Insular cortex has extended connections with different autonomic centers and with the limbic system that is why other studies showed reversed responses, possibly explained by the predominance of the autonomic activity from the controlateral, non-ischemic hemisphere [15].

These conflicting results regarding specific autonomic roles of the central nervous system structures justify further studies using functional brain imagery in stroke patients, in order to better understand a possible cortical lateralization and eventually describe other cerebral structures involved in post stroke cardiac dysautonomia patients. Overall, our data suggest that there is a differential cerebral modulation of autonomic function depending on the side of the brain.

There is a strong relationship among nonlinear indices SD1 and DFA $\alpha 1$ and linear parameters in ischemic stroke patients in short term recordings, which could provide supplementary confirming data on the sympatho-vagal impaired modulation at cardiac level, following an acute neurovascular lesion. As proven by previous studies, early cardiac monitoring of the stroke patients using HRV linear and nonlinear parameters in order to identify a sympathetic overactivation on the control of the heart rate, may improve the therapeutically approach and impact the short-term prognostic.

Randomized trials are needed for confirmation of the benefits of ACE inhibitors or beta-blockers to stabilize the sympatho-vagal balance in patients prone to neurogenic heart disease and fatal cardiac arrhythmia. The role of cardiodefibrillator in order to decrease mortality rate can be discussed. Multiple clinical trials documented significant survival benefits of implantable cardioverter defibrillator in certain subsets of patients (experiencing decreased left ventricle ejection fraction secondary to cardiomyopathy, sustained ventricular arrhythmias, etc.) with high risk of sudden cardiac death [85,86]. However, progress in cardiac monitoring protocols in stroke units, but also pragmatic analysis of cost-effectiveness issues are still necessary to determine the precise use of defibrillator in patients with documented ventricular dysrhythmias. Furthermore, animal models in experimental studies showed that vagal nerve stimulation and rehabilitative training enhanced the forelimb recovery after ischemic stroke [87]. Preventing sympathetic hyperactivity and secondary cardiac arrhythmia by rising vagal activity could be achieved by transcranian magnetic stimulation [88,89]. It still remains to be clarified if vagal nerve stimulation would be a possible preventive strategy for cardiac arrhythmias in post-stroke patients.

Since clear guidelines outlining an approach for stroke patients more prone to develop autonomic dysfunction are still needed, this data points out potentially effective predictive parameters to be used in clinical routine in stroke and rehabilitation units to assess severe arrhythmic risk and cerebral outcome. The presence and magnitude of autonomic dysfunction, as shown by our results, may foster the elaboration of prognostic scores, necessary for a global approach of neurological patients at risk.

One limitation of our study is the low number of participants which may decrease the statistical power. Therefore, further studies with larger groups are needed in order to confirm and strengthen these results.

6. Conclusions

Our results indicate that the autonomic nervous system disposes asymmetric, lateralized responses to different stimulation autonomic tests in stroke patients. Right hemisphere stroke has a more pronounced sympathetic control on the HR than left hemisphere in right handed patients.

Disclosure

All authors have approved the final version of the article and each author had a significant contribution for the writing, interpretation, supervision and correction of the article.

Victor Constantinescu, Daniela Matei – concept and design, acquisition of data, analysis and interpretation of data.

Dan Cuciureanu, Victor Costache, Catalina Arsenescu-Georgescu – supervision and correction of the article.

Conflict of interest

None declared.

Acknowledgement and financial support

The support of the staff at the Neurology Department, as well as the enduring cooperation of the participants in this study is gratefully acknowledged.

REFERENCES

[1] Orlandi G, Fanucchi S, Strata G, Pataleo L, Landucci Pellegrini L, Prontera C, et al. Transient autonomic nervous system dysfunction during hyperacute stroke. Acta Neurol Scand 2000;102:317–21.
[2] Bassi A, Colivicchi F, Santini M, Caltagirone C. Cardiac autonomic dysfunction and functional outcome after ischaemic stroke. Eur J Neurol 2007;14:917–22.
[3] Sykora M, Diedler J, Turcani P, Hacke W, Steiner T. Baroreflex: a new therapeutic target in human stroke? Stroke 2009;40(12):e678–82.
[4] Craig AD. Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 2003;13(4):500–5.
[5] Critchley HD, Harrison NA. Visceral influences on brain and behavior. Neuron 2013;77(4):624–38.
[6] LeDoux J. The amygdala. Curr Biol 2007;17(20):R868–74.
[7] Daniele O, Caravaglios G, Fierro B, Natale E. Stroke and cardiac arrhythmias. J Stroke Cerebrovasc Dis 2002;11(1):28–33.
[8] Oppenheimer SM, Hachinski VC. The cardiac consequences of stroke. Neurol Clin 1992;10:167–76.
[9] Davis AM, Natelson BH. Brain-heart interactions. The neurocardiology of arrhythmia and sudden cardiac death. Tex Heart Inst J 1993;20(3):158–69.
[10] Samuels MA. Neurogenic heart disease: a unifying hypothesis. Am J Cardiol 1987;60(18):15J–9J.
[11] Oppenheimer SM. Neurogenic cardiac effects of cerebrovascular disease. Curr Opin Neurol 1994;7(1):20–4.
[12] Ozdemir O, Hachinski V. Brain lateralization and sudden death: its role in the neurogenic heart syndrome. J Neurol Sci 2008;268(1–2):6–11.
[13] Critchley HD, Elliott R, Mathias CJ, Dolan RJ. Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. J Neurosci 2000;20(8):3033–40.
[14] Rincon F, Dhamoon M, Moon Y, Paik MC, Boden-Albala B, Homma S, et al. Stroke location and association with fatal cardiac outcomes: Northern Manhattan Study (NOMAS). Stroke 2008;39:2425–31.
[15] Al-Qudah Z, Yacoub HA, Souayah N. Serial heart rate variability testing for the evaluation of autonomic dysfunction after stroke. J Vasc Interv Neurol 2014;7(5):12–7.
[16] Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043–65.
[17] Stein PK, Fauchier L, Babuty D. Sudden death, arrhythmic events and measurements of heart rate variability. J Am Coll Cardiol 1999;34(7):2148–9.
[18] Graff B, Gąsecki D, Rojek A, Boutouyrie P, Nyka W, Laurent S, et al. Heart rate variability and functional outcome in ischemic stroke: a multiparameter approach. J Hypertens 2013;31(8):1629–36.
[19] Chen C-H, Huang P-W, Tang S-C, Shieh JS, Lai DM, Wu AY, et al. Complexity of heart rate variability can predict stroke-in-evolution in acute ischemic stroke patients. Sci Rep 2015;5:17552.
[20] Woo MA, Stevenson WG, Moser DK, Trelease RB, Harper RM. Patterns of beat-to-beat heart rate variability in advanced heart failure. Am Heart J 1992;123(3):704–10.
[21] Tulppo MP, Mäkikallio TH, Seppänen T, Laukkanen RT, Huikuri HV. Vagal modulation of heart rate during exercise: effects of age and physical fitness. Am J Physiol 1998;274: H424–9.
[22] Karmakar CK, Gubbi J, Khandoker AH, Palaniswami M. Analysing temporal variabililty of standard descriptors of Poincaré plots. J Electrocardiol 2010;43:719–24.
[23] Hoshi RA, Pastre CM, Vanderlei LC, Godoy MF. Poincaré plot indexes of heart rate variability: relationships with other nonlinear variables. Auton Neurosci 2013;177(2):271–4.
[24] Brennan M, Palaniswami M, Kamen P. Do existing measures of Poincaré plot geometry reflect nonlinear features of heart rate variability? IEEE Trans Biomed Eng 2001;48(11):1342–7.
[25] Lerma C, Infante O, Pérez-Grovas H, José MV. Poincaré plot indexes of heart rate variability capture dynamic adaptations after haemodialysis in chronic renal failure patients. Clin Physiol Funct Imaging 2003;23:72–80.
[26] Tulppo MP, Makikallio TH, Takala TE, Seppanen T, Huikuri HV. Quantitative beat-to-beat analysis of heart rate dynamics during exercise. Am J Physiol 1996;271:H244–52.
[27] Huikuri H, Makikallio TH, Perkiomaki J. Measurement of heart rate variability by methods based on nonlinear dynamics. J Electrocardiol 2003;36:95–9.
[28] Mourot L, Bouhaddi M, Perrey S, Cappelle S, Henriet MT, Wolf JP, et al. Decrease in heart rate variability with overtraining: assessment by the Poincaré plot analysis. Clin Physiol Funct Imaging 2004;24:10–8.
[29] Mourot L, Bouhaddi M, Perrey S, Rouillon JD, Regnard J. Quantitative Poincaré plot analysis of heart rate variability: effect of endurance training. Eur J Appl Physiol 2004;91:79–87.
[30] De Vito G, Galloway SD, Nimmo MA, Maas P, McMurray JJ. Effects of central sympathetic inhibition on heart rate variability during steady-state exercise in healthy humans. Clin Physiol Funct Imaging 2002;22:32–8.
[31] Porta A, Gnecchi-Ruscone T, Tobaldini E, Guzzetti S, Furlan R, Montano N. Progressive decrease of heart period variability entropy-based complexity during graded head-up tilt. J Appl Physiol 2007;103:1143–9.
[32] Lewis MJ, Short AL. Sample entropy of electrocardiographic RR and QT timeseries data during rest and exercise. Physiol Meas 2007;28:731–44.
[33] Richman JS, Moorman JR. Physiological time-series analysis using approximante entropy and sample entropy. Am J Physiol 2000;278(6):H2039–4.
[34] Javorka M, Zila I, Balhárek T, Javorka M. Heart rate recovery after exercise: relations to heart rate variability and complexity. Braz J Med Biol Res 2002;32(8):991–1000.

[35] Penttilä J, Helminen A, Jartti T, Kuusela T, Huikuri HV, Tulppo MP, et al. Effect of cardiac vagal outflow on complexity and fractal correlation properties of heart rate dynamics. Auton Autacoid Pharmacol 2003;23(3):173–9.
[36] Acharya UR, Lim CM, Joseph P. Heart rate variability analysis using correlation dimension and detrended fluctuation analysis. ITBM-RBM 2002;23:333–9.
[37] Carvalho TD, Pastre CM, de Godoy MF, Fereira C, Pitta FO, de Abreu LC, et al. Fractal correlation property of heart rate variability in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2011;6:23–8.
[38] Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos 1995;5(1):82–7.
[39] Mäkikallio TH, Tulppo MP, Seppänen T, Huikuri HV. Analysis of nonlinear heart rate dynamics in cardiac arrhythmias. Herzschr Elektrophys 2000;11:131–8.
[40] Acharya UR, Kannathal N, Sing OW, Ping LW, Chua T. Heart rate analysis in normal subjects of various age groups. BioMed Eng 2004;3:24–31.
[41] Ewing DJ, Clarke BF. Autonomic neuropathy: its diagnosis and prognosis. Clin Endocrinol Metab 1986;15:855–88.
[42] Kollai M, Mizse G. Respiratory sinus arrhythmia is a limited measure of cardiac parasympathetic control in man. J Physiol 1990;424:329–42.
[43] Parati G, di Rienzo M, Castiglioni P, Mancia G, Taylor JA, Studinger P. Point: counterpoint: cardiovascular variability is/is not an index of autonomic control of circulation. J Appl Physiol 2006;101:676–82.
[44] Taylor JA, Myers CW, Halliwill JR, Seidel H, Eckberg DL. Sympathetic restraint of respiratory sinus arrhythmia: implications for vagal-cardiac tone assessment in humans. Am J Physiol Heart Circ Physiol 2001;280(6):H2804–1.
[45] Eckberg D. Human sinus arrhythmia as an index of vagal cardiac outflow. J Appl Physiol 1975;54:961–6.
[46] Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, et al. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985;248:H151–3.
[47] Randall DC, Brown DR, Raisch RM, Yingling JD, Randall WC. SA nodal parasympathectomy delineates autonomic control of heart rate power spectrum. Am J Physiol 1991;260:H985–8.
[48] Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991;84:482–92.
[49] Berntson GG, Bigger JT, Eckberg DL, Grossman P, Kaufmann PG, Malik M, et al. Heart rate variability: origins, methods, and interpretive caveats. Pyschophysiology 1997;34:623–48.
[50] Billman GE. Heart rate variability – a historical perspective. Front Physiol 2011;2:86.
[51] Goldstein DS, Bentho O, Park MY, Sharabi Y. Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp Physiol 2011;96(12):1255–61.
[52] Heathers JA. Sympathovagal balance from heart rate variability: an obituary. Exp Physiol 2012;97(4):556.
[53] Eckberg DL. Sympathovagal balance: a critical appraisal. Circulation 1997;96:3224–32.
[54] Houle MS, Billman GE. Low-frequency component of the heart rate variability spectrum: a poor marker of sympathetic activity. Am J Physiol 1999;267:H215–23.
[55] Billman GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Front Physiol 2013;4:26.
[56] Reyes del Paso GA, Langewitz W, Mulder LJ, Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of previous studies. Psychophysiology 2013;50(5):477–87.
[57] Hopf HB, Skyschally A, Heusch G, Peters J. Low-frequency spectral power of heart rate variability is not a specific marker of cardiac sympathetic modulation. Anesthesiology 1995;82:609–19.
[58] Shahani BT, Day TJ, Cros D, Khalil N, Kneebone CS. RR interval variation and the sympathetic skin response in the assessment of autonomic function in peripheral neuropathy. Arch Neurol 1990;47:659–64.
[59] Kleiger RE, Miller JP, Bigger JTMA. Multicenter postinfarction research group: decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256–62.
[60] Ernst G, Watne LO, Frihagen F, Wyller TB, Dominik A, Rostrup M. Decreases in heart rate variability are associated with postoperative complications in hip fracture patients. PLOS ONE 2017;12(7):e0180423.
[61] Ernst G, editor. Heart Rate Variability. London: Springer; 2014.
[62] de Bruyne MC, Kors JA, Hoes AW, Klootwijk P, Dekker JM, Hofman A, et al. Both decreased and increased heart rate variability on the standard 10-second electrocardiogram predict cardiac mortality in the elderly: the Rotterdam Study. Am J Epidemiol 1999;150:1282–8.
[63] Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol 2010;141 (2):122–31.
[64] Goldberger AL. Fractal variability versus pathologic periodicity: complexity loss and stereotypy in disease. Perspect Biol Med 1997;40(4):543–61.
[65] Goldberger AL. Non-linear dynamics for clinicians: Chaos theory, fractals, and complexity at the bedside. Lancet 1996;347:1312–4.
[66] West BJ, Goldberger AL. Physiology in fractal dimensions. Am Scientist 1987;75:354–65.
[67] Goldberger AL, Rigney DR, West BJ. Chaos and fractals in human physiology. Sci Am 1990;262:40–9.
[68] Glass L, Mackey MC, editors. From Clocks to Chaos: The Rhythms of Life. Princeton: Princeton Univ. Press; 1988.
[69] O'Neal WT, Chen LY, Nazarian S, Soliman EZ. Reference ranges for short-term heart rate variability measures in individuals free of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). J Electrocardiol 2016;49 (5):686–90.
[70] Lee CH, Lee JH, Son JW, Kim U, Park JS, Lee J, et al. Normative values of short-term heart rate variability parameters in Koreans and their clinical value for the prediction of mortality. Heart Lung Circ 2017. pii: S1443-9506(17)30471-7.
[71] Nunan D, Sandercock GR, Brodie DA. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. Pacing Clin Electrophysiol 2010;33(11):1407–17.
[72] Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac autonomic derangement and arrhythmias in right-sided stroke with insular involvement. Stroke 2004;35:2094–8.
[73] Naver HK, Blomstrand C, Wallin BG. Reduced heart rate variability after right-sided stroke. Stroke 1996;27:247–51.
[74] Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllyä VV. Abnormal heart rate variability as a manifestation of autonomic dysfunction in hemispheric brain infarction. Stroke 1996;27:2059–63.
[75] Mäkikallio AM, Mäkikallio TH, Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllylä VV. Heart rate dynamics predict poststroke mortality. Neurology 2004;62(10):1822–6.
[76] Lakusić N, Mahović D, Babić T, Sporis D. Changes in autonomic control of heart rate after ischemic cerebral stroke. Acta Med Croat 2003;57(4):269–73.

[77] Baranchuk A, Nault MA, Morillo CA. The central nervous system and sudden cardiac death: what should we know? Cardiol J 2009;16:105–12.
[78] Van Bree MD, Roos YB, van der Bilt IA, Wilde AA, Sprengers ME, de Gans K, et al. Prevalence and characterization of ECG abnormalities after intracerebral hemorrhage. Neurocrit Care 2010;12:50–5.
[79] Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S. Predictors of early cardiac morbidity and mortality after ischemic stroke. Stroke 2007;38:2295–302.
[80] Oppenheimer SM, Gelb AW, Girvin JP, Hachinski VC. Cardiovascular effects of human insular stimulation. Neurology 1992;42:1727–32.
[81] Hilz MJ, Dutsch M, Perrine K, Nelson PK, Devinsky O. Hemisheric influence on autonomic modulation and baroreflex sensitivity. Ann Neurol 2001;49:575–84.
[82] Oppenheimer SM, Cechetto DF. Cardiac chronotropic organization of the rat insular cortex. Brain Res 1990;533:66–72.
[83] Saad MA, Huerta F, Trancard J, Elghozi JL. Effects of middle cerebral artery occlusion on baroreceptor reflex control of heart rate in the rat. J Auton Nerv Syst 1989;27:165–72.
[84] McLachlan CS, Ocsan R, Spence I, Hambly B, Matthews S, Wang L, et al. Increased total heart rate variability and enhanced cardiac vagal autonomic activity in healthy humans with sinus bradycardia. Proc (Bayl Univ Med Cent) 2010;23(4):368–70.
[85] Ding L, Hua W, Niu H, Chen K, Zhang S. Primary prevention of sudden cardiac death using implantable cardioverter defibrillators. Europace 2008;10(9):1034–41.
[86] Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Heart Rhythm 2013;10.
[87] Hays SA, Ruiz A, Bethea T, Khodaparast N, Carmel JB, Rennaker RL, et al. Vagus nerve stimulation during rehabilitative training enhances recovery of forelimb function after ischemic stroke in aged rats. Neurobiol Aging 2016;43:111–8.
[88] Yoshida T, Yoshino A, Kobayashi Y, Inoue M, Kamakura K, Nomura S. Effects of slow repetitive transcranial magnetic stimulation on heart rate variability according to power spectrum analysis. J Neurol Sci 2001;184:77–80.
[89] Clarke BM, Upton ARM, Kamath MV, Al-Harbi T, Castellanos CM. Transcranial magnetic stimulation for migraine: clinical effects. J Headache Pain 2006;7:341–6.