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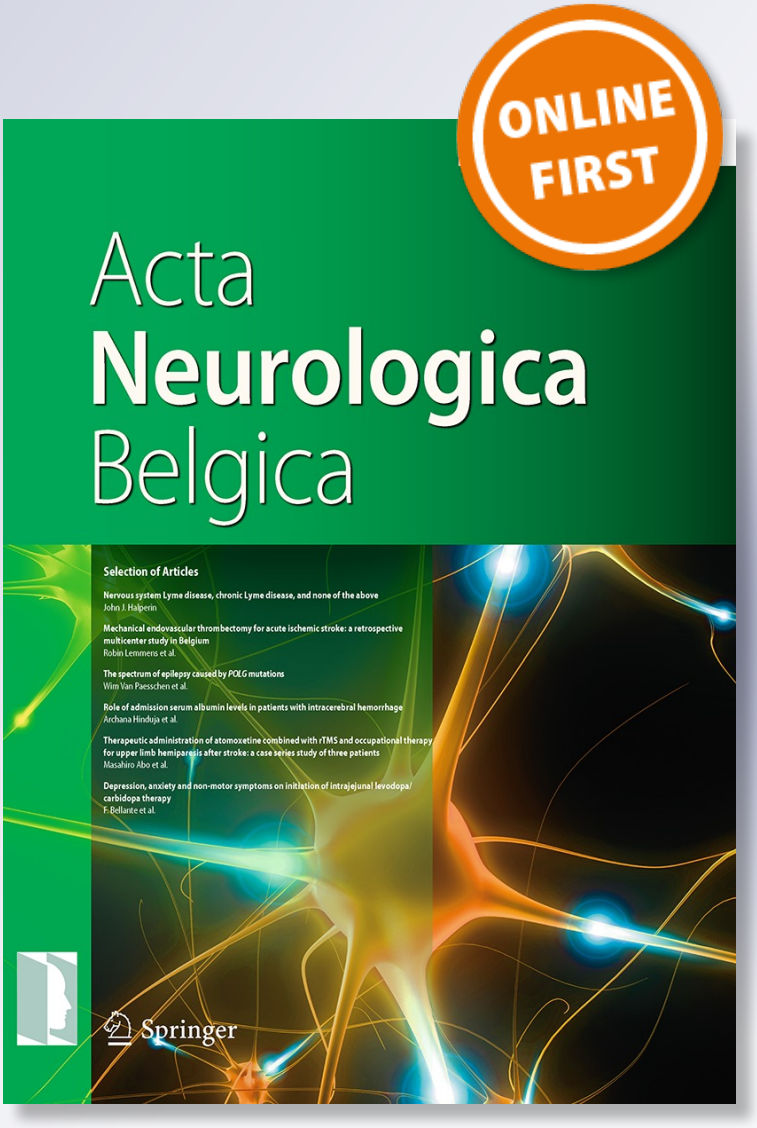

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ORIGINAL ARTICLE

Cortical modulation of cardiac autonomic activity in ischemic stroke patients

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Abstract The cardiovascular system is regulated by the autonomic nervous system, under cortical modulation. Stroke can induce cardiac autonomic imbalance, therefore, causing secondary cardiovascular complications. Heart rate variability (HRV) analysis is a simple method to appraise the autonomic nervous function. The purpose of this study was to investigate the cardiac autonomic activity in patients that suffered an ischemic stroke in middle cerebral artery (MCA) territory. Using Biopac Acquisition System, we monitored ECG in rest condition and during Ewing's tests. From these measurements, HRV parameters (using time and frequency domain analysis) were determined in 20 right MCA and 20 left MCA ischemic stroke patients, in the first 6 months after the acute event. Data were compared with 20 age- and sex-matched healthy controls. All the patients were right handed. In ischemic stroke patients, HRV parameters were significantly modified compared to controls ($p < 0.05$) and we found asymmetric responses to different stimulation autonomic tests between right and left hemisphere. Parameters illustrating the parasympathetic predominance in time domain (RMSSD) and frequency domain (HF) analysis were higher in left hemisphere stroke compared to right hemisphere stroke patients ($p < 0.01$) in resting state. From Ewing's battery test, patients with left hemisphere ischemic stroke showed predominance of parasympathetic activity to deep breathing ($p < 0.01$), while HRV parameters in right hemisphere ischemic stroke patients described a reduced cardiac parasympathetic innervation ($p < 0.01$). Cardiac autonomic imbalance occurs more often after right hemisphere ischemic stroke. HRV study may highlight cardiac dysfunctions that increase the risk of cardiovascular complications and portends a poor long-term outcome.

Keywords Autonomic cardiac dysfunction · Ischemic stroke · Heart rate variability

Introduction

Stroke represents a major public health issue, being worldwide, the second cause of death, after ischemic heart disease and the first cause of long term acquired disability [1, 2]. As we assist to a growth in life expectancy and global aging of population, cerebrovascular pathology becomes an important aspect. In Europe, the incidence of stroke varies, being estimated between 100 and 200 new cases for each 100,000 inhabitants annually, variations that depend on the importance of risk factors, among which hypertension plays a major role [3].

Approximately, 40 % of stroke patients present a risk of recurrence in the first 5 years [4] and a higher risk for myocardial infarction, uncontrolled hypertension, cardiac arrhythmias and cardiogenic shock [5, 6]. Cardiac arrhythmias, especially malignant ventricular arrhythmias, are frequently in acute stroke due to autonomic dysfunctions, triggered by the impairment of the central autonomic nervous system (ANS) structures and catecholamine storm [7, 8]. Increased sympathetic nervous system and reduced parasympathetic nervous system activity is common in acute stroke patients [9, 10]. These disturbances of

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autonomic cardiac function, and also, the preexisting cardiac disease, may be responsible for 2–6 % of the total mortality 3 months after acute ischemic stroke [11].

Considerable evidence regarding the role of cortical lateralization in cardiovascular autonomic dysregulation exists in patients with ischemic and hemorrhagic stroke [12]. Animal studies support the asymmetry in central nervous control of cardiac function showing that experimental stroke in right hemisphere induced more pronounced sympathetic effects than lesions on the left side [13, 14]. Clinical observations also suggest an association between right hemispheric lesions and supraventricular tachycardia [15].

The power spectral analysis of heart rate variability (HRV) is a simple method to assess ANS activity, especially the modulation of the sympathetic and parasympathetic tone upon heart rate under experimental and clinical conditions [16]. Power spectral analysis of heart rate has shown a pronounced reduction of spectral power in the field of sinus arrhythmia after right-sided lesions when compared with left-sided lesions [17].

The purpose of this study was to investigate ANS function in patients with monofocal ischemic stroke in middle cerebral artery (MCA) territory. Another objective was to determine, using Ewing's battery of autonomic function tests and power spectral analysis of HRV, whether autonomic function is impaired depending on cortical localization of the ischemic stroke.

Subjects and methods

Participant recruitment and inclusion criteria

40 consecutive ischemic stroke patients were recruited from Department of Neurology Rehabilitation Hospital Iasi, Romania, between June 2014 and May 2015. The study was approved by our institutional ethics committee and all the 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 for stroke, evaluated in the first 6 months after the acute event, computed tomography (CT) or magnetic resonance imaging (MRI) showing a single ischemic lesion within the left or right hemisphere (superficial and/or profound MCA territory), 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 dysmetabolic pathologies generating polyneuropathy, no present medication interfering with heart rate (medication with beta blockers), fever, hypoxia, alterations in consciousness or any relevant hemodynamic compromise on admission.

Clinical, psychological and biochemical assessment

Every patient was clinically assessed, the motor deficit being scored upon the Medical Research Council (MRC) scale from 0 (no contraction) to 5 (normal strength and movement of the limb). We also analyzed the anthropometric data (body weight, body mass index), bioclinical parameters, such as blood count, glycemia, cholesterol with fractions low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglyceride, hepatic function—ALAT, ASAT, renal function—urea, creatinine.

Systolic and diastolic blood pressure (SBP and DBP) were measured in supine and upright positions using an aneroid sphygmomanometer with an adult cuff. Hypertension was defined as a SBP $>$ 140 mmHg or a DBP $>$ 90 mmHg or both, with or without the use of blood pressure lowering drugs.

Clinical autonomic function tests and measurement of heart rate variability

Heart rate shows a continuous variability that is altered in autonomic dysfunction. The HRV can be assessed under resting conditions and during challenge.

Using Biopac MP150 Acquisition System, we monitored HRV in resting condition and during Ewing's tests (Valsalva maneuver, heart rate difference during six deep breaths, changing heart rate after standing, blood pressure measurement after 5 min of supine position and sustained handgrip) [18]. The first two are used for the assessment of the parasympathetic function and the last two are used for the assessment of the sympathetic function. Data were afterwards processed using Kubios HRV 2.2—Heart Rate Variability Analysis Software (Biosignal Analysis and Medical Imaging Group—University of Eastern Finland). We used the time domain analysis that calculates the Standard Deviation of Normal-to-Normal beat (SDNN), the square root of the mean squared differences of successive NN intervals (RMSSD), the proportion of differences in consecutive, the so-called normal-to-normal RR intervals that are longer than 50 ms and reflects the percentage of such intervals in comparison to the total number of analyzed intervals (pNN50). We also used frequency domain methods 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 (characteristic to parasympathetic activity), low frequency (LF) from 0.04 to

0.15 Hz (characteristic to sympathetic activation, but depending on more complex mechanisms) and the very low frequency (VLF) from 0.0033 to 0.04 Hz (influenced by the thermoregulatory and renin–angiotensin system) [19]. In this respect, we preferred to use the LF/HF ratio to describe the predominance of the sympathetic nervous system or parasympathetic nervous system, and also the normalized units for the LF and HF, which represent the relative value of each power component in proportion to the total power minus the VLF component [19].

The statistical analysis was performed using the MaxStat Lite software. The values are presented as mean values and standard deviation. Test *t* Student or variance analysis (ANOVA) was used to determine the differences between the groups. The values $p < 0.05$ were considered statistically significant.

Results

Clinical and biochemical features in the groups study

The above mentioned parameters were determined in 40 ischemic stroke patients, within 6 months post stroke. Data were compared with 20 age- and sex-matched healthy controls, volunteers from community dwelling people, with no previous history of transient ischemic attack or stroke and no evidence of dementia.

The subjects were divided in two groups: 20 right hemisphere (first group) and 20 left hemisphere (second group) ischemic stroke patients, in the MCA territory, in both groups. The ratio male/female was 23/17, with a mean age 64.7 years old for the first group and 63.9 years old for the second group. The control group had a mean age 62.7 years old (Table 1).

85 % of patients had hypertension in first group, 90 % of patients in the second group while only 7 patients (46.6 %) were hypertensive in control group ($p < 0.05$). Values of systolic blood pressure were higher in right hemisphere compared to left hemisphere stroke ($p < 0.01$) and also compared to control group ($p < 0.01$).

90 % of patients had dyslipidemia in both first and second group, compared to 55.4 % in the control group. The stroke group had lower total cholesterol and triglycerides levels compared to controls since they were under treatment with different statins, in secondary prevention.

We found orthostatic hypotension (defined as a decrease in systolic blood pressure of 20 mmHg or a decrease in diastolic blood pressure of 10 mmHg within 3 min of standing when compared with blood pressure from the supine position) in 40 % of patients with left hemispheric stroke when compared with control group ($p < 0.05$) (Table 1).

In resting state, heart rate was higher in right hemisphere stroke patients compared both to control group ($p < 0.01$) and left hemisphere stroke patients ($p < 0.05$).

QTc values measured on resting state ECG were superior in left hemisphere stroke patients compared both to right hemisphere stroke patients ($p < 0.05$) and to controls ($p < 0.05$) (Table 1).

Clinical autonomic function tests and measurement of heart rate variability

Ischemic stroke patients presented significantly modified HRV parameters compared to controls ($p < 0.05$).

Time domain analysis in resting state showed low values for HF in normalized units (HFnu) (expressing the parasympathetic activity) in right hemisphere stroke patients compared to left hemisphere stroke patients ($p < 0.01$) and to control patients ($p < 0.01$) suggesting low parasympathetic activity in right MCA stroke patients. The sympathetic tone (LF/HF ratio) was more pronounced in right sided MCA stroke patients ($p < 0.01$) compared to contralateral stroke patients (Table 2). Moreover, RMSSD values in resting state showed predominant parasympathetic activity in left MCA infarcts compared to right MCA infarcts ($p < 0.05$) and to control group ($p < 0.05$).

HRV parameters in deep breathing test illustrated predominant parasympathetic tone in left hemisphere stroke patients compared to control group (for RMSSD parameters $p < 0.05$). Also, heart rate values were lower in left MCA territory ischemic stroke patients compared to contralateral stroke patients ($p < 0.05$) and in right MCA stroke when compared to control group (average heart rate 79 ± 7.9 b/min vs. 67.3 ± 5.24 b/min, $p < 0.01$). Frequency domain analysis for HRV parameters in deep breathing showed high parasympathetic predominance in left hemisphere stroke patients (HF nu) $p < 0.05$ when compared to control, higher LFnu and absolute values for LF in milliseconds squared (Table 3). Sympathetic activity, evaluated by LF/HF ratio was predominant in right hemisphere stroke group when compared to left MCA stroke group ($p < 0.01$) and to controls ($p < 0.05$).

Valsalva maneuver revealed lower frequency domain values, with HF and HFnu lower in right hemisphere stroke ($p < 0.01$ for HFnu) when compared to left hemisphere stroke and increased LF/HF ratio in right MCA stroke group compared to contralateral stroke patients ($p < 0.05$). This data suggest that right hemisphere stroke patients had prevalent sympathetic activity, when compared to left hemisphere stroke patients and to control group (as shown in Table 3).

Analysis of HRV time and frequency domain measures in orthostatic position, revealed that right hemisphere stroke patients displayed a decreased parasympathetic tone

Table 1 General parameters

Parameter	Right hemisphere stroke, $N = 20$	Left hemisphere stroke, $N = 20$	Control group, $N = 20$
Age (years)	64.7 ± 8.45	63.9 ± 9.55	62.7 ± 8.26
Hypertension (%)	85 %$^{\bullet}$	90 %	46.6 %*
SBP (mmHg)	136.7 ± 25.5$^{\bullet\bullet}$	124.3 ± 8.45††	125.21 ± 10.5
DBP (mmHg)	79.8 ± 13.4	76.5 ± 7.1	75.14 ± 8.34
Dyslipidemia	90 %$^{\bullet}$	90 %	55.4 %*
MRC superior limb (average)	3–4	2–4	–
MRC inferior limb (average)	3–4	3–4	–
Epileptic seizures	40 %	20 %†	–
Orthostatic hypotension	25 %$^{\bullet}$	40 %†	10 %*
Glycemia (mg/dl)	107.1 ± 16.4	100.8 ± 17.8	94.9 ± 13.25
Total cholesterol (mg/dl)	152 ± 50.2	154.3 ± 44.1	175 ± 22.9
Triglyceride (mg/dl)	101.5 ± 44.8	111.5 ± 54.13	127.7 ± 31.5
ALAT (UI)	21.1 ± 7.41	20.3 ± 7.48	20.5 ± 7.15
ASAT (UI)	26.5 ± 14.3	24.5 ± 11.4	24.2 ± 12.7
Urea (mg/dl)	37.45 ± 11.12	39.6 ± 12.1	35.3 ± 1.45
Uric acid (mg/dl)	4.57 ± 1.36	5.41 ± 1.74	3.21 ± 1.45*
Creatinine (mg/dl)	1.15 ± 0.41	0.96 ± 0.34	0.98 ± 0.46
Heart rate (b/min)	81.28 ± 6.4$^{\bullet\bullet}$	72.5 ± 10.2†	67.3 ± 10.26*
PR (msec)	169.1 ± 24.2	168.2 ± 29.3	168.6 ± 24.5
QRS (msec)	94.61 ± 11.7	93.44 ± 11.34	97.2 ± 11.62
QT (msec)	389.76 ± 31.73	404 ± 38.6	395.1 ± 30.82
QTc	414.4 ± 28.19	434 ± 29.6†	411 ± 28.6*
QTd	45.42 ± 7.93	48.6 ± 7	45.4 ± 15.71
RV5 (mV)	1.46 ± 0.34	1.43 ± 0.17	1.43 ± 0.21
SV1 (mV)	0.76 ± 0.45	0.76 ± 0.38	0.76 ± 0.32

Values are calculated as mean ± standard deviation

* $p < 0.05$, ** $p < 0.01$ when comparing left hemispheric stroke patients with control group

$^{\bullet}$ $p < 0.05$, $^{\bullet\bullet}$ $p < 0.01$ when comparing right hemispheric stroke patients with control group

† $p < 0.05$, †† $p < 0.01$ when comparing stroke patients (first and second group)

compared to control group (higher HF in absolute values, $p < 0.01$). Moreover, they showed predominant sympathetic activity compared to left hemisphere stroke, illustrated by elevated LF/HF ratio ($p < 0.01$). Higher time domain parameters in left hemispheric stroke patients, were consistent with parasympathetic tone dominance in these patients, when compared to other groups (Table 4).

In "hand grip" test, most of the HRV parameters in time domain showed a clear difference between right and left hemisphere stroke patients, with better represented parasympathetic activity in left hemisphere stroke group (SDNN, RMSSD, HF).

Elevated LF/HF ratio describes important sympathetic activity in right MCA stroke patients when compared to left hemisphere stroke patients ($p < 0.01$) and to controls (Table 4).

Cardiac parasympathetic innervation was more reduced in right hemisphere ischemic stroke patients ($p < 0.01$) in resting state. Parameters illustrating the parasympathetic tone in time domain (RMSSD) and frequency domain (HF) left hemisphere stroke patients had higher values compared to those in the right hemisphere stroke.

Patients with left hemisphere ischemic stroke showed predominant parasympathetic activity in deep breathing test ($p < 0.01$), while right hemisphere ischemic stroke patients showed impairment in two parasympathetic activation tests (heart rate response to deep breathing and Valsalva) when compared to controls (Table 3).

In all autonomic activation tests and in resting state there is a parasympathetic predominance in left hemisphere stroke patients, compared to right hemisphere and to control group, as described by HFnu values ($p < 0.01$) (Fig. 1). Consistent with the findings, in resting state and in all tests, right hemispheric stroke patients presented higher values of LF/HF ratio illustrating greater sympathetic tonus ($p < 0.01$) (Fig. 2).

Table 2 Heart rate variability parameters in resting state

HRV parameters in resting state	Right hemisphere stroke, $N = 20$	Left hemisphere stroke, $N = 20$	Control group, $N = 20$
RR (msec)	777.1 ± 87.8	789.2 ± 99	823.2 ± 74
SDNN	33.9 ± 17.6	44.9 ± 5.2	37.5 ± 7.8
Heart rate (b/min)	77.4 ± 7.4	74.3 ± 8.8	68.7 ± 6.4
RMSSD	37 ± 35.2†	54.8 ± 38.2$^{\bullet}$	38.8 ± 11.3
pNN50	3.54 ± 3.2	4.2 ± 1.34	6.05 ± 1.5
VLF (ms^2)	245.1 ± 226.5	96.6 ± 86.5$^{\bullet\bullet}$	362.3 ± 83.8*
LF (ms^2)	427.1 ± 410.8††	496.5 ± 107.1	539.4 ± 175.1
HF (ms^2)	210.7 ± 187.4††	513.6 ± 226.1	526.7 ± 67.8**
LFnu	65.9 ± 17.5††	40.4 ± 21.5$^{\bullet}$	56.8 ± 14.1
HFnu	34.2 ± 18.56††	59.7 ± 21.5	51.4 ± 12.2**
LF/HF	2.07 ± 2.21††	0.97 ± 0.82	1.14 ± 0.29*

Values are expressed as a mean ± standard deviation

† $p < 0.05$, †† $p < 0.01$ when comparing stroke patients

* $p < 0.05$, ** $p < 0.01$ right hemispheric stroke patients compared with control patients

$^{\bullet}$ $p < 0.05$, $^{\bullet\bullet}$ $p < 0.01$ left hemispheric stroke patients compared with control patients

Table 3 Heart rate variability parameters in deep breathing test and Valsalva test

HRV parameters in deep breathing test (inhale/exhale)	Right hemisphere stroke, $N = 20$	Left hemisphere stroke, $N = 20$	Control group, $N = 20$
RR (msec)	773.7 ± 79.2	751.29 ± 103.5	806.7 ± 81.3
SDNN	48.9 ± 5.6	56.5 ± 4.7$^{\bullet}$	33.9 ± 5.33
Heart rate (b/min)	79.28 ± 7.9	71.1 ± 11.3$^{\bullet}$	67.3 ± 5.24**
RMSSD	42 ± 25.1	69.8 ± 32.5$^{\bullet}$	49.5 ± 12.8
pNN50 %	4.47 ± 3.1	3.66 ± 3.35	5.01 ± 3.2
VLF (ms^2)	184.7 ± 159.1	199.2 ± 156.2$^{\bullet\bullet}$	441 ± 162.4**
LF (ms^2)	612.9 ± 466.7†	498.2 ± 130.7$^{\bullet\bullet}$	556.7 ± 123.5**
HF (ms^2)	378.7 ± 327.2†	545 ± 331.4$^{\bullet}$	882.6 ± 426.8**
LFnu	65.2 ± 12.4††	38.3 ± 16.3	31.6 ± 12.2**
HFnu	35.12 ± 10.20††	60.9 ± 15.29$^{\bullet}$	42.9 ± 11.6
LF/HF	1.93 ± 0.73††	0.76 ± 0.42	0.83 ± 1.08*
HRV parameters in Valsalva test			
RR (msec)	774 ± 61.8	765.9 ± 112.5	799.2 ± 66.9
SDNN	63.3 ± 25.1	83.2 ± 58.4$^{\bullet}$	35.7 ± 7.95*
Heart rate (b/min)	78.4 ± 6.2	71.9 ± 12.47	69.8 ± 9.7*
RMSSD	53.9 ± 43.3	82.1 ± 64.3	45.7 ± 13.3
pNN50 %	5.21 ± 6.6	6.3 ± 5.03	8.85 ± 11.4
VLF (ms^2)	166.3 ± 127.9†	271.7 ± 158.2	417.2 ± 42.2**
LF (ms^2)	979.4 ± 861.3	935.8 ± 826$^{\bullet}$	752.7 ± 318*
HF (ms^2)	660.4 ± 510.1	945.8 ± 754	727.5 ± 340.6
LFnu	69.5 ± 18.4†	45.02 ± 21.3	44.4 ± 14.3*
HFnu	31.1 ± 16.7††	47.8 ± 21.9$^{\bullet}$	38.4 ± 14.8
LF/HF	2.4 ± 1.92†	0.98 ± 0.61	1.03 ± 0.76*

Values are expressed as a mean ± standard deviation

† $p < 0.05$, †† $p < 0.01$ when comparing stroke patients

* $p < 0.05$, ** $p < 0.01$ right hemispheric stroke patients compared with control group

$^{\bullet}$ $p < 0.05$, $^{\bullet\bullet}$ $p < 0.01$ left hemispheric stroke patients compared with control group

Table 4 HRV parameters in orthostatism and during "hand grip" test

HRV parameters in orthostatism	Right hemisphere stroke, $N = 20$	Left hemisphere stroke, $N = 20$	Control group, $N = 20$
RR (msec)	714 ± 69.5	721.2 ± 134.2	765.7 ± 75.2
SDNN	57.3 ± 26.4	65.7 ± 23.7	42.5 ± 7.35
Heart rate (b/min)	89.6 ± 13.1	83.6 ± 8.77	78.7 ± 5.07*
RMSSD	36.7 ± 32.9	60.9 ± 41.7	32.4 ± 5.28
pNN50 %	4.95 ± 2.45	6.01 ± 4.93	6.89 ± 4.2
VLF (ms^2)	142.7 ± 129.5	126.8 ± 112.7••	419.2 ± 44.4**
LF (ms^2)	359.5 ± 312.6	278.2 ± 130••	742.4 ± 359.5*
HF (ms^2)	131.2 ± 112.6	295.8 ± 251•	514.1 ± 240.4**
LFnu	72.5 ± 22.6††	44.7 ± 14.8•	65.5 ± 17.8
HFnu	31.15 ± 10.20†	49.2 ± 19.3	46.4 ± 17.26*
LF/HF	2.74 ± 1.59††	1.06 ± 0.72	1.62 ± 0.68*
HRV parameters "hand grip" test			
RR (msec)	725 ± 59.2	705.5 ± 106.2	763.4 ± 85.2
SDNN	52.5 ± 18.4	63.2 ± 56.4	51.9 ± 28.5
Heart rate (b/min)	82.4 ± 7.1	81.4 ± 18.4	77.3 ± 8.6
RMSSD	27.5 ± 25.3	47.2 ± 42.5	32.3 ± 17.7
pNN50 %	4.22 ± 3.6	5.3 ± 5	7.3 ± 6.4
VLF (ms^2)	191.1 ± 166	308.8 ± 256.2	283.4 ± 193.9
LF (ms^2)	519.8 ± 490.3	462.6 ± 431.2	881.4 ± 708
HF (ms^2)	341.5 ± 200.1	694.2 ± 654	276.9 ± 248.6
LFnu	78.2 ± 17.7†	54.6 ± 25.7•	78.8 ± 4.8
HFnu	32.6 ± 19.2	44.6 ± 25.4•	30.3 ± 4.1
LF/HF	3.72 ± 3.65††	1.12 ± 1.04•	2.7 ± 1.04

Values are calculated as mean ± standard deviation

† $p < 0.05$, †† $p < 0.01$ when comparing stroke patients

* $p < 0.05$, ** $p < 0.01$ when comparing right hemisphere stroke group to control group

• $p < 0.05$, •• $p < 0.01$ when comparing left hemisphere stroke group to control group

Discussion

In the past decades, post stroke autonomic nervous system dysregulation has attracted vivid interest and there are facts that still need to be clarified, with possible implication in short term evolution and prognostic. The cardiac dysfunctions secondary to destruction of cerebral structures involved in central control, particularly the insular cortex, located in the vascular territory of the MCA, and amplified by catecholaminergic storm, may induce cardiac

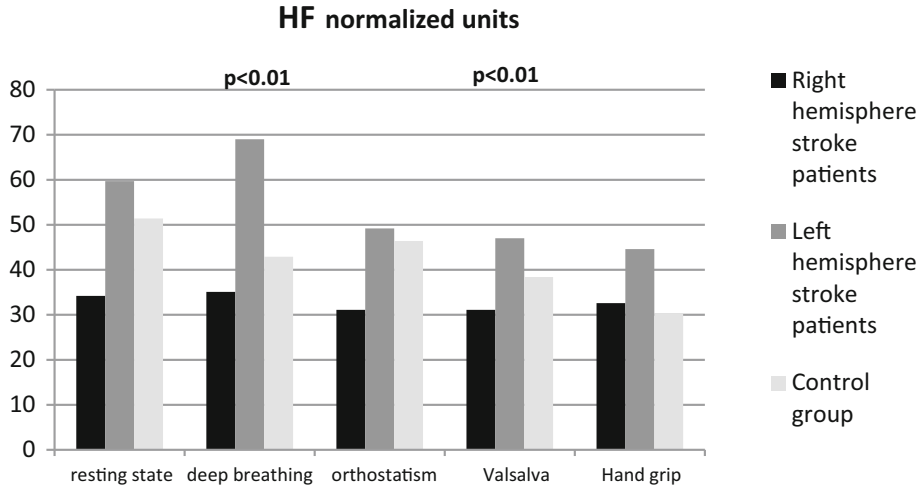

Fig. 1 HFnu in resting state and in different autonomic activation tests in study groups

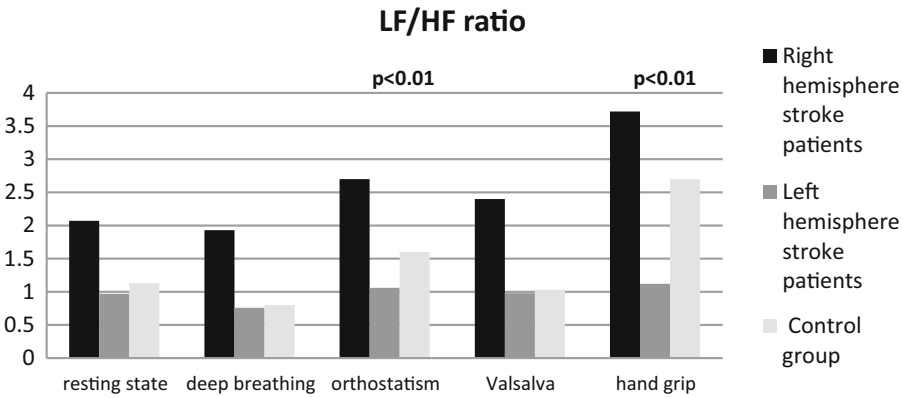

Fig. 2 LF/HF ratio in resting state and in different autonomic activation tests in study groups

ventricular arrhythmias or myocardial detriment, which are often associated with sudden death [20, 21]. Moreover, insular cortex involvement is associated with non-dipper profile of blood pressure [22], myocardial injury and sleep-related disordered breathing [23]. Additionally, patients with right insular cortex ischemia had increased incidence of ECG abnormalities (atrial fibrillation, A–V block, ectopic beats and inverted T wave) [24], higher blood pressure values compared to left insular cortex ischemia [25]. High norepinephrine levels were correlated to right insular infarction and QTc prolongation [26]. However, it is not clear whether cardiac injury and ECG abnormalities result from elevated serum catecholamine levels or from direct neural intervention [27].

Atrial fibrillation is the most frequent cardiac arrhythmia after stroke, as well as a risk factor for secondary cardiac complications such as ventricular tachycardia or fibrillation and heart failure, which can increase the risk of sudden death [28, 29]. Actually, many of these arrhythmias such as atrial fibrillation could be the cause and not the result of the acute cerebral event [30].

In our study, we tried to evaluate the ANS dysregulation in stroke patients and to explore the correlations between cerebral lateralization of the ischemic lesion and post stroke autonomic changes which may predict the outcome. This should provide new cues for stroke outcome, and thus, contribute to the development of new clinical evaluation algorithms based on dysautonomic changes in these patients.

Patients from the studied groups presented higher sympathetic activation in right hemisphere stroke (MCA territory). All the patients were right handed. These data are according to other results of similar studies, where it was proved that right insular cortex seems to modulate the sympathetic tone and left insular cortex the parasympathetic activity in these patients [31]. HRV study in the first 6 months after stroke may be useful to highlight the cardiac dysfunctions with potential clinical involvement. The risk of developing cardiac arrhythmias such as atrial fibrillation or other ECG abnormalities (QT prolongation, A–V block, T wave inversion) in ischemic stroke patients is higher in those with predominant sympathetic activity, with poorer prognostic for cardiac or cerebral events on long term [32, 33].

The cardiac arrhythmias following stroke may be related to the degree of sympathetic predominance. The presence of electrocardiographic abnormalities and cardiac arrhythmias is very common after acute cerebrovascular events, even in the absence of structural heart disease, but determining a causal relationship has been difficult as patients with stroke associate usually risk factors for coronary artery disease, such as hypertension, diabetes mellitus and smoking.

The autonomic dysregulation measured by HRV is not routinely assessed in everyday practice in stroke patients, but HRV might be a useful tool to predict and prevent secondary vascular events. This data may be effective in finding predictive parameters for severe arrhythmic risk and cerebral outcome. Therefore, as clear guidelines for clinicians outlining an approach of patients who might develop ANS dysfunctions after stroke are still needed, new stratification scores that may predict the outcome according to the presence/magnitude of dysautonomia can emerge. One limitation of this study is represented by the low number of participants which may decrease the statistical power. Therefore, further studies with larger groups of study are needed to confirm these results. Also, important might be taking into consideration left handed patients.

Conclusions

In conclusion, HRV represents a simple method of monitoring post ischemic stroke cardiac autonomic activity. Our results indicate that in ischemic stroke the autonomic nervous system dispose asymmetric responses to different stimulation autonomic tests between right and left hemisphere. The right hemisphere stroke has a more pronounced

sympathetic tonus than left hemisphere in right handed patients. This should provide new cues for the stratification of the outcome in stroke patients, and thus, contribute to the development of new clinical evaluation algorithms based on dysautonomic changes in these patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethical standard The study was carried out in accordance with the Helsinki Declaration.

Informed consent The study was approved by our institutional ethics committee and all the patients gave consent in accordance with ethical principles.

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