

## Gradual recovery of impaired cardiac autonomic balance within first six months after ischemic cerebral stroke

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### Abstract

*Background :* The level of autonomic dysbalance in the first months after acute ischemic cerebral stroke has not been thoroughly investigated, and the available data are incomplete. The aim of this research is to establish the degree and dynamics of impaired cardiac autonomic balance recovery within the first six months following the acute ischemic cerebral stroke.

*Methods :* This prospective study included 78 patients who had suffered the first ischemic cerebral stroke and 78 sex and age-matched healthy subjects. We have analyzed heart rate variability (HRV) from a 24-hour Holter ECG. In the group of patients with ischemic cerebral stroke, HRV was measured after two and six months following the acute phase, respectively.

*Results :* Two and six months after the acute ischemic cerebral stroke, all HRV variables, except low to high frequency ratio (LF/HF), were significantly lower in the group of stroke patients when compared to the control group. Furthermore, we found a significant increase in the overall HRV between months 2 and 6 after the acute phase of cerebral stroke ;  $p = 0.03$  for Standard deviation of all normal R-R intervals (SDNN) and  $p = 0.01$  for Total power.

*Conclusions :* The results point to the gradual recovery of impaired cardiac autonomic balance in the patients with ischemic cerebral stroke within the first months following the acute phase. Nevertheless, HRV remains significantly lower even six months after the acute phase in comparison to healthy subjects.

*Key words :* Heart rate ; autonomic nervous system ; cerebral stroke ; ischemic.

### Introduction

Like an acute myocardial infarction (MI) (6), acute ischemic cerebral stroke leads to autonomic dysbalance and lowered heart rate variability (HRV) (15). The mechanism of HRV decrease in the acute ischemic cerebral stroke is the damage of brain structures located in the insular cortex that are modulating the autonomic heart activity (4, 16, 18). The level of autonomic dysbalance in the first months following ischemic cerebral stroke has not

been thoroughly investigated, and available literature data are incomplete (8).

The aim of this research is to establish the degree and dynamics of impaired cardiac autonomic balance recovery within the first six months following the acute ischemic cerebral stroke.

### Patients and methods

This prospective study included 78 consecutive patients who had suffered the first ischemic cerebral stroke (53 male and 25 female, mean age  $59 \pm 11$  year) within 10 weeks after the acute phase during rehabilitation treatment, and 78 age and sex-matched healthy subjects.

Inclusion criteria were : age under 70 years, ischemic hemispheric lesions verified by a CT scan (52% with the left and 48% with the right hemispheric infarction), and ECG sinus rhythm.

Exclusion criteria were : hemorrhagic stroke, atrial fibrillation, sick sinus syndrome, AV block of II or III degree, previous MI, percutaneous coronary intervention, coronary artery bypass grafting (CABG), diabetes mellitus, heart failure and beta-adrenergic blockers or antiarrhythmic drugs in therapy.

Cardiac autonomic balance was evaluated by analysis of HRV. All HRV variables were measured through the 23.2-hour period (ranged 21 to 24 hours). Ambulatory ECG recordings were made by 3-channel Medilog Digital Holter recorders FD3, Oxford, with 1024 Hz resolution. HRV was analyzed by computer and over-read manually. A commercial system (Oxford Instruments, with software Medilog Holter Management System Excel 2, Version 7.1) was used. Algorithms for arrhythmia analysis gave a label to each QRS complex. An operator cleaned all recordings from artefacts, reviewed beats and modified them if needed, under the cardiologist supervision. Only recordings with less than 15% of ectopic beats were used. Periods with the highest and lowest average R-R intervals, detected from R-R interval histograms, were always validated. The corrected data were processed

and HRV was computed. Raw tachogram was used for time domain analysis. The power spectral analysis was computed using fast Fourier transformation. R-R intervals that included ectopic beats were excluded and extrapolated by linear interpolation for the spectral analysis. Details have been published elsewhere (13).

In the group of patients with ischemic stroke, HRV was measured two ( $58 \pm 6$  days) and six months ( $178 \pm 12$  days) after the acute phase and once in healthy subjects. Most of the variables proposed by the Task Force on the HRV (17) were analyzed. Time domain analysis included: Mean RR - mean of R-R intervals for normal beats, SDNN - standard deviation of all normal R-R intervals, SDANN-i - standard deviation of the 5-minute means of R-R intervals, SDNN-i - mean of the 5-minute standard deviations of RR intervals, rMSSD - square root of the mean of the squared successive differences in R-R intervals and pNN50 - percentage of R-R intervals that are at least 50 ms different from the previous interval. Frequency domain analysis covered: TP - Total power (0.0-0.5 Hz), VLF - very low (0.003-0.04 Hz), LF - low (0.04-0.15 Hz) and HF - high (0.15-0.4 Hz) frequency components, with LF/HF - low to high frequency ratio. LF and HF variables are expressed in  $\text{ms}^2$ , as well as in normalised units (n. u.), which is calculated using the formula: LF or HF norm / (TP - VLF)  $\times$  100 (17).

Statistical package Microsoft SPSS for Windows, Version 10.0 was used. The results are expressed by mean values and standard deviations. The normality of distribution of the variables was tested using the Kolmogorov - Smirnov test. Differences in HRV were tested by analysis of variance (ANOVA) with post hoc comparison using the Tukey test. The value  $p < 0.05$  is considered statistically significant.

## Results

HRV was analyzed in 74 (95%) out of total of 78 included patients six months after the acute phase. This was due to the fact that in the follow-up period one patient had died, one patient had a new stroke and two patients had been excluded due to atrial fibrillation.

After two months from the acute ischemic cerebral stroke, all HRV variables, except LF/HF ratio, were significantly lower in the group of stroke patients compared to the control group:  $p = 0.02$  for Mean RR;  $p < 0.001$  for SDNN, SDANN-i, SDNN-i, pNN50, TP and LF norm;  $p = 0.006$  for rMSSD;  $p = 0.01$  for VLF;  $p = 0.001$  for LF and HF norm; and  $p = 0.008$  for HF.

Furthermore, in stroke patients, all HRV variables, except LF/HF ratio, remained significantly lower six months after the acute phase in comparison to healthy control subjects:  $p = 0.03$  for Mean

RR, VLF and HF norm;  $p = 0.004$  for SDNN, pNN50;  $p = 0.002$  for SDANN-i and TP;  $p = 0.001$  for SDNN-i;  $p = 0.01$  for rMSSD and LF norm;  $p = 0.008$  for LF and  $p = 0.02$  for HF.

Moreover, an increase in all HRV parameters was found between the second and sixth month after the acute ischemic cerebral stroke, and significant differences were found in the following variables:  $p = 0.03$  for SDNN, SDNN-i and LF norm;  $p = 0.01$  for TP;  $p = 0.02$  for SDANN-i and LF (Table 1).

## Discussion

The obtained results point to the gradual recovery of impaired cardiac autonomic balance within the first months after ischemic cerebral stroke, but HRV remains significantly lower even six months after the acute phase when compared to healthy controls. It is interesting that the LF/HF ratio didn't show any change whereas TP was reduced. In addition, the time domain measures of parasympathetic regulation were reduced compared to controls. Although LF/HF ratio generally accepted as measure of sympatho-vagal balance (17), LF/HF ratio might fail to describe sympatho-vagal balance in a clinical practice, particularly when long term Holter recordings are analysed (10). It seems that LF/HF ratio correctly present sympatho-vagal balance in healthy subjects, while LF/HF ratio is useless in patients with seriously decreased overall HRV and sympathetic overactivity (11, 19). By a decrease in overall HRV, TP lose signal in LF and HF and most of the residual energy is distributed in lower frequencies, explicitly in the VLF band (2). Furthermore, the possible explanation for limited benefit from LF/HF ratio in the analysis of sympatho-vagal balance in cardiac, as well as in stroke patients, is that disease progression shifts HRV spectra leftward (14). These findings explain why we didn't find significant changes between stroke patients and healthy controls when we analyzed LF/HF ratio. Regarding to that, we conclude that within first six months after the acute phase of disease, in patients who had suffered ischemic cerebral stroke there exist lower parasympathetic modulation activities and a higher sympathetic tone when compared to healthy persons of the same age.

Previously, a similar investigation in a markedly smaller sample was performed by Korpelainen JT *et al.* (8). Although Korpelainen JT *et al.* reported that abnormal HRV persisted up to six months after hemispheric infarction, their results were contradictory to the results of our investigation. Bearing in mind that Korpelainen *et al.* measured HRV from a 24-hour Holter ECG, it is difficult to explain the low values of SDNN even six months after stroke, the values of which were within the borders of pathological HRV. Besides the mean SDNN value of 46 ms in the acute phase, or 51 ms six

Table 1

Values of heart rate variability (HRV) in the patients who suffered ischemic cerebral stroke two and six months after acute phase of disease and control group of healthy subjects

HRV variables	Stroke patients		Control group
	Two months after stroke	Six months after stroke	
Mean RR (ms)	867 ± 102	875 ± 103	892 ± 117
SDNN (ms)	96 ± 21	107 ± 24	136 ± 31
SDANN-i (ms)	84 ± 22	92 ± 26	122 ± 20
SDNN-i (ms)	42 ± 12	47 ± 13	55 ± 16
rMSSD (ms)	23 ± 16	27 ± 18	31 ± 18
pNN50 (%)	4.5 ± 3.9	6.0 ± 4.8	8.0 ± 6.4
TP (ms <sup>2</sup> )	1989 ± 1305	2638 ± 1617	3968 ± 2857
VLF (ms <sup>2</sup> )	1568 ± 642	1786 ± 745	2134 ± 979
LF (ms <sup>2</sup> )	362 ± 291	576 ± 316	792 ± 485
LF norm (n.u.)	48.2 ± 19.7	59.3 ± 24.5	68.1 ± 28.4
HF (ms <sup>2</sup> )	154 ± 126	212 ± 107	309 ± 234
HF norm (n.u.)	20.1 ± 8.6	22.8 ± 10.1	26.2 ± 11.7
LF/HF	2.4 ± 1.4	2.6 ± 1.3	2.6 ± 1.6

Mean RR - mean of R-R intervals for normal beats, SDNN - standard deviation of all normal R-R intervals, SDANN-i - standard deviation of the 5-minute means of R-R intervals, SDNN-i - mean of the 5-minute standard deviations of RR intervals, rMSSD - square root of the mean of the squared successive differences in R-R intervals and pNN50 - percentage of R-R intervals that are at least 50 ms different from the previous interval, TP - total power (0.0-0.5 Hz), VLF - very low (0.003-0.04 Hz), LF - low (0.04-0.15 Hz), HF - high (0.15-0.4 Hz) frequency components, LF/HF - low to high frequency ratio.

months after stroke, the measured mean values of TP were 1936 ms<sup>2</sup>, or 2336 ms<sup>2</sup>, while Mean RR was 896 ms, or 935 ms six months after stroke (8), what is very doubtful according to our experience and to results of this study. Such low SDNN values cannot be related to normal TP values, what on the other hand correlates well with SDNN values in the time domain (17). Furthermore, the mean SDNN values (68 ms) measured in the control group of healthy subjects are difficult to accept in comparison to the high values of TP (4772 ms<sup>2</sup>). In our previous studies, we have analyzed HRV on a sample of more than 2500 patients and we have offered standards for HRV for different groups of cardiac patients (13). In this study, SDNN value considered normal for the "general cardiological population" was 93 ms, the cut point for pathologically decreased SDNN was 59 ms, and the cut point for normal TP was 1312 ms<sup>2</sup>. If we follow the analogy from the HRV analysis in patients after MI published by Bigger JT *et al.* (3), it is to be expected that there would be at least partial recovery from diminished levels of HRV in the first months after the acute phase of cerebral stroke and that trend we found in our investigation.

The cognition that cerebral infarction causes autonomic dysbalance is not only of academic and scientific character, but it also has clinical implications. Therefore, each patient should be monitored during the acute phase of stroke and it would be ideal if the degree of the autonomic dysbalance could be quantified by the HRV analysis. By that screening, we believe that could be possible to identify patients with high risk of malignant arrhythmias and sudden death. Keeping in mind that some groups of antihypertensives and antiar-

rhythmic drugs have a favourable effect on the HRV (7, 9, 12), by selection of medications in those patients we could try to affect on the improvement of autonomic cardiac activity or lowering the autonomic dysbalance, respectively. This finally could reduce the early and late mortality rate from stroke.

A possible limitation of this research is the fact that HRV had not been measured in the first days of the disease. However, the aim of this investigation was to analyze HRV after the acute phase. The severe exclusion criteria from the study were been necessary to eliminated the impact of other disease and condition like MI (6), CABG (5), diabetes mellitus (1), etc., on HRV. Further investigations should be designed to follow up patients with ischemic stroke from the acute phase of the disease. HRV should be measured in the first days, and also more times up to a year after the acute phase in order to establish in what degree and in which period recovery of impaired cardiac autonomic balance occurs, and also whether it comes to its complete recovery.

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