

## AUTONOMIC DYSFUNCTION AND PROGRESSION OF PARKINSON'S DISEASE

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### Abstract

An exact quantitative evaluation method of autonomic dysfunction in Parkinson's disease (PD) for everyday clinical use has not been developed yet.

The aim of this study was to evaluate autonomic cardiovascular regulation in mild and advanced stages of PD with the use of heart rate variability (HRV) examination.

Twenty-five patients entered the study and passed short-term HRV examination in supine position with metronome-controlled breathing  $f = 0.33$  Hz.

The following parameters of power spectral analysis were evaluated: Total Power (TP;  $\text{ms}^2$ ), Low Frequency Power (0.04-0.14 Hz; Power LF;  $\text{ms}^2$ ), High Frequency Power (0.15-0.4 Hz; Power HF;  $\text{ms}^2$ ), and Ratio Power LF / Power HF (LF/HF).

The results show a statistically significant decrease of TP (438 vs. 123  $\text{ms}^2$ ), Power LF (132 vs. 40  $\text{ms}^2$ ), and Power HF (251 vs. 47  $\text{ms}^2$ ) in the group of patients with a higher mean H&Y (1.3 vs. 2.3; T test). The change of LF/HF was not statistically significant.

The short-term examination of heart rate variability fulfils the criteria for test objectivity, reproducibility, reliability, and validity. We proved a higher impairment of autonomic cardiovascular regulation in the group of PD patients with advanced PD (H&Y = 2.3) than in mild PD (H&Y = 1.3). Short-term HRV examination is also sensitive enough to be used for comparison of the difference of autonomic dysfunction corresponding to the change of impairment by 1 grade in H&Y score.

### Key words

Parkinson's disease, Autonomic dysfunction, Heart rate variability, UPDRS, Hoehn & Yahr score, Metronome-controlled breathing, Rehabilitation

### INTRODUCTION

Dysfunctions of the autonomic nervous system are an integral part of symptomatology of idiopathic Parkinson's disease (PD) from its very outset (19, 21, 24, 29, 36, 37).

Clinical studies examine the function of the autonomic nervous system by means of standard autonomic tests - orthostatic test (32), Valsalva maneuver

(5, 40), isometric exercise test (40), ratio of heart rate increase to 15th heartbeat after supine position to its decrease to 30th heartbeat (30:15 ratio; 4), ratio of the longest RR interval in expiration to the shortest RR interval in inhalation (E:I ratio; 4), evaluation of the reaction of heart rhythm and blood pressure to the deep breathing test (5, 40) and the tilt table test (4, 25), sympathetic skin response (4, 43), etc.

A number of studies support dysfunction progression of the autonomic nervous system proportionally to the course of development of other PD symptoms depending on the applied method of examination (5, 23, 25, 28, 32, 40).

Measurement of heart rate variability (HRV) and its analysis is a non-invasive examination revealing autonomic dysfunction in mild stage of PD already (6). Decrease of spectral power in the mild stage of PD disablement was documented in short-term HRV examination by *Rodriguez* (34); in 24-hour examination *Haapaniemi* (11) gives consistent results of HRV analysis.

Even if spectral power of HRV decreases naturally with increasing age, the influence of age as a unique factor bringing out this decrease was not confirmed in PD patients. Dysfunction of the autonomic nervous system in PD patients demonstrates a marked dependence mainly on the disease progression evaluated according to the motoric scale UPDRS III or H&Y score (H&Y) UPDRS V (40).

The influence of medication as the only factor conditioning the development of symptomatology of autonomic dysfunction was disproved as well. The presence of autonomic dysregulation is indicated also in studies evaluating spectral power of HRV in patients with idiopathic PD even before starting this medication (9, 20, 26).

Evaluation of the measure of dysfunctions of the autonomic nervous system is a permanent subject of the research (1, 4, 5, 7, 23, 30, 41). Most preceding studies, however, have not yet been dealing adequately with important factors of daytime in carrying out a short-term examination of HRV, differences in the extent of disablement by PD, type of dopaminergic or other pharmacotherapy, changes of breathing rate in examination, etc. (s).

#### PURPOSE OF THE STUDY

Evaluation of disorder of autonomic cardiovascular regulation in PD patients in mild and advanced stages according to H&Y score by means of methodology of spectral analysis of short-term HRV examination.

#### METHODOLOGY

Twenty-five PD patients, whose diagnosis was established in the 1st Department of Neurology of St. Anne's Faculty Hospital in Brno, were included into the study (8). The absence of other diseases or other pharmacological therapy influencing

the results of HRV examination was the condition of inclusion into the study (2, 3, 12, 14, 16, 22, 27, 33, 40). The patients included into the study also met the criteria of stable medication without any change in the last 4 weeks before the examination, observance of the usual daily schedule including medication, in the day before the examination without excessive physical activity, in the night before the examination at least 6 hours of good sleep, in the morning before the examination only light breakfast without coffee, tea, alcohol, with regard to the age of patients, at least 2 hours before the examination.

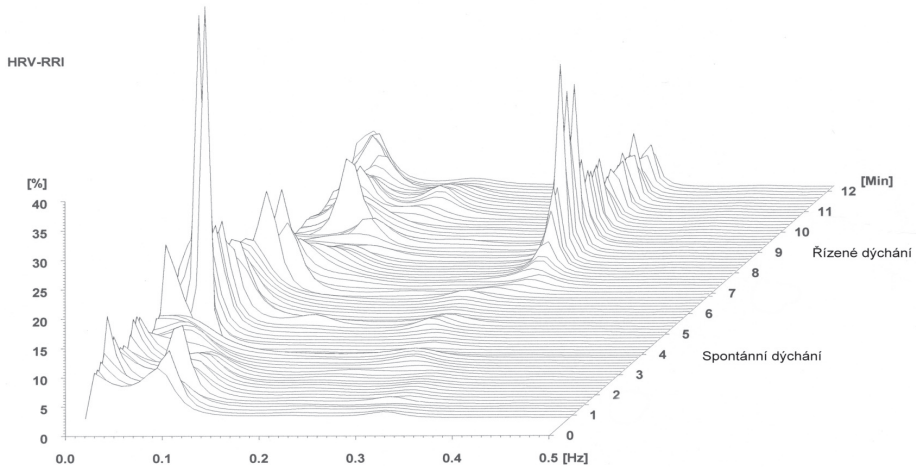
The patients were divided into two groups according to the measure of clinical disablement. H&Y score in the range of 1-1.5 was the criterion for inclusion into the group "SI" ; H&Y score in the range of 2-3 was the criterion for inclusion into the group "SII".

The basic anthropometric characteristics of the groups are given below in *Table 1* as mean  $\pm$  SD:

*Table 1*  
Basic anthropometric characteristics of evaluated groups

	H&Y	AGE (years)	BMI	PD DURATION (years)
Group SI	1.3 $\pm$ 0.3	65.7 $\pm$ 11.0	24.7 $\pm$ 2.5	7.6 $\pm$ 3.9
Group SII	2.3 $\pm$ 0.4	68.2 $\pm$ 7.1	26.7 $\pm$ 2.1	5.7 $\pm$ 3.0

The patients examined were subjected to short-term measurement and spectral analysis of heart rate variability in supine position (15, 20). The methodology of the metronome-controlled breathing rate  $f = 0.33$  Hz (18, 34, 38, 39, 42) was used for reducing the effect of the different rate of spontaneous breathing on spectral power in the groups of patients subjected to examination (5, 13, 28, 31, 40). A graphical representation of the effect of controlled breathing on spectral power is given below in *Graph 1*.



*Graph 1*

Example of graphical representation of the results of spectral analysis of heart rate variability by the system Task Force Monitor, CNSystems Medizintechnik GmbH.

All HRV tests were made always in the morning hours between 9 and 11 a.m.

The measure of autonomic dysfunction evaluated by means of spectral analysis of HRV was compared between the groups of patients with a different degree of clinical disablement according to H&Y.

The differences of values of selected parameters of spectral analysis of HRV between the groups SI and SII were statistically evaluated by means of the Kolmogorov-Smirnov test (tests of distribution) and the T test (Statistica, StatSoft Inc., version 7, 2004).

The study was accepted by the ethical committee of Masaryk University in Brno and all participants of the study signed their informed consent. The study was supported by grant MSM0021622402.

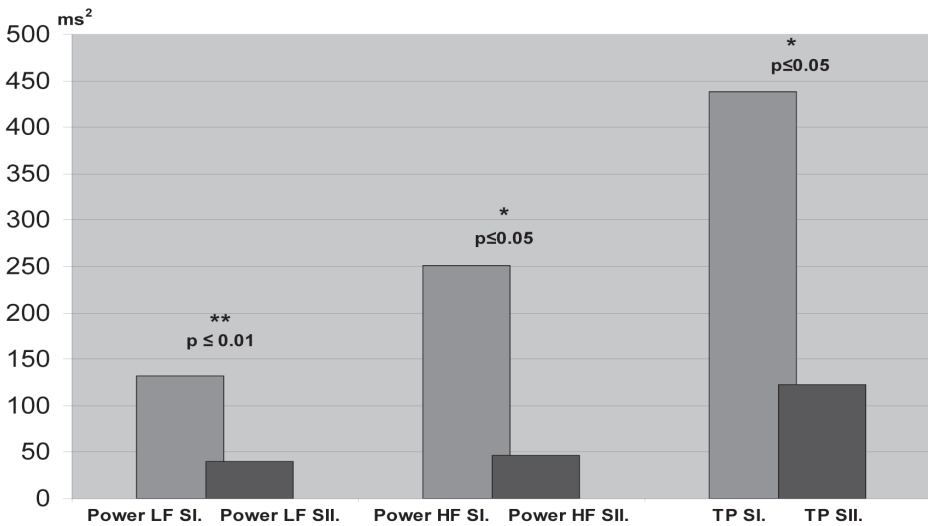
## RESULTS

The results of the evaluated parameters of spectral analysis of short-term examination of HRV are given below in *Table 2* (mean  $\pm$  SD): total power (TP,  $\text{ms}^2$ ), power in low-frequency band (0.04-0.14 Hz; Power LF;  $\text{ms}^2$ ), power in high-frequency band (0.15-0.4 Hz; Power HF;  $\text{ms}^2$ ), and ratio of both powers (LF/HF).

*Table 2*  
Results of spectral analysis of HRV for metronome-controlled breathing ( $f = 0.33$  Hz)

	TP (ms <sup>2</sup> )	Power LF (ms <sup>2</sup> )	Power HF (ms <sup>2</sup> )	LF/HF
Group SI	438 ± 411	132 ± 95	251 ± 315	1.0 ± 0.6
Group SII	123 ± 108	40 ± 37	47 ± 62	1.9 ± 2.3
P	*0.018	**0.005	*0.038	N.S.

A graphical representation of the difference of monitored parameters of spectral analysis of short-term examination of HRV for metronome-controlled breathing ( $f = 0.33$  Hz) is given below (*Graph 2*).



*Graph 2*  
Comparison of parameters of spectral analysis of HRV

In a statistical comparison of monitored parameters of spectral analysis of HRV a significant difference was found between the group SI with a milder degree of disablement and the group SII with a more advanced degree of disablement according to H&Y. In group SII a statistically significant decrease of the total power and of the power in low-frequency and high-frequency spectral components occurred. The change of ratio of low-frequency power and high-frequency power LF/HF was not statistically significant.

## DISCUSSION

Autonomic dysfunctions in PD patients progress in connection with progression of the disease (25, 32, 40). Their exact examination and scoring in the present clinical practice are more and more important.

Examination of short-term heart rate variability meets the exacting criteria of a non-invasive and nevertheless objective, reproducible, reliable, and valid test of autonomic regulation (10, 15, 34). *Kallio* (20) recommends, because of a higher sensitivity, application of spectral analysis (frequency domain) of HRV before time analysis (time domain). It was proved that the measure of disorder of autonomic control of heart function is identical with the dopaminergic system disorder (1, 4).

We have demonstrated statistically in two examined groups, SI with a mild degree of disablement (H&Y = 1.3) and SII with a more advanced degree of disablement (H&Y = 2.3), with the difference in the measure of clinical disablement of 1 degree, a significant difference of the total power and the power in low-frequency and high-frequency spectral components in the short-term examination of HRV. We consider the short-term examination and its spectral analysis also to be sufficiently sensitive for evaluation of the progression of autonomic dysfunctions in PD.

Our results are in accordance with the testing of other authors using similar methods of HRV examination. *Linden* (25) made a comparative study with two groups of an average age of 67.6 years with a higher H&Y (2.1 vs. 3.3) and found out also a significant decrease of the low-frequency and high-frequency spectral power in the group with a higher H&Y in comparison with the group with a lower H&Y.

*Rodriguez* (34) presents a decrease of power in all spectral bands in the group of examined patients with PD of an average age of 30.8 years in comparison with the group of examined patients with PD of an average age of 61.9 years and a higher H&Y.

The same results found out by means of spectral analysis of HRV, autonomic dysfunction progression in connection with the disease development, are given also by *Deiseroth* (5) in his study made on 30 patients in the age of 39–84 years.

*Van Dijk* (40) determined dependence of a reduced autonomic response in the short-term examination of HRV on age, duration of medication and higher H&Y and, on the contrary, excluded a direct relation with the duration of the disease.

*Devos* (6), unlike the preceding authors, takes into consideration in the methodology of examination also the daytime of examination, pharmacotherapy, breathing rate, and previous physical load. He compares the results of a short-term examination of HRV of three groups of examined PD patients with a different degree of motor dysfunction according to the motor scale UPDRS III (7 vs. 8.9 vs. 19) and of the check group, the average age being always 61 years. In all groups of examined PD patients he finds significant differences in all spectral bands of HRV.

The results of Hisayoshi's study (17) prove, in the mild stage of PD disease in comparison with the corresponding check group of healthy population, only a

decrease of the spectral power in the low-frequency band.

The difference in spectral power in the short-term examination of HRV between the group of healthy population and age corresponding to examined PD patients in the mild stage is denied only by *Krygowska-Wajs* (23). Her methodology of examination, however, does not take into consideration all factors influencing the results of the short-term examination of HRV and does not use the methodology of controlled breathing. In another study (24), where she evaluates the changes of heart rate in the mild stage of PD by means of the tilt table test (30:15 ratio), a statistically significant difference between the examined patients in the mild stage of PD and the check group of healthy population of the corresponding age and sex is already confirmed.

*Piha* (32) comes to the same conclusions on the basis of testing orthostatic hypotension.

Statistically significant changes of spectral power in comparison with the check group of healthy population already in the mild stage of the disease ( $H\&Y = 1.5$ ) are also given by *Haapaniemi* in his study (11) based on the results of 24-hour examination of HRV in PD.

#### CONCLUSION

We established a larger disorder of autonomic regulation of heart rate in the group of patients in the advanced stage of PD ( $H\&Y = 2.3$ ) in comparison with the group in the mild stage of PD ( $H\&Y$  score = 1.3). On the basis of our results demonstrating a statistically significant difference between the groups with an average  $H\&Y$  score differing by one degree (1.3 vs. 2.3) in the spectral power values (TP 438 vs. 123  $ms^2$ , Power LF 132 vs. 40  $ms^2$ , Power HF 251 vs. 47  $ms^2$ ), we consider spectral analysis of a short-term examination of HRV to be a suitable method of evaluation of autonomic dysfunction in PD patients.

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