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Abnormal cardiovascular autonomic regulation in Parkinson's disease

T. Szili-Török¹, L. Rudas¹, G. Dibó², D. Paprika¹, A. Kardos³

Parkinson's disease (PD) is often associated with an autonomic neuropathy. The extent of autonomic involvement, however is poorly defined and unpredictable. In order to assess the autonomic cardiovascular regulation time and frequency domain indices of heart rate and frequency domain indices of blood pressure the variability was determined non-invasively in 20 patients (age: 66 ± 8 years) with PD. The arbitrarily chosen level of spontaneous linear baroreflex sensitivity (BRS) of 3.5 ms/mmHg served to divide PD patients into subgroups. 12 PD patients exhibited a normal (nBRS), and 8 an impaired (iBRS) BRS. The results were compared with those from 18 healthy age-matched volunteers. The group of iBRS PD patients exhibited marked abnormalities in the other indices of cardiovascular autonomic regulation. In contrast, nBRS PD patients displayed only modest deviations. It is concluded that a decreased BRS is a distinctive feature of the impaired cardiovascular autonomic regulation in this heterogeneous population, and may serve as a selection marker for further assessment. *J Clin Basic Cardiol* 1999; 2: 245–7.

Key words: Parkinson's disease, baroreflex sensitivity

It is well documented that Parkinson's disease may be associated with a dysfunction of the autonomic nervous system. In idiopathic Parkinson's disease, this dysfunction can be explained by damage to neurological structures. Histological studies have proven the presence of Lewy's bodies in sympathetic and parasympathetic preganglionic neurons and also in central structures associated with the autonomic regulation [1]. To characterize the cardiovascular autonomic regulation, reflex tests of various complexity, such as the Valsalva maneuver or active orthostasis were traditionally used. These tests were often carried out in panels as a test series [2, 3]. A well-known example is the Ewing Panel [4]. In recent years, several studies have been reported in which Parkinson's disease patients were tested by this method. [5–15]. These tests require an active participation of the patients, and thus the hypokinesia, rigidity and tremor characteristic of Parkinson's disease led to serious limitations. It is obvious that with some patients these tests are infeasible or the results are meaningless. The measurement of autonomic parameters using power spectrum analysis of heart rate (HR) and blood pressure (BP) and a non-invasive determination of baroreflex sensitivity (BRS) does not require the active participation of patients.

One aim of the present study was to determine the markers of heart rate and blood pressure variability (HRV and BPV) in Parkinson's disease. A further goal was to verify our presumption that the pathological BRS level separates the disordered autonomic regulation and autonomically intact subgroups of Parkinson's disease patients.

Methods

Patient population

The study involved 20 patients with Parkinson's disease who were recruited from the Parkinson's Outpatient Clinic of the Neurological Department at Albert Szent-Györgyi Medical University. Patients without history of any cardiovascular disease, and with negative physical examination and normal 12-lead ECG were selected for this study. Neurological characteristics of the patients are shown in Table 1. The average age was 66 ± 7 years. The average age at the time of the diag-

nosis was 60 ± 8 years. The duration of the Parkinsonian signs was on average 71 ± 62 months. 76 % of the patients were on L-DOPA, 63 % on a MAO inhibitor, 25 % on an anticholinergic drug, 67 % on amantadine and 31 % on bromocriptine. 36 % of the patients took antidepressants and 15 % beta-blockers. All measurements were conducted in the afternoon, 4–5 hours following the last meal. The participants were requested to avoid smoking and to refrain from caffeine-containing beverages for 6 hours prior to the examinations. The subjects were equipped with the peripheral unit of the Penaz system non-invasive BP monitor (Finapres 2300) and ECG electrodes. Continuous BP and HR measurements were started after a 10-min resting period. BP and HR were monitored and recorded in a supine position for 20 mins. Data were analysed off-line. By means of the 3.5 ms/mmHg limit the Parkinson's disease patients were divided into two subgroups: those with a normal BRS (nBRS; 12 patients) and those with an impaired BRS (iBRS; 8 patients). Most of the previous studies utilized pharmacological (phenylephrine) BRS tests. It has been documented that phenylephrine and spontaneous BRS values are closely related but not interchangeable [16]. Therefore we selected our cut off point at 3.5 ms/mmHg.

Table 1. Clinical characteristics and neurodiagnostic test scores of subjects

	Control N = 18	PD nBRS N = 12	PD iBRS N = 8
Age (years)	65 ± 9	64 ± 6	67 ± 7
Sex (M/F)	9/9	6/6	3/5
Age at onset of disease (years)	-	60 ± 7	59 ± 8
MMSE score	29 ± 0.9	27.3 ± 0.7	27.8 ± 0.6
UPDRS	-	26.5 ± 0.3	25.9 ± 0.4
HY	-	2.0 ± 0.1	2.1 ± 0.1

Data are mean $\pm$ SD; PD = Parkinson's disease with normal BRS (nBRS) and with impaired BRS (iBRS); M = male, F = female, MMSE = Mini Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale; HY = Modified Hoehn and Yahr staging

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From the ¹Medical Intensive Care Unit, the ²Department of Neurology, and the ³Second Department of Internal Medicine, Albert Szent-Györgyi Medical University, Szeged, Hungary.

Correspondence to: Tamás Szili-Török, MD, Belgyógyászati Intenzív Osztály, Szeged, Korányi fasor 7, H-6725, Hungary;

E-mail: torok@comser.szote.u-szeged.hu

Measurements and calculations

The ECG was continuously recorded with a Sirecust 730 (Siemens) monitor. Blood pressure was measured non-invasively with a Finapres 2300 (Ohmeda) device, which reliably reflects blood pressure spectral changes. The Penaz system photoplethysmographic finger blood pressure monitor reconstructs a continuous blood pressure curve that closely follows the invasively recorded blood pressure fluctuations. The R wave of the ECG and the plethysmographic signals were fed through an amplifier, filter and analog-digital converter into an IBM-AT-compatible computer. The computer measured the interval between successive R waves with a precision of 2 ms. The accuracy of ECG signal detection was 40 microvolts and 1 mmHg of the blood pressure measurement. The cardiogram and trend-grams of the BP values were continuously recorded on-line. Spectral analysis of the R-R interval and systolic BPV was performed by fast Fourier transformation, using the Hamming window over two frequency bands: low-frequency power (0.04 to 0.14 Hz) and high-frequency power (0.15 to 0.4 Hz). The total frequency power range from 0.01 to 0.4 Hz was considered. The short-term measures of time domain indices as the average normal R-R intervals (mean R-R), SDNN, pNN50, rMSSD were also calculated. BRS was characterized by the spontaneous sequences method as described earlier [17, 18]. It has been established that 3 or more cardiac cycles of unidirectional BP increase or decrease with the corresponding lengthening or shortening of the interbeat intervals to form spontaneous "up-" or "down-sequences". These sequences are analogous to those induced by pharmacological maneuvers, and a spontaneous BRS could be determined as an average of several individual slopes. In this study, all of the changes in systolic blood pressure (delta SBP) were paired with the changes in the subsequent RR intervals (delta RR). This method is referred to as the lag1 technique [17, 18].

Statistical analysis

HRV, BPV and BRS values of patients with Parkinson's disease showed non-gaussian distribution. These data were analysed using the Friedman test. An α level of $p < 0.05$ was considered to be significant.

Results (Table 2)

The average RR interval length was shorter in both Parkinson's disease groups than in the healthy volunteers. The systolic blood pressure, however, was very similar in all three groups. rMSSD was almost the same in the control group and the nBRS group. In the iBRS group, the rMSSD was significantly lower than in the other two groups. There was an even more marked difference in pNN50: the values for the healthy volunteers and the nBRS group were very similar, while that in the iBRS group was 0. There was a similar tendency in the spectral parameters of heart rate variability. TFHRV, LFHRV and HFHRV for the nBRS group were all slightly below those for the healthy volunteers, whereas statistically significant differences were observed between the iBRS group and the healthy volunteer group. The spectral markers of systolic blood pressure variability behaved differently from the other parameters. TFBPV and LFBPV for the iBRS group were significantly higher than those for the control group.

Discussion

Parkinson's disease is a clinical diagnosis. Pathological examinations reveal another syndrome, multiple systemic atrophy (MSA) in one-fourth of patients diagnosed as having Parkinson's disease. The extent and frequency of autonomic involvement differ in the two syndromes [15]. It is even more important that the prognosis and the effect of the applied anti-Parkinson drugs also differ in the two entities, and their differentiation remains an important task for the future [6, 19]. Bordet et al. consider that, because of the difficulties with traditional reflex tests, spectral analysis of heart rate variability may be used even more widely to study the autonomic regulation in Parkinsonian patients in the future [6]. Frontoni et al. have already applied spectral analysis for the same reasons in studies of multiple sclerosis [20]. To the best of our knowledge, this is the first publication relating to a spectral analysis of the HRV and BRS test in patients with Parkinson's disease. The HR spectrum is divided into "high-" and "low"-frequency bands at a commonly agreed value [21]. The high-frequency band is equivalent to breathing arrhythmias and is generated mainly by parasympathetic modulation. The genesis of the low-frequency range is influenced by both sympathetic and parasympathetic nervous mechanisms. While this view is somewhat simplistic, it may be of significance that both frequency ranges were reduced by spectral analysis in the iBRS group, and thus both the sympathetic and the parasympathetic components could be assessed as pathological. Spectral analysis of BPV has not been carried out on Parkinson's disease patients so far. Netten et al. have reported studies on Parkinson's disease patients in which the Finapres blood pressure monitor was used [11], but they targeted the examination of orthostasis tolerance and handgrip-induced vasoconstrictor response. It is of importance that only one of the 23 patients studied by Netten et al. had to be excluded because of hand tremor induced blood pressure artifacts. In our group of 20 patients, we had no such difficulties at all. BRS in Parkinson's disease patients was first examined by Appenzeller and Goss. They used the blood pressure and heart rate response in the overshoot phase of the Valsalva maneuver to characterize BRS, and concluded that these BRS values were pathological in some Parkinson's disease patients [22]. Our study confirms this and demonstrates some more general aspects of this early observation. The time and frequency domain indices of HRV were

Table 2. Comparison of spectral autonomic parameters and BRS values between control, PDn and PDi groups

	Control subjects N = 18	PD nBRS N = 12	PD iBRS N = 8
BRS (ms/mmHg)	9.9 ± 4	9.65 ± 6	2.1 ± 1*
Mean RR (ms)	855 ± 100	689 ± 140	697 ± 9*
Mean SBP (mmHg)	126 ± 21	117 ± 17	117 ± 22
SDNN (ms)	52.4 ± 4.6	49.1 ± 3.1	34.9 ± 2.9*
rMSSD (ms)	27.7 ± 8	27.2 ± 22	11.4 ± 4*
pNN50 (%)	8 ± 7	11 ± 18	0 ± 0*
TFHRV (ms ² /Hz)	847 ± 595	382 ± 662	85 ± 63*
LFHRV (ms ² /Hz)	187 ± 152	63 ± 51	28 ± 23*
HFHRV (ms ² /Hz)	463 ± 480	261 ± 586	28 ± 36*
TFBPV (mmHg ² /Hz)	18 ± 16	15 ± 13	34 ± 51*
LFBPV (mm Hg ² /Hz)	1 ± 2	7 ± 8*	8 ± 10*
HFBPV (mm Hg ² /Hz)	8 ± 8	2 ± 3*	7 ± 11

Data are mean ± SD; * = $p < 0.05$ compared with control group; PD = Parkinson's disease with normal BRS (nBRS) and with impaired BRS (iBRS); BRS = baroreflex sensitivity; SBP = systolic blood pressure; rMSSD, pNN50, TFHRV, LFHRV, HFHRV, TFBPV, LFBPV, HFBPV: explanation in method section.

also pathological in the group of patients classified as iBRS. A somewhat controversial tendency could be observed in the spectral parameters of systolic BPV. The function of HRV is commonly known to be to buffer changes in BP. Accordingly, it is not surprising that the amplitude of BP surges increases with decreasing HR fluctuation [23]. The significance of the abnormalities in cardiovascular regulation among Parkinson's disease patients is not yet fully known. It is possible that the dysbalance of the sympathetic and the parasympathetic tone is connected with the arrhythmias developing in the ischaemic heart muscles. The pathological BRS that signalled an autonomic dysbalance in the acute phase of myocardial infarction was a sensitive predictor of ventricular arrhythmias and sudden death [18]. The connection between autonomic dysregulation and arrhythmia-related death has recently been considered in other, non-cardiovascular diseases, such as depression [24]. Analogously, we can presume a connection between the autonomic dysbalance and the high mortality among Parkinson's disease patients [25, 26]. The mortality of Parkinson's disease patients is almost twice that for age and sex-matched healthy control groups [25]. The 20-year follow-up study by Ben-Shlomo and Marmot suggested that this increased mortality is connected with an increase in heart ischaemia-related deaths [26]. That study, however, did not distinguish sudden cardiac deaths, and thus the real importance of arrhythmia-related deaths could not be assessed. However, the available data indicate that a wide-ranging prospective examination of autonomic regulation in Parkinson's disease patients would be justified. The examination of spontaneous BRS involves a non-invasive procedure that does not need the active cooperation of the patients and it can therefore be used with disabled or weak patients, too. Our results demonstrate that the procedure is quite suitable for screening autonomic involvement among Parkinson's disease patients. The predictive nature of the pathological BRS in this group necessitates further investigations.

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