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Cardiac responses to orthostatic stress deteriorate in Parkinson disease patients who begin to fall

Wystąpienie upadków w chorobie Parkinsona wiąże się z pogorszeniem regulacji czynności serca w czasie pionizacji

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Abstract

Background and purpose: It is not clear how cardiovascular autonomic nervous system dysfunction can affect falls in Parkinson disease (PD) patients. The aim of the study was to evaluate cardiovascular autonomic responses to orthostatic stress and occurrence of falls in PD patients over a period of 1-2 years.

Material and methods: In 53 patients, who either experienced at least one fall during 12 months preceding the study onset (fallers) or did not fall (non-fallers), we monitored RR intervals (RRI), heart rate (HR) and systolic (SBP) and diastolic (DBP) blood pressure, and calculated the coefficient of variation of RRI (RRI-CoV) and the ratio of low to high frequency spectral powers of RRI oscillations (LF/HF) at rest and upon tilting at study entry and after at least 12 months. Based on the number of falls at study closure, we identified three subgroups: non-fallers, chronic fallers, and new fallers.

Results: At study entry, RR-CoV, SBP, or DBP did not differ between fallers and non-fallers, while LF/HF ratios were lower in fallers than non-fallers at rest and upon tilting. After the follow-up period, HR and RRI-CoV responses to head-up tilt were reduced in new fallers as compared to study entry,

Streszczenie

Wstęp i cel pracy: Do tej pory nie ustalono, czy istnieje związek pomiędzy zaburzeniami czynności autonomicznego układu nerwowego (AUN) a występowaniem upadków u osób z chorobą Parkinsona (ChP). Celem badania była ocena odpowiedzi AUN na pionizację oraz ocena częstości występowania upadków u chorych na ChP w czasie obserwacji wynoszącej 1–2 lata.

Materiał i metody: W badaniu uczestniczyło 53 chorych, którzy na wstępie zostali podzieleni na pacjentów z upadkami w wywiadzie (co najmniej jeden upadek w ciągu 12 miesięcy poprzedzających badanie) i pacjentów bez upadków. Monitorowano odstępy RR (RRI), częstość rytmu serca (HR), ciśnienie skurczowe (SBP) i rozkurczowe (DBP), obliczono współczynnik wariancji odstępów RR (RRI-CoV) oraz iloraz mocy widm oscylacji RRI w zakresie niskich i wysokich częstotliwości (LF/HF) w pozycji leżącej i po pionizacji. Powyższe zmienne oceniono na początku badania i po co najmniej 12 miesiącach. Uczestnicy badania zostali podzieleni na 3 grupy: grupę pacjentów bez upadków w wywiadzie i w czasie obserwacji, grupę pacjentów, którzy upadali przed badaniem i podczas badania, oraz grupę pacjentów, którzy zaczęli upadać w trakcie obserwacji.

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whereas these variables remained unchanged during the study in non-fallers and chronic fallers. Prevalence of orthostatic hypotension did not differ between subgroups of patients. **Conclusions:** Cardiac responses to orthostatic stress deteriorate in PD patients who begin to fall. Orthostatic blood pressure responses remain unchanged over time and are not associated with falls in PD.

Key words: Parkinson disease, autonomic nervous system, orthostatic hypotension, falls, syncope.

Wyniki: Na początku badania RRI-CoV, SBP i DBP nie różniły się pomiędzy chorymi z upadkami i bez upadków, natomiast wartości LF/HF w pozycji leżącej i po pionizacji były mniejsze u pacjentów upadających w stosunku do chorych bez upadków. W badaniu końcowym odpowiedzi HR oraz RRI-CoV na pionizację były mniejsze niż w badaniu wstępnym u chorych bez upadków w wywiadzie, którzy zaczęli upadać dopiero w czasie okresu obserwacji, podczas gdy te zmienne nie uległy zmianie u chorych bez upadków i stale upadających. Nie stwierdzono różnic w występowaniu niedociśnienia ortostatycznego w badanych podgrupach pacjentów. **Wnioski:** Odpowiedź HR na pionizację pogarsza się u tych chorych na ChP, którzy zaczynają upadać. Odpowiedź ciśnienia tętniczego na pionizację nie zmienia się w czasie rocznej do dwuletniej obserwacji i nie ma związku z obecnością upadków w ChP.

Słowa kluczowe: choroba Parkinsona, układ autonomiczny, niedociśnienie ortostatyczne, upadki, omdlenie.

Introduction

Autonomic nervous system dysfunction is a relatively common and well documented feature of Parkinson disease (PD). It has been estimated that approximately 60-80% of PD patients present with various autonomic nervous system symptoms [1,2]. As demonstrated by cardiovascular reflex tests [3,4], cardiac neuroimaging [5-7] and postmortem pathological studies [8-10], PD-associated autonomic dysfunction involves both the sympathetic and parasympathetic systems. Although prominent autonomic disturbances at the disease onset may be indicative of parkinsonism associated with e.g. multiple system atrophy (MSA) rather than PD [11,12], there is a growing body of evidence that a mild to moderate impairment of cardiovascular control occurs early in the course of PD [1,13,14]. It is not clear, however, how this impairment progresses with disease duration and severity. In a study by Holmberg *et al.*, decreases in mean blood pressure upon orthostasis were greater with longer duration of PD [15]. Magerkurth *et al*. described more pronounced blood pressure decreases during active standing and passive tilt that accompanied more advanced stages of the disease [16]. While some studies correlated PD symptoms with autonomic indices, others found no correlation between autonomic complaints and the PD duration or severity, which – according to the authors – might even suggest separate mechanisms underlying autonomic and motor symptoms in the course of PD [1,16,17].

Falls constitute the most common motor complication associated with PD [17,18]. Trauma, mostly due to falls, has been described as the most frequent comorbid event leading to hospitalization in PD [17,19]. Previous studies report a 38-68% risk of falling in PD patients [20-22], which is up to two-fold higher than in the general population [22]. As with the autonomic dysfunction, early falls in the presence of parkinsonian symptoms may suggest a disease other than PD, e.g. progressive supranuclear palsy (PSP) or MSA [23-25]. In a study by Williams *et al*., median latency from disease onset to first fall estimated for a group of 279 PD patients was 108 months, while it was only 42 months in MSA and 47 months in PSP-parkinsonism patients [25]. The most consistently documented risk factors for falling in PD include advanced age, longer duration and greater disease severity, balance impairment, functional improvement following levodopa administration, on-off phenomena and dyskinesias, multiple medication, depression and dementia [22,25,26].

Little is known about the possible impact of autonomic dysfunction in PD patients on the risk of falls. A positive correlation between carotid sinus hypersensitivity and falls has been found in the general population [27,28], but not in PD [22]. Furthermore, most studies failed to show any significant correlation between falls and frequency of autonomic symptoms or abnormal results of autonomic function tests [17,20,26]. To our knowledge, there has been only one report by Williams *et al*. that demonstrated a positive association

between occurrence of falls and autonomic dysfunction defined as two abnormal tests of autonomic function [25]. Moreover, studies on falls in PD performed so far have not been conducted along with a prospective assessment of the autonomic impairment. Because autonomic instability can affect falling [25,27,28], it seems possible that cardiovascular disturbances might contribute to falls also in PD. Therefore, we hypothesized that the presence or exacerbation of autonomic dysfunction may be associated with the occurrence of at least some falls in PD and that the deterioration of autonomic function in PD might be different in the falling and non-falling patients. In the present prospective study, we evaluated changes in cardiovascular autonomic function in PD patients with and without falls over a period of 1-2 years.

Material and methods

Study participants

Fifty-three patients (29 men and 24 women), aged 39-80 (mean 63.9, standard deviation [SD] 9.3 years), with the diagnosis of idiopathic PD were enrolled into the study between February 2004 and February 2005. The participants were recruited from the in- and outpatient population at the Department of Neurology, Jagiellonian University Medical College. Inclusion criteria were as follows: diagnosis of PD according to the United Kingdom PD Society Brain Bank criteria [29], stage II-IV on the Hoehn and Yahr scale, disease duration of at least 3 years, sustained (longer than 1 year) response to levodopa therapy. Exclusion criteria were: severe gait disability due to any reason, disorders other than PD which might cause weakness or instability (stroke or myocardial infarction that occurred later than 3 months prior to enrolment into the study, severe hepatic or renal failure, cancer, ankylosing spondylitis, severe coxarthrosis, etc.), history of orthopaedic surgery of the hip or knee causing gait difficulties, other chronic disorders of the musculoskeletal system that cause mobility limitation, epilepsy, and moderate or severe dementia (Mini-Mental State Examination [MMSE] score < 17 points).

Study design

All patients underwent a multidisciplinary assessment for the evaluation of non-parkinsonian causes of falls including: neurological, laryngological and ophthalmological examination, electroencephalography (EEG), standard 12-lead electrocardiogram (ECG), ultrasonographic examination of the carotid and vertebral arteries, electronystagmographic evaluation of vestibular function with response asymmetry of 20% or more considered as abnormal, cognitive function assessment using the MMSE, X-ray of the cervical spine, and magnetic resonance imaging (MRI) of the brain. During the history-taking, patients were asked to describe the circumstances of falls that had occurred during the last 12 months. A fall was defined as 'an unexpected event where the person inadvertently came to rest on the ground or other lower level'. The same investigator (S.B.) guided history-taking and classified the causes of falls according to the St. Louis Oasis Study Fall Classification [30]. Participants were obliged to report each fall during the one-year follow-up of our study. Every patient or caregiver was obliged to report the occurrence of a fall within 3 days following the event. The investigator guided the survey in order to ascertain all the information needed to classify a fall according to the St. Louis Oasis Study Fall Classification.

Severity of PD was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr staging at the beginning of the study and after one year of follow-up.

Twenty patients had experienced at least one fall, classified as a fall not due to extrinsic factors according to the St. Louis Oasis Study Fall Classification, during the 12-month period preceding enrolment into the study and were described as 'fallers'. Thirty-three patients did not report falls and, thus, were categorized as 'non-fallers'.

The study protocol was approved by the local ethics committee and all patients gave their written informed consent to participate in this study.

Procedures

Study procedures were performed in a quiet room with an ambient temperature of 24°C and stable humidity. All participants were tested twice: at baseline and after a follow-up period of at least 12 months. After having taken a short history, we performed neurological examination and assessed patients' clinical status using the Unified Parkinson's Disease Rating Scale (UPDRS). Subsequently, details of the testing procedure were explained. Patients were laid down on a tilt table and the monitoring devices were attached. To ensure stabilization of the cardiovascular system, the

participants rested in the supine position for at least 20 minutes prior to data collection.

Electrocardiographic RR intervals (RRI) and heart rate were continuously monitored using a standard 5-lead electrocardiogram with superficial skin electrodes in standard locations. Blood pressure was recorded from the right brachial artery using automated oscillometric cuff measurements (SpaceLabs Medical Inc., Redmond, WA, USA) performed at 1-minute intervals.

We monitored RRI, and systolic (SBP), diastolic (DBP) and mean blood pressures (MBP) during a 5-minute period of supine rest and during 60-degree head-up tilt for a subsequent period of 5 minutes, or until syncope occurred, or the patient experienced marked presyncope symptoms and requested the test to be terminated.

At the study closure, patients were questioned in detail on the number and circumstances of falls experienced between the two visits.

Data acquisition and analysis

All data were digitized by an analogue-to-digital converter (Medea, Gliwice, Poland) at a sampling rate of 300 Hz, fed to a PC computer, manually cleaned from artefacts by linear interpolation, and stored for off-line analysis. The system identified all QRS complexes, located the peak of each R wave, and the time series were constructed and used for further analyses in the time and frequency domains.

We calculated the mean heart rate (HR) and RRI values and the coefficient of variation of RRI (RR-CoV) to evaluate heart rate variability (HRV) both at rest and during tilting. Standard deviation of RRI (RR-SD) reflects both sympathetic and parasympathetic heart rate modulation and is also largely dependent on mean RRI [31], whereas RRI-CoV (calculated as the ratio of RR-SD to mean RRI) reflects primarily the parasympathetic function and is not affected by mean RRI [32]. Further, we applied power spectral analysis by means of the autoregressive algorithm to assess the contribution of the sympathetic and parasympathetic autonomic nervous systems to HR modulation [33] and calculated the ratio of the low (LF: 0.04-0.15 Hz) to high frequency (HF: 0.15-0.40 Hz) RRI spectral powers (LF/HF). LF oscillations of RRI are considered to be mediated by combined sympathetic and parasympathetic activity, while HF oscillations in RRI are associated with respiratory sinus arrhythmia and reflect parasympathetic activity [31,34]. The LF/HF ratio can be considered a measure of the sympathovagal balance [35]. According to Ewing [36], we evaluated the initial response to orthostasis as the '30 : 15' ratio (i.e., the ratio between the highest RRI around the 30th heart beat and the lowest RRI around the 15th heart beat after tilting). We averaged SBP, DBP and MBP values over the 5-minute period in the supine position and the 5-minute period of head-up tilt and calculated SBP, DBP and MBP responses to orthostatic stress as blood pressure changes (differences) from baseline (ΔSBP, ΔDBP, ΔMBP). Additionally, we determined the lowest SBP (SBP_{min}) and DBP (DBP_{min}) values during the first 3 minutes of tilt. Orthostatic hypotension was diagnosed if there was a fall in SBP (ΔSBP_{min}) of 20 mm Hg or more or in DBP (ΔDBP_{min}) of 10 mm Hg or more (i.e. $\Delta SBP_{min} \leq -20$ mm Hg or $\Delta DBP \leq -10$ mm Hg) during the first 3 minutes of head-up tilt [37].

Statistical analysis

Categorical variables (e.g. gender, prevalence of orthostatic hypotension) were statistically assessed using the χ^2 test. Continuous variables were first tested for normal distribution using the Kolmogorov-Smirnoff test. To compare the normally distributed continuous variables between 'fallers' and 'non-fallers' at the study entry, we used the Student's t-test. The Mann-Whitney U-test was used in cases where the variables were not normally distributed. To assess changes in cardiovascular parameters after the follow-up period in each patient group, we used paired Student's t-test or the Wilcoxon signed rank test where appropriate. The level of statistical significance was set at $p < 0.05$.

Results

Baseline

Basic demographic and clinical characteristics of study participants at the time of entry are shown in Table 1. There was no significant difference between 'fallers' and 'non-fallers' with regard to age, gender distribution, daily levodopa dose, PD duration, total and motor UPDRS scores, or the MMSE scores. In the ultrasound examination of carotid and vertebral arteries, atherosclerotic plaques were found in a similar number of 'fallers' (63.2%) and 'non-fallers' (56.0%); these changes, however, were not associated with blood flow disturbances within the insonated arteries in any of the

Table 1. Clinical characteristics and baseline cardiovascular variables of study participants recorded during supine rest at the time of entry into the study

	Fallers (n = 20)	Non-fallers (n = 33)	Total (n = 53)
Gender [male/female]	8/12	21/12	29/24
Age [years]	66 (53-80)	66 (39-76)	66 (39-80)
Disease duration [years]	5 (1-14)	5 (2-15)	5 (1-15)
Levodopa dose [mg]	800 (100-1300)	600 (0-1400)	600 (0-1400)
UPDRS total score	51 (18-80)	45 (15-81)	47 (15-81)
UPDRS part III score	30 (11-53)	28 (0-48)	28 (0-53)
MMSE score	27.3 (17-30)	28.4 (22-30)	28.0 (17-30)
Comorbidity			
Ischaemic heart disease	7 (35%)	11 (33%)	18 (34%)
Hypertension	11 (55%)	10 (30%)	21 (40%)
Diabetes mellitus	3 (15%)	3 (9%)	6 (11%)
Heart rate [bpm]	69.7 ± 7.8	74.3 ± 8.1	72.6 ± 6.9
RR-CoV	0.036 ± 0.012	0.034 ± 0.009	0.035 ± 0.013
SBP [mm Hg]	125.5 ± 8.5	123.2 ± 6.8	124.1 ± 9.3
DBP [mm Hg]	73.7 ± 9.1	75.4 ± 5.5	74.8 ± 7.3
MBP [mm Hg]	91.1 ± 8.9	93.2 ± 6.1	91.3 ± 8.7

Values are medians with ranges, absolute numbers with percentages or means ± standard error of the mean
UPDRS – Unified Parkinson's Disease Rating Scale, MMSE – Mini Mental State Examination, RR-CoV – coefficient of variation of RR intervals, SBP, DBP, MBP – systolic, diastolic, and mean blood pressures, respectively

study participants. Furthermore, prevalence of cervical spine instability, as demonstrated by the functional X-ray examination, did not differ between the group of 'fallers' (35.0%) and 'non-fallers' (33.3%). Side-to-side differences of above 20% in vestibular function were observed in a similar percentage of PD patients with falls (30.0%) and those who did not report falls (27.8%).

In 2 of the 53 patients, we only assessed blood pressure changes, but did not perform HRV analysis, because of chronic atrial fibrillation in one case (female, 74, 'faller') and an implanted cardiostimulator in another (male, 69, 'non-faller'). At the time of entry, there was no difference in HR, RR-CoV, SBP, DBP or MBP between the two patient groups, either at rest or upon tilting. In contrast, LF/HF ratios were significantly lower in 'fallers' than in 'non-fallers', both at rest and during head-up tilt (24.9 ± 6.2 vs. 37.1 ± 5.5 at rest, $p = 0.035$; 18.1 ± 3.1 vs. 42.1 ± 12.3 during tilt, $p = 0.012$). Upon tilting, 'fallers' and 'non-fallers' presented with similar responses of HR, SBP, DBP, and MBP as well as similar 30 : 15 ratios. Maximum decreases in SBP and DBP during the first 3 minutes of orthostatic stress (i.e. changes from supine SBP and DBP values to their minima during head-up tilt) [37] did not differ between the two groups. Furthermore, prevalence of orthostatic hypotension was similar in 'fallers' and 'non-fallers'.

Follow-up

Patients were followed up for 12-25 months (median, 18 months). According to their reports on falls experienced within the follow-up period, we identified three distinct subgroups of patients. Those who fell neither before nor after the enrolment were classified as 'non-fallers' (n = 23), those who had had falls before and kept falling after the enrolment as 'chronic fallers' (n = 15, 6 males), those who started to fall after enrolment into the study as 'new fallers' (n = 10, 5 males). Five patients who had falls, but did not report any falls during the follow-up period, were excluded from further analyses because of the small sample size. In the non-fallers group, mean age was 62.4 ± 8.9 years; median PD duration was 6.5 years (range, 2-15); median levodopa dose was 550 mg (range, 0-1200). Mean age in the chronic fallers group was 65.9 ± 9.1 years, median

Table 2. Changes in cardiovascular variables after 12-25 months of follow-up in 53 patients with Parkinson disease

	Baseline	Follow-up	*P*-value
ΔHR (tilt – rest)	8.9 ± 1.1	6.5 ± 0.8	0.028
RR-CoV (rest)	0.035 ± 0.002	0.029 ± 0.002	0.048*
RR-CoV (tilt)	0.043 ± 0.003	0.033 ± 0.003	0.002*
ΔLF/HF (tilt – rest)	0.4 ± 5.4	5.6 ± 5.1	NS*
30 : 15 ratio	1.091 ± 0.007	1.084 ± 0.009	NS
ΔSBP (tilt – rest)	–11.7 ± 9.8	–13.8 ± 11.3	NS
ΔDBP (tilt – rest)	–3.9 ± 3.4	–3.6 ± 3.2	NS
ΔMBP (tilt – rest)	–6.5 ± 4.3	–2.8 ± 2.1	NS
ΔSBP_{min} (tilt – rest)	–17.5 ± 12.0	–16.1 ± 11.8	NS
ΔDBP_{min} (tilt – rest)	–6.8 ± 9.1	–6.2 ± 8.8	NS
Number of patients with orthostatic hypotension	24 (45.3%)	21 (39.6%)	NS**

*Values are means ± standard error of the mean or absolute numbers with percentages. P-values are derived from paired t-test unless otherwise indicated (*Wilcoxon signed rank test, **χ^2 test)*
ΔHR – tilt-induced heart rate change, RR-CoV – coefficient of variation of RR intervals, LF/HF – ratio of low to high frequency powers of RR oscillations,
ΔSBP, ΔDBP, ΔMBP – tilt-induced changes in systolic, diastolic, and mean blood pressures, ΔSBP_{min}, ΔDBP_{min} – greatest falls in systolic and diastolic blood pressures during tilt

PD duration was 4 years (range 1-14), median levodopa dose was 800 mg (range 100-1100). In the new fallers group, mean age was 64.2 ± 9.4 years, median PD duration 5 years (range, 2-10), and median levodopa dose 600 mg (range, 0-1400). Again, the groups did not differ with regard to age, gender, duration of the disease, or levodopa dose.

In all study patients, mean values of HR, SBP, DBP, and MBP at rest and during tilting did not change after the follow-up period as compared to the first visit. Similarly, tilt-induced responses of blood pressure expressed as changes from supine rest did not differ between the first and the second visit. Furthermore, prevalence of orthostatic hypotension did not change significantly during the follow-up period. In contrast, HR responses to head-up tilt decreased significantly from 8.9 ± 1.1 bpm at study entry to 6.5 ± 0.8 bpm after the follow-up period (paired t-test, $p = 0.028$). Time domain analysis of HRV performed at study onset and after the follow-up period revealed a decrease both in RR-CoV assessed at rest (from 0.035 ± 0.002 to 0.029 ± 0.002, Wilcoxon signed rank test, $p = 0.048$), and during tilt (from 0.043 ± 0.003 to 0.033 ± 0.003, Wilcoxon signed rank test, $p = 0.002$). The LF/HF ratios, however, did not change after the follow-up period.

Analysing the three patient groups separately, we observed similar changes in total UPDRS, the motor part of UPDRS and in MMSE scores among non-fallers, chronic fallers, and new fallers over the follow-up period, as compared to the first visit. Cardiovascular variables within the group of chronic fallers remained unchanged during the follow-up period. In contrast, new fallers presented with a significant decrease in HR responses to head-up tilt (from 11.4 ± 2.6 bpm during the first visit to 5.4 ± 1.4 bpm during the second visit, paired t-test, $p = 0.025$). However, there was a significant decrease in RR-CoV assessed during tilting both in the non-fallers and new fallers (non fallers: 0.044 ± 0.005 during the first visit vs. 0.033 ± 0.004 after the follow-up, Wilcoxon signed rank test, $p = 0.002$; new fallers: 0.048 ± 0.009 vs. 0.032 ± 0.007, Wilcoxon signed rank test, $p = 0.002$). Additionally, only in the new fallers group was the tilt-induced change (difference) in RR-CoV from supine baseline significantly reduced at study closure (0.001 ± 0.006) as compared to study entry (0.014 ± 0.007, Wilcoxon signed rank test, $p = 0.014$). Mean values of HR, SBP, DBP, and MBP at rest and upon tilting, the LF/HF and 30 : 15 ratio, or the prevalence of orthostatic hypotension did not change significantly during the follow-up period in any of the patient groups. Detailed results of the prospective part of the study are shown in Tables 2 and 3.

Discussion

We found that HR, but not blood pressure, responses to orthostatic stress deteriorate in patients with PD, as demonstrated by a reduction in orthostatic HR increases observed after the follow-up period. Furthermore, HR variability also decreased with time, both at rest and during head-up tilt, as indicated by the changes in RR-CoV. Conversely, we did not observe any reduction in the 30 : 15 ratio, known as a marker of early HR responses to orthostasis, in our group of patients. This may be explained by the fact that in our patients, orthostatic stress was induced by passive tilting, while the 30 : 15 ratio best describes cardiac responses to more rapid changes in the cardiovascular system typically occurring during active standing [31,36]. Slower, gradual tilting may not have elicited sufficiently pronounced initial orthostatic stress to appropriately evaluate early HR responses accounting for the 30 : 15 variable [36,38]. Yet, most patients with PD are unable to quickly stand up from the supine position because of bradykinesia. Therefore, we used a tilt table to evaluate cardiovascular responses to orthostatic stress. In this setting, changes in mean values of HR or variables calculated using longer, several-minute recordings, such as RR-CoV, seem to better describe cardiac orthostatic responses [31,38].

In our study, we demonstrated that the reduction in orthostatic HR responses occurred in those PD patients who started to experience falls. Interestingly, we did not observe such changes in non-fallers or even in patients who kept falling for a longer time (chronic fallers). This may suggest that the onset of falls in PD is preceded by a deterioration of cardiac responses to orthostatic stress. It seems possible that an impaired parasympathetic adaptation to the upright posture might account for early falls in PD patients. In contrast, we did not find any differences in BP values and their responses to tilting over the follow-up period in any group of study participants. The prevalence of orthostatic hypertension also remained unchanged. This suggests that the association between aggravation of orthostatic hypotension and falls in PD patients does not seem to be straightforward. Moreover,

Table 3. Changes in cardiovascular variables after 12-25 months of follow-up in three groups of patients with Parkinson disease (non-fallers, chronic fallers and new fallers)

	Non-fallers (n = 23)			Chronic fallers (n = 15)			New fallers (n = 10)		
	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value
ΔHR [bpm]	9.1 ± 1.8	8.3 ± 1.5	NS	7.2 ± 1.9	5.6 ± 1.3	NS	11.4 ± 2.6	5.4 ± 1.4	0.025
RR-CoV (rest)	0.034 ± 0.003	0.030 ± 0.003	NS*	0.039 ± 0.007	0.027 ± 0.003	NS*	0.033 ± 0.004	0.031 ± 0.006	NS*
RR-CoV (tilt)	0.044 ± 0.005	0.033 ± 0.004	0.001*	0.044 ± 0.007	0.036 ± 0.005	NS*	0.048 ± 0.009	0.032 ± 0.007	0.004*
ΔRR-CoV	0.010 ± 0.005	0.003 ± 0.003	NS*	0.005 ± 0.006	0.009 ± 0.003	NS*	0.014 ± 0.007	0.001 ± 0.006	0.019*
ΔLF/HF [%]	+11.4 ± 10.9	+9.1 ± 9.7	NS*	–7.1 ± 6.3	+5.6 ± 10.0	NS*	–9.0 ± 8.7	–0.3 ± 6.3	NS*
30 : 15 ratio	1.09 ± 0.01	1.09 ± 0.01	NS	1.09 ± 0.02	1.08 ± 0.02	NS	1.11 ± 0.02	1.08 ± 0.01	NS
ΔSBP [mm Hg]	–11.26 ± 8.7	–15.30 ± 11.2	NS	–13.53 ± 10.0	–11.99 ± 9.2	NS	–10.31 ± 8.1	–14.58 ± 11.2	NS
ΔDBP [mm Hg]	–1.19 ± 0.9	–3.84 ± 2.2	NS	–4.00 ± 2.8	–3.27 ± 2.7	NS	–7.59 ± 4.7	–4.27 ± 2.5	NS
ΔMBP [mm Hg]	–4.54 ± 3.6	–4.90 ± 4.1	NS	–7.18 ± 5.4	–2.24 ± 3.7	NS	–8.50 ± 5.9	–1.31 ± 1.4	NS
ΔSBP_{min} [mm Hg]	–14.8 ± 7.3	–15.0 ± 8.4	NS	–21.5 ± 16.8	–18.5 ± 15.3	NS	–17.2 ± 9.8	–16.1 ± 10.8	NS
ΔDBP_{min} [mm Hg]	–4.3 ± 2.5	–4.1 ± 2.0	NS	–10.1 ± 8.6	–9.6 ± 8.4	NS	–6.1 ± 3.2	–5.9 ± 3.7	NS
Number of patients with orthostatic hypotension	8 (34.8%)	8 (34.8%)	NS**	9 (60%)	6 (40%)	NS**	4 (40%)	4 (40%)	NS**

*P-values are derived from paired t-test unless otherwise indicated (*Wilcoxon signed rank test, **χ^2 test), ΔHR – tilt-induced heart rate change, RR-CoV – coefficient of variation of RR intervals, ΔRR-CoV – tilt-induced changes in RR-CoV reflecting changes in RRI variability in response to orthostasis, LF/HF – ratio of low to high frequency powers of RR oscillations, ΔLF/HF – tilt-induced changes in LF/HF, ΔSBP, ΔDBP, ΔMBP – tilt-induced changes in systolic, diastolic, and mean blood pressures, ΔSBP_{min}, ΔDBP_{min} – greatest falls in systolic and diastolic blood pressures during tilt*

studies conducted so far did not identify orthostatic hypotension as a risk factor for falls in PD [17,20, 26,39]. The findings that orthostatic hypotension does not contribute to falls may be related to the fact that blood pressure falls in PD are moderate and, unlike in MSA, are rarely associated with severe orthostatic intolerance [40-43]. Changes in BP are normally counteracted by changes in cerebrovascular resistance to maintain stable cerebral blood flow, i.e. by the mechanisms of cerebral autoregulation [38]. Relatively limited orthostatic falls in blood pressure observed in PD might be compensated by cerebral autoregulation, thus preventing occurrence or at least limiting symptoms of orthostatic intolerance. Indeed, cerebral autoregulation was found to be preserved in patients with PD despite impaired control of systemic circulation [41,44]. While blood pressure responses during orthostatic stress depend on the sympathetic activity and changes in peripheral vascular resistance, heart rate changes during orthostatic stress are mainly vagally mediated and contribute to a lesser extent to blood pressure [31,38]. However, the contribution of heart rate to maintaining blood pressure becomes more important in the elderly [31,45], especially since the sympathetic tone decreases with age [46]. Therefore, the attenuation of HR response to orthostatic stress in PD patients who have started to experience falls, observed in our study, might in part explain the mechanisms of at least some falls in PD. Because vagally mediated changes in HR account for early, short-term changes in blood pressure [31,38], certain more abrupt changes in body position during everyday life of PD patients might induce blood pressure alterations that are not readily compensated by HR changes, thus possibly contributing to transient decreases in cerebral blood flow resulting in presyncope and reduction in postural tone. Responses of cerebral resistance vessels might also be less pronounced, as cerebral autoregulation better counteracts oscillatory than phasic changes in blood pressure [47-50].

In our study, we evaluated both falls and autonomic function in PD in a prospective manner, whereas there have been no data describing the effects of progression of cardiovascular disturbances on falls in PD. Previous studies investigating predictive risk factors for falls in PD were based exclusively on baseline measurements of autonomic system function, i.e. measurements that were not repeated during the follow-up period [22,26,39]. Nevertheless, several studies on HRV measures in PD do, in part, support our findings. In a study by Niehaus *et al.*, head-up tilt provoked smaller HR increases in PD patients than in healthy subjects [41]. Mihci *et al*. demonstrated marked reductions in multiple time-domain parameters as well as in LF and HF of orthostatic HRV in patients, as compared to controls [14]. Other authors found the VLF, LF and HF spectral components of HRV in PD to be also decreased in conditions of daily living, using 24-hour ambulatory ECG monitoring [51,52]. Another study documented a reduction in the diurnal LF power and the LF/HF ratio along with a nocturnal decrease in the HF power in more advanced stages of PD [53]. In our patients, LF/HF ratios differed at baseline between the fallers and non-fallers, with fallers having lower values at rest and upon tilting than non-fallers. We observed, however, no change in the LF/HF ratio among study participants over the follow-up period. Simultaneous reduction in both LF and HF components of RRI oscillations may explain this finding.

Prevalence of orthostatic hypotension in our study ranged from near 35% in non-fallers and 40% in new fallers to 60% in chronic fallers. According to a recent meta-analysis by Goldstein, there are many discrepancies with respect to the evaluation of this condition in PD patients [54]. Various authors use different diagnostic criteria and assess different PD populations. However, studies conforming to the Consensus Committee criteria [37] report orthostatic hypotension prevalence of 30-58%, which is similar to our findings [42, 55-58]. Despite the relatively high prevalence of orthostatic hypotension in PD, the majority of patients with orthostatic hypotension do not experience pronounced symptoms of orthostatic intolerance [42,43], which was also observed in our study. Furthermore, although there is evidence of a positive correlation between the magnitude of orthostatic falls in BP and PD severity or duration [15,16], only symptomatic orthostatic hypotension seems to be related to duration of the disease or daily levodopa dose [42]. This is in accordance with our study results, which did not demonstrate any progression of orthostatic hypotension over the period of 18 months. Moreover, only one of the study participants reported frequent episodes consistent with symptomatic orthostatic hypotension and this could be attributed to treatment with an alpha-antagonist.

Because of the large number of concomitant disorders in the screened PD population, patients with conditions known to affect autonomic function were not excluded from the study. Arterial hypertension, ischaemic heart disease and diabetes mellitus may all have biased the study results. Some of the study participants

received pharmacotherapy for benign prostate hyperplasia, pain and depression, known to affect the autonomic nervous system. Nevertheless, the proportion of patients suffering from diseases other than PD was similar in all study groups. Modification of anti-Parkinson treatment was allowed during the follow-up period if required; thus some of the results may be due to the modified treatment and not to the natural course of PD. Yet, modifications of levodopa or dopamine agonist dosages were similar across the study groups and thus unlikely to have affected the incidence of falls in our patients. Furthermore, our study participants were followed up for approximately 18 months. Considering the slow progression of both motor and autonomic deterioration in PD, such a short follow-up period may not have been sufficient to obtain a complete picture of the associations between the cardiovascular autonomic system and the motor function in PD.

Several factors possibly contributing to falls, such as vestibular dysfunction, large vessel disease, or changes in the cervical spine, that were also found in our patients might have affected our results. Moreover, atherosclerosis in the carotid arteries may affect baroreflex control [59]. However, a similar number of patients with these conditions was found in each group and, therefore, it is unlikely that these co-morbidities had any significant impact on the differences observed among the subgroups of our PD patients. Furthermore, pathological changes observed in the carotid arteries were relatively small and were not associated with stenosis or blood flow disturbances.

The question why further deterioration was not observed in chronically falling patients is still open. It seems possible that the onset of falls in PD patients occurs when the cardiac autonomic impairment reaches a certain threshold. We do not know whether, after having passed the threshold, the deterioration stops or merely slows down. Extension of the follow-up period might answer this question.

Dysfunction of cerebral autoregulation might be another mechanism that contributes to falls in PD. However, a study investigating both cardiovascular and cerebrovascular regulation in PD patients during tilting showed that while the autonomic circulatory control is impaired during both rest and head-up tilt, cerebral autoregulation remains intact [41]. This may also explain why no effect of blood pressure on falls was observed in our or other studies. However, it is not known whether cerebral autoregulation is preserved to a similar degree in falling and non-falling PD patients or whether control of the cerebral vessels changes over time in PD. It might be beneficial to perform a prospective study that employs measurements of indices of cerebral autoregulation in falling and non-falling patients with PD.

Conclusion

Our study demonstrated that in PD, cardiac responses to orthostatic stress deteriorate with disease progression and that this deterioration might contribute to falls, whereas orthostatic blood pressure responses, although reduced, remain unchanged over longer periods of time and are not associated with falls in PD.

Disclosure

Authors report no conflict of interest.

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