JMD
http://dx.doi.org/10.14802/jmd.16001 / J Mov Disord 2016;9(2):97-103
pISSN 2005-940X / eISSN 2093-4939

ORIGINAL ARTICLE

Cardiovascular Autonomic Dysfunction in Mild and Advanced Parkinson's Disease

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ABSTRACT

Objective The purpose of the present study was to investigate cardiovascular autonomic dysfunction in patients with Parkinson's disease (PD) with mild to severe stages of motor symptoms and to compare cardiovascular autonomic dysfunction between drug-naïve and dopaminergic drug-treated groups.

Methods This study included 188 PD patients and 25 age-matched healthy controls who underwent head-up tilt-testing, 24-h ambulatory blood pressure (BP) monitoring and 24-h Holter monitoring. Autonomic function test results were evaluated among groups categorized by motor symptom severities (mild vs. moderate vs. severe) and treatment (drug-naïve or dopaminergic drug treatment).

Results Orthostatic hypotension and supine hypertension were more frequent in patients with PD than in healthy controls. The frequencies of orthostatic hypotension, supine hypertension, nocturnal hypertension and non-dipping were not different among groups. Additionally, no significant differences were detected in supine BP, orthostatic BP change, nighttime BP, nocturnal BP dipping, or heart rate variabilities among groups.

Conclusions Cardiovascular autonomic dysfunction is not confined to moderate to severe PD patients, and starts early in the course of the disease in a high proportion of PD patients. In addition, dopaminergic drug treatments do not affect cardiovascular autonomic function.

Key Words Parkinson's disease; Autonomic dysfunction; Cardiovascular; Symptom severity; Dopaminergic treatment.

Cardiovascular autonomic dysfunctions are commonly observed in Parkinson's disease (PD), and some of these abnormalities can cause disabling symptoms in many patients. These include orthostatic hypotension (OH), supine hypertension (SH), nocturnal hypertension (NH), labile blood pressure (BP), absence of decrease in BP during the night ("non-dipping"), and heart rate variability (HRV).[1,2]

These abnormalities are interrelated in patients with PD. SH is found in a considerable proportion of untreated PD patients with OH.[3-5] Although drugs to treat PD can exert hemodynamic effects (mainly decreased BP from systemic vasodilation), cardiovascular autonomic abnormalities observed in PD can occur independently of drug treatment.[6]

A few studies have shown that OH in patients with PD was associated with disease duration and severity and with the use of high daily levodopa dose or other dopaminergic drugs.[6-9] However, results have been inconsistent and have not provided a clear pathophysiological mechanism. There were no comprehensive studies addressing cardiovascular autonomic function in the early and late stage of disease.

The purposes of the present study were 1) to investigate cardiovascular autonomic dysfunction in patients with mild to severe PD and 2) to evaluate cardiovascular autonomic dysfunction between drug-naïve and dopaminergic drug treated groups.

Received: January 5, 2016 **Revised:** February 27, 2016 **Accepted:** March 4, 2016
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MATERIALS & METHODS

Patients

This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital and a waiver of consent was obtained for a Health Insurance Portability and Accountability Act-compliant retrospective study. The study included 188 diagnosed PD patients. The clinical diagnosis of PD was made according to the UK Brain Bank criteria.[10] At the time of the study, 55 patients had taken dopaminergic medications for PD. Twenty-five age-matched healthy subjects free from neurological disease were enlisted to serve as controls.

Clinical information included age, sex, symptom duration, history of arterial hypertension, diabetes mellitus, cigarette smoking, and current medication. All patients were evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) part I–III and classified by modified Hoehn and Yahr (H&Y) stage. Positron emission tomography using ^{18}F-N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane was used to exclude suspected cases of secondary Parkinsonism.

Excluded from the study were patients: 1) with a history of diabetic neuropathy or other peripheral/autonomic neuropathy; 2) with a history of neuropathy or other previous relevant cardiac disease, or any abnormalities on routine chest radiography or electrocardiography; and 3) who were taking medications known to influence cardiovascular autonomic functions except anti-parkinsonian medications.

All BP and heart rate tests were performed after discontinuing any antihypertensive medications for more than 7 days (7.4 ± 0.3 days); during this period, no serious clinical problems were observed. In 55 patients, dopaminergic medications were continued during the tests.

Tilt testing

Continuous electrocardiographic and noninvasive BP monitoring leads were connected for each patient (YM6000, Mediana Tech, Redmond, WA, USA). After 30 min of supine rest, the head-up tilt test (20 min at 60°) was performed using the Manumed Special Tilt 1-section (ENRAF NONIUS, Rotterdam, the Netherlands). BP was obtained every 5 minutes before and 1, 3, 5, 10, 15, and 20 minutes during tilt, 1 minute post-tilt, and as indicated for patient safety. The mean supine baseline and lowest tilt values for BP were then recorded. For statistical analyses, the lowest values recorded between 3 and 5 minutes were selected. OH was defined as a decline of at least 20 mm Hg in systolic blood pressure (SBP) and/or 10 mm Hg in diastolic BP as measured between 2 and 5 minutes after tilting.[11,12] Subjects with systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg were categorized as having SH.[5,13,14]

Ambulatory blood pressure monitoring

Automated 24-h BP recording instruments (Mobil-O-Graph NG, I.E.M., Stolberg, Germany) were used to measure ambulatory BP every 15 min during the day and every 30 min at night. Average SBP and diastolic BP and heart rate during the daytime, nighttime, and over 24-h periods was evaluated. Nocturnal falls in BP and heart rate were reported as percent changes between daytime and nighttime mean values. Subjects with a < 10% nocturnal fall in mean BP were considered "non-dippers".[15] NH was defined according to the 2007 European Hypertension Society/European Cardiology Society guidelines (i.e., average nighttime BP ≥ 120/70 mm Hg).[16,17]

Heart rate variability analysis

In all subjects, 24-h Holter monitoring was conducted using an Aria recorder. The recordings were subsequently analyzed with the Impresario Solo system (Delmar Reynolds, Hertford, UK). While being monitored, participants were instructed to maintain their normal daily routines while recording their activities in diaries. The participants also recorded the number of hours of night rest. Time-domain analyses of HRV were also conducted for all participants.

Time-domain HRV analyses were derived from a direct measurement of normal-to-normal R-R over a 24-hour period. The following time-domain HRV parameters were calculated: normal R-R interval means (mRR); N-N interval standard deviations (SDNN); 5-min standard deviation N-N interval duration means (SDNN index); root mean square successive N-N deltas (RMS-SD); the difference in percentile between adjacent normal R-R intervals greater than 50 ms (pnn50); and 5-min means of N-N interval standard deviations (SDANN).[18] The first three parameters reflect both sympathetic and parasympathetic functions. The next two parame-

ters are associated with parasympathetic function specifically, and the final is related to sympathetic function only.[18]

Data analysis

Patients were initially stratified to a mild motor symptom group (modified H&Y stage score 1 and 1.5), a moderate motor symptom group (modified H&Y stage score 2 and 2.5), or a severe motor symptom group (modified H&Y stage score ≥ 3). We also grouped patients into a drug-naïve patient group or a dopaminergic drug-treated group ("treated" group). Independent means *t*-tests, one-way analyses of variance or analyses of covariance and Pearson's χ^2 tests were used to make comparisons between groups. The relationships among the levodopa-equivalent dose and the duration of dopaminergic drugs and cardiovascular autonomic functions were assessed with Spearman's rank correlation test. Statistical tests were performed using SPSS 15.0 software for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

RESULTS

Of the 188 patients, 101 (53.7%) were women. The mean age (± standard deviation) was 68.4 ± 10.4 years, and the mean disease duration was 3.4 ± 3.7 years. Total UPDRS and H&Y stage scores were 27.2 ± 25.2 and 1.8 ± 0.9, respectively.

Patients with PD frequently exhibited OH (PD vs. controls, 29.8% vs. 4.0%, $\chi^2 = 7.487$, $p = 0.006$) and SH (PD vs. controls, 31.4% vs. 12.0%, $\chi^2 = 4.107$, $p = 0.045$) compared to controls. In addition, the PD group tended to have more NH than controls (PD vs. controls, 25.0% vs. 8.0%, $\chi^2 = 3.600$, $p = 0.058$).

In the patient group, OH was associated with NH (OH vs. no OH = 35.7% vs. 20.5%, $\chi^2 = 4.883$, $p = 0.027$) and non-dipping (OH vs. no OH = 91.1% vs. 77.3%, $\chi^2 = 4.941$, $p = 0.026$). NH was also related to SH (NH vs. no NH = 72.3% vs. 17.7%, $\chi^2 = 48.818$, $p < 0.001$) and non-dipping (NH vs. no NH = 95.7% vs. 76.6%, $\chi^2 = 8.531$, $p = 0.003$).

Among the patients with PD, 106 had mild and unilateral disease (modified H&Y stage score 1 and 1.5), 51 had moderate and bilateral disease (modified H&Y stage score 2 and 2.5), and 31 had severe motor symptoms (modified H&Y stage score ≥ 3).

Table 1. Demographics of age-matched controls and patients with Parkinson's disease stratified by motor symptom severities

	Controls (n = 25)	Mild (H&Y 1 or 1.5, n = 106)	Moderate (H&Y 2 or 2.5, n = 51)	Severe (H&Y ≥ 3, n = 31)	p	Post-hoc comparison				
						Controls vs. mild	Controls vs. moderate	Controls vs. severe	Mild vs. moderate	Mild vs. severe	Moderate vs. severe
Age, yr	67.4 ± 10.9	66.1 ± 10.9	71.8 ± 8.6	70.5 ± 9.9	0.003	1.000	0.392	1.000	0.004	0.152	1.000
No. of men (%)*	6 (24.0)	57 (53.8)	16 (31.4)	14 (45.2)	0.009						
Disease duration, yr	–	2.2 ± 2.5	4.5 ± 4.4	5.8 ± 4.3	< 0.001	-	-	-	< 0.001	< 0.001	0.297
Hypertension (%)*	6 (24.0)	41 (38.7)	19 (37.3)	9 (29.0)	0.467						
Used antihypertensive agents	ARB 4, CCB 2	ARB 22, CCB 15, ACE 3, DU 1	ARB 13, CCB 5, no use 1	ARB 3, CCB 2, no use 4							
Diabetes mellitus (%)*	4 (16.0)	8 (7.5)	11 (21.6)	3 (9.7)	0.077						
Current or ex-smoker (%)*	7 (28.0)	23 (21.7)	8 (15.7)	4 (12.9)	0.427						
UPDRS	-	16.8 ± 11.5	31.3 ± 15.6	64.2 ± 30.4	< 0.001	-	-	-	< 0.001	< 0.001	< 0.001
UPDRS part 1	-	1.9 ± 1.9	2.8 ± 1.8	4.6 ± 3.3	< 0.001	-	-	-	0.110	< 0.001	0.005
UPDRS part 2	-	5.2 ± 4.0	8.8 ± 5.5	19.8 ± 11.0	< 0.001	-	-	-	0.002	< 0.001	< 0.001
UPDRS part 3	-	9.6 ± 7.1	19.7 ± 10.2	39.8 ± 19.6	< 0.001	-	-	-	< 0.001	< 0.001	< 0.001
H&Y	-	1.1 ± 0.2	2.2 ± 0.2	3.2 ± 0.5	< 0.001	-	-	-	< 0.001	< 0.001	< 0.001

Values represent the mean with standard deviation or numbers of patients (percentage), *analyses were performed by one-way analysis of variance with Bonferroni post-hoc comparison or by χ^2 test. H&Y: Hoehn & Yahr stage, ARB: angiotensin II receptor blocker, CCB: calcium channel blocker, ACE: angiotensin converting enzyme inhibitor, DU: diuretics, UPDRS: Unified Parkinson's Disease Rating Scale.

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Table 2. Blood pressure and heart rate monitoring results of age-matched controls and patients with Parkinson's disease stratified by motor symptom severities

	Controls (n = 25)	Mild (H&Y 1 or 1.5, n = 106)	Moderate (H&Y 2 or 2.5, n = 51)	Severe (H&Y ≥ 3, n = 31)	p	Post-hoc comparison					
						Controls vs. mild	Controls vs. moderate	Controls vs. severe	Mild vs. moderate	Mild vs. severe	Moderate vs. severe
Orthostatic hypotension, n (%)*	1 (4.0)	31 (29.2)	16 (31.4)	9 (29.0)	0.056						
Supine hypertension, n (%)*	3 (12.0)	31 (29.2)	16 (31.4)	12 (38.7)	0.168						
Non-dipper, n (%)*	19 (76.0)	86 (81.1)	40 (78.4)	27 (87.1)	0.717						
Nocturnal hypertension, n (%)*	2 (8.0)	28 (26.4)	9 (17.6)	10 (32.3)	0.102						
Supine SBP	122.5 ± 14.1	129.1 ± 19.5	132.1 ± 16.2	137.4 ± 21.5	0.028	0.409	0.288	0.017	1.000	0.322	0.921
ΔSBP during tilt	3.3 ± 9.0	13.1 ± 17.6	12.3 ± 16.0	15.5 ± 17.6	0.012	0.011	0.136	0.022	1.000	1.000	1.000
Nighttime SBP	107.1 ± 11.6	111.7 ± 15.0	112.0 ± 14.7	115.9 ± 14.7	0.135	0.655	1.000	0.114	1.000	1.000	1.000
Dipping	7.5 ± 6.8	4.4 ± 14.2	3.2 ± 7.6	1.0 ± 6.9	0.150	0.964	0.536	0.157	1.000	0.988	1.000
SD SBP, day	12.0 ± 4.8	13.7 ± 4.4	13.9 ± 5.0	13.9 ± 4.1	0.362	0.769	0.514	1.000	1.000	1.000	1.000
SD SBP, night	10.0 ± 3.1	12.1 ± 4.5	12.2 ± 5.2	12.2 ± 3.2	0.196	0.305	0.308	0.428	1.000	1.000	1.000
HRV of all qualified beats (SDNN)	120.9 ± 24.9	125.8 ± 36.3	117.9 ± 46.9	110.3 ± 40.4	0.379	1.000	1.000	1.000	1.000	0.559	1.000
RMS of successive NN deltas (RMS-SD), msec	32.1 ± 18.3	42.7 ± 44.2	46.5 ± 63.1	37.8 ± 47.7	0.573	1.000	0.965	1.000	1.000	1.000	1.000
SD of successive NN delta (SDSD), msec	25.0 ± 17.5	31.9 ± 31.9	33.1 ± 41.9	28.5 ± 32.4	0.681	1.000	1.000	1.000	1.000	1.000	1.000
Triangular index (HRV index)	18.1 ± 3.8	18.0 ± 5.7	16.2 ± 6.1	18.9 ± 20.7	0.757	1.000	1.000	1.000	1.000	1.000	1.000
Triangular interpolation (TINN), msec	534.4 ± 137.7	557.5 ± 173.9	495.4 ± 189.9	446.6 ± 177.3	0.026	1.000	1.000	0.352	0.345	0.030	1.000
Mean RR, msec	824.4 ± 80.7	884.1 ± 117.0	847.5 ± 126.6	836.2 ± 122.9	0.128	0.325	1.000	1.000	1.000	0.474	1.000
pnn50, %	4.6 ± 3.7	9.1 ± 15.1	11.2 ± 21.2	7.9 ± 16.8	0.414	1.000	0.564	1.000	1.000	1.000	1.000
Mean of interval HRVs (SDNN index), msec	35.3 ± 9.3	20.4 ± 24.2	18.8 ± 35.4	17.8 ± 19.6	0.053	0.063	0.097	0.218	1.000	1.000	1.000
SD of interval rates (SDANN), bpm	10.4 ± 2.1	9.5 ± 3.0	9.1 ± 2.7	9.4 ± 3.7	0.316	1.000	0.395	1.000	1.000	1.000	1.000
SD of interval rates (SDANN), msec	113.4 ± 26.2	112.4 ± 36.9	104.7 ± 36.5	101.9 ± 34.2	0.349	1.000	1.000	1.000	1.000	0.751	1.000

Values represent the mean with standard deviation or numbers of patients (percentage). *analysis was performed by analyses of covariance controlling age, sex, hypertension, and diabetes mellitus or by χ^2 test. H&Y: Hoehn & Yahr stage, SBP: systolic blood pressure, SD: standard deviation, HRV: heart rate variability, SDNN: N-N interval standard deviations, mean RR: mean normal R-R interval means, pnn50: the difference percentile between adjacent normal R-R intervals that are greater than 50 ms, SDNN index: 5-min standard deviation N-N interval duration means, SDANN: 5-min means of N-N interval standard deviations.

Patients with severe motor symptoms were older and with a longer disease duration. As expected, they scored higher on the UPDRS than mild and moderate groups (Table 1). The proportion of OH (mild vs. moderate vs. severe = 29.2% vs. 31.4% vs. 29.0%, $\chi^2 = 0.085$, $p = 0.959$), SH (mild vs. moderate vs. severe = 29.2% vs. 31.4% vs. 38.7%, $\chi^2 = 0.998$, $p = 0.607$), NH (mild vs. moderate vs. severe = 26.4% vs. 17.6% vs. 32.3%, $\chi^2 = 2.455$, $p = 0.293$) and non-dipping (mild vs. moderate vs. severe = 81.1% vs. 78.4% vs. 87.1%, $\chi^2 = 0.966$, $p = 0.617$) did not vary among groups (Table 2). There were no significant differences among the three groups regarding supine BP, orthostatic ΔSBP, nighttime BP, nocturnal BP dipping, or HRV (Table 2).

Fifty-five patients were being treated with dopaminergic drugs (39: levodopa + dopamine agonist; 16: levodopa only). As expected, the treated group had a longer disease duration, higher UPDRS and higher H&Y stage score than the drug-naïve group (Table 3). The frequency of OH, SH, NH, and non-dipping were not different between the treated group and drug-naïve group (Table 4). Levodopa-equivalent dose and duration of dopaminergic treatment were not correlated with supine BP, orthostatic ΔSBP, nighttime BP, or nocturnal BP dipping, and almost HRV domains (Table 5). The treated group had a tendency towards higher supine BP and lower nocturnal BP dipping although these results were not statistically significant. The treated group also had similar heart rate variations in the almost time domains compared to controls (Table 4).

DISCUSSION

The present study found that cardiovascular autonomic dysfunctions were neither related to parkinsonian motor symptom severity nor the use of dopaminergic drugs.

Cardiovascular autonomic dysfunctions are frequent in patients with PD, manifesting mainly as dizziness, faintness, orthostatic intolerance, and syncope. These abnormalities are also associated with cognitive impairments, white matter hyperintensity, carotid wall thickening, and mortality.[1,5,19-21] Cardiovascular autonomic dysfunction may result from myriad episodes of cerebral hypo- and hyper-perfusion, contributing to microvascular injury. These dysfunctions in PD are associated with sympathetic

Table 3. Demographics of patients with Parkinson's disease categorized by dopaminergic drug treatment

	Drug-naïve (*n* = 133)	On dopaminergic treatment (*n* = 55)	*p*
Age, yr	67.9 ± 10.5	69.5 ± 10.3	0.335
No. of men (%)*	66 (49.6)	21 (38.2)	0.151
Disease duration, yr	2.0 ± 2.4	7.0 ± 4.0	< 0.001
Hypertension (%)*	56 (42.1)	13 (23.6)	0.017
Diabetes mellitus (%)*	17 (12.8)	5 (9.1)	0.474
Current or ex-smoker (%)*	30 (22.6)	5 (9.1)	0.031
Duration of treatment, yr	-	6.0 ± 3.6	
Levodopa-equivalent dose, mg	-	513.5 ± 302.4	
UPDRS	24.5 ± 18.0	34.1 ± 29.5	0.021
UPDRS part 1	2.4 ± 2.1	3.0 ± 2.4	0.004
UPDRS part 2	7.0 ± 6.2	10.9 ± 9.2	< 0.001
UPDRS part 3	15.1 ± 11.6	20.1 ± 19.2	0.057
Hoehn & Yahr stage	1.6 ± 0.7	2.1 ± 1.0	< 0.001

Values represent the mean with standard deviation or numbers of patients (percentage). *analyses were performed by independent sample *t*-test or by χ^2 test. UPDRS: Unified Parkinson's Disease Rating Scale.

Table 4. Blood pressure and heart rate monitoring results with Parkinson's disease categorized by dopaminergic drug treatment

	Drug-naïve (*n* = 133)	On dopaminergic treatment (*n* = 55)	*p*
Orthostatic hypotension, *n* (%)*	36 (27.1)	20 (36.4)	0.205
Supine hypertension, *n* (%)*	39 (29.3)	20 (36.4)	0.344
Non-dipper, *n* (%)*	106 (79.7)	47 (85.5)	0.356
Nocturnal hypertension, *n* (%)*	31 (23.3)	16 (29.1)	0.405
Supine SBP	129.4 ± 18.8	135.7 ± 19.5	0.080
ΔSBP during tilt	12.4 ± 16.8	15.4 ± 17.9	0.588
Nighttime SBP	111.6 ± 14.2	114.6 ± 16.3	0.263
Dipping	4.6 ± 13.0	1.0 ± 7.7	0.117
SD SBP, day	13.9 ± 4.6	13.5 ± 4.3	0.428
SD SBP, night	12.2 ± 4.5	12.0 ± 4.5	0.768
HRV of all qualified beats (SDNN)	127.2 ± 41.0	106.6 ± 35.4	0.003
RMS of successive NN deltas (RMS-SD), msec	43.2 ± 52.0	42.0 ± 45.7	0.777
SD of successive NN delta (SDSD), msec	31.6 ± 35.7	31.8 ± 32.4	0.650
Triangular index (HRV index)	17.8 ± 5.7	17.5 ± 16.1	0.904
Triangular interpolation (TINN), msec	544.9 ± 182.3	469.1 ± 174.5	0.017
Mean RR, msec	873.7 ± 123.6	848.9 ± 116.0	0.238
pnn50, %	9.6 ± 17.2	9.0 ± 16.8	0.863
Mean of interval HRVs (SDNN index), msec	17.7 ± 24.2	24.0 ± 32.0	0.077
SD of interval rates (SDANN), bpm	10.6 ± 9.1	8.3 ± 2.4	0.311
SD of interval rates (SDANN), msec	115.1 ± 35.6	93.2 ± 33.8	< 0.001

Values represent the mean with standard deviation or numbers of patients (percentage). *analysis was performed by analyses of covariance controlling age, sex, hypertension, and diabetes mellitus or by χ^2 test. SBP: systolic blood pressure, SD: standard deviation, HRV: heart rate variability, SDNN: N-N interval standard deviations, mean RR: mean normal R-R interval means, pnn50: the difference percentile between adjacent normal R-R intervals that are greater than 50 ms, SDNN index: 5-min standard deviation N-N interval duration means, SDANN: 5-min means of N-N interval standard deviations.

Table 5. Simple correlation analysis results between the levodopa-equivalent dose and the duration of dopaminergic drugs and cardiovascular autonomic functions

	Levodopa-equivalent dosage	Duration of dopaminergic treatment
Supine SBP	0.200 (0.143)	-0.049 (0.724)
ΔSBP during tilt	-0.230 (0.091)	-0.029 (0.831)
Nighttime SBP	0.115 (0.408)	0.152 (0.273)
Dipping	-0.093 (0.504)	-0.128 (0.355)
SD SBP, day	-0.175 (0.204)	-0.070 (0.617)
SD SBP, night	-0.078 (0.576)	-0.062 (0.655)
HRV of all qualified beats (SDNN)	-0.065 (0.682)	0.063 (0.691)
RMS of successive NN deltas (RMS-SD), msec	-0.026 (0.871)	-0.038 (0.810)
SD of successive NN delta (SDSD), msec	-0.065 (0.681)	-0.115 (0.470)
Triangular index (HRV index)	-0.063 (0.693)	-0.026 (0.869)
Triangular interpolation (TINN), msec	-0.108 (0.495)	0.027 (0.867)
Mean RR, msec	0.093 (0.557)	0.330 (0.033)*
pnn50, %	-0.103 (0.516)	-0.090 (0.572)
Mean of interval HRVs (SDNN index), msec	-0.017 (0.917)	-0.133 (0.401)
SD of interval rates (SDANN), bpm	-0.113 (0.477)	-0.179 (0.258)
SD of interval rates (SDANN), msec	-0.023 (0.885)	0.156 (0.324)

Data are *r* (*p* value) of the correlation. Analyses were performed using Spearman's rank correlation analysis. *$p < 0.05$. SBP: systolic blood pressure, SD: standard deviation, HRV: heart rate variability, SDNN: N-N interval standard deviations, mean RR: mean normal R-R interval means, pnn50: the difference percentile between adjacent normal R-R intervals that are greater than 50 ms, SDNN index: 5-min standard deviation N-N interval duration means, SDANN: 5-min means of N-N interval standard deviations.

noradrenergic neurons, resulting in cardiac and extra-cardiac noradrenergic denervation.[22] As with the Braak et al.[23] schema for the pathogenetic sequence in synucleinopathies, the progression of midbrain alpha-synuclein disease manifests in cognitive/mood and autonomic disturbances and sleep disorders. Therefore, we can speculate that patients with late stage PD would have a greater impairment in these autonomic test variables. However, this was not the case. Previous studies indicated that sympathetic noradrenergic dysfunctions occur independently of striatal dopamine transporter uptake, which is associated with the motor features of PD.[24] These suggest that cardiovascular autonomic symptoms are related to a different pathophysiology than that of PD motor symptoms.

A number of studies have investigated cardiovascular autonomic dysfunction irrespective of levodopa treatment. Many researchers have supposed that cardiovascular autonomic dysfunction in patients with PD was associated with the use of levodopa and/or dopamine agonists.[25] However, the results have been contradictory; some studies suggested that OH is associated with levodopa treatment and others did not.[6-8] In this study, the chronic dopaminergic treatment did not influence cardiovascular autonomic functions. Because the present study was carried out in a large group of patients with PD and the procedures for assessing cardiovascular autonomic function of PD were very comprehensive, we can suggest that the cardiovascular autonomic abnormalities associated with PD occur independently of levodopa treatment.

Our study also has several limitations. First, because the study design was cross-sectional, we did not compare autonomic function tests before and after dopaminergic treatment. Additional longitudinal studies would be needed to confirm the hemodynamic effects of dopaminergic drugs. Second, our results should be interpreted cautiously because the chronic use of anti-hypertensive medication can contribute to OH. In addition, because patents were tested after discontinuing antihypertensive medications for more than 7 days, the tested autonomic parameters could have been affected by drug withdrawal. Finally, a discrepancy of sample numbers between patients and controls could be a limitation for interpreting this study. The severe motor symptom group and control group were relatively smaller than the mild symptom group.

In conclusion, cardiovascular autonomic dysfunction is frequent in PD, it is not confined to late stage patients, and it begins early in the course of the disease in a high proportion of patients. In addition, levodopa treatments might not affect cardiovascular autonomic functions. These findings have potential implications for a targeted therapeutic approach in PD.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgments

The authors wish to acknowledge the financial support of the Catholic Medical Center Research Foundation in the program year of 2014.

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