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Title: Sudomotor and cardiovascular dysfunction in patients with early untreated Parkinson's disease

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ABSTRACT

BACKGROUND: According to Braak staging of Parkinson's disease (PD), detection of autonomic dysfunction would help with early diagnosis of PD.

OBJECTIVE: To determine whether the autonomic nervous system is involved in the early stage of PD, we evaluated cardiovascular and sudomotor function in early untreated PD patients.

METHODS: Orthostatic blood pressure regulation, heart rate variability, skin vasomotor function, and palmar sympathetic sweat responses were examined in 50 early untreated PD patients and 20 healthy control subjects.

RESULTS: The mean decrease in systolic blood pressure during head-up tilt in PD patients was mildly but significantly larger than in controls ($p = 0.0001$). There were no differences between the 2 groups in heart rate variability, with analysis of low frequency (LF; mediated by baroreflex feedback), and high frequency (HF; mainly reflecting parasympathetic vagal) modulation. However, LF/HF, an index of sympatho-parasympathetic balance, was lower in the PD group than in controls ($p = 0.02$). Amplitudes of palmar sweat responses to deep inspiration ($p = 0.004$), mental arithmetic ($p = 0.01$), and exercise ($p = 0.01$) in PD patients were lower than in controls, with negative correlations with motor severity. Amplitudes of palmar skin vasomotor reflexes in PD patients did not differ from controls.

CONCLUSIONS: Our study indicates impairment of sympathetic cardiovascular and sudomotor function with orthostatic dysregulation of blood pressure control, reduced LF/HF and reduction in palm sweat responses even in early untreated PD patients.

Key words: Parkinson's disease, autonomic nervous system, cardiovascular system, sudomotor function

1. Introduction

Non-motor features of Parkinson's disease (PD) are increasingly being defined, with a considerable number attributable to dysfunction of the autonomic nervous system. Autonomic abnormalities in PD may result from the disease itself and/or be caused by anti-parkinsonian medication. They are known to be more prevalent in advanced PD, but also may occur in early stages of the disease[1, 2]. Certain autonomic features, such as constipation, can precede the onset of motor symptoms [3]. A proposed six-stage pathological staging of PD suggests a predictable sequence of lesions with ascending progression from medullary or olfactory nuclei to the cortex. The first two stages are correlated with incidental Lewy body disease, or non-motor symptoms, such as hyposmia and constipation [4-6]. Several studies using ^{123}I-meta-iodobenzylguanidine (MIBG) scintigraphy indicate that cardiac sympathetic denervation occurs in early PD [7] suggesting predominant peripheral cardiovascular autonomic involvement. Lewy body pathology may initially occur in the autonomic nervous system [5]. To determine whether the autonomic regulation is involved in the early stages of PD, we investigated orthostatic blood pressure regulation, heart rate variability and skin vasomotor and sudomotor function, as measures of autonomic cardiovascular and sudomotor activity in PD patients who had not been treated with anti-Parkinsonian drugs.

2. Subjects and Methods

2.1 Subjects

Participants included 50 untreated PD patients (mean age 64.2 ± 8.9 years, 28 men and 22 women, disease duration 1.8 ± 1.4 years).Modified Hoehn & Yahr stage [8] ranged from 1 to 3 (mean 1.62 ± 0.69). All met the criteria of the United Kingdom Brain Bank [9]. None were taking anti-parkinsonian drugs or any medication that could affect autonomic function. Brain MRI scans were performed in all patients, and there were no findings to indicate other neurodegenerative disorders, such as multiple system atrophy and ischemic lesions. Twenty

age-matched healthy volunteers (mean age, 63.7 ± 7.9 years; 10 men and 10 women) were examined as controls. None were taking any medications that could affect autonomic function, or had any neurologic disorders or clinically significant illnesses that could affect autonomic nervous function, including hypertensive or chronic heart disease. Participants were recruited from 2008 to 2010. All patients were under regular follow up (intervals of 4 or 8 weeks) for at least 2 years after the study and clinical diagnosis of PD was further confirmed by their response to dopaminergic therapy and exclusion of atypical features. All participants were recruited in Chiba University Hospital. Informed consent was obtained from all participants. The ethics committee of Chiba University School of Medicine approved the protocol and all procedures.

2.2 Evaluation of autonomic nervous system function

Details of autonomic symptoms were obtained in all patients by a neurologist. Cardiovascular, sudomotor, bowel and bladder autonomic symptoms were evaluated with a non-validated questionnaire in PD patients. Postural symptoms included dizziness, visual disturbance and syncope. Urinary symptoms included storage [urinary urgency, daytime urinary frequency (>8 times /day), nocturia (> once/night) and incontinence] and voiding (urinary hesitancy and feeling of incomplete emptying) symptoms.

Autonomic function testing was performed in a quiet room at an ambient temperature of 22–26°C. Each subject was asked to relax, stay awake, and remain in a supine position for at least 15 min before each test. Before, during and after head-up tilt, blood pressure and heart rate were measured by a sphygmomanometer (BP-8800FS; Nihon Colin Co., Tokyo, Japan) at 1-min intervals. After 5 min of baseline measurement, each subject was passively tilted on an electrically driven tilt table to 70° for 10 min. Orthostatic hypotension was defined as a reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least

10 mmHg within 3 min of tilting [10]. In addition, 'late' orthostatic hypotension was diagnosed when blood pressure fell after 3 min of tilting [11]. For evaluating heart rate variability, the electrocardiogram was recorded with the subject in a supine position as 300 consecutive R-R intervals with an accuracy of 1 ms during normal breathing. As an index of time-domain analysis, the coefficient of variation of R-R intervals (CV_{R-R}) was calculated as the standard deviation divided by the mean of 100 R-R intervals. The average of 3 series was used as the CV_{R-R} value. An abnormal CV_{R-R} value was judged according to age-matched data from our laboratory (data not shown). Power spectral analysis of 300 R-R intervals was computed using fast Fourier transformation. The power spectrum was quantified into frequency-domain measurements; high-frequency oscillations (HF, 0.15–0.4 Hz) and low frequency oscillations (LF, 0.04–0.14 Hz) were estimated from the spectra. In addition the ratio between low-frequency and high-frequency oscillations (LF/HF) was calculated [12].

As indices of sudomotor and skin vasomotor function, the sympathetic sweat response (SSwR) and skin vasomotor reflex (SkVR) were recorded [13, 14]. Sweat output was measured on the tip of the thumb (palm side) by a sudorometer (SKD-1000, Skinos, Japan), and cutaneous blood flow was measured at the tip of an index finger (palm side) by a Doppler flowmeter (ALF21D, Advance, Japan) during sympathetic activation that included deep inspiration, mental arithmetic (serial 7 subtraction), and exercise (raising both lower limbs to 30° for 10 s). These procedures increase sweat output (SSwR) and reduce cutaneous blood flow (SkVR). The SSwR amplitude was measured from the baseline to the peak response, and the SkVR reduction rate was calculated as the percentage of the peak reduction in blood flow from basal blood flow [(reduced flow/basal flow) × 100%].

2.3 Statistical methods

Comparisons between 2 groups were analyzed using the Mann-Whitney U test. Spearman correlation coefficients were used to examine the relationship between disease duration or modified Hoehn & Yahr stage and results of autonomic function tests. Significance was set at 0.05.

3. Results

Clinical features of autonomic dysfunction included postural symptoms (lightheadedness) in 2 out of 50 PD patients (4%), constipation in 23 (46%), and urinary symptoms (frequency or urgency) in 18 (36%). There were no significant differences in baseline blood pressure and heart rate while supine between the PD and control groups (**Table 1**). During head-up tilt, orthostatic hypotension occurred in 4 PD patients (8 %), and 'late' orthostatic hypotension was identified in 4 PD patients (8 %). These 9 patients were asymptomatic during head-up tilting, but one patient with orthostatic hypotension and one with 'late' orthostatic hypotension had a history of recurrent lightheadedness according to the questionnaire. The decrease in systolic blood pressure during head-up tilt in PD was significantly greater than in controls ($p = 0.0001$). There were no significant differences in the changes in diastolic blood pressure and heart rate between the 2 groups (**Table 1**).

Abnormally low values of $CV_{R\text{-}R}$ were observed in 3 PD patients (6 %). The $CV_{R\text{-}R}$ values in PD patients (2.21 ± 1.37 %) did not significantly differ from that of the controls (2.14 ± 0.89 %). There were no significant differences in LF and HF between the PD (128.7 ± 240.1 ms^2 and 122.4 ± 304.0 ms^2) and control (117.7 ± 91.0 ms^2 and 52.1 ± 49.8 ms^2) groups, while the LF/HF ratio in the PD group (1.88 ± 1.45) was significantly lower than that in controls (3.4 ± 2.38, $p = 0.01$, **Fig. 1**).

There was no significant difference in baseline sweat output between the PD (0.21 ± 0.19 ml/cm^2/min) and controls (0.22 ± 0.11 ml/cm^2/min). SSwRs were evoked in all controls, while 3 PD patients (6%) showed absent SSwR for all of the procedures. SSwR amplitudes in PD patients were significantly lower than in controls for deep inspiration (0.17 ± 0.24 ml/cm^2/min vs. 0.35 ± 0.33 ml/cm^2/min, p = 0.007), mental arithmetic (0.23 ± 0.27 ml/cm^2/min vs. 0.41 ± 0.37 ml/cm^2/min, p = 0.02), and exercise (0.21 ± 0.23 ml/cm^2/min vs. 0.41 ± 0.35 ml/cm^2/min, p = 0.02, **Fig. 2**). There was no significant difference in baseline skin blood flow between the groups. SkVRs were evoked in all controls and PD patients. The SkVR amplitudes in PD did not differ from those in controls (**Table 1**). **Table 2** shows the correlations between the results of autonomic function tests and the disease duration or severity. The modified Hoehn & Yahr stage was significantly and negatively correlated with the SSwRs for deep inspiration, mental arithmetic and exercise ($p < 0.05$), and the modified Hoehn & Yahr stage tended to be positively correlated with the LF/HF ratio ($p = 0.05$) in the PD group. Age was significantly and negatively correlated with changes in diastolic blood pressure during head-up tilting, SSwRs for deep inspiration and exercise and $CV_{R\text{-}R}$ in the PD group. Age also showed a negative correlation with $CV_{R\text{-}R}$ in the control group. There were no significant differences in any parameters of autonomic tests between male (n = 28) and female (n = 22) patients, between patients with (n = 39) and without (n = 11) tremor or between PD patients with (n = 23) and without (n = 27) constipation.

4. Discussion

Post-mortem studies in the premotor phase of PD suggest that Lewy body pathology initially appears in anterior olfactory structures, the dorsal motor nucleus of the vagal nerve [4-6], paravertebral sympathetic chain [15] and the enteric nervous system [16]. Because cardiac parasympathetic nerves arise from the dorsal motor nucleus of the vagal nerve, cardiac parasympathetic function may be impaired in the early or premotor phase of PD. However, our

study in early PD did not find abnormalities in the HF component, which mainly reflects respiratory sinus arrhythmia mediated by parasympathetic vagal nerves. Our results support previous studies on the HF component in untreated PD patients, where the HF component was preserved [17, 18], except for one study [19], where the HF component was mildly but significantly reduced. Early untreated PD patients do not appear to have severe parasympathetic cardiac dysfunction. The unchanged HF components suggest that the proposed pathology in the dorsal motor nucleus of the vagus nerve was not overtly present in our group of early PD patients, and may thus is not consistent with the Braak staging hypothesis. Another possibility is that compensatory mechanisms may help maintain cardiovascular autonomic control, despite involvement of the dorsal motor nucleus. As an example, vagal control after unilateral vagotomy is recovered by peripheral and central compensatory changes in the intact contralateral vagus nerve in rabbits [20]. Thus, function observed may not proportionally reflect pathological change. Alternatively, analysis of heart rate variability has a low sensitivity for detecting cardiac autonomic dysfunction, despite published evidence accepting it in the evaluation of autonomic function [21].

In our study, the LF/HF ratio was reduced in untreated PD patients compared to controls. LF is mainly produced by baroreflex feedback loops, in which cardiac sympathetic modulation plays an important role, and HF mainly reflexes cardiac parasympathetic modulation. Therefore, LF/HF is used as an index of sympatho-parasympathetic balance. The reduced LF/HF in our untreated PD patients imply a predominant parasympathetic drive to the heart. Accumulation of MIBG, which is actively taken up in the sympathetic nerve terminals in the myocardium, is reduced even in the early stages of PD [22], and cardiac sympathetic denervation, also using tyrosine hydroxylase staining, has been pathologically confirmed in incidental Lewy body disease [23]. In addition, LF/HF appeared to show a positive correlation with disease severity (modified Hoehn & Yahr stage). Cardiac sympathetic dysfunction may precede parasympathetic

dysfunction in PD, and parasympathetic activity may be relatively preserved compared with sympathetic activity in the early stages of PD.

Out of our 50 patients, 5 fulfilled the criteria of orthostatic hypotension [10], and an additional 4 patients showed 'late' orthostatic hypotension [11]. However, no patient complained of postural symptoms during head-up tilting. Our results are similar to those in a previous report, where 7 of 51 untreated PD patients (14%) had a decrease in systolic blood pressure of more than 20 mmHg on standing and symptoms of hypotension occurred in only 1 patient [24]. The mean blood pressure fall during head-up tilt testing in the PD group was statistically significant but small. Dysregulation of systemic blood pressure control appears to be mild in the majority of early untreated PD patients. Proposed mechanisms of orthostatic blood pressure dysregulation in PD include central and peripheral lesions [25]. The sympathetic pathway of blood pressure regulation is shown in **Fig. 3A**. In PD patients, Lewy body pathology is observed in the rostral ventrolateral medulla [26-28], which participates in the maintenance of blood pressure [29], and also in the intermediolateral nucleus of the thoracic cord [26]. Lewy body deposition has also been reported in sympathetic ganglia [15, 26], and cardiac MIBG scintigraphy indicates postganglionic sympathetic denervation even in the early stages of PD [22]. Plasma noradrenaline concentrations, which reflect postganglionic sympathetic activity, have recently been reported to be maintained in the early stages of PD [30], but are unlikely to be a sensitive indicator of sympathetic function because of the many processes influencing plasma catecholamine levels. In addition, SkVR amplitudes, an index of sympathetic skin vasoconstriction function [13, 31, 32], were preserved in our PD patients. These findings suggest that functional cardiovascular deficits due to central and peripheral sympathetic lesions are evident but of mild severity in the early stages of PD.

Previous studies in treated PD patients using the SSwR [13, 33] or sympathetic skin responses [34], which is considered to be the electrical reflection of the SSwR [13, 32], report diminished palmar sweat responses. Our study confirmed similar results even in early untreated PD patients. Sweating on the palm is classified as so-called 'emotional sweating'. **Fig. 3B** shows the pathway of emotional sweating [35]. The precise central pathway of palmar sweating remains unclear with the amygdala, anterior cingulate cortex [36], the reticular formation of the brain stem [37] of importance. In addition, the basal ganglia is considered to be important for emotional sweating [35]. In our study, SSwR amplitudes showed a negative correlation with motor dysfunction severity caused by degeneration of the substantia nigra. Our results support previous studies, where sympathetic skin responses were correlated with motor disability in treated PD patients [38-40]. Additionally, in our untreated PD patients, sympathetic cardiovascular dysfunction was mild compared with sudmotor dysfunction. In a previous study, patients with progressive supranuclear palsy, where the substantia nigra is severely affected [41], showed diminished SSwR in spite of an intact autonomic nervous system [13]. It is thought that the basal ganglia participates in the generation of emotional sweating [35]. Thus, the reduced SSwR amplitudes in our PD patients may have reflected dysfunction of the nigrostriatal dopamine pathway as well as lesions in the sympathetic nervous system, such as the nucleus intermediolateralis and sympathetic ganglia [15, 26], the limbic system, such as the amygdala [6], and the reticular formation of the medulla [27].

Our study has revealed impairment of sympathetic cardiovascular and sudomotor function in early untreated PD patients. The findings indicate dysregulation of blood pressure control during head-up tilt, reduced LF/HF (parasympathetic dominancy of cardiac sympatho-sparasympathetic balance) and diminution of the emotional sweat response (SSwR). However, sympathetic cardiovascular dysfunction was mild in our early PD patients. Cemorouardiovascular autonomic function tests may be insufficient as biomarker tools for early

PD detection unlike MIBG scintigraphy. On the other hand, attenuation of SSwR amplitudes was prominent in our early PD patients. Furthermore, reductions in SSwR correlated with disease severity in our PD patients and may reflect nigral dopaminergic deficiency, as well as lesions in the central and peripheral autonomic nervous systems.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Table 1. Results in the head-up tilt test and skin vasomotor reflex.

	PD	Control	p-values
Age	64.2 ± 8.9	63.6 ± 7.9	NS
Sex (M : F)	28 : 22	10 : 10	NS
Disease duratin (year)	1.8 ± 1.4		
Modified Hoehn & Yahr stage	1 ~ 3		
Head-up tilt test			
Supine baseline			
SBP (mmHg)	128.3 ± 17.2	128.3 ± 19.2	NS
DBP (mmHg)	71.8 ± 11.0	74.0 ± 10.7	NS
HR beats/min)	69.3 ± 9.4	67.6 ± 8.1	NS
Changes during head-up tilt			
SBP change (mmHg)	-4.7 ± 11.9	5.9 ± 7.8	P = 0.0001
DBP change (mmHg)	0.7 ± 9.4	2.0 ± 9.5	NS
HR change (beats/min)	7.6 ± 6.3	7.6 ± 6.7	NS
Skin vasomotor reflex			
Baseline skin blood flow (mg/100g/min)	42.3 ± 14.4	40.8 ± 14.5	NS
Reduction rate (%)			
Deep inspiration	53.9 ± 22.9	58.4 ± 18.6	NS
Mental arithmetics	41.8 ± 20.6	40.5 ± 23.3	NS
Exercise	45.8 ± 20.7	46.0 ± 22.2	NS

SBP, systolic blood pressur; DBP, diastolic blood pressur; HR, heart rete

Table 2. Correlation btween results of autonomic function tests and disease duration, severity or age

	Parkinson's disease (n = 50)			Control (n = 20)
	Duration	H&Y stage	Age	Age
SBP change	0.013	-0.191	**-0.388** *	-0.309
DBP change	-0.044	-0.098	-0.240	-0.308
SSwR amplitudes for DI	0.077	**-0.344** *	**-0.486** *	-0.281
SSwR amplitudes for MA	0.031	**-0.344** *	**-0.380** *	-0.300
SSwR amplitudes for Ex	0.008	-0.261	**-0.561** *	-0.063
RR for DI	-0.026	-0.203	0.149	-0.010
RR for MA	-0.010	-0.071	0.073	0.005
RR for Ex	0.105	-0.110	0.152	0.084
LF	0.020	-0.012	-0.245	-0.156
HF	-0.152	-0.169	-0.122	0.044
LF/HF	0.249	0.277	**-0.460** *	-0.243
CV_{RR}	-0.238	-0.127	**-0.529** *	**-0.369** *

Values are shown as r (correlation coefficient). SBP, systolic blood pressure; DBP, diastolic blood pressure; SSwR, sympathetic sweat response; DI, deep inspiration; MA, mental arithmetics; Ex, exercise; RR, reduction rate of skin vasomotor reflex; LF, low frequency component of heart rate variavility; HF, high frequency; CV_{R-R}, coefficient of variation of R-R intervals.

* $p < 0.05$

Figure Legends

Fig 1.

Means of the LF (A), HF (B), LF/HF ratios (C) and $CV_{R\text{-}R}$ (D) in patients with Parkinson's disease (PD) and control healthy subjects. LF, HF and LF/HF are presented as logarithmic transformations.

Fig. 2.

Mean amplitudes in SSwRs for deep inspiration (A), mental arithmetic (B) and exercise (C) in Parkinson's disease (PD) and control healthy subjects.

Fig. 3.

Descending sympathetic pathways for regulation of blood pressure (A), heart rate (B) and palmar sweating (C).

Am: amygdala, In: insular cortex, AC: anterior cingulate cortex, HT: hypothalamus, BG: basal ganglia, FC: frontal cortex, RVLM: rostral ventrolateral medulla, RVMM: rostral ventromedial medulla, IML: intermediolateral nucleus, SG: sympathetic ganglia.

Fig. 1

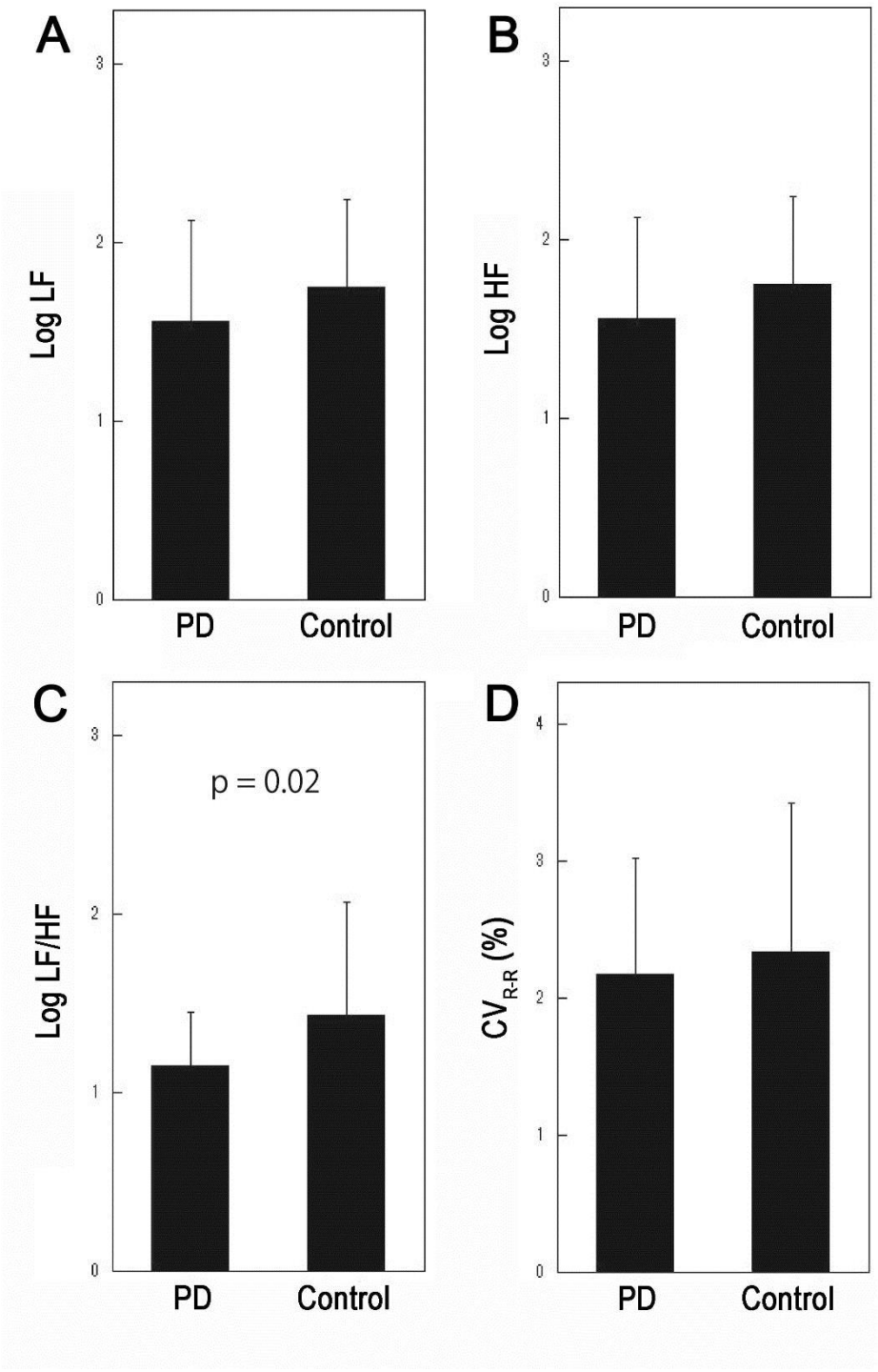

A
Log LF
3
2
1
0
PD
Control
B
Log HF
3
2
1
0
PD
Control
C
Log LF/HF
p = 0.02
3
2
1
0
PD
Control
D
CV R-R (%)
4
3
2
1
0
PD
Control

Fig. 2

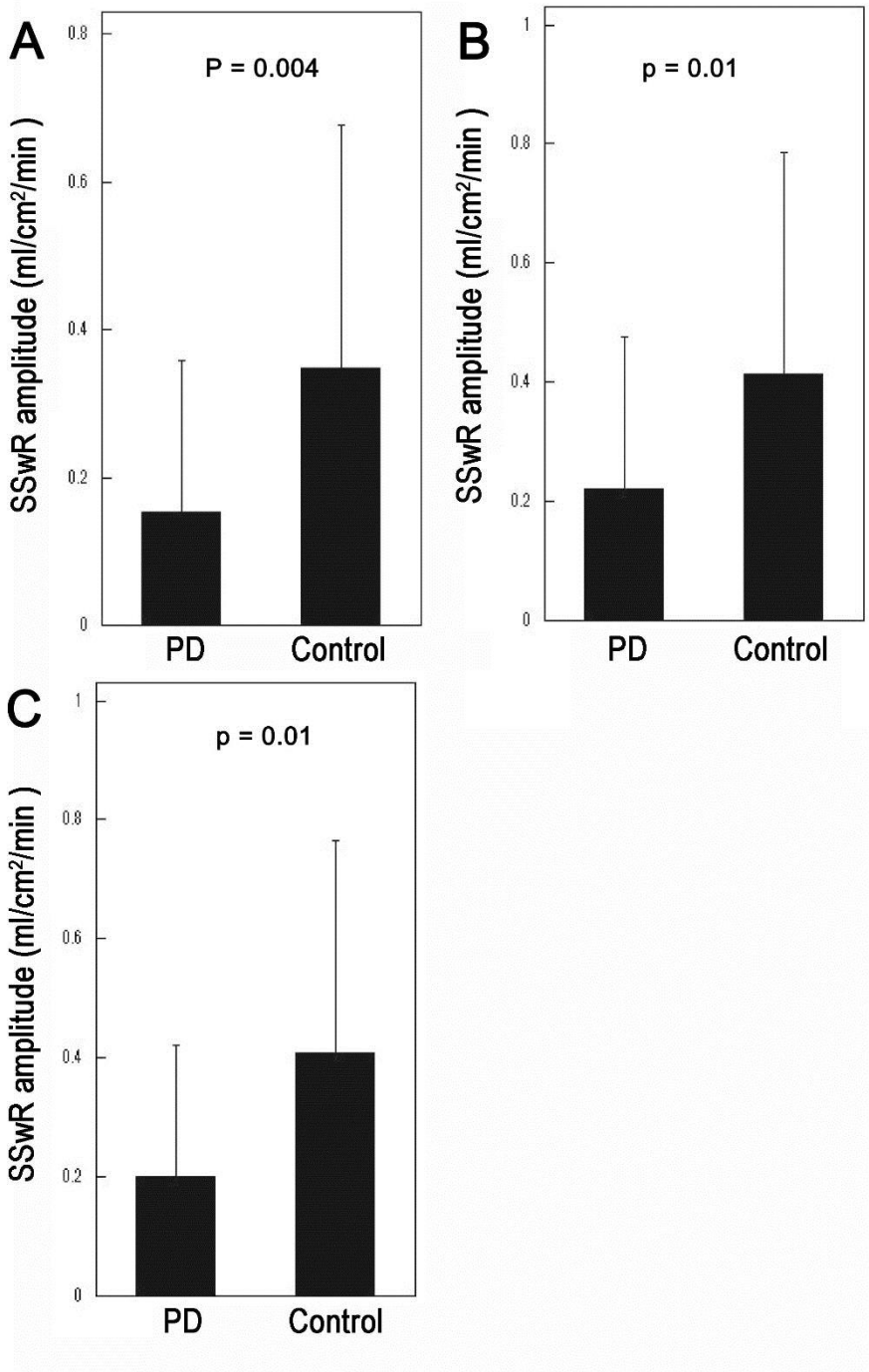
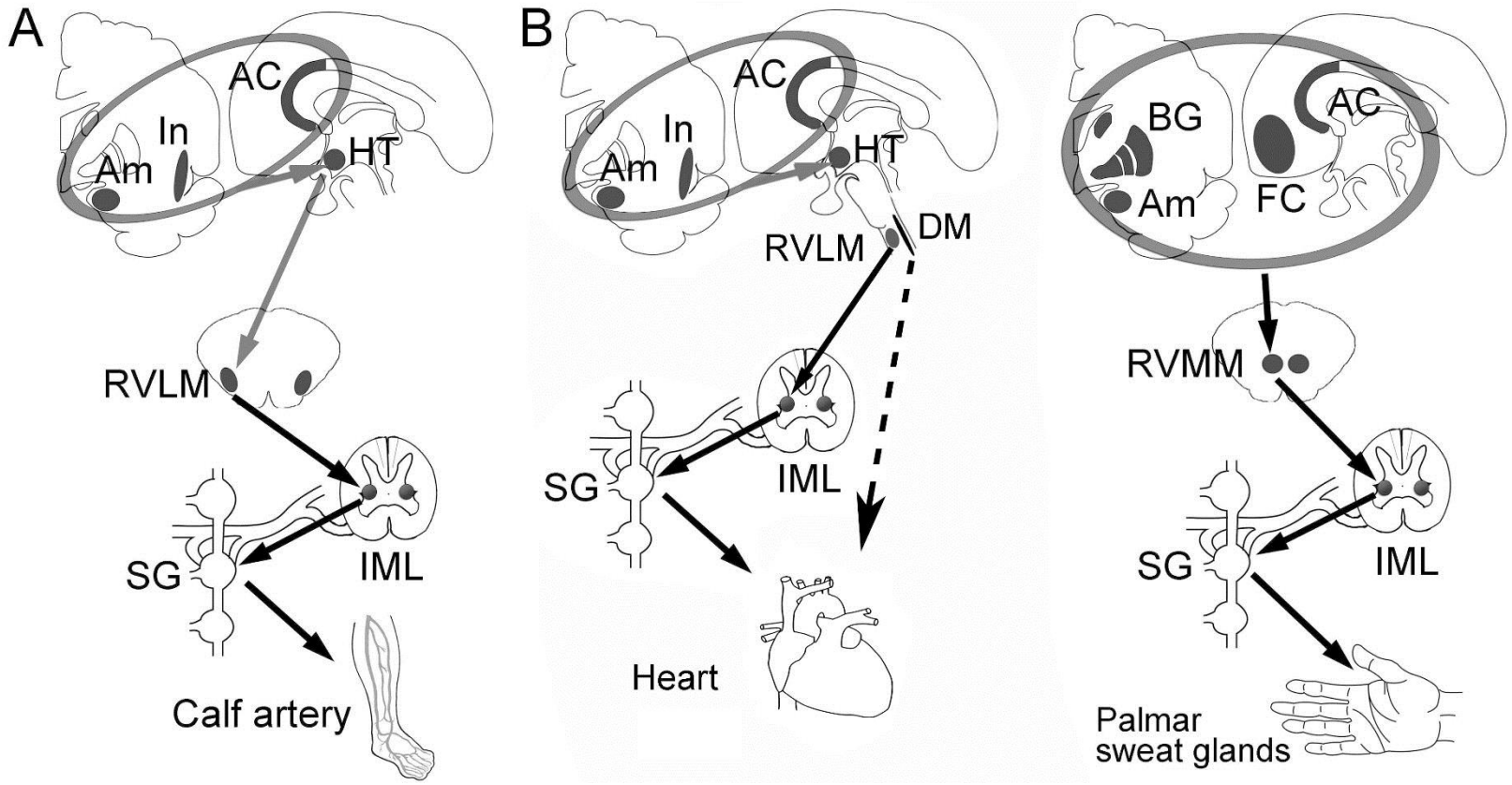

A
P = 0.004
SSwR amplitude (ml/cm²/min)
0.8
0.6
0.4
0.2
0
PD
Control
B
p = 0.01
SSwR amplitude (ml/cm²/min)
1
0.8
0.6
0.4
0.2
0
PD
Control
C
p = 0.01
SSwR amplitude (ml/cm²/min)
1
0.8
0.6
0.4
0.2
0
PD
Control

Fig. 3


A
AC
In
Am
HT
RVLM
SG
IML
Calf artery
B
AC
In
Am
HT
RVLM
DM
SG
IML
Heart
BG
AC
Am
FC
RVMM
SG
IML
Palmar
sweat glands