Cardiovascular dysautonomia in de novo Parkinson’s disease

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Abstract

Background. Clinical symptoms of Parkinson’s disease (PD) include not only motor distress, but also autonomic dysfunction.

Objective. To clarify the progression of autonomic nervous dysfunction in PD.

Methods. The subjects were 44 patients with de novo PD. Autonomic nervous function, including cardiac sympathetic gain, was evaluated on the basis of cardiac radioiodinated metaiodobenzylguanidine (MIBG) uptake, the response to the Valsalva maneuver, and spectral analyses of the RR interval and blood pressure.

Results. Decreased cardiac MIBG uptake was found even in patients with early stage PD. MIBG uptake gradually decreased with increased disease severity. Hemodynamic studies using the Valsalva maneuver revealed that patients with early stage PD had reduced baroreceptor reflex sensitivity (BRS) in phase II, but not phase IV. Blood pressures normally rose in phases II and IV, but the increments decreased with disease progression. In early stage PD, the low frequency power of the RR interval (RR-LF) and the ratio (LF/HF) of RR-LF to the high frequency component of the RR interval (RR-HF) were significantly lower than the respective control values, despite no significant difference in RR-HF; these variables decreased with disease progression.

Conclusion. Our results show that latent sympathetic nervous dysfunction without parasympathetic dysfunction, especially that involving the sinus node, is already present in early stage de novo PD. It is unclear whether the responsible lesion is central or peripheral.

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Keywords. Parkinson’s disease; Cardiovascular sympathetic dysautonomia; Cardiac radioiodinated metaiodobenzylguanidine (123I-MIBG) scintigraphy; Valsalva maneuver; Baroreceptor reflex sensitivity

1. Introduction

Parkinson’s disease (PD) is characterized by resting tremor, rigidity, bradykinesia, and gait disturbance. It is an important degenerative disease because of its high prevalence [1]. The pathological hallmark of PD is loss of nigrostriatal dopaminergic neurons [2]. Significant dysfunction, such as constellation and orthostatic and postprandial hypotension, can occur in progressive PD; however, the autonomic dysfunction in PD is less severe than that in multiple system atrophy [3–6].

Recent studies have shown that sympathetic noradrenergic dysfunction has a clinical importance in PD; orthostatic hypotension occurs in 20–50% of patients with PD and can contribute to falls and other accidental trauma [7–9]. Sympathetic dysfunction due to abnormal cardiac and peripheral sympathetic innervation in patients who have PD with orthostatic hypotension can lead to disturbances resulting from the loss of postganglionic sympathetic nervous fibers; norepinephrine concentrations are lower in these patients than in patients who have PD without orthostatic hypotension [10–12].

Myocardial concentrations of radioiodinated metaiodobenzylguanidine (MIBG) are also decreased in PD [13–15].
MIBG is a physical analogue of noradrenaline that is transported into sympathetic nerve terminals [16]. MIBG imaging has been used to assess efferent postganglionic neuronal function in the heart [17]. Many authors have concluded that the sympathetic nervous disturbance in PD is caused by postganglionic lesions [13 – 15]. However, the pathogenesis of the parasympathetic nervous dysfunction in PD remains unclear. The cardiac parasympathetic nervous system may be relatively preserved in patients with PD. In fact, many studies have shown that the baroreceptor reflex in patients who have early stage PD without orthostatic hypotension is not severely impaired [18 19]. Cardioagal efferent innervation, which produces a reflex bradycardia, is mainly mediated by the nucleus ambiguous, which does not appear to suffer cell loss in patients with PD [20].

The aims of this study were 1) to determine whether cardiovascular dysfunction occurs in previously untreated early stage PD and 2) to examine whether the development of cardiovascular autonomic deregulation involves mainly the sympathetic nervous system, including cardiac and noradrenergic function, or the cardiovascular nervous system.

2. Patients and methods

2.1. Study groups

The subjects were 44 patients with de novo PD (17 men and 27 women, age 66.1 ± 6.3 years, range 41–89 years) with a disease duration of 1–9 years (mean 2 years). The diagnosis of PD was based on the assessments of three neurologists according to the criteria of Calne et al. [21]. The diagnoses were retrospectively confirmed by clinical observation over a period of at least 3 years. No patient had abnormal findings on magnetic resonance imaging, including evidence of brain ischemia, brain stem atrophy, or cerebellar atrophy. All patients were ultimately treated with levodopa or a dopa agonist, to which they had a good response.

Eleven patients had stage I disease, 21 stage II disease, and 12 stage III disease according to the Hoehn–Yahr classification. No patient had signs or symptoms of cardiac disease or any abnormalities on chest radiography, electrocardiography, or cardiac echography. No patient had previously received drugs with potential effects on 123I-MIBG uptake at sympathetic nerve terminals.

2.2. Control group

An age-matched group of 25 persons with no neurological disorders (age 64.8 ± 5.2 years) served as control. None of the controls had clinically significant diseases potentially affecting the cardiac autonomic nervous system, or any form of neurological disorders.

2.3. 123I-MIBG myocardial scintigraphy

All patients and control subjects underwent 123I-MIBG scintigraphy. All examinations were done before they received any therapy for PD (including levodopa, dopa agonists, and other antiparkinson drugs).

The subjects rested in a supine position for 20 min and were given an intravenous injection of 111 MBq 123I-MIBG (Daichi Radioisotope Laboratories Co., Tokyo, Japan). A planar image of the chest was obtained with the use of a double-headed gamma camera (PRISM-AXIS, Shimadzu Co., Japan) after 15 min (early phase) and after 3 h (delayed phase). Photopack energy was centered at 159 keV 123I-MIBG with a 25% window. For the anterior planar image, the data acquisition matrix was 512 × 512, and a presentation time of 3 min was used for image acquisition. Relative organ uptake of 123I-MIBG was determined by region-of-interest (ROI) analysis in the anterior view. The ratio of the average pixel count in the heart (H) to that in the mediastinum (M) was calculated (H/M ratio) after 15 min (early) and after 3 h (delayed). Background subtraction was not performed for any ROI count.

2.4. Hemodynamic autonomic function using the Valsalva maneuver

The Valsalva maneuver was done by having the subjects exhale into a mouthpiece at an expiratory pressure of 40 mm Hg for 15 s. Blood pressure and RR intervals were measured during the Valsalva maneuver by tonometry, using a noninvasive blood pressure monitoring system (CBM3000, Nihon Colin Co., Ltd.) [22,23]. Fig. 1 shows the blood pressure and RR interval changes during the Valsalva maneuver in a control. Fig. 2 shows the measurement of baroreceptor reflex sensitivity (BRS) in the second and fourth phases of the Valsalva maneuver.

Fig. 1. Blood pressure and RR interval changes during the Valsalva maneuver in a control. The upper figure shows systolic (SBP), mean (MBP), and diastolic pressures (DBP). The lower figure shows RR intervals. Hp is the increase of SBP in the late second phase, and IVP is the overshoot of SBP in the fourth phase. The horizontal arrow indicates on and off of the Valsalva maneuver.
2.5. Spectral analysis of the RR interval and systolic blood pressure

RR intervals (RR) and systolic blood pressures (SBP) were recorded continuously by tonometry, using a noninvasive blood pressure monitoring system. The spectral analyses of RR intervals and SBP were performed using the fast Fourier transformation on an IBM computer. A series of 256 consecutive points were analyzed to determine RR intervals and SBP, with the subjects in a supine position after a 20 min rest. ANS508 software (Nihon Colin Co., Ltd.) was used for analysis. The subjects were asked not to cough or breathe deeply during the test, but to breathe regularly (from 10 to 15 times a minute). The areas of the two frequency components of the RR interval (RR) and the low frequency component of the SBP were measured by integration. The low frequency component (LF) of the RR interval (RR-LF) ranged from 0.04 to 0.15 Hz, and the high frequency component (HF) of the RR interval (RR-HF) ranged from 0.15 to 0.4 Hz. The LF of the SBP (SBP-LF) ranged from 0.04 to 0.15 Hz. The ratio of RR-LF to RR-HF (LF/HF) was also calculated.

2.6. Changes in blood pressure and noradrenaline concentrations in serum on a head up tilt test

The SBP and norepinephrine concentrations in serum were measured with the subjects in a supine position after a 20 min rest and in a tilted position (60°) after 10 min on a tilt table. Venous blood was drawn through an indwelling catheter. Plasma concentrations of noradrenaline were assayed by high performance liquid chromatography according to methods validated by SRL Inc.

The ethics committee of Ato Hospital, Jikei University School of Medicine reviewed the protocol, and all subjects gave their informed consent before enrollment.

2.7. Statistical analysis

Data are presented as means ± standard deviation (SD). Statistical analyses were performed with Excel statistical data analysis software (Esumi Co., Ltd.). Groups were compared with the use of Welch’s t test. A p value of <0.05 was considered to indicate statistical significance.

3. Results

3.1. 123I-MIBG myocardial scintigraphy in de novo PD

H/M ratios of the early and delayed images were significantly lower in the patients with PD than in the control subjects (early: 1.77 ± 0.34 (PD) vs. 2.49 ± 0.21 (control), delayed: 1.65 ± 0.42 (PD) vs. 2.40 ± 0.26 (control), p < 0.001 for both). The H/M ratios of the early and delayed images in the patients with PD decreased gradually with an increase in disease severity graded according to Hoehn–Yahr stage (Table 1).

3.2. Hemodynamic autonomic function using the Valsalva maneuver

BRSII and IVp were significantly smaller in patients with PD than in control (BRSII: 1.9 ± 0.8 (PD) vs. 4.3 ± 1.9 (control), IVp: 13.7 ± 7.6 (PD) vs. 21.6 ± 6.9 (control),...
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 25)</th>
<th>PD (n = 44)</th>
<th>Hoehn–Yahr I (n = 11)</th>
<th>II (n = 21)</th>
<th>III (n = 12)</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>68.9 ± 5.3</td>
<td>65.7 ± 6.5</td>
<td>64.6 ± 6.0</td>
<td>69.1 ± 6.9</td>
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<tr>
<td>Early H/M</td>
<td>2.49 ± 0.21</td>
<td>1.89 ± 0.28a</td>
<td>1.83 ± 0.38a</td>
<td>1.57 ± 0.21a</td>
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<tr>
<td>Delay H/M</td>
<td>2.40 ± 0.26</td>
<td>1.76 ± 0.37a</td>
<td>1.74 ± 0.48a</td>
<td>1.40 ± 0.24a</td>
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\* p < 0.01 as compared with control.

\( p < 0.001 \) for both. Ilp was slightly but not significantly smaller in patients with PD than in control (8.3 ± 6.7 (PD) vs. 11.8 ± 4.9 (control), \( p < 0.1 \)). BRSIV did not differ significantly between patients with PD and control (5.2 ± 2.7 (PD) vs. 6.4 ± 1.5 (control)).

BRSII was already reduced in early stage PD (Hoehn–Yahr stage I). BRSIV was preserved in early stage PD, but decreased significantly in Hoehn–Yahr stage III. Ilp and IVP also decreased in association with increasing severity of PD. There were no significant differences between the controls and patients with Hoehn–Yahr stage II or I PD. Ilp and IVP were significantly smaller in patients with Hoehn–Yahr stage III disease than in control (Table 2).

3.3. Spectral analysis of the RR interval and SBP

The RR-LF was significantly lower in patients with PD than in control, irrespective of the Hoehn–Yahr stage of disease. RR-LF decreased with increasing disease severity. RR-HF tended to decrease with increasing disease severity and was significantly lower than control in patients with Hoehn–Yahr stage III PD. As compared with control, LF/HF was already reduced in early stage disease (Hoehn–Yahr stage I). LF/HF was also significantly smaller in patients with Hoehn–Yahr stage II or III disease than in control. LF/HF did not differ significantly according to Hoehn–Yahr stage. SBP-LF was significantly lower in patients with PD than in control (0.29 ± 0.23 (PD) vs. 0.49 ± 0.22 (control), \( p < 0.002 \)). SBP-LF was also significantly lower in patients with Hoehn–Yahr stage III PD than in control, but SBP-LF did not differ significantly between control and patients with Hoehn–Yahr stage I or II PD (Table 3).

Table 2

<table>
<thead>
<tr>
<th>Hemodynamic autonomic function using the Valsalva maneuver</th>
<th>Control (n = 25)</th>
<th>PD (n = 44)</th>
<th>Hoehn–Yahr I (n = 11)</th>
<th>II (n = 21)</th>
<th>III (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRSII (ms/mm Hg)</td>
<td>4.3 ± 1.9</td>
<td>2.0 ± 0.5a</td>
<td>2.1 ± 1.0a</td>
<td>1.6 ± 0.7a</td>
<td></td>
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<tr>
<td>BRSIV (ms/mm Hg)</td>
<td>6.4 ± 1.5</td>
<td>7.2 ± 3.9</td>
<td>5.5 ± 2.2</td>
<td>2.9 ± 1.1b</td>
<td></td>
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<tr>
<td>Ilp (mm Hg)</td>
<td>11.8 ± 4.9</td>
<td>10.6 ± 6.6</td>
<td>8.8 ± 7.3</td>
<td>5.2 ± 4.8a</td>
<td></td>
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<tr>
<td>IVP (mm Hg)</td>
<td>21.6 ± 6.9</td>
<td>15.4 ± 7.1</td>
<td>16.1 ± 8.6</td>
<td>8.2 ± 6.0b</td>
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\* p < 0.02 as compared with control.

\( p < 0.01 \) as compared with control.

Table 3

<table>
<thead>
<tr>
<th>Spectral analyses of RR interval and systolic blood pressure</th>
<th>Control (n = 25)</th>
<th>PD (n = 44)</th>
<th>Hoehn–Yahr I (n = 11)</th>
<th>II (n = 21)</th>
<th>III (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR-LF (ms²)</td>
<td>41.4 ± 24.9</td>
<td>14.3 ± 11.5a</td>
<td>14.1 ± 12.6b</td>
<td>6.6 ± 5.2b</td>
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<tr>
<td>RR-HF (ms²)</td>
<td>34.5 ± 23.5</td>
<td>23.1 ± 19.0</td>
<td>22.6 ± 20.4</td>
<td>7.1 ± 3.7a</td>
<td></td>
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<tr>
<td>LF/HF (ms²)</td>
<td>1.6 ± 0.8</td>
<td>0.8 ± 0.4a</td>
<td>0.7 ± 0.4a</td>
<td>0.8 ± 0.4a</td>
<td></td>
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<tr>
<td>SBP-LF (mm Hg)</td>
<td>0.49 ± 0.22</td>
<td>0.45 ± 0.26</td>
<td>0.29 ± 0.23</td>
<td>0.13 ± 0.10a</td>
<td></td>
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</table>

\* p < 0.05 as compared with control.

\( p < 0.01 \) as compared with control.

3.4. Changes in blood pressure and noradrenaline concentrations in serum on head up tilt test

Blood pressure response during the tilt table test was slightly but not significantly reduced in patients with Hoehn–Yahr stage I or II PD compared with control. The decrease in blood pressure during the tilt table test was not significantly greater than in control. Patients with Hoehn–Yahr stage I PD had slightly higher norepinephrine concentrations in the supine and upright positions than did control. Patients with Hoehn–Yahr stage II PD had slightly lower norepinephrine concentrations than control and patients with Hoehn–Yahr stage III PD. Furthermore, in patients with Hoehn–Yahr stage III PD, norepinephrine concentrations in the supine and upright positions were significantly lower than those in control (Table 4).

4. Discussions

Our results show that the cardiac MIBG uptake of patients with PD was lower than that of control. This finding is in accordance with the results of previous studies [13–15]. In our patients, MIBG uptake was reduced even in early
stage PD. MIBG uptake gradually decreased with increasing disease severity. A reduced norepinephrine level at rest, denervation hypersensitivity to norepinephrine infusions, and reduced cardiac MIBG uptake indicated that the sympathetic failure was caused by postganglionic lesions. MIBG can be used to evaluate cardiac sympathetic denervation because MIBG uptake by myocardial sympathetic nerve terminals is qualitatively similar to norepinephrine uptake [16,17]. Therefore, our MIBG results show that cardiac postganglionic sympathetic dysfunction in patients with PD is already present in early disease.

Our hemodynamic study using the Valsalva maneuver revealed that BRS in phase II but not in phase IV was reduced in patients with early stage PD, whereas the blood pressure responses in phases II and IV were similar to those of control. The shortening of the RR interval in phase II of the Valsalva maneuver is regulated by both the withdrawal of parasympathetic activity and the excitation of sympathetic nerve activity [24–26]. In contrast, elongation of the RR interval in phase IV is caused by parasympathetic nerve activation [27–29]. Previous studies have demonstrated that results obtained with techniques using the Valsalva maneuver are highly reproducible and closely correlated with results obtained by pharmacological methods, such as the phenylephrine or nitroprusside infusion test [27]. We measured BRS by using the Valsalva maneuver, because this method is simple and noninvasive. With pharmacological methods, BRS derived from nitrate-induced decreases in pressure is smaller than that derived from phenylephrine-induced increases in pressure [30]. In our study, BRS in phase II of the Valsalva maneuver was smaller than that in phase IV, even in controls. In patients with early stage de novo PD, BRS was impaired only in phase II and was preserved in phase IV, suggesting that cardiac sympathetic activity to the heart, especially to the sinus node, is reduced without impairing parasympathetic vagal function.

In the Valsalva maneuver, blood pressure elevation during the late second phase (IIp) pharmacologically indicates vasomotor function (vascular sympathetic function), and blood pressure elevation during the fourth phase (IVp) indicates vascular and cardiac sympathetic function (mainly cardiac muscle contraction) [31]. IIp and IVp did not differ significantly between early stage PD and control, but did differ significantly between stage III PD and control. Our findings suggested that vasomotor and cardiac sympathetic functions were not impaired in early disease; however, in stage III PD vasomotor and cardiac dysfunction became obvious.

Blood pressure responses during tilt were similar to control in patients with early disease stage PD, but were significantly decreased in patients with Hoehn–Yahr stage III PD. These findings indicated that orthostatic hypotension occurred even in patients with de novo PD. This orthostatic hypotension was related to the severity of disease and was independent of effects of levodopa on autonomic cardiovascular control. Furthermore, norepinephrine concentra-

Available evidence thus indicates that patients with de novo PD have nearly intact vasomotor sympathetic denervation in early disease, such as Hoehn–Yahr stage I. Nonetheless, orthostatic hypotension due to the loss of postganglionic sympathetic nervous fibers can occur with the progression of disease, even in de novo PD.

Spectral analysis of RR interval variations showed that the RR-LF and the LF/HF ratios in early PD are significantly reduced as compared with control, whereas RR-HF did not differ from control. The high frequency power of the RR interval is significantly affected by vagal gains and is quite independent of sympathetic gains [33–35]. This finding has been confirmed in clinical and experimental studies of autonomic maneuvers such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy. Therefore, previous reports have consistently proposed that vagal activity primarily contributes to the RR-HF component. In contrast, interpretation of the RR-LF component remains controversial. Some studies have suggested that RR-LF reflects both sympathetic activity and vagal activity, whereas others have regarded LF to be a quantitative marker of sympathetic modulations. Consequently, RR-LF is considered to be influenced by a balance of sympathetic and parasympathetic activities. The LF/HF ratio is also considered by some investigators to mirror sympathovagal balance or to reflect sympathetic modulations [36,37]. This claim was supported by our finding that sympathetic nerve dysfunction in the sinus node was present in patients who had early stage de novo PD without parasympathetic nerve dysfunction.

SBP-LF in early stage PD was similar to that of control, while SBP-LF in Hoehn–Yahr stage III PD was significantly smaller than that of control. Spectral analysis of systolic blood pressure also demonstrated two major
components: low frequency components and high frequency components, similar to those of the RR interval. Available evidence suggests that the low frequency component of blood pressure variability is mediated by changes in peripheral vascular resistance, which in turn are controlled by changes in vascular sympathetic nerve activity. In contrast, the high frequency component of blood pressure variability has been considered to be independent of the autonomic nervous system [38]. Therefore, vascular sympathetic function was not impaired in early PD such as Hoehn–Yahr stage I or II, but gradually decreased with progression of disease to Hoehn–Yahr stage III. This finding is consistent with the results of our hemodynamic studies using the Valsalva maneuver.

Our studies of the autonomic nervous system by 123I-MIBG scintigraphy, the Valsalva maneuver, and spectral analyses of the RR interval and blood pressure suggested that latent cardiac sympathetic nervous dysfunction, especially that involving the sinus node, has already occurred in patients who have de novo PD without clinical evidence of autonomic dysfunction. Nonetheless, cardiac parasympathetic and vasomotor peripheral sympathetic functions were preserved in early stage PD.

In PD, lesions are considered to develop in the dorsal motor nucleus of the vagal and the glossopharyngeal nerves, as well as the anterior olfactory nucleus. With disease progression, the pontine tegmentum structures, such as the coeruleus–subcoeruleus complex, are gradually involved [39]. The locus coeruleus is thought to have an important role in the central regulation of cardiovascular function and in the regulation of sympathetic cardiovascular mechanisms [40]. The reduction in cardiac sympathetic nerve activity observed in our study may be associated with central sympathetic damage to the locus coeruleus and other structures. However, our study also showed that patients with early stage PD have decreased cardiac MIBG uptake, apparently arising from the loss of functional cardiac sympathetic nerve terminals. It thus remains unclear whether cardiac sympathetic dysfunction in PD was caused by peripheral or central lesions in our study.

In conclusion, our findings indicate that cardiac parasympathetic and vasomotor peripheral sympathetic dysfunction is preceded by reduced cardiac sympathetic nervous function in the sinus node in patients with early stage de novo PD.

References


