



Cardiac parasympathetic dysfunction concurrent with cardiac sympathetic denervation in Parkinson's disease

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ABSTRACT

We aimed to characterize the relationship between cardiac sympathetic and parasympathetic dysfunction employing cardiac ¹²³I-meta-iodobenzylguanidine (MIBG) uptake and other autonomic function parameters in Parkinson's disease (PD). 79 PD patients were studied. We performed ¹²³I-MIBG myocardial scintigraphy to assess the extent of cardiac sympathetic denervation. Electrocardiogram readings at rest and postural change in blood pressure were also examined. Coefficient variation of RR intervals (CVR-R) was used as an index for cardiac parasympathetic activity. Cardiac ¹²³I-MIBG uptake did not vary significantly among the Hoehn–Yahr (H–Y) stages. There was a significant correlation between cardiac ¹²³I-MIBG uptake and CVR-R (early, $r=0.457$, $p<0.001$; late, $r=0.442$, $p<0.001$). While the correlation was present among the patients who had had the disease less than two years (early, $r=0.558$, $p<0.001$; late, $r=0.530$, $p<0.001$), the patients with the disease duration longer than two years did not have such a significant correlation. Age, disease duration, corrected QT interval, or postural blood pressure change did not correlate with cardiac ¹²³I-MIBG uptake. Orthostatic hypotension was observed in 13 out of 72 subjects, and reduced CVR-R was a major determinant for the development of orthostatic hypotension. We conclude that cardiac parasympathetic dysfunction occurs concurrent with sympathetic denervation as revealed by ¹²³I-MIBG myocardial scintigraphy in PD and contributes to the development of orthostatic hypotension.

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1. Introduction

Recent evidence shows that Parkinson's disease (PD) is a neurodegenerative disease that manifests a constellation of neurological symptoms beyond classic Parkinsonian features, such as resting tremor and rigidity, and forms a continuum with dementia with Lewy bodies (DLB) characterized by limbic and neocortical degeneration responsible for cognitive impairment [1]. Braak et al. [2] clarified that pathological processes in PD begin in the anterior olfactory nucleus and medulla, the latter of which harbors the dorsal motor nucleus of the vagal nerve, one of major autonomic centers. Accordingly, hyposmia and autonomic dysfunction, particularly constipation, are now appreciated as early clinical manifestations relevant to PD. Recognition of these symptoms will become more important with attempts to institute preventive therapy against this disabling disease.

The peripheral autonomic system is also affected in PD. Pathological studies have demonstrated the presence of Lewy bodies in myenteric and submucosal plexuses [3–5]. As for the cardiac autonomic system, many nuclear radiological studies using ¹²³I-meta-iodobenzylguanidine

(MIBG) or 6-[¹⁸F]fluorodopamine have reported cardiac sympathetic denervation in PD patients, and the degeneration of postganglionic sympathetic fibers was confirmed by postmortem pathological examinations [6,7]. However, the absence of obvious cardiovascular symptoms, like orthostatic hypotension, in many of cases displaying reduced cardiac ¹²³I-MIBG uptake is an enigma [8,9]. This implies a need for a comprehensive understanding of cardiovascular autonomic status including cardiac parasympathetic and peripheral vasomotor activity and cardiac sympathetic function. Despite the presence of several hemodynamic studies showing the involvement of cardiac parasympathetic system in PD [9–13], its incidence and temporal profile relative to cardiac sympathetic denervation remain elusive.

Here, we demonstrate that cardiac parasympathetic dysfunction occurs with sympathetic denervation in PD by examining heart rate variability at rest and cardiac ¹²³I-MIBG uptake. Concurrent development of parasympathetic and sympathetic dysfunction is obvious in the early stages of PD.

2. Methods

2.1. Subjects

79 PD patients (39 men and 40 women) who visited our outpatient clinic were studied. All patients fulfilled United Kingdom Parkinson's

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Table 1

Comparisons of demographic and autonomic function parameters other than H/M ratio of ^{123}I -meta-iodobenzylguanidine (MIBG) among the Hoehn–Yahr stages

Hoehn–Yahr stage	I	II	III	IV	V	<i>p</i>
N	20	29	23	5	2	
Age, y	71.0±5.2	72.5±6.9	76.4±5.5	75.2±5.5	74.0±4.2	NS
Gender (M:F)	8:12	15:14	10:13	3:2	0:2	NS
Disease duration, y	1.4±1.1	3.5±4.0	4.2±4.6	6.0±6.1	10.5±6.4	NS
Age of onset, y	69.4±5.4	69.0±8.7	72.3±8.0	69.2±10.7	63.5±10.6	NS
WR (%)	32.7±7.1	33.0±6.3	33.2±6.1	29.9±3.5	26.2±5.0	NS
CVR-R (%)	2.50±1.26	2.11±0.89	2.26±1.23	1.40±0.40	0.81±0.13	NS
QTc (ms)	412±15	408±16	411±15	425±21	433±1	NS
ΔSBPp (mm Hg)	−4.2±15.3	−6.5±17.6	−4.9±16.5	−11.0±15.7	−5.5±16.2	NS

Data are mean±SD. NS=not significant.

^a Post-hoc comparison I vs. V.

Disease Society Brain Bank Clinical Diagnosis Criteria [14]. Other Parkinsonian disorders such as vascular parkinsonism, multiple system atrophy, and progressive supranuclear palsy were excluded from clinical features and MRI findings. None of the subjects exhibited marked dementia or visual hallucination. Those who had ischemic heart disease, diabetes mellitus, or were undergoing treatment with selegiline hydrochloride (L-deprenyl) or tricyclic antidepressants were not included in consideration of the potential effects of these factors on cardiac ^{123}I -MIBG uptake. We employed the Hoehn–Yahr (H–Y) stage to assess the disease severity. 44 of the 79 subjects were on medication for PD at the time of investigation. We evaluated motor symptoms during the “off” period when we examined medicated patients. The mean age±SD was 73.4±6.2 years, and the mean disease duration±SD, 3.5±4.1 years.

Informed consent was obtained from every patient prior to enrollment. This study was approved by the institutional review board for clinical research of the National Hospital Organization Tokyo Medical Center.

2.2. ^{123}I -MIBG myocardial scintigraphy

The patients were asked not to have breakfast on the day of examination. Each subject was relaxed in the supine position for 20 min and was intravenously injected with 111 MBq of ^{123}I -MIBG (Daiichi Radioisotope Laboratories Co., Tokyo, Japan) around 10:00 AM. A thoracic planar image was acquired in a static fashion for 5 min

using a dual-headed rotating scintillation camera (HITACHI gamma-view-i RPC-DC) equipped with low-energy, high-resolution parallel-hole collimators after 15 min (early phase) and 3 h (late phase) following the administration of ^{123}I -MIBG. The acquisition matrix was 256×256. Energy discrimination was centered on 159 keV with a 10% window. In each case, an oval region of interest (ROI) was set on the left ventricular part of the heart with a rectangular reference ROI placed on the upper mediastinum of the anterior ^{123}I -MIBG planar image. Average counts per pixel were made in these ROIs. The heart-to-mediastinum (H/M) ratios for the early and late images were calculated to evaluate the integrity of cardiac sympathetic nerve fiber densities. The washout ratio (WR) was defined as $100 \times (\text{Ec} - \text{Lc}) / \text{Ec} \%$ (Ec: the early cardiac count density, Lc: the decay-corrected late cardiac count density).

2.3. Electrocardiogram analysis and postural change in systolic blood pressure

After a bed rest for 5 min, an electrocardiogram (EKG) recording in the supine position with normal breathing was carried out for 5 min using ECG-1550 (Nihon Kohden). For analysis of coefficient variation of RR intervals (CVR-R), successive 200 RR intervals were sampled during the recording period. CVR-R was automatically calculated as a percentage of the standard deviation of the RR intervals divided by their mean. CVR-R measured at rest under normal breathing is an established index for parasympathetic activity [15,16]. QTc was computed according to Bazett's formula; $\text{QTc} = \text{QT} / (\text{RR})^{1/2}$. Blood pressure was measured in the supine position. Subsequently, blood pressure in the upright position was recorded after 60-second-long orthostasis. Postural change in systolic blood pressure (ΔSBPp) was also calculated.

2.4. Statistical analysis

The data were analyzed using the SPSS software, version 15.0 Family (SPSS Inc., Chicago, IL). Inter-group differences were evaluated using one-way analysis of variance (ANOVA) combined with Tukey's post-hoc test or unpaired *t*-test. χ^2 calculations were used for frequency data. Correlations for the H/M ratio of MIBG uptake, CVR-R, QTc, heart rate (HR), and postural change in systolic blood pressure were assessed using Pearson's correlation coefficient. Multiple regression analyses were performed on the correlation of H/M ratio of MIBG uptake with other parameters. *p* value <0.01 was considered statistically significant.

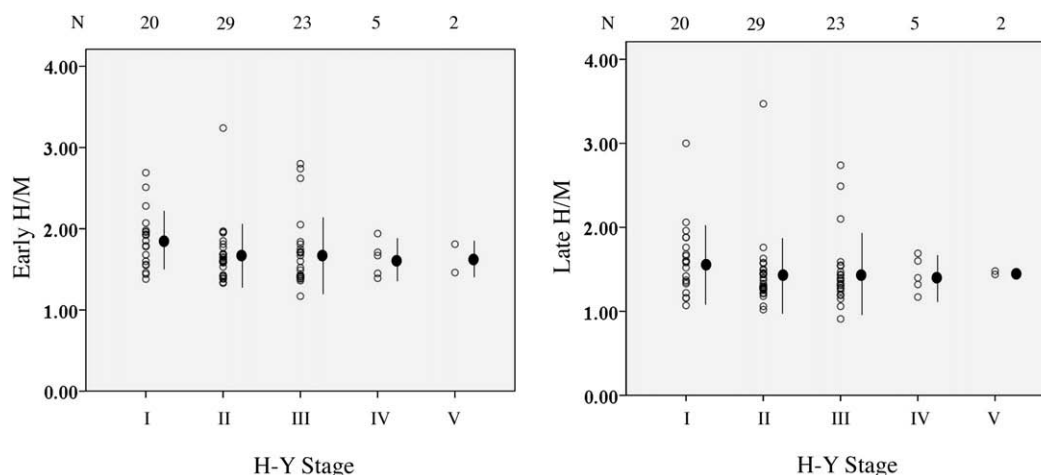


Fig. 1. Comparisons of H/M ratio of ^{123}I -meta-iodobenzylguanidine (MIBG) uptake among the Hoehn–Yahr (H–Y) stages. The dot and bar data represent mean±SD. The data were analyzed using one-way analysis of variance and Tukey's post-hoc test.

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