Pattern of Cardiac Sympathetic Denervation in Idiopathic Parkinson Disease Studied with ^{11}C Hydroxyephedrine PET¹

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Purpose:

To determine whether cardiac sympathetic denervation in idiopathic Parkinson disease (IPD) affects the left ventricle in a distinct regional pattern versus a more global pattern with use of carbon 11 (^{11}C) *meta*-hydroxyephedrine (HED) positron emission tomography (PET).

Materials and Methods:

This prospective study was approved by the institutional review board and was compliant with HIPAA. Informed consent was obtained from all subjects. Cardiac PET was performed with ^{11}C HED in 27 patients with IPD (20 men and seven women aged 50–74 years; mean age, 62 years $\pm$ 6 [standard deviation]). ^{11}C HED retention indexes (RIs), which reflect nerve density and integrity, were determined. RIs for 33 healthy control subjects (15 men and 18 women aged 20–78 years; mean age, 47 years $\pm$ 17) were used as a control database. Patients with IPD were compared with control subjects by using *z* score analysis. Global and segmental measurements of sympathetic denervation were expressed as percentage extent, *z* score severity, and severity-extent product (SEP). Group comparisons were performed with the Student *t* test.

Results:

The mean ^{11}C HED RI was 0.086 mL of blood per minute per milliliter tissue $\pm$ 0.015 for control subjects and 0.043 mL of blood per minute per milliliter tissue $\pm$ 0.016 for patients with IPD ($P < .0001$). When compared with normative data from the control database, profound cardiac denervation (global extent $>50\%$) was seen in most patients (19 of 27 patients, 70%). Four patients had normal ^{11}C HED studies and four had mild denervation (global extent $<25\%$). The mean global denervation extent was $62\% \pm 38$, the mean severity *z* score was -2.7 ± 1.2 , and the mean SEP was -202 ± 131 (range, -358 to 0). Segmental analysis revealed relative sparing of anterior and proximal septal segments (mean extent, 48%–51%; mean severity *z* score, -2.47 to -2.0 ; mean SEP, -167 to -139), with lateral and proximal inferior segments more severely affected (mean extent, 68%–73%; mean severity *z* score, -2.8 to -2.62 ; mean SEP, -271 to -230). Patients with normal findings or preserved denervation did not significantly differ in mean age ($t = 1.09$) or disease duration ($t = 0.44$) compared to patients with severe sympathetic denervation.

Conclusion:

Cardiac sympathetic denervation in IPD is extensive, with a segmental pattern that involves the proximal lateral left ventricular wall most severely, with relative sparing of the anterior and proximal septal walls.

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Idiopathic Parkinson disease (IPD) is associated with multiple autonomic comorbidities, including cardiac postganglionic, presynaptic sympathetic denervation (1). Previous studies of IPD with iodine 123 (^{123}I) metaiodobenzylguanidine (MIBG), a false neurotransmitter with affinity for the presynaptic norepinephrine transporter of postganglionic sympathetic neurons, have demonstrated extensive reductions in cardiac ^{123}I MIBG uptake indicative of cardiac sympathetic neuronal loss (2–22). The pathobiologic mechanism appears to be neurodegenerative, associated with α -synuclein accumulation in the autonomic cardiac plexus and distal axons (6,13,23–25).

Cardiac scintigraphy with ^{123}I MIBG has been proposed as a diagnostic test with which to differentiate IPD with postganglionic autonomic dysfunction from other Parkinsonian syndromes such as multiple system atrophy with central and preganglionic sympathetic dysfunction (3,4,15,18,20). However, much of the sequence and process of cardiac sympathetic denervation in IPD remains poorly understood. Most

studies using ^{123}I MIBG have relied on heart-to-mediastinal ratios derived from early and delayed planar imaging. Cardiac sympathetic imaging with carbon 11 (^{11}C) meta-hydroxyephedrine (HED) positron emission tomography (PET) has been reported in small numbers of patients with IPD (26,27). Cardiac PET has advantages of increased sensitivity and more accurate measurements of tissue radioactivity concentrations as compared with planar single-photon scintigraphy. ^{11}C HED PET provides quantitative measurements of cardiac radiotracer retention, which reflects sympathetic nerve density, enabling global and segmental analysis of cardiac sympathetic denervation (1,28–30).

The purpose of the current study was to determine whether cardiac sympathetic denervation in IPD affects the left ventricle in a distinct regional pattern versus a more global pattern with use of ^{11}C HED PET.

Materials and Methods

This study was not funded by industrial or commercial sources nor did it evaluate products for commercial purposes.

Study Population

The institutional review board of the University of Michigan, Ann Arbor, approved this investigation of patients with IPD and healthy control subjects. Informed consent was obtained from all participants. This prospective study was compliant with the Health Insurance Portability and Accountability Act (clinicaltrials.gov identifier: NCT01565473). We studied 27 patients with mild to moderate IPD (20 men and seven women aged 50–74 years; mean age $\pm$ standard deviation, 62

years $\pm$ 6). The diagnosis of IPD was established by means of published research criteria (31) on the basis of clinical neurologic examination (conducted by N.I.B., a neurologist with 20 years of experience) and confirmed by the presence of nigrostriatal dopaminergic denervation at dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) PET based on putaminal dopaminergic losses greater than caudate nucleus that are often asymmetric (32). Each DTBZ scan was reviewed and confirmed to be consistent with IPD by PET neuroimaging experts (N.I.B., K.A.F., S.G.) at monthly consensus meetings.

Cardiac sympathetic denervation has been reported to occur as a result of a range of cardiac diseases, including diabetic cardiac autonomic neuropathy (33), after myocardial infarction, owing to congestive cardiac failure, and in cardiac transplant recipients (28). Therefore, patients with IPD were screened to exclude those with a history of cardiac disease or diabetes as

Advances in Knowledge

- Most patients with Parkinson disease have severe cardiac sympathetic denervation.
- With three-dimensional tomographic analysis of carbon 11 (^{11}C) hydroxyephedrine (HED) retention in the left ventricle, it was demonstrated that the cardiac sympathetic denervation in Parkinson disease follows a distinct regional pattern.
- The lateral wall of the left ventricle is affected most severely and frequently, whereas the anterior and septal walls are relatively spared in comparison.
- Knowledge of the regional pattern of cardiac sympathetic denervation contributes to our understanding of Parkinson disease as a degenerative disease of autonomic neurons.

Implication for Patient Care

- ^{11}C HED PET provides three-dimensional tomographic data demonstrating severe cardiac sympathetic denervation in most patients with Parkinson disease and may have a role as a diagnostic test.

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Abbreviations:

DTBZ = dihydrotetrabenazine
HED = hydroxyephedrine
IPD = idiopathic Parkinson disease
MIBG = metaiodobenzylguanidine
RI = retention index
SEP = severity-extent product
VMAT2 = vesicular monoamine transporter type 2

Author contributions:

Guarantors of integrity of entire study, K.K.W., K.A.F., N.I.B., S.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, K.K.W., D.M.R., K.A.F., N.I.B., S.G.; clinical studies, N.I.B., S.G.; statistical analysis, K.K.W., D.M.R., R.A.K., K.A.F., N.I.B.; and manuscript editing, K.K.W., D.M.R., N.I.B., S.G.

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well as those with abnormal Q waves at echocardiography. Nine patients with IPD were taking a combination of a dopamine agonist and carbidopa-levodopa, 14 patients were taking carbidopa-levodopa alone, one patient was taking a dopamine agonist alone, and three patients were not taking dopaminergic drugs. Patients taking tricyclic antidepressants, bupropion, calcium channel blockers, or β -blockers were not eligible for the study because these drugs may interfere with HED metabolism.

Radiochemistry

^{11}C HED was prepared by ^{11}C methylation of (–)-metaraminol as the free base and purified by means of high-performance liquid chromatography (34). This procedure provided ^{11}C HED at specific activities of 18.5–55.5 TBq/mmol and radiochemical purities of greater than 98%.

^{11}C HED PET Cardiac Imaging

With the patient lying comfortably in the PET scanner, a mean of $740 \text{ MBq} \pm 74$ of ^{11}C HED was injected intravenously and a dynamic sequence of cardiac scans was acquired over 40 minutes (framing rates = 12×10 seconds, 2×30 seconds, 2×60 seconds, 2×150 seconds, 2×300 seconds, and 2×600 seconds). A low-dose (74 MBq) nitrogen 13 ammonia cardiac localizer scan was obtained before administration of HED to position the heart in the center of the scanner field of view. All scans were obtained with an ECAT Exact HR+ PET scanner (Siemens Medical Solutions, Hoffman Estates, Ill), which has an intrinsic resolution of approximately 4.6 mm full width at half maximum. Sixty-three planes with a 2.425-mm center-to-center separation were imaged simultaneously. Attenuation correction using three germanium 68 line sources was applied to the measured transmission scan data, which were then segmented and reprojected into sinogram space. The resolution of the reconstructed images was approximately 8–9 mm at full width at half maximum based on the PET camera resolution and the selected matrix size. The cardiac images were resectioned into short-axis images for

further quantitative analysis as previously described (35). A region of interest was placed over the left ventricular chamber in a short-axis section near the base of the heart (performed by D.M.R., a physicist with 20 years of experience), and a time-activity curve for total activity in blood was generated. Next, the left ventricular wall in each of the eight short-axis sections from the apex to the base was automatically subdivided into 60 angular sectors to generate a total of 480 sectors. The apical sections had at least four pixels per sector, whereas the basal section had at most 14 pixels per sector. The time-activity curve for tissue ^{11}C HED concentration was determined for each sector. As a semiquantitative measure of nerve density and neuronal integrity, tissue ^{11}C HED concentrations in the final image frame (30–40 minutes after injection) were normalized by dividing them by the integral of the blood time-activity curve over the 40-minute scan, as has been previously described (30). This procedure provided a ^{11}C HED retention index (RI, in milliliters of blood per minute per milliliter of tissue) for each myocardial region. The RI reflects the ability of the sympathetic neurons to take up and store norepinephrine.

Healthy control subjects who did not have a history of cardiac or neurologic disease, diabetes mellitus, or other chronic medical conditions were recruited for this study. None of the control subjects were taking any medications that could have an effect on cardiac sympathetic neurons. The RIs for 33 healthy control subjects (15 men and 18 women aged 20–78 years; mean age, 47 years $\pm$ 17) were used to define a normal HED retention database in which the means and standard deviations for each myocardial sector were calculated. Measured RI data for each patient with IPD were compared with the healthy control database by means of z score analysis. For this analysis, a z score was calculated for each sector in a patient's polar map, as follows: $z_i = (\mu_i - q_i)/\sigma_i$, where q_i is the patient's RI for the i th sector of the polar map, μ_i the healthy population mean RI for that sector, and σ_i the corresponding

across-subject standard deviation of the healthy population for that sector. Left ventricular sectors with z scores of less than 2.5 (ie, their ^{11}C HED RI values were more than 2.5 standard deviations below the healthy population mean) were considered to have abnormal ^{11}C HED retention. An age-adjustment factor was applied to the HED RI values of the patients with IPD, normalizing to an age of 50 years. The control group had a very modest decline of the HED RI with age (1.3% decline per decade). The effect of age adjustment was considered minimal because the largest age correction performed in any one sector's RI was an increase of 3% in one of the oldest patients with IPD.

We calculated the fraction of 480 sectors in each patient's polar map that was abnormal as a measure of the extent of abnormal ^{11}C HED retention in the left ventricle. Regional extent measures were generated for the left ventricle on the basis of perfusion territories of the three main coronary arteries: the left circumflex, left anterior descending, and right coronary arteries. In addition, the basal-to-apical gradient of sympathetic innervation was assessed with a nine-segment model on the polar map as previously described (30). Global, regional, and segmental measurements of abnormal cardiac sympathetic denervation were expressed as percentage extent, z score severity, and severity-extent product (SEP), which was obtained by multiplying the percentage extent and the z score severity integers. The SEP measurement combines percentage extent and severity of sympathetic denervation into a single product in a manner akin to the summed stress score used in routine myocardial perfusion imaging.

^{11}C DTBZ PET Neuroimaging

All subjects with IPD also underwent brain magnetic resonance (MR) imaging and (+)- ^{11}C DTBZ VMAT2 PET for confirmation of nigrostriatal dopaminergic denervation consistent with Parkinson disease diagnosis. DTBZ PET was performed in three-dimensional imaging mode by using an ECAT HR+ tomograph (Siemens Molecular Imaging,

Knoxville, Tenn). No-carrier-added (+)- ^{11}C DTBZ (9.25–37.0 TBq/mmol at the time of injection) was prepared as reported previously (36). Dynamic PET was performed for 60 minutes immediately after injection of a bolus of 55% of 555 MBq of (+)- ^{11}C DTBZ dose over the first 15–30 seconds of the study, whereas the remaining 45% of the dose was continuously infused over the next 60 minutes, resulting in stable arterial tracer levels and equilibrium with brain tracer levels after 30 minutes (37). All subjects underwent imaging while supine, with eyes and ears unoccluded, resting quietly in a dimly lit room.

All dynamic PET imaging frames were spatially coregistered within subjects with a rigid body transformation to reduce the effects of subject motion during the imaging session. These motion-corrected PET frames were spatially coregistered to the MR images by using SPM8b software (Wellcome Trust Centre for Neuroimaging, London, England). Interactive Data Language image analysis software (Research Systems, Boulder, Colo) was used to manually trace volumes of interest on the MR image, including the striatum (caudate and putamen). Time-activity curves for each volume of interest were generated from the spatially aligned PET frames. DTBZ distribution volume ratio was then estimated by using the Logan plot graphical analysis method (38) with the time-activity curves as the input function and the neocortex as reference tissue for DTBZ, a reference region very low in VMAT2 binding sites, with the assumption that the nondisplaceable distribution is uniform across the brain at equilibrium (39). The imaging protocols are summarized in Figure 1.

Data Analysis

Statistical analyses were performed with software (version 9.1, SAS Institute, Cary, NC; STATA, version 11.1, StataCorp, College Station, Tex). Group comparisons between two subgroups of IPD patients, those with normal findings or mild cardiac sympathetic denervation and those with severe cardiac sympathetic denervation, were performed by using the Student *t* test.

Results

Patient Characteristics

Disease severity in patients with IPD was classified as mild to moderate, with a mean disease duration of 5.4 years $\pm$ 3.4 (range, 1–14 years) and mean Hoehn and Yahr score of 2.2 ± 0.4 (range, 1–2.5). An IPD nigrostriatal denervation pattern typically consisted of asymmetric dopaminergic losses that were greater in the putamen than in the caudate nucleus. An example is shown in Figure 2. Patients had a mean Unified

Parkinson's Disease Rating Scale motor score of 28.6 ± 10.9 (range, 7–52).

Cardiac ^{11}C HED Retention

In the 33 control subjects, the mean ^{11}C HED RI was 0.086 mL of blood per minute per milliliter of tissue $\pm$ 0.015. Table E1 (online) summarizes the demographic and clinical features and the global and regional ^{11}C HED retention measurements in the 27 patients with IPD. The mean ^{11}C HED RI in patients with IPD was 0.043 mL of blood per minute per milliliter of tissue $\pm$ 0.016 ($P < .0001$ vs control subjects). For the

Figure 1: Summary of functional sympathetic cardiac PET and nigrostriatal PET neuroimaging protocols.

Figure 2: Transaxial parametric DTBZ PET VMAT2 binding images at level of striatum show normal intense uptake in control subject (left) and asymmetric predominant putaminal losses in patient with IPD (right).

Figure 3: A, B, Comparison polar maps of mean HED RI in, A, control subjects and, B, patients with IPD demonstrate severe global cardiac sympathetic denervation in patients with IPD. C, Segmental z score severity polar map generated by means of sector-to-sector comparison of HED RI in patients with IPD and control subjects shows the “characteristic” regional pattern of sympathetic denervation in IPD. Proximal lateral wall is most severely affected, with relative sparing of anterior and proximal septal walls. There is concordance in segmental distribution on both the z score severity polar map and, D, the frequency polar map representing the percentage of patients with IPD with an abnormal sector z score of 2.5 or less (ie, number of patients/27 × 100) displayed on a color scale of 0%–100%.

cohort of patients with IPD, the mean global denervation extent was $62\% \pm 38$ (range, 0%–100%), the mean severity z score was -2.7 ± 1.2 (range, -3.6 to -2.63), and the mean SEP was -202 ± 131 (range, -358 to 0). As expected, profound cardiac denervation (global extent >50%) was seen in most patients (19 of 27 patients, 70%). Four patients had normal ^{11}C HED studies (global extent = 0%) and four had partial, mild cardiac denervation (global extent <25%). Figure 3 displays polar maps illustrating the mean ^{11}C HED retention in the left ventricle of healthy control subjects and patients with IPD, the z score severity, and the frequency distributions of abnormal sympathetic innervation in these patients.

We performed a segmental analysis comparing mean global extent, severity, and SEP to the mean values in each of the nine segments. This analysis revealed relative sparing of proximal and distal anterior septal segments and proximal septal segments (mean extent, 48%–51%; severity z score, -2.47 to -2.0 ; SEP, -167 to -139). The proximal and distal lateral segments and proximal inferior segments were more severely affected (mean extent, 68%–73%; severity z score, -2.8 to -2.62 ; SEP, -271 to -230). Figure 4 presents a bull’s-eye representation of the segmental mean extent, severity, and SEP measurements.

Figure 4: Bull’s-eye plots obtained with nine-segment model summarize segmental distribution of sympathetic denervation with respect to mean percentage extent, z score severity, and SEP in comparison to global mean measurements. Mean global denervation extent was $62\% \pm 38$ (range, 0%–100%), mean severity z score was -2.7 ± 1.2 (range, -3.6 to -2.5), and mean SEP was -202 ± 131 (range, -358 to 0). Lateral wall displays greater extent and more severe reduction of ^{11}C HED retention compared with anterior and proximal septal walls.

Figure E1 (online) shows the global and segmental distributions of SEP. The SEPs were used to divide patients into three categories: (a) those with normal findings (SEP = 0), (b) those with mild to moderate denervation (SEP <0 to greater than -200), and (c) those with severe denervation (SEP less than or equal to -200). This distribution is summarized for the nine segments in Table E2 (online). Using these categories, we compared sympathetic denervation of the proximal lateral segment (normal findings = 6, severe denervation = 21) to that of the proximal anterior segment (normal findings = 9, mild to moderate denervation = 6, severe denervation = 12), finding that the proximal lateral segment is affected more severely and more frequently than other segments.

Relationship with Clinical and Nigrostriatal DTBZ PET Variables

The Table shows the results of the group comparison of the clinical and DTBZ PET measures in the eight patients with either normal findings or partial mild cardiac denervation (global extent <25%) versus the 19 patients with more extensive cardiac denervation. There were no significant differences in age or duration of disease between the two groups. There were no significant differences in the extent of nigrostriatal denervation between the two groups.

Discussion

To our knowledge, this investigation reports on the largest number of IPD

patients studied with ^{11}C HED PET imaging thus far. We have previously reported our initial experience in a mixed group of Parkinsonian subjects, including nine patients with IPD (27). Our current study confirms previous findings of extensive cardiac sympathetic denervation documented by using ^{123}I MIBG imaging, supporting the notion that cardiac sympathetic imaging might be used as a relatively sensitive diagnostic test for IPD. Many authors have endorsed the potential of cardiac sympathetic imaging to differentiate IPD from other Parkinsonian disorders (3,12,15,18,20,26,40). Nevertheless, we and others have reported that cardiac sympathetic neuronal loss also occurs in multiple system atrophy (4,13,25,27).

We did not find significant differences in the degree of nigrostriatal denervation between the patients with normal findings or relatively preserved cardiac sympathetic innervation and those with more severe cardiac sympathetic denervation. Furthermore, we did not find differences in mean age or duration of motor disease between those groups. Reductions in ^{123}I MIBG uptake in IPD have been previously reported to correlate with Hoehn and Yahr severity scores (7,15,17,40), the presence of visual hallucinations (10), midline symptoms of speech, posture, and gait dysfunction (8), and deficits in olfactory testing (8,11). There is currently no consensus regarding a relationship between MIBG uptake and patient outcome measurements in IPD, and no studies

comparing ^{11}C HED PET and ^{123}I MIBG imaging have been reported to date.

Histopathologic studies of degeneration of cardiac sympathetic nerves in IPD, using paravertebral sympathetic ganglia tissue and cardiac tissue derived from anterior left ventricular walls, stained with tyrosine hydroxylase and neurofilament antibodies to confirm sympathetic nervous tissue, demonstrated α -synuclein aggregates in the neuronal somata with absent tyrosine hydroxylase and neurofilament immunoreactivity in the distal sympathetic axons (13,23,25). Fluorine 18 (^{18}F) fluorodopamine PET studies in patients with IPD have shown relatively lower sympathetic innervation in the lateral wall, with sparing of the septum, which was attributed to loss of functional cardiac sympathetic nerve terminals (41,42). Furthermore, in patients who underwent serial ^{18}F fluorodopamine PET imaging with a mean interval of 2 years from the first scan, radioactivity on the second study was decreased by 31% in the left ventricle free wall compared with only 16% in the septum (42). Therefore, the segmental patterns of left ventricular sympathetic denervation in IPD appear comparable between ^{11}C HED PET and previous ^{18}F fluorodopamine PET imaging studies.

Cardiac sympathetic neurons within the right coronary, left coronary, and left lateral cardiac nerves travel with the coronary arteries in the subepicardial layer before penetrating the myocardium. The segmental pattern we observed is not explained by either

Comparison of Clinical and DTBZ PET Variables in Patients with Normal Findings or Partial Mild Cardiac Denervation (Global Extent <25%) versus Patients with More Extensive Cardiac Denervation

Variable*	Patients with Normal Findings or Relatively Preserved Sympathetic Cardiac Innervation (n = 8) [†]	Patients with More Extensive Sympathetic Cardiac Denervation (n = 19) [†]	t Value [‡]
Age (y)	63.1 $\pm$ 5.1	60.5 $\pm$ 5.9	1.09 (.29)
Duration of motor disease (y)	5.9 $\pm$ 4.0	5.2 $\pm$ 3.2	0.44 (.66)
Hoehn and Yahr stage	2.25 $\pm$ 0.38	2.24 $\pm$ 0.39	0.08 (.94)
Striatal DTBZ DVR	2.03 $\pm$ 0.25	1.95 $\pm$ 0.30	0.70 (.49)

* DVR = distribution volume ratio.

[†] Data are means $\pm$ standard deviations.

[‡] Data were determined with the Student t test. Numbers in parentheses are P values.

greater susceptibility to injury of the neurons supplying the lateral left ventricular wall or regional differences in neuronal density. First, the ^{11}C HED distribution in the hearts of healthy subjects has been described as homogeneous (28,30). Second, z score analysis would correct for any regional differences in ^{11}C HED distribution.

Autonomous cardiac sympathetic innervation in humans is complex, with efferent cardiopulmonary and more distal cardiac nerves demonstrating overlapping segmental territories in the left ventricle. A plausible explanation for the observed pattern, based on human anatomy and experiments in nonhuman species, is that the lateral wall and, to a lesser extent, posterior (inferior) wall supplied by the left lateral cardiac nerve has the least amount of overlapping innervation (43). Conversely, the anterior and septal walls are innervated by the left coronary cardiac nerve, which derives branches from right and left dorsal mediastinal (medial and lateral) cardiopulmonary nerves that contain axonal projections from the right and left stellate and middle cervical ganglia, respectively (43). In a canine model, sectioning of the left lateral cardiac nerve led to decreased inotropic responses in the lateral and posterior walls following left middle cervical ganglion stimulation (44). However, sectioning of individual major sympathetic cardiopulmonary nerves failed to abolish left ventricular inotropic responses after ipsilateral middle cervical ganglion stimulation, suggesting possible redundant innervation from contralateral cervical ganglia (44).

A limitation of this study was that concurrent myocardial perfusion imaging was not performed in our patient cohort, unlike for studies investigating ^{11}C HED PET in patients with congestive cardiac failure, diabetic autonomic neuropathy, or myocardial infarction. Despite this, we do not believe that undiagnosed coronary artery disease could have contributed to our observed findings. None of the patients with IPD had angina-like symptoms, a history of cardiac disease, or abnormal electrocardiographs. In addition, none of the

patients was taking antianginal medications. Furthermore, the pattern of more severe proximal lateral left ventricle involvement is not typical for coronary artery disease. Early ^{11}C HED PET images at 5 minutes after injection during the “perfusion” phase were inspected for the four patients with IPD and mild denervation and did not reveal any defects. Another limitation of our study was that we were unable to perform any comparison between ^{11}C HED PET and ^{123}I MIBG. To more fully understand the process of cardiac denervation in IPD, it may be necessary to evaluate patients at even earlier stages of disease with short-interval serial studies and to perform comparative studies between ^{11}C HED PET and ^{123}I MIBG imaging to determine which radiotracer more closely correlates with clinical parameters.

In conclusion, cardiac sympathetic denervation is extensive in IPD and affects most patients at an early stage in the disease course. The segmental pattern of cardiac sympathetic denervation involves the proximal lateral left ventricular wall most severely, with relative sparing of the anterior and proximal septal walls. This suggests a characteristic pattern of neuronal sympathetic degeneration in IPD.

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