

DAVID S. GOLDSTEIN, MD, PhD

Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Bethesda, MD

YEHONATAN SHARABI, MD

Clinical Neurocardiology Section, NINDS, NIH, Bethesda, MD

BARBARA I. KARP, MD

Clinical Neurosciences Program, NINDS, NIH, Bethesda, MD

OLADI BENTHO

Clinical Neurocardiology Section, NINDS, NIH, Bethesda, MD

AHMED SALEEM, MD

Clinical Neurocardiology Section, NINDS, NIH, Bethesda, MD

KAREL PACAK, MD, PhD

Reproductive Biology and Medicine Branch, National Institute of Child Health and Development, NIH, Bethesda, MD

GRAEME EISENHOFER, PhD

Clinical Neurocardiology Section, NINDS, NIH, Bethesda, MD

Cardiac sympathetic denervation preceding motor signs in Parkinson disease*

■ ABSTRACT

There is substantial interest in identifying biomarkers to detect early Parkinson disease (PD). Cardiac noradrenergic denervation and attenuated baroreflex-cardiovascular function occur in de novo PD, but whether these abnormalities can precede PD has been unknown. Here we report the case of a patient who had profoundly decreased left ventricular myocardial 6-[¹⁸F]fluorodopamine-derived radioactivity and low baroreflex-cardiovascular gain, 4 years before the onset of symptoms and signs of PD. The results lead us to hypothesize that cardiac noradrenergic denervation and decreased baroreflex-cardiovascular function may occur early in the pathogenesis of PD.

In Parkinson disease (PD), by the time the movement disorder develops, most of the nigrostriatal dopamine terminals have been lost. Identification of biomarkers of PD should improve early diagnosis and spur development of effective treatments.

Braak has proposed a pathogenetic sequence beginning outside the brain, with invasion of peripheral, vulnerable autonomic neurons, followed by alpha-synucleinopathy in lower brainstem nuclei and then by alpha-synucleinopathy in the midbrain substantia nigra and then finally in the cerebral cortex.^{3,4} Consistent with early involvement of peripheral autonomic or lower brainstem centers, several studies of de novo PD have reported evidence of cardiac noradrenergic denervation^{5,8,14,22} or of decreased baroreflex-cardiovascular function.^{1,2,6,14,18}

Whether these abnormalities can actually precede

symptomatic PD has been unknown. Here we report the case of a patient who had cardiac noradrenergic denervation, detected by 6-[¹⁸F]fluorodopamine positron emission tomography, and decreased baroreflex-cardiovascular gain, detected by abnormal beat-to-beat blood pressure and heart rate responses to the Valsalva maneuver, 4 years before the clinical onset of PD.

■ CASE REPORT

A 56-year-old man was referred for possible pheochromocytoma, based on episodic hypertensive episodes and symptoms suggesting excessive catecholamine effects.

He had no serious health problems until about 1998, when he began to experience malaise and exercise intolerance and episodes of hypertension or hypotension, palpitations, and chest tightness. He also had a long history of constipation and dyspepsia, a tendency to urinary retention, and complained of a sense of fullness in the left neck. The patient's career was in marketing and business development, until he quit work due to his symptoms. His mother had died of PD. Cardiac catheterization showed normal coronary arteries. Gastrointestinal endoscopy was unrevealing. Biochemical testing showed elevated plasma levels and urinary excretion of epinephrine. Thyroid function was normal.

Because of the hypertensive paroxysms, pheochromocytoma was suspected. In April 2000, the patient had a plasma epinephrine level about twice the upper limit of normal and a plasma metanephrine level about 50% above normal. In July 2001, he was evaluated at the National Institutes of Health (NIH). Normal follow-up plasma metanephrine, and failure of 6-[¹⁸F]fluorodopamine PET to detect an adrenal or extra-adrenal focus of radioactivity, excluded pheochromocytoma.¹⁷ At that time the concentration of 6-[¹⁸F]fluorodopamine-derived radioactivity was found to be markedly decreased in the left ventricular myocardium (**Figure 1**).

Autonomic function testing included measure-

* This article is reprinted, with permission, from *Clinical Autonomic Research* (Goldstein DS, et al. Clin Auton Res 2007; 17:118–121). The original publication is available at www.springerlink.com.

No author conflicts of interest were reported in the original publication of this article.
doi:10.3949/ccjm.76.s2.10

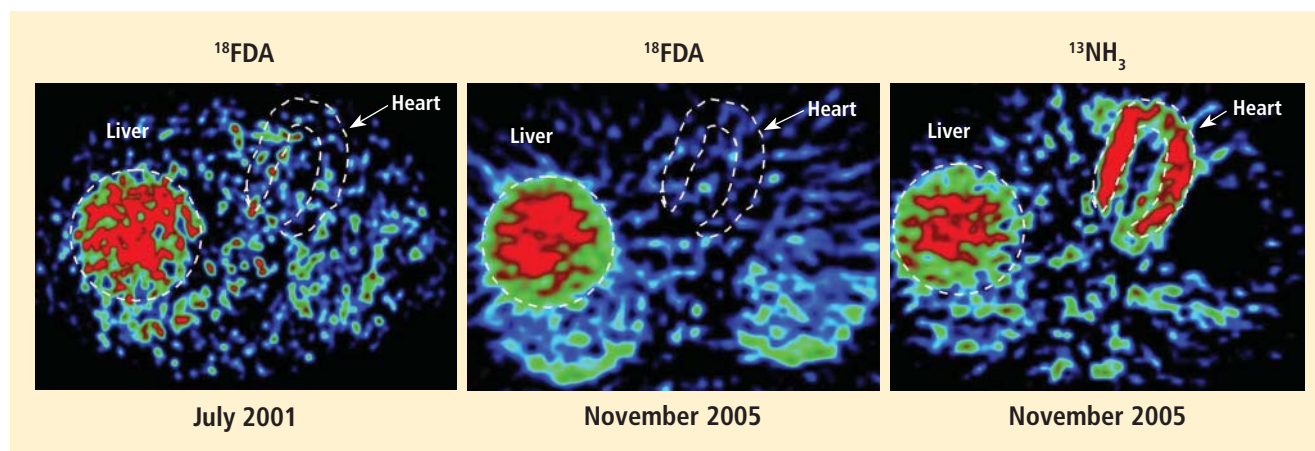


FIGURE 1. Thoracic 6- ^{18}F fluorodopamine (^{18}F FDA) and ^{13}N -ammonia (^{13}N NH_3) images in July 2001 and November 2005. Note absence of left ventricular myocardial 6- ^{18}F fluorodopamine-derived radioactivity at both times, indicating cardiac sympathetic denervation. Myocardial perfusion, as indicated by ^{13}N NH_3 -derived radioactivity, was normal.

ments of beat-to-beat blood pressure and heart rate during and after performance of the Valsalva maneuver. Blood pressure decreased early in Phase II and then leveled off, and there was an overshoot in pressure during Phase IV (dashed line in **Figure 2**), which are normal findings. Baroreflex-cardiovagal gain, calculated from the slope of the relationship between cardiac interbeat interval (with one beat delay) and systolic blood pressure during Phase II of the maneuver, was decreased at 3.2 msec/mm Hg; baroreflex-cardiovagal gain calculated from the data in Phase IV after release of the maneuver was also decreased at 3.1 msec/mm Hg).^{11,14,15}

Over several months in 2005 the patient noted progressive slowing of movement and inability to relax the arms, small handwriting, decreased facial expression, and decreased voice volume. The patient returned to the NIH in November 2005, to participate in a protocol on pseudopheochromocytoma, the evaluation again including 6- ^{18}F fluorodopamine positron emission tomographic scanning and beat-to-beat blood pressure and heart rate associated with the Valsalva maneuver. 6- ^{18}F fluorodopamine PET again revealed severely decreased 6- ^{18}F fluorodopamine-derived radioactivity throughout the left ventricular myocardium (**Figure 1**). In the interventricular septum, radioactivity at the midpoint of the scanning frame between 5 and 10 minutes after initiation of injection of 6- ^{18}F fluorodopamine was 1,286 nCi/kg/cc-mCi, more than 2 standard deviations below the normal mean and one of the lowest values we have recorded so far (**Figure 3**). Blood pressure decreased progressively in Phase II of the Valsalva maneuver, to a greater extent than in 2001, there was no over-

shoot of pressure after release of the maneuver, and the return of pressure toward baseline was prolonged, findings pointing to failure of sympathetically mediated reflexive vasoconstriction.^{12,23} Baroreflex-cardiovagal gain was also lower than in 2001 (1.2 msec/mm Hg from the results in Phase II, 2.6 msec/mm Hg from those in Phase IV), both because the range of heart was smaller and the extent of change in systolic pressure larger in 2005 than in 2001.

As a test of the status of the adrenomedullary hormonal system, blood was obtained via an indwelling arm catheter during supine rest and after bolus i.v. injection of 1 mg of glucagon and assayed for plasma catecholamines in our laboratory. Both in July 2001 and November 2005, the ratio of plasma epinephrine (in pg/mL) to norepinephrine (in pg/mL) was relatively high during supine rest (76:99 and 101:234), and the patient had large increases of plasma epinephrine levels in response to glucagon (peak values more than 250 pg/mL, more than six times the normal peak value).

Neurological consultation in November 2005 noted stooped posture and axial instability, cogwheel rigidity in all four extremities, paucity of spontaneous movements, masked face with infrequent blinking, and monotone voice, but with normal speed of gait and no resting tremor. The patient was diagnosed with mild PD.

DISCUSSION

In this patient, results of 6- ^{18}F fluorodopamine PET scanning indicated cardiac sympathetic denervation 4 years before the clinical onset of PD. Considering that in PD loss of cardiac noradrenergic innervation progresses slowly over years,¹³ and that the patient

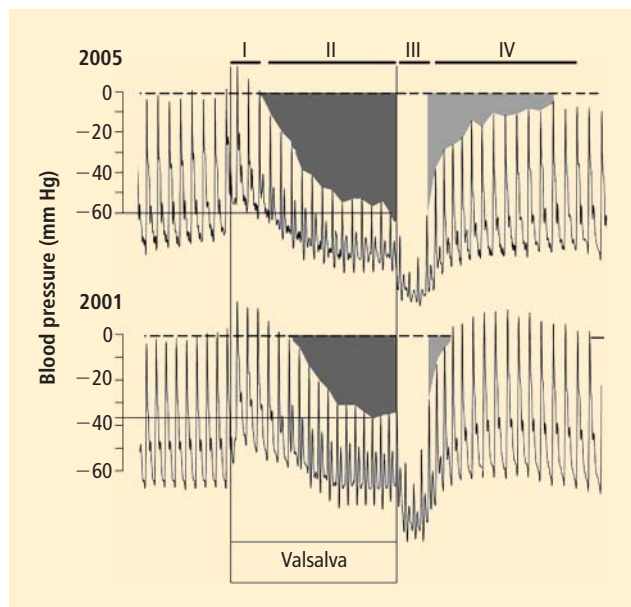


FIGURE 2. Beat-to-beat heart rate and blood pressure responses to the Valsalva maneuver (12-second duration, 30 mm Hg) in July 2001 and November 2005. In the latter recording, note progressive decline in blood pressure during Phase II, smaller pressure overshoot, and delayed return of pressure toward baseline in Phase IV, consistent with worsening baroreflex-sympathoneural function. Heart rate responses during and after the maneuver were also smaller in 2005 than in 2001, despite larger changes in blood pressure, consistent with worsening baroreflex-cardiovascular function.

already had evidence for markedly decreased cardiac noradrenergic innervation at the time of initial evaluation, loss of cardiac sympathetic nerves probably preceded the movement disorder by many more than the 4 years between initial testing and the onset of PD.

The findings in this case fit with previous reports of cardiac noradrenergic denervation in *de novo* PD and with the concept of a peripheral-to-central and caudal-to-rostral pathogenetic sequence. Orimo and co-workers have noted loss of noradrenergic terminal innervation of the myocardium before loss of cell bodies in sympathetic ganglia in PD.¹⁶

Our patient also had evidence for decreased baroreflex-cardiovascular function 4 years before the movement disorder. The baroreflex is a homeostatic arc, and abnormalities of afferent neurotransmission, central integration by brainstem centers, or vagal efferent pre-ganglionic or post-ganglionic fibers could result in the same clinical laboratory finding of low baroreflex-cardiovascular gain. In particular, the extent to which baroreflex-cardiovascular failure in PD reflects a brainstem lesion, as opposed to an afferent lesion or loss of parasympathetic cholinergic efferents, remains unknown. The results in our patient are consistent

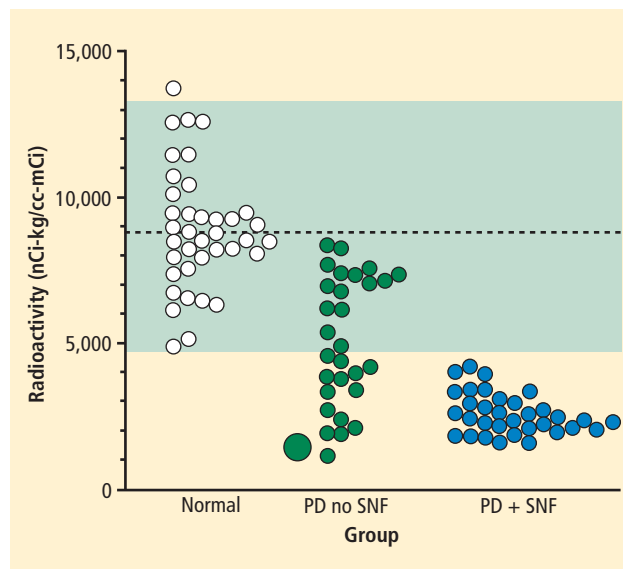


FIGURE 3. Individual values for septal myocardial 6-[¹⁸F]fluorodopamine-derived radioactivity, in normal control subjects (white circles), patients with Parkinson disease without sympathetic neurocirculatory failure (PD no SNF, green circles), patients with Parkinson disease and sympathetic neurocirculatory failure (PD + SNF, blue circles), and the case reported here (large green circle). Dashed line shows the normal mean value and light green shaded area 2 standard deviations from the normal mean. Note markedly decreased 6-[¹⁸F]fluorodopamine-derived radioactivity in the current case.

with the view that baroreflex-cardiovascular function worsens over years before the onset of PD.

Chronic constipation, which also preceded parkinsonism in our case, would be consistent with early dysregulation of gastrointestinal autonomic function. Accumulations of alpha-synuclein in enteric neurons and in the dorsal motor nucleus of the vagus nerve, the central neural site of origin of parasympathetic innervation of much of the gastrointestinal tract, has been reported to be an early pathological finding.³ As noted above, however, the occurrence of central neural pathology would not exclude a concurrent afferent or efferent lesion, and studies have found Lewy bodies in the myenteric plexus of both the esophagus and colon,⁹ as well as loss of enteric dopaminergic neurons in PD with chronic constipation.¹⁹

Evidence for abnormalities of the sympathetic noradrenergic and parasympathetic cholinergic components of the autonomic nervous system in our patient occurred without evidence for compromised adrenomedullary function. On the contrary, the patient had augmented plasma epinephrine responses to glucagon injection, both upon initial evaluation and at follow-up. The patient therefore did not appear to have diffuse loss of catecholaminergic cells. Although studies have noted decreased adrenomedullary catecholamine

concentrations in patients with severe PD,^{7,20,21} plasma levels of epinephrine and its O-methylated metabolite, metanephrine, have been reported to be normal.¹⁰

Combined cardiac sympathetic denervation (with attendant denervation supersensitivity), baroreflex-cardiovascular hypofunction, and adrenomedullary hyper-responsiveness might explain the symptoms and signs of cardiovascular instability, such as episodic hypertensive paroxysms, tachycardia, palpitations, and chest pain despite normal coronary arteries, that led to clinical suspicion of pheochromocytoma in this patient.

The results in this case lead us to propose that cardiac sympathetic denervation and decreased baroreflex-cardiovascular gain may be biomarkers of early autonomic involvement in PD. Studies in progress about autonomic function in relatives of patients with familial PD should help test this hypothesis.

Acknowledgments

This research was supported by the Intramural Research Program of the NIH, National Institute of Neurological Disorders and Stroke.

REFERENCES

1. Bonuccelli U, Lucetti C, Del Dotto P, et al. Orthostatic hypotension in de novo Parkinson disease. *Arch Neurol* 2003; 60:1400–1404.
2. Bouhaddi M, Vuillier F, Fortrat JO, et al. Impaired cardiovascular autonomic control in newly and long-term-treated patients with Parkinson's disease: involvement of L-dopa therapy. *Auton Neurosci* 2004; 116:30–38.
3. Braak H, de Vos RA, Bohl J, Del Tredici K. Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett* 2006; 396:67–72.
4. Braak H, Rub U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm* 2003; 110:517–536.
5. Braune S. The role of cardiac metaiodobenzylguanidine uptake in the differential diagnosis of parkinsonian syndromes. *Clin Auton Res* 2001; 11:351–355.
6. Camerlingo M, Aillon C, Bottacchi E, et al. Parasympathetic assessment in Parkinson's disease. *Adv Neurol* 1987; 45:267–269.
7. Carmichael SW, Wilson RJ, Brimijoin WS, et al. Decreased catecholamines in the adrenal medulla of patients with parkinsonism. *N Engl J Med* 1988; 318:254.
8. Druschky A, Hilz MJ, Platsch G, et al. Differentiation of Parkinson's disease and multiple system atrophy in early disease stages by means of I-123-MIBG-SPECT. *J Neurol Sci* 2000; 175:3–12.
9. Edwards LL, Quigley EM, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease: frequency and pathophysiology. *Neurology* 1992; 42:726–732.
10. Goldstein DS, Holmes C, Sharabi Y, Brentzel S, Eisenhofer G. Plasma levels of catechols and metanephrines in neurogenic orthostatic hypotension. *Neurology* 2003; 60:1327–1332.
11. Goldstein DS, Horwitz D, Keiser HR. Comparison of techniques for measuring baroreflex sensitivity in man. *Circulation* 1982; 66:432–439.
12. Goldstein DS, Tack C. Noninvasive detection of sympathetic neurocirculatory failure. *Clin Auton Res* 2000; 10:285–291.
13. Li ST, Dendi R, Holmes C, Goldstein DS. Progressive loss of cardiac sympathetic innervation in Parkinson's disease. *Ann Neurol* 2002; 52:220–223.
14. Oka H, Mochio S, Onouchi K, Morita M, Yoshioka M, Inoue K. Cardiovascular dysautonomia in de novo Parkinson's disease. *J Neurol Sci* 2006; 241:59–65.
15. Oka H, Mochio S, Yoshioka M, Morita M, Onouchi K, Inoue K. Cardiovascular dysautonomia in Parkinson's disease and multiple system atrophy. *Acta Neurol Scand* 2006; 113:221–227.
16. Orimo S, Amino T, Itoh Y, et al. Cardiac sympathetic denervation precedes neuronal loss in the sympathetic ganglia in Lewy body disease. *Acta Neuropathol (Berl)* 2005; 109:583–588.
17. Pacak K, Eisenhofer G, Carrasquillo JA, Chen CC, Li ST, Goldstein DS. 6-[¹⁸F]fluorodopamine positron emission tomographic (PET) scanning for diagnostic localization of pheochromocytoma. *Hypertension* 2001; 38:6–8.
18. Quadri R, Comino I, Scarzella L, et al. Autonomic nervous function in de novo parkinsonian patients in basal condition and after acute levodopa administration. *Funct Neurol* 2000; 15:81–86.
19. Singaram C, Ashraf W, Gaumnitz EA, et al. Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. *Lancet* 1995; 346:861–864.
20. Stoddard SL, Ahlskog JE, Kelly PJ, et al. Decreased adrenal medullary catecholamines in adrenal transplanted parkinsonian patients compared to nephrectomy patients. *Exp Neurol* 1989; 104:218–222.
21. Stoddard SL, Tyce GM, Ahlskog JE, Zinsmeister AR, Carmichael SW. Decreased catecholamine content in parkinsonian adrenal medullae. *Exp Neurol* 1989; 104:22–27.
22. Takatsu H, Nishida H, Matsuo H, et al. Cardiac sympathetic denervation from the early stage of Parkinson's disease: clinical and experimental studies with radiolabeled MIBG. *J Nucl Med* 2000; 41:71–77.
23. Vogel ER, Sandroni P, Low PA. Blood pressure recovery from Valsalva maneuver in patients with autonomic failure. *Neurology* 2005; 65:1533–1537.

Correspondence: David S. Goldstein, MD, PhD, Clinical Neurocardiology Section, NINDS, NIH, 10 Center Drive MSC-1620, Building 10, Room 6N252, Bethesda, MD 20892-1620; goldsteind@ninds.nih.gov