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Cardiac denervation in patients with Parkinson disease

Until relatively recently, Parkinson disease (PD) was viewed as mainly a movement disorder, resulting from loss of nigrostriatal dopamine terminals in the brain. Almost all patients with PD, however, have symptoms or signs of dysfunction of the autonomic nervous system,[1] such as constipation, urinary incontinence, orthostatic or postprandial light-headedness, heat or cold intolerance, and orthostatic hypotension. Recent studies focusing on the sympathetic noradrenergic component of the autonomic nervous system have supported the concept that PD is not only a movement disorder but also a form of dysautonomia. This review provides an update on the status of the innervation of the heart in PD.

SYMPATHETIC INNERVATION OF THE HEART

The autonomic nervous system has multiple components—enteric, parasympathetic cholinergic, sympathetic cholinergic, sympathetic noradrenergic, and adrenomedullary hormonal—and failure of a particular component produces characteristic clinical manifestations. In particular, sympathetic noradrenergic failure presents as orthostatic hypotension, which can cause or contribute to susceptibility to falls and other accidental trauma. Moreover, orthostatic hypotension is amenable to treatment, and administration of drugs for the movement disorder can worsen orthostatic tolerance and decrease blood pressure when the patient stands. Orthostatic hypotension occurs in about 40% of patients with PD and can be an early finding.[2]

Sympathetic nerves in the heart emanate from thoracic ganglia and course with the epicardial coronary arteries before diving into the myocardium. The fibers seem to develop along the coronary vascular trunk, since after cardiac transplantation, reinnervation begins in and often is confined to the anteroseptal base of the heart.

EVIDENCE FOR CARDIAC AND EXTRACARDIAC NORADRENERGIC DENERVATION IN PD

Since 1997, more than 40 neuroimaging studies have assessed the sympathetic innervation of the heart in PD. There has been universally consistent evidence for loss of sympathetic noradrenergic nerves. Several postmortem pathology studies demonstrating profoundly decreased tyrosine hydroxylase immunoreactivity in epicardial nerves or myocardial tissue have confirmed cardiac sympathetic denervation in PD.[3] In remarkable contrast, more than 15 neuroimaging studies have reported intact cardiac noradrenergic innervation in multiple system atrophy, a finding confirmed also by postmortem immunohistochemistry.

Cardiac denervation and orthostatic hypotension: Association but no causation

Although orthostatic hypotension in patients with parkinsonism has been thought to be a side effect of treatment with levodopa, the neurocirculatory abnormalities attending PD with orthostatic hypotension occur independently of levodopa treatment.[4]

Whereas cardiac sympathetic denervation, as indicated by 6-[^{18}F]fluorodopamine-derived radioactivity, seems to be virtually universal in PD patients who have neurogenic orthostatic hypotension, about one half of patients with PD who do not have orthostatic hypotension also have neuroimaging evidence for loss of cardiac noradrenergic innervation **(Figure 1)**. Therefore, cardiac noradrenergic denervation does not cause the orthostatic hypotension in PD.

Etiologic link with alpha-synucleinopathy

Patients with familial PD from mutation of the gene encoding alpha-synuclein or from triplication of the normal gene have low myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity,[5,6] whereas

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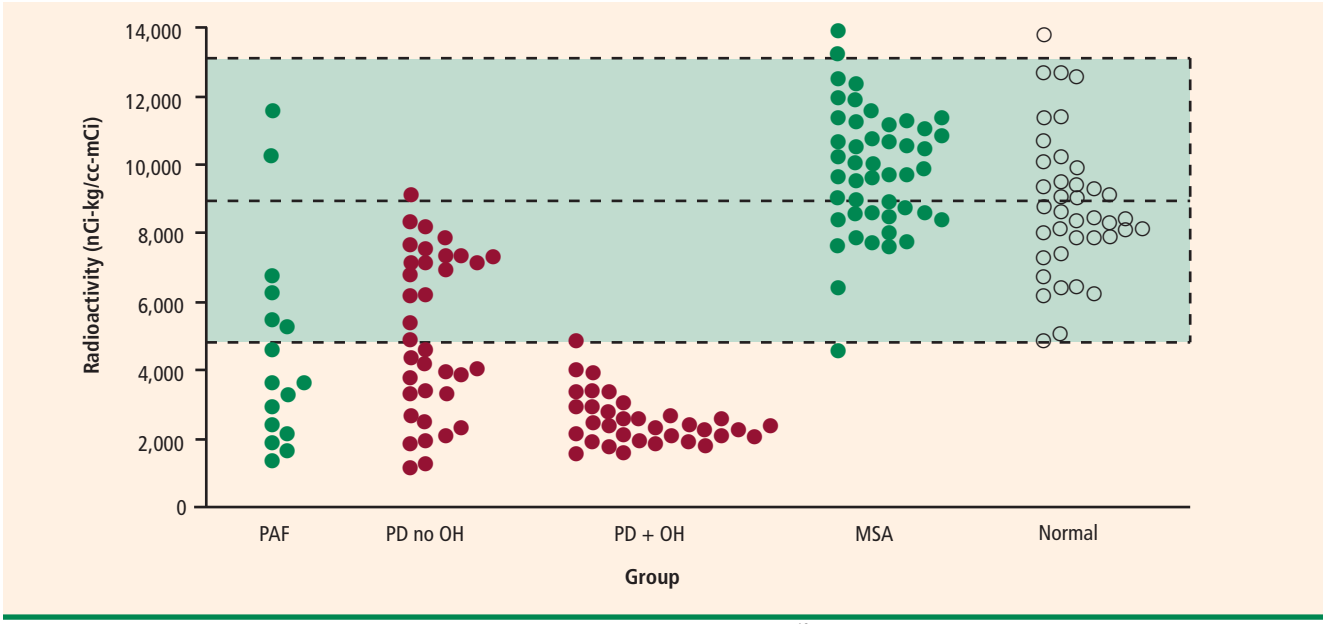

FIGURE 1. Individual values for interventricular septal myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity in patients with pure autonomic failure (PAF) or multiple system atrophy (MSA) (green circles), patients with Parkinson disease (PD) with or without orthostatic hypotension (OH) (red circles), and normal volunteers (empty circles). Rectangles with dashed lines indicate normal mean value ± 2 standard deviations. Note that virtually all "PD + OH" patients have low radioactivity and that virtually all MSA patients have normal radioactivity.

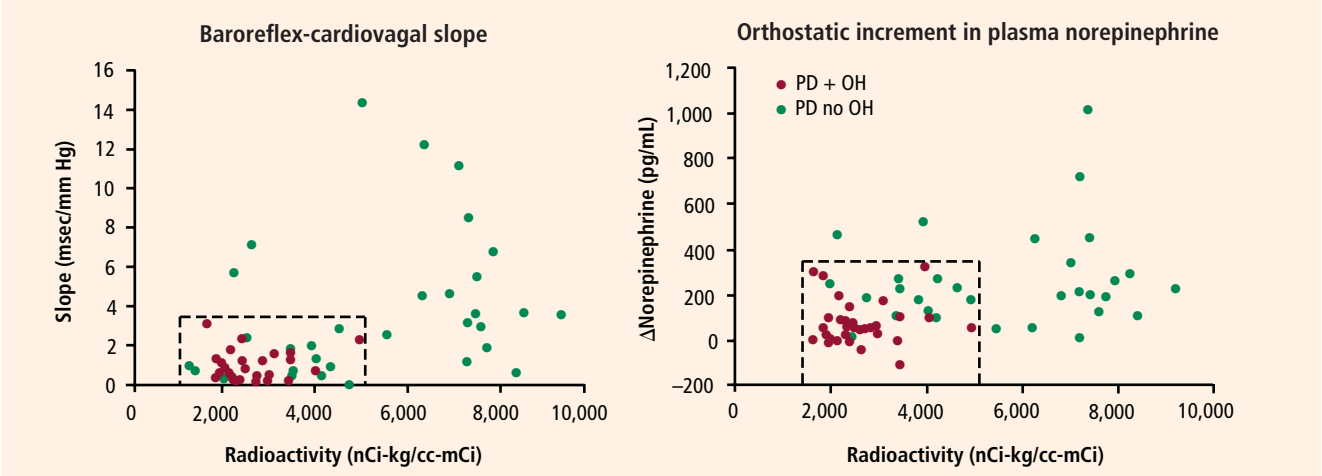

FIGURE 2. Individual values for baroreflex-cardiovagal slope and the orthostatic increment in plasma norepinephrine, expressed as functions of interventricular septal myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity, in patients with Parkinson disease (PD) with (red circles) or without (green circles) orthostatic hypotension (OH). Note the low values for both baroreflex-cardiovagal slope and the orthostatic increment in plasma norepinephrine in patients with OH.

patients with familial PD from mutation of the gene encoding parkin have normal cardiac innervation,[7] indicating an etiologic link between cardiac sympathetic denervation and alpha-synucleinopathy.

Progression over years

The loss of cardiac innervation in PD progresses over years, in a pattern suggesting a "dying-back" pathogenetic sequence[8] that seems to be the mirror image of the sequence of partial reinnervation after cardiac transplantation.[9] Compared with patients who do not have orthostatic hypotension, PD patients with orthostatic hypotension have lower plasma levels of norepinephrine and of its main neuronal metabolite, dihydroxyphenylglycol, consistent with extracardiac noradrenergic denervation.

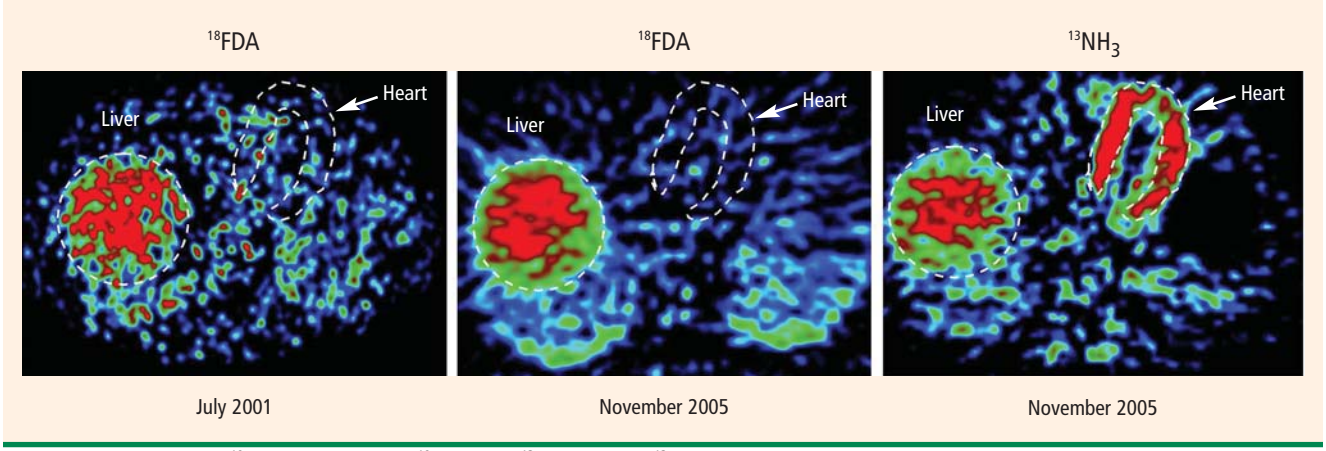

FIGURE 3. Thoracic 6-[^{18}F]fluorodopamine (^{18}FDA) and ^{13}N-ammonia ($^{13}NH_3$) images from July 2001 and November 2005 in a patient who first developed symptoms of Parkinson disease in about May 2005. Note the absence of left ventricular myocardial ^{18}FDA-derived radioactivity in both 2001 and 2005, indicating cardiac sympathetic denervation. Myocardial perfusion, as indicated by $^{13}NH_3$-derived radioactivity, was normal.

Extracardiac denervation

Patients with PD and orthostatic hypotension also have relatively low concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity in the renal cortex, indicating noradrenergic denervation not only of the heart but also of the kidneys.[10]

Associations with baroreflex-cardiovagal and baroreflex-sympathoneural failure

The arterial baroreflex constitutes a classic, frequently studied neurocirculatory reflex. Distortion of stretch-sensitive cells in the walls of large arteries and the heart evokes reflexive increases in vagal outflow to the heart, resulting in bradycardia, and also decreased sympathetic outflows to the cardiovascular system, resulting in vasodilation and decreased force of contraction of the heart. One can estimate baroreflex-cardiovagal gain from the slope of the relationship between interbeat interval and systolic blood pressure during phase II of the Valsalva maneuver.[11] Baroreflex-sympathoneural gain can be assessed by the increment in plasma norepinephrine during orthostasis. In PD patients with orthostatic hypotension, both baroreflex-cardiovagal and baroreflex-sympathoneural gain are virtually universally very low and correlated with the myocardial concentration of 6-[^{18}F]fluorodopamine-derived radioactivity **(Figure 2)**. Thus, PD with orthostatic hypotension features not only cardiac noradrenergic denervation but also baroreflex-cardiovagal and baroreflex-sympathoneural failure.

The site or sites of central neural lesions producing baroreflex failure in PD remain largely unknown. Cells of the rostral ventrolateral medulla that contain phenylethanolamine-*N*-methyltransferase, the enzyme catalyzing conversion of norepinephrine to epinephrine (C1 cells), project to sympathetic preganglionic neurons, and PD patients have been reported to have a loss of C1 cells.[12] The dorsal motor nucleus of the vagus nerve can have cell loss or Lewy bodies in PD,[13,14] but the main source of vagal effer-

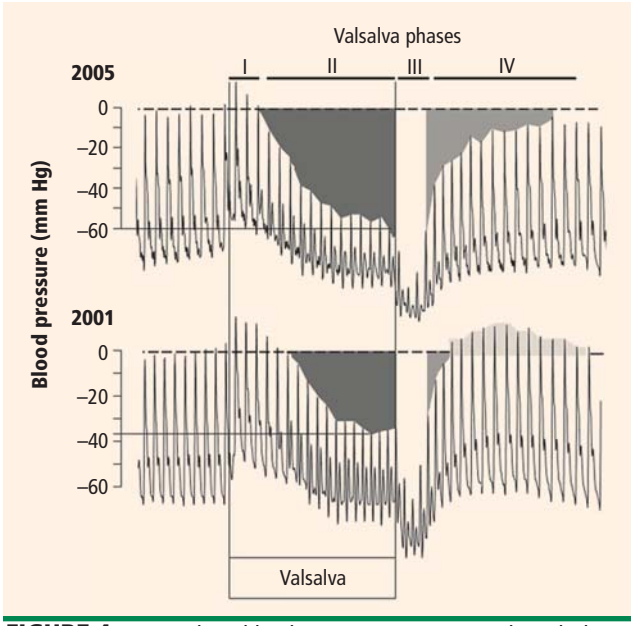

FIGURE 4. Beat-to-beat blood pressure responses to the Valsalva maneuver in November 2005 and July 2001 in the same patient as in Figure 3. In 2001, 4 years before the onset of PD, the patient had relatively little increase in heart rate for a given decrease in blood pressure during phase II of the Valsalva maneuver. In the 2005 recording, note the progressive decline in blood pressure during phase II and the absence of pressure overshoot and delayed return of pressure toward baseline in phase IV, consistent with declining baroreflex-sympathoneural function.

ents mediating reflexive bradycardia is the nucleus ambiguus, and the nucleus ambiguus does not appear to be involved.[15]

NEUROCARDIOLOGIC TESTING FOR DETECTING EARLY PD?

As indicated by the data in **Figure 2**, combined cardiac denervation and baroreflex hypofunction characterizes virtually all patients with PD and orthostatic hypotension. Others have reported this combination in de novo PD,[16,17] consistent with early involvement of peripheral autonomic or lower brainstem centers. Whether these abnormalities can actually *precede* symptomatic PD has been unknown. We recently evaluated a patient who had both cardiac noradrenergic denervation, detected by 6-[^{18}F]fluorodopamine positron emission tomography, and baroreflex-cardiovagal failure, detected by abnormal beat-to-beat blood pressure and heart rate responses to the Valsalva maneuver, 4 years before the onset of PD **(Figures 3 and 4)**. The findings in this potentially important case suggest that neurocardiologic testing may provide a biomarker for detecting presymptomatic or early PD.

SUMMARY

More than 40 neuroimaging studies have reported evidence for loss of sympathetic noradrenergic nerves in PD. Cardiac sympathetic denervation is virtually universal in patients with PD and neurogenic orthostatic hypotension. About one half of patients with PD who do not have orthostatic hypotension also have evidence for loss of noradrenergic innervation. The loss progresses over years, in a pattern suggesting "dying-back." Because patients with familial PD from mutation of the gene encoding alpha-synuclein or from triplication of the normal gene have low myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity, cardiac sympathetic denervation seems linked etiologically with alpha-synucleinopathy. Baroreflex-cardiovagal failure and cardiac sympathetic denervation can occur before onset of the movement disorder, suggesting that neurocardiologic testing might provide a biomarker for detecting presymptomatic or early PD and for following responses to putative neuroprotective treatments.

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