Neurocirculatory Abnormalities in Parkinson Disease With Orthostatic Hypotension
Independence From Levodopa Treatment

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Abstract—Patients with Parkinson disease often have orthostatic hypotension. Neurocirculatory abnormalities underlying orthostatic hypotension might reflect levodopa treatment. Sixty-six Parkinson disease patients (36 with orthostatic hypotension, 15 off and 21 on levodopa; 30 without orthostatic hypotension) had tests of reflexive cardiovagal gain (decrease in interbeat interval per unit decrease in systolic pressure during the Valsalva maneuver; orthostatic increase in heart rate per unit decrease in pressure); reflexive sympathoneural function (decrease in pressure during the Valsalva maneuver; orthostatic increment in plasma norepinephrine); and cardiac and extracardiac noradrenergic innervation (septal myocardial 6-[18F]fluorodopamine-derived radioactivity; supine plasma norepinephrine). Severity of orthostatic hypotension did not differ between the levodopa-untreated and levodopa-treated groups with Parkinson disease and orthostatic hypotension (−52±6 [SEM] versus −49±5 mm Hg systolic). The 2 groups had similarly low reflexive cardiovagal gain (0.84±0.23 versus 1.33±0.35 ms/mm Hg during Valsalva; 0.43±0.09 versus 0.27±0.06 bpm/mm Hg during orthostasis); and had similarly attenuated reflexive sympathoneural responses (97±29 versus 71±23 pg/mL during orthostasis; −82±10 versus −73±8 mm Hg during Valsalva). In patients off levodopa, plasma norepinephrine was lower in those with (193±19 pg/mL) than without (348±46 pg/mL) orthostatic hypotension. Low values for reflexive cardiovagal gain, sympathoneural responses, and noradrenergic innervation were strongly related to orthostatic hypotension. Parkinson disease with orthostatic hypotension features reflexive cardiovagal and sympathoneural failure and cardiac and partial extracardiac sympathetic denervation, independent of levodopa treatment. (Hypertension. 2005; 46:1333-1339.)

Key Words: hypotension ■ sympathetic nervous system ■ norepinephrine ■ baroreflex

Primary chronic autonomic failure syndromes have been classified clinically in 3 forms: pure autonomic failure (PAF), multiple system atrophy (MSA), and Parkinson disease (PD) with autonomic failure.1 All 3 forms feature neuropathic orthostatic hypotension (OH), supine hypertension,2,3 and attenuation of the orthostatic increase in the plasma level of norepinephrine (NE), the sympathetic neurotransmitter.4,5 Levodopa is a precursor of dopamine and therefore of NE. In the treatment of PD, levodopa is usually combined with an inhibitor of L-aromatic-acid-decarboxylase, such as carbidopa, which does not penetrate the blood–brain barrier. Combined levodopa/carbidopa treatment therefore augments delivery of levodopa to the brain and mitigates nausea and vomiting thought to result from occupation of dopamine receptors outside the blood–brain barrier. Combined levodopa/carbidopa treatment attenuates but does not prevent catecholamine synthesis from levodopa outside the brain.6,7 Reflexive cardiovagal gain has been reported to be variably decreased in PD8,9 and markedly decreased in PD+OH.10 Levodopa treatment of PD can affect reflexive cardiovagal function,11 and decreased reflexive cardiovagal gain is more prominent in patients with long-standing PD,12 who would be expected to be on levodopa. This study explored whether levodopa treatment is related to abnormal neurocirculatory function in PD+OH.

Several homeostatic reflexes maintain blood pressure during orthostasis, a complex stimulus that decreases venous return to the heart and alters proprioceptive and vestibular inputs to the brain. In this study, we used 2 methods to assess reflexive cardiovagal gain: the extent of increase in heart rate per unit decrease in systolic pressure during orthostasis and the extent of decrease in interbeat interval per unit decrease in systolic pressure during the Valsalva maneuver, which should not entail altered proprioceptive and vestibular inputs.

In phase II of the Valsalva maneuver, cardiac stroke volume decreases, and reflexive sympathetically mediated vasoconstriction normally prevents the blood pressure from
falling progressively; in phase IV, the heart ejects a normal volume of blood into the reflexively constricted vasculature, so that blood pressure temporarily overshoots the baseline value. An abnormal pattern of beat-to-beat blood pressure, in which pressure falls progressively in phase II and fails to overshoot the baseline value in phase IV, can detect reflexive sympathetic neurocirculatory failure; however, this is a qualitative and somewhat subjective measure. In the present study, we measured the extent of fall in systolic pressure during the Valsalva maneuver, which would be expected to be excessive in reflexive sympathetic neurocirculatory failure. Plasma NE levels normally approximately double within 5 minutes of an individual’s standing up from the supine position. The extent of increase in plasma NE during orthostasis provides another quantitative index of sympathetic neurocirculatory function. In this study, we used both indices to examine whether levodopa-treated PD + OH patients differ from levodopa-untreated PD + OH patients in terms of reflexive sympathetic neurocirculatory function. It should be noted that the magnitude of the orthostatic increment in plasma NE does not decrease as a function of normal aging.

More than 25 studies using cardiac sympathetic neuroimaging have agreed that patients with PD have a loss of noradrenergic innervation of the heart. Postmortem pathologic studies have confirmed marked loss of tyrosine hydroxylase immunoreactivity in myocardial nerves; and most patients with PD have Lewy body pathology or α-synucleinopathy in sympathetic ganglia. The status of noradrenergic innervation outside the heart in PD has been much less clear. Without stratification in terms of levodopa treatment, PD + OH patients have normal plasma levels of NE and its neuronal metabolite dihydroxyphenylglycol (DHPG), though the same patients have neuroimaging and neurochemical evidence for loss of cardiac noradrenergic nerves. Release of NE into the venous drainage of the heart normally contributes negligibly to NE concentrations in the systemic circulation. Therefore, systemic plasma levels of NE and DHPG provide an indication of extracardiac sympathetic innervation. Our previous work did not address whether and to what extent levodopa treatment would affect the physiological and neurochemical results in PD + OH. We have accumulated sufficient data from PD + OH patients who were off or on levodopa at the time of evaluation to analyze the data after stratification of the groups and examine possible interactions of levodopa treatment with plasma NE and DHPG as neurochemical indices of extracardiac noradrenergic innervation in PD + OH.

Methods
A total of 64 patients with PD were studied: 34 with and 30 without OH. Mean ages were 72 ± 1 (SEM) and 60 ± 2 years, with ranges of 51 to 84 and 41 to 82 years. Of the PD patients with OH, 21 were men and 13 were women, and of those without OH, 26 were men and 4 were women. Twenty-eight of the 34 PD + OH patients and 28 of the 30 PD patients without OH were white. Of patients with OH, 14 were off and 20 on levodopa, and of patients without OH, 5 were off and 25 on levodopa at the time of evaluation. All patients had been referred for evaluation of autonomic function at the National Institutes of Health Clinical Center. Each patient gave informed written consent before participating in ≥1 research protocols approved by the institutional review board of the National Institute of Neurological Disorders and Stroke.

Comparison data were used from patient groups with MSA (n = 42) or PAF with cardiac sympathetic denervation (n = 28). Normal data were obtained from an ongoing database of healthy volunteers.

All subjects were studied in a dedicated patient observation room, with ambient temperature kept at 73°F to 76°F and humidity ~50%. Most subjects were studied in the morning after fasting overnight except for noncaloric liquids. For orthostasis, the subject was tilted to a full upright position within ~7 seconds. OH was defined by a persistent, consistent fall in systolic blood pressure ≥20 mm Hg and diastolic pressure ≥10 mm Hg, between lying supine for ≥15 minutes and standing or upright tilting for 5 minutes, using automated devices enabling measurement of beat-to-beat pressure (Colin 7000; Colin Instruments, Inc.; Finometer; TNO), with the probe kept at heart level.

Patients were considered to be off levodopa at the time of testing if plasma levels of dopa, dopamine, and dihydroxyphenylacetic acid were all normal. Reflexive cardiovagal responsiveness was quantified from the slope of the relationship between cardiac interbeat interval and systolic blood pressure during phase II of the Valsalva maneuver. For the Valsalva maneuver, the patient, while supine with head on pillow, blew into a tube connected to a sphygmomanometer to maintain a pressure of 30 mm Hg for 12 seconds. Cardiovagal responsiveness was also measured from the reflexive increment in heart rate per unit decrease in systolic pressure between lying supine and after upright posture for 5 minutes among subjects in whom blood pressure fell.

Reflexive sympathetic neurocirculatory function was quantified from the orthostatic increment in plasma NE and from the fall in systolic blood pressure during the Valsalva maneuver (difference between maximum pressure and minimum pressure) among subjects in whom blood pressure fell.

Cardiac noradrenergic innervation was assessed by thoracic positron emission tomographic scanning and quantification of the septal myocardial concentration of radioactivity in the interval 5 to 10 minutes after initiation of a 3-minute intravenous injection of 1 mCi of 6-[18F]fluorodopamine. Extracardiac noradrenergic innervation was assessed by plasma levels of NE and DHPG in subjects after ≥15 minutes of supine rest. Blood was obtained via an indwelling arm catheter and assayed by liquid chromatography with electrochemical detection after batch alumina extraction, as described previously by our group.

Data were analyzed by independent-means t tests, ANOVA with Fisher’s protected least significant difference post hoc test, and calculation of correlation coefficients and χ2.

Results
Orthostatic Vital Signs
During supine rest, the groups with PD + OH, PD without OH, MSA, or PAF did not differ in systolic, diastolic, or mean arterial pressure or in heart rate. Among the group with PD + OH, the subgroup off levodopa did not differ from that on levodopa in mean values for these variables (160 ± 2 versus 154 ± 2 mm Hg; 88 ± 2 versus 83 ± 2 mm Hg; 112 ± 3 versus 106 ± 3 mm Hg; 69 ± 2 versus 72 ± 2 bpm). In marked contrast, the groups differed clearly in orthostatic mean changes in systolic, diastolic, and mean arterial pressure (F = 12.5, P < 0.0001; F = 12.0, P < 0.0001; F = 13.8, P < 0.0001; Figure 1) but not in heart rate (F = 1.3). The PD + OH group off levodopa did not differ from that on levodopa in terms of orthostatic changes in blood pressure or heart rate (Figure 1).
Reflexive Cardiovagal Function

Reflexive cardiovagal gain during the Valsalva maneuver was very low in PD+OH patients (0.96±0.16 ms/mm Hg; n=31), similar to values in MSA and PAF and far below normal (Figure 2). Reflexive cardiovagal gain in the PD group without OH did not differ from a previously published value in middle-aged patients with essential hypertension.30 The PD+OH subgroups off or on levodopa had similarly low reflexive cardiovagal gain (Figure 2). The PD+OH group did not differ from the PD group without OH in the extent of increase in heart rate during the Valsalva maneuver (11±2 versus 13±2 bpm), and the PD+OH subgroups off or on levodopa also did not differ in the extent of the heart rate increase (12±3 versus 10±2 bpm).

The increase in heart rate for a given decrease in systolic pressure during orthostasis varied with patient group (F=16.6; P<0.0001), with much lower mean values in the groups with PD+OH, PAF, or MSA than in the group with PD lacking OH (P<0.0001 for each comparison). In contrast, the magnitude of the tachycardia response to orthostasis, without adjustment for blood pressure, did not differ between the PD+OH group and the PD group without OH (14±2 versus 13±3 bpm) or between the PD+OH subgroups off versus on levodopa (16±2 versus 11±3 bpm/mm Hg).

Across all subjects, individual values for reflexive cardiovagal gain during the Valsalva maneuver correlated positively with the extent of increase in heart rate for a given decrease in systolic pressure during orthostasis (r=0.61; P<0.0001).

Reflexive Sympathetic Neurocirculatory Function

The mean orthostatic increment in plasma NE varied with the subject group (F=9.5; P<0.0001) and was smaller in the PAF, MSA, and PD+OH groups than in the PD group without OH or in the normal volunteer group (Figure 3). The PD+OH subgroups off versus on levodopa had similarly attenuated orthostatic plasma NE responses (Figure 3). The PD+OH group had a larger mean decrease in systolic pressure than did PD patients without OH (P=0.01). The PD+OH groups off or on levodopa had similarly augmented falls in systolic pressure during the Valsalva maneuver.

Across all subjects, the extent of fall in systolic blood pressure during orthostasis correlated negatively with the
corresponding orthostatic increment in plasma NE \((r=-0.47; P<0.0001)\) and with the fall in systolic pressure during the Valsalva maneuver \((r=0.26; P=0.03)\). The orthostatic increment in plasma NE also correlated negatively with the fall in pressure during the Valsalva maneuver \((r=0.21; P=0.05)\).

### Sympathetic Noradrenergic Innervation

Plasma NE during supine rest varied with subject group \((F=4.2; P=0.003)\). Compared with the normal volunteer group, patients with PAF had low plasma NE, patients with PD who did not have OH had high plasma NE, and patients with MSA or PD+OH groups had normal plasma NE (Figure 5A). PD+OH patients off levodopa had lower mean plasma NE \((193\pm20 \text{ pg/mL})\) than did healthy controls \((280\pm18 \text{ pg/mL}; t=2.6; P=0.01)\) but higher levels than did PAF patients \((88\pm19 \text{ pg/mL}; t=3.9; P=0.0006)\).

Plasma DHPG during supine rest also varied with subject group \((F=3.7; P=0.006)\). Compared with the normal volunteer group, patients with PAF had low plasma DHPG, patients with PD who did not have OH had high plasma DHPG, and patients with MSA or PD+OH groups had normal plasma DHPG (Figure 5B). PD+OH patients off levodopa had lower mean plasma DHPG \((634\pm34 \text{ pg/mL})\) than did healthy controls \((280\pm18 \text{ pg/mL}; t=2.6; P=0.01)\) but higher levels than did PAF patients \((415\pm51 \text{ pg/mL}; t=3.6; P=0.001)\).

Among PD+OH patients, the SD of plasma NE during supine rest \((415 \pm \text{ pg/mL})\) was \(>5\times\) that in PD+OH patients off levodopa \((75 \pm \text{ pg/mL})\). Because of the marked interindividual variability of plasma NE levels in PD+OH patients on levodopa, the subgroups off versus on levodopa did not differ significantly in mean plasma NE during supine rest. Among PD+OH patients on levodopa, the SD of plasma DHPG \((1248 \pm \text{ pg/mL})\) was \(\approx10\times\) that among PD+OH patients off levodopa \((133 \pm \text{ pg/mL})\).

Across all patients off levodopa, plasma DHPG correlated positively with plasma NE \((r=0.66; P=0.0001)\). For a given NE level, the PD+OH group had lower plasma DHPG than did the group with PD lacking OH \((\chi^2=13.2; P=0.0002)\).

As expected, PD+OH patients who were on levodopa at the time of evaluation had higher and more variable plasma levels of dopamine and 3,4-dihydroxyphenylacetic acid than did PD+OH patients who were off levodopa \((293\pm115 \text{ versus } 21\pm9 \text{ pg/mL}; t=2.0; P=0.06; 17 \ 325\pm4214 \text{ versus } 1117\pm104 \text{ pg/mL}; t=3.4; P=0.002)\).

Of 11 PD patients off levodopa who had combined reflexive cardiovagal failure and extracardiac noradrenergic denervation, as indicated by reflexive cardiovagal gain <2.0 ms/mm Hg during the Valsalva maneuver and plasma NE <300 pg/mL during supine rest, all had OH, whereas of 4 patients off levodopa who had cardiovagal gain and plasma NE greater than these amounts, none had OH \((\chi^2=19; P<0.0001)\). Conversely, of 14 PD+OH patients off levodopa, 13 had cardiovagal gain <2.0 ms/mm Hg, and all had
plasma NE <300 pg/mL, whereas of 5 PD patients without OH studied off levodopa, all had cardiovagal gain >2.0 ms/mm Hg and 4 had plasma NE >300 pg/mL ($\chi^2=15$; $P=0.0001$).

**Discussion**

In this study, we obtained evidence for associations of OH with reflexive cardiovagal failure, reflexive sympathetic neurocirculatory failure, and extracardiac noradrenergic denervation in PD, independently of levodopa treatment.

Studies of reflexive cardiovagal function have sometimes found\(^9,31\) and sometimes not found\(^8,12\) abnormalities overall in PD. PD+OH patients have attenuated reflexive cardiovagal gain assessed by heart rate and blood pressure changes during phase II of the Valsalva maneuver and have attenuated orthostatic increments in plasma NE\(^2\) consistent with decreased reflexive cardiovagal and sympathetic neurocirculatory function. The present results confirmed and extended this interpretation by an additional quantitative measure of reflexive cardiovagal function, the extent of increase in heart rate per unit decrease in systolic pressure during orthostasis, and an additional measure of reflexive sympathoneural function, the extent of fall in systolic pressure during the Valsalva maneuver.

Because patients with baroreflex failure typically do not have OH\(^32,33\) reflexive cardiovagal and sympathetic neurocirculatory failure might be insufficient to explain OH in PD. The present results highlight the additional factor of extracardiac sympathetic denervation. Previous studies of PD overall have noted elevated plasma NE during supine rest\(^34,35\) or normal levels.\(^36–39\) In the present study, we separately analyzed neurochemical data for patients who were off levodopa. Patients were considered to be off levodopa only if their plasma 3,4-dihydroxymandelate, dopamine, and dihydroxyphenylacetic acid levels all were normal. Using this criterion, PD+OH patients who were off levodopa had low plasma NE levels during supine rest, compared not only with PD patients without OH, as reported previously,\(^36–40,41\) but also with elderly healthy volunteers. Nevertheless, PD+OH patients had plasma NE levels that were clearly higher than those in PAF patients, consistent with more severe loss of extracardiac noradrenergic nerves in PAF.\(^42\) The results therefore fit with partial loss of extracardiac noradrenergic nerves in PD+OH.

Among healthy volunteers and patients with uncomplicated essential hypertension who do not have OH, baroreflex–cardiovagal gain varies inversely with plasma NE.\(^30\) PD+OH patients had lower plasma NE than would be expected from concurrent baroreflex–cardiovagal failure, again consistent with at least partial loss of extracardiac noradrenergic nerves.

PD+OH patients who were treated with levodopa all had clearly larger SDs of plasma NE and DHPG levels than did groups with the same diagnoses who were off levodopa. In previous studies, individual variability could have resulted in false-negative results for group differences in plasma NE.

It is well accepted that PD involves not only loss of dopamine cells of the substantia nigra but also of NE cells of the locus ceruleus, especially in demented or depressed patients.\(^43,44\) PD also entails loss of cells in medullary nuclei that participate in autonomic outflows or baroreflex regulation, such as C1 cells of the rostral ventrolateral medulla,\(^45\) the dorsal motor nucleus of the vagus nerve,\(^46\) noradrenergic cells of the nucleus of the solitary tract,\(^47\) and serotonergic raphe nuclei.\(^48\) Destruction of the nigrostriatal dopamine system in rats attenuates baroreflex responses,\(^49\) and Braak has noted $\alpha$-synuclein accumulations in the dorsal motor nucleus of the vagus as one of the earliest pathologic changes in PD.\(^50,51\) These findings fit with the concept that brain stem neuropathology may underlie deficient neurocirculatory reflex function in PD+OH. Considering more extensive loss of catecholaminergic cells of the ventrolateral medulla in MSA than in PD,\(^52\) the same amount of OH in the 2 diseases might reflect relatively greater peripheral neuronal loss in the latter.

**Study Limitations**

Failure of effectors can obscure or prevent assessments of other components of homeostatic negative feedback loops. The present evidence of partial extracardiac noradrenergic denervation in PD+OH prevented concluding that sympathetic neurocirculatory failure reflected baroreflex failure in this group.

Heart rate responses to the Valsalva maneuver depend mainly on modulation of parasympathetic cardiovagal outflow. If there were parasympathetic cholinergic denervation of the heart in PD+OH, then the denervation would obviate assessment of the rest of the reflex arc, and, again, one could not conclude that cardiovagal failure reflected baroreflex failure in PD+OH. Whether patients with PD+OH have cardiovagal denervation is unknown. It is known that these patients have intact sympathetic cholinergic innervation of sweat glands, indicating that such patients do not have a diffuse cholinergic lesion.\(^53\) In the present study, PD+OH patients did not differ from PD patients lacking OH in terms of the extent of increase in heart rate during the Valsalva maneuver or during orthostasis, although the patients had markedly smaller heart rate responses for given decreases in systolic pressure during these maneuvers. These findings would tend to favor baroreflex–cardiovagal failure over parasympathetic denervation as a cause of attenuated heart rate responses in PD+OH.

**Perspectives**

The present findings support the view that PD is not only a movement disorder but also a form of cardiovascular dysautonomia, in which OH occurs as part of the disease process because of a combination of reflexive cardiovagal failure, sympathetic neurocirculatory failure, and partial extracardiac noradrenergic denervation, independently of levodopa treatment. This combination might constitute a pathophysiological substrate upon which treatment of the movement disorder in PD using drugs that directly or indirectly elicited vasodilatation could worsen orthostatic tolerance and decrease orthostatic blood pressure, as has been reported for levodopa\(^54,55\) and dopamine receptor agonists.\(^37,56–58\)

**Acknowledgments**

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


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_Hypertension_. 2005;46:1333-1339; originally published online October 10, 2005; doi: 10.1161/01.HYP.0000188052.69549.e4

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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