Published in final edited form as:

J Neurol Sci. 2011 November 15; 310(1-2): 123–128. doi:10.1016/j.jns.2011.06.047.

Mechanisms of orthostatic hypotension and supine hypertension in Parkinson disease[☆]

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Abstract

Non-motor aspects of Parkinson disease (PD) are now recognized to be important both clinically and scientifically. Among these facets are abnormalities in blood pressure regulation. As much as 40% of PD patients have orthostatic hypotension (OH), which is usually associated with supine hypertension (SH). Symptoms of OH range from light-headedness to falls with serious trauma. SH, while typically asymptomatic, poses a significant increased risk for cardiovascular morbidity and mortality. Neuroimaging, neurochemical, and neuropharmacological studies indicate cardiac and extra-cardiac sympathetic noradrenergic denervation and baroreflex failure in virtually all PD patients with OH, and cardiac sympathetic denervation has been confirmed histopathologically. Mechanisms of SH in PD+OH remain poorly understood. The diurnal blood pressure profile shows increased variability that is correlated with decreased baroreflex gain and with increased morbidity and mortality. Treatment should be individually tailored according to the timing of OH or SH, using primarily short-acting sympathomimetic medications in the daytime for OH and short-acting antihypertensive in the nighttime for SH. Future research is needed to understand better and attenuate blood pressure fluctuations through manipulations that improve baroreflex function.

Keywords

Parkinson; Supine hypertension; Orthostatic hypotension; Baroreflex; Blood pressure; Autonomic

1. Introduction

Parkinson disease (PD) has been considered to be primarily a movement disorder. Over the past decade, however, substantial evidence has documented non-motor aspects of the disease, including dementia, chronic constipation, loss of sense of smell, REM behavior disorder, chronic fatigue, daytime sleepiness, and orthostatic intolerance [1–4]. These symptoms can dominate the clinical picture, and in at least in some cases they can precede

[☆]The authors have no conflicts of interest to disclose.

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the motor findings required for diagnosing PD [5]. In PD the process of sympathetic denervation begins before the denervation is apparent clinically but can be appreciated based on subtle abnormalities such as a decrease Phase IV overshoot of blood pressure after the Valsalva maneuver [6].

Among the most clinically important non-motor features of PD is altered blood pressure regulation. In this report we focus on orthostatic hypotension (OH) and supine hypertension (SH). Typically, PD+OH patients also have SH, and fluctuations between OH and SH can result in a variety of morbid consequences.

2. Orthostatic hypotension in PD

OH is defined as a persistent, consistent, orthostatic fall in systolic blood pressure of 20 mm Hg or diastolic pressure of 10 mm Hg by 3 min of standing up [7]. OH can be an asymptomatic sign or manifest as symptoms that range from lightheadedness to loss of consciousness. In our experience PD+OH patients do not typically present with recurrent syncope, because they come to recognize and respond to premonitory symptoms such as generalized weakness, dizziness, fading vision, or lightheadedness while standing that are relieved by lying down. PD+ OH patients often present with recurrent falls, an obvious and important risk factor for potentially lethal consequences such as hip fracture and head trauma.

OH occurs fairly commonly in PD, occurring in about 40% of patients [8]. The OH attending PD is virtually always neurogenic and can dominate the clinical picture. A simple yet sensitive test to screen for a neurogenic cause of OH is by analyzing blood pressure responses to the Valsalva maneuver. Typically, blood pressure decreases during the straining portion (Phase II), but in the late part of Phase II (Phase II_L) the pressure increases from its nadir. Following the maneuver, in Phase IV the blood pressure rapidly increases to above the baseline level. Both the increase in pressure in Phase II_L and the noticeable pressure overshoot in Phase IV require an intact sympathetic nervous system to evoke the reflexive cardiovascular responses. In PD+OH, blood pressure typically decreases progressively during the maneuver, and there is no overshoot after the maneuver, revealing baroreflex-sympathoneural failure (Fig. 1). Consistent with this view, PD+OH patients have attenuated orthostatic increments in plasma levels of norepinephrine (NE), the sympathetic neurotransmitter. Blunted increases in heart rate for given systolic pressure decreases in Phase II of the Valsalva maneuver indicate concurrent baroreflex-cardiovagal failure.

The sympathetic neurocirculatory failure underlying OH in PD also involves important and substantial sympathetic noradrenergic denervation. Several neuroimaging, neurochemical, and neuropharmacological studies by our group and others have addressed this matter. 6-[¹⁸F]Fluorodopamine (¹⁸F-DA) is a positron emission tomographic (PET) imaging agent that is taken up by sympathetic nerve endings via the cell membrane NE transporter and radiolabeled storage vesicles in sympathetic nerves [9,10]. Using ¹⁸F-DA PET scanning we found that PD+OH patients consistently have very low ¹⁸F-DA-derived radioactivity diffusely in the left ventricular myocardium (Fig. 2) [11]. Many studies using 123I-metaiodobenzylguanidine single photon emission computed tomography have reported

analogous evidence of cardiac sympathetic denervation in PD, which post-mortem neuropathology has by now amply confirmed. The clinical use of MIBG in the assessment of cardiac sympathetic denervation should be emphasized. This technique is available in most parts of the world, and a large body of evidence has demonstrated the ability of MIBG scanning to serve as a tool for semi-quantitative assessment of cardiac sympathetic innervation [6,12]. PD+OH patients have a lower mean plasma NE level compared to PD patients without OH. Several neuropharmacological tests distinguish PD±OH. The plasma DHPG response to infusion of tyramine (an indirect sympathomimetic amine that displaces NE from vesicles into the cytosol), NE response to infusion of isoproterenol (a beta-adrenoceptor agonist that evokes exocytotic NE release), and blood pressure responses to trimethaphan (a ganglion blocker) and yohimbine (a central sympathomimetic) are blunted in PD±OH, and the DHPG concentration in skeletal muscle microdialysate is low—all indicating a decreased complement of sympathetic noradrenergic nerves in the body as a whole in PD+OH (Fig. 3).

In the setting of decreased cardiovascular sympathetic innervation and baroreflex failure, vasodilation and hypovolemia elicited by dopamine produced from levodopa might decrease the blood pressure, both during supine rest and when standing in patients with PD. Therefore, orthostatic intolerance and OH may occur in patients with PD while taking levodopa/carbidopa or dopamine receptor agonists, not directly from effects of these drugs alone but from interactions with baroreflex and sympathoneural denervation occurring as part of the disease process.

Early, prominent OH in patients with Parkinsonism has been considered to exclude PD and to support another diagnosis, such as the Parkinsonian form of multiple system atrophy (MSA) [13], which is characterized by OH [14]. Among patients with PD+OH, in a substantial proportion OH comes on before, at the time of, or within one year of onset of the movement disorder [15], and idiopathic OH initially diagnosed as pure autonomic failure (PAF) can evolve into PD+OH [16]. Symptomatic OH can come on late in the course of PD [17] or can already be prominent in *de novo* PD [15,18,19]. Considering that PD is far more prevalent than MSA or PAF, one should consider PD in the differential diagnosis of neurogenic OH [20].

At least four factors related to cardiovascular autonomic regulation distinguish PD+OH from PD without OH. PD+OH patients have failure of both the cardiovascular and sympathoneural limbs of the baroreflex, whereas PD patients without OH have normal or near normal baroreflex gains [21–23]. The baroreflex abnormalities may be related to markedly decreased numbers of catecholaminergic neurons in the nucleus of the solitary tract [24], which is the site of the initial synapse of baroreflexes. Second, PD+OH patients all have loss of cardiac sympathetic noradrenergic innervation that is diffuse throughout the left ventricular myocardium, whereas about half of PD patients without OH have intact or locally decreased innervation [25]. Third, PD+OH patients have neuroimaging evidence for decreased renal sympathetic innervation [26], which may promote natriuresis and diuresis and increase susceptibility to blood volume depletion. Finally, PD+OH entails neuropharmacologic, neurochemical, and neuroimaging evidence for decreased noradrenergic innervation in the body as a whole, whereas PD without OH does not [27,28].

3. Supine hypertension in PD+OH

In PD, as in other forms of primary chronic autonomic failure, OH is associated with supine hypertension (SH) [21,29], which sometimes is severe (Fig. 4). Review of the NIH experience to date shows that the magnitude of SH in PD is directly related to the magnitude of OH ($r=0.57$, $p<0.0001$) and inversely related to the log of baroreflex-cardiovagal gain ($r=-0.39$, $p=0.01$).

Unlike OH, which often manifests with symptoms related to the orthostatic fall in blood pressure when the patient first arises in the morning, SH often occurs late in the day or at night and typically elicits no symptoms. Schmidt et al. reviewed 24-hour blood pressure recordings of patients with various extrapyramidal syndromes and control subjects [30]. They found that 48% of PD patients had nocturnal hypertension, particularly among those with OH.

The authors also suggested a link between the nocturnal hypertension and increased cardiovascular risk in these patients. SH with a blood pressure above 150/90 mm Hg while supine is known to be associated with elevated risk for several adverse outcomes such as left ventricular hypertrophy, congestive heart failure, atrial fibrillation, and chronic renal failure. Moreover, the risk of stroke or myocardial infarction is high late at night, when PD+OH patients can have extremely high blood pressure. The extent to which results of studies of patients with sustained hypertension apply to PD+OH, in which blood pressure can be quite low during ambulatory activities, remains unclear.

The mechanism for SH associated with PD+OH is unknown. It is unlikely to be driven by increased sympathetic outflows, because as noted above PD + OH patients have cardiac and extra-cardiac sympathetic denervation. Hardly any research has been done to understand this important phenomenon. Garland et al. examined kidney function as a determinant of high blood pressure in 64 pure autonomic failure (PAF) patients and found a slight increase in plasma creatinine among PAF patients and a lower glomerular filtration rate in PAF patients with than without SH. The resemblance in clinical and pathophysiological features with regards to blood pressure dysregulation in PAF and PD patients might lead one to speculate about a similar pattern in PD+OH; however, such a small impairment in renal function seems unlikely to explain the severe SH that PD+OH patients have. Further research is needed, with attention to denervation supersensitivity of alpha-adrenoceptors, blood volume, baroreflex gain, endothelial dysfunction, increased arterial stiffness, and increased arteriolar wall:lumen ratios.

4. Blood pressure variability

A hallmark of baroreflex failure is blood pressure variability (Fig. 4), and since PD+OH patients have profound baroreflex failure, it is expected that they should also have variable pressure. As noted by Schmidt et al. through 24-hour ambulatory blood pressure monitoring [30], blood pressure variability expressed as the standard deviation of daytime and nighttime pressure readings is 30–50% greater in PD patients than in control subjects.

Target organ damage in hypertension is determined to an important extent by blood pressure variability. Thus, for any given average blood pressure, future development of left ventricular hypertrophy is significantly higher when hypertensive patients are stratified based on blood pressure variability [31]. Furthermore, the development of carotid atherosclerosis is increased in patients with high blood pressure variability [32]. The combination of advanced age, increased blood pressure variability, and SH results in high risk of stroke [33]. This combination is frequent in PD patients and poses a critical clinical challenge. An elegant prospective study by Driver et al. [34] demonstrated a hazard ratio of 1.6 for cardiac mortality and hazard ratio of 3.26 for cerebrovascular mortality among PD patients compared to matched controls.

5. The spectrum of OH and SH in PD

Co-occurrence of OH and SH in PD suggests a common mechanism. Because of the renal function curve, which relates urinary sodium excretion to renal perfusion pressure, SH might evoke pressure natriuresis, resulting in relative daytime hypovolemia and OH; however, day-night differences in blood volume have not been assessed in PD+OH patients.

Another practical aspect is counteracting effects of medications. Some patients are on antihypertensive medications for SH and in addition sympathomimetics for OH. Inappropriate timing might worsen morning OH or night-time SH.

As noted above, a key determinant of high blood pressure variability is baroreflex failure. In a study of PD patients with or without OH, baroreflex-cardiovagal gain was calculated from the relation between the interbeat interval and systolic pressure during the Valsalva maneuver. PD+OH entailed SH that was similar in severity to that in essential hypertension. Among patients with PD, those with OH had much lower mean baroreflex-cardiovagal gain (Fig. 5). It should be noted that early PD can be associated with decreased baroreflex-cardiovagal gain [6]. In our experience, however, as a group PD±OH patients have far worse baroreflex-cardiovagal and baroreflex-sympathoneural function than do PD without OH patients.

Baroreflex failure may be a common determinant of OH, SH, and high blood pressure variability and help explain adverse outcomes associated with the wide fluctuations in pressure [35,36]. In animal models, low baroreflex sensitivity results in substantial increases in inflammatory and atherosclerotic changes in the arterial wall [36].

6. Management of OH–SH

OH and SH pose different clinical challenges, and accordingly the clinician should divide efforts to control OH and SH. One must make note of the circumstances under which each patient suffers from OH and SH. For this purpose, 24-hour blood pressure monitoring is highly recommended. This monitoring enables objective measures of diurnal variation and the timing and extent of blood pressure fluctuations.

For OH the main therapeutic goal should not be to reduce the magnitude of fall in blood pressure in response to standing but to provide symptomatic relief. PD+OH patients often

can tolerate large decreases in blood pressure without symptoms. Low blood pressure during orthostasis and OH should first be treated using non-pharmacological approaches. Patients should be instructed to take frequent small meals, have a relatively high rate of water intake, and avoid rapid changes in posture or prolonged standing. Elastic hose to the waist may be tried; sometimes these help, but often they are not worth the effort and inconvenience. Patients should be informed that rapid ingestion of tap water can elicit a substantial, sustained increase in blood pressure [37] and that performing physical counter-maneuvers such as crossing the legs, squatting, tensing the muscles of the legs, abdomen, or buttocks may help maintain blood pressure briefly [38]. Rigorous review of medications and times of the day when they are taken is important. Levodopa should not be avoided, as OH occurs irrespective of treatment with levodopa [23], and improvement in muscle tone and control might increase the efficiency of muscle pumping during orthostasis and ambulation.

When these interventions do not suffice in providing symptomatic relief, medications to increase blood pressure are needed. In view of the sympathodeficient state in PD+OH, adrenoceptor agonist drugs are used. The most extensive experience is with midodrine. L-dihydroxyphenylserine (L-DOPS, droxidopa, Northera) is an alternative [39,40]. One must take into account the relatively short half-lives of these drugs. In the setting of OH-SH this can be an advantage, as the timing can be adjusted to the hours of activity without a negative effect on the high blood pressure at night. In severe cases, where symptoms persist or are associated with injuries, treatment with fludrocortisone, desmopressin, octreotide, methylphenidate, or yohimbine may be warranted.

SH should be addressed regardless of symptoms. As for OH, non-pharmacological treatments should be tried first—particularly sleeping with the head of the bed elevated on blocks. Usually this approach is not sufficient to lower blood pressure below 150/90 mm Hg, and antihypertensive medications are considered. The appropriate drugs are short acting and with minimal OH as a known side effect, as PD+OH patients may get up at night, sometimes several times. Short acting angiotensin converting enzyme inhibitors such as enalapril or captopril or short acting angiotensin receptor blockers such as losartan are reasonable choices. Some reports suggest the use of clonidine at bedtime, but this should be done with caution, as rebound hypertension has been described with this drug. Transdermal nitroglycerin as paste or patch is another option with a practical advantage, since the effect can be stopped quickly when the patient removes the drug from the skin [41,42]. Another option that has been studied but is not approved as an antihypertensive agent is sildenafil, which not only exerts a blood pressure lowering effect but also can assist with improving erectile function [43].

In summary, OH, SH, and variable blood pressure are frequent and often occur together in PD. All three severely affect quality of life or increase risks of morbidity. OH is associated with cardiac and extra-cardiac sympathetic denervation and baroreflex failure. Mechanisms of SH in PD are unknown. The clinical assessment of this triad should include 24 h blood pressure monitoring. Because of denervation supersensitivity, adrenoceptor agonists should be considered early in drug treatment of OH in PD. Nocturnal SH should be treated by short-acting drugs such as angiotensin receptor blockers, nitroglycerine, or clonidine. Future

research is needed to understand better and attenuate blood pressure fluctuations through manipulations that increase baroreflex sensitivity.

Abbreviations

PD	Parkinson disease
OH	orthostatic hypotension
SH	supine hypertension
SNS	sympathetic nervous system
MSA	multiple system atrophy
PAF	pure autonomic failure
NE	norepinephrine

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Fig. 1.

Heart rate and blood pressure responses in the 4 phases of the Valsalva maneuver in (left) a control subject and (right) a patient with Parkinson disease and orthostatic hypotension. Neurogenic orthostatic hypotension is characterized by a progressive decline in blood pressure in phase II (arrow), slow recovery of blood pressure in phases III and IV and absence of overshoot in pressure above baseline in phase IV (thick black line).

Fig. 2. Cardiac positron emission tomographic scans after intravenous injection of 6- ^{18}F fluorodopamine (6- ^{18}F FDA) or the perfusion imaging agent ^{13}N -ammonia (^{13}N NH₃) in patients with pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson disease with neurogenic orthostatic hypotension (NOH) and normal volunteers (NV). Note absence of detectable 6- ^{18}F fluorodopamine-derived radioactivity in the left ventricular myocardium, despite normal perfusion as indicated by ^{13}N -ammonia-derived radioactivity, in the patient with Parkinson disease.

Fig. 3.

Group comparison between subjects with pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson disease with neurogenic orthostatic hypotension (NOH) and normal volunteers (NV) in (A) plasma dihydroxyphenylglycol glycol (DHPG) responses (means $\pm$ SEM) to tyramine infusion; (B) plasma norepinephrine (NE) responses (means $\pm$ SEM) to isoproterenol infusion; (C) Skeletal muscle microdialysate concentrations (means $\pm$ SEM) of dihydroxyphenylglycol glycol (DHPG); and (D) change in systolic blood pressure (PBs) to yohimbine or trimethaphan infusion.

Fig. 4.
24-hour blood pressure monitoring of a 73 years old patients with Parkinson disease and orthostatic hypotension.

Fig. 5.

Log baroreflex slope, derived from heart rate response to blood pressure changes in patients with Parkinson disease with orthostatic hypotension (PD+OH), Parkinson disease without orthostatic hypotension (PD no OH) and healthy volunteers (Normal).