Early Abnormalities of Vascular and Cardiac Autonomic Control in Parkinson’s Disease Without Orthostatic Hypotension

Franca Barbic, Francesca Perego, Margherita Canesi, Michela Gianni, Sara Biagiotti, Giorgio Costantino, Giovanni Pezzoli, Alberto Porta, Alberto Malliani, Raffaello Furlan

Abstract—Cardiac autonomic abnormalities have been described in Parkinson’s disease. Little is known about possible alterations of vascular sympathetic regulatory activity in patients without orthostatic hypotension or symptoms of orthostatic intolerance. Nineteen patients with Parkinson’s disease without orthostatic hypotension (PD), 21 with orthostatic hypotension (PDOH), and 20 healthy controls underwent ECG, beat-to-beat arterial pressure, and respiration recordings while recumbent and during a 75° head-up tilt. Spectrum analysis of RR interval and systolic arterial pressure (SAP) variability provided indices of cardiac sympathovagal interaction (low frequency [LF]/high frequency [HF]) to the sinoatrial node and sympathetic vasomotor control (LFSAP). Arterial baroreceptor mechanisms were assessed by the spontaneous sequences technique and bivariate spectrum analysis (α index). Plasma catecholamines provided the neurohormonal profile. At rest, hemodynamics and spectral markers of autonomic function were similar in PD and control subjects. Norepinephrine was lower in PD and PDOH than in control subjects. In PDOH, SAP was higher, whereas LF/HF ratio and LFSAP were lower compared with control subjects. During tilt, SAP was unchanged in PD; however, similar to PDOH, the increase of heart rate, LF/HF ratio, and LFSAP was blunted compared with control subjects. Baroreflex indices were unmodified in PD and PDOH compared with control subjects. Initial alterations in both cardiac and vascular sympathetic modulatory activity were found in PD and revealed by a gravitational stimulus. Prompt recognition of sympathetic abnormalities might result in earlier therapeutic intervention, reduced orthostatic intolerance, and increased quality of life. (Hypertension. 2007;49:1-7.)

Key Words: nervous system ■ sympathetic ■ arterial baroreceptors ■ power spectrum analysis ■ tilt test ■ Parkinson’s disease

Hypertension during orthostasis1–3 is a common finding4,5 in the advanced phases of Parkinson’s disease. It leads to additional disabling symptoms and may worsen movement capability and increase the number of falls, thus further impairing a patient’s self-sufficiency. In addition, orthostatic hypotension is often accompanied by remarkable hypertension while recumbent.6,7 The latter is also a cardiovascular risk factor in patients with dysautonomia,8 thus requiring appropriate antihypertensive drug treatment that, in turn, may worsen blood pressure decrease during standing.9

Abnormalities of cardiovascular autonomic control have been proposed as possible underlying mechanisms leading to the decrease of arterial pressure during standing,10–13 although most of the drugs used to control symptoms in Parkinson’s disease may promote orthostatic hypotension.14

Presently, the large majority of studies have focused on cardiac autonomic abnormalities, and different methodologies have been used to address both the morphological15 and functional alterations of heart innervation in Parkinson’s disease. A study based on spectral analysis of heart rate variability reported a reduction in absolute values of both the high-frequency (HF) and low-frequency (LF) spectral components in patients compared with age-matched controls.16 Reduced uptake of meta-[(123)I]iodobenzylguanidine (MIBG), suggestive of partial cardiac sympathetic denervation, has been observed in patients with Parkinson’s disease by means of MIBG myocardial scintigraphy.17 In a study based on cardiac norepinephrine spillover and positron emission tomography scan using radiolabeled interventricular fluorodopamine, a selective cardiac sympathetic denervation has also been described.18

To the best of our knowledge, only 1 study has simultaneously described the alterations of cardiac and vascular autonomic control in patients with Parkinson’s disease and orthostatic hypotension.10 However, it is still unclear whether early abnormalities in sympathetic vasomotor control are also
present in patients not suffering from symptoms because of orthostatic intolerance or from orthostatic hypotension. These aspects share potential clinical implications because the early detection of abnormalities in vascular sympathetic control might help to alert patients and physicians about the importance of promptly identifying symptoms of orthostatic hypotension and starting treatment with fluids and salt load to prevent falls.

In the present study, we tested the hypothesis that even in the absence of orthostatic hypotension and symptoms because of orthostatic intolerance, patients with Parkinson’s disease are characterized by a certain degree of alteration in cardiovascular autonomic control in response to the gravitational stimulus. Healthy control subjects and a second group of patients with Parkinson’s disease and orthostatic hypotension served as reference for intact and markedly impaired cardiovascular autonomic functions, respectively.

**Methods**

**Population**

We studied 40 consecutive patients with Parkinson’s disease characterized by a mild/medium motor impairment, referred to the outpatient clinic of the Parkinson’s Disease Center of Istituti Clinici di Perfezionamento in Milan. Parkinson’s disease was diagnosed on the basis of clinical criteria. Radiographic (MRI) signs were also used to exclude other dysautonomias and neuro-degenerative diseases. Patients characterized by a motor disability accounted for by stages 1 to 3 of the Hoehn-Yahr scale were eligible to be enrolled. Patients were excluded if liver, kidney, lung, heart diseases, or secondary causes of autonomic dysfunction were present on the basis of medical evaluation and routine tests.

According to changes in systolic arterial pressure (SAP) after 5 minute standing they were assigned to the group without orthostatic hypotension ([PD] N=19; 13 men; age 66±2 years) or to the group with orthostatic hypotension ([PDOH] N=21; 15 men; age 69±1 years). Patients without orthostatic hypotension who suffered either from syncope or >3 episodes of presyncope symptoms during the previous 12 months were excluded from the study. In all of the patients, therapy for Parkinson’s disease was maintained unchanged for the 30 days preceding and during the study procedure.

Control subjects (N=20; 12 men; age 64±2 years) were gender- and age-matched healthy volunteers without evidence of organic disease on the basis of interview and physical examination. They were not taking any medication affecting autonomic profile. The characteristics of the 3 populations are illustrated in Table 1.

**Recorded Variables and Protocol**

In every subject we continuously recorded the ECG and noninvasive beat-to-beat blood pressure using the volume-clamp technique (Finapres, Ohmeda 2300). Respiratory activity was concomitantly evaluated by a thoracic bellows connected to a pressure transducer. A catheter was placed on the nondominant arm for blood withdrawal. ECG, arterial blood pressure, and respiratory activity were digitized at 300 samples per second per channel by an analogical-to-digital converter (National Instruments, AT-MIO 16E2) and stored on the hard disk of a personal computer.

Each subject was placed on a motorized tilt table with a footrest and underwent instrumentation as described above. Thirty minutes after instrumentation, baseline data acquisition was initiated, and a blood sample was obtained for plasma catecholamine assessment. Thereafter, subjects were tilted until the 75° head-up position was reached. This position was maintained, if tolerated, for 30 minutes. A second blood sample was taken at minute 5 of the tilt procedure. The tilt procedure was interrupted whenever presyncope signs and symptoms developed. Plasma norepinephrine and epinephrine from venous blood samples were determined by high-performance liquid chromatography with electrochemical detection. The experimental protocol was approved by the ethical committee of the hospital, and written informed consent was obtained from all of the participants.

**Data Analysis**

Analog data were analyzed offline after analog-to-digital conversion at 300 samples per second per channel. Software techniques for data acquisition, spectrum, and cross-spectrum analysis of RR interval and SAP variability and respiration activity have been described in detail elsewhere. As for RR spontaneous variability, there are 2 major spectral components, the amplitude of which are affected by changes in neural autonomic control. One is the HF component (HFRR, ~0.25 Hz at rest), synchronous with the respiratory activity, a recognized index of the vascular efferent modulation to the sinoatrial node discharge. The other spectral component is indicated as LF (LFRR, ~0.1 Hz), and when expressed in normalized units has been proposed to primarily reflect the sympathetic efferent modulation to the sinoatrial node and its changes. Both spectral components of RR variability are provided in absolute units (ms²) and normalized units (n.u.). Absolute values of each component were computed as the integral of the oscillatory components (LFRR, HFRR). Normalization was achieved by dividing the absolute power of each component by total variance minus the power of the very-low-frequency component (~0.03 Hz) and subsequently multiplying by 100. The LF/HF ratio, a nondimensional index, was also calculated to assess the reciprocal changes of sympathetic and vagal modulation of the sinoatrial node discharge. The LF oscillatory component of SAP variability (LFVAP, ~0.1 Hz) was expressed in absolute values and can be used as a marker of the sympathetic modulation of vasoconstrictor activity.

Arterial baroreflex function was assessed by both a frequency domain and a time domain approach at rest and during tilt. The first method is based on cross-spectral analysis of RR and SAP variability. After having obtained a squared coherence function (K²) >0.5, the index α was computed as the square root of the ratio between the powers of the LF (0.1 Hz) spectral components of RR interval and SAP variability and used as an index of arterial baroreceptor activity.

The second method is derived from the detection of spontaneous sequences of ~3 SAP and RR values that simultaneously increase (positive sequences) or decrease (negative sequences). Sequences were considered to reflect baroreceptor activity if the following criteria had been accomplished: (1) RR interval variations were >5 ms, (2) SAP modifications were >1 mm Hg, and (3) sequences were >4 beats. For each sequence, a linear regression between the 2 variables was computed, and the slopes characterized by a correlation coefficient >0.85 were averaged. The final value was taken as the gain of arterial baroreflex control of heart rate (BRS).

Data are expressed as mean±SEM. One-way ANOVA with Bonferroni posttest correction for multiple testing and Student t test for paired observation were used when appropriate. Differences were considered significant at values of P<0.05.

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of Control, PD, and PDOH Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Male/female</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>HY</td>
</tr>
<tr>
<td>L-dopamine, mg/d</td>
</tr>
<tr>
<td>Dopamine agonists (no. of patients)</td>
</tr>
<tr>
<td>Duration of disease, y</td>
</tr>
</tbody>
</table>

HY indicates Hoehn-Yahr scale.
Barbic et al  Sympathetic Alterations in Parkinson’s Disease  3

Results

Demographic and clinical features of patients with Parkinson’s disease and control subjects are summarized in Table 1.

Baseline Hemodynamic and Neurohumoral Data

At rest, the hemodynamics and spectral markers of cardiovascular autonomic modulation of PD were similar to those of healthy control subjects (Tables 2 and 3). PDPOH subjects showed higher values of SAP than control subjects (Table 2). PD and PDPOH subjects were characterized by higher respiratory rate than control subjects (Table 2).

In spite of heart rate values similar in the 3 groups, LF/HF ratios were lower in PDPOH subjects than in the other 2 groups (Table 3). Plasma norepinephrine was slightly higher in the 2 groups of patients compared with control subjects (Table 3).

In spite of heart rate values similar in the 3 groups, LF/HF ratios were lower in PDPOH subjects than in the other 2 groups (Table 3). Plasma norepinephrine was slightly higher in the 2 groups of patients compared with control subjects (Table 3).

TABLE 2. Hemodynamic and Respiratory Parameters of Control, PD, and PDPOH Subjects at Rest and During 75° Head-Up Tilt

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Subjects</th>
<th>PD Subjects</th>
<th>PDPOH Subjects</th>
<th>Control Subjects</th>
<th>PD Subjects</th>
<th>PDPOH Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>69±2</td>
<td>75±2</td>
<td>72±2</td>
<td>83±3</td>
<td>82±3</td>
<td>79±3</td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>120±3</td>
<td>129±4</td>
<td>132±4*</td>
<td>126±3</td>
<td>128±5</td>
<td>96±3†</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>76±2</td>
<td>80±2</td>
<td>82±2</td>
<td>82±2</td>
<td>83±2</td>
<td>70±2†</td>
</tr>
<tr>
<td>Resp, cycles/min</td>
<td>16±1</td>
<td>22±1†</td>
<td>19±1*</td>
<td>19±1</td>
<td>22±1</td>
<td>20±1†</td>
</tr>
</tbody>
</table>

HR indicates heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; Resp, respiration; other abbreviations as in Table 1.

*P<0.05 PDPOH vs control subjects; †P<0.05 PDPOH vs PD subjects; ‡P<0.05 PD vs control subjects.

TABLE 3. Indices of Autonomic Activity and Baroreflex Sensitivity of Control, PD, and PDPOH Subjects at Rest

<table>
<thead>
<tr>
<th>Indices</th>
<th>Control Subjects</th>
<th>PD Subjects</th>
<th>PDPOH Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR variance, ms²</td>
<td>777±141</td>
<td>793±310</td>
<td>286±75</td>
</tr>
<tr>
<td>LFRR, ms²</td>
<td>198±30</td>
<td>225±131</td>
<td>46±17</td>
</tr>
<tr>
<td>n.u.</td>
<td>55.1±3.6</td>
<td>48.0±6.9</td>
<td>36.9±4.5*</td>
</tr>
<tr>
<td>HFRR, ms²</td>
<td>96.5±22</td>
<td>42.2±15.5</td>
<td>52.4±17.9</td>
</tr>
<tr>
<td>n.u.</td>
<td>26.3±3.4</td>
<td>27.8±4.9</td>
<td>44.1±4.0†</td>
</tr>
<tr>
<td>LF/HF</td>
<td>3.1±0.6</td>
<td>3.7±1.0</td>
<td>1.3±0.3†</td>
</tr>
<tr>
<td>LFSAP, mm Hg²</td>
<td>3.5±0.8</td>
<td>3.7±0.8</td>
<td>1.2±0.3†</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>262±12</td>
<td>141±34†</td>
<td>118±20*</td>
</tr>
<tr>
<td>E, pg/mL</td>
<td>27.1±5.3</td>
<td>28.2±5.2</td>
<td>21.6±4.4</td>
</tr>
<tr>
<td>αLF, ms/mm Hg</td>
<td>10.3±1.3</td>
<td>6.5±1.5</td>
<td>7.4±1.4</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>9.2±4.8</td>
<td>7.1±1.0</td>
<td>2.6±0.7</td>
</tr>
</tbody>
</table>

NE indicates norepinephrine; E, epinephrine; αLF, index of arterial baroreceptor sensitivity assessed by bivariate power spectrum analysis; BRS, index of arterial baroreceptor sensitivity assessed by the spontaneous sequences method. For NE and E: control subjects n=9; PD n=8; PDPOH, n=11.

*p<0.05 PDPOH vs control subjects; †p<0.05 PDPOH vs PD; ‡p<0.05 PD vs control subjects.

TABLE 4. Changes Induced by the Tilt Maneuver on the Indices of Cardiac and Vascular Autonomic Control and of Baroreflex Sensitivity in Control, PD, and PDPOH Subjects

<table>
<thead>
<tr>
<th>Indices</th>
<th>Control Subjects</th>
<th>PD Subjects</th>
<th>PDPOH Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR variance, ms²</td>
<td>76±228</td>
<td>−291±208</td>
<td>−176±58</td>
</tr>
<tr>
<td>LFRR, ms²</td>
<td>41.9±64.5</td>
<td>8.2±41.5</td>
<td>−38.7±17.9</td>
</tr>
<tr>
<td>n.u.</td>
<td>20.5±4.1</td>
<td>9.7±7.0</td>
<td>−5.4±5.8*</td>
</tr>
<tr>
<td>HFRR, ms²</td>
<td>−46.7±14.2</td>
<td>−0.3±27.8</td>
<td>−35.5±18.3</td>
</tr>
<tr>
<td>n.u.</td>
<td>−14.5±3.3</td>
<td>−8.9±4.9</td>
<td>−1.7±6.6</td>
</tr>
<tr>
<td>LF/HF</td>
<td>6.7±1.7</td>
<td>1.9±1.3†</td>
<td>1.4±0.7*</td>
</tr>
<tr>
<td>LFSAP, mm Hg²</td>
<td>3.9±0.7</td>
<td>0.66±1.3†</td>
<td>−0.2±0.3*</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>234.3±37.4</td>
<td>145.1±68.5</td>
<td>88.1±28.3</td>
</tr>
<tr>
<td>E, pg/mL</td>
<td>25.5±12.8</td>
<td>15.3±17.0</td>
<td>0.4±7.0</td>
</tr>
<tr>
<td>αLF, ms/mm Hg</td>
<td>−5.0±1.4</td>
<td>−0.7±2.5</td>
<td>−0.8±1.3</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>−3.9±0.8</td>
<td>−3.5±0.9</td>
<td>−0.9±0.6*</td>
</tr>
</tbody>
</table>

NE indicates norepinephrine; E, epinephrine; αLF, index of arterial baroreceptor sensitivity assessed by bivariate power spectrum analysis; BRS, index of arterial baroreceptor sensitivity assessed by the spontaneous sequences method.

*p<0.05 PDPOH vs control subjects. †p<0.05 PDPOH vs PD subjects.
During tilt, the increase of plasma norepinephrine was slightly lower in PD and PDOH subjects compared with control subjects (Table 4 and Figure 1). In control subjects, α and BRS decreased (P < 0.05) during tilt. In contrast, in PD subjects the indices α and BRS were not modified by the tilt procedure (P value not significant), although their mean values were not statistically different compared with control subjects.

Individual data of the relationships between changes in SAP induced by the tilt maneuver and concomitant modifications in RR interval, LF/HF ratio, and LFSAP are depicted in Figure 2. PD subjects showed a blunted capability of increasing the index of vascular sympathetic modulation LFSAP compared with control subjects, in spite of the absence of orthostatic hypotension. In addition, the reduced increase of heart rate and LF/HF ratio during tilt suggested a concomitant alteration of the cardiac sympathovagal relationship with a decreased sympathetic modulatory activity to the sinoatrial node.

**Discussion**

In the present study, we addressed the hypothesis that, even in the absence of symptoms of orthostatic intolerance and orthostatic hypotension, patients with Parkinson’s disease are characterized by some degree of vascular sympathetic impairment.

We found that in the supine position, PD subjects showed a cardiovascular neural modulation indiscernible from that observed in healthy age-matched control subjects. The gravitational stimulus enabled us to reveal abnormalities in the vascular autonomic response of PD subjects consisting of a blunted increase of the spectral index of sympathetic vasomotor control LFSAP compared with control subjects, in spite of the absence of orthostatic hypotension. In addition, the decline of RR interval and the enhancement of LF/HF ratio were less than in control subjects similar to PDOH subjects.

**Cardiovascular and Autonomic Profile of Parkinson’s Disease at Rest**

The results of the present study indicate that, in the supine position, abnormalities in the hemodynamics and in the indices of autonomic function could be observed only in PDOH subjects, whereas patients with Parkinson’s disease without orthostatic hypotension were comparable to healthy subjects. In PDOH, systolic blood pressure was higher and the spectral index of sympathetic vasomotor control LFSAP was lower than in control subjects. These apparently contradictory findings may be reconciled when considering that in similar dysautonomias, a residual sympathetic activity to the vessels has been described and hypothesized to underlie the abnormal increase of blood pressure observed when patients were supine. Similarly, the enhancement of arterial pressure observed in the present study in PDOH subjects at...
rest might be mediated by a residual vascular sympathetic modulation, quantified by \( LF_{SAP} \) in a setting of a likely denervation hypersensitivity\(^6,31\) and reduced baroreflex restraint.\(^32\) In keeping with the latter, it must be pointed out that, in our study, both BRS and \( \alpha \) indices of baroreflex sensitivity were slightly lower in PDOH subjects than in control subjects, although not statistically significant.

As to the potential alterations of cardiac autonomic control at rest, we found reduced LFRR (although not significant) and diminished LF/HF ratio in PDOH subjects, suggesting an impaired cardiac sympathetic modulation only in patients suffering from orthostatic hypotension. This finding is in accordance with previous studies using thoracic PET scanning of the heart and cardiac norepinephrine spillover in patients of similar age, duration, and severity of disease, although in a subset of those patients therapy was withdrawn.\(^11,18,33\) In those studies, a cardiac sympathetic denervation was observed in all of the patients with orthostatic hypotension. However, at difference from our results, in \( \approx 50\% \) of patients without hypotension, a certain degree of cardiac sympathetic abnormalities could be identified in the supine position.\(^11,18,33\) Inequalities in the sensitivity of the methodologies used and minor dissimilarities in the studied populations might account for these discordances.

In keeping with our results, a cardiac sympathetic denervation has already been hypothesized in patients with severe orthostatic hypotension by means of MIBG myocardial scintigraphy\(^17\) and on the basis of a reduced LF component in the power spectrum of RR variability both on short\(^16\) and 24-hour periods.\(^34\) Finally, immunohistochemical staining of postmortem specimens of cardiac tissue showed a decreased number of sympathetic axons innervating the left anterior ventricular wall of the heart of 4 patients suffering from Parkinson’s disease.\(^15\)

Based on cardiac norepinephrine spillover,\(^18\) immunohistochemical staining\(^15\) methodologies, and the presence of Lewy bodies in ganglionic cells and axons of the paravertebral sympathetic chain,\(^35\) the concomitant presence of a peripheral sympathetic denervation disease has been hypothesized recently in Parkinson’s disease.\(^15\) Such an issue was beyond the aims of the present study. Yet, in keeping with the above-mentioned hypothesis, both PD and PDOH patients showed lower values of plasma norepinephrine compared with control subjects, a pattern that resembled what has already been described in patients with pure autonomic failure, namely, in subjects with a peripheral postganglionic sympathetic degeneration.\(^36\)

Finally, an unexpected observation of the present study is the finding of higher values of HFRR n.u. in PDOH subjects than in control subjects at rest. Because HFRR is a recognized marker of cardiac vagal modulation,\(^23,25\) one might infer an increased vagal drive to the sinoatrial node in the group of patients with orthostatic hypotension compared with control subjects. In this context we are convinced that this is not the case. Indeed, in the presence of markedly reduced variance, the HF component of RR variability mainly reflects the mechanics of respiration.\(^36\) As to the LF component in n.u., its use in the presence of very low variance of RR interval seems rather dubious and should be avoided. Therefore, we
restricted the evaluation of cardiac autonomic profile to the LF/HF ratio, a widely accepted index.\textsuperscript{23,24,27} In conclusion, as already observed in dysautonomias with very low total RR variability,\textsuperscript{36} the use of the normalization procedure without considering the absolute power of the different spectral components may be misleading.

**Cardiovascular and Autonomic Changes Induced by a Gravitational Stimulus**

So far, most of the studies but 1\textsuperscript{10} aimed at addressing potential alterations in the neural control of the cardiovascular system in Parkinson’s disease have used methodologies that could focus only on the cardiac autonomic profile and were unable to evaluate both the sympathetic vasomotor control and the patient during dynamic conditions. In the present investigation we assessed both the cardiac and vascular autonomic profile in the supine position and during passive orthostasis focusing on patients without orthostatic hypotension who did not yet suffer from symptoms of orthostatic hypotension.

The gravitational stimulus was associated with an expected decline of blood pressure in PDOH subjects. In addition, the increase of heart rate induced by the tilt maneuver was blunted in both PDOH and PD subjects, thus suggesting that in asymptomatic patients without orthostatic hypotension a cardiac sympathetic abnormality was present and detectable by means of a gravitational stimulus. In keeping with such an inability to shift the cardiac sympathovagal balance toward a sympathetic predominance, the increase of the LF/HF ratio during tilt was reduced in PD compared with control subjects, similarly to PDOH subjects. A dynamic impairment of cardiac sympathetic modulation in accordance with our results has already been described by power spectrum analysis of RR variability during 24-hour ECG recordings\textsuperscript{34} and the tilt maneuver.\textsuperscript{10}

In the PD group, despite the absence of orthostatic hypotension, the tilt-induced increase of LF\textsubscript{SAP} was blunted compared with control subjects, similar to PDOH subjects. This observation suggests that in PD subjects the neural control of blood pressure is, to some extent, different from that of its spontaneous variability as compared with PDOH subjects in whom orthostatic hypotension was mirrored by a blunted increase of LF\textsubscript{SAP}. Therefore, it is possible to hypothesize that, in Parkinson’s disease, initial alterations of sympathetic vasomotor control may primarily affect blood pressure variability, that is, spontaneous systolic pressure 0.1-Hz oscillations, and only subsequently induce changes in the SAP mean values leading to orthostatic hypotension. We highlighted this concept in Figure 2 by showing that PD patients are in between normal control subjects and subjects with a severe cardiovascular autonomic impairment (PDOH), as far as the potential continuum of the relationship between SAP and LF\textsubscript{SAP} changes during tilt is concerned. However, other mechanisms might account for the maintained blood pressure values during standing in PD, including a noradrenergic hypersensitivity likely to be present in our patients because of reduced norepinephrine values at rest. This aspect, however, was not specifically addressed in the present study.

**Limitations**

For ethical reasons, in the present study patients were studied under full regimen therapy that was not modified for $\geq$30 days before the protocol was performed. This might obviously have interfered with patients’ hemodynamics, particularly during the upright position, because of the potential hypotensive effects of dopamine presence. We admit, however, that few patients with orthostatic hypotension might have been classified in the PD group if therapy had been discontinued. In addition, drugs might have influenced the autonomic profile both at rest and during tilt. However, we do believe that overall the main findings of the present study were not affected by possible misdiagnosed orthostatic hypotension, because both groups of patients were under analogous treatment. On the other hand, this approach added an important feature to the present study that enabled us to assess the hemodynamic and autonomic changes likely to be present during a patient’s daily life.

**Perspectives**

The elucidation of the possible initial abnormalities of sympathetic vasomotor control during upright posture has important clinical and social implications. It can be hypothesized that, even in the absence of a recognized orthostatic hypotension, our findings may help patients and physicians to promptly identify symptoms and early signs of orthostatic intolerance and starting treatment with pressor drugs, salt, and water. This might decrease the intensity of symptoms of orthostatic intolerance, thus reducing the number of falls, enhancing self-sufficiency and the quality of life of patients.

**Source of Funding**

This work was funded by an Autogrill S.p.A. grant 2003.

**Disclosures**

None.

**References**


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_Hypertension_. published online November 13, 2006;

_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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