Age and duration related changes in muscle sympathetic nerve activity in Parkinson’s disease

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Objective: To clarify the characteristics of sympathetic vasomotor function in Parkinson’s disease by sympathetic neurographic analysis.

Methods: Muscle sympathetic nerve activity (MSNA) was recorded using a microneurographic technique at rest and during head up tilt in 18 patients with idiopathic Parkinson’s disease and 21 healthy controls. Resting MSNA showed a negative correlation with age in patients with Parkinson’s disease (p<0.05) and a positive correlation with age in controls (p<0.01). There was a negative correlation between duration of disease or disability levels and MSNA (p<0.01).

Conclusions: Sympathetic vasomotor function may be related to age and disease duration in Parkinson’s disease.

Findings or symptoms of autonomic dysfunction are common in patients with Parkinson’s disease, as reported by many investigators. Among autonomic abnormalities, orthostatic intolerance or hypotension is often observed, especially in advanced stages of Parkinson’s disease, probably because preganglionic or postganglionic sympathetic neurones are progressively impaired. However, decreased activity of sympathetic outflow to muscles—an important factor in the control of blood pressure—has not been confirmed conclusively in patients with Parkinson’s disease.

To clarify the characteristics of sympathetic vasomotor function in idiopathic Parkinson’s disease, we recorded muscle sympathetic nerve activity (MSNA) by microneurography in patients with Parkinson’s disease and control subjects with a similar age distribution.

Methods

Patients

We studied 18 patients with Parkinson’s disease (six men, 12 women; mean (SD) age, 67.9 (9.3) years; range 53 to 86) whose modified Hoehn-Yahr disability stages ranged from 2.5 to 4.0 (mean, 3.3 (0.6)) during on periods. We selected patients with idiopathic Parkinson’s disease whose diagnoses were confirmed by at least three years of clinical observation, a good response to levodopa treatment, and absence of demonstrable atrophy of the brain stem or cerebellum on magnetic resonance imaging. The interval from the apparent onset of Parkinson’s disease to the time of study ranged from 2.5 to 4.0 (mean, 3.3 (0.6)) during on periods.

Results: Heart rate and blood pressure at rest did not differ between control and patients. The increase in these variables and MSNA in response to tilting was slightly blunted in the Parkinson’s group. Resting MSNA showed a negative correlation with age in patients with Parkinson’s disease (p<0.05) and a positive correlation with age in controls (p<0.01). There was a negative correlation between duration of disease or disability levels and MSNA (p<0.01).

Conclusions: Sympathetic vasomotor function may be related to age and disease duration in Parkinson’s disease.

Microneurography

Sympathetic neurograms to muscles were recorded using microneurographic techniques, after informed consent had been obtained from each patient. The procedure was approved by the local ethics committee.

Subjects were tested in the supine position. MSNA was recorded directly from peroneal nerve fascicles in the right popliteal fossa using tungsten microelectrodes. Neurograms were obtained using previously described methods.

Identification of MSNA was done on the basis of the following three criteria:

- spontaneous and pulse synchronous rhythmic burst discharge;
- modulation by respiration;
- marked accentuation by a manoeuvre to increase intrathoracic pressure such as the Valsalva manoeuvre.

The electrodes were connected to a preamplifier (DAM50, WPI, Sarasota, Florida, USA) using a gain setting of ×100.
and to an amplifier (AVM-10, Nihon Kohden, Tokyo, Japan) with a gain setting of ×500. A band-pass filter of 500 to 2000 Hz was used. To obtain the mean voltage neurogram, the filtered neurogram was fed into an RC integrating unit (EI-601G, Nihon Kohden) using a time constant of 0.1 s.

Measurement and analysis
ECGs were recorded using chest wall surface electrodes. Heart rate was monitored by ECG. Blood pressure was measured by sphygmomanometry (Finapres, Ohmeda, Madison, Wisconsin, USA). The cuff was attached to the arm by a regression formula based on data from the appropriate parts of the analysis, and corrected for age by a regression formula based on data from the appropriate parts of the analysis. Burst frequency was measured before breakfast in both the resting supine and the standing positions, using high performance liquid chromatography.

MSNA was quantified as only burst frequency (bursts/100 heart beats) in this comparative study, because the number of bursts per minute is easily influenced by heart rate. In appropriate parts of the analysis, burst frequency was corrected for age by a regression formula based on data from controls expressed by percentile. Heart rate, blood pressure, and MSNA measurements were averaged over each minute for 10 minutes. Investigators, who were blinded to clinical findings in individual patients, identified muscle sympathetic bursts by inspecting the mean voltage neurogram.

Parasymptomatic nervous activity was assessed as the variance of RR intervals at rest (CVRR; standard deviation × mean interval−1 × 100) on the ECG. In all subjects, the plasma noradrenaline (norepinephrine) concentration was measured before breakfast in both the resting supine and the standing positions, using high performance liquid chromatography.

Results are expressed as mean (SD). Data were evaluated by Student’s unpaired t test; a probability (p) value of <0.05 defined statistical significance.

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<td>C, UF, OH</td>
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C, constipation; F, female; H, hyperhidrosis; L+C, levodopa+carbidopa; M, male; OD, orthostatic dizziness; OH, orthostatic hypotension; UF, urinary frequency.

Results
In representative recordings, MSNA at rest in a relatively young Parkinson’s disease patient was similar to that in a control subject, but an older patient showed less MSNA at rest than a control subject (fig 1). The response of MSNA to head up tilting was slightly attenuated in both younger and older patients.

No differences in age, heart rate, blood pressure, or CVRR at rest were evident between patient and control groups. The burst frequency of MSNA at rest was negatively correlated with age in the patients with Parkinson’s disease (p<0.05), and positively in the controls (p<0.01, fig 2).

In four patients, head up tilting was not done because the inserted electrodes were pulled out of nerve fascicles by leg movement. The increase in heart rate and MSNA in response to head up tilting was slightly reduced in the patients with Parkinson’s disease. The response of blood pressure during tilting was blunted in Parkinson’s disease (p<0.05, tables 2 and 3), as three patients with orthostatic hypotension were involved. Plasma noradrenaline in the patients with Parkinson’s disease increased less on standing than in the control subjects (p<0.05, table 3).

A negative correlation between duration of disease or disability levels and age adjusted burst frequency of MSNA was observed in Parkinson’s disease (p<0.01, tables 1 and 2, fig 3). No significant relation was found between the degree of increase in MSNA, blood pressure, or noradrenaline in response to tilting or standing and age or disease duration. There was also no significant correlation between sex or body mass index and MSNA. Other tests of sympathetic failure, such as the Valsalva manoeuvre, were only possible in a few patients because of technical difficulties resulting from the parkinsonian symptoms.

Discussion
Recent microneurographic studies have confirmed that resting MSNA gradually increases with age in healthy subjects because of reduced sensitivity of the baroreceptors or a reduction in parasymptomatic tone with advancing age. In contrast, MSNA at rest in our patients with Parkinson’s disease gradually decreased with age, and also
with duration of disease. Older patients showed less MSNA than normal subjects, reflecting the long duration of disease in these patients. Although increases in heart rate, blood pressure, and MSNA during head up tilting in Parkinson’s disease were less than in control subjects, these variables did not show a significant relation to age or disease duration. The lack of a chronological relationship in our study may reflect the exclusion of patients with severe manifestations of autonomic failure, such as frequent syncope with orthostatic hypotension. Actual autonomic deficits would not be present, as an MSNA response during tilt was preserved in all the patients studied, even though resting MSNA was at a low level. The observed reduction in sympathetic activity may be relevant to postural hypotension.

Many investigators have examine associations between Parkinson’s disease and orthostatic intolerance or hypotension. It is reported that 70% of patients with Parkinson’s disease show a mild to severe orthostatic fall in blood pressure. Furthermore, all patients with Parkinson’s disease had postural dizziness, and obvious postural hypotension was observed in 27%. Moreover, a significant fall in systolic blood pressure was seen in patients with Parkinson’s disease even before the initiation of antiparkinsonian treatment.
In contrast, some investigators have reported no differences in the blood pressure response to upward tilt between Parkinson’s disease patients and controls.\textsuperscript{16, 17} However, most recent studies have shown that mild to severe orthostatic hypotension is common in Parkinson’s disease, and is related to the duration and severity of the disease.\textsuperscript{7, 8, 18, 19} As parasympathetic function was normal in our study, abnormalities of cardiovascular reflexes in Parkinson’s disease related to MSNA are suggestive of a generalised neural dysfunction. Our present results are consistent with previous observations of sympathetic vasomotor impairment in Parkinson’s disease. It may be important to confirm the presence of a characteristic autonomic dysfunction in Parkinson’s disease by direct recordings of the sympathetic outflow to muscles.

This study was undertaken while the patients continued to take their antiparkinsonian drugs, so as to prevent the malignant neuroleptic syndrome or any possible effects on the autonomic nervous system from exacerbation of akinesia or body bradykinesia. In relation to possible effects of antiparkinsonian drugs on orthostatic hypotension, many investigators have reported that levodopa treatment has no effect on the orthostatic blood pressure response.\textsuperscript{24, 25, 6} However, several studies have shown that the administration of levodopa or dopamine agonists aggravated the fall in blood pressure in response to upward tilting because of the arterial and venous relaxing effects of these agents.\textsuperscript{82, 0} Although it is possible that MSNA at rest may be increased after administration of antiparkinsonian drugs, this tendency was not observed in our study except in some of the younger patients. While there is still no consensus about these drug effects on autonomic function in Parkinson’s disease, the long term administration of antiparkinsonian drugs appears to have had relatively little effect on sympathetic nerve activity in our study, as our results were not affected by the type of drugs used or the dose given.

Previous neurographic recordings have shown that the increase in MSNA resulting from the administration of levodopa was significantly attenuated in subjects with Parkinson’s disease.\textsuperscript{21} In that study, resting MSNA was similar to that in normal controls, but the investigators did

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not evaluate the relation between age and MSNA. The present report is the first to confirm that orthostatic intolerance or hypotension may reflect an age and duration dependent reduction in outflow from sympathetic vasomotor neurons in Parkinson’s disease, and not a diminution in the vasoconstrictor response of peripheral blood vessels. The related decline in sympathetic function indicates that the intermediolateral nucleus or sympathetic ganglion may be involved during the advanced stages of Parkinson’s disease. It would be helpful if more patients with Parkinson’s disease and orthostatic hypotension are included in future studies of sympathetic activity. The effects of age and disease duration should be considered when assessing autonomic function in patients with Parkinson’s disease.

### Authors’ affiliations

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Competing interests: none declared

### Table 3

Comparison of each variable in patients with Parkinson’s disease and control subjects

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<th>Variable</th>
<th>At rest</th>
<th>Tilt up</th>
<th>Noradrenaline (ng/mL)</th>
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<tr>
<td></td>
<td>HR (beats/min)</td>
<td>MBP (mm Hg)</td>
<td>MSNA (bursts/100 heart beats)</td>
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<tr>
<td>Control (n = 21)</td>
<td>74.5 (9.0)</td>
<td>88.2 (16.0)</td>
<td>64.2 (15.5)</td>
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<tr>
<td>Parkinson’s disease (n = 14–18)</td>
<td>76.8 (10.5)</td>
<td>93.7 (15.9)</td>
<td>58.3 (12.4)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

*p<0.05 vs controls.

CVRR, coefficient of RR interval variability on ECG (standard deviation – mean RR interval * 100); HR, heart rate (beats/min); MBP, mean blood pressure (mm Hg); MSNA, muscle sympathetic nerve activity (bursts/100 heart beats).

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### REFERENCES