Sympathetic neurocirculatory failure in PAF and MSA is due to lesions in the peripheral (post-ganglionic sympathetic neurons) and central autonomic pathways (olivopontocerebellar system, brain stem nuclei and pre-ganglionic neurons), respectively. Increase in arginine vasopressin (AVP) following a head-up tilt (HUT) confirms the presence of central autonomic integrity [1]. Normal basal nor-adrenaline (NA), and an increase in NA following HUT confirms the integrity of peripheral autonomic pathway [2, 3]. Therefore patients with MSA fail to increase AVP following HUT, whereas patients with PAF have low basal NA, and fail to increase NA following HUT. It has been suggested that the mechanism of OH in PD is similar to that of PAF [4].

However, the mechanism of sympathetic neurocirculatory failure in PD is unclear and we hypothesise that it is due to the lesions in both central and peripheral autonomic pathways, because Lewy bodies (LB), which are a marker of neurodegeneration have been demonstrated in both central and peripheral autonomic pathways [5, 6]. In this study, we assessed the autonomic integrity in patients with PD to establish the site of lesion in sympathetic neurocirculatory failure.

**Methods**

We identified patients with PD from the movement disorder clinic register, all of whom fulfilled the UK Brain Bank diagnostic criteria. We excluded subjects with any medical condition or current drug therapy (except medications for PD) that would affect their autonomic function based on medical review and assessment. Also, patients with significant cognitive impairment were excluded. We identified an age and sex-matched healthy controls free from any known diseases and not on any drugs from a general practitioner’s list.

**Protocol**

We carried out the study in the morning and did the following assessments: blood pressure (BP) in the supine position, blood samples for estimation of basal NA and AVP, continuous ECG monitoring, BP every minute using an automated BP monitor, and used the tilt table to perform HUT. We assessed the severity of PD [using full Unified Parkinson’s Disease Rating Scale (UPDRS)], cognitive function [Mini-Mental Status Examination (MMSE)], depressive symptomatology [GDS-15 Geriatric Depression Scale (GDS)] and autonomic symptoms [Autonomic Symptoms Scale (ASS) [7]]. We defined OH as a fall in systolic pressure of 20 mm Hg or diastolic BP of 10 mmHg within 3 min.
of standing or tilt [8]. The local ethics committee approved study protocol and we analysed the statistical difference using the Mann–Whitney U test.

**Results**

Results are shown in Table 1. Out of 262 patients with a clinical diagnosis of PD, only 32 patients were suitable for the study. Although 21 patients agreed to take part in the study, only 13 completed the study. Of the 24 healthy subjects identified, only 6 completed the study.

BP response to handgrip manoeuvre and heart rate response to valsalva manoeuvre were difficult to perform and interpret because of fatigue, tremor and dyskinesia. Therefore, patients were divided into two groups based on presence or absence of OH. In the end, the study cohort consisted of 13 patients with PD (6 with OH, 7 without OH) and 6 controls. Eight patients were on levodopa (four in each group), two were on ropinirole (one in each group) and three (one in OH group) were not on any drugs.

All patients with PD had low basal NA and a smaller increase in NA following HUT compared to controls. In particular, patients with OH had the least increase (statistically significant, P<0.05) in NA following HUT, compared to the other two groups. Three patients with OH had a decrease in NA following HUT, one had negligible increase and the remaining two had an increase comparable to patients without OH. None in the other two groups showed a decrease in NA following HUT.

The OH group also had a statistically smaller increase in AVP (P<0.05) following HUT compared to the other two groups. In this group, four patients had a decrease in AVP, one had negligible increase and the other had an increase comparable to the group without OH. Patients without OH had the largest increase in AVP following HUT. No associations were found between the duration and severity of disease, dose of levodopa, depression and mental state examination. Patients with OH had a significantly higher score on ASS compared to controls.

**Discussion**

The current investigation revealed low basal NA levels and only a small increase in NA following HUT in all patients with PD. Patients with OH had the lowest basal NA levels and the smallest increase in NA following HUT. This indicates the involvement of peripheral post-ganglionic sympathetic neurons in all patients with PD, more so in patients with OH. Patients with OH also showed a blunted response of AVP following HUT confirming the involvement of central sympathetic pathway. These two results demonstrate that PD patients with sympathetic neurocirculatory failure have lesions in both central and peripheral autonomic pathways.

Patients without OH had an increase in AVP following HUT suggesting an intact central autonomic pathway. Also they had a much higher increase in AVP compared to controls. This could possibly be a compensatory mechanism for the inadequate peripheral sympathetic response mediated through NA, as circulating AVP could increase the BP through V1 receptors [9].

It is likely that peripheral sympathetic neurons are involved first, followed by involvement of central autonomic pathway leading to sympathetic failure. Cardiac sympathetic denervation has been demonstrated in all PD patients with OH and in around 50% PD patients without OH [10]. Progressive loss in this pattern has led to the ‘dying-back’ hypothesis in patients with PD having sympathetic neurocirculatory failure. This ascending AF mirrors the recent theory that neurodegeneration in PD follows an ascending course [11].

The hypothalamus has been considered the ‘highest’ level of integration of autonomic function and it remains under the influence of the cortex and the ‘limbic system’. The final
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outputs of these central regulatory circuits are mediated by sympathetic pre-ganglionic neurons of the intermediolateral column of the spinal cord and vasopressin secreting neurons of the hypothalamus.

In a pathological study of 30 patients with PD, LB were identified in every hypothalamic nucleus, with highest counts in postero-lateral areas and tubero-mamillary nucleus [5]. Because AVP is predominantly secreted by paraventricular nuclei in the postero-lateral area, lesions here would explain the impaired AVP release following HUT. LB have also been identified in other structures involved in autonomic regulation such as the reticular formation, the intermediolateral column and the sympathetic ganglia [5, 6, 12].

We found lower NA levels in all patients with PD, more so in patients with OH, as demonstrated previously [2, 4, 13, 14]. Our novel finding is the impaired AVP release following HUT in patients with OH. We are confident that our PD patients with OH did not have MSA. None of these patients fulfilled the clinical criteria for MSA and none had early onset urinary disturbance. Also these patients had low basal NA, unlike patients with MSA who have been shown to have normal basal NA [2, 15].

In the last decade, PD, MSA, PAF and dementia with LB have been classified as α-synucleinopathies. A recent study in dementia with LB has demonstrated similar results [16]. Therefore, it is likely that we are looking at a spectrum of neurodegenerative diseases associated with primary AF involving the peripheral and central sympathetic pathways and propose the following mechanism (Table 2).

In conclusion, this investigation suggests that the pathophysiological mechanism of sympathetic neurocirculatory failure in patients with PD is due to a compromise in both central and peripheral autonomic integrity. Presence of peripheral lesions in all patients and central lesions in only patients with overt sympathetic failure suggest that AF might follow an ascending pattern in PD.

Key points

- Primary autonomic failure associated with neurodegenerative diseases is due to involvement of peripheral and central autonomic pathways.
- Sympathetic neurocirculatory failure in PD is due to a compromise in both central and peripheral autonomic integrity.
- Presence of peripheral lesions in all patients and central lesions in only patients with overt sympathetic failure suggest that AF might follow an ascending pattern in PD.

Conflicts of interest

None.

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References


Table 2. Mechanism of AF

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline NA</th>
<th>NA after HUT</th>
<th>AVP after HUT</th>
<th>Pre-ganglionic lesion</th>
<th>Post-ganglionic lesion</th>
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</tr>
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<tr>
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</tr>
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<td>−</td>
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</tr>
<tr>
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</table>
The influence of positioning upon cerebral oxygenation after acute stroke: a pilot study

Sir—Passive postural changes may have an effect on a number of physiological parameters after stroke [1]. For example, standing, sitting or even elevating the head after stroke might reduce cerebral blood flow due to poor collateral circulation and an inability to regulate and augment cerebral blood flow in ischaemic regions of the brain [2–5]. Optimal positioning for patients in the acute stage after stroke is still unknown [6–8]. Variation in clinical practice is evident in the literature [5–9] and has been observed [10]. This variation could be because of the paucity of experimental findings to inform a scientific rationale for positioning early after stroke. The relatively new technology of near infrared spectroscopy (NIRS), a minimally invasive technique, offers the possibility of making such measurements [17]. The aim of this pilot study is to explore whether changes in position, involving different placements of the head and upper body in relation to gravity, in the first week after a middle cerebral artery cortical ischaemic stroke produce changes in cerebral oxygenation in the region of the arterial territory.

Methods

A replicated single case study design was used with the phase sequence ABACA (details in procedure section below). The study was approved by the Local Research Ethics Committee and participants provided either written informed consent or, if that was not possible, assent was provided by their next-of-kin.

Participants were adults who had suffered a middle cerebral artery cortical ischaemic stroke, confirmed by computer tomography (CT) no more than 7 days prior to testing. Exclusion criteria were: a previous stroke in the same division of the ipsilesional medial cerebral artery (MCA) territory; critical illness (peripheral oxygen saturations <90% on air, pulse >100 beats per min, systolic BP <90 mmHg, Glasgow Coma Score <10); inability to follow one-stage command; and, inability to sit upright on the edge of a bed with support from one person. Participants were seated in a multi-position chair (see instrumentation below) in a quiet room adjacent to the acute stroke unit. Two optodes were placed bihemispherically on their scalp with a 4 or 5 cm distance between the receiving and emitting probes over each hemisphere. Positional accuracy of the optodes was achieved through superficial scalp marking over the ischaemic lesion using laser guidance at CT scanning and mirrored over the opposite hemisphere. An electronic topical recorder was used to record peripheral oxygen saturations, pulse and blood pressure at 2-min intervals. This ensured systematic haemodynamic changes were demonstrated independently of cerebral monitoring. Each participant then completed the standardised five-phase posture sequence designed to reproduce positions often used during the first week after stroke:

(1) A phase—supine lying.
(2) B phase—45° back-rest/seat with legs raised up straight as if lying propped up in bed.
(3) A phase—supine lying.
(4) C phase—sitting upright with hips, knees and ankles at 90° as if sitting in a chair.
(5) A phase—supine lying.

penumbra might be at risk from a reduction in cerebral blood flow mediated through positional changes after stroke [1]. To be relevant clinically, cerebral oxygenation needs to be measured in relation to changes in posture. It also needs to be measured in real time at the bedside to enable appropriate clinical decisions about positioning. The relatively new technology of near infrared spectroscopy (NIRS), a minimally invasive technique, offers the possibility of making such measurements [17]. The aim of this pilot study is to explore whether changes in position, involving different placements of the head and upper body in relation to gravity, in the first week after a middle cerebral artery cortical ischaemic stroke produce changes in cerebral oxygenation in the region of the arterial territory.