Hypocapnia and Cerebral Hypoperfusion in Orthostatic Intolerance

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Background and Purpose—Orthostatic and other stresses trigger tachycardia associated with symptoms of tremulousness, shortness of breath, dizziness, blurred vision, and, often, syncope. It has been suggested that paradoxical cerebral vasoconstriction during head-up tilt might be present in patients with orthostatic intolerance. We chose to study middle cerebral artery (MCA) blood flow velocity (BFV) and cerebral vasoregulation during tilt in patients with orthostatic intolerance (OI).

Methods—Beat-to-beat BFV from the MCA, heart rate, CO₂, blood pressure (BP), and respiration were measured in 30 patients with OI (25 women and 5 men; age range, 21 to 44 years; mean age, 31.3 ± 1.2 years) and 17 control subjects (13 women and 4 men; age range, 20 to 41 years; mean age, 30 ± 1.6 years); ages were not statistically different. These indices were monitored during supine rest and head-up tilt (HUT). We compared spontaneous breathing and hyperventilation and evaluated the effect of CO₂ rebreathing in these 2 positions.

Results—The OI group had higher supine heart rates (P<0.001) and cardiac outputs (P<0.01) than the control group. In response to HUT, OI patients underwent a greater heart rate increment (P<0.001) and greater reductions in pulse pressure (P<0.01) and CO₂ (P<0.001), but total systemic resistance failed to show an increment. Among the cerebrovascular indices, all BFVs (systolic, diastolic, and mean) decreased significantly more, and cerebrovascular resistance (CVR) was increased in OI patients (P<0.01) compared with control subjects. In both groups, hyperventilation induced mild tachycardia (P<0.001), a significant reduction of BFV, and a significant increase of CVR associated with a fall in CO₂. Hyperventilation during HUT reproduced hypocapnia, BFV reduction, and tachycardia and worsened symptoms of OI; these symptoms and indices were improved within 2 minutes of CO₂ rebreathing. The relationships between CO₂ and BFV and heart rate were well described by linear regressions, and the slope was not different between control subjects and patients with OI.

Conclusions—Cerebral vasoconstriction occurs in OI during orthostasis, which is primarily due to hyperventilation, causing significant hypocapnia. Hypocapnia and symptoms of orthostatic hypertension are reversible by CO₂ rebreathing. (Stroke. 1998;29:1876-1881.)

Key Words: hypotension, orthostatic ■ hypocapnia ■ hypoperfusion ■ orthostatic intolerance ■ ultrasonography, Doppler, duplex

Orthostatic intolerance is characterized by symptoms of lightheadedness, tiredness, palpitations, blurred vision, and, occasionally, by loss of consciousness during standing, all of which are relieved on recumbency. Previous studies suggested that mild peripheral autonomic neuropathy affecting sudomotor and adrenergic fibers is associated with excessive orthostatic tachycardia. Orthostatic symptoms are predominantly those of cerebral hypoperfusion, and they occur in the absence of orthostatic hypotension. Cerebral autoregulation maintains constant cerebral blood flow despite changes in systemic blood pressure (BP). There is some evidence that disorders associated with orthostatic intolerance may also have impaired autoregulation. Previous studies have suggested that abnormal cerebral vasoreactivity is found in patients with vasodepressor syncope. A fall of blood flow velocity (BFV) in the middle cerebral artery (MCA) preceded the onset of syncope with rapid reduction of BP, during lower body negative pressure testing. Similarly, an increase in the cerebrovascular resistance (CVR) preceded the onset of syncope during head-up tilt (HUT). These studies suggested that paradoxical vasoconstriction is overriding the results of autoregulatory vasodilation, causing a rightward shift on the autoregulatory curve.

This study was designed to evaluate cerebral vasoregulation in patients with orthostatic intolerance (OI) during HUT. The objective was to evaluate whether paradoxical cerebral vasoconstriction occurred in OI and its mechanism. We hypothesized that cerebral hypoperfusion might be related to

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changes in CO₂, which has a predictable effect on cerebral perfusion. Therefore, we undertook a series of studies to evaluate the effect of HUT on respiration, CO₂ cerebral blood flow, and systemic cardiovascular peripheral responses in OI patients and healthy control subjects. We also evaluated the effect of correction of CO₂ on the recorded abnormalities and symptoms of orthostatic intolerance.

Subjects and Methods

Subjects
Thirty patients suffering from OI and 17 healthy subjects participated in the study. Inclusion criteria required (1) sinus rhythm with no evidence of arrhythmia or cardiac disease; (2) heart rate increment >30 beats per minute (bpm) from the baseline and >100 bpm for >60% of the duration of the 10-minute tilt-table test; (3) stable BP profile without syncope, presyncope, or orthostatic hypotension; and (4) the presence of 3 or more of the following clinical symptoms for at least 3 months: dizziness, fatigue, palpitations, blurred vision, breathing difficulties, abnormal sweating, nausea, gastrointestinal dysmotility, headache. Patients were excluded if they received medications that could cause OI, if they were hypovolemic due to blood volume or fluid loss, or if they suffered from any medical condition that was known to cause OI (such as diabetes or peripheral neuropathy). Detailed clinical evaluation included a general medical, cardiological, and neurological history; physical examination; and laboratory evaluation. The evaluation typically included Holter monitoring, determination of plasma volume, determination of catecholamine level, thyroid function testing, electroencephalography, electrocardiography, and MRI or CT head scanning, if indicated. No cardiac or other pathology that could explain episodes of tachycardia and OI was found. All medications were withheld for 5 half-lives before autonomic testing. None of the patients used cardioactive or anticholinergic medication. All patients and subjects refrained from tobacco and caffeine use on the day of the study.

Protocols
In protocol 1, the patients (n=22) performed the Valsalva maneuver and underwent hyperventilation in the supine position. After a period of rest, they underwent HUT. Eight of the patients also participated in protocol 2, in which they underwent hyperventilation after HUT, followed by rebreathing of CO₂ in an upright position.

Head-Up Tilt
After 10 minutes of rest in the supine position, the patient underwent HUT to 80° for 10 minutes and then was returned to the supine position for a further 5 minutes.

Hyperventilation
After 10 minutes of rest in the supine position, the patient was instructed to hyperventilate at a frequency of 1 Hz for 4 minutes and then to breathe quietly and spontaneously.

CO₂ Rebreathing
After 5 minutes of rest, the patient was tilted up to an angle of 80° and underwent 4 minutes of hyperventilation to induce hypocapnia. The patient then underwent CO₂ rebreathing for 5 minutes or until CO₂ returned to baseline values. During CO₂ rebreathing, the patients maintained spontaneous breathing frequency, inhaling and exhaling from a 1500-mL rebreathing bag. ECG, BP, respiration, and CO₂ were measured continuously at 250 Hz, simultaneous with the transcranial Doppler (TCD) signal.

Data Acquisition and Analysis
Time series of R-R intervals, systolic (SBP), and diastolic (DBP) BP were measured beat to beat. Heart rate was calculated from R-R intervals. BP was measured via the finger using the photopletysmographic method (Finapres; Ohmeda Monitoring Systems), which provides a reliable estimate during both short- and long-term recordings of intra-arterial BP. Respiratory and CO₂ signals were equidistantly sampled at 4 Hz.

Transcranial Doppler Testing
Cerebral BFV was measured using the Transcranial Doppler System (Multigon Industries). The left MCA was insonated from the anterior temporal window. A TCD probe (2 MHz) was positioned to record the maximal MCA velocity and fixed in the desired angle using a specially designed Teflon probe holder. The envelope of maximal BFV is similar to the BP waveform. Systolic (BFVₛ), diastolic (BFVₐ), and mean (BFVₐ) BFVs were detected from analog signals on a beat-to-beat basis. CVR was defined as mean blood pressure (MBP)/BFVₐ.

Impedance Cardiography
Changes in thoracic impedance during the cardiac cycle largely reflect changes in thoracic aortic volume and hence in left ventricular outflow. All subjects were tested using an impedance plethysmograph (Bomed NCCOM3 R-7), had normal cardiovascular function, and were free of intraventricular conduction defects, intracardiac shunts, or valvular insufficiency that may confound stroke volume (SV) and cardiac output (CO) measurements. The equation for calculation of SV and CO used adjustments for the body surface area, which may account for interindividual variation of the impedance estimate. SV and CO were also acquired beat to beat, simultaneously with other signals.

Respiration and CO₂
Respiratory excursion was measured using a nasal thermistor and sampled at 4 Hz. CO₂ was measured from the expiratory flow using a Puritan-Bennett 254 airway gas monitor calibrated with 5% CO₂. All data were simultaneously acquired; outlying values and extrasystoles were carefully removed. Time series were then averaged over 30-second intervals for each parameter to obtain individual temporal profiles; group averaged profiles were also obtained.

Statistical Analysis
For comparison of groups, unpaired 2-tailed t test was used. When a comparison of multiple groups was made, we used ANOVA with a repeated-measure design and Schefé’s test was used for post hoc analysis. Statistical analysis of sex distribution was done using χ² with Yates correction and 2×2 contingency table. The relationships of BFVₛ to CO₂ and heart rate to CO₂ were evaluated using linear regression analysis. Data was expressed as mean±SEM, and significance was accepted at the 5% level.

Results

Clinical Characteristics
Sex and age distributions of patients (25 women and 5 men; age range, 21 to 44 years; mean age, 31.3±1.2 years) and healthy control subjects (13 women and 4 men; age range, 20 to 41 years; mean age, 30±1.6 years) were not statistically different. All patients experienced typical symptoms of OI such as dizziness, lightheadedness, and fatigue. None of the healthy control subjects reported symptoms of OI during HUT.

Head-Up Tilt
In all orthostatically intolerant patients, supine heart rate (P<0.001) and cardiac output (P<0.01) were greater than in the control group (Table 1). BP, BFV, end-diastolic volume, total peripheral resistance (TPR), and CVR for the OI patient group were not different from those of the control group during supine rest. Figure 1 shows the mean average temporal profile of all variables in the OI and control groups during HUT (Figure 1). Data for each subject were reduced to 30-second averages, and the mean averages were obtained.
TABLE 1. Cardiovascular and TCD Parameters in Control Subjects and OI Patients During HUT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supine-Control</th>
<th>Supine-OI</th>
<th>HUT-Control</th>
<th>HUT-OI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>60.2±1.5</td>
<td>81.5±3.0‡</td>
<td>79.8±2.4†</td>
<td>123.2±3.7¶</td>
</tr>
<tr>
<td>SBP</td>
<td>114.8±1.9</td>
<td>120.6±3.9</td>
<td>113.4±2.3</td>
<td>112.4±4.5</td>
</tr>
<tr>
<td>DBP</td>
<td>58.4±1.8</td>
<td>62.7±2.7</td>
<td>65.9±1.9</td>
<td>71.3±3.6</td>
</tr>
<tr>
<td>MBP</td>
<td>75.3±1.6</td>
<td>80.1±2.9</td>
<td>80.2±1.9</td>
<td>83.6±3.8</td>
</tr>
<tr>
<td>PP</td>
<td>56.4±1.7</td>
<td>57.8±2.4</td>
<td>47.5±1.6</td>
<td>41.1±1.7¶</td>
</tr>
<tr>
<td>BFVp</td>
<td>118.5±4.8</td>
<td>115.9±3.5</td>
<td>109.9±4.7</td>
<td>94.2±4.5¶</td>
</tr>
<tr>
<td>BFV0</td>
<td>58.0±2.7</td>
<td>57.4±1.6</td>
<td>53.8±2.5</td>
<td>46.5±2.4¶</td>
</tr>
<tr>
<td>BFVd</td>
<td>76.2±3.3</td>
<td>75.0±2.0</td>
<td>70.7±3.1</td>
<td>61.0±2.9¶</td>
</tr>
<tr>
<td>BFVm</td>
<td>60.5±2.5</td>
<td>58.5±2.6</td>
<td>56.1±2.7</td>
<td>47.7±2.7¶</td>
</tr>
<tr>
<td>TPR</td>
<td>20.7±1.1</td>
<td>17.7±2.0</td>
<td>24.8±1.56</td>
<td>17.1±1.7†</td>
</tr>
<tr>
<td>CVR</td>
<td>1.0±0.05</td>
<td>1.1±0.0</td>
<td>1.2±0.1</td>
<td>1.5±0.1†¶</td>
</tr>
<tr>
<td>CO</td>
<td>3.8±0.19</td>
<td>5.0±0.4†</td>
<td>3.4±0.19</td>
<td>5.0±0.3‡</td>
</tr>
<tr>
<td>EDV</td>
<td>101.4±4.5</td>
<td>100.2±7.7</td>
<td>80.2±4.6i</td>
<td>69.6±4.3i</td>
</tr>
<tr>
<td>CO2</td>
<td>42.8±1.6</td>
<td>41.2±1.4</td>
<td>38.8±1.3</td>
<td>31.9±1.6i¶</td>
</tr>
<tr>
<td>CO2 %</td>
<td>100.0±0.0</td>
<td>100.0±0.0</td>
<td>90.8±1.2i</td>
<td>77.4±3.0i¶</td>
</tr>
</tbody>
</table>

Data are mean±SEM; controls n=17; OI n=22.

†P<0.05; †P<0.01; †P<0.001.

Tilt vs supine, same condition (OI or control); §P<0.05; †P<0.01; ¶P<0.001.

and displayed for each group for visual clarity. In response to HUT, compared with control subjects, OI patients had significantly higher heart rates (P<0.001), greater COs (P<0.001), and lower pulse pressures (P<0.05) and CO2 levels (P<0.01) (Table 1, Figure 1). Among the cerebrovascular indices, all MCA BFVs (BFVs, BFVd, BFVd, P<0.05; BFVd, P<0.05; BFVd, P<0.05; and pulse [BFVp], P<0.05) were also significantly lower during HUT in the patients with OI. In contrast, CVR increased during HUT in OI patients (P<0.01) but not in control subjects. TPR significantly increased with HUT in control subjects (P<0.05) but not in patients with OI, and TPR values during HUT were lower (P<0.01) in OI patients than in control subjects. EDV, an index of preload, was not different between groups either in the supine position or during HUT. HUT resulted in the following symptoms: lightheadedness, palpitations, weakness, and, less commonly, chest aching and acral paresthesias.

In control subjects, respiratory frequency and CO2 did not significantly change during HUT. In contrast, OI patients underwent a significant degree of hypocapnia during HUT (P<0.01). Mean respiratory frequency for the OI group during HUT (0.25 Hz) did not differ significantly from that of the control group (0.23 Hz), although the range of respiratory frequencies was wider during HUT in the OI group (from 0.06 to 0.39 Hz) than in the control group (0.12 to 0.31 Hz). In OI patients, spontaneous rhythmic breathing was interrupted by episodes of deep breaths, faster respiratory rate, irregular respiration, or apneas. We have not quantified these differences.

**Hyperventilation**

During supine rest, OI patients had higher heart rates (P<0.001). In both groups, hyperventilation induced mild tachycardia (P<0.001), a significant reduction of BFV (BFVs, BFVd, and BFV), and a significant increase in CVR (Table 2); TPR was significantly reduced in the control subjects. Hyperventilation significantly increased CO in control subjects (P<0.05) but not in OI patients.

**Vasomotor Sensitivity to CO2**

Vasomotor sensitivity was evaluated during protocol 2 (HUT with hyperventilation and CO2 rebreathing) in OI patients. HUT with hyperventilation induced significant reductions of MCA BFV and CO2 and a significant increase in heart rate and CVR. BP was not significantly different. The symptoms of OI were more severe during HUT with hyperventilation. The indices of cerebral perfusion (MCA BFV and CVR)
TABLE 2. Cardiovascular and TCD Parameters in Control Subjects OI Patients During Hyperventilation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest-Control</th>
<th>Rest-OI</th>
<th>HV-Control</th>
<th>HV-OI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>61.5 ± 1.7</td>
<td>82.1 ± 2.3</td>
<td>78.6 ± 3.3</td>
<td>95.8 ± 3.4</td>
</tr>
<tr>
<td>SBP</td>
<td>115.5 ± 21.4</td>
<td>117.8 ± 2.9</td>
<td>116.7 ± 2.3</td>
<td>117.6 ± 3.6</td>
</tr>
<tr>
<td>DBP</td>
<td>59.9 ± 2.4</td>
<td>64.0 ± 2.7</td>
<td>58.7 ± 2.5</td>
<td>62.3 ± 2.8</td>
</tr>
<tr>
<td>MBP</td>
<td>76.6 ± 2.3</td>
<td>80.2 ± 2.6</td>
<td>76.1 ± 2.2</td>
<td>78.9 ± 3.0</td>
</tr>
<tr>
<td>PP</td>
<td>55.6 ± 1.8</td>
<td>53.8 ± 1.9</td>
<td>58.0 ± 2.1</td>
<td>55.3 ± 2.1</td>
</tr>
<tr>
<td>BFV_M</td>
<td>124.5 ± 4.7</td>
<td>112.9 ± 3.4</td>
<td>96.9 ± 4.0</td>
<td>95.2 ± 4.0</td>
</tr>
<tr>
<td>BFV_0</td>
<td>61.4 ± 2.5</td>
<td>56.1 ± 1.8</td>
<td>38.1 ± 2.3</td>
<td>40.1 ± 3.2</td>
</tr>
<tr>
<td>BFV_M'</td>
<td>80.2 ± 3.1</td>
<td>73.2 ± 2.1</td>
<td>55.8 ± 2.6</td>
<td>56.9 ± 3.2</td>
</tr>
<tr>
<td>BFV_0'</td>
<td>63.1 ± 2.9</td>
<td>56.9 ± 2.5</td>
<td>58.89 ± 2.6</td>
<td>55.8 ± 2.6</td>
</tr>
<tr>
<td>TPR</td>
<td>20.6 ± 1.0</td>
<td>19.6 ± 2.0</td>
<td>17.0 ± 11.6</td>
<td>16.2 ± 1.5</td>
</tr>
<tr>
<td>CVR</td>
<td>1.0 ± 0.0</td>
<td>1.1 ± 0.0</td>
<td>1.4 ± 0.1</td>
<td>1.5 ± 0.09</td>
</tr>
<tr>
<td>CO</td>
<td>3.8 ± 0.2</td>
<td>4.8 ± 0.4*</td>
<td>4.7 ± 0.3§</td>
<td>5.6 ± 0.47</td>
</tr>
<tr>
<td>EDV</td>
<td>99.6 ± 5.6</td>
<td>97.3 ± 7.7</td>
<td>100.8 ± 6.9</td>
<td>101.0 ± 11.8</td>
</tr>
<tr>
<td>CO₂</td>
<td>41.6 ± 2.3</td>
<td>41.1 ± 1.2</td>
<td>26.3 ± 1.0</td>
<td>30.4 ± 1.3</td>
</tr>
<tr>
<td>CO₂, %</td>
<td>100.0 ± 0.0</td>
<td>100.0 ± 0.0</td>
<td>64.5 ± 3.9</td>
<td>75.0 ± 3.7</td>
</tr>
</tbody>
</table>

HV indicates hyperventilation.

Data are mean ± SEM; control n = 17; OI, n = 22.

OI vs control, same condition (Rest or HV): †P<0.05; ‡P<0.01; ¶P<0.001.

HV vs Rest, same condition (OI or Control): §P<0.05; ¶P<0.01; ¶¶P<0.001.

Discussion

We originally defined “postural tachycardia syndrome” (POTS) as an increase in heart rate exceeding 30 bpm associated with orthostatic symptoms. We subsequently found that this definition included a rather heterogeneous group of patients, including patients with deconditioning, POTS, and constitutional OI. We subsequently redefined POTS as “requiring an orthostatic heart rate ≥120 bpm.” When we used this definition, not all of our patients qualified, so we chose the more inclusive term of OI for this article.

The main findings in this study were that symptoms of orthostatic intolerance in this group of patients were associated with cerebral hypoperfusion and increased CVR. This paradoxical cerebrovascular arteriolar vasoconstriction is caused by hypocapnia and can be reversed by CO₂ rebreathing. The improvement in cerebral perfusion was associated with resolution of symptoms.

To quantify the sources of error in the use of the Finapres to measure beat-to-beat BP, impedance cardio- graphy for measuring indices of preload and afterload, and TCD ultrasonography for measuring cerebral blood flow, Finapres measures digital arterial pressure using a volume clamp method from the digital artery of the index finger. SBP-, DBP-, and MBP-recorded pressures measured using the Finapres compare accurately with simultaneous brachial and radial intra-arterial recordings and reproduce the continuously changing intra-arterial waveform during the Valsalva maneuver and during sudden changes in posture. Determinations of CO using the thoracic electrical bioimpedance technique have been found to correlate strongly with results from indicator or thermodilution measurements taken with indwelling catheters, and this technology tracks changes in SV and CO very reliably, including beat-to-beat changes of left ventricular SV from simultaneous left ventriculograms. These techniques accurately measure relative changes in a wide range of conditions. MCA flow velocity correlates with cerebral blood flow, measured with xenon clearance techniques or with laser Doppler flux and flow velocity estimates. Flow velocity can increase because of an increased flow through the arterioles distal to the probe or a constriction of the insonated trunk. Changes of the caliber of MCA stem (the insonated segment in TCD) in response to BP and CO₂ are small (<4%). Larger changes in trunk caliber can occur, but only under extreme circumstances such as subarachnoid hemorrhage or injury to the vessel.

During HUT, heart rate increment, reduction of cerebral BFV, and increase of CVR strongly correlated with end-tidal CO₂. This hypocapnia was associated with symptoms of lightheadedness and weakness. Correction of hypocapnia during CO₂ rebreathing in an upright position reduced orthostatic tachycardia and normalized cerebral BFV, and the symptoms of orthostatic intolerance abated. During hyperventilation in the supine position, none of the cerebral blood flow and resistance indices differed between the OI patient group and the control group. Additionally, the slope of the regression line relating BFV to CO₂ was not different when the OI group was compared with the control group. These data suggest that vasomotor reactivity is preserved in OI patients.
A key question is why hypocapnia occurs in OI patients. The hyperventilation syndrome per se is not a psychiatric diagnosis but is often associated with anxiety, depression, and panic attacks. We need to ask whether these patients develop hyperventilation because HUT evokes orthostatic anxiety or panic attacks or whether there is a physiological basis for their orthostatic hyperventilation. Hyperventilation is associated with a variety of symptoms that overlap with those of OI. These include cardiac (palpitations, chest pain), neurological (dizziness, syncope, paresthesias, tetany), and psychiatric (feeling of unreality, intense fear, hallucinations, euphoria) symptoms. As with OI and POTS, the hyperventilation syndrome is more prevalent in women. This syndrome is associated with cerebral vasoconstriction, resulting in dizziness, vision disturbance, and, often, paresthesias; with a reduction of up to 60% of BFV; and with a concomitant increase of spectral powers in slower rhythms on the electroencephalograph that are suggestive of ischemia. A recent study of 85 subjects attempted to segregate the contributions of anxiety and somatic manifestations to symptoms associated with hyperventilation. Anxiety was considered to explain approximately 30% of symptoms, whereas somatic symptoms such as cardiac symptoms, dizziness, and fainting correlated with reduced CO2.

However, there are some significant differences between POTS and the hyperventilation syndrome. The respiratory rate and end-tidal CO2 in POTS with the patient at rest are identical to those of control subjects. Hyperventilation that consists of an increased depth without an increased rate only occurs during orthostatic stress. Patients increase their depth of respiration after they develop a transient reduction in BP and a persistent reduction in pulse pressure. An increase in respiratory depth is a well-known mechanism that results in an increase in BP by increasing preload mechanically and by vasoconstriction. Deep inspiration also activates a vasoconstrictor reflex with a spinal pathway. Finally, respiratory neurons modulate the rostral ventrolateral medulla and hence vasomotor tone.

Our tentative position is that OI and anxiety-panic states share a common efferent pathway involving sympathetic activation but that they are evoked by quite different mechanisms. Evidence exists to implicate the noradrenergic system in the

![Figure 2. Temporal profile of beat-to-beat heart rate (HR), mean blood pressure (MBP), and mean flow velocity (BFV_M) data from 1 patient (23-year-old woman with OI) during HUT with hyperventilation and CO2 rebreathing. There is a significant reduction of BFV_M during tilt, with hyperventilation accompanied by tachycardia. HR and BFV_M improved during tilt with CO2 rebreathing. The first arrow indicates HUT and commencement of hyperventilation; the second arrow, rebreathing of CO2; and the third arrow, tilt-back.](http://stroke.ahajournals.org/)

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However, there are some significant differences between POTS and the hyperventilation syndrome. The respiratory rate and end-tidal CO2 in POTS with the patient at rest are identical to those of control subjects. Hyperventilation that consists of an increased depth without an increased rate only occurs during orthostatic stress. Patients increase their depth of respiration after they develop a transient reduction in BP and a persistent reduction in pulse pressure. An increase in respiratory depth is a well-known mechanism that results in an increase in BP by increasing preload mechanically and by vasoconstriction. Deep inspiration also activates a vasoconstrictor reflex with a spinal pathway. Finally, respiratory neurons modulate the rostral ventrolateral medulla and hence vasomotor tone.

Our tentative position is that OI and anxiety-panic states share a common efferent pathway involving sympathetic activation but that they are evoked by quite different mechanisms. Evidence exists to implicate the noradrenergic system in the
development of the anxiety-panic state. Even small alterations in noradrenergic function can produce significant cardiovascular, gastrointestinal, and respiratory symptoms in patients with panic disorder that are similar to symptoms experienced by patients with OI. However, the mechanisms evoking those similar symptoms appear to be quite different. OI patients hyperventilate as a compensatory response to OI. However, continued hyperventilation is counterproductive because it causes hypocapnia, which induces a reduction in cerebral perfusion, and worsens symptoms of OI. Furthermore, although a single breath will transiently increase, continued hyperventilation reduces total systemic peripheral resistance, further aggravating OI. For individuals with panic disorder, changes in respiratory rate (ie, hyperventilation) produce panic symptoms rather than being a compensatory phenomenon as seen in patients with OI. Hyperventilation produces hypocapnia and precipitates panic symptoms in individuals with panic disorders. However, hypocapnia has also been associated with the induction of panic. The reason why hypo- and hypocapnia both produce panic symptoms is unclear, and this raises the question of whether POTS patients are unduly sensitive to hypocapnia. We found no difference in the slope between heart rate and BFV responses to changes in PCO₂ in OI patients and control subjects (Figure 3), indicating that supersensitivity is not present.

Although the focus of this article is on the contributions of hypocapnia to cerebral hypoperfusion, it is clear that there are also changes that occur at rest in OI patients. They have a higher resting heart rate, CO, and TPR than control subjects. These findings are in keeping with a hyperadrenergic state causing peripheral vasoconstriction and an increase in heart rate and CO. There is also heterogeneity in mechanisms in these patients. In the present study, we demonstrated the failure of TPR to vary incrementally with HUT. In an earlier study, we demonstrated that POTS patients who had a tendency toward syncope have a progressive decrease in TPR, whereas another group (who tend not to faint) have a normal or higher TPR with HUT. With the patient supine, a part of the peripheral vasoconstriction is in the veins, which show derangement supersensitivity; these same veins fail to maintain their tone with the patient standing, resulting in venous pooling. In summary, patients with OI respond to HUT-induced cardiovascular alterations with an increased depth of respiration, which augments the oscillations in BP. This in turn results in hypocapnia and cerebral hypoperfusion, worsening OI.

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