Oscillatory Cerebral Blood Flow Is Associated With Impaired Neurocognition and Functional Hyperemia in Postural Tachycardia Syndrome During Graded Tilt

Julian M. Stewart, Andrew T. Del Pozzi, Akash Pandey, Zachary R. Messer, Courtney Terilli, Marvin S. Medow

Abstract—We hypothesize that upright cognitive impairment in patients with postural tachycardia syndrome (POTS) is caused by reduced cerebral blood flow (CBF). The CBF velocity (CBFv) measured by transcranial Doppler ultrasound decreased excessively during 70° tilt in a minority of patients with intermittent hyperpnea/hypocapnia. Incremental tilt showed no difference in mean CBFv. But N-back memory tasking indicated progressive compromised memory, reduced functional hyperemia, and reduced neurovascular coupling. Orthostasis caused slow oscillations in CBFv, linked to oscillations in arterial pressure in patients with POTS. We also hypothesize that oscillatory CBFv degrades neurovascular coupling. We performed 2-back testing when subjects were in supine position and during incremental tilts to 15°, 30°, 45°, and 60° in 11 patients with POTS and 9 controls. Oscillatory arterial pressure, oscillatory CBFv, and neurovascular coupling were similar in supine position. The oscillatory arterial pressure increased by 31%, 45%, 67%, and 93% in patients with POTS during tilt and remained unchanged in the controls. Oscillatory CBFv increased by 61%, 82%, 161%, and 264% in patients with POTS during tilt and remained unchanged in the controls. Functional hyperemia decreased from 4.1% to 3.0%, 1.1%, 0.2%, and to 0.04% in patients with POTS, but it was unchanged at 4% in the controls. Percent correct N-back responses decreased from 78% to 33% in patients with POTS, whereas they remained at 89% in the controls. In patients with POTS, oscillatory CBFv was linearly correlated with functional hyperemia ($r^2=0.76$). Increased oscillatory CBFv is associated with reduced neurovascular coupling and diminished cognitive performance in patients with POTS. (Hypertension. 2015;65:636-643. DOI: 10.1161/HYPERTENSIONAHA.114.04576.)

Key Words: cognition ■ orthostatic intolerance

Orthostatic intolerance is defined by signs and symptoms of lightheadedness, tachycardia, diaphoresis, heat, hypotension, hyperpnea, headache, nausea, fatigue, cognitive deficits, and exercise intolerance while the patient in upright position, which are relieved by recumbency.1,2 Postural tachycardia syndrome (POTS) is a chronic orthostatic intolerance associated with excess upright tachycardia without hypotension.3–7 Patients with POTS often report “brain fog” while upright to describe impaired awareness, mental confusion, lightheadedness, mental fatigue, and cognitive deficits, especially of working memory.9

We initially hypothesized that brain fog is caused by orthostatic reductions of cerebral blood flow (CBF), impairing neuronal activation.9 Although CBF decreases excessively in patients with POTS compared with controls,10 we later showed that mean CBF was abnormally reduced only in some patients during rapid orthostasis.11 In these patients, large reductions in CBF occurred intermittently and in response to a rapid initially decreased central blood volume.11 Excessively reduced CBF does not occur in most patients with POTS, although brain fog is consistently present. Thus, reduced CBF is not a prerequisite for orthostasis-induced diminished central nervous system function.

Changes in CBF do not explain brain fog because decreased CBF did not occur with incremental upright tilts, and mean CBF, although decreasing with tilt angle, was similar for patients with POTS and for controls.12 Here, we used N-back tasking to quantify working memory, concentration, and information processing of progressive difficulty.13 We combined N-back task with transcranial Doppler (TCD) ultrasound of the middle cerebral artery (MCA) during incremental tilt. During N-back, the CBF velocity (CBFv) in the MCA increases above the mean in control subjects14 in the absence of blood pressure (BP) or end-tidal CO2 (ETCO2) changes,15 as shown in...
Figure S1 in the online-only Data Supplement. This increase is called functional- or neural activity–related hyperemia. The relationship between neural activity and functional hyperemia is called neurovascular coupling (NVC), and it involves interactions among components of the neurovascular unit.16

The accuracy of N-back responses and functional hyperemia deteriorated with tilt angle in patients with POTS but not in the controls,17 signifying that progressive orthostatic stress impairs cognitive performance and NVC. Decreased functional hyperemia and blunted NVC17 may therefore result in cognitive dysfunction in patients with POTS.

We recently observed greatly increased slow CBFv oscillations (<0.40 Hz) in patients with POTS compared with the controls during 70° upright tilt,18 suggesting that oscillatory CBF (OCBF) power interferes with cognition and NVC. Therefore, we used incremental upright tilt and related the increases in OCBF to the decreases of functional hyperemia and cognitive performance in patients with POTS but not in healthy volunteers.

Methods

Outline

We tested neurocognition during incremental tilt by administering an N-back memory task to measure executive working memory, concentration, and information processing.13,14 We used a 2-back memory task that best discriminated between controls and patients with POTS in previous work.12 The CBFv of the left MCA, which assessed the functional hyperemic response during 2-back cognitive activation,13,19,20 was measured at 0°, 15°, 30°, 45°, and 60°; 75° was not used because it resulted in vasovagal syncope in patients with POTS and in the controls.

Subjects

We enrolled 11 subjects with POTS aged 18 to 26 years (median age, 22.3 years; 9 women and 2 men), with POTS defined by standard criteria.1 All had symptoms for >6 months. POTS was identified during a separate tilt to 70° by signs and symptoms of orthostatic intolerance and excessive increase in the heart rate (HR) without hypotension within 10 minutes of head-up tilt.21 Medical problems that could explain these signs or symptoms had been previously ruled out.

Nine healthy volunteers were enrolled as controls. They were aged 17 to 27 years (median age, 21.4 years; 6 women and 3 men), were nonsmokers with no previously known medical conditions or illness, were taking no medications, and had normal physical exams and ECGs. Healthy control subjects never experienced orthostatic intolerance, including orthostatic hypotension, POTS, or syncope. All refrained from medications for 2 weeks before study except for contraceptives and stopped intake of xanthine-, caffeine-, or alcohol-containing substances 72 hours before the study.

The New York Medical College Institutional Review Board reviewed and approved this protocol. Each subject received a detailed description of all protocols. Signed informed consent was obtained from all participants or their parents.

Instrumentation

All subjects were instrumented by the same operators while in the supine position on an electric powered tilt table (Colin Medical Instruments Corp, San Antonio, TX) with a footboard. Beat-to-beat BP was monitored using finger arterial plethysmography (Finometer; FMS, Amsterdam, The Netherlands), corrected for tilt angle, and calibrated to brachial artery pressure. A single-lead ECG measured the HR. A nasal cannula connected to a capnograph with a pulse oximeter (Smiths Medical, Waukesha, WI) measured ETCO2 and O2 saturation. TCD (Neurovision; Multigon, Yonkers, NY) measured the CBFv of the left MCA using a 2-MHz probe fixed to the subject’s head by a custom-made headband. All analog signals were digitized at 200 Hz with custom signal processing software and analyzed off-line.

N-Back Task

A parametric N-back test21 using 2-back levels comprised the mental task. The visually presented stimulus duration was 1 s, and interstimulus duration was 1 s.13 Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s. Subjects responded to perceived correct stimulus duration was 1 s, and interstimulus duration was 1 s.

Protocol

Subjects practiced responding, rested for 5 minutes, and then underwent three 2-back practice sessions. Baseline measurements of arterial pressure, CBFv, HR, and ETCO2 were taken during the last 5 minutes. Subjects rested for 5 minutes, and then tilted upright to 15° for 10 minutes. The data obtained in the first minute were omitted to allow for HR and BP stabilization. One to 6 minutes of the tilt were used to obtain the mean and oscillatory data for that angle. The 2-back tasking started at minute 6 and lasted ≈1 minute. After 10 minutes, the subjects were incrementally tilted to 30°, 45°, and 60°, and stabilization, baseline data collection, and 2-back tasking were repeated at each angle.

A priori stopping criteria during incremental tilt were signs and symptoms of presyncope, a decrease in systolic BP to 80 mm Hg, a decrease in systolic BP to 90 mm Hg, or lightheadedness, nausea, sweating, or diaphoresis, or a request to discontinue testing. Presyncope subjects were immediately returned to supine position, and testing was ended. If the subjects completed all the angles of tilt, they were returned to the supine position.

Table 1. Supine Hemodynamic Measurements

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Patients With POTS</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>114±3</td>
<td>111±4</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>62±2</td>
<td>61±2</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>80±2</td>
<td>78±3</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>76±5*</td>
<td>65±3</td>
</tr>
<tr>
<td>ETCO2, mm Hg</td>
<td>41±1</td>
<td>43±1</td>
</tr>
<tr>
<td>Mean CBFv, cm/s</td>
<td>79±3</td>
<td>76±4</td>
</tr>
<tr>
<td>OCBF power</td>
<td>11.3±1.8</td>
<td>14.9±4.4</td>
</tr>
<tr>
<td>VLF power</td>
<td>6.6±1.2*</td>
<td>10.1±1.6</td>
</tr>
<tr>
<td>LF power</td>
<td>3.4±0.7</td>
<td>3.6±1.3</td>
</tr>
<tr>
<td>HF power</td>
<td>1.3±0.2</td>
<td>1.2±0.6</td>
</tr>
<tr>
<td>OAP power</td>
<td>10.6±2.7</td>
<td>11.4±3.0</td>
</tr>
<tr>
<td>VLF power</td>
<td>7.2±3.1</td>
<td>8.0±1.7</td>
</tr>
<tr>
<td>LF power</td>
<td>3.3±0.8</td>
<td>2.8±1.5</td>
</tr>
<tr>
<td>HF power</td>
<td>0.3±0.1</td>
<td>0.6±0.3</td>
</tr>
<tr>
<td>2-back number correct</td>
<td>6.9±0.9</td>
<td>7.9±0.2</td>
</tr>
<tr>
<td>Functional hyperemia, % change CBFv/min</td>
<td>4.1±0.9</td>
<td>3.6±1.2</td>
</tr>
</tbody>
</table>

Unit for OCBF is (cm3/s) and for OAP is mm Hg2. CBFv indicates cerebral blood flow velocity; DBP, diastolic blood pressure; ETCO2, end-tidal CO2; HF, very low frequency; HR, heart rate; LF, low frequency; MAP, mean arterial pressure; OAP, oscillatory arterial pressure; OCBF, oscillatory cerebral blood flow velocity; POTS, postural tachycardia syndrome; SBP, systolic blood pressure; and VLF, very low frequency.

*P<0.05 compared with control.

Functional Hyperemia

We used the change of CBFv (Δ [(centimeter per second) per minute]) as an index of functional hyperemia during the 2-back task. This
Table 2. MAP→CBF, Transfer Function Analysis: Gain, Phase, and Coherence

<table>
<thead>
<tr>
<th></th>
<th>0°</th>
<th>15°</th>
<th>30°</th>
<th>45°</th>
<th>60°</th>
</tr>
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<tbody>
<tr>
<td>OCBF, power</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POTS</td>
<td>11.3±1.8</td>
<td>11.8±1.3</td>
<td>14.4±1.4</td>
<td>20.3±1.7</td>
<td>26.4±2.1†</td>
</tr>
<tr>
<td>VLF</td>
<td>6.6±1.2</td>
<td>6.4±1.6</td>
<td>5.8±0.7</td>
<td>5.6±1.0</td>
<td>5.3±1.1</td>
</tr>
<tr>
<td>LF</td>
<td>3.4±0.7</td>
<td>4.1±0.9</td>
<td>7.6±1.2</td>
<td>13.3±1.3</td>
<td>18.7±1.7†</td>
</tr>
<tr>
<td>HF</td>
<td>1.3±0.2</td>
<td>1.3±0.2</td>
<td>1.0±0.1</td>
<td>1.4±0.2</td>
<td>2.3±0.7</td>
</tr>
<tr>
<td>OCBF, power</td>
<td>16.9±2.5</td>
<td>11.3±1.9</td>
<td>11.2±1.9</td>
<td>11.8±1.9</td>
<td>12.5±2.4</td>
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<tr>
<td>control</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLF</td>
<td>10.1±1.6</td>
<td>6.5±1.2</td>
<td>6.7±2.2</td>
<td>6.4±1.9</td>
<td>5.9±1.9</td>
</tr>
<tr>
<td>LF</td>
<td>3.6±1.3</td>
<td>3.4±0.9</td>
<td>3.5±1.0</td>
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<td>4.8±1.1</td>
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<tr>
<td>HF</td>
<td>1.2±0.6</td>
<td>1.4±0.6</td>
<td>1.0±0.3</td>
<td>1.3±0.3</td>
<td>1.8±0.5</td>
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<tr>
<td>OAP power</td>
<td>10.6±2.7</td>
<td>13.9±1.8</td>
<td>15.4±1.3</td>
<td>17.7±1.4</td>
<td>20.5±2.3†</td>
</tr>
<tr>
<td>POTS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>VLF</td>
<td>7.2±3.1</td>
<td>8.3±2.6</td>
<td>5.9±1.0</td>
<td>3.0±0.4</td>
<td>4.4±1.4</td>
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<tr>
<td>LF</td>
<td>3.3±0.8</td>
<td>4.6±1.1</td>
<td>8.5±1.2</td>
<td>13.4±1.5</td>
<td>14.7±1.2†</td>
</tr>
<tr>
<td>HF</td>
<td>0.3±0.1</td>
<td>1.0±0.1</td>
<td>1.0±0.1</td>
<td>1.3±0.2</td>
<td>1.4±0.6</td>
</tr>
<tr>
<td>OAP power</td>
<td>11.4±3.0</td>
<td>11.3±1.9</td>
<td>10.5±1.9</td>
<td>11.7±2.2</td>
<td>13.9±2.4</td>
</tr>
<tr>
<td>control</td>
<td></td>
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<tr>
<td>VLF</td>
<td>8.0±1.7</td>
<td>7.2±1.9</td>
<td>6.3±1.8</td>
<td>6.4±1.9</td>
<td>7.2±1.3</td>
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<tr>
<td>LF</td>
<td>2.8±1.5</td>
<td>3.1±0.4</td>
<td>3.4±0.8</td>
<td>4.1±0.8</td>
<td>6.2±1.1</td>
</tr>
<tr>
<td>HF</td>
<td>0.6±0.3</td>
<td>1.0±0.2</td>
<td>0.9±0.2</td>
<td>1.2±0.2</td>
<td>1.5±0.2</td>
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<tr>
<td>Gain POTS</td>
<td></td>
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<tr>
<td>VLF</td>
<td>0.5±0.08</td>
<td>0.57±0.08</td>
<td>0.50±0.10</td>
<td>0.72±0.13</td>
<td>0.50±0.10</td>
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<tr>
<td>LF</td>
<td>0.8±0.11</td>
<td>0.85±0.06</td>
<td>0.87±0.07</td>
<td>1.0±0.05</td>
<td>1.17±0.07†</td>
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<tr>
<td>HF</td>
<td>1.0±0.12</td>
<td>1.04±0.07</td>
<td>0.93±0.10</td>
<td>0.90±0.06</td>
<td>1.01±0.08</td>
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<tr>
<td>VLF</td>
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<td>0.66±0.10</td>
<td>0.55±0.07</td>
<td>0.58±0.21</td>
<td>0.55±0.12</td>
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<td>LF</td>
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<td>0.86±0.05</td>
<td>0.79±0.09</td>
<td>0.72±0.10</td>
<td>0.76±0.06</td>
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<tr>
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<td>1.20±0.16</td>
<td>1.07±0.12</td>
<td>0.94±0.08</td>
<td>0.90±0.10</td>
<td>0.86±0.09</td>
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<td>Phase POTS</td>
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<tr>
<td>VLF</td>
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<td>−29±16</td>
<td>−31±12</td>
<td>−46±24</td>
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<tr>
<td>LF</td>
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<td>−41±6</td>
<td>−36±4</td>
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<tr>
<td>HF</td>
<td>−19±8</td>
<td>−12±6</td>
<td>−17±15</td>
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<td>−21±4</td>
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<tr>
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<td>−68±17</td>
<td>−54±11</td>
<td>−40±11</td>
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<tr>
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<td>−53±7</td>
<td>−49±8</td>
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<td>−40±4</td>
</tr>
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<td>−8±4</td>
<td>−19±4</td>
<td>−21±4</td>
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<td>Coherence POTS</td>
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<td>0.89±0.02</td>
<td>0.93±0.03†</td>
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<tr>
<td>HF</td>
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<td>0.84±0.03</td>
<td>0.85±0.04</td>
<td>0.88±0.02</td>
<td>0.76±0.04</td>
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<td>Coherence control</td>
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<tr>
<td>VLF</td>
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<td>0.29±0.08</td>
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<td>0.37±0.08</td>
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<td>LF</td>
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<td>0.73±0.08</td>
<td>0.75±0.09</td>
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<td>HF</td>
<td>0.72±0.09</td>
<td>0.80±0.04</td>
<td>0.81±0.08</td>
<td>0.76±0.06</td>
<td>0.74±0.10</td>
</tr>
</tbody>
</table>

Unit for OCBF, is (cm/s)², for OAP is mmHg², for gains is (cm/s) mmHg⁻¹, and for phases is degree. Coherence is dimensionless. OAP indicates oscillatory arterial pressure; OCBF, oscillatory cerebral blood flow velocity; HF, high frequency; LF, low frequency; POTS, postural tachycardia syndrome; and VLF, very low frequency.

*P<0.05 compared with 0°.
†P<0.05 compared with control.

was quantified by the slope of the CBF during each 2-back task at each angle of tilt as shown in Figure S1. CBF varied from subject to subject in part because of the differences in the angle of insonation. Therefore, we normalized the CBF slope to the average CBF during measurement. Results are expressed as percent change in CBF per minute.

\[
\frac{100 \times \frac{\Delta CBF}{C_{BF} \Delta t}}{C_{BF}}
\]

This quantity is positive for a net increase in CBF, (increased functional hyperemia) and negative for decreased functional hyperemia during mental activation.

Power Spectra and Transfer Function Analysis

Baseline and tilted mean arterial pressure (MAP) autospectra, mean CBF autospectra, and transfer function analyses were obtained from the data collected in supine position and during 1–6 minutes at each angle of tilt. Specific details of these calculations are shown in the online-only Data Supplement.

Data Analysis

All data were continuously sampled at 200 Hz, converted with an analog-to-digital converter (DI-720 DataQ Ind, Milwaukee, WI), and analyzed off-line. NCSS 2007 (NCSS; LCC, Kaysville, UT) statistical software was used in the analysis. The mean CBF for each pulse was computed as a time average over a cardiac cycle. Analysis of 2-back outcome and neuronal activation of CBF (functional hyperemia) used a repeated-measures ANOVA conducted using 1 between factors (patients with POTS versus controls) and 1 within factor (tilt angle at 5 preselected degrees). Data were mean±SEM. Significance was set at P<0.05.

Results

Supine: Baseline Data

Supine data are tabulated in Table 1. There was no significant difference in systolic BP, diastolic BP, or MAP, or MAP, and mean CBF between patients with POTS and the controls. There was a significantly higher supine HR in patients with POTS compared with controls (P<0.05).

Autospectral Power: Oscillatory Data

Supine autospectral data (oscillatory arterial pressure [OAP], OCBF, equivalently MAP, and mean CBF, variability data) are also shown in Table 1. Very low-frequency (VLF) OCBF was significantly reduced in patients with POTS compared with controls (P<0.01). There were no significant differences in total, LF, and high-frequency OCBF. There were no differences in oscillatory MAP power either total or divided among VLF, LF, and high-frequency bands.

Transfer Function Analysis

Supine coherence, gain, and phase are shown in Table 2. There was a lower gain in VLF in patients with POTS compared with the controls. Otherwise, there were no significant differences at any frequency band. Note that VLF coherence was always <0.5, implying either no relationship, a missing
interacting term, a nonlinear relationship, or the presence of excessive noise. Typically, gain and phase data are often regarded as unreliable linear estimates under these circumstances.

Two-Back Test Results and Functional Hyperemia
There was no significant difference between patients with POTS and the controls in the number of correct responses during 2-back testing and in the functional hyperemic response associated with 2-back testing in supine position.

Imposition of Graded Orthostatic Challenge

Hemodynamic Data
Figure 1 shows that CBF, and systolic BP, diastolic BP, and MAP changed similarly with the angle of tilt for patients with POTS and for the controls, whereas HR was increased in patients with POTS and ETCO₂ was somewhat decreased. Thus, although there were small significant differences observed in ETCO₂, these did not result in decreased CBF. In the upright position, CBF was reduced \( (P<0.025) \) compared with that in the supine position in both patients with POTS and controls, but it did not differ between groups while the patients and the controls were in the upright position.

Autospectral Power: Oscillatory Data
Figure 2 shows data from a representative patient with POTS and a control subject. This illustrates the progressive increase
in CBF oscillations with the angle of tilt in the patient with POTS but not in the control subject.

Figure 3 shows the percent change in oscillatory mean CBF and oscillatory MAP during incremental upright tilt. OAP and OCBF increase significantly \((P<0.001)\) in patients with POTS but not in the controls. There are significant between-group differences \((P<0.001)\), which are more marked for OCBF than for OAP.

Table 2 shows data averaged over all subjects within each group. Significances within group and between groups are shown. Total OCBF velocity and OAP power summed over all frequency bands increased progressively with the angle of tilt in patients with POTS \((P<0.001)\) but did not increase in control subjects. Table 2 also shows that the significant difference in total power between patients with POTS and the controls results predominantly from an increase in LF power in patients with POTS but not seen in the controls.

Transfer Function Analysis
Transfer function analysis data are also shown in Table 2. LF gain increases with the angle of tilt in patients with POTS \((P<0.025)\) but not in the controls, whereas VLF and high-frequency gains were not different. Increasing gain was associated with increasing coherence and decreasing phase difference in patients with POTS during incremental tilt.

Two-Back Test Results and Functional Hyperemia
These data are depicted in Figure 4. There is a significant decrease in the accuracy of the 2-back test results \((P<0.01)\) and a significant reduction \((P<0.001)\) in measured functional hyperemia in patients with POTS but not in the controls in whom 2-back response and functional hyperemia remained unchanged.

Discussion
Our data show progressive reduction in 2-back performance and functional hyperemia and progressive increase in OCBF in patients with POTS but not in controls during stepwise incremental upright tilt. However, the average magnitude of CBF decreases similarly in patients with POTS and in the controls with the angle of tilt. We observed stepwise-increased oscillations in arterial pressure that produce larger stepwise increases in OCBF. Increased OCBF in patients with POTS results primarily from enhanced LF oscillatory power that occurs in patients with POTS and not in the controls. This results
from the combined effects of increased OAP in the LF band and increased LF transfer gain from OAP to OCBF in patients with POTS. We have shown greatly increased CBF, in patients with POTS when upright, which is protected by an autoregulatory mechanism that comprises the properties of the vasculature that, in the absence of large environmental or metabolic changes, maintain CBF relatively unchanged despite changes in BP. Although the use of these oscillations is poorly understood, our data suggest that OCBF interferes with NVC and that altered OCBF might serve as a marker for brain fog in patients with POTS.

Progressively Increased OCBF Implies Progressively Decreased Cerebral Autoregulation in Patients With POTS

The use of Fourier method–based transfer function analysis is suitable for the evaluation of cerebral autoregulation (CA) in linear time-invariant systems that are approximated during stepwise incremental tilt. CA is most effective at lower frequencies $\leq 0.1$ Hz; therefore, OAPs at frequencies corresponding to HR are transmitted to OCBF. However, they are highly damped at the tissue level, with only LF and VLF oscillations effectively penetrating into the microvasculature. Although reduced coherence and increased phase difference between OAP and OCBF indicate relative independence of OAP and OCBF and thus effective autoregulation, high gain, increased coherence, and decreased phase difference indicate ineffective autoregulation because of the great linear dependence of OCBF on OAP. Thus, in patients with POTS but not in the controls, CA in the predominant LF band is progressively impaired as incremental tilt proceeds. This also implies that in patients with POTS, at least, OCBF is driven by OAP at low frequency and is not predominantly the result of spontaneous vasomotion. Vasomotion may contribute to VLF oscillations between 0.01 and 0.04 Hz that are present in arterial pressure and CBF and are the predominant oscillations in the controls, and it may reflect the aspects of intact autonomous cerebrovascular myogenic regulation resulting in high CA because coherence is so poor.

Progressively Increased OCBF Is Associated With Progressively Decreased Cognition and NVC in Patients With POTS

Increasing OCBF power correlates fairly well with reductions in functional hyperemia and 2-back performance. Mechanisms by which LF oscillations could perturb NVC during mental tasking may involve activation of astrocytic receptors, resulting in arteriolar vasodilation. Although neural activity controls local CBF via NVC, the homoneural hypothesis proposes that local CBF reciprocally affects neuronal activity, ie, a state of vasoneural coupling. OCBF could exert direct effects on neurons and axons or indirect effects via astrocytes. Investigators have demonstrated the linkage between vascular stretch, astrocyte depolarization, and release of vascular mediators, promoting neuronal activity, and arachidonic acid metabolites. Oscillatory shear stress couples vascular deformation to astrocyte depolarization and astrocyte depolarization to neuronal activity. Interference with NVC and neuronal depolarization may then result. Therefore, it is reasonable to infer that slow oscillations could interfere with NVC and that such interference could account for reduced cognitive performance in patients with POTS.

Limitations

We show an associative rather than causal nature of the relationship between OCBF and functional hyperemia/NVC and of 2-back performance and NVC. Although it is difficult to show statistical associations between physiological measurements and subjective phenomena, ie, between OCBF and brain fog, we will need to devise experiments to show that altering OCBF velocity affects working memory. We do not know whether 2-back task-activated deficiencies in functional hyperemia in patients with POTS during incremental tilt are related to reduced neural activity or to reduced NVC; our techniques do not provide information about neuronal activity.

TCD measures OCBF velocity rather than OCBF that depends on the cross-section area of the insonated artery. However, MCA cross-section may be relatively resistant to change during orthostatic stress. Also, oscillations of CBF correspond to oscillations of CBF and to oscillations of MAP. Even under conditions of changing BP, CA can be estimated by TCD, although the results may be a bit underestimated.

TCD measures only blood flow through specific cerebral blood vessels with good temporal resolution. The MCA was used because it is the main vessel that perfuses the brain area activated during working memory testing. Although CBF data represent an average compared with MCA-perfused areas, perfusion during orthostatic stress may vary with brain location, but such variations are often small. We did not measure TCD values in both hemispheres because MCA CBF was not different between hemispheres during orthostatic stress.

Fourier transfer function analysis depends on linear time-independent system characteristics. The linear hypothesis is an approximation but provides useful information. An additional drawback is the relatively small range of amplitudes of arterial pressure and CBF that are interrogated, at least in the supine position and at lower angles of tilt. This improves with progressive increases in the tilt angle. Also, relatively small variations in BP occur in patients with POTS.

Perspectives

Upright cognitive deficits are a defining feature of POTS, the mechanisms of which are unknown. It might be logical to hypothesize that a reduction in CBF would play some role as it does in neurogenic orthostatic hypotension and postural vasovagal syncope. Indeed, previous work suggested that CBF was on average reduced in patients with POTS compared with the controls. Subsequent work did not show reduced mean CBF in most patients with POTS, leaving a gap in our understanding of potential pathophysiological origins of brain fog in our patients. This
study offers correlative data that may bridge that gap by showing associations among the deterioration of memory, NVC, and increasing OCBF during progressive orthostatic stress. We hypothesize that causal vasoconverging exists alongside of NVC and can result in malfunction of the neurovascular unit, which is mediated by oscillatory blood flow. We speculate that our findings in patients with POTS might generalize to other illnesses in which there is cognitive loss.

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Disclosures
None.

References
What Is New?

- We show progressive reduction in neurocognitive performance and functional hyperemia and a progressive increase in oscillatory cerebral blood flow in patients with postural tachycardia syndrome (POTS) but not in the controls during incremental upright tilt. This arises from a combination of increased oscillations in arterial pressure and reduced cerebral autoregulation in patients with POTS.

What Is Relevant?

- Increased oscillatory cerebral blood flow is thus associated with decreased cognition and decreased neurovascular coupling in patients with POTS and may signify a causal relationship.

Novelty and Significance

Increased oscillatory cerebral blood flow is associated with reduced neurovascular coupling, diminished cognitive performance, and deficient autoregulation in patients with POTS. Altered oscillatory cerebral blood flow might serve as a marker for brain fog in POTS.
Oscillatory Cerebral Blood Flow Is Associated With Impaired Neurocognition and Functional Hyperemia in Postural Tachycardia Syndrome During Graded Tilt
Julian M. Stewart, Andrew T. Del Pozzi, Akash Pandey, Zachary R. Messer, Courtney Terilli and Marvin S. Medow

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Oscillatory Cerebral Blood Flow Is Associated With Impaired Neurocognition And Functional Hyperemia In Postural Tachycardia Syndrome During Graded Tilt.


ONLINE SUPPLEMENT

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Running Head: Oscillatory Cerebral Blood Flow and Neurovascular coupling

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Power Spectra and Transfer Function Analysis

Baseline and tilted MAP autospectra, mean CBFv autospectra, and transfer function analyses were obtained from data collected while supine and during minute 1-6 at each angle of tilt. We report results at each angle of tilt as averages over the following frequency bands: very low frequency (VLF) = 0.0078-0.04Hz, low frequency (LF) = 0.04-0.13 Hz, high frequency (HF) = 0.13-0.4Hz. Power within a band is the autospectral power integrated over frequencies falling within a given frequency band. Total power is the sum of power over all frequency bands.

Data was preprocessed by discrete wavelet smoothing using Daubechies least asymmetric (LA12) mother wavelet function ¹. The mother wavelet generated a dyadic orthonormal basis and multiresolution analysis was used to retain signals from 0.0078 Hz through 0.4Hz. The extended version of the discrete wavelet transform described by Percival and Walden ² was used to produce a maximal overlap transform which fills all time points at each scale, allows precise alignment of the signal and its wavelets, allows for any sample size, and has zero phase-shifted details. The signal was detrended by removing the smoothed signal residua obtained from the scaling function.

Thereafter, OAP and OCBF autospectra (power spectra), and cross-spectral density were obtained from preprocessed signals using Welch’s method ³ with overlapping intervals 128 seconds in length. The lowest detectible frequency was then 1/128 = 0.0078Hz. Additional transfer function analysis followed the methods of Zhang ⁴. The strength of a linear relation between OAP and OCBF was quantitated by the squared coherence function, defined as the ratio of squared cross spectrum divided by the product of the OAP and OCBF autospectra. The transfer function was derived as the ratio of the cross spectral density to the MAP autospectrum ⁵. Gain was defined as the magnitude or amplitude of the transfer function at a given frequency, while phase difference was defined by the phase of the transfer function.

References


Figure S1 shows the increase in activated cerebral blood flow velocity in the top panel corresponding to a 2-Back task shown in the bottom panel for a representative control subject. Data is shown in gray while a linear fit to CBFv is shown by the black line. Cerebral blood flow velocity increases during the 2-Back task indicated by the positive slope of the line.
体位性心动过速综合征（摘要）

波动性脑血流与体位性心动过速综合征分级倾斜试验中受损的神经认知及功能性充血有关

Oscillatory Cerebral Blood Flow Is Associated With Impaired Neurocognition and Functional Hyperemia in Postural Tachycardia Syndrome During Graded Tilt

Julian M. Stewart, Andrew T. Del Pozzi, Akash Pandey, Zachary R. Messer, Courtney Terilli, Marvin S. Medow

浦晓东 译

我们假设体位性心动过速综合征（postural tachycardia syndrome，POTS）患者直立位认知损害是由于脑血流（cerebral blood flow，CBF）减少所导致。在少数间歇性过度呼吸/低碳酸血症的患者中，倾斜70°时经颅多普勒超声测定的CBF速度（CBFv）明显减慢。斜率增加平均CBFv没有明显变化。但是N-back记忆训练显示进行性记忆损害，功能性充血减轻和减少神经血管连接。静态平衡位引起CBFv缓慢波动使POTS患者的脑血流量波动有关。我们还擅自波性CBFv降低神经血管相互作用。我们对11例POTS患者和9例对照组进行了仰卧位后以及逐渐增加倾斜至15°、30°、45°和60°的2-Back测试。仰卧位时波性动脉压，波性CBFv和神经血管连接均相似。POTS患者倾斜试验时波动性动脉压分别增加31%、45%、67%和93%，对照组保持不变；波动性CBFv分别增加61%、82%、161%和264%，对照组保持不变；功能性充血从4.1%减至3.0%、1.1%、0.2%和0.04%，而对照组保持在4%。POTS患者N-back正确响应率从78%减至33%，而对照组保持在89%。POTS患者波动性CBFv与功能性充血呈线性相关（γ² = 0.76）。增加的波性CBF与POTS患者神经血管连接及认知表现减弱有关。

（Hypertension. 2013;65:636-643.）

心血管风险预测（摘要）

中心动脉储备波形分析有助于老年高血压患者的心血管风险预测

Central Aortic Reservoir-Wave Analysis Improves Prediction of Cardiovascular Events in Elderly Hypertensives

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郭芊卉 译 李燕 审校

中心动脉压力波的一些形态学参数被认为是心血管风险的标志物，然而，目前没有研究证实任何一种波形参数，在已知危险因素外对老年高血压患者提供额外预测价值。储备波的概念结合了波传导和Windkessel模型元素，定义一个基本储备血压及其基础上叠加的额外血压。目前尚不清楚从储备波分析中获得的压力速率常数是否可以用于预测心血管事件发生风险。澳大利亚全国第二次血压研究的一个子项目中的838例研究对象在随机分组治疗前进行了颈动脉压力波形测量。储备波分析获得收缩期、舒张期压力速率常数等反映动脉功能的指标。我们利用生存分析来研究储备波参数与心血管事件之间的关系，并评估了除了弗雷明汉风险评估之外储备波参数的预测价值。结果显示：基线的收缩期速率常数能独立预测临床终点事件（对死亡及非致死性脑卒中和心肌梗死的危险比为0.33，95%可信区间：0.13~0.82，P=0.016；对包括所有心脑血管事件在内的复合终点的危险比为0.38，95%可信区间：0.20~0.74，P=0.004）。通过净重新分类改善指数（net reclassification improvement indices，NRI）和综合判定改善指数（integrated discrimination improvement，IDI）分析显示，在弗雷明汉风险评估基础上增加这个储备波参数能够提高心血管风险预测的准确性。此项研究说明基线的收缩期速率常数能够预测老年高血压患者的临床结局，进一步改善心血管病预后的风险评估。

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