Nervous System

Reduced Cerebral Blood Flow With Orthostasis Precedes Hypocapnic Hyperpnea, Sympathetic Activation, and Postural Tachycardia Syndrome

Andrew T. Del Pozzi, Christopher E. Schwartz, Deepali Tewari, Marvin S. Medow, Julian M. Stewart

Abstract—Hyperventilation and reduced cerebral blood flow velocity can occur in postural tachycardia syndrome (POTS). We studied orthostatically intolerant patients, with suspected POTS, with a chief complaint of upright dyspnea. On the basis of our observations of an immediate reduction of cerebral blood flow velocity with orthostasis, we hypothesize that the resulting ischemic hypoxia of the carotid body causes chemoreflex activation, hypocapnic hyperpnea, sympathetic activation, and increased heart rate and blood pressure in this subset of POTS. We compared 11 dyspeptic POTS subjects with 10 healthy controls during a 70° head-up tilt. In POTS subjects during initial orthostasis before blood pressure recovery; central blood volume and mean arterial pressure were reduced ($P<0.025$), resulting in a significant ($P<0.001$) decrease in cerebral blood flow velocity, which temporally preceded (17±6 s; $P<0.025$) a progressive increase in minute ventilation and decrease in end tidal CO$_2$ ($P<0.05$) when compared with controls. Sympathoexcitation, measured by muscle sympathetic nerve activity, was increased in POTS ($P<0.01$) and inversely proportional to end tidal CO$_2$ and resulted in an increase in heart rate ($P<0.001$), total peripheral resistance ($P<0.025$), and a decrease in cardiac output ($P<0.025$). The decrease in cerebral blood flow velocity and mean arterial pressure during initial orthostasis was greater ($P<0.025$) in POTS. Our data suggest that exaggerated initial central hypovolemia during initial orthostatic hypotension in POTS results in reduced cerebral blood flow velocity and postural hypocapnic hyperpnea that perpetuates cerebral ischemia. We hypothesize that sustained hypocapnia and cerebral ischemia produce sympathoexcitation, tachycardia, and a statistically significant increase in blood pressure. *(Hypertension. 2014;63:1302-1308.)* • Online Data Supplement

Key Words: autonomic nervous system • orthostatic intolerance

Orthostatic intolerance (OI), the inability to tolerate upright posture, relieved by recumbency,¹ can result in lightheadedness, cognitive deficits, abnormal blood pressure (BP), and heart rate (HR) regulation.² Some with OI complain of dyspnea associated with hyperventilation and hypocapnia.³,⁴ Thus, neurogenic orthostatic hypotension and vasovagal syncope are frequently associated with hyperventilation. In addition, induced hypotension of healthy controls results in hyperventilation and hypocapnia.⁵,⁶ Hypotension also evokes hyperventilation via the ventilatory baroreflex.⁷

Hyperventilation and hypocapnia occur in postural tachycardia syndrome (POTS),⁸ defined as OI with excessive upright tachycardia without hypotension.⁹ Patients with POTS are often categorized as neuropathic or hyperadrenergic. Neuropathic POTS has regional adrenergic denervation, resulting in a redistributive central hypovolemia and associated reflex tachycardia.¹² In hyperadrenergic POTS, widespread sympathoexcitation drives the tachycardia.¹³

We associate hyperventilation with neuropathic POTS,¹³ especially in those with splanchnic pooling after orthostasis.¹⁴ We previously attributed hyperventilation to splanchnic hypoxemia, resulting in thoracic hypovolemia, baroreflex unloading, and consequent sympathoexcitation and activation of respiratory centers.¹⁵ In addition, hyperventilation is facilitated by enhanced hypoxic and reduced hypercapnic ventilatory responses in POTS because of altered peripheral and central chemoreceptor sensitivity.¹⁶ Hyperventilation produces large reductions in cerebral blood flow (CBF)¹⁷ and neuronal ischemia.

We evaluated patients with POTS and the chief complaint of shortness of breath and large reductions of CBF velocity (CBFv) followed by hyperventilation on change from supine to upright. On the basis of this response, we hypothesize a paradigm for hyperventilation sequentially comprising a large immediate reduction in CBFv on orthostasis, ischemic (stagnant) hypoxia-driven carotid chemoreflex activation, followed by hypocapnic hyperpnea, sympathetic activation, increased BP, and tachycardia. This is a CBF-driven form of POTS. To test this hypothesis, we compared POTS subjects with immediate postural hyperpnea to healthy subjects during orthostatic challenge.
Methods

Subjects
Twenty-one subjects (11 POTS: 8 women and 3 men; 10 healthy control subjects: 7 women and 3 men) were tested supine and during 70° upright tilt (HUT). All were referred for suspected POTS with OI lasting >6 months, comprising excessive tachycardia, lightheadedness, exercise intolerance, headache, fatigue, neurocognitive deficits, palpitations, nausea or abdominal pain, blurred or altered vision, shortness of breath, or sensation of heat while upright, with no other medical explanation for the symptoms. We confirmed POTS by HUT, which required symptoms of OI with an increase in HR exceeding 35 bpm in patients aged >21 years or exceeding 40 bpm in patients aged <21 years during the first 10 minutes of HUT.16,17 POTS subjects were only enrolled if they had a chief complaint of shortness of breath. All had normal pulmonary function tests and no cardiopulmonary or systemic illness. Thus, these patients represent a subgroup because not all patients with POTS present with the chief complaint of shortness of breath.

All subjects were nonsmokers and normotensive. Healthy control subjects had no previously known medical conditions, no OI, and were free of systemic illness, with normal physical examination, ECG, and echocardiogram. Subjects were not taking any medications or ceased their medications for a minimum of 2 weeks before study. All stopped caffeine- and xantine-containing products and did not exercise for 24 hours before testing. All protocols were approved by the New York Medical College Institutional Review Board and conformed to the Declaration of Helsinki. All participants signed an informed consent.

Protocol
Testing began at 10 a.m. using an electronic motorized tilt table (Colin Medical Instruments Corp, San Antonio, TX). Measurements were made, supine, after a 30-minute resting period using methods as described.

Participants were instrumented for electrocardiography, respiratory photoplethysmography using a Respitrace device (NIMS, Inc, North Bay Village, FL) calibrated against pneumotachography (Hans Rudolph Inc, Shawnee, KS) via facemask, SaO2 by pulse oximetry, and combined capnography (Smith Medical PM Inc, Waukesha, WI) to measure end tidal carbon dioxide (ETCO2). Transcranial Doppler (Neurovision; Multigun, Yonkers, NY) measured CBFV of the left middle cerebral artery using a 2-MHz probe.

Occlusion cuffs were placed around the midcalf to measure supine calf blood flow in response to venous occlusion photoplethysmography. Impedance photoplethysmography detected internal volume shifts during orthostatic stress and Tetrapolar High Resolution Impedance Monitor digital impedance photoplethysmography (model 2904D, UPI, Inc, Morro Bay, CA)18 to estimate the changes in thoracic and splanchnic blood volume (BV).

Continuous electrocardiography measured HR (Finapress Medical Systems, Amsterdam, The Netherlands). Beat-to-beat BP was recorded using finger photoplethysmography (Finapress Medical Systems, Amsterdam, Netherlands) calibrated every 5 minutes by automated brachial sphygmomanometer (Colin Medical Instruments Corp).

Muscle sympathetic nerve activity (MSNA) was recorded using a tungsten microelectrode (FHC, Corp, Bowdoin, ME) inserted into the common peroneal nerve near the leg’s fibular head, as previously reported.19 All measurements were sampled at 200 Hz. All recordings were obtained and analyzed using custom data acquisition software. All data were analyzed by the same trained scientist.

After 30 minutes of supine acclimatization, there was an additional 30-minute resting period, where ETCO2 was obtained by capnography. Mean ETCO2 for the past 5 minutes of the rest period was defined as baseline isocapnia for the particular subject throughout the protocol. Beat-to-beat BP, transcranial Doppler, HR, impedance measurements, respirations, and MSNA were recorded to obtain 10-min baseline data. After baseline measurements, all participants had HUT to 70° for 10 minutes while measurements continued.

Data Analysis
Baseline data were recorded for 10 minutes before HUT. The first minute of active standing or HUT often includes a period of hemodynamic instability known as initial orthostatic hypotension (IOH) characterized by translocation of blood from cephalic toward the caudal portion of the body causing a fall in central BV and BP and concomitant rise in HR attributed to a lag in compensatory adrenergic vasoconstriction.20,21 Often the first minute of tilting is not used for analysis. However, we retained all of these physiological measurements because early non-equilibrium changes in hemodynamics are critical to understanding the initial hyperventilatory response. Thus, we tabulated the lowest value for the decreased BP, CO, central BV, and the highest value for the increased HR and total peripheral resistance (TPR) during the initial tilt. Thereafter, upright measurements were divided into 4 additional stages: 1 to 2, 2 to 4, 4 to 6, and 8 to 10 minutes from the onset of HUT. Data were time averaged during these time periods.

Beat-to-beat changes in systolic pressure, diastolic pressure, mean arterial pressure (MAP), and relative changes in CO were determined from Finometer data using ModelFlow software.22 TPR was obtained by dividing MAP by CO and HR derived from the ECG. MSNA was compared with diastolic arterial pressure after correcting for a 1.3-s lag time from a triggering R-wave. Bursts of MSNA activity were used if they had a >3:1 burst:noise ratio. Burst frequency (bursts per minute) and total MSNA (bursts per minute ×area underneath the bursts) were obtained. Total activity was normalized to the largest single burst occurring during the baseline period assigned a value of 1000. We successfully recorded MSNA in 6/11 POTS and 6/10 controls supine and during all time stages.

Normalized respiratory impedance data were used to calculate respiratory rate and estimate tidal volume and expiratory minute volume (V̇e). Data were detrended to remove artifact, and tidal volume was obtained as peak–trough volume per breath. V̇e was determined by averaging tidal volume >1 minute and multiplying by respiratory rate. Changes in electric impedance were measured continuously from baseline, throughout, and after HUT.

Statistics
SPSS 16 (SPSS Inc, Chicago, IL) was used for statistical calculations. Systolic BP, diastolic BP, MAP, HR, TPR, ETCO2, respiratory

<table>
<thead>
<tr>
<th>Measurements</th>
<th>POTS</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>85±6*</td>
<td>60±2</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>114±5</td>
<td>122±4</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>58±3</td>
<td>60±3</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>76±12</td>
<td>81±11</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>56±3</td>
<td>61±3</td>
</tr>
<tr>
<td>Calf blood flow, mL/100 mL per minute</td>
<td>2.7±0.2</td>
<td>2.6±0.2</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>13±1</td>
<td>13±1</td>
</tr>
<tr>
<td>V̇e, L/min</td>
<td>7.3±0.9</td>
<td>6.6±0.8</td>
</tr>
<tr>
<td>ETCO2, Torr</td>
<td>41.4</td>
<td>43.6±0.8</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.1±0.4</td>
<td>5.5±0.3</td>
</tr>
<tr>
<td>TPR, mm Hg/L per minute</td>
<td>15.2±0.8</td>
<td>14.2±1.0</td>
</tr>
<tr>
<td>Mean CBFV, cm/s</td>
<td>78±4</td>
<td>73±4</td>
</tr>
<tr>
<td>CBF Conductance Index (CBFv/MAP)</td>
<td>1.07±0.10</td>
<td>0.96±0.05</td>
</tr>
<tr>
<td>MSNA burst area, AU</td>
<td>2055±802</td>
<td>1894±242</td>
</tr>
<tr>
<td>MSNA burst count, burst/min</td>
<td>17±4</td>
<td>15±2</td>
</tr>
</tbody>
</table>

*Different from controls, P<0.05.
rate, \( V_e \), CBFv, and MSNA were analyzed using a repeated measure ANOVA. Bonferroni post hoc analysis was performed when findings were significant. Because of intersubject variability in baseline arterial pressures, CBFv, MSNA, and impedance measurements of regional volume changes, we also expressed repeated measure data as percentage change from baseline. Changes in impedance and estimated compartmental variance were analyzed using a 2-tailed Student \( t \) test. All measures were reported as mean±SEM. Statistical significance was set a priori at \( P<0.05 \) for all tests.

**Results**

POTS subjects mean age was 19±3 years and controls 23±3 years. The height of POTS subjects was 169±7 cm, whereas the height of controls was 169±5 cm; and the weight of POTS subjects was 65±12 kg, whereas the weight of controls was 71±9 kg; thus body mass indices were the same with 22.9±4.4 kg/m² for POTS and 24.4±2.8 kg/m² for controls. Of the 11 POTS subjects, 9 were able to complete 10 minutes of HUT; 2 POTS subjects were unable because of orthostatic precipitation of presyncope. All 10 control subjects withstood the complete duration of the HUT.

**Supine Hemodynamics**

The Table shows that supine HR was significantly increased for POTS subjects when compared with that for controls (\( P<0.01 \)). Although systolic BP in POTS was lower than in controls, the difference was not significant. None of the other parameters shown were different when compared POTS with controls.

**Response to Orthostatic Stress**

**Respiratory Responses**

Respiratory data for all subjects are shown in Figure 1. Although an increased tidal volume accounts for most of the \( V_e \) increase, some also had a significant (\( P<0.05 \)) increase in respiratory rate at the initial and 1 to 2 minutes stages of HUT when compared with supine baseline. There was an obvious and significant (\( P<0.001 \)) decrease in ETCO₂ for POTS subjects at each stage of HUT when compared with controls, in which ETCO₂ decreased to a lesser extent with time and was not different than baseline. \( V_e \) increased significantly (\( P<0.001 \)) after HUT in POTS for all time points after the 1- to 2-minute period. Controls showed no significant increase in \( V_e \). Maximum ventilation in POTS subjects was achieved 2 to 4 minutes after HUT and was maintained through.

**Neurocardiopulmonary Responses to Tilt**

Figure 2 compares respiratory, hemodynamic, and MSNA data for the same representative POTS subject shown in Figure S1 in the online-only Data Supplement. \( V_e \) illustrates the differences in timing of the neurocardiopulmonary response to HUT. Total MSNA increased in parallel to \( V_e \) and was inversely related to ETCO₂. CBFv fell immediately on HUT in synchrony with a brief, abrupt fall in BP comprising IOH.\(^{23} \) Notably, the fall in CBFv preceded the increased \( V_e \) and reciprocal decreased ETCO₂. Figure S2 shows the time delay between CBFv fall and onset of hyperventilation in 1 representative subject; in all POTS subjects, there was a delay of 17±6 s (\( P<0.025 \)). Hyperventilation was not elicited by HUT in controls. Figure 3, the hemodynamic response of all participants, shows that HR was significantly increased at baseline in POTS subjects when compared with that in controls (\( P<0.001 \)). The increase in HR during HUT in POTS was greater than that in controls (\( P<0.001 \)) and associated with a decreased CO (\( P<0.025 \)) and increased TPR (\( P<0.025 \)) when compared with controls. The short-lived initial decrease in MAP, associated with IOH, was larger in POTS when compared with that in controls (\( P<0.025 \)).

Because baseline values differed between POTS and controls, Figure 4 shows the percentage change from baseline averaged for all subjects within each group. There was a 2-fold larger emptying of the thorax (central BV) in POTS when compared with that in controls, with reciprocal filling.

**Figure 1.** Averaged respiratory data for all participants (black line, controls; gray line, postural tachycardia syndrome [POTS]) before and during a 10-minute 70° head-up tilt. Expiratory minute volume (\( V_e \)) is expressed as liters per minute, end tidal carbon dioxide (ETCO₂) as Torr, respiratory rate (Rate) as breaths per minute, and tidal volume (TV) expressed as milliliters. *Different from controls, \( P<0.05 \).
of the splanchnic reservoir. However, BV redistribution was only transiently different between the 2 groups during the initial tilt. Initial decreases in CBFv were synchronous with and proportionate to initial changes in central BV ($r^2=0.80$) and were significantly greater in POTS when compared with that in controls ($P<0.01$). Once hyperventilation and hypocapnia occurred, CBFv decreased further in POTS subjects.

MSNA (Figure 4) increased similarly after HUT for POTS and controls. Thereafter, MSNA increased directly with $V_E$ and inversely to ETCO2 for POTS subjects, whereas remaining stable for controls. Because of sympathetic activation, MAP and TPR were increased in POTS subjects when compared with that in controls for the remainder of the HUT.

**Discussion**

Changing from supine to standing transfers >500 mL of central BV caudally, initially decreasing central BV and increasing BV within the splanchnic vasculature and lower extremities.20,21,24 There is often a period of IOH during which BP and CBF transiently decrease, sometimes markedly, reaching their nadir 10 to 20 s after standing.25 A reflex tachycardia results, and BP and CBFv are restored within 30 to 60 s.

**Figure 2.** Arterial blood pressure (AP) expressed as millimeters of mercury, cerebral blood flow velocity (CBFv) as centimeters per second, heart rate (HR) as beats per minute, expiratory minute volume ($V_E$) in liters per minute, end tidal carbon dioxide (ETCO2) in Torr, and muscle sympathetic nerve activity (MSNA) expressed as arbitrary units shown for a representative patient with postural tachycardia syndrome before, during, and after a 10-minute 70° head-up tilt. BP indicates blood pressure.

**Figure 3.** Hemodynamic data for all participants (black line, controls; gray line, postural tachycardia syndrome [POTS]) before and during a 10-minute 70° head-up tilt. Heart rate (HR) is expressed as beats per min, mean arterial pressure (MAP) as millimeters of mercury, cardiac output (CO) as liters per minute, and total peripheral resistance (TPR) as millimeters of mercury per liter per minute. *Difference from controls, $P<0.05$. #Overall effect different from controls, $P<0.05$. 
IOH results from the normal delay of arterial baroreflex detection and autonomic response to gravitational BV redistribution. Thereafter upright HR slows remaining elevated when compared with supine; CBFv recovers to somewhat less than supine26; and BP is restored with a slightly higher MAP but reduced pulse pressure because of musculoskeletal mechanisms,23,27 arterial vasoconstriction, elastic recoil of pooled blood in dependent veins, and active venoconstriction of splanchnic veins.28 IOH is common and occurs in healthy individuals who do not develop OI during prolonged postural stress.25 Hitherto, studies of POTS subjects have not distinguished differences in IOH from controls.

We describe here for the first time a subset of patients with POTS and the chief complaint of dyspnea in which IOH during HUT is exceptional, comprising an exaggerated initial decrease in CBFv that coincides with a notably large fall in central thoracic BV before BP restitution. Moreover, the reduced CBFv is immediately followed by hyperpnea and hypocapnia, perpetuating the reduced CBFv. Finally, sympathetic activity, measured by MSNA, increases in parallel with hyperpnea and hypocapnia at least until orthostatic stress is discontinued. We hypothesize that hyperpnea and hypocapnia increase brain-wide vasoconstriction and hypoxia-ischemia via the Bohr Effect,29 resulting in increased cerebral oxygen demand, neuronal excitability, and continued sympathetic activation (Figure 4).30

**Posturally Increased Ventilation Can Also Occur in Control Subjects and in POTS**

A modest increase in ventilation and decrease in ETCO₂ are observed during transitions from supine to upright.31,32 However, these changes are often exaggerated in POTS subjects when compared with that in controls.3,10,28,33 It has been assumed that a reduction in CBF in these patients with POTS follows hypocapnia.3,10,33 However, here we show that the reverse may be true; a reduction in CBFv precedes hyperventilation in these POTS subjects.

Hyperventilation in POTS may be a mechanism for compensation of reduced thoracic BV34 and teleologically may be an explanation for hyperpnea and hyperventilation. However, voluntary hyperventilation fails to induce POTS symptoms,10 and the respiratory pump (increased intra-abdominal and decreased intrathoracic pressures) does not improve CO in POTS subjects.3 Indeed, in past studies, spontaneous hyperventilation in POTS subjects occurs after HUT is well underway. Also, increased ventilation has no effect on reductions of peripheral blood flow in arms, legs, and pelvic regions when compared with normocapnic POTS subjects and healthy controls.3 Moreover, hyperpneic breathing, causing increased abdominal pressure during inspiration and expiration, can restrict venous return to the heart as observed in our patients with POTS.35

**What Causes the Exaggerated Decrease in CBFv?**

Transduction from BV, to arterial BP, to CBF can function as a high pass filter system in which a rapid decrease in central BV during IOH results in a rapid decrease in AP that drives similar decreases in CBF.36 This attenuates slow variations and permits pressure to drive CBF only at higher frequencies (with periods of seconds or smaller). However, central BV and AP can also modulate cerebral autoregulation.37 Central BV is linked by the baroreflexes to cerebrovascular regulation via the extrinsic (extracerebral) vascular innervation system, and excessive baroreflex unloading causes parasympathetic withdrawal and reduction of nitric oxide–dependent dilatation of the extrinsic cerebral vasculature resulting in cerebral
vasoconstriction. Our work supports the ability of this extrinsic vasculature to respond well to nitric oxide in humans. Thus, we propose that the exaggerated initial fall in CBFv is directly caused by the initial decrease in BP of IOH and indirectly by reflex loss of NO-dependent dilation of the extracerebral brain vasculature because of parasympathetic withdrawal.

What Causes the Exaggerated Hyperpnea and Hypocapnia?

A decreased chemoreflex response to CO₂ and increased hypoxic ventilatory response found in POTS subjects contribute to hyperventilation. CBF derives largely from carotid artery blood flow. If CBF were reduced, carotid artery blood flow would also be reduced, causing decreased carotid body blood flow and increased chemoreflex sensitivity to hypoxia. Although these data are from rabbits, they are closely paralleled in primates by stagnant ischemia or ischemic hypoxia in which large reductions in carotid body blood flow is similar to the response to hypoxic hypoxia. Once engaged, hyperventilation and hypocapnia sustain reduced CBFv. Central nervous system hypocapnia and ischemia result in neuronal excitation and sympathetic activation.

Limitations

We used transcranial Doppler that only measures CBFv; however, changes in CBFv accurately reflect changes in CBF during orthostatic stress. The decrease in arterial BP with IOH is larger during standing than during HUT although present in both. Nevertheless, these patients uniformly identified their symptoms, including dyspnea, during tilt with symptoms that occur during real-world orthostasis.

We did not capture MSNA during all tilts because the electrode position was sometimes lost with HUT. However, the time-dependent responses of respiratory measurements, BP and CBFv, were similar in all subjects and recorded successfully during all studies.

Subjects for this study were recruited if they were first referred to our clinic for evaluation of suspected POTS. Thus, we have no insight into how this subgroup of patients with POTS fits into the larger sphere of patients affected by POTS. Custom data acquisition software is used; however, it has been used extensively in previously validated experiments.

Perspectives

Hyperventilation is associated with POTS. Its mechanism was unknown but, based on teleological arguments, it was assumed to subserve the respiratory-abdominal pump, supporting cardiac output and brain blood flow. This study indicates that hyperventilation takes the form of hyperpnea, resulting in a decrease in cardiac output and a disproportionate fall in CBF in POTS. Hyperpnea seems caused by a profound reduction of central BV early during the initial hypotensive phase of orthostasis. We hypothesize that this results in stagnant ischemic stimulation of the carotid body and consequent hyperpnea, sympathetic activation, tachycardia, and an increase in BP.

Acknowledgments

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Disclosures

None.

References


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**Novelty and Significance**

**What Is New?**

- To our knowledge, this is the first report of decreased cerebral blood flow initiating hypocapnic hyperpnea.

**What Is Relevant?**

- Hyperpnea and hypocapnia perpetuate brain-wide vasoconstriction and hypoxia-ischemia via the Bohr effect resulting in increased cerebral oxygen demand, neuronal excitability, and continued sympathetic activation with tachycardia.

**Summary**

The ensuing potentiating and sustained effects of hypocapnia on reducing cerebral blood flow and the effects of respiratory alkalosis on oxygen dissociation cause a state of severe hypoxia-ischemia that severely limits brain oxygen and substrate supply while increasing oxygen demand. An ischemia-reperfusion mechanism with oxidative stress could ensue.
Reduced Cerebral Blood Flow With Orthostasis Precedes Hypocapnic Hyperpnea, Sympathetic Activation, and Postural Tachycardia Syndrome
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REDUCED CEREBRAL BLOOD FLOW WITH ORTHOSTASIS PRECEDES HYPOCAPNIC HYPERPNEA, SYMPATHETIC ACTIVATION AND POTS.

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Running head: Attenuated cerebral blood flow; one cause of POTS

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**Figure S1.** Respiratory data from a representative postural orthostatic tachycardia (POTS) patient for time period before, during and after (Supine) a 10 min 70° head-up tilt (Tilt). Minute volume ($V_E$) is expressed as liters per minute ($L \cdot min^{-1}$), Tidal Volume as liters (L), and Respiratory Rate as breaths per minute (bpm).
Figure S2. A magnified view of the time course of the changes in cerebral blood flow velocity (CBFv) in $\text{cm} \cdot \text{s}^{-1}$, and Respiratory Volume in liters (L). The vertical line marks the beginning of the fall in CBFv which temporally precedes the increase in ventilation following a head-up tilt to 70°. The data shown is for a single representative POTS patient.