Baroreceptor unloading in postural tachycardia syndrome augments peripheral chemoreceptor sensitivity and decreases central chemoreceptor sensitivity

Indu Taneja,1,2,3 Marvin S. Medow,1,4 Debbie A. Clarke,1 Anthony J. Ocon,1 and Julian M. Stewart1,2,4

Departments of 1Pediatrics, 2Medicine, 3Pharmacology, and 4Physiology, New York Medical College, Valhalla, New York

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Taneja I, Medow MS, Clarke DA, Ocon AJ, Stewart JM. Baroreceptor unloading in postural tachycardia syndrome augments peripheral chemoreceptor sensitivity and decreases central chemoreceptor sensitivity. Am J Physiol Heart Circ Physiol 301: H173–H179, 2011. First published May 2, 2011; doi:10.1152/ajpheart.01211.2010.—While orthostatic tachycardia is the hallmark of postural tachycardia syndrome (POTS), orthostasis also initiated increased minute ventilation (VE) and decreased end-tidal CO2 in many patients. We hypothesized that chemoreflex sensitivity would be increased in patients with POTS. We therefore measured chemoreceptor sensitivity in 20 POTS (16 women and 4 men) and 14 healthy controls (10 women and 4 men), 16–35 yr old by exposing them to eucapneic hypoxia (30% O2), eucapneic hypoxia (10% O2), and hypercapnic hypoxia (30% O2+5% CO2) while supine and during 70° head-upright tilt. Heart rate, mean arterial pressure, O2 saturation, end-tidal CO2, and VE were measured. Peripheral chemoreflex sensitivity was calculated as the difference in VE during hypoxia compared with room air divided by the change in O2 saturation. Central chemoreflex sensitivity was determined by the difference in VE during hypoxia divided by the change in CO2. POTS subjects had an increased peripheral chemoreflex sensitivity (in 1·%oxygen−1) in response to hypoxia (0.42±0.38 vs. 0.19±0.17) but a decreased central chemoreflex sensitivity (1·Torr−1) CO2 response (0.49±0.38 vs. 1.04±0.18) compared with controls. CO2 sensitivity was also reduced in POTS subjects when supine. POTS patients are marked sensitized to hypoxia when upright but desensitized to CO2 while upright or supine. The interactions between orthostatic baroreflex unloading and altered chemoreflex sensitivities may explain the hyperventilation in POTS patients.

Orthostatic intolerance is defined by symptoms of light-headedness, nausea, cognitive disability, diaphoresis, headache, fatigue, palpitations, and heat, which are present upright and resolve when recumbent. Postural tachycardia syndrome (POTS) is defined by orthostatic intolerance associated with excessive postural tachycardia, and in adults by an increase in sinus heart rate (HR) of >30 beats/min or to a HR >120 beats/min during 10 min of orthostasis (16).

Many POTS patients have dyspnea and hyperventilation when upright. Our group has reported the association of hyperventilation with thoracic hypovolemia and splanchnic hypervolemia in POTS (33). Large decrements in end-tidal CO2 (ETCO2), often reaching 25 Torr or less, following change of position from supine to upright are driven by increased ventilation (18). This results in cerebral vasoconstriction (25), which may account, in part, for central symptoms of orthostatic intolerance. Evidence of hyperventilation in POTS patients occurs in the absence of any functional or structural cardiac or respiratory abnormalities. Candidate mechanisms for hyperventilation include a defect in chemoreflex response or in ventilatory control in these patients. There is no evidence supporting an intrinsic defect in chemoreception. Thus far baroreflex–chemoreflex interactions have not been studied in patients with POTS.

Respiratory chemoreceptors are of two types: peripheral and central. The peripheral receptors primarily respond to arterial hypoxia and to a lesser extent to hypercapnia (17). The central receptors are far more sensitive to hypercapnia (increase in hydrogen ions) (4). The peripheral chemoreceptors are contained within the carotid and aortic bodies, whereas the central chemoreceptors are currently believed to be distributed mainly in the medulla (5).

Respiratory chemoreceptors can modulate the autonomic nervous system. The modulation can be indirect, via changes in blood O2 and CO2 concentration, or by inhibiting K+ channels, depolarizing chemosensitive neurons, and thereby increasing their firing rate (27, 31). Modulation can also be direct via sympathetic facilitation (30).

Baroreceptors can also modulate chemoreflex activity and ventilation. For example, ventilatory responses to chemoreceptor stimulation are augmented by arterial baroreflex unloading and are depressed by baroreceptor loading (12).

Based on these relationships, we tested the hypothesis that chemoreflex sensitivities are increased in POTS patients and are potentiated by orthostatic baroreflex unloading causing hyperventilation.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of New York Medical College, and informed consent was obtained from all subjects.

Subjects

We studied 20 POTS [16 women (W) and 4 men (M)] and 14 healthy subjects (10 W and 4 M) between the ages of 16 and 35 yr and with height of 169±9 cm, weight of 63.8±10.3 kg, and body mass index of 22.4±0.8 kg/m2 (means±SE). All subjects were non-smokers and normotensive. Subjects were not taking medications, and none of them had been at high altitude (>1,500 m) for at least 5 mo. Hemoglobin concentrations were normal and ranged from 10.2 to 17.4 mg/dl. Since hypovolemia and dehydration may increase ventilation, POTS patients were screened for evidence of hypovolemia and abnormal renin-angiotensin-aldosterone levels. None of the enrolled patients was hypovolemic or had any other hormonal or hematologic abnormalities. Because of the effects of the menstrual cycle on cardiovascular regulation (21), all female subjects were studied during their early follicular phase (1–4 days after the onset of menstruation).

Experimental Setup

The ventilatory responses to eucapnic hypoxia and hyperoxic hypervacapnia were obtained using the “dynamic end-tidal forcing”
This technique allows for the manipulation of end-tidal concentration of one gas while maintaining the end-tidal concentration for another gas constant. We used four gas conditions intended to separate the effects of hypoxia and hypercapnia on chemoreflex function: eucapnic normoxia (breathing room air), eucapnic hypoxia (10% O₂ balanced with N₂ while maintaining ETCO₂ unchanged from breathing room air), eucapnic hyperoxia (30% O₂ while maintaining ETCO₂ unchanged from breathing room air), and hypercapnic hyperoxia (30% O₂ + 5% CO₂).

Eucapnic hypoxia was used to assess the hypoxic response attributed to peripheral chemoreflex sensitivity (PCS). Thirty percent O₂ (hypoxia) was used to minimize the PCS. Hyperoxic hypercapnia was used to measure the hypercapnic [central chemoreceptor sensitivity (CCS)] chemoreflex function by suppressing the effect of peripheral chemoreceptors (carotid body) with O₂ and stimulating central chemoreceptors with CO₂ (23). An open circuit was used to control inspired gases during each of these gas conditions. Open circuit breathing uses two-way valves to eliminate exhaled CO₂ and uses premixed gases for inhalation.

Subjects breathed through a face mask connected to a pneumotachograph (Hans Rudolph, Shawnee, KS), from which we obtained inspired minute volumes. The other end of this pneumotachograph was connected through a low-resistance two-way nonrebreathing valve (Hans Rudolph), which had two outlets. One outlet of this nonrebreathing valve was used for expired gas and connected to a room air exhaust; the other end of the nonrebreathing valve was connected to a 30-liter breathing bag (Rusch, Teleflex Medical). The gas in the bag was constantly replenished with gases (O₂, CO₂, and N₂), mixed to the desired concentration using a rotameter (model FL-6GP, Omega Engineering, Stamford, CT). The inspired content of the bag was changed by varying the concentrations of O₂, CO₂, and N₂. The breathing bag was always fully inflated at the start of inspiration, and excess gas was vented through an exhaust valve. The flow was modulated to ensure that a sufficient amount of gas was available during the increased ventilation induced by hypercapnia.

Two stage gas flow regulators connected to each of the three air cylinders (O₂, N₂, and CO₂) were used to achieve constant flow at the desired concentration of the air mixture, balanced with N₂ (5% CO₂, 10% O₂, 30% O₂, balanced by N₂). Inhaled O₂ concentration was measured continuously and directly by an O₂ sensor (S-3A/I Oxygen Analyzer with N-22M Sensor, AEI Technologies, Naperville, IL), attached near the face mask. ETCO₂ was measured by nasal prongs connected to a side stream capnograph (Capnocheck sleep capnograph/oximeter, Smiths Medical, St. Paul, MN). The pneumotachograph was calibrated using a 3-liter syringe, and the O₂ sensor was calibrated using known concentrations of O₂ before each testing session. A schematic diagram of the experimental setup is shown in Fig. 1.

For eucapnic normoxia, the valves were adjusted so that subjects breathed room air. For eucapnic hypoxia, the level of O₂ was titrated so that subjects breathed 10% O₂ (monitored by O₂ sensor) for 8 min. During this time, subjects typically achieved an arterial O₂ saturation (SaO₂) of ~80–85% as assessed by pulse oximetry of the earlobe. For hyperoxia, the level of O₂ was titrated so that subjects breathed 30% O₂ (monitored by O₂ sensor) for 8 min. For hypercapnic hyperoxia, the level of O₂ and CO₂ was titrated so that subjects breathed 30% O₂ plus 5% CO₂ to increase ETCO₂ to 60 Torr or to 10 Torr more than baseline level (monitored by O₂ sensor and by capnograph) for 8 min. The ETCO₂ levels were displayed in real time on the capnograph screen, ETCO₂ giving an accurate noninvasive measurement of arterial Pco₂ (28). Subjects rested and breathed room air in between the hypoxic and hyperoxic conditions. Measurements of all respiratory and cardiovascular parameters were made once a steady state was achieved.

Protocol

Testing began at 10:00 AM after 4 h of fast. Subjects refrained from beverages containing xanthine and caffeine for at least 72 h before testing. Subjects were familiarized with the procedures used in the
study. Subjects were instrumented for electrocardiography, respiratory plethysmography, \( S_{aO_2} \), by pulse oximetry, pneumotachography via a facemask, impedance plethysmography, continuous blood pressure recording, and capnography. After an initial 20 min of acclimatization, subjects were monitored during a 20-min rest period in which ETCO\(_2\) was measured via a nasal cannula. Mean ETCO\(_2\) over the last 5 min of rest period was defined as isocapnia for the particular subject for the remainder of the protocol. Subjects then underwent four measurement periods separated by 30-min rest periods. Each measurement period corresponded to one of the following gas conditions presented in random order: eucapnic normoxia (room air), eucapnic hypoxia, eucapnic hyperoxia, and hypercapnic hyperoxia. We randomized the order of conditions between eucapnic normoxia, eucapnic hyperoxia, hyperoxic hypercapnia, and eucapnic hypoxia because the order of gas might effect the responses (13). Subjects breathed gases for 8 min or until the subject requested to stop.

After all supine data collections were complete, the subjects were reintroduced to each gas condition for 1 min while supine and were tilted head-upright to 70° (HUT) for a maximum of 8 min in each gas condition. Continuous HR, mean arterial pressure (MAP), \( S_{aO_2} \), ETCO\(_2\), and minute ventilation (\( V\dot{E} \)) were recorded. Subjects were tilted back to the supine position if fainting ensued or if the subject requested to stop. Cardiac output (CO) was estimated using the model flow method contained within the Finometer.

**Data Analysis**

Data were digitized at 200 Hz with signal processing software and analyzed off-line. Beat-to-beat data were collected during the last 3 min for HR, MAP (Finometer, TNO, Amsterdam, The Netherlands), \( S_{aO_2} \), ETCO\(_2\), and expired \( V\dot{E} \) during supine and HUT in each of the gas conditions.

Cardiovascular responses were further assessed by measuring MAP, systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, CO, total peripheral resistance (TPR), and stroke volume (SV) during ventilatory changes.

MAP was calculated from SBP and DBP with the formula MAP = (SBP + 2DBP)/3. TPR was calculated as MAP/CO.

Ventilation versus gas content function curves were constructed with \( V\dot{E} \) on the ordinate and the gas measure on the abscissa. The operating point was defined by room air (normoxia-eucapnia) for each subject.

Ventilatory PCS (response to hypoxia) was determined by calculating linear regression slopes between \( V\dot{E} \) and \( S_{aO_2} \) (gas measure) during eucapnic hyperoxia to eucapnic hypoxia (the hypoxic ventilatory response).

Ventilatory central chemoreflex sensitivity (CCS) (response to hypercapnia) was determined by calculating linear regression slopes between \( V\dot{E} \) and ETCO\(_2\) (gas measure) during eucapnic hypoxia and hypercapnia.

**Statistics**

Measurements across the conditions were computed for PCS and CCS for each subject. Individual regression slopes between \( V\dot{E} \), hypoxia, and hypercapnia were averaged across each condition and compared for supine and HUT. Regressions for chemoreflex responses were compared across the two conditions during supine and HUT conditions using a two-way repeated-measures analysis of variance. Likewise, cardiovascular responses (HR, MAP, SBP, DBP, CO, TPR, and SV) were compared across supine and HUT conditions. When appropriate, post hoc comparisons were performed using Tukey’s test. Primary outcome variables were correlated to find causal associations. Differences were considered significant when \( P < 0.05 \). All values are reported as means ± SE unless otherwise indicated.

**RESULTS**

Out of 20 POTS (16 W and 4 M) and 14 control (10 W and 4 M) subjects, 19 POTS (15 W and 4 M) and 12 control (8 W and 4 M) subjects completed the eucapnic normoxia (room air HUT) protocol, 13 POTS (9 W and 4 M) and 6 control (5 W and 1 M) subjects completed the hyperoxic HUT protocol, 13 POTS (9 W and 4 M) and 6 control (5 W and 1 M) subjects completed the hypercapnic hypoxia HUT protocol. Data of patients completing each gas condition have been averaged and compared across groups. Group-averaged data for POTS and control subjects for every gas condition are shown for the supine position (Table 1) and upright position (Table 2).

**Eucapnic Normoxia: Room Air**

**Supine: baseline conditions.** POTS and control subjects had no significant differences in \( S_{aO_2} \), ETCO\(_2\), and respiratory rate while supine. However, POTS patients had a higher \( V\dot{E} \) \((P < 0.05 \) compared with controls.

### Table 1. Ventilatory and cardiovascular measures for peripheral and central chemoreflex sensitivity in supine position

<table>
<thead>
<tr>
<th>Supine</th>
<th>Central Chemoreflex</th>
<th>Peripheral Chemoreflex</th>
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<tbody>
<tr>
<td></td>
<td>Eucapnic normoxia</td>
<td>Hyperoxic normoxia</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>POTS</td>
</tr>
<tr>
<td>Arterial oxygen saturation, %</td>
<td>97.5 ± 0.6</td>
<td>97.2 ± 0.2</td>
</tr>
<tr>
<td>Minute ventilation, l/min</td>
<td>4.1 ± 0.4</td>
<td>5.5 ± 0.4</td>
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<tr>
<td>Respiratory rate, beats/min</td>
<td>16.7 ± 1.1</td>
<td>16.8 ± 0.7</td>
</tr>
<tr>
<td>ETCO(_2), Torr</td>
<td>43.0 ± 0.7</td>
<td>42.2 ± 1.0</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>63.7 ± 3.2</td>
<td>75.4 ± 3.2</td>
</tr>
<tr>
<td>Systolic arterial pressure, mmHg</td>
<td>121.2 ± 2.8</td>
<td>112.7 ± 1.9†</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mmHg</td>
<td>62.9 ± 1.7</td>
<td>61.7 ± 1.6</td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
<td>84.0 ± 1.9</td>
<td>79.0 ± 1.5</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>4.9 ± 0.4</td>
<td>4.9 ± 0.2</td>
</tr>
<tr>
<td>TPR, mmHg·l⁻¹·min⁻¹</td>
<td>17.9 ± 1.3</td>
<td>16.6 ± 1.1</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>81.1 ± 8.1</td>
<td>66.1 ± 2.1†</td>
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</table>

Values are means ± SE. POTS, postural tachycardia syndrome; ETCO\(_2\), end-tidal CO\(_2\); TPR, total peripheral resistance. *\( P < 0.05 \) compared with eucapnic normoxia; †\( P < 0.05 \) compared with controls.
Table 2. Ventilatory and cardiovascular measures for peripheral and central chemoreflex sensitivity in HUT70

<table>
<thead>
<tr>
<th></th>
<th>Central Chemoreflex</th>
<th>Peripheral Chemoreflex</th>
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<tbody>
<tr>
<td></td>
<td>Eucapnic normoxia</td>
<td>Hyperoxic hypercapnia</td>
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<tr>
<td></td>
<td>Controls</td>
<td>POTS</td>
</tr>
<tr>
<td>Arterial oxygen saturation, %</td>
<td>97.5 ± 0.6</td>
<td>97.2 ± 0.2</td>
</tr>
<tr>
<td>Minute ventilation, l/min</td>
<td>4.6 ± 0.8</td>
<td>8.8 ± 1.2‡</td>
</tr>
<tr>
<td>Respiratory rate, beats/min</td>
<td>16.7 ± 1.1</td>
<td>18.6 ± 1.4</td>
</tr>
<tr>
<td>ETCO2, Torr</td>
<td>41.2 ± 1.2</td>
<td>34.4 ± 1.8†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>82.8 ± 3.9</td>
<td>101.5 ± 5.4‡‡</td>
</tr>
<tr>
<td>Systolic arterial pressure, mmHg</td>
<td>118.8 ± 3.9</td>
<td>114.1 ± 2.5</td>
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<tr>
<td>Diastolic arterial pressure, mmHg</td>
<td>67.3 ± 3.8</td>
<td>64.3 ± 2.5</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>86.2 ± 3.4</td>
<td>81.8 ± 2.4</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>4.3 ± 0.3</td>
<td>4.9 ± 0.3</td>
</tr>
<tr>
<td>TPR, mmHg·l−1·min−1</td>
<td>21.1 ± 1.4</td>
<td>17.9 ± 1.3‡</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>52.1 ± 4.1‡</td>
<td>57.1 ± 3.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. HUT70, head-up tilt at 70° position. *P < 0.05 compared with eucapnic normoxia; †P < 0.05 compared with controls; ‡ compared with supine (Table 1).

0.05), lower SBP (P < 0.05), and higher HR (P < 0.05) than control subjects. CO and TPR were not different, but SV was reduced in POTS compared with control subjects (P < 0.05) (Table 1).

HUT. Head-up tilt to 70° was used to unload the baroreflexes. Baroreflex unloading during HUT did not affect SaO2 and respiratory rate (Table 2) in either POTS or control subjects. When compared with controls, POTS patients had significantly higher VE (P < 0.05), lower ETCO2 (P < 0.01), and higher HR (P < 0.01) than control subjects.

HUT decreased CO (P < 0.01) in controls. SV decreased (P < 0.001), HR increased (P < 0.001), and peripheral resistance increased (P < 0.05) in both POTS and control subjects (Table 2) compared with supine.

PCS: Eucapnic Hypoxia

Hypoxia supine. Hypoxia in the supine position decreased SaO2 in both POTS and control subjects (P < 0.001). However, controls tended toward larger decreases in SaO2 compared with POTS patients (Table 1). A decrease in SaO2 initiates an increase in ventilation (29) in both POTS and control subjects (P < 0.05). Despite smaller decreases in SaO2, POTS patients had a higher VE during hypoxia than control subjects (P < 0.05) (Fig. 2). Thus, in the supine position, POTS patients had a trend toward higher hypoxic ventilatory response/PCS (in l·min−1·%oxygen−1) than controls (PCS vs. controls, 0.2 ± 0.11 vs. 0.15 ± 0.05, P = 0.08). Both POTS and control subjects had an increase in their HR (P < 0.05) (PCS > controls, P < 0.01) and an increase in their COs (Table 1).

Hypoxia HUT. When compared with room air HUT, hypoxia HUT decreased SaO2 (P < 0.001), increased VE, and increased HR in both POTS and control subjects (P < 0.001). However, POTS patients had higher VE (P < 0.05) and higher HR (P < 0.05) than controls (Fig. 2). Hypoxia HUT did not change CO, TPR, MAP, CO, or SV (Table 2).

Baroreflex unloading during hypoxia did not change the PCS in controls (supine vs. HUT, 0.15 ± 0.05 vs. 0.19 ± 0.017, P = not significant) but increased PCS in POTS patients (0.2 ± 0.11 to 0.42 ± 0.38, P < 0.05). Thus PCS during HUT was higher in POTS than in control subjects (P < 0.05, Fig. 2).

In addition, the hypoxic response was reset, shifted upwards and to the right so that POTS patients had a higher VE and higher SaO2 than control subjects (Fig. 2).

CCS: Hyperoxic Hypercapnia

Hyperoxic hypercapnia increased ventilation in both POTS and control subjects. During spontaneous breathing, hypercapnia is some 3–5 times stronger than hypoxia as a ventilatory stimulus under our experimental conditions (Table 1).

Hypercapnia supine. When supine, POTS and control subjects had no significant differences in ETCO2. Hypercapnia increased ETCO2 in both POTS and control subjects to similar levels with a trend toward higher VE in controls compared with POTS patients (P = 0.08) (Fig. 3, and Table 1). The hypercapnic ventilatory response/CCS for POTS patients was lower than that for controls (0.68 ± 0.34 vs. 1.0 ± 0.18, P < 0.05).

At room air supine position, POTS patients had a trend toward higher ventilation than did controls (Table 1). Room air hypercapnia caused a higher increase in ventilation in controls compared with POTS patients. Room air hypercapnia increased MAP and HR in both POTS and control subjects.

Hypercapnia HUT. Baroreflex unloading during hypercapnia HUT led to higher VE in controls compared with POTS patients (P < 0.05, Fig. 3). SaO2 was not different between POTS and control subjects (Table 2).

When compared with room air HUT, hypercapnia HUT did not change CCS in controls (supine vs. HUT, 0.84 ± 0.27 vs. 1.04 ± 0.18, P = not significant) but decreased CCS in POTS patients (0.68 ± 0.34 vs. 0.49 ± 0.38, P < 0.05). Upright CCS for POTS patients was markedly lower than for controls (HUT-CCS, POTS vs. controls, 0.49 ± 0.38 vs. 1.04 ± 0.18, P < 0.05).

DISCUSSION

The results of this study demonstrated an increased respiratory chemoreflex response to hypoxia and a decreased respiratory chemoreflex response to hypercapnia in POTS compared with control subjects, even while supine. These differences were enhanced by orthostasis. We therefore infer that PCS
measured by the hypoxic ventilatory response was increased in POTS patients, whereas CCS measured by the hypercapnic ventilatory response was reduced in POTS patients. Baroreflex unloading during HUT potentiated the hypoxic response while further blunting the hypercapnic response. Therefore, in POTS patients, baroreflex unloading during HUT stimulates peripheral O2-dependent chemoreflexes causing hyperventilation that is unopposed by the restraining effects of hypocapnia. Thus it seems that respiratory chemoreflexes are impaired in POTS patients, and their function is further perturbed by baroreflex unloading resulting in hyperventilation.

Increased PCS and Set Point in POTS

Increased ventilation can be induced in healthy humans during severe orthostatic stress that produces extreme reductions in central blood volume and CO (14). The hyperpneic response is therefore physiological in extremis.

In our earlier studies of POTS, we found that modest orthostatic stress initiates hyperpnea and hyperventilation, but not in control subjects. Hyperpnea in POTS patients was related to the enhanced thoracic hypovolemia and reduced CO in these patients (33, 35). Enhanced thoracic hypovolemia results in excessive baroreflex unloading in POTS compared with control subjects, resulting in marked sympathoexcitation (3). In addition to increased peripheral O2 chemoreceptor sensitivity in POTS patients, we observed a resetting of the hypoxic ventilatory response toward higher SaO2 and Ve. This is directionally similar to orthostatic resetting of the arterial baroreflex known to occur in all subjects but enhanced in POTS patients (10). Thus a resetting of the peripheral chemoreceptor set point is expected when upright.

Baroreflex unloading could increase ventilation through direct sympathoexcitation of the respiratory center (33, 35), through effects on the peripheral chemoreflex (6), or through interactions of baroreflex and chemoreflex afferents in the intermediate area of the nucleus tractus solitarius (22). This could also be due to more localized effects of baroreflex-mediated sympathetic vasoconstriction of arterioles supplying the carotid and aortic bodies. Reduced local blood flow might result in a neural discharge similar to that evoked by asphyxia, anoxemia (2), or nicotine and cyanide (1, 7, 19). Indeed, McCloskey (20) showed that increased impulse traffic of the carotid sinus nerve is easily elicited by hypotension-induced reductions in carotid body blood flow.

Although overt hypotension is uncommon in POTS, intermittently reduced blood flow occurs whenever upright and might engender chemoreflex potentiation similar to potentiation caused by chronic intermittent hypoxia. Indeed, POTS patients have increased Ve supine, similar to long-lasting increases in baseline respiratory activity and long-term facilitation of respiratory motor output in humans with intermittent hypoxia (26).
Reduced Central Chemoreceptor Sensitivity in POTS

In contrast to the increased response to hypoxia, POTS patients demonstrated depressed $V_E$ responses to hypercapnia compared with control subjects. Hypercapnia is usually a strong ventilatory stimulus and excites the medullary respiratory center via changes in blood pH (9). Hypercapnia may also influence sympathoexcitation at the rostral ventrolateral medulla (9). We used hyperoxic hypercapnia to examine the ventilatory effects of central chemoreceptor stimulation while minimizing the effects of peripheral chemoreceptors that are primarily $O_2$ sensitive (15, 23). The stimulation of carotid chemoreceptors facilitates central chemoreceptors; conversely, the inhibition of carotid chemoreceptors can blunt central chemoreceptors (24). However, physiological blunting of the central chemoreceptors must have been small because no such effects were observed in control subjects. Thus the peripheral effects on central chemoreceptors cannot account for the reduced central chemoreceptor sensitivity in POTS compared with control subjects. One potential explanation for this reduced chemoreceptor sensitivity may relate to the profound reduction of the cardiovagal baroreflex in POTS patients despite enhanced sympathoexcitation (32). The application of cholinergic agents on the ventrolateral surface of the medulla in areas where the central chemoreceptors may be located stimulates breathing, whereas the application of atropine inhibits ventilation (11). Thus vagal withdrawal could account for central chemoreflex suppression; however, these experiments have only been performed in nonhuman mammals.

Clinical Implications for POTS

POTS patients have increased ventilation, especially when upright, related to sympathetic baroreflex stimulation and almost complete cardiovagal baroreflex withdrawal. Hypocapnia results because POTS patients have decreased sensitivity to $CO_2$, whereas the response of the peripheral chemoreceptors to hypoxia is enhanced. Enhanced hypoxic sensitivity may contribute to the long-term facilitation of sympathoexcitation in these patients. Upright hyperventilation and hypocapnia reduces cerebral blood flow (8) and contributes to light-headedness and to cognitive impairment during daily life.

Limitations

Our study has several limitations. First, the cardiorespiratory effects observed in our study were induced by acute chemoreflex activation but suggest a chronic change in chemoreflex sensitivity whose origins remain unclear. Second, we did not test the effects of hypoxic hypercapnia. However, we were primarily interested in separating the ventilatory effects of $O_2$ and $CO_2$. In retrospect, this could have further delineated the role and contribution of carotid bodies in peripheral and central chemoreceptor interactions.
Summary

The present study demonstrates the enhanced ventilation in response to hypoxia and the blunting of the ventilation response to hypercapnia particularly during baroreflex unloading in POTS patients compared with healthy control subjects.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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