Baroreflex control of muscle sympathetic nerve activity in postural orthostatic tachycardia syndrome

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Muenter Swift, N., N. Charkoudian, R. M. Dotson, G. A. Suarez, and P. A. Low. Baroreflex control of muscle sympathetic nerve activity in postural orthostatic tachycardia syndrome. Am J Physiol Heart Circ Physiol 289: H1226–H1233, 2005. First published April 29, 2005; doi:10.1152/ajpheart.01243.2004.—Postural orthostatic tachycardia syndrome (POTS) is characterized by excessive tachycardia during orthostasis. To test the hypothesis that patients with POTS have decreased sympathetic neural responses to baroreflex stimuli, we measured heart rate (HR) and muscle sympathetic nerve activity (MSNA) responses to three baroreflex stimuli including vasoactive drug boluses (modified Oxford technique), Valsalva maneuver, and head-up tilt (HUT) in POTS patients and healthy control subjects. The MSNA response to the Valsalva maneuver was significantly greater in the POTS group (controls, 26 ± 7 vs. POTS, 48 ± 6% of baseline MSNA/mmHg; P = 0.03). POTS patients also had an exaggerated MSNA response to 30° HUT (controls, 123 ± 24 vs. POTS, 208 ± 30% of baseline MSNA; P = 0.03) and tended to have an exaggerated response to 45° HUT (controls, 137 ± 27 vs. POTS, 248 ± 58% of baseline MSNA; P = 0.10). Sympathetic baroreflex sensitivity calculated during administration of the vasoactive drug boluses also tended to be greater in the POTS patients; however, this did not reach statistical significance (P = 0.15). Baseline MSNA values during supine rest were not different between the groups (controls, 23 ± 4 vs. POTS, 16 ± 5 bursts/100 heartbeats; P = 0.30); however, resting HR was significantly higher in the POTS group (controls, 58 ± 3 vs. POTS, 82 ± 4 beats/min; P = 0.0001). Our results suggest that POTS patients have exaggerated MSNA responses to baroreflex challenges compared with healthy control subjects, although resting supine MSNA values did not differ between the groups.

intolerance; blood pressure; heart rate; Valsalva maneuver; head-up tilt

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS) is a chronic, potentially debilitating condition that often occurs in otherwise healthy individuals who are most often young women. Patients with this condition (also known as idiopathic orthostatic intolerance) exhibit excessive tachycardia [increase in heart rate (HR) of >30 beats/min] during head-up tilt (HUT) in the absence of significant orthostatic hypotension. They also develop dizziness, fatigue, headache, and/or anxiety with standing or HUT (24, 34). Although POTS has become better recognized clinically in recent years, the mechanisms underlying the pathophysiology of this condition remain unclear.

In humans, normal baroreflex physiology involves increased HR, increased vascular sympathetic nerve activity, and peripheral vasoconstriction in response to decreased venous return during upright posture (31). These normal responses result in maintenance of arterial pressure with the upright posture and an absence of symptoms such as those reported by POTS patients. It is not clear whether the excessive tachycardia with orthostasis in POTS patients is the cause or the consequence of one or more abnormal steps in the baroreflex pathway. For example, evidence is conflicting regarding baroreflex control of HR in patients with orthostatic intolerance. Some researchers have reported decreased sensitivity of baroreflex control of HR in these patients (9, 19), whereas others did not find a significant difference in sensitivity between controls and patients in similar studies (11, 22).

With regard to baroreflex responses to orthostasis, it is possible that in POTS patients, excessive tachycardic responses are secondary consequences of defects at other points in the baroreflex pathway. It has been reported (4) that peripheral vasoconstrictor responses are important predictors of successful orthostasis in humans. If patients with POTS have decreased sympathetic neural responses to orthostasis, the augmented tachycardia in these patients may be a compensatory response in the face of decreased peripheral vasoconstriction. For example, Furlan et al. (11) reported higher frequency of muscle sympathetic nerve activity (MSNA; measured in bursts/min) at rest, smaller changes in this variable with 75° HUT, and similar total burst frequencies in patients compared with control subjects during tilt. These data are consistent with the idea of decreased sympathetic responsiveness (smaller change with tilt) in the patient group.

In this context, an important element in quantification of sympathetic nerve activity is burst size or area (a reflection of the number of action potentials firing in that individual burst of sympathetic activity). That is, total integrated activity of the sympathetic nerves is a combination of burst frequency and burst area, and thus is not reflected in analysis of burst frequency alone (13). Furthermore, because MSNA is dependent upon the cardiac cycle, it is not clear from the report of Furlan et al. (11) whether the MSNA data reported (in bursts/min) are a consequence of the higher HRs seen in the patient group.

With this information as a background, our aim in the present study was to comprehensively assess MSNA responses to several baroreflex stimuli in POTS patients and healthy control subjects. We tested the hypothesis that the total integrated activity of sympathetic nerves in response to baroreflex stimuli is decreased in patients with POTS compared with healthy control subjects. We directly measured MSNA and HR responses to administration of vasoactive drug boluses (mod-
Modified Oxford technique. Arterial pressure was first lowered and then raised by sequential bolus injections of sodium nitroprusside (100 mcg) and phenylephrine (150 mcg), and the resultant HR and MSNA responses were measured to determine baroreflex sensitivity and function. This technique was recently evaluated to be a simple and efficient method of assessing cardiac and sympathetic baroreflex responses (32). Phenylephrine was administered when the nitroprusside-induced decrease in SBP reached 30 mmHg or at 60 s after the nitroprusside injection, whichever came first. The phenylephrine injection was followed by a minimum of 20 min of recovery before the start of baseline for the Valsalva maneuvers; this was done to insure that the drugs were not affecting autonomic responses to the subsequent tests.

Valsalva maneuver. Subjects were asked to blow against a closed airway (i.e., into a plastic bugle) at an expiratory pressure of 40 mmHg for 15 s. If a subject was unable to generate 40 mmHg of expiratory pressure, the subject was asked to perform the maneuver at the highest pressure that could comfortably be generated. This sustained increase in intrathoracic pressure followed by its abrupt release causes a characteristic four-phase response in arterial pressure (5, 23, 33). Phase II consists of two parts; in early phase II (PhIIE), arterial pressure decreases due to decreased venous return, and in late phase II, pressure begins to increase due to the appropriate HR and MSNA responses elicited by PhIIE. The sympathoexcitatory response to PhIIE of the Valsalva maneuver provides a measure of sympathetic baroreflex function. After 5 min of baseline data collection, Valsalva maneuvers were performed in triplicate with ≥5 min of recovery between maneuvers. The last Valsalva maneuver was followed by ≥5 min of recovery before HUT baseline data collection began.

Head-up tilt. HUT provides an orthostatic and thus baroreflex challenge by using gravity to decrease venous return and cardiac output. HR, MSNA, and arterial pressure responses to HUT provide information on baroreflex sensitivity and function. After 5 min of baseline data collection, subjects were tilted to an angle of 30° for 2 min and then further tilted to an angle of 45° for 3 min.

Data Analyses

All data signals were stored on a computer (sample rate, 250 Hz) for later analyses using Windaq signal processing software (Dataq Instruments; Akron, OH). For MSNA analyses, relative baseline (i.e., zero activity) was set by selecting a section of the integrated neurogram in which no bursts occurred, calculating the signal average of that section, and setting that average equal to zero. Average burst area was then calculated relative to that zero baseline. All muscle sympathetic bursts were associated with the appropriate DBPs by correcting for baroreflex latency (8). Specifically, the peak of an MSNA burst occurs ~1.2 to 1.5 s after the ECG R wave associated with the end of the diastole that triggered the burst. Baroreflex latency, which is primarily due to nerve conduction time, is linearly correlated to body height and extremity length and is consistent and reproducible within an individual (8). By correcting for baroreflex latency, we insured that all MSNA bursts triggered by diastoles occurring within a time period of interest (i.e., during PhIIe of the Valsalva maneuver, for instance) were included as part of the MSNA response to that time period.

For comparisons of baseline MSNA between groups, burst frequency (number of bursts/min) and burst incidence (number of bursts/100 heartbeats) values were calculated. MSNA bursts were identified manually based on burst shape, amplitude, and appropriate baroreflex latency. Total activity, which takes into consideration not only the number of bursts but also the area (amplitude and duration) of the bursts, cannot be used for interindividual comparisons unless a normalization procedure is first performed on the data, because the quality of the MSNA signal can affect burst area. To allow comparisons of total activity between groups, MSNA responses to baroreflex tests were normalized as follows: MSNA total activity responses were calculated as a percentage of baseline (i.e., each subject’s baseline was

**Methods**

**Subjects**

This study was approved by the Mayo Clinic Rochester Institutional Review Board. Twelve healthy control individuals and nine POTS patients participated in the study after giving their written informed consent. All female subjects tested negative for pregnancy before participation. Control subjects completed a medical questionnaire and autonomic symptom profile and underwent an autonomic reflex screen to establish good health and normal autonomic function. POTS patients fulfilled all of the following criteria during a 70° HUT test: 1) a sustained increase in HR of ≥30 beats/min or a sustained HR of ≥120 beats/min, 2) absence of orthostatic hypotension defined as a sustained drop in systolic blood pressure (SBP) of >20 mmHg and/or in diastolic blood pressure (DBP) of >10 mmHg, and 3) presence of orthostatic symptoms including lightheadedness, dizziness, nausea, head pressure, and dyspnea. All POTS patients were sufficiently bothered by their orthostatic symptoms that they sought medical treatment; if an individual were on medications that could affect autonomic function, he or she was removed from those medications at least 5 half-life time periods before the study. Subjects abstained from vigorous exercise and alcohol for 24 h before the study and from caffeine for 12 h before and were at least 3 h postprandial the time of the study.

**Measurements**

HR was measured using a standard three-lead ECG. Arterial blood pressure (BP) was measured noninvasively at the finger from beat-to-beat photoplethysmographic recordings (Finapres blood pressure monitor 2300; Ohmeda; Englewood, CO). This technique has been demonstrated to compare accurately with simultaneous intraarterial recordings and to reproduce the continuously changing intraarterial waveform during the Valsalva maneuver and HUT (15, 16, 30). A thoracic respiratory monitoring band placed around the subject’s ribcage monitored respiratory movements. Effluent multunit, postganglionic MSNA was measured directly using standard microneurographic techniques as previously described (39, 40). Briefly, two sterile tungsten microelectrodes (tip diameter, 5–10 μm; Frederick Haer; Bowdoinham, ME) were inserted, one into the peroneal nerve for recording of MSNA and the other ~3 cm away (not in a nerve) to serve as a reference. A signal processing system (662C-3 Nerve Traffic Analysis System; University of Iowa Biomedical Engineering; Iowa City, IA) amplified (9 × 10^4 times), band-pass filtered (700–2,000 Hz), rectified, and integrated (time constant, 0.1 s) the nerve signal.

**Protocol**

Studies were performed in a temperature-controlled room (23°C) with subjects in the supine position. An intravenous cannula was placed in an antecubital vein a minimum of 45 min before baseline recordings. Upon arrival in the laboratory, subjects were instrumented for recording of ECG, arterial pressure, respiration, and MSNA. Finapres monitor readings were verified with manual phasmohancy to insure accuracy. After instrumentation, 10 min of baseline data were recorded. A series of three baroreflex challenges (described below) were then performed in the following order: modified Oxford technique, Valsalva maneuver, and HUT. Owing to the fragile nature of the MSNA recording, the order of the tests was not randomized; rather, they were performed in order according to the greatest likelihood of maintaining the nerve recording. This was done to maximize data collection.
For example, the last diastolic BP of PhIIE was performed after omission of threshold and saturation points. Averaged over 2-mmHg bins of SBP, and a weighted linear regression was performed separately for decreasing and increasing pressures. HR was assessed using the relationship of MSNA to DBP. Responses to decreasing arterial pressure (using nitroprusside) and increasing arterial pressure (using phenylephrine) were analyzed separately. To determine sympathetic baroreflex sensitivity for each individual, MSNA was integrated over 3-mmHg “bins” of DBP. This binning procedure reduces the statistical impact of non-baroreflex-mediated changes in MSNA (such as those due to respiration, etc.; Refs. 6, 7). In brief, a single average value for MSNA (total activity/heartbeat) was calculated for each 3-mmHg bin using the Halliwill program. The MSNA average value for each bin was then converted to percent of baseline activity. Alternatively, when the data were normalized using the traditional Halliwill method (13), the total activity-per-heartbeat values generated by the Halliwill program were not converted. A weighted linear regression (weighted by number of heartbeats/bin) was then performed between MSNA and DBP. Because the true relationship between MSNA and DBP is sigmoid rather than linear, threshold and/or saturation data points were omitted from the regression analyses.

Cardiac baroreflex sensitivity was similarly calculated and also performed separately for decreasing and increasing pressures. HR was averaged over 2-mmHg bins of SBP, and a weighted linear regression was performed after omission of threshold and saturation points.

Valsalva maneuver. The MSNA response to PHII was of the Valsalva maneuver was used to quantify sympathetic baroreflex function as illustrated in Fig. 1. The beginning of PHII was defined as the first decrease in DBP after the phase I BP upshoot. The end of PHII was defined as the point at which DBP began to increase again. Because the MSNA response depends on the strength of the stimulus (i.e., the magnitude of the drop in DBP), the responses are expressed as MSNA (as percent of baseline) divided by ΔDBP, where ΔDBP equals the decrease in DBP from the beginning to the end of PHII as defined above. To reduce confusion, the responses are expressed as positive numbers (because MSNA is increased from baseline) despite the fact that ΔDBP is negative. For each subject, MSNA responses to individual Valsalva maneuvers were averaged over the three trials.

Head-up tilt. MSNA, HR, and arterial pressure responses were calculated at both 30° and 45° tilt. The first minute after tilt was not used for data analyses to allow for stabilization. Data segments of 30–60 s in length were selected from each tilt angle for analyses; sections containing large breaths or inconsistent respiratory activity were omitted.

**Statistical Analyses**

To determine whether the baroreflex control of POTS patients differed from that of healthy control subjects, HR and MSNA values at baseline and responses to baroreflex challenges were compared using unpaired two-sample t-tests. The level of significance (α) was set at 0.05. All data are expressed as means ± SE.

**RESULTS**

**Subjects**

The control group consisted of six females and six males (age, 30 ± 2 yr), whereas the POTS patient group consisted of eight females and one male (age, 32 ± 2 yr). The age difference between the groups was not significant (P = 0.50). In addition, there were no significant differences between the female and male control subjects for any variables either during baseline or in response to any of the baroreflex challenges. Furthermore, separate comparisons of data from only the females in the control group with only the females in the POTS group (data not shown) showed similar group differences to those seen when the whole groups were compared.

Two of the control subjects and two of the POTS patients did not complete the modified Oxford technique due to difficulties obtaining or maintaining the intravenous line or due to the potential for an allergic reaction (the phenylephrine solution...
Baseline

Baseline averages for the two groups are summarized in Table 1. There was no significant difference between the POTS group and the control group in baseline MSNA, whether expressed as burst incidence \((P = 0.30)\) or burst frequency \((P = 0.85)\). Likewise, there was no difference in average resting DBP \((P = 0.69)\) or mean arterial pressure (MAP) \((P = 0.52)\); however, SBP was higher in the control subjects \((P = 0.04)\). Average resting HR was significantly higher in the POTS group \((P = 0.0001)\).

### Modified Oxford Technique

Sympathetic baroreflex sensitivity calculated from the nitroprusside-induced decrease in BP was approximately double in the POTS patients compared with control subjects \((controls, 26.2 \pm 3.0 \text{ vs. POTS, } -57.0 \pm 34.1 \% \text{ of baseline MSNA/mMgHg}; P = 0.15)\). Sympathetic baroreflex sensitivity calculated from the phenylephrine-induced increase in BP was also not statistically different between the groups \((controls, -20.9 \pm 4.5 \text{ vs. POTS, } -31.7 \pm 15.7 \% \text{ of baseline MSNA/mMgHg}; P = 0.24)\).

Sympathetic baroreflex sensitivities calculated in the traditional Halliwill method \(i.e.,\) utilizing Halliwill’s normalization procedure \(Ref. 13\) \(were\) also not statistically different between the groups either during the nitroprusside-induced decrease in pressure \(control, -8.67 \pm 1.17 \text{ vs. POTS, } -10.18 \pm 4.58 \text{ arbitrary integrated units (aiu)beat}\(^{-1}\)-mMgHg\(^{-1}\); \(P = 0.36)\) or the phenylephrine-induced increase in pressure \(control, -6.39 \pm 1.09 \text{ vs. POTS, } -7.42 \pm 2.83 \text{ aiu} \text{-beat}\(^{-1}\)-mMgHg\(^{-1}\); \(P = 0.36)\). In addition, sympathetic baroreflex sensitivity calculated during the nitroprusside-induced decrease in BP did not significantly differ from sympathectic baroreflex sensitivity calculated during the phenylephrine-induced increase in BP for either subject group \(both, P > 0.3)\).

POTS patients exhibited decreased cardiac baroreflex sensitivity during the nitroprusside-induced decrease in arterial pressure \(controls, -1.3 \pm 0.2 \text{ vs. POTS, } -0.8 \pm 0.1 \text{ beats}\cdot\text{min}^{-1}\text{-mMgHg}^{-1}; P = 0.05)\). Cardiac baroreflex sensitivity during the phenylephrine-induced increase in pressure was not different between the two groups \(controls, -1.1 \pm 0.2 \text{ vs. POTS, } -1.3 \pm 0.2 \text{ beats}\cdot\text{min}^{-1}\text{-mMgHg}^{-1}; P = 0.55)\).

### Table 1. Baseline average values

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>POTS</th>
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<tbody>
<tr>
<td>Muscle sympathetic nerve activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>as burst incidence</td>
<td>23 ± 4</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>as burst frequency</td>
<td>13 ± 2</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>58 ± 3</td>
<td>82 ± 4*</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>133 ± 3</td>
<td>119 ± 6†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>69 ± 2</td>
<td>71 ± 5</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>90 ± 2</td>
<td>87 ± 5</td>
</tr>
<tr>
<td>Respiratory frequency, breaths/min</td>
<td>16 ± 1</td>
<td>19 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. Baseline resting averages for healthy control and postural orthostatic tachycardia syndrome (POTS) patients. Muscle sympathetic nerve activity did not differ between the two groups; however, POTS patients had higher heart rate and lower systolic blood pressure compared with control subjects. Burst incidence, no. of bursts per 100 heartbeats; burst frequency, no. of bursts per minute. *\(P = 0.0001\); †\(P < 0.05\).

### Valsalva Maneuver

Valsalva maneuver expiratory pressures ranged from 29–40 mmHg; all maneuvers were sufficient to produce the four characteristic phases and thus provided the baroreflex stimulus intended. Figure 2 shows average data for the MSNA response to \(\Phi_{IIE}\) of the Valsalva maneuver. As can be seen in this figure, the sympathoexcitatory response was significantly greater in the POTS group compared with the control group \(controls, 26 ± 7 \text{ vs. POTS, } 48 ± 6 \% \text{ of baseline MSNA/mMgHg}; P = 0.03)\). In addition, the decrease in DBP from the beginning to the end of \(\Phi_{IIE}\) was significantly less in the POTS group \(controls, -19 ± 2 \text{ vs. POTS, } -10 ± 1 \text{ mmHg}; P < 0.01)\).
The HR increment in response to PhilE was not different between patients and controls (controls, 18 ± 2 vs. POTS, 16 ± 6 beats/min; P = 0.73). Likewise, the maximum change in HR induced by Valsalva (all phases included) was also not different between groups (controls, 37 ± 3 vs. POTS, 39 ± 11 beats/min; P = 0.78).

**Head-Up Tilt**

A representative raw-data tracing illustrating the MSNA response to tilt of a control subject and a POTS patient is depicted in Fig. 3. As shown in Fig. 4, the overall average sympathoexcitatory response to 30° HUT was significantly greater in the POTS group compared with control subjects (controls, 123 ± 24 vs. POTS, 208 ± 30% of baseline MSNA; P = 0.03). The MSNA response at 45° HUT tended to be greater in the POTS patients but did not reach statistical significance (controls, 137 ± 27 vs. POTS, 248 ± 58% of baseline MSNA; P = 0.10); a likely contributing factor to the lack of significance is the decrease in control sample size from six subjects at 30° HUT to four subjects at 45° HUT.

The HR increment was significantly greater in the POTS group at both angles of tilt (at 30°: controls, 6 ± 1 vs. POTS, 11 ± 2 beats/min; P = 0.02; at 45°: controls, 13 ± 2 vs. POTS, 23 ± 3 beats/min; P = 0.03). Despite the greater MSNA and HR responses in the POTS group at 30° HUT, the DBP increment was not greater in the POTS group at this angle of tilt (controls, 11 ± 2 vs. POTS, 13 ± 3 mmHg; P = 0.66) nor at 45° HUT (controls, 15 ± 5 vs. POTS, 18 ± 4 mmHg; P = 0.60).

**DISCUSSION**

The major new findings of the present study are that patients with POTS had significantly augmented sympathetic neural responses to the Valsalva maneuver and 30° HUT compared with control subjects, and that responses to 45° HUT and vasoactive drug administration (modified Oxford technique) tended to be greater in POTS patients. These findings contrast with our original hypothesis that sympathetic neural responses to baroreflex stimuli are diminished in POTS patients.
Our findings also contrast with the conclusions of Furlan et al. (11), who reported that patients with orthostatic intolerance had increased resting MSNA (in bursts/min), decreased responsiveness to HUT (such that the numbers of total bursts/min during HUT were not different between patients and controls), and similar supine MSNA baroreflex gain values (via vasoactive drug infusions) compared with healthy control subjects. In the present study, we did not observe a difference in resting MSNA between control subjects and POTS patients, whether calculated as burst frequency or burst incidence (no. of bursts/100 heartbeats). Expression of MSNA as burst incidence allows comparison among individuals independent of HR (25). Similar to our study, Furlan et al. (11) reported significantly greater resting HR in patients compared with control subjects; however, it is unclear whether resting MSNA, if calculated as burst incidence, was significantly augmented in their patient group. Additionally, we showed that baroreflex responsiveness in terms of total integrated MSNA was greater in patients compared with control subjects. In the study by Furlan et al. (11), total activity of sympathetic nerves was not reported, so we cannot directly compare their data with those of the present study. However, Bonyhay and Freeman (1) recently observed increased sympathetic activation in POTS patients compared with healthy control subjects in response to bolus nitroprusside injections. In the present study, we used several baroreflex tests in the same set of patients to assess whether the response differences that we observed can be generalized to more than one type of stimulus.

Even within groups of relatively homogeneous POTS patients, cardiovascular autonomic responses can be somewhat variable (14, 18, 20). As such, even the augmented MSNA responses to baroreflex stimuli that were not statistically significant in the present study may be quite physiologically significant in a large subgroup of patients with POTS. This augmented sympathoexcitation may be a compensatory response to dysfunction in one or more cardiovascular control mechanisms necessary for normal baroreflex responses. For example, there is evidence to suggest that POTS patients have decreased vasoconstrictor responses to orthostasis. Bush and colleagues (3) reported that patients with POTS had significantly impaired forearm vascular resistance responses to orthostatic stress. In addition, Novak et al. (28) observed that calculated total peripheral resistance did not increase during HUT in POTS patients. Data from the present study suggest that decreased sympathoexcitation is not an explanation for this decreased vasoconstriction. Although the mechanism(s) remains unclear, possible sources of dysfunction include decreased norepinephrine release from vascular sympathetic nerve endings, decreased postsynaptic adrenergic responsiveness, and/or decreased production of nonadrenergic vasoconstrictors such as angiotensin II.

Decreased norepinephrine release is suggested by the work of Jacob and colleagues (17, 19), who reported attenuated increments in norepinephrine spillover in response to the cold pressor test, nitroprusside infusion, and tyramine infusion in POTS patients, and they found that this response deficit occurred selectively in the legs (17). However, POTS patients characteristically have greater systemic plasma norepinephrine concentrations during orthostasis compared with healthy controls (11, 17, 19, 35, 38). Such chronic repeated elevations in plasma norepinephrine could lead to receptor desensitization in POTS patients and result in decreased adrenergic vasoconstrictor responsiveness. If blood vessels of patients with POTS exhibit less vasoconstriction to a given level of adrenergic stimulation, increased sympathetic activity could be a compensatory response in an attempt to “normalize” vasoconstriction. Yet studies have shown that patients with orthostatic intolerance have similar SBP responses to phenylephrine compared with control subjects both before and after ganglionic blockade (20, 22). Also in the present study, POTS patients tended to have an increased DBP response to phenylephrine (controls, 24 ± 2 vs. POTS, 33 ± 5 mmHg; \( P = 0.08 \)), and another study (19) reported hypersensitivity of pressor responses to phenylephrine in POTS patients. Thus present evidence suggests decreased norepinephrine release from sympathetic neurons in POTS patients but does not support impairment of pressor responses to adrenergic agonists in patients with POTS. However, whether cardiac output and/or local flow responses to adrenergic agonists are altered in patients with POTS awaits further study.

Impairment of the renin-angiotensin system may also contribute to the decreased vasoconstrictor responses to orthostasis in POTS. In addition to being a direct vasoconstrictor, angiotensin II increases norepinephrine release from adrenergic nerve terminals and augments the postsynaptic response (29, 30a). Plasma renin activity (PRA) normally increases in response to an orthostatic challenge (12, 26, 27, 41), but this response may be attenuated in some POTS patients (18, 21). Jacob et al. (18) observed that a subgroup of POTS patients had significantly decreased supine and standing PRA compared with healthy subjects. In addition, Jordan et al. (21) studied two POTS patients along with their identical twins; one of these POTS patients had inappropriately low PRA during orthostasis that was not observed in her asymptomatic twin. However, the other POTS patient and her twin, both symptomatic, had normal PRA responses to orthostasis. Thus it appears that impairment of the renin-angiotensin system may importantly contribute to the development of symptoms in some but not all POTS patients.

Another potential area of dysfunction for which exaggerated sympathoexcitation could be compensating is increased venous pooling and/or capillary filtration during orthostasis in POTS patients. For example, we were interested to note in the present study that the increased sympathoexcitatory responses in POTS patients translated into better maintenance of DBP compared with control subjects during theValsalva maneuver but not during HUT. (Sympathoexcitation was significantly greater at 30° HUT in POTS patients and likely would have reached statistical significance at 45° HUT were it not for a loss of signal in two subjects at that angle.) This suggests that during HUT in particular, the increased HR and MSNA responses observed in POTS patients were appropriate and necessary to maintain arterial pressure similar to control subjects (SBP and MAP responses to HUT were also not different between the two groups; \( P > 0.68 \)). One condition that is present during HUT but not during the Valsalva maneuver is gravity-induced venous pooling in the lower limbs. Excessive venous pooling and/or capillary filtration in the legs of POTS patients would result in a smaller effective circulating plasma volume and a greater requirement for sympathoexcitation to maintain arterial pressure. Streeten et al. (38) reported significantly greater venous pooling during orthostasis in POTS patients. They also
demonstrated that application of external pressure of 45–50 mmHg to the legs and abdomen of patients via a medical antishock-trousers (MAST) suit significantly improved their orthostatic tachycardia. Another study (37) found the increase in calf volume with HUT to be significantly greater in adolescent POTS patients compared with healthy age-matched control subjects, which suggests increased venous compliance and pooling and/or increased capillary filtration. In contrast, other investigators have reported decreased calf venous compliance in POTS patients compared with controls (9, 10) and similar decreases in central venous pressure with HUT between POTS patients and controls (11). The reason for these discrepancies in the literature is unclear but may relate to different measurement and analysis techniques among studies.

We found that cardiac baroreflex sensitivity (i.e., the slope or gain of the linear portion of the cardiac baroreflex curve) calculated during the nitroprusside-induced decrease in arterial pressure was reduced in POTS patients compared with healthy control subjects but found no difference between the groups in response to the phenylephrine-induced increase in pressure. Considering the excessive tachycardic response to orthostasis, it is interesting that the POTS group had decreased cardiac baroreflex sensitivity during the decrease in arterial pressure (which induces a reflex increase in HR). In previous studies, investigators have reported either a decrease (9, 19), a trend for a decrease ($P < 0.08$; Ref. 11), or no difference (22) in cardiac baroreflex sensitivity in patients with orthostatic intolerance compared with healthy control subjects. Taken together with the present data, this suggests that in the POTS population as a whole, cardiac baroreflex sensitivity may range from normal to decreased.

The variability among patients with POTS is well recognized and contributes to the difficulty of studying this patient group both clinically and with regard to basic mechanisms. This may relate to certain combinations of genetics and environment in patients with POTS. For example, a norepinephrine-transporter gene polymorphism that results in a 98% loss of transporter function was identified and shown to track with orthostatic tachycardia among members of an individual family (36). However, POTS symptoms varied among the family members who shared the polymorphism, which suggests important contributions of other genetic and/or environmental factors in determining phenotype. A similar genotype/environment interaction could explain the variability in cardiac baroreflex sensitivity among POTS patients.

During the baseline supine rest period, average SBP in POTS patients was significantly lower than in healthy control subjects, whereas average HR was significantly greater. This suggests that in POTS patients, the cardiac baroreflex curve may be shifted upward and leftward (i.e., a shift in the operating range to higher HRs and lower pressures), that the operating point may be located further to the left on the cardiac baroreflex curve, or a combination of both. However, due to a limited range of arterial pressure changes that can safely be performed in humans, we often did not collect data that encompassed the entire sigmoidal range of the baroreflex curve. Therefore, we can only speculate on such aspects of the function curve as operating range or location of the operating point upon the curve.

In summary, we report in the present study that directly measured sympathetic neural responses to baroreflex stimuli are augmented in patients with POTS compared with age-matched control subjects. These augmented responses were statistically significant for the Valsalva maneuver and HUT tests but may be physiologically significant for all tests in a majority of patients. We propose that this augmented neural responsiveness in POTS represents a compensatory response to other cardiovascular impairments that affect BP regulation during orthostasis including diminished norepinephrine release, decreased responsiveness of the renin-angiotensin system, and increased venous pooling and/or capillary filtration.

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