Sympathetic Nerve Activity in Response to Hypotensive Stress in the Postural Tachycardia Syndrome

Istvan Bonyhay, MD, PhD; Roy Freeman, MD

Background—Increased central sympathetic activity and/or deficient peripheral sympathetic nerve function are among the proposed pathophysiological changes in patients with the postural tachycardia syndrome (POTS). Little is known about sympathetic nerve outflow and its role in hemodynamic control in this disorder.

Methods and Results—We recorded peroneal muscle sympathetic nerve activity in 9 POTS patients and 9 control subjects at rest and during a nitroprusside-induced hypotensive stimulus. Baseline blood pressure (BP) and heart rate were significantly higher in POTS patients than in controls. At rest, the burst frequency was similar in POTS patients and controls (18.1±6.2 and 20.1±7.9 bursts/min, respectively; P=NS), whereas the burst incidence was significantly lower (23.1±6.8 versus 32.2±11.4 bursts/100 heartbeats, P<0.05). Nitroprusside increased sympathetic outflow significantly more in POTS patients than in controls despite a similar BP decrease (burst frequency 20.4±7.5 versus 12.1±4.1 bursts/min, P=0.008, and burst incidence 21.8±8.4 versus 14.4±5.2 bursts/100 heartbeats, P=0.03). The change in mean burst area, a measure of the number of actively firing sympathetic neurons, was similar in patients and controls (117±15% versus 114±21%, P=NS).

Conclusions—At rest, the tachycardia and normal burst frequency result in normal or even elevated BP in POTS patients. During a hypotensive stimulus, cardiovascular homeostasis is maintained by the increased sympathetic outflow and normal heart rate response despite the lack of concomitant increase in mean burst area that is most likely due to sympathetic denervation. (Circulation. 2004;110:3193-3198.)

Key Words: nervous system, autonomic ■ nervous system, sympathetic ■ blood pressure ■ tachycardia
recruited for the study from patients referred to the Center for Autonomic and Peripheral Nerve Disorders at Beth Israel Deaconess Medical Center for assessment of orthostatic intolerance. All patients had symptoms of orthostatic intolerance and an increase in heart rate of >30 bpm within 10 minutes of standing without orthostatic hypotension.1,2 All participants gave their written informed consent before the study. The protocol was approved by the Committee on Clinical Investigation of Beth Israel Deaconess Medical Center.

Study Preparation
In the week preceding the study, subjects were instructed to follow a diet that contained ~100 mEq of sodium, 75 mEq of potassium, 2500 mL of fluid, and at least 1800 kcal per day. Subjects refrained from caffeine and alcohol for at least 48 hours before the study. Patients were withdrawn from medications that affect autonomic function at least 5 half-lives before the studies.

Standard Autonomic Testing
A standard tilt-table test of 20 minutes was performed on all subjects. There was no insertion of intravenous lines or isoproterenol use during or before the tilt-table test. The tilt angle was 60°.

Study Protocol
Subjects were studied in the morning, while supine, after a light breakfast. A cannula was inserted into a forearm vein for drug administration. Heart rate and cardiac interval were measured continuously from a standard monitor lead ECG. Arterial blood pressure was monitored noninvasively (Finapres [Ohmeda] and Dinamap [Critikon]). Sympathetic bursts were identified by their characteristic morphology and relationship to R waves on the ECG by an automated neurogram analysis program.12 Only bursts with a signal-to-noise ratio >3:1 were included for analysis.

Muscle Sympathetic Nerve Activity
MSNA was recorded directly from the leg with a unipolar, tungsten microelectrode inserted into a fascicle of the peroneal nerve. The correct electrode position was confirmed by the characteristic response of neural activity to quick expiration and a Valsalva maneuver. Neural signal was filtered (bandwidth 0.7 to 2.0 kHz), rectified, and integrated (time constant 0.1 second; Nerve Traffic Analyzer, model 662c-3, University of Iowa Bioengineering). Sympathetic bursts were identified by their characteristic morphology and relationship to R waves on the ECG by an automated neurogram analysis program.12 Only bursts with a signal-to-noise ratio >3:1 were included for analysis.

MSNA, quantified by counting the number of bursts in the mean voltage neurogram, was expressed as burst incidence (bursts/100 heartbeats) and burst frequency (bursts/min). Burst area was used to denote burst strength (burst intensity) and was calculated for each individual burst. The mean burst area during the baroreflex run was expressed as percentage of the mean area of bursts during baseline recording. Only this relative measure for burst area was used for interindividual comparison.

Assessment of Baroreflex Characteristics
After a 15-minute baseline, the modified Oxford technique was used to assess sympathetic baroreflex function.13 A bolus injection of 100 µg of sodium nitroprusside, followed 60 seconds later by a bolus injection of 150 µg of phenylephrine hydrochloride, produced a drop in pressure of ~15 mm Hg followed by a rise above baseline of ~15 mm Hg. The falling-pressure segment of the test was considered for sympathetic baroreflex assessment (Figure 1). The hypotensive period was delimited by the start of the nitroprusside-induced decrease in diastolic blood pressure (DBP) and the lowest DBP achieved during the pressure fall. Baroreflex control of MSNA was assessed (1) by changes of burst frequency and burst incidence between the baseline and hypotensive period and (2) by regression of total integrated activity against DBP, averaged over 2-mm Hg changes of DBP.13 The percent change of burst frequency and burst incidence relative to baseline was also calculated to permit comparison with the change of burst strength (burst area) in response to hypotension. Baroreflex tests were performed 2 or 3 times with a 15-minute recovery period between each trial. Resting data were the average of at least two 3- to 5-minute baseline recordings.

All study subjects completed an autonomic symptom questionnaire, orthostatic intolerance questionnaire, and fatigue severity questionnaire.14 Symptoms were graded as follows: on the autonomic symptom questionnaire with a 100-mm visual analog scale in which 0 represents “never experience symptom” and 100 represents “always experience symptom;” on the orthostatic tolerance questionnaire with a 0 to 3 score scale in which 0 represents “never experience the symptom” and 3 represents “frequently experience the symptom;” on the fatigue severity questionnaire with a 1 to 7 score scale in which 1 represents “strongly disagree” and 7 represents “strongly agree” with the statement.

Statistical Analysis
Data are presented as mean±SD. Data that were not normally distributed (heart rate in response to the decrease in blood pressure and baroreflex-sympathetic data) were normalized by logarithmic transformation. Paired and unpaired t tests and ANOVA with repeated measures were used for within-group and between-group response comparisons. Relations between variables were determined by computing Pearson’s correlation coefficient (r) and linear regression.

Results
Subject Characteristics
Patients and controls did not differ in age (36±12 versus 40±12 years), gender, weight (73.3±12.5 versus 74.1±19.4 kg), and body mass index (26.6±5.4 versus 26.7±5.9 kg/m²). A preceding viral infection was present in 5 of 9 patients. The onset of symptoms of orthostatic intolerance was acute in 4 patients and subacute in 5.

All POTS patients and no controls reported symptoms of lightheadedness and dizziness with standing. Mean scores for the 2 corresponding questions of the Orthostatic Intolerance Questionnaire were 2.3 and 1.8 in patients versus 0.1 and 0.1 in controls. Other frequently reported autonomic symptoms are shown in Table 1. All patients reported fatigue as a major symptom. Seven of the 9 patients met the revised Centers for Disease Control criteria for a diagnosis of chronic fatigue syndrome.15 The mean Fatigue Severity Scale score of
Response to Passive Head-Up Tilt

patients was significantly different from that of controls (5.3 versus 2.1, \(P<0.001\)).

Baseline Cardiovascular Assessment

Baseline systolic blood pressure, DBP, and heart rate were significantly higher in POTS patients than in controls. Maximal heart rate and DBP during the passive head-up tilt test were significantly higher in POTS patients (Table 2). The heart rate increment was significantly higher in POTS patients than in control subjects (37±13.8 versus 24±9.3 bpm, \(P<0.05\)).

Cardiovascular Response to the Modified Oxford Procedure

Nitroprusside induced a similar decrease in blood pressure in patients and controls. Although the maximum pressure change from baseline to nadir was not different, the blood pressure decrease, averaged over the entire hypotensive period, was slightly less in patients (Figure 2). The blood pressure change data were normally distributed and had the same relative dispersion in both groups. Baroreflex-mediated pressure change data were normally distributed and had the same relative dispersion in both groups.

At rest, burst frequency was similar in POTS patients and controls. Burst incidence was significantly lower in patients than in controls (Table 3). Both groups exhibited a pronounced increase in MSNA in response to the blood pressure fall (Figure 3); however, POTS patients increased burst incidence and burst frequency significantly more than controls. Burst frequency averaged over the blood pressure fall was 20.4±7.5 bursts/min higher than baseline in POTS patients and 12.1±4.1 bursts/min higher than baseline in controls \((P=0.008)\). The burst incidence in POTS patients during blood pressure fall increased over baseline by 21.8±8.4 bursts/100 heartbeats, whereas burst incidence in control subjects increased by 14.4±5.2 bursts/100 heartbeats \((P=0.03);\) Figure 3). The relative change in burst frequency and burst incidence compared with baseline was significantly higher in patients than in controls, whereas the change in mean burst area was not different between the 2 groups (Figure 4). There was a significant linear relationship between changes in burst incidence and mean burst area in both groups \((P<0.01);\) however, the slope of the relation was lower in patients \((b=1.89)\) than in controls \((b=2.82)\).

Although the baroreflex-mediated increase in burst frequency and burst incidence was greater in POTS patients, the sympathetic baroreflex gain, calculated by the total integrated activity, was not different between the 2 groups (Table 3). Burst incidence and mean burst area did not correlate with cardiac cycle length during sympathetic activation in POTS patients and controls (cardiac interval with burst incidence: \(r=0.29\) in POTS patients and \(r=0.45\) in controls, both \(P=NS\); cardiac interval with mean burst area: \(r=0.09\) in POTS patients and \(r=0.04\) in controls, both \(P=NS\)).

Discussion

The main findings of the present study are that (1) baroreflex-mediated sympathetic nerve activity in response to a hypotensive challenge is greater in POTS patients than controls, (2) the increase in sympathetic activity in POTS patients manifests as higher sympathetic burst incidence and burst frequency but without a concomitant increase in burst strength (burst area), and (3) resting sympathetic activity is not enhanced in POTS patients. In the present study, recumbent POTS patients had an increased sympathetic baroreflex response to an acute hypotensive challenge. Although nitro-
prusside induced a similar blood pressure decrease in patients and controls, POTS patients responded with a significantly greater burst incidence and burst frequency change to baroreceptor unloading than controls; the probability of sympathetic burst during a cardiac cycle almost doubled in POTS patients, whereas it increased only 1.5 times in controls.

The pathophysiological mechanisms behind the enhanced sympathetic response in POTS patients are not fully elucidated. The occurrence of sympathetic bursts is modulated by baroreflex function, which results in pulse synchronous burst activity of a multiunit nerve fiber. Whether a cardiac cycle has an associated sympathetic burst depends on central sympathetic drive, DBP, cardiac interval length, the threshold for burst generation,17 the individual characteristics of sympathetic fiber firing and recruitment,19 and unknown central factors that govern the interaction between baroreceptor signal and the central sympathetic generator.20

There are thus several possible explanations for the augmented increase in sympathetic burst incidence in response to hypotension in the POTS patients. Because the decrease in DBP was similar, it is not likely to explain the intergroup differences (averaged over the entire hypotensive period, the blood pressure fall was actually slightly less in the POTS patients). The cardiac cycle length was shorter in POTS patients and therefore also not likely to promote a greater increase in MSNA burst number. A more likely explanation is that the enhanced sympathetic drive in response to the hypotensive stress is due to intergroup differences in the muscle sympathetic nerve firing and/or recruitment characteristics. Several reports have drawn attention to the presence of impaired peripheral sympathetic nerve function in the lower extremity in POTS patients.2,4,11 Thus, a plausible pathophysiological explanation for the present findings is that, owing to sympathetic fiber denervation, POTS patients increase firing frequency and/or recruitment of the residual muscle sympathetic fibers to maintain cardiovascular homeostasis in response to a hypotensive stimulus.

The discrepancy between the increase in sympathetic burst activity and sympathetic burst area (strength) lends support to

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**TABLE 3. Cardiovascular and Sympathetic Response to Modified Oxford Test: Summary of Physiological Parameters in Baroreflex Assessment**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>POTS (n=9)</th>
<th>Control (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum heart rate change to nitroprusside, bpm</td>
<td>23±7.6</td>
<td>19±9.3</td>
</tr>
<tr>
<td>Average heart rate change over blood pressure fall, bpm</td>
<td>8.5±6.7</td>
<td>7.2±7.1</td>
</tr>
<tr>
<td>Maximum DBP change to nitroprusside, mm Hg</td>
<td>12.7±4.3</td>
<td>13.4±3.9</td>
</tr>
<tr>
<td>Mean DBP change during nitroprusside response, mm Hg</td>
<td>5.8±1.7</td>
<td>7.3±2.0</td>
</tr>
<tr>
<td>Burst frequency at rest, burst/min</td>
<td>18.1±6.2</td>
<td>20.1±7.9</td>
</tr>
<tr>
<td>Burst incidence at rest, burst/100 heart beats</td>
<td>23.1±6.8*</td>
<td>32.2±11.4</td>
</tr>
<tr>
<td>Sympathetic BRS: total activity, AIU/heart beat/mm Hg</td>
<td>−8.0±2.8</td>
<td>−7.4±3.0</td>
</tr>
<tr>
<td>Sympathetic BRS: burst frequency, burst/min/100 heart beats</td>
<td>−3.9±1.7*</td>
<td>−1.8±0.6</td>
</tr>
<tr>
<td>Sympathetic BRS: burst incidence, burst/100 heart beats</td>
<td>−4.4±2.3*</td>
<td>−2.2±0.8</td>
</tr>
</tbody>
</table>

BRS indicates baroreflex sensitivity; AIU, arbitrary integrated units.

Data are mean±SD.

*P<0.05 vs control.

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**Figure 3.** Change in burst frequency (top) and burst incidence (bottom) in response to sodium nitroprusside (NP)-induced blood pressure fall. There was a significant increase in burst frequency and burst incidence from baseline in POTS patients and controls (all *P*<0.001). Changes in burst frequency and burst incidence were significantly higher in POTS patients. †*P*<0.01 vs control; ‡*P*<0.05 vs control.

**Figure 4.** Relative change in burst frequency, burst incidence, and mean burst area in POTS patients and controls during baroreflex-mediated sympathetic activation. *P*<0.05 vs control.
the notion that sympathetic denervation plays a role in the increased MSNA. Furthermore, this finding may provide additional insight into the pathophysiology of sympathetic dysfunction in POTS patients. Sympathetic activation typically results in an increase in sympathetic burst activity (burst incidence and burst frequency, as seen in both POTS patients and controls) and also an increase in the area or strength of the individual bursts. Because the area of individual multiunit sympathetic bursts is determined mainly by the number of active neurons, the lack of a proportional increase in burst area in response to sympathetic activation in POTS despite the increased burst activity (Figure 4) suggests that the increase in MSNA is due to increased firing of individual muscle sympathetic neurons and not recruitment of additional silent sympathetic fibers. These observations are consistent with the firing characteristics of sympathetic neurons determined with single-unit recordings at rest in patients with moderate to severe congestive heart failure, a disorder associated with marked sympathoexcitation. We cannot exclude the possibility that primary central factors also play a role in the increased sympathetic activation in POTS patients; however, it is of interest that the increase in sympathetic outflow in response to mental stress (a condition characterized by a central increase in sympathetic outflow that is not provoked by hypotension) is associated with an increase in both burst number and burst amplitude.

In contrast to the enhanced sympathetic burst activity in response to baroreceptor unloading in POTS patients, sympathetic nerve activity in the supine resting condition was characterized by a lower burst incidence. The lower probability of burst generation during a cardiac cycle at rest in POTS patients may be attributable to the following, acting alone or in combination: (1) increased resting blood pressure, (2) shorter cardiac interval, (3) lower-extremity sympathetic denervation, and (4) impairment of the central sympathetic burst generator.

The increased resting blood pressure, which is commonly observed in POTS patients, provides the most plausible explanation for the lower burst incidence. Specifically, diastolic pressures that are higher than the burst appearance threshold during spontaneous blood pressure fluctuations within each cardiac cycle cause a lower probability of burst generation. The cardiac interval also may play a role in the lower resting burst incidence. If the influence of cardiac interval on the occurrence of sympathetic bursts is identical in patients and controls, then a higher heart rate may result in a lower burst occurrence in POTS patients. However, a dominant role for the cardiac interval length in the burst incidence difference appears to be unlikely, because if cardiac interval were to have a significant influence on the probability of sympathetic burst at rest, one would not anticipate that burst occurrence would significantly increase in POTS patients during the even shorter cardiac cycles that occur in response to baroreceptor unloading. Sympathetic denervation may also be responsible for the lower resting burst incidence in POTS patients. This measure is proposed as an early index of autonomic neuropathy by some but not all investigators. The enhanced increase in sympathetic burst incidence in response to baroreflex unloading excludes impairment of the central sympathetic generator in the POTS patients; the possibility of discordant central generation of sympathetic bursts to high and low blood pressures in POTS patients appears unlikely.

This finding is at variance with an earlier report that concluded that resting sympathetic outflow is increased but baroreflex-mediated sympathetic response is normal in patients with POTS. There are several possible explanations for the differences between these studies. First, in the study by Furlan et al., resting blood pressure was similar in patients and controls. Second, the hypotensive challenge in that study was elicited by a nitroprusside infusion, whereas in the present study, nitroprusside was administered as a bolus. Finally, we cannot exclude differences in patient populations, especially because it appears likely that the POTS patient population is heterogeneous.

Our findings, which are in accordance with those suggesting that patients with POTS have mild distal sympathetic denervation, elucidate the possible physiological mechanisms whereby circulatory homeostasis in POTS patients is maintained in both resting conditions and during a brief hypotensive stimulus. First, the greater increase in sympathetic burst frequency may compensate for the smaller bursts, thereby providing effective sympathetic vascular control during a hypotensive challenge. This assumption is supported by the finding that sympathetic baroreflex gain determined by total integrated activity was similar in POTS patients and controls. Second, the tachycardia in POTS patients contributes to hemodynamic control by increasing cardiac output. Finally, the sympathetic nervous system and heart rate may have an additional functional interaction, because the tachycardia can amplify sympathetic nerve outflow by providing a multiplicative effect on sympathetic burst incidence. This functional coupling has been reported in the postural change of healthy subjects and in patients with congestive heart failure. Thus, in POTS patients, the higher heart rate compensates for the lower burst incidence at rest, which results in a burst frequency similar to that in controls, and amplifies the burst incidence change during hypotension, which results in an enhanced sympathetic burst frequency response. Because of the response characteristics of the vasculature for burst effects, the total burst number as a function of time (burst frequency) is physiologically more relevant to the vasoconstrictor response than the burst incidence.

Because the arterial baroreflex has a major role in the circulatory adaptation to postural change, the present findings may be extrapolated to the upright posture and may explain, at least in part, the maintained or even elevated blood pressure seen in POTS patients in response to orthostatic change. The exaggerated tachycardia in POTS patients during orthostatic change may represent functional coupling between the heart and sympathetic outflow that maintains cardiovascular homeostasis in response to hemodynamic stress.

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References


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