Arterial baroreflex control of heart rate during exercise in postural tachycardia syndrome

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POSTURAL TACHYCARDIA SYNDROME (POTS) is a clinical syndrome of orthostatic intolerance characterized by excessive increases in heart rate (HR) during orthostatic stress in the absence of orthostatic hypotension (3, 13, 15). Although clinicians and investigators have focused on the responses during orthostasis in this syndrome, patients with POTS also exhibit excessive tachycardia during exercise and they often complain of chronic fatigue and exercise intolerance (15, 32). However, there have been few studies demonstrating pathophysiological mechanisms of excessive tachycardia during exercise in the patients (19). In this context, we recently found that stroke volume in the POTS patients was reduced compared with healthy controls during exercise whereas cardiac output and arterial pressure were generally maintained by greater elevations in HR (19). Thus the greater elevation in HR might be seen largely as a compensatory response for the reduced stroke volume. These observations raise the possibility that baroreflex control of HR might be “normal” in POTS.

By contrast, HR is one of the key effectors of arterial baroreflex in response to changes in arterial pressure. Because of the exaggerated elevation of HR in the absence of discernible changes in arterial pressure, clinicians and investigators have speculated that abnormalities in baroreflex control of HR might result in an inappropriate tachycardia during exercise in these patients (1, 11). However, there have been no studies to assess baroreflex control of HR during exercise in POTS patients.

Along these lines, baroreflex sensitivity of HR is blunted during exercise in healthy subjects (2, 27, 28), whereas overall baroreflex control of arterial pressure is maintained (23). Therefore, the purpose of the present study was to test the hypothesis that excessive tachycardia during exercise in POTS patients is not due to abnormal baroreflex control of HR. If so, baroreflex sensitivity of HR would be blunted during exercise in the patients similar to healthy controls. Because baroreflexes buffer dynamic changes in arterial pressure, a second aim was to determine whether any blunted baroreflex sensitivity of HR during exercise affects stability of arterial pressure in the patients. To examine these hypotheses, we measured arterial pressure and HR continuously during exercise in POTS patients and healthy control subjects, and we also assessed baroreflex sensitivity of HR. Moreover, we used both upright and supine exercise, because supine exercise provides a condition facilitating venous return by minimizing peripheral pooling of blood. This is important because HR responses in the patients are very sensitive to venous pooling (18) and because there are important interactions between arterial baroreflex control of HR during exercise and cardiopulmonary baroreflexes (22, 30).

METHODS

Subjects. The studies were approved by the Institutional Review Board of the Mayo Clinic, and each participant gave prospective written informed consent. Thirteen POTS patients (29 ± 2 yr; 11 women, 2 men; weight, 68 ± 2 kg; height, 171 ± 2 cm; body mass...
index, 23 ± 1 kg/m²) participated in this study. We deliberately recruited typical POTS patients, and they were not consecutive patients with postural tachycardia seen in the Mayo Autonomic laboratory. For comparison, we matched 10 healthy normal community-dwelling control subjects (32 ± 3 yr; 8 women, 2 men: weight, 66 ± 2 kg; height, 167 ± 2 cm; body mass index, 23 ± 1 kg/m²). Data were collected as part of a large series of studies, and criteria for inclusion in the POTS patients and healthy control subjects were described in the preceding study (18, 19).

Arterial and venous catheterization. Under aseptic conditions, a 5-cm 20-gauge catheter was inserted into the radial or brachial artery of the nondominant arm under local anesthesia (1% lidocaine). The arterial catheter was connected to a pressure transducer for determination of arterial pressure and continuously flushed at 3 ml/h with heparinized saline (8). A 3-cm 18-gauge catheter was inserted into an antecubital vein in the contralateral arm the day before the study and was used for phenylephrine (PE) boluses. HR was monitored by using a three-lead electrocardiogram.

Protocol. All studies were performed in the General Clinical Research Center (GCRC). All participants were advised to refrain from caffeine, alcohol, and exercise at least 24 h before GCRC admission. They reported to the GCRC between 8 and 9 AM the day before the study, and in the afternoon they participated in an orthostatic trial that has been previously published (18). After the trial, subjects received a standardized light meal at 4 PM and a standardized evening meal at 7 PM. After 10 PM, subjects fasted and received overnight intravenous fluid hydration (saline, 125 ml/h for 8 h) to ensure both adequate and comparable hydration in all the subjects.

The subjects received a standardized very light meal the next day at 9 AM, and they were studied at 10 AM. After arterial catheterization, they rested for 30 min in the supine position. A stand test was then performed to assess the severity of orthostatic tachycardia (19). After resumption of the supine position and stabilization of vital signs, they performed a bout of exercise. The bout included a 10-min supine resting period, and incremental supine cycling exercise at 25, 50, and 75 W (~60 revolutions/min) for 7 min each, while arterial pressure and HR were continuously measured.

Baroreflex sensitivity of HR was determined from the HR response to change in systolic arterial pressure (SAP) after an intravenous infusion of PE as a bolus in each workload (2, 29, 33). PE was infused at 7 min of rest and at ~5 min of each workload after confirmation that hemodynamic variables were stable. The dose of PE used at rest and at 25-, 50-, and 75-W exercise was 1.5, 2.0, 2.5, and 3.0 μg/kg, respectively, to increase SAP ~20 mmHg over a short period of time. A higher dose of PE was necessary with increasing workload due to blunted adrenergic vasoconstriction during exercise (9, 35). After supine exercise, subjects rested while sitting on a chair for 70 min, and they had a glass of water. The bicycle exercise trial was then repeated while the subjects were sitting upright on the bicycle.

The protocols were designed to increase the chances that the patients could complete part or all of the study; thus we did not randomize for exercise posture due to the possibility that POTS patients would exhibit orthostatic symptoms and fatigue during upright exercise and that the study would have to be terminated. Consequently, all patients and controls completed the supine and upright exercise trials in this study. The laboratory temperature was maintained at 19–21°C during the study.

Arterial pressure and HR analyses. Data were digitized at 600 Hz, stored on a computer, and analyzed offline with signal-processing software (Windaq, Dataq Instruments, Akron, OH). SAP and diastolic arterial pressure (DAP) were derived from the arterial pressure waveform. Pulse pressure (PP) was calculated as SAP − DAP. HR and R-R interval (RRI) were determined from the electrocardiogram signal. Mean values for arterial pressure and HR reported represent an average of minutes 2–3 during resting or during each workload. To assess the stability of the hemodynamic variables, coefficient of variation [CV, (standard deviation/mean) × 100] for SAP, DAP, PP, and HR was also determined during this period, and it was used as an index of variability for each parameter (16, 17). Furthermore, to assess the effect of POTS on variability of arterial pressure during upright exercise more precisely, the frequency distribution of PP during upright exercise at 75 W was also determined using the same data used for CV analysis (7). Because the individual means are variable, we preformed frequency distribution analysis after the values were normalized for changes in PP from the mean for each subject.

Baroreflex analyses and SAP response to PE. We assessed baroreflex sensitivity using the relationship between SAP and HR after a PE bolus. The slope of the linear portion of this relationship was used as an index of baroreflex sensitivity (4, 5, 12). Values for HR from the baroreflex test were pooled over 2-mmHg pressure ranges for analysis to minimize variability due to nonbaroreflex influences such as respiration (4, 5).

Data are expressed in terms of HR, and it was used as our main index of cardiac baroreflex sensitivity. Our rational for using HR vs RRI is that HR is linearly related to cardiac output during exercise. Moreover, the reciprocal relationship between HR and RRI can result in a decrease in RRI slope with changes in baseline HR due to the fact that (mathematically) a given change in HR results in less of a change in RRI when baseline HR is higher (24). However, to be comprehensive in our analysis, we also analyzed the present data in terms of RRI.

In addition, we determined change in SAP after an injection of PE in each workload and used it as an index of α-adrenergic vasoconstrictor responsiveness, because α-adrenergic vasoconstrictor responsiveness can also affect beat-to-beat stability of arterial pressure (17, 20).

Statistics. Two-sample t-tests were used to test for differences in demographic measurements between the POTS patients and controls. Repeated-measures models were used to predict the outcomes of the mean and CV for hemodynamic values, baroreflex sensitivity, and change in SAP after PE infusion, where wattage levels were the repeated effect. Unstructured correlation matrices (unique correlations between pairs of wattage levels) were used in the model fitting. The models included main effect terms for group (POTS and controls) and wattage (rest, 25, 50, and 75 W). Interaction terms were investigated as well. If the global F test for the interaction terms was significant at the α = 0.05 level, they were left in the model. Otherwise, they were removed. For models with interaction terms, we estimated the mean difference in the outcome between the POTS patients and controls at each level of wattage. For models without interaction terms, the main effect mean group difference was sufficient.

RESULTS

There were no differences in age, height, body weight, or body mass index between POTS patients and controls (P > 0.1). Arterial pressure and HR. Table 1 summarizes the mean and CV for SAP, DAP, PP, and HR at rest and during exercise in the supine and upright positions. SAP, DAP, and PP at rest and the responses to exercise were not different in the patients and controls in either position (P > 0.1). HR in the patients was significantly higher than the controls at rest and during exercise in both the supine and upright positions (P < 0.01), whereas the change from rest to exercise was not different between the groups in either position (P > 0.1).

The CV for SAP, DAP, PP, and HR at rest and during exercise were not different in the patients and controls in the supine position (P > 0.2). On the other hand, in the upright position, CV for SAP and PP during exercise at 50 and 75 W was significantly higher in the patients than the controls (P < 0.05), indicating that SAP and PP fluctuated more in the patients, whereas there were no differences in CV for DAP and HR at rest and during exercise between the groups (P > 0.6).
Table 1. Arterial pressure and HR at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Supine Workload</th>
<th>Upright Workload</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>25 W</td>
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<tr>
<td><strong>Control (n = 10)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP Mean, mmHg</td>
<td>133±3</td>
<td>148±2</td>
</tr>
<tr>
<td>CV, %</td>
<td>2.2±0.2</td>
<td>2.2±0.2</td>
</tr>
<tr>
<td>DAP Mean, mmHg</td>
<td>69±2</td>
<td>73±1</td>
</tr>
<tr>
<td>CV, %</td>
<td>4.4±0.6</td>
<td>3.8±0.3</td>
</tr>
<tr>
<td>PP Mean, mmHg</td>
<td>64±2</td>
<td>75±2</td>
</tr>
<tr>
<td>CV, %</td>
<td>4.7±0.6</td>
<td>4.0±0.4</td>
</tr>
<tr>
<td>HR Mean, beats/min</td>
<td>62±4</td>
<td>90±3</td>
</tr>
<tr>
<td>CV, %</td>
<td>6.8±1.3</td>
<td>2.8±0.4</td>
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<tr>
<td><strong>POTS (n = 13)</strong></td>
<td></td>
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</tr>
<tr>
<td>SAP Mean, mmHg</td>
<td>136±3</td>
<td>151±4</td>
</tr>
<tr>
<td>CV, %</td>
<td>2.2±0.2</td>
<td>2.6±0.2</td>
</tr>
<tr>
<td>DAP Mean, mmHg</td>
<td>67±2</td>
<td>72±2</td>
</tr>
<tr>
<td>CV, %</td>
<td>3.6±0.4</td>
<td>4.3±0.3</td>
</tr>
<tr>
<td>PP Mean, mmHg</td>
<td>69±3</td>
<td>79±3</td>
</tr>
<tr>
<td>CV, %</td>
<td>3.8±0.4</td>
<td>4.3±0.3</td>
</tr>
<tr>
<td>HR Mean, beats/min</td>
<td>76±3†</td>
<td>107±3†</td>
</tr>
<tr>
<td>CV, %</td>
<td>5.8±0.7</td>
<td>3.0±0.3</td>
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</table>

Values are means ± SE; n, no. of subjects. POTS, postural tachycardia syndrome; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; PP, pulse pressure; HR, heart rate; CV, coefficient of variation. Significant differences from the controls: *P < 0.05; †P < 0.01; ‡P < 0.001, respectively.

Figure 1 shows original traces of arterial pressure during upright exercise at 75 W in a control subject and a POTS patient. As shown in the figure, arterial pressure in the control was maintained within a narrow range, whereas arterial pressure, especially PP, in the patient fluctuated more.

Figure 2 shows the frequency distribution of PP during upright exercise at 75 W. Because cardiac cycles used for this analysis were higher in the patients than the controls (164 ± 3 vs. 131 ± 7, P < 0.001), the frequency distributions were expressed as percentage of the total cardiac cycles. The PP distribution was wider in the patients than the controls with a significantly higher standard deviation (6.8 ± 0.9 vs. 4.3 ± 0.3 mmHg, P = 0.03).

Baroreflex sensitivity. Figure 3 shows typical examples of the data obtained during the baroreflex tests from a control subject and a POTS patient at rest and during exercise at 25, 50, and 75 W in upright position. As summarized in Fig. 4, supine and upright exercise produced a significant decrease (i.e., a less negative slope) in baroreflex sensitivity in terms of HR for the patients and controls (P < 0.001). While supine, there were no differences in the sensitivity between the groups (P > 0.6). On the other hand, upright baroreflex sensitivity in
POTS patients was 50% higher than the controls at rest \((P = 0.01)\), but as exercise intensity increased this finding reversed, such that baroreflex sensitivity in POTS patients was 70% less than the controls during 75-W exercise \((P = 0.02)\).

In terms of RRI, supine and upright exercise produced a significant decrease in baroreflex sensitivity for the patients and controls \((P < 0.001)\). While supine, there were no differences in the sensitivity in the patients and controls at rest \((15.8 \pm 2.5 \text{ vs. } 27.4 \pm 4.2 \text{ ms/mmHg})\), at 25-W \((6.9 \pm 1.1 \text{ vs. } 10.3 \pm 1.9 \text{ ms/mmHg})\), 50-W \((5.2 \pm 0.8 \text{ vs. } 6.1 \pm 1.4 \text{ ms/mmHg})\), and 75-W exercise \((2.6 \pm 0.5 \text{ vs. } 3.5 \pm 0.8 \text{ ms/mmHg})\) \((P > 0.6)\). Upright baroreflex sensitivity of RRI was not different in the patients and controls at rest \((11.0 \pm 1.7 \text{ vs. } 12.1 \pm 2.7 \text{ ms/mmHg}; P > 0.7)\), whereas it tended to be lower in the patients than the controls at 25 W \((4.1 \pm 0.5 \text{ vs. } 9.3 \pm 2.8 \text{ ms/mmHg}; P = 0.07)\), and lower at 50 W \((1.5 \pm 0.5 \text{ vs. } 4.2 \pm 1.3 \text{ ms/mmHg}; P = 0.05)\) and 75 W \((0.2 \pm 0.1 \text{ vs. } 1.5 \pm 0.5 \text{ ms/mmHg}; P = 0.02)\) as seen in HR sensitivity.

To consider the baroreflex sensitivity at a given HR, baroreflex sensitivity of HR was plotted against HR during supine and upright exercise (Fig. 5). As shown in the figure, the baroreflex sensitivity was reduced with increasing HR. Moreover, in the upright position, baroreflex sensitivity of HR at a given HR in the patients was much higher than in the controls at rest, but it tended to normalize with exercise.

SAP response to PE. Table 2 shows SAP response to PE at rest and during exercise in the supine and upright positions. In the patients and controls, 1.5, 2.0, 2.5, and 3.0 \(\mu g/kg\) of PE increased SAP by \(-20 \text{ mmHg at rest and at 25, 50, and 75 W exercise, respectively (}P < 0.001\). There were no differences in the responses to PE between the groups in either position \((P > 0.8)\).

DISCUSSION

The present study attempted to determine whether altered baroreflex control of HR might responsible for excessive tachycardia during exercise in the POTS patients. It appears from our observations that the tachycardia is not due to major differences in arterial baroreflex control of HR in POTS. Thus the major findings in the present study are as follows. 1) During a given level of exercise, HR in the patients was elevated relative to controls. 2) During upright exercise, baroreflex sensitivity of HR in the patients was only lower than the controls during the highest workload, whereas supine baroreflex sensitivity was similar between the groups, and these differences appear less obvious when differences in HR are accounted for (Fig. 5). 3) Upright SAP and PP during exercise fluctuated more in the POTS patients than the controls at higher workloads, whereas supine arterial pressure was controlled in a narrow range similar to the controls. Together, these observations argue that reduced stroke volume and/or cardiac filling during upright exercise are the primary causes of the differences in HR and arterial pressure responses seen in POTS patients vs. controls during exercise, and they further suggest that arterial baroreflex control of HR is normal in this condition.

In this context, we recently found that stroke volume was reduced in POTS patients compared with healthy controls during exercise (e.g., supine exercise at 75 W, 97 \pm 5 vs. 111 \pm 7 ml; upright exercise at 75 W, 70 \pm 4 vs. 94 \pm 6 ml), whereas the level of cardiac output and arterial pressure was maintained by greater elevation in HR (19). Thus we postulated that the greater elevation in HR might be a compensatory response for the reduced stroke volume. However, the higher HR in the absence of discernible changes in arterial pressure also raised the possibility that abnormalities in the baroreflex control of HR might result in an inappropriate tachycardia during exercise.
Baroreflex sensitivity. In the present study, baroreflex sensitivity of HR was reduced during exercise both in the patients and controls. Several experiments have been conducted to assess baroreflex sensitivity during exercise in healthy subjects. It has been reported that sensitivity for baroreflex control of HR was similar at rest and during exercise (cycle ergometer) at any intensity when it was determined using neck pressure and suction to alter carotid sinus transmural pressure (21, 25, 31). On the other hand, when baroreflex sensitivity was determined by bolus infusions of vasoactive drug, the sensitivity of RRI was reduced during cycling exercise with increasing workload (2, 27, 28). Similarly, in terms of HR, the sensitivity, recalculated from RRI values in each subject reported in the previous studies (2, 27, 28), was still reduced progressively during middle- to high-intensity exercise (we did this because the relationship between RRI and its reciprocal, HR, is non-linear (24)). In this study, we confirmed that baroreflex sensitivity of HR, determined by vasoactive drug infusion, was reduced during exercise in the POTS patients as well as in control subjects (Figs. 3 and 4).

Although there are no clear reasons why baroreflex sensitivity of HR was unchanged by neck pressure and suction but was reduced by infusions of vasoactive drug, this might be due to the fact that the former method selectively stimulates carotid baroreceptors, whereas the latter globally stimulates both carotid and aortic baroreceptors. Additionally, more recent studies using neck pressure and suction suggest that as HR approaches 150 beats/min, baroreflex control of HR is indeed blunted (23). More importantly, baroreflex control of mean arterial pressure is generally maintained even during relatively heavy exercise (23).

In the present paper, the reduction in baroreflex sensitivity of HR during upright exercise was greater in the patients than the controls, whereas supine baroreflex sensitivity was similar between the groups. This might be explained by an interaction between arterial and cardiopulmonary baroreflexes. It has been reported that unloading of cardiopulmonary baroreceptors with orthostatic stress altered arterial baroreflex control of HR at rest and during exercise (26, 30). In this study, at rest, supine baroreflex sensitivity of HR was similar between the patients and controls, whereas upright sensitivity was higher in the patients than the controls, suggesting that unloading cardiopulmonary baroreceptors enhanced arterial baroreflex sensitivity in the patients compared with the controls. Although this might contribute to the maintenance of arterial pressure, the ability of baroreflex control of HR to influence arterial pressure regulation might be limited during orthostasis (6).

On the other hand, during upright exercise, baroreflex sensitivity of HR in the patients was lower than the controls at highest workload. To clarify the mechanisms, we determined the baroreflex sensitivity at a given HR (Fig. 5). We did this because baroreflex control of HR can be reduced with increasing exercise intensity and HR, and thus the lower baroreflex sensitivity of HR in the patients during upright exercise could be simply explained by higher HR. As shown in Fig. 5, baroreflex sensitivity of HR at a given HR in the patients was much higher at rest but greatly decreased with exercise. These results suggest that in upright position, cardiopulmonary baroreflexes enhanced arterial baroreflex sensitivity of HR in the patients at rest but not during exercise. While we have no clear mechanistic explanation for this observation, it is possible that the enhanced venous return during either the supine position (rest or exercise) or with upright exercise (muscle pump) was responsible for the normal pattern of baroreflex control of HR seen in the patients under these conditions.

Fluctuations in arterial pressure. Based on the discussion above, it appears that baroreflex control of HR is surprisingly normal in POTS patients, and the higher HR likely reflects their low stroke volume and general state of deconditioning (19) vs. a primary defect in baroreflex control of HR. In this context, hyperventilation may affect the stability of arterial pressure in the patients. It has been reported that arterial pressure variability at high frequency is largely mediated by mechanical effects of respiration (36). Moreover, some POTS patients demonstrate hyperventilation during orthostasis (34).

Along these lines, SAP and PP in the patients fluctuated more during upright exercise whereas DAP was relatively stable (Fig. 1, Table 1). Why is the increase in fluctuations of arterial pressure specific to SAP and PP? While the etiology of POTS is heterogeneous (15), our data and those of the Dallas group suggest that deconditioning and cardiac atrophy may be a major contributing factor to the reduced stroke volume in the patients (10, 19). Moreover, a smaller and less distensible heart after bed rest results in a steeper Frank-Starling relationship (14). These results suggest that small changes in left ventricular end-diastolic pressure cause greater changes in stroke volume via steeper Frank-Starling relationship in POTS patients, translating into greater variability of arterial pressure, especially SAP and PP. Additionally, such changes would likely amplify the effects of respiration on arterial pressure variation during exercise.

Another possible explanation for the greater fluctuations in SAP and PP is the impaired control of vascular resistance. Ogoh et al. (23) reported that with increasing exercise intensity, the contribution of vascular resistance to baroreflex-mediated changes in arterial pressure increased and those of HR or cardiac output declined in healthy subjects. In our companion paper (19), the total peripheral resistance response

### Table 2. SAP response to phenylephrine at rest and during exercise

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<tr>
<th>Workload</th>
<th>Supine Workload</th>
<th>Upright Workload</th>
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<tbody>
<tr>
<td></td>
<td>Rest (1.5 μg/kg PE)</td>
<td>25 W (2.0 μg/kg PE)</td>
</tr>
<tr>
<td></td>
<td>12 0 12 2 12 4 12 6</td>
<td>25 W (2.0 μg/kg PE)</td>
</tr>
<tr>
<td>Control (n = 10)</td>
<td>15±2</td>
<td>17±2</td>
</tr>
<tr>
<td>POTS (n = 13)</td>
<td>17±2</td>
<td>16±1</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. PE, phenylephrine.
to exercise was not different in the patients and controls in either supine or upright position. Moreover, in this study, SAP response to PE during exercise was similar between the patients and controls, suggesting that α-adrenergic vasoconstrictor response during exercise is normal in the patients. However, it is unknown whether baroreflex control of sympathetic nerve activity functions effectively to stabilize arterial pressure as exercise intensity increases. Therefore, further studies are needed to assess how dynamic changes in vascular resistance relate to greater fluctuations in arterial pressure during upright exercise in the patients.

In summary, the present study explored the pathophysiological mechanisms responsible for excessive tachycardia during exercise in the POTS patients. It appears from our observations that the tachycardia during exercise is not due to abnormal baroreflex control of HR but is likely a compensatory response to a low stroke volume. Additionally, the greater fluctuations in arterial pressure during upright exercise might be due to either mechanical factors acting on venous return and stroke volume or impaired dynamic control of vascular resistance, but the mechanisms remain to be determined.

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REFERENCES


