Reduced stroke volume during exercise in postural tachycardia syndrome

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Masuki S, Eisenach JH, Schrage WG, Johnson CP, Dietz NM, Wilkins BW, Sandroni P, Low PA, Joyner MJ. Reduced stroke volume during exercise in postural tachycardia syndrome. J Appl Physiol 103: 1128–1135, 2007. First published July 12, 2007; doi:10.1152/japplphysiol.00175.2007.—Postural tachycardia syndrome (POTS) is characterized by excessive tachycardia without hypotension during orthostasis. Most POTS patients also report exercise intolerance. To assess cardiovascular regulation during exercise in POTS, patients (n = 13) and healthy controls (n = 10) performed graded cycle exercise at 25, 50, and 75 W in both supine and upright positions while arterial pressure (arterial catheter), heart rate (HR; measured by ECG), and cardiac output (open-circuit acetylene breathing) were measured. In both positions, mean arterial pressure, cardiac output, and total peripheral resistance at rest and during exercise were similar in patients and controls (P > 0.05). However, supine stroke volume (SV) tended to be lower in the patients than controls at rest (99 ± 5 vs. 110 ± 9 ml) and during 75-W exercise (97 ± 5 vs. 111 ± 7 ml) (P = 0.07), and HR was higher in the patients than controls at rest (76 ± 3 vs. 62 ± 4 beats/min) and during 75-W exercise (127 ± 3 vs. 114 ± 5 beats/min) (both P < 0.01). Upright SV was significantly lower in the patients than controls at rest (57 ± 3 vs. 81 ± 6 ml) and during 75-W exercise (70 ± 4 vs. 94 ± 6 ml) (both P < 0.01), and HR was much higher in the patients than controls at rest (103 ± 3 vs. 81 ± 4 beats/min) and during 75-W exercise (164 ± 3 vs. 131 ± 7 beats/min) (both P < 0.001). The change (upright − supine) in SV was inversely correlated with the change in HR for all participants at rest (R2 = 0.32), at 25 W (R2 = 0.49), 50 W (R2 = 0.60), and 75 W (R2 = 0.32) (P < 0.01). These results suggest that greater elevation in HR in POTS patients during exercise, especially while upright, was secondary to reduced SV and associated with exercise intolerance.

Cardiovascular regulation during exercise in POTS patients and healthy control subjects, and we also determined SV and total peripheral resistance (TPR). Moreover, to assess the possibility of exaggerated venous pooling and inadequate cardiac venous return (31–34) during exercise, we included both upright and supine exercise, because supine exercise provides a condition facilitating venous return by minimizing peripheral pooling of blood.

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. 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). All subjects were Caucasian American, non-smokers, and normotensive. All women had a negative serum pregnancy test the day before the study. They were also studied during

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days 15–21 of the menstrual cycle (midluteal) or during the second week of hormone pills in a standard cycle of oral contraceptives to minimize variability in autonomic control of cardiovascular function due to reproductive hormone status (9, 22).

The POTS patients were selected on the basis of a preexisting tilt-test diagnosis, including 1) a sustained increase in HR of ≥30 beats/min or a sustained HR of ≥120 beats/min within 10 min of initiation of the tilt; 2) absence of orthostatic hypotension defined as a sustained drop in systolic arterial pressure (SAP) of ≥20 mmHg and/or in diastolic arterial pressure (DAP) of ≥10 mmHg; and 3) presence of orthostatic symptoms, including light-headedness, dizziness, nausea, head pressure, and dyspnea. All POTS patients were sufficiently bothered by their orthostatic symptoms that they sought medical treatment, but they were free of organ system dysfunction or systemic illness that could affect the study results. Medications that could affect autonomic function were withdrawn for at least five half-lives before the study.

Control subjects were recruited from the local community and selected based on the following criteria: 1) no history of systemic diseases; 2) no history of neurological disorders, including syncope or orthostatic intolerance; and 2) no history of taking medications that are indicated for the aforementioned disorders and not taking medications except oral contraceptives. Data were collected as part of a large series of studies (21, 21a), and more detailed criteria for inclusion in the subjects were described in the preceding study (21).

Measurements

Arterial catheterization. Under aseptic conditions, a 5-cm 20-gauge catheter was inserted into the radial artery of the nondominant arm under local anesthesia (1% lidocaine). Because one female control subject and one female patient had a radial artery that was difficult to catheterize, the catheter was inserted into the brachial artery of the nondominant arm in these two participants. The arterial catheter was connected to a pressure transducer for determination of arterial pressure and continuously flushed at 3 ml/h with heparinized saline (6). While supine the arm was positioned at heart level, and while upright the arm was also positioned at heart level using an arm holder. Arterial blood samples were obtained at selective time points for measurement of plasma catecholamines (norepinephrine, epinephrine, and dopamine). These samples were centrifuged and stored at −70°C for later measurement of plasma catecholamines via high-performance liquid chromatography (29).

HR and CO. HR was monitored by using a three-lead electrocardiogram. CO (l/min) was estimated using an open-circuit acetylene washin method (15). This method allows the noninvasive determination of CO and can be repeated every 4–6 min.

Forearm blood flow. To assess blood flow in a nonactive vascular bed, brachial artery diameter and blood velocity of the nondominant arm were measured with a 12-MHz linear-array Doppler probe (model M12L, Vivid 7, General Electric, Milwaukie, WI) with a probe insonation angle previously calibrated to 60°. Diameter measurements corresponded to the QRS complex (end diastole) of the electrocardiogram. Forearm blood flow (FBF) was calculated as brachial blood velocity multiplied by brachial artery cross-sectional area and expressed as milliliters per minute (7, 25, 30). Because one female and one male control (but none of the POTS patients) had a brachial artery that bifurcated into smaller arteries further upstream, we could not determine FBF in these two controls. Therefore, the presented FBF responses to exercise in controls represent the values in eight control subjects.

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 a forearm intravenous line was started. A standardized very light meal was served at 10 AM, and in the afternoon the subjects participated in an orthostatic trial that has been previously published (21). After the trial, the 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.

Venous blood samples were obtained at noon the day before the study and at 7 AM the day of the study to determine hematocrit, hemoglobin concentration, and plasma osmolality. The percent change in plasma volume to overnight saline infusion was calculated using hematocrit and hemoglobin concentration (11). Because we were unable to obtain venous blood samples from one female POTS patient, the data reported represent the values in 12 POTS patients.

After arterial catheterization, the subjects rested for 30 min in supine position. A stand test was then performed to assess the severity of orthostatic tachycardia. After a 2-min supine baseline period, the subjects stood for 2 min while HR and arterial pressure were monitored. A 2-min standing period was chosen to minimize the duration of any orthostatic symptoms in the patients. After resumption of the supine position and stabilization of vital signs, the subjects performed a bout of exercise (see protocol, Fig. 1). No participants complained of light-headedness or other orthostatic symptoms before the 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 HR, arterial pressure, and FBF were continuously measured. CO was measured at 3.5 and 9.5 min of each workload and at 3.5 min of each workload. Arterial blood samples were obtained at 5 min of rest and at ~4.2 min of each workload to assess the effect of POTS on catecholamine responses to exercise. After supine exercise, subjects rested while sitting on a chair for 70 min, and they had a glass of water (150 ml) at 10–15 min of the intermission. Although drinking much more water (480 ml) can affect HR in POTS patients (35), the amount we provided was small, and it has been reported that it does not change plasma volume or plasma osmolality (16). The bicycle exercise trial was then repeated while 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 because of the possibility that POTS patients would exhibit orthostatic symptoms and fatigue during upright exercise and 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.
Analyses

Data were digitized at 600 Hz, stored on a computer, and analyzed offline with signal processing software (Windaq, Dataq Instruments, Akron, OH). HR was determined from the electrocardiogram signal. SAP, DAP, and mean arterial pressure (MAP) were derived from the arterial pressure waveform. Pulse pressure (PP) was calculated as \( \text{SAP} - \text{DAP} \). Forearm vascular conductance (FVC) was calculated as \( \frac{\text{FFB}\times\text{MAP}}{100} \), and expressed as milliliters per minute per 100 millimeters of Hg. Although we did not use forearm venous pressure to calculate FVC, it has been reported that in either supine or upright position, forearm venous pressure was not different in POTS patients and healthy controls (32, 33). HR, arterial pressure, FBF, and FVC reported represent an average of minutes 2–3 during resting or during each workload. Resting CO represents an average of two measurements at rest. SV was calculated as CO/HR, and it was expressed as milliliters per liter per minute.

Statistics

Values are expressed as means ± SE. Group differences in subject characteristics were tested by a one-way ANOVA. Group differences in the HR, arterial pressure, CO, SV, TPR, FVC, and catecholamine responses to exercise, and HR and arterial pressure responses to standing were tested by a two-way ANOVA for repeated measures. The effects of overnight saline infusion on hematocrit, hemoglobin, plasma osmolality, and plasma volume were tested by a two-way ANOVA for repeated measures. Subsequent post hoc tests to determine significant differences in the various pairwise comparisons were performed using Fisher’s least significant difference test. All \( P \) values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics and Stand Test

There were no differences in age, height, body weight, or body mass index between POTS patients and controls (\( P = 0.17–0.70 \)). Overnight saline infusion produced a significant decrease in hematocrit (38.1 ± 0.9 vs. 37.4 ± 0.9%; pre- vs. postinfusion), hemoglobin concentration (13.2 ± 0.3 vs. 13.0 ± 0.3 g/dl; pre- vs. postinfusion), and plasma osmolality (286 ± 1 vs. 284 ± 1 mosmol/kgH₂O; pre- vs. postinfusion) in the patients (\( P = 0.02–0.04 \)), but it did not change hematocrit (37.2 ± 0.9 vs. 36.9 ± 0.8%; pre- vs. postinfusion), hemoglobin concentration (12.6 ± 0.3 vs. 12.5 ± 0.3 g/dl; pre- vs. postinfusion), and osmolality (286 ± 1 vs. 287 ± 1 mosmol/kgH₂O; pre- vs. postinfusion) in the controls (\( P = 0.33–0.56 \)), and there were no differences in these parameters between the groups (\( P = 0.27–0.58 \)). Similarly, overnight saline infusion significantly increased plasma volume by 3.1 ± 1.2% in the patients (\( P = 0.03 \)), but it did not increase in the controls (1.4 ± 1.9%; \( P = 0.47 \)).

Table 1 shows HR and arterial pressure responses to stand test. At baseline, HR was significantly higher in the patients than the controls (\( P = 0.001 \)), but SAP, DAP, and MAP were not different between the groups (\( P = 0.53–0.92 \)). The HR response to standing was greater in the patients (\( P < 0.001 \)), but the SAP and MAP responses to standing were not different between the groups (\( P = 0.24–0.32 \)), whereas the DAP response was significantly greater in the patients (\( P = 0.0099 \)).

**HR and Arterial Pressure**

As shown in Fig. 2, supine and upright cycling produced a significant increase in HR, MAP, and PP in the patients and controls (\( P < 0.001 \)).

While supine, HR in the patients was significantly higher than the controls at rest (76 ± 3 vs. 62 ± 4 beats/min; \( P = 0.004 \)) and during exercise (highest workload, 127 ± 3 vs. 114 ± 5 beats/min; \( P = 0.006 \)). Upright posture further increased HR in the patients, and the HR in the patients was much higher than the controls at rest (103 ± 5 vs. 81 ± 4 beats/min; \( P < 0.001 \)) and during exercise (highest workload, 164 ± 3 vs. 131 ± 7 beats/min; \( P < 0.001 \)), whereas the change from rest to exercise was not different between the groups in either position (\( P = 0.12–0.99 \)).

SAP, MAP, and DAP at rest and the responses to exercise were not different in the patients and controls in either position (\( P = 0.13–0.86 \)). Similarly, PP at rest and the response to exercise were not different in the patients and controls in either position (\( P = 0.19–0.83 \)).

**CO, SV, and TPR**

As shown in Fig. 3, supine and upright cycling produced a significant increase in CO and SV, and decrease in TPR in the patients and controls (\( P < 0.02 \)), except for supine SV in either group (\( P = 0.28–0.84 \)).

CO at rest and the response to exercise were not different in the patients and controls in either position (\( P = 0.38–0.88 \)). Similarly, TPR at rest and the response to exercise were not different in the patients and controls in either position (\( P = 0.07–0.20 \)).

Supine SV in the patients tended to be lower than the controls at rest (99 ± 5 vs. 110 ± 9 ml) and during exercise (highest workload, 97 ± 5 vs. 111 ± 7 ml) (\( P = 0.07 \)). Upright posture further decreased SV in the patients, and the SV in the patients was significantly lower than the controls at rest (57 ± 3 vs. 81 ± 6 ml; \( P = 0.003 \)) and during exercise (highest

<table>
<thead>
<tr>
<th>Table 1. HR and arterial pressure responses to standing</th>
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<tr>
<td><strong>Control (n = 10)</strong></td>
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<tr>
<td><strong>Baseline</strong></td>
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<td>HR, beats/min</td>
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<td>MAP, mmHg</td>
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Values are means ± SE; \( n \), no. of subjects. POTS, postural tachycardia syndrome; HR, heart rate; SAP, DAP, and MAP, systolic, diastolic, and mean arterial pressure, respectively; Δ, difference between baseline and standing. Significant differences from the controls: *\( P < 0.01 \) and †\( P < 0.001 \). Significant differences from the values at baseline in each group. ‡\( P < 0.01 \) and §\( P < 0.001 \). 

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workload, 70 ± 4 vs. 94 ± 6 ml; \( P = 0.003 \)), whereas the change from rest to exercise was not different between the groups in either position \( (P = 0.45–0.96) \).

To assess whether decrease in SV with a change from supine to upright position is associated with increase in HR, delta SV \( (\text{upright} - \text{supine}) \) was plotted against delta HR \( (\text{upright} - \text{supine}) \) at rest and at 25-, 50-, or 75-W exercise in all the subjects. Consequently, the delta SV was inversely and significantly correlated with the delta HR at rest \( (R^2 = 0.32, P = 0.005) \), 25-W \( (R^2 = 0.49, P < 0.001) \), 50-W \( (R^2 = 0.60, P < 0.001) \), and 75-W exercise \( (R^2 = 0.32, P = 0.005) \) (Fig. 4).

**Catecholamine Values**

The catecholamine responses to cycling exercise are summarized in Table 2. Supine and upright cycling produced a significant increase in norepinephrine and epinephrine in the patients and controls \( (P = 0.003) \), whereas dopamine did not increase \( (P = 0.17–0.56) \) except for upright cycling for the patients \( (P = 0.008) \). The norepinephrine was significantly higher at higher workloads in the patients than in the controls in the upright position \( (P = 0.04) \), but it was not different in the supine position \( (P = 0.33) \). Epinephrine and dopamine responses to exercise were similar between the groups in both positions \( (P = 0.48–0.78) \).
DISCUSSION

To our knowledge, this is the first study that has evaluated the cardiovascular responses to exercise in POTS patients. The major findings in the present study are as follows. 1) In either the supine or upright position, arterial pressure, CO, TPR, and FVC at rest and the responses to exercise were not different in the patients and controls. 2) At rest and during exercise, SV in the patients tended to be lower than controls in supine position, and it was significantly lower than controls in upright position. 3) Coincident with the smaller SV, the patients had higher HR than controls, especially in upright position. Thus our results suggest that greater elevation in HR during exercise in POTS is related to a reduced SV rather than to an excessive vasodilation in the exercising muscles.

Reduced SV in POTS

Reduced SV during exercise in POTS patients may be caused by deconditioning. Saltin et al. (26) reported that in healthy young men, a 20-day period of bed rest reduced SV during submaximal exercise by 20% in the supine position and by 30% in the upright position and that the reduction in SV was entirely responsible for a fall in maximal oxygen consumption. They also mentioned that a decrease in plasma volume after bed rest (8%) cannot fully account for the reduction in SV. In this study, we performed overnight saline infusion (vs. overt volume loading) to eliminate the potential effect of acute hypovolemia, because hypovolemia and chronic “underhydration” has been reported in some POTS patients (8, 25). We confirmed that the infusion decreased hematocrit, hemoglobin concentration, and plasma osmolality, and increased plasma volume, in the patients, whereas it did not change these parameters in the controls. Nevertheless, SV in the POTS patients tended to be lower than controls in supine position at rest and during exercise, and it was much lower compared with the controls in upright position. Thus, although SV can be reduced after hypovolemia, factors other than acute hypovolemia may also contribute to the reduced SV in POTS.
Recently, Fu et al. (10) reported that left ventricular mass was much smaller in female POTS patients than in healthy women. A smaller (and therefore, less “distensible”) heart would result in a steeper Frank-Starling relationship, leading to an excessive reduction in SV during orthostasis (10, 17), which might contribute to a much lower SV during upright exercise in the POTS patients in the present study. Along these lines, POTS patients often become significantly disabled, during even simple activities such as eating, showering, or low-intensity exercise (19). To cope with these symptoms, patients often reduce their standing time and activity level (2). Perhaps this behavioral pattern then leads to a cycle of inactivity and secondary deconditioning that induces cardiac atrophy (23).

Taken together, these results suggest that secondary deconditioning and cardiac atrophy may be a major contributing factor to the reduced SV in POTS patients.

Another possible factor contributing to the reduced SV in POTS is exaggerated venous pooling. Streten et al. (34) reported that patients with orthostatic tachycardia had excessive venous pooling in the leg while standing. Stewart et al. (32, 33) reported in POTS patients that calf blood volume increased twice as much and thoracic blood volume decreased markedly compared with controls during head-up tilt, and this indicated that POTS is related to inadequate cardiac venous return during orthostasis. However, to date, no studies have evaluated venous return during exercise in POTS. In the present study, we included supine exercise to provide a condition facilitating venous return by minimizing peripheral pooling of blood. However, we observed reduced SV in POTS patients during supine as well as upright exercise. Thus, although increased venous pooling may partially explain the marked reduction in SV during the upright posture, because CO during exercise was the same in the patients and controls in both positions, venous return during exercise was also likely similar. Therefore, other factors such as the reduced cardiac size reported by Fu and colleagues (10) that would lead to reduced SV during exercise should also be considered as major explanations for the reduced SV in the POTS patients.

**Higher HR in POTS**

We observed higher HR in the POTS patients during exercise, especially in the upright position, which may be a compensatory response to reduced SV to maintain CO. In the classic study comparing nonathletes vs. athletes, CO for a given workload is similar but HR is higher in nonathletes than athletes due to a smaller SV (4). Similarly, after bed rest CO for a given workload is slightly lower but relatively maintained in most of the subjects, whereas HR is higher after bed rest than before due to a smaller SV (26). In this study, HR was higher and SV was lower in the POTS patients than controls during exercise (Figs. 2 and 3). Moreover, as shown in Fig. 4, the decrease in SV was inversely correlated with the increase in HR, suggesting that HR is increased more when SV is reduced. Consequently, CO in the patients was well maintained in the same level as the control subjects (Fig. 3). On the other hand, HR in the patients would reach a maximal level at a lower workload. Therefore, if exercise had been maximal, we would almost certainly have seen dramatically reduced maximal CO in the patients due to a lower SV. Thus the higher HR in POTS patients may serve as a compensatory response to

### Table 2. Catecholamine response to exercise

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<th>Control (n = 10)</th>
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<th>POTS (n = 13)</th>
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<td>Rest 25 W 50 W 75 W</td>
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<tr>
<td>Norepinephrine, pg/ml</td>
<td>170±21</td>
<td>215±27</td>
<td>237±29‡</td>
<td>296±44§</td>
<td>195±24</td>
<td>286±43§</td>
<td>292±40§</td>
<td>358±55§</td>
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<td>Epinephrine, pg/ml</td>
<td>35±6</td>
<td>39±6</td>
<td>49±9†</td>
<td>58±8§</td>
<td>44±13</td>
<td>56±17†</td>
<td>60±14‡</td>
<td>66±17§</td>
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<td>Dopamine, pg/ml</td>
<td>14±2</td>
<td>11±1</td>
<td>17±6</td>
<td>16±4</td>
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<td>Norepinephrine, pg/ml</td>
<td>301±32</td>
<td>372±38</td>
<td>479±53‡</td>
<td>818±114§</td>
<td>363±31</td>
<td>522±49</td>
<td>742±81§</td>
<td>1227±166§</td>
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<tr>
<td>Epinephrine, pg/ml</td>
<td>60±9</td>
<td>58±8</td>
<td>80±11</td>
<td>141±21§</td>
<td>60±13</td>
<td>69±16</td>
<td>91±17†</td>
<td>143±25§</td>
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<tr>
<td>Dopamine, pg/ml</td>
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<td>14±2</td>
<td>17±4</td>
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<td>21±7</td>
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Values are means ± SE; n, no. of subjects. *Significant differences from the controls, $P < 0.05$. Significant differences from the values at rest in each group: †$P < 0.05$, ‡$P < 0.01$, and §$P < 0.001$. 

![Graph](image-url)
reduced SV that maintains CO during submaximal exercise in the patients. This interpretation is consistent with our laboratory's recent observations (in the same groups of subjects) that the exaggerated HR response to orthostatic stress is a physiological response to venous pooling in the POTS patients and not of psychogenic origin (21).

Another possible explanation for the increased levels of HR in the patients is a reflex response to the excessive vasodilation in exercising muscles. When sympathetic restraint of blood flow to active muscles is absent, in autonomic failure, blood pressure falls by ∼40 mmHg with exercise even in supine position (20, 29). However, as shown in Figs. 2 and 3, the TPR and MAP responses to exercise were not different in the POTS patients and controls in either position, indicating that sympathetic restraint of muscle blood flow is well preserved in POTS. In addition, FVC (in noneexercising forearm) responses to exercise were not different in the POTS patients and controls in either position. Taken together, these results suggest that the increased levels of HR in the patients are not a response to excessive vasodilation in peripheral vessels during exercise, but may be a compensatory response to reduced SV.

Norepinephrine concentrations were higher at higher workloads in the patients than the controls in the upright position, whereas they were similar between the groups in supine position (Table 2). Although the mechanisms responsible for the higher norepinephrine concentrations are not clear, it might be partially explained as a characteristic of POTS. POTS patients frequently have high systemic plasma norepinephrine concentrations during orthostasis compared with healthy controls (12, 14, 28). Jacob et al. (14) reported that the decrease in norepinephrine clearance during standing was greater in patients than control subjects, although the increase in norepinephrine spill-over was similar in patients and control subjects, indicating that much of the increase in plasma norepinephrine was due to a decrease in clearance. By contrast, the higher norepinephrine during upright exercise might be simply explained by higher relative exercise intensity in the patients than the controls with an associated greater level of sympathetic activation. However, we observed the higher norepinephrine during upright but not supine exercise, suggesting that the increase had a postural component.

**Experimental Considerations**

There are five main experimental considerations that deserve additional discussion. First, we performed overnight saline infusion, which might have altered the native physiology in POTS patients. It has been reported that acute volume loading greatly blunts orthostatic tachycardia in POTS (13). However, our goal was to ensure a normovolemic state, without overt volume loading. Indeed, the increase in plasma volume after overnight saline infusion was only 3%, which is equivalent to ∼70 ml based on the plasma volume reported in the previous study of POTS (24). Also, excessive tachycardia during standing was seen in the patients after overnight saline infusion. Thus the effect of overnight saline infusion on the response to exercise in the POTS patients was likely minor in this study.

Second, we did not randomize the order of the supine and upright exercise trials because of concerns about excessive fatigue and orthostatic symptoms in the patients. However, the results in the patients were compared with controls subjects who underwent the same protocol. Unexpectedly, the patients were not exhausted by the supine exercise, likely because the exercise workloads we used were relatively low. Therefore, we believe it is unlikely that the order affected the main outcomes of the study. Additionally, participating in an orthostatic trial prior to the present investigation might have exacerbated the symptoms in POTS (19). However, no patients complained of severe symptoms compared with their daily lives before the present investigation.

Third, we used the term “upright” as “sitting upright on the bicycle,” but this may be a little different from standing or head-up tilt. For example, norepinephrine at rest in upright position tended to be higher in our patients than controls but this was nonsignificant, whereas high systemic norepinephrine concentrations have been reported during standing in POTS patients (12, 14, 28). This is likely because the level of orthostatic stress is lower during sitting upright on the bicycle (in this study) than during standing for POTS patients. Probably for the same reason, CO at rest in upright position was not different in our patients and controls, whereas inadequate venous return has been reported during head-up tilt in POTS patients (31, 32).

Fourth, we did not directly measure blood flow to the muscle or other noneexercising organs except forearm. Because partial sympathetic denervation in the legs (12) and splanchnic hyperemia (31, 36) are reported in some POTS patients, further studies are needed to assess how redistribution of blood flow occurs during exercise in these patients so that TPR and arterial pressure are maintained similar to controls.

Fifth, we did not measure cardiac volume in this study. However, based on the SV responses we observed, the study of Fu et al. (10), and classic ideas about cardiac size and exercise tolerance (4, 23, 26), it seems reasonable to suggest that “cardiac atrophy” is a major contributing factor to exercise intolerance in POTS.

**Perspectives**

How can we apply the implications of the present findings to physiological strategies in POTS? Saltin et al. (26) reported that physical training after bed rest dramatically increased SV, CO, and oxygen uptake at maximal exercise compared with those values after bed rest, whereas there was no change in maximal HR. This suggests that graded physical training may have beneficial effects in POTS.

In summary, the results from the present investigation demonstrate that in both supine and upright positions, arterial pressure, CO, TPR, and FVC responses to exercise were similar in the POTS patients and controls, and that to maintain CO during exercise, HR in the patients was elevated with reduced SV. Furthermore, the inverse relationship between HR and SV suggests that greater elevation in HR may serve as a compensatory adaptation to reduced SV in POTS.

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