Excessive heart rate response to orthostatic stress in postural tachycardia syndrome is not caused by anxiety

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Submitted 22 August 2006; accepted in final form 9 November 2006

Masuki S, Eisenach JH, Johnson CP, Dietz NM, Benrud-Larson LM, Schrage WG, Curry TB, Sandroni P, Low PA, Joyner MJ. Excessive heart rate response to orthostatic stress in postural tachycardia syndrome is not caused by anxiety. J Appl Physiol 102: 896–903, 2007. First published November 16, 2006; doi:10.1152/japplphysiol.00927.2006.—Postural tachycardia syndrome (POTS) is characterized by excessive increases in heart rate (HR) during orthostasis. The relationship between the tachycardia and anxiety is uncertain. Therefore, we tested whether the HR response to orthostatic stress in POTS is primarily related to psychological factors. POTS patients (n = 14) and healthy controls (n = 10) underwent graded venous pooling with lower body negative pressure (LBNP) to −40 mmHg while wearing deflated antishock trousers. "Sham" venous pooling was performed by LBNP with trouser inflation marked by lower body negative pressure (P < 0.01). LBNP with trouser inflation markedly blunted the HR responses in the patients (9 ± 2 beats/min) and controls (2 ± 1 beats/min), and there was no HR increase during vacuum application without LBNP in either group. HR responses during mental stress were not different in the patients and controls (18 ± 2 vs. 19 ± 1 beats/min; P > 0.6). Anxiety, somatic vigilance, and catastrophic cognitions were significantly higher in the patients (P < 0.05), but they were not related to the HR responses during LBNP or mental stress (P > 0.1). These results suggest that the HR response to orthostatic stress in POTS patients is not caused by anxiety but that it is a physiological response that maintains arterial pressure during venous pooling.

orthostatic intolerance; venous pooling; blood pressure; sympathetic nervous system; mental stress

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. It generally affects young and middle-aged women (20, 33). Symptoms include fatigue, light-headedness, and nausea, and POTS can be quite debilitating with significant limitations to activities of daily living (1, 18, 30). Although POTS is now better recognized, the mechanisms underlying this condition remain unclear.

Clinical observations suggest that these patients often experience marked anxiety and other psychological symptoms (19, 20, 30), and many POTS patients report being told by at least one physician that the cause of their tachycardia is psychogenic (1). On the other hand, several studies have consistently demonstrated that the excessive tachycardia may be a compensatory response to other cardiovascular impairments during orthostasis (14, 34–37). However, there have been no attempts to assess the direct psychogenic component of the tachycardia in POTS. Therefore, we tested the hypothesis that the HR response to orthostatic stress in POTS patients is not due to anxiety. Utilizing several experimental approaches, our findings indicate that anxiety is not the primary cause for the excessive orthostatic tachycardia seen in POTS. In a larger context, our findings suggest that although psychological symptoms are common in POTS, they may not be causal.

METHODS

Subjects

Fourteen POTS patients (29 ± 3 yr; 12 women, 2 men; weight, 68 ± 2 kg; height, 170 ± 2 cm) participated in this study (Table 1). For comparison, we matched 10 healthy control subjects (32 ± 3 yr; 8 women, 2 men; weight, 66 ± 2 kg; height, 167 ± 2 cm). The studies were approved by the Institutional Review Board of the Mayo Clinic, and each participant gave prospective written informed consent. All subjects were nonsmokers and normotensive. All women had a negative serum pregnancy test the day of the study. They were also studied during 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, 21).

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 blood pressure of ≥20 mmHg and/or in diastolic blood pressure 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 (Table 1). However, some of the drugs that were being used for psychological or other reasons were continued, unless voluntarily stopped for 5 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 psychological disorders, including anxiety disorders, 3) no history of neurological disorders, including syncope.
LBNP when venous pooling was prevented by random order) a ramped LBNP protocol and two bouts of "sham" mented while supine in the LBNP box. They then underwent (in AM, and the study began at 12:30 PM. reported to the GCRC between 8 and 9 AM, and a forearm intrave- alcohol, and exercise at least 24 h before GCRC admission. They

Table 1. POTS patient characteristics

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Gender</th>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>Medication Discontinued Before Study</th>
<th>Medication Continued During Study</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>46</td>
<td>25</td>
<td>Sodium chloride tablets</td>
<td>Nortriptyline, paroxetine</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>22</td>
<td>23</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>25</td>
<td>25</td>
<td>Atenolol, pyridostigmine</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>28</td>
<td>22</td>
<td>Propranolol</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>22</td>
<td>23</td>
<td>Pyridostigmine, aceticaminophen/dichloralphenazon/ isomeethene mucate (Midrin)</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>21</td>
<td>21</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>28</td>
<td>22</td>
<td>Sodium chloride tablets, atomoxetine</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>21</td>
<td>25</td>
<td>Pyridostigmine</td>
<td>Nortriptyline, venlafaxine</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>23</td>
<td>25</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>44</td>
<td>23</td>
<td>Propranolol, bismuth subsalicylate</td>
<td>Sertraline</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>25</td>
<td>21</td>
<td>Metoprolol, tizanidine</td>
<td>Rabeprazole</td>
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<tr>
<td>12</td>
<td>F</td>
<td>48</td>
<td>29</td>
<td>Atenolol, dexamethasone, zolpidem, estrogen patch</td>
<td>Citalopram, somatropin, oxaprin</td>
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<tr>
<td>13</td>
<td>F</td>
<td>28</td>
<td>24</td>
<td>Atenolol, glycipyrofolate, lorazepam</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>25</td>
<td>21</td>
<td>Pyridostigmine, sodium chloride/potassium chloride (Thermotabs), electrolyte solution (Pedialyte), esomeprazole, metoclopramide, cetirizine</td>
<td>Sertraline, venlafaxine, mirtazapine, clonazepam</td>
</tr>
</tbody>
</table>

Mean±SE 29±3 24±1

POTS, postural tachycardia syndrome; BMI, body mass index; M, male; F, female. Medication Discontinued, these medications were discontinued for at least 5 half-life time periods before the study. Medication Continued, medications were not discontinued for at least 5 half-life time periods before the study, or subjects remained on medications during study.

or orthostatic intolerance, and 4) no history of taking medications that are indicated for the aforementioned disorders and not taking medications except oral contraceptives.

Measurements

HR. HR was monitored by using a three-lead electrocardiogram. Beat-by-beat arterial pressure was measured by using a Finapres adjusted to heart level, and regularly verified by automated sphygmomanometry.

Forearm blood flow. Forearm blood flow (FBF) was measured every 15 s using venous occlusion plethysmography with mercury-in-Silastic strain gauges (11).

Lower body negative pressure. The lower body of the subject was sealed in an airtight box above the iliac crests. The box was attached to a pump so that graded suction up to 40 mmHg could be rapidly produced. The subject was supported by a bicycle seat mounted within the box and was kept supine throughout the lower body negative pressure (LBNP) protocol.

Medical antishock trousers. Subjects were segmented medical antishock trousers (MAST III-A, David Clark, Worcester, MA). When in use, the trousers in the leg region (but not abdominopelvic region) were inflated to 5 mmHg (relative to outside the negative pressure box), which negates superimposed LBNP and greatly attenuates reflex tachycardia and vasoconstriction in healthy subjects (5, 12). A low pressure was chosen to avoid squeezing the legs and evoking either reflex increases in arterial pressure (43) or potential fluid shifts from the lower body (10). It has been previously observed that trouser inflation to 5 mmHg does not alter baseline hemodynamics (12).

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, and a forearm intravenous line was started. A standardized very light meal was served at 10 AM, and the study began at 12:30 PM.

LBNP. Participants donned the antishock trousers and were instrumented while supine in the LBNP box. They then underwent (in random order) a ramped LBNP protocol and two bouts of “sham” LBNP when venous pooling was prevented by 1) trouser inflation during LBNP and 2) vacuum pump activation without suction in the box. Each bout included a 3-min baseline period, LBNP at levels of −10, −20, −30, and −40 mmHg for 3 min with or without medical antishock trouser inflation, or with vacuum sound but no changes in box pressure. Observations were continued for 3 min of recovery. HR, arterial pressure, and FBF were monitored throughout the trials, and the participants were blinded to the specific aims and order of LBNP trials. The three trials were separated by 20 min of quiet rest. Data were averaged during the last 2 min of each period. Because one female control and one female patient exhibited presyncopal signs during the last 30 s of −40 mmHg period during LBNP (but not the 2 sham trials) and the trial was terminated, data were averaged during the second minute of −40 LBNP for these two participants.

Mental stress. At least 20 min after LBNP, the Stroop colored word test was performed to induce nonorthostatic anxiety-provoking stress (6, 40). Following 3 min of baseline measure and 30 s of printed instructions read aloud, the computerized test was administered for 3 min, with consistent monologue from one investigator urging the participant to respond faster and to concentrate fully. During this protocol, HR, arterial pressure, and FBF were measured as described above. Data were averaged during 3 min of baseline and during each minute of mental stress.

Psychological variables. After the Stroop test, participants completed validated questionnaires measuring anxiety sensitivity, somatic vigilance, and catastrophic cognitions. Anxiety sensitivity was measured with the Anxiety Sensitivity Index (25), a 16-item scale developed to measure anxiety-related bodily sensations. The score was calculated as a sum of the 16 items. Multiple studies have demonstrated the reliability and validity of the Anxiety Sensitivity Index in both clinical and nonclinical samples (25). Somatic vigilance was measured with the Body Vigilance Scale (31), a four-item scale developed to assess attentional focus to internal bodily sensations. The score was measured with the Anxiety Sensitivity Index in both clinical and nonclinical samples (25). Somatic vigilance was measured with the Body Vigilance Scale (31), a four-item scale developed to assess attentional focus to internal bodily sensations. The score was calculated as a sum of the 4 items. The Body Vigilance Scale has been validated in nonclinical and anxiety disorder populations (31). Catastrophic cognitions were measured with a modified version of the Coping Strategies Questionnaire Catastrophizing Scale (29). The Catastrophizing Scale includes six items that reflect thoughts of helplessness and an inability to cope with pain. The score was calculated as an average of the six items. Instructions were modified to ask respondents to rate how much they have these thoughts when experiencing POTS-related symptoms. This scale has

J Appl Physiol • VOL. 102 • MARCH 2007 • www.jap.org
been well validated in pain samples (28). Additionally, all three instruments have demonstrated good reliability in previous research with POTS (2, 3).

Stand test. After the questionnaires, 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). On the second experimental day at 10 AM, a stand test was performed to assess the severity of orthostatic tachycardia in euhydrated patients and controls. After a 2-min supine baseline period, subjects stood for 2 min, while HR and arterial pressure were monitored. Arterial pressure was measured via a 5-cm 20-gauge catheter that was inserted into the radial or brachial artery of the nondominant arm under aseptic conditions after local anesthesia (1% lidocaine). The arterial pressure catheter was available because we were conducting an exercise trial in these patients on day 2. Data were averaged during 2 min of baseline and during 2 min of standing.

Analyses

HR was determined from the electrocardiogram signal, and mean arterial pressure (MAP) was derived from the arterial pressure waveform. FBF was determined from the derivative of the forearm plethysmogram and was expressed as milliliters per 100 milliliters of tissue per minute. To account for any potential changes in blood pressure, forearm vascular conductance (FVC) was calculated as \( \frac{\text{FBF}}{\text{MAP}} \times 100 \), and it was expressed as arbitrary units.

Statistics

Values are expressed as means ± SE. Group differences in subject characteristics, baseline hemodynamic values, arterial pressure and HR responses to standing, and psychological variables were determined by a one-way ANOVA. Group differences in the MAP, HR, and FVC responses to LBNP trials and mental stress were determined by a two-way ANOVA for repeated measures. All \( P \) values < 0.05 were considered statistically significant.

RESULTS

There were no differences in age, height, body weight, or body mass index between POTS patients and controls (\( P > 0.3 \)). Baseline HR was significantly higher in the patients (77 ± 3 beats/min) than in the controls (62 ± 3 beats/min) (\( P < 0.01 \)). Baseline systolic pressure, diastolic pressure, and MAP were not significantly different in the patients and controls (135 ± 2, 67 ± 2, and 89 ± 2 mmHg vs. 134 ± 4, 68 ± 2, and 91 ± 3 mmHg, respectively; \( P > 0.5 \)). The HR response to standing was greater in the patients (Fig. 1), but the systolic and mean pressure responses to standing were not different between the groups, whereas the diastolic pressure response was significantly greater in the patients.

LBNP

Figure 2A shows typical examples of HR and MAP responses to the three LBNP trials in a POTS patient and a control subject. During standard LBNP, the HR response in the patient was much greater than that in the control. During sham LBNP with either trouser inflation or vacuum sound but no changes in box pressure, there was little HR response in both the patient and the control.

Figure 2B shows mean HR and MAP responses to three different types of LBNP. At baseline for all three trials, HR in POTS patients was significantly higher than in the controls (\( P < 0.05 \)), but MAP was not different (\( P > 0.7 \)). Standard LBNP (no trouser inflation) induced suction-dependent in-
creases in HR ($P < 0.001$) that were significantly greater in the patients than controls ($P < 0.01$). For example, the increase at $-40$ mmHg was $39 \pm 5$ vs. $19 \pm 3$ beats/min in the patients vs. controls. During LBNP with trouser inflation, the increase in HR was markedly blunted in both groups ($P < 0.001$), but the change from baseline was significantly higher in POTS patients than the controls ($P < 0.01$). The increase at $-40$ mmHg was $9 \pm 2$ vs. $2 \pm 1$ beats/min in the patients vs. controls. During vacuum-sound LBNP (no change in box pressure), the increase in HR was completely abolished in both groups ($P < 0.001$). Additionally, MAP did not change in the patients or controls during any LBNP trial ($P > 0.3$), and there were no differences between groups in the MAP response to LBNP in any trial. ($P > 0.5$).

Forearm vasoconstrictor responses to LBNP trials were similar between POTS patients and controls. Baseline FVC for
standard LBNP was 3.1 ± 0.4 units in the patients and 2.9 ± 0.5 units in controls, similar to baseline for other trials (P > 0.8). During standard LBNP at −40 mmHg, FVC decreased to 1.6 ± 0.3 units in the patients vs. 1.5 ± 0.3 units in controls (P > 0.6). During LBNP at −40 mmHg with trouser inflation, FVC decreased to 2.0 ± 0.3 units in the patients vs. 1.9 ± 0.3 units in controls (P > 0.7). During vacuum sound LBNP, FVC did not change throughout the trial (P > 0.7).

Mental Stress

Figure 3 shows typical examples (A) and mean values (B) of HR and MAP responses to mental stress. At baseline, HR in POTS patients was significantly higher than in the controls (P < 0.05), but MAP was not different (P > 0.9). Mental stress produced a significant increase in HR, MAP, and FVC (P < 0.001), but there was no difference in the pattern between the patients and controls (P > 0.2).

Psychological Variables

Figure 4 shows participants’ scores on the Anxiety Sensitivity Index, Body Vigilance Scale, and Catastrophizing Scale. Scores were significantly higher in POTS patients than in controls (P < 0.05). In previously reported studies, mean Anxiety Sensitivity Index scores in normal populations have ranged from 13.1 to 22.5, whereas mean scores in samples from patients with panic disorder have ranged from 30.5 to 36.6 (24, 25, 32, 42). In this study, the score of 21.1 in the POTS patients is lower than that seen in panic disorder but seems likely to be at the upper limits of the normal population. For the Body Vigilance Scale, normal populations have

![Graphs showing HR and MAP responses to mental stress and psychological variables](image-url)
achieved mean scores of 15.8 and 17.9, with samples from patients with panic disorder achieving a mean of 22.6 (23, 31). In this study, the score of 19.1 in the POTS patients might, again, be slightly above the mean for a normal population. The Catastrophizing Scale is primarily used with pain samples. Reported mean scores for chronic pain patients have ranged from 2.3 to 2.6 (4, 15, 29). In one study, scleroderma patients achieved a mean score of 1.4 (7), which is similar to that seen in POTS patients. On the other hand, scores for the Anxiety Sensitivity Index, Body Vigilance Scale, and Catastrophizing Scale in the control group confirm that the control subjects were relatively free of anxiety-related symptoms.

To assess possible relationships between psychological variables and HR during standard LBNP or mental stress, the psychological variables were plotted against the increase in HR at \(-40\) mmHg during standard LBNP or against the increase in HR during mental stress. However, none of the psychological scores was correlated with the changes in HR during LBNP or mental stress \((P > 0.1)\).

Because most common antidepressants act on catecholamine pathways, we performed a subsidiary analysis that excluded these patients \((patients 1, 8, 10, 12–14; Table 1)\). HR, MAP, and FVC responses to LBNP trials and mental stress in the patients not taking antidepressants were similar to all patients, and none of the psychological scores was correlated with the changes in HR during LBNP or mental stress in this subset. Additionally, Anxiety Sensitivity Index scores in these patients were significantly higher than in the controls \((P < 0.05)\), whereas Body Vigilance Scale and Catastrophizing Scale scores were not \((P > 0.1)\).

**DISCUSSION**

This study shows that HR in POTS patients only increased markedly during periods of significant venous pooling and that the HR responses to “sham” orthostatic stress and mental stress were similar between the patients and controls. Additionally, the HR responses to both orthostatic stress and mental stress were not related to scores on several psychological indexes associated with POTS. Taken together, these findings suggest that anxiety is not the primary cause for the excessive orthostatic tachycardia seen in POTS.

POTS is characterized by orthostatic symptoms and tachycardia without orthostatic hypotension. The nonspecific nature of the symptoms and the absence of orthostatic hypotension have probably resulted in a lack of recognition of this syndrome by both clinicians and investigators. Clinical observations suggest that many POTS patients report being told by at least one physician that the cause of their augmented HR responses to standing are primarily psychogenic and have been misdiagnosed as a panic disorder \((1, 18, 19)\).

In this general context, POTS may be explained by physiological mechanisms. In this study, we used LBNP to simulate orthostasis. Our rational for using LBNP vs tilting is that we could also conduct sham LBNP with the combination of the medical antishock trouser inflation that prevents venous pooling or with vacuum pump activation without LBNP. As expected, the HR responses to LBNP in POTS patients were enhanced. This excessive tachycardia may be caused by central hypovolemia, because LBNP induces venous pooling and also accentuates extravasation within the interstitium of the leg, thereby reducing plasma volume \((13)\), which may be exaggerated in POTS patients \((34, 36, 37)\). Additionally, hypovolemia \((8, 26)\) and cardiac atrophy due to deconditioning \((Refs. 16, 17; BD Levine, personal communication)\) may also contribute to an enhanced HR response to LBNP and orthostatic intolerance via an excessive fall in stroke volume in some patients. These results suggest that the increased HR during orthostasis in POTS is a physiological response and, if so, should be attenuated when venous pooling is prevented.

During sham LBNP conducted with the medical antishock trouser inflation or with vacuum pump activation without LBNP, the patients had “normal” HR responses, even though they showed increased levels of anxiety-related characteristics compared with controls. These findings are consistent with previous studies demonstrating that anti-gravity suit inflation reduced tachycardia during standing in patients with orthostatic intolerance, although their anxiety level was not reported and these patients were not blinded to the order or timing of the suit inflation \((38, 39)\). Nevertheless, the collective data from all of these studies suggest that enhanced HR in POTS is not seen unless there is significant venous pooling.

In this study, during medical antishock trouser inflation to \(5\) mmHg during LBNP, the POTS patients had slightly higher increases in HR compared with the controls. Under these circumstances, there might still be venous pooling in the abdomen or pelvis and this observation is consistent with reports of excessive venous pooling in these regions in POTS \((35, 36, 41)\). Moreover, factors such as excessive splanchnic or pelvic vascular capacity and deconditioning may also account for higher resting HR in the patients \((22, 35, 41)\). Finally, in this study, the HR response to mental stress was similar between the patients and controls, but the HR responses to both orthostatic stress and mental stress were not related to scores on several psychological indexes. Thus we found little evidence that anxiety is the primary cause for the excessive orthostatic tachycardia seen in POTS. An unanswered question is how might differences in psychological variables relate to POTS.

The onset of autonomic dysfunction may result in heightened somatic vigilance and other indexes \((3)\). Also, reductions in day-to-day physical activity and increased perceptions of disability may heighten psychological indexes. POTS patients often become significantly disabled, during even simple activities such as eating, showering, and low-intensity exercise \((18)\), and data have shown that functional disability is correlated with psychological variables in POTS patients \((3)\). To cope with symptoms, patients often reduce their standing time and activity level \((3)\). Perhaps this pattern of reaction then leads to a cycle of inactivity and deconditioning that makes the HR responses to venous pooling worse instead of better over time. However, there have been no longitudinal studies to clarify the relationship between psychological abnormalities and POTS. Therefore, further studies are necessary to determine how differences in psychological variables are related to and influence the course of the syndrome.

In this study, 6 of the 14 POTS patients had an orthostatic tachycardia <30 beats/min with standing, which seems discordant with the definition used to determine POTS. However, Raj et al. \((27)\) reported that orthostatic increase in HR in POTS patients was smaller with standing than with tilt by 14 beats/
min, and the results indicated that higher degrees of skeletal muscle pump activation with standing decreases the orthostatic tachycardia. Thus the reason that the six patients did not meet the HR criterion of POTS might be due to the physiological differences between standing and tilt, although we confirmed that the HR response to standing was much greater in the patients than controls.

Limitations of this study should be acknowledged. Although most of the medications were withdrawn for at least 5 half-lives before the study, some of the drugs that were being used for psychological reasons were continued (Table 1), which might have affected the results in this study. However, patients both taking and not taking antidepressants showed similar physiological responses.

In summary, HR in POTS patients increased markedly during significant venous pooling, whereas the patients had normal HR responses to sham orthostatic stress and mental stress. Additionally, the HR responses to both orthostatic stress and mental stress were not related to scores on several psychological indexes associated with POTS. Thus anxiety is not the primary cause for the excessive orthostatic tachycardia seen in POTS.

ACKNOWLEDGMENTS

We thank Ruth Kraft, Karen Krucker, Shelly Roberts, Branton Walker, Lynn Sokolnicki, and Jessica Abenstein for excellent technical assistance and the subjects who participated in this study.

GRANTS

This research was supported by National Institutes of Health (NIH) Grant NS-32352 (to M. J. Joyner), National Center for Research Resources Grant K23-17520 (to J. H. Eisenach), NIH General Clinical Research Center Grant RR-00585 (to the Mayo Clinic, Rochester, MN), and the Uehara Memorial K23-17520 (to J. H. Eisenach), NIH General Clinical Research Center Grant GRANTS in POTS.

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