Inspiratory Resistance Improves Postural Tachycardia
A Randomized Study

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Background—The objective of this study was to determine the effect of inspiratory resistance through an impedance threshold device (ITD) on orthostatic tolerance in patients with postural tachycardia syndrome. We hypothesized that the ITD would result in a greater negative intrathoracic pressure to enhance cardiac venous return, improve stroke volume, and reduce heart rate in these patients.

Methods and Results—We compared the effect of a sham device (sham, no resistance) versus an ITD (increased inspiratory resistance) in 26 patients with postural tachycardia syndrome in a randomized, single-blind, crossover study. Hemodynamic assessments were performed at baseline while supine and during head-up tilt to 70° for 10 minutes. We did not find differences in baseline hemodynamic parameters between the ITD and the sham devices. After 10 minutes of head-up tilt, the heart rate was lower with the ITD versus sham device (102±4 versus 109±4 beat/min, respectively; P=0.003). The ITD also improved stroke volume compared with the sham device (35±2 versus 26±1 mL; P=0.006).

Conclusions—These findings suggest that increasing negative intrathoracic pressure with ITD breathing improves heart rate control in patients with postural tachycardia syndrome during upright posture.

Clinical Trial Registration—clinicaltrials.gov; Unique Identifier: NCT00962728.

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Key Words: autonomic nervous system ■ postural tachycardia syndrome ■ stroke volume ■ tachycardia

Postural tachycardia syndrome (POTS) is a common form of chronic orthostatic intolerance that primarily affects premenopausal women. This heterogeneous disorder is characterized by excessive sustained tachycardia on standing, which is unrelated to medications or other medical conditions, and is accompanied by orthostatic symptoms, such as light-headedness, nausea, blurred vision, fatigue, and mental clouding. Although the underlying cause of POTS remains unclear, several mechanisms have been proposed, including sympathetic activation, deconditioning, hypovolemia,1-4 and reduced stroke volume attributed to cardiac atrophy coupled with this hypovolemia.2,5 Although several pharmacological and behavioral approaches have been tested in POTS, an optimal treatment strategy has not been identified for these patients.

The use of an impedance threshold device (ITD) has been proposed for the treatment of orthostatic intolerance6 and was demonstrated to attenuate the fall in blood pressure with standing and to improve presyncopal symptoms in patients with orthostatic hypotension.7,8 Breathing through the ITD increases negative intrathoracic pressure during spontaneous inspiration to improve venous return and ventricular preload through a thoracic suction effect.9 This suction effect increases blood pressure, cardiac output, and stroke volume in patients after cardiac arrest10 and during central hypovolemia.11 The use of an ITD also blunted the fall in blood pressure during acute induction of orthostatic intolerance in healthy subjects.11,12

Given these findings, we hypothesized that breathing through an ITD would reduce tachycardia in POTS patients, by improving stroke volume. To test this hypothesis, we compared the effects of the ITD versus a sham device on heart rate in patients with POTS in the supine position and during orthostatic stress test created by head-up tilt (HUT). As a secondary objective, we examined the hemodynamic mechanisms underlying any effect of the ITD on heart rate in these patients.

Methods

Standard Protocol Approvals, Registration, and Patient Consents
The Vanderbilt Institutional Review Board approved this study. Written informed consent was obtained from all participants.
WHAT IS KNOWN

- Postural tachycardia syndrome (POTS) is a common disorder that primarily affects premenopausal women. It is characterized by excessive sustained tachycardia on standing and is accompanied by debilitating orthostatic symptoms, such as lightheadedness, nausea, blurred vision, fatigue, and mental clouding.
- The underlying cause of POTS still remains unclear, but several pharmacological and behavioral approaches have been tested in POTS. Despite this, an optimal treatment strategy has not been identified for these patients.

WHAT THE STUDY ADDS

- We assessed the effects of increased inspiratory resistance on orthostatic tolerance and symptoms in patients with POTS in a randomized, crossover study.
- We found that increased negative intrathoracic pressure reduces upright heart rate and increases stroke volume while maintaining cardiac output and blood pressure.
- These overall findings suggest that an impedance threshold device (increases inspiratory resistance) could be used as a nonpharmacological approach to help restrain upright heart rate in patients with POTS.

Study Participants

We enrolled 39 POTS patients admitted to the Vanderbilt Autonomic Dysfunction Center for evaluation between November 2008 and October 2011. Patients met all the following criteria for POTS: (a) a heart rate increase ≥30 beats per minute within 10 minutes of standing or HUT; (b) the absence of orthostatic hypotension (defined as a fall in blood pressure >20/10 mm Hg)16,17; (c) at least a 6-month history of orthostatic symptoms; and (d) the absence of medications or an additional chronic medical condition known to cause tachycardia (eg, bedridden, severe dehydration). All patients were at least 18 years of age and were not smokers, pregnant, or endurance-trained athletes.

General Protocol

POTS patients were studied on an inpatient basis and were placed on a low-monoamine, methylxanthine-free, fixed sodium (150 mEq/d), and potassium (70 mEq/d) diet on admission. Medications affecting the autonomic nervous system, blood pressure, or blood volume were withheld at least 5 half-lives before testing.

Orthostatic Stress Testing

All patients underwent standardized orthostatic stress testing, in the morning at 8:00 AM after an overnight fast. Patients remained supine after overnight rest and then were asked to stand for 30 minutes or as long as tolerated. Blood pressure and heart rate were recorded in the supine and upright positions using an automated sphygmomanometer cuff. Blood samples were collected at the end of the supine and standing periods via an antecubital vein catheter that was placed at least 30 minutes before testing. Supine and standing plasma norepinephrine and epinephrine levels were measured by high-performance liquid chromatography with electrochemical detection, as previously described.15

Study Design

We performed a randomized, single-blind (patient blinded to intervention), crossover study assessing the effects of the ITD versus sham device on heart rate during HUT to 70° in patients with POTS. The primary outcome was defined a priori as the heart rate after 10 minutes of HUT. As a secondary objective, we compared the effects of the ITD versus sham device on stroke volume, cardiac output, blood pressure, and total peripheral resistance. The order of interventions was randomized using computer-generated random numbers, and a 20-minute washout period was allowed between interventions.

Protocol

All testing was performed in the afternoon and at least 2 hours after a meal. Patients were strapped into a tilt table (Medical Positioning Inc., Kansas City, MO) and allowed to rest in the supine position for 30 minutes before data collection. Baseline blood pressure and heart rate were recorded for 5 minutes, and then patients were instrumented with a low-resistance mouthpiece connected to a bag to measure cardiac output using the Innocor inert gas rebreathing technique (Innovision, Denmark). Patients were asked to breath spontaneously for at least 5 minutes in the supine position through the active (ITD, ResQGARD, Advanced Circulatory Systems Inc.) or sham resistance devices. Patients were tilted head-up to 70° for 10 minutes or as long as tolerated (Figure 1). Blood pressure (oscillometric device, Vital-Guard 450C; Ivy Biomedical Systems Inc.) and cardiac output (Innocor) were measured at baseline and every 5 minutes during testing. Heart rate was measured by continuous ECG. Stroke volume was calculated as cardiac output divided by heart rate (CO/HR). Total peripheral resistance was calculated as 80 times the mean blood pressure divided by cardiac output [(80×mean BP)/CO] and reported in SI units (dyne×seconds×cm⁻⁵).

Symptoms

Patients were asked to self-report symptom burden immediately after being tilted back to the supine position using the validated Vanderbilt POTS symptom score.16,17 Patients were asked to rate the severity of 9 symptoms on a 0 to 10 scale, with 0 reflecting absence of symptoms. The sum of the scores at each time point was used as a measure of the overall symptom burden. The symptoms evaluated were mental clouding, blurred vision, shortness of breath, rapid heartbeat, tremulousness, chest discomfort, headache, lightheadedness, and nausea.

Statistical Analysis

We tested the null hypothesis that the heart rate at 10 minutes after HUT, the primary outcome, would not be different between ITD and sham devices in patients with POTS. Secondary outcomes included stroke volume, cardiac output, blood pressure, and total peripheral resistance. Outcomes were compared using paired t tests. A 2-tailed P<0.05 was defined as statistically significant. Data are presented as mean±SEM. They were also analyzed with linear mixed-effects models. Each variable in Table 1 was regressed against indicator covariates for whether a device was used and whether this was a sham or ITD device. An interaction term for these 2 covariates was included in these models. The device, ITD, and interaction covariates were treated as fixed effects. Data from each patient were treated as a random effect. This analysis was restricted to data collected from supine patients. Analogous analyses were run for the data in Table 2; only here data collected without any device were excluded, and the dependent variable was regressed against position (supine or tilted) and ITD. These analyses were run using Stata’s mixed command (version 13.1; StataCorp LP, College Station, TX). Tests of contrasts from these analyses gave results that were comparable with those of analogous t tests in Tables 1 and 2. We only present the t tests because the regression analyses, while theoretically more powerful, also make assumptions that are not required by the t tests. Other analyses were performed using SPSS (version 22.0; IBM Corp). GraphPad Prism (version 6.0; GraphPad Software, San Diego, CA) was used to generate figures.

Sample Size

This study was powered to detect a difference in tilt-induced heart rate of 10 beats per minute between ITD and sham interventions,
which would reflect a clinically meaningful reduction. Assuming that the pooled standard deviation in upright heart rate will be 15 beats per minute, a final sample size of 26 patients would provide 90% power to detect this difference with an \( \alpha \) level of 0.05 using a paired sample \( t \) test (PS software, version 3.0.43).

### Results

#### Study Participants

Thirty-nine patients with POTS were enrolled in this study (Figure 2). Two patients were excluded before randomization...
Table 1. Effect of Breathing Devices on Supine Hemodynamic Parameters at Baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Without Device</th>
<th>With Device</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>102±13</td>
<td>100±13</td>
<td>0.302</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>63±8</td>
<td>64±9</td>
<td>0.066</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>76±9</td>
<td>76±10</td>
<td>0.454</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76±13</td>
<td>76±13</td>
<td>0.773</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>6.1±1.2</td>
<td>5.9±1.5</td>
<td>0.474</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>82±25</td>
<td>81±30</td>
<td>0.808</td>
</tr>
<tr>
<td>Total peripheral resistance, dyne×sec×cm−5</td>
<td>1041±5</td>
<td>1087±11</td>
<td>0.146</td>
</tr>
</tbody>
</table>

**Table 2. Hemodynamic Effects of ITD and Sham Devices During Head-Up Tilt**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham</th>
<th>ITD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>100±3</td>
<td>105±4</td>
<td>0.016</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>64±2</td>
<td>64±2</td>
<td>1.000</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>76±2</td>
<td>78±2</td>
<td>0.200</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76±3</td>
<td>78±3</td>
<td>0.013</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.9±0.3</td>
<td>5.6±0.2</td>
<td>0.300</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>81±6</td>
<td>75±4</td>
<td>0.081</td>
</tr>
<tr>
<td>Total peripheral resistance, dyne×sec×cm−5</td>
<td>1087±56</td>
<td>1143±57</td>
<td>0.164</td>
</tr>
</tbody>
</table>

Table 2; Figure 3). There was no effect of the sham device on supine hemodynamic function when compared with baseline (Table 1; Figure 3). At the end of the supine breathing period, systolic blood pressure (105±4 versus 100±3 mmHg; P=0.016) and heart rate (78±13 versus 76±13 beats per minute; P=0.013) were higher with the ITD compared with sham device, with no differences in other hemodynamic measures (Table 2).

Effect of ITD Versus Sham Device on Hemodynamics During Orthostatic Challenge

The HUT elicited similar hemodynamic changes with the ITD versus sham devices. As shown in Figure 4, HUT with the ITD resulted in increased heart rate (23±4 beats per minute; P<0.001), mean arterial pressure (7±2 mmHg; P<0.001), and total peripheral resistance (967±105 dyne×sec×cm−5; P<0.001) and decreased stroke volume (40±3 mL; P<0.001). Similarly, HUT with the sham device increased heart rate (33±3 beats per minute; P<0.001), mean arterial pressure (6±2 mmHg; P<0.001), and total peripheral resistance (992±78 dyne×sec×cm−5; P<0.001) and decreased stroke volume (50±4 mL; P<0.001). The ITD, however, attenuated these hemodynamic changes to HUT when compared with the sham device (Table 2; Figure 4). At 10 minutes after HUT, heart rate was lower (P=0.007) and stroke volume was higher (P=0.026) with the ITD versus sham device, with no differences in mean arterial pressure or total peripheral resistance (Table 2; Figure 4).

Baseline Patient Characterization

The clinical characteristics of patients with POTS in this study are shown in Table 3. All but one patient was female, reflecting the strong gender predominance of this disorder. During orthostatic stress testing (Table 3), patients with POTS exhibited a significant increase in heart rate on standing (43±4 beats per minute; P<0.001), with no differences in systolic (3±4 mmHg) or diastolic (6±3 mmHg) blood pressure. This orthostatic tachycardia was accompanied by a significant increase in plasma norepinephrine (174±16 supine versus 656±59 pg/mL standing; P<0.001) and epinephrine (18±4 supine versus 100±28 pg/mL standing; P<0.001) levels.

Effect of ITD Versus Sham Device on Supine Hemodynamics

There were 2 supine baseline periods in this study without devices: (1) before the first tilt test and (2) between the 2 tilt tests. When compared with the first baseline period, patients with POTS had decreased stroke volume (86±2 versus 82±6 mL; P=0.001) and cardiac output (6.4±0.2 versus 6.0±0.3 L/min; P=0.002), with no difference in heart rate (77±2 and 76±2 beats per minute; P=0.581) during the second baseline period. When stratified by intervention (ITD versus sham), this pattern was similar in both groups, suggesting that the randomization was effective in equalizing hemodynamic carryover effects. In the supine position, the ITD did not change HR or MAP but resulted in a decrease in SV (P=0.002) and an increase in TPR (P=0.002; Table 1; Figure 3). There was no effect of the sham device on supine hemodynamic function when compared with baseline (Table 1; Figure 3). At the end of the supine breathing period, systolic blood pressure (105±4 versus 100±3 mmHg; P=0.016) and heart rate (78±13 versus 76±13 beats per minute; P=0.013) were higher with the ITD compared with sham device, with no differences in other hemodynamic measures (Table 2).
Effect of Interventions on Symptom Scores
The overall symptom scores were similar between the ITD and the sham interventions (18±2 versus 19±2; P=0.897). Interestingly, although the ITD could potentially make it harder to breath, the shortness of breath symptom was rated equally between interventions (4.1±0.6 ITD versus 3.5±0.6 sham; P=0.382).

Discussion
We assessed the effects of increased inspiratory resistance using an ITD on orthostatic tolerance and symptoms in patients with POTS in a randomized, crossover study. The main finding is that increased negative intrathoracic pressure reduces upright heart rate in POTS. This attenuation in orthostatic tachycardia was associated with increased stroke volume and maintenance of cardiac output and blood pressure, perhaps reflecting improved cardiac venous return through a thoracic suction effect. These overall findings suggest that an ITD could be used as a nonpharmacological approach to help restrain upright heart rate in patients with POTS.

Hemodynamic Adaptations to Standing in POTS
The assumption of upright posture requires rapid cardiovascular adaptations to maintain blood pressure, including activation of afferent autonomic neural pathways to induce reflex-mediated increases in efferent sympathetic outflow, vasoconstriction, and subsequently venous return. Although the underlying cause of POTS remains unclear, many patients have low blood volume, which can reduce venous return and stroke volume even in the supine position. This reduction in stroke volume is thought to elicit tachycardia as a compensatory mechanism to maintain cardiac output and blood pressure in these patients.

Potential Benefits of ITD in POTS
Given the heterogeneity of POTS, this disorder is challenging to treat, and there are currently limited therapeutic options for these patients. The primary treatment approaches in patients with POTS involve either attempting to restrain heart rate (eg, β-blockers or pyridostigmine) or increasing circulating blood volume (eg, increased dietary salt and water, fludrocortisone,

Table 3. Clinical Characteristics of POTS patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>POTS Patients (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>25 (96%)</td>
</tr>
<tr>
<td>Age, y</td>
<td>30±2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166±2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65±3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23±1</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>69±2</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>107±3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>66±2</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>173±16</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>21±4</td>
</tr>
<tr>
<td>Standing</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>112±4</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>110±4</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>72±3</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>654±61</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>101±28</td>
</tr>
<tr>
<td>Change from supine to standing</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>43±4</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>3±4</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>6±3</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>482±27</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>82±51</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. POTS indicates postural tachycardia syndrome.
desmopressin). As with many medications, potential side effects may limit their use. In this regard, nonpharmacological interventions have an intuitive appeal because they do not produce off-target pharmacological adverse effects. In this study, we tested a nonpharmacological intervention that has the potential to increase venous return and stroke volume,

![Graphs showing hemodynamic changes](image1)

**Figure 3.** Effect of impedance threshold device (ITD) breathing on supine hemodynamic parameters. All panels show supine hemodynamic parameters at baseline breathing without any device (WO, blank bars) or using a breathing device (with, black bars). The left side of each panel shows the change with the ITD and the right side with the sham device. Breathing with the ITD did not change heart rate (HR; A) or mean arterial pressure (MAP; B) but decreased stroke volume (SV; C) and increased total peripheral resistance (TPR; D). Breathing with the sham device did not alter any of the hemodynamic parameters studied. The heart rate at the end of the supine period, however, was significantly higher while breathing with the ITD compared with the sham device (A).

![Graphs showing hemodynamic changes](image2)

**Figure 4.** Hemodynamic changes during head-up tilt with the impedance threshold device (ITD) or sham device. Changes in hemodynamic parameters from baseline (white bars for ITD, gray bars for sham) to 70° of head-up tilt (black bars for ITD and checkered bars for sham). Breathing through both the ITD and sham devices resulted in an increase in heart rate (HR; A), mean arterial pressure (MAP; B) and total peripheral resistance (TPR; D) and a decrease in stroke volume (SV; C). At 10 minutes after head-up tilt, however, heart rate was lower (A) and stroke volume was higher (C) with the ITD versus sham device.
and by partially reversing these abnormal hemodynamic responses, to reduce upright heart rate in patients with POTS.

Venous return is a passive process that is determined by a pressure gradient (venous-right atrial pressure) and venous resistance. During inspiration, the intrathoracic pressure is negative, whereas abdominal pressure is positive. The resulting increase in the pressure gradient pulls blood toward the right atrium to increase venous return. With deeper inspiration or with the use of ITD, both of which increase intrathoracic negative pressure, there could be an enhancement of venous return because of the larger negative pressure generated. In fact, breathing through an ITD has been shown to increase stroke volume and improve orthostatic tolerance in healthy subjects during hypovolemic challenges. It has also been recently shown that slow breathing can improve orthostatic tolerance and the proposed mechanism being through the generation of negative intrathoracic pressure.21 The ITD can force an increase in the depth of breathing by generating increased respiratory resistance. We hypothesized that this would increase stroke volume to decrease tachycardia in patients with POTS.

In the supine position, the ITD produced a modest increase in systolic blood pressure, an increase in total peripheral resistance, and a decrease in stroke volume, without altering heart rate. We speculate that the bigger respiratory effort required by the ITD caused an increase in sympathetic tone and total peripheral resistance, with a resultant decrease in venous return and stroke volume. During orthostatic stress, the ITD effectively reduced heart rate and increased stroke volume during in patients with POTS when compared with the sham device. Importantly, there were no differences in self-reported symptom scores between devices, although breathing through an ITD requires more effort. Given these findings, it is possible that the ITD could be used as a rescue measure or as a coadjuvant to other therapies to acutely reduce orthostatic tachycardia in POTS, without worsening symptoms.

Limitations
This study has some potential limitations. First, we only tested responses to the ITD during an acute tilt protocol. This was designed as a proof of concept study to show that the ITD could favorably restrain heart rate and alter hemodynamics and in POTS. The results are reported after 10 minutes of HUT. We actually see a trend toward a restraining effect of the ITD on the continuous increase in heart rate during tilt, but the study was not adequately powered to study such a pattern of effect. Further studies are needed to assess the practical use of ITD for the treatment of POTS and to study its long-term efficacy. It is possible that the ITD could be used as a rescue therapy for patients when they are feeling symptomatic while upright. Second, we focused on the hemodynamic mechanisms of the ITD but did not examine for neurohormonal changes or other potential mechanisms that could contribute to its beneficial effects. Finally, our patients were enrolled at a specialized care center for the treatment of autonomic disorders and therefore may not reflect the broader, and perhaps less severe, POTS population.

Conclusions
Breathing through an ITD device can acutely restrain upright heart rate and increase stroke volume in patients with POTS. Further studies are needed to explore the chronic effects of ITD breathing, but these data suggest that it may be an effective rescue therapy for some patients with POTS to reduce tachycardia during orthostatic stress.

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