Acute volume loading and exercise capacity in postural tachycardia syndrome

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Figieroa RA, Arnold AC, Nwazue VC, Okamoto LE, Paranjape SY, Black BK, Diedrich A, Robertson D, Biaggioni I, Raj SR, Gamboa A. Acute volume loading and exercise capacity in postural tachycardia syndrome. J Appl Physiol 117: 663–668, 2014. First published July 24, 2014; doi:10.1152/japplphysiol.00367.2014.—Postural tachycardia syndrome (POTS) is associated with exercise intolerance, hypovolemia, and cardiac atrophy, which may contribute to reduced stroke volume and compensatory exaggerated heart rate (HR) increases. Acute volume loading with intravenous (iv) saline reduces HR and improves orthostatic tolerance and symptoms in POTS, but its effect on exercise capacity is unknown. In this study, we determined the effect of iv saline infusion on peak exercise capacity (V˙O2peak) in POTS. Nineteen patients with POTS participated in a sequential study. V˙O2peak was measured on two separate study days, following administration of placebo or 1 liter of iv saline (NaCl 0.9%). Patients exercised on a semirecumbent bicycle with resistance increased by 25 W every 2 min until maximal effort was achieved. Patients exhibited blood volume deficits (~13.4 ± 1.4% ideal volume), consistent with mild to moderate hypovolemia. At baseline, saline significantly increased stroke volume (saline 80 ± 8 ml vs. placebo 64 ± 4 ml; P = 0.010), increased cardiac output (saline 6.9 ± 0.5 liter/min vs. placebo 5.7 ± 0.2 liter/min; P = 0.021), and reduced systemic vascular resistance (saline 992.6 ± 70.0 dyn-s/cm5 vs. placebo 1,184.0 ± 50.8 dyn-s/cm5; P = 0.011), with no effect on HR or blood pressure. During exercise, saline did not produce differences in V˙O2peak (saline 26.3 ± 1.2 mg·kg−1·min−1 vs. placebo 27.7 ± 1.8 mg·kg−1·min−1; P = 0.615), peak HR [saline 174 ± 4 beats per minute (bpm) vs. placebo 175 ± 3 bpm; P = 0.672] or other cardiovascular parameters. These findings suggest that acute volume loading with saline does not improve V˙O2peak or cardiovascular responses to exercise in POTS, despite improvements in resting hemodynamic function.

METHODS

Study design. In the present study, we tested the hypothesis that intravenous (iv) saline would improve maximal exercise capacity in POTS. We used a sequential trial to compare the effects of pretreatment with iv saline vs. placebo in patients with POTS on peak oxygen consumption and measures of hemodynamic function during semirecumbent cycling exercise to maximal effort. Maximal oxygen consumption (V˙O2 max) is the gold standard measure of exercise capacity (21); however, in cases in which the V˙O2 plateau is not evident, the highest achieved value is used (V˙O2peak) (22).

Protocol approvals, registrations, and patient consent. The Vanderbilt University Institutional Review Board approved this study. Written informed consent was obtained from all patients, and this protocol was registered at www.clinicaltrials.gov under the study title Intravenous (IV) Saline and Exercise in Postural Tachycardia Syndrome (POTS) (NCT01000350).

Study participants. This study included 19 patients with POTS between ages 18–65 yr who had been admitted to the Vanderbilt Autonomic Dysfunction Center for evaluation between October 2009 and December 2011. All patients met consensus criteria for POTS including sustained tachycardia (≥30 bpm) within 10 min of standing, absence of orthostatic hypotension, and chronic symptoms (≥6 mo) of cerebral hypoperfusion (4, 8, 16, 20). Patients were screened with a comprehensive medical history, physical examination, and routine laboratory testing. Patients were excluded if they had other medical conditions (e.g., acute dehydration, bed-ridden or chair-ridden), were taking medications that could explain significant orthostatic tachycardia, were pregnant, or were trained athletes. All patients received a low-monoamine, methylxanthine-free, fixed sodium (150 meq/day) and potassium (60–80 meq/day) diet upon admission, and medica-
tions affecting the autonomic nervous system, blood pressure (BP), or blood volume were withheld ≥5 half-lives before testing.

**Clinical characterization of patients with POTS.** All patients were characterized with orthostatic stress testing performed at 8:00 A.M. to minimize circadian differences in hemodynamic and biochemical measurements (2). Patients remained supine after an overnight rest and then stood for up to 30 min, or as long as tolerated. BP and HR were measured in the supine and standing positions. BP was measured with an arm cuff by automated oscillometric method and HR by continuous electrocardiogram (ECG) (VitalGuard 450C; Ivy Biomedical, Branford, CT). Supine and standing fasting blood samples were collected via an antecubital vein catheter placed at least 30 min before testing for measurement of plasma catecholamines by high-performance liquid chromatography with electrochemical detection (12). Total blood volume was measured using the indicator dye-dilution technique with 131I-labeled human serum albumin as previously described (27). The ideal total blood volume was determined for each patient from the height, weight, and gender. Individual blood volume deficits were determined by calculating the ideal minus measured volumes. This difference was divided by the ideal volume and expressed as a percent deficit, to control for individual variation in the ideal plasma volumes.

**Spectral analysis.** Continuous BP and HR were recorded using a WINDAQ acquisition system (DI720; DATAQ, Akron, OH). Data segments of at least 300 s were processed with PhysioWave software (Visual Numerics, Boulder, CO), with power spectral densities estimated in low-frequency (0.04–0.15 Hz) and high-frequency (0.15–0.40 Hz) ranges (33a).

**Exercise testing.** Patients with POTS participated in exercise testing to maximal effort on 2 separate study days, which were at least 3 days apart within a 2-wk period, in a sequential design. On the first study day, exercise testing was performed on 22 patients within 2 h after receiving a placebo pill (lactose tablet, Cebocaps; Forest Pharmaceuticals, New York, NY). The first study day was considered valid if two of the following criteria were met: 1) predicted peak HR was obtained; 2) the respiratory exchange ratio (RER) reached >1.1 (satisfactory effort); or 3) VO2peak reached a plateau (25). Subjects were considered deconditioned if VO2peak was <80% VO2max predicted and severely deconditioned if VO2peak was <65%. Predicted VO2max was calculated from established thresholds for sedentary women. Predicted peak HR was determined from the following formula: predicted HR (bpm) = [210 – (age × 0.65)] (30).

**Sample size calculation.** In our previous study, there was an improvement in VO2peak of 3.1 ml·kg⁻¹·min⁻¹, with a standard deviation of 3.9 ml·kg⁻¹·min⁻¹, following propranolol administration in patients with POTS (1). Assuming a similar effect size and variance, we estimated that 19 patients would provide 90% power to reject the null hypothesis in this study. Power calculations were performed on the basis of a paired t-test analysis (PS software, version 3.0.43) (5).

**RESULTS**

**Clinical characteristics.** This study included 19 patients with POTS (18 women, 1 man; age 31 ± 2 yr), with clinical characteristics shown in Table 1. During orthostatic stress testing, HR increased by 46 ± 4 bpm from the supine to standing positions, consistent with the diagnosis of POTS.

Standing produced a modest increase in systolic BP (P = 0.011), with no difference in diastolic BP, and an approximate threefold increase in plasma norepinephrine levels (supine
Table 1. Clinical characteristics of patients with POTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SE</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>Total blood volume</td>
<td></td>
</tr>
<tr>
<td>Measured, ml</td>
<td>3,596 ± 116</td>
</tr>
<tr>
<td>Predicted, ml</td>
<td>4,152 ± 111</td>
</tr>
<tr>
<td>Deficit, ml</td>
<td>557 ± 57</td>
</tr>
<tr>
<td>Deficit, %</td>
<td>13.4 ± 1.4</td>
</tr>
<tr>
<td>Orthostatic stress testing</td>
<td></td>
</tr>
<tr>
<td>Supine SBP, mmHg</td>
<td>109 ± 3</td>
</tr>
<tr>
<td>Supine DBP, mmHg</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>Supine HR, bpm</td>
<td>73 ± 2</td>
</tr>
<tr>
<td>Standing SBP, mmHg</td>
<td>118 ± 4*</td>
</tr>
<tr>
<td>Standing DBP, mmHg</td>
<td>71 ± 4</td>
</tr>
<tr>
<td>Standing HR, bpm</td>
<td>120 ± 5*</td>
</tr>
<tr>
<td>ΔHR, standing – supine</td>
<td>46 ± 4</td>
</tr>
<tr>
<td>Supine plasma norepinephrine, pg/ml</td>
<td>208 ± 22</td>
</tr>
<tr>
<td>Standing plasma norepinephrine, pg/ml</td>
<td>738 ± 119*</td>
</tr>
<tr>
<td>ΔNorepinephrine, standing – supine</td>
<td>530 ± 106</td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; HR, heart rate; POTS, postural tachycardia syndrome; SBP, systolic blood pressure. Values are means ± SE. *P < 0.05 between supine and standing.

Discussions

The main finding of this study is that an iv saline infusion given prior to exercise does not increase siemicumbent maximal exercise capacity in patients with POTS. Furthermore, although there was improvement in resting hemodynamic function, saline did not alter cardiovascular responses to exercise in these patients. Collectively, these findings suggest that acute volume loading may not be sufficient to improve exercise tolerance in POTS.

Saline and exercise capacity in POTS. Hypovolemia is observed in various conditions of orthostatic intolerance such as syncope and bed rest deconditioning (7, 14, 17), and pharmacologic and nonpharmacologic strategies to augment blood volume are often used in management of these patients. Many patients with POTS also exhibit low blood and plasma volume, with previous studies showing deficits ranging from 13 to 20% of expected values (9, 23, 27). Although we did not select for blood volume status in this study, all patients had total blood volume deficits with average levels consistent with mild to moderate hypovolemia. The hypovolemia coupled with cardiac atrophy is believed to contribute to reductions in SV and compensatory tachycardia in patients with POTS (9). Rapid iv saline infusion to expand intravascular and extracellular fluid volume has been shown to increase SV and CO and reduce HR to improve orthostatic intolerance in bed rest deconditioning (33). Because saline also reduces HR in POTS (15), we hypothesized that this strategy could improve exercise tolerance by increasing SV to control excessive tachycardia during exercise. We expected HR to decrease after volume expansion with normal saline infusion; however, in contrast to our hypothesis, there was no effect of saline on maximal exercise capacity or cardiovascular responses to exercise in patients with POTS. In addition, there was no effect of saline on submaximal exercise capacity (measured at 75 W), a measure that is independent from maximal effort and may better reflect daily activity.

There are several potential explanations for these findings. First, an acute saline infusion may not be sufficient, and more chronic treatments may be needed (i.e., dietary sodium and fluid increases, fludrocortisone, the vasopressin analog DD-
AVP) to improve exercise capacity in POTS. Second, because the treatment order was not randomized, it is possible that any beneficial effect of saline was confounded by prolonged fatigue or training effect (time effect) from the first study day. The possibility of prolonged fatigue seems unlikely, however, because the exercise tests were performed ≥3 days apart. The treatments were also not blinded and it is possible that patients perceived that saline infusion would limit exercise performance. This explanation is also unlikely, given that measures of exertion were similar on both study days. Third, acute saline infusions have been reported to increase fatigue and ventilation during maximal exercise in healthy subjects and to impair exercise capacity (28). It is possible that patients with POTS experienced increased symptoms following saline. This was not assessed in the present study, but it would contradict the usual improvement in symptoms that patients with POTS experience with iv saline. Finally, volume status may not be a major determinant for exercise tolerance in patients with POTS, at least in an acute setting. Indeed, we found no correlation between blood volume deficits and difference in VO2peak following placebo vs. saline (\( r^2 = 0.008, P = 0.733 \)). In support of this, rapid volume expansion also does not improve VO2peak during acclimatization to high altitude in healthy subjects (3), or during exercise in the heat in trained subjects (34).

Saline and cardiovascular hemodynamic function. Compared with healthy subjects, patients with POTS have increased HR, reduced SV, and no difference in BP in the supine position, with varying results for CO and SVR (1, 9, 10, 19). It is expected that acute volume expansion with saline would increase venous return to the heart to improve SV and decrease HR and SVR, possibly in part through reductions in sympathetic activation. In this study, saline infusion, in fact, decreased SVR and sympathetic modulation of vasomotor tone (LF\(_{SYS}\)), without alteration in vagal tone (HF\(_{RRI}\)) or baroreflex modulation. At baseline, saline infusion also increased SV and CO, but in contrast to our previous report (15), there was no effect on resting HR. These collective hemodynamic changes may suggest an uncoupling of baroreflex-volume pathways in these patients. Furthermore, despite some improvement to resting hemodynamic function, iv saline did not alter cardiovascular responses to exercise in POTS, consistent with the lack of effect on exercise capacity in these patients. These findings are in contrast to the hemodynamic and symptomatic improvement to postural challenges following saline infusions in patients with orthostatic intolerance (13, 15, 33).

Fig. 2. Effect of saline on exercise capacity. Exercise capacity was determined following placebo or iv saline infusion in patients with POTS in a semirecumbent position. There were no differences in resting oxygen consumption (VO2) (A), resting heart rate (HR) (B), VO2 at 75 W (C), HR at 75 W (D), peak VO2 (E), or peak HR (F) during exercise testing following placebo vs. saline administration.
Deconditioning in POTS. The cardiovascular phenotype of patients with POTS resembles that of subjects exposed to prolonged bed rest or microgravity deconditioning. It has been suggested that deconditioning is an almost universal finding in POTS and may play a central role in the pathophysiology of this disorder (16). A recent retrospective study showed that >90% of patients with POTS were deconditioned during upright treadmill exercise (24). In contrast to these findings, we recently reported that only 18% of studied patients with POTS were deconditioned during semirecumbent exercise with placebo, with no effect of saline. Overall, the varying degrees of deconditioning among these studies may reflect differences in patient selection, use of upright vs. recumbent protocols, and selection of the predicted VO2peak cutoff.

Study limitations. There are some limitations to this study. First, patients with POTS were evaluated at a specialized care center for autonomic disorders and thus may not be representative of the broader population. Second, although the number of patients in this study was similar to that of other clinical trials in POTS, some parameters may have been statistically significant with a larger sample size. This study was powered to detect differences in the primary outcome of VO2peak. Given the data in this study, 171 patients would have been needed to have 80% power to detect a significant difference in this outcome following saline vs. placebo, suggesting that we did not miss a meaningful difference. Third, we did not have a control group to assess whether the effects of saline on exercise capacity would be different depending on health status. Fourth, we did not evaluate blood volume after saline infusion, and it is possible that the saline effect may have been minimal at the time of measure; however, patients with POTS report symptoms improvement for as long as a week after the infusion. Fifth, we chose a pill as placebo to avoid possible effects of substances contained in other crystalloids and colloids such as dextrose and electrolytes.

Conclusions. Although acute volume expansion with iv saline improved resting hemodynamic function and decreased sympathetic activity in POTS, there was no effect on maximal exercise capacity or cardiovascular responses to exercise in these patients, at least when measured at 2 h after the intervention. It is possible that chronic sodium supplementation or pharmacologic strategies to correct plasma volume deficits would have been more effective in improving exercise tolerance in these patients, but this remains to be tested. Finally, this study provides further evidence that not all patients with POTS are deconditioned, and raises the possibility that varying degrees of deconditioning may result secondary to orthostatic tachycardia, rather than as a primary pathophysiological phenomenon.

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DISCLOSURES

Dr. Biaggioni is a consultant for Chelsea Therapeutics and Astra Zeneca and receives research support from Astra Zeneca and Forest Laboratories. Dr. Raj is involved in expert medical consulting for law firms regarding POTS.

AUTHOR CONTRIBUTIONS

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