Acute volume loading and exercise capacity in postural tachycardia syndrome

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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 compensated 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 (\(V\dot{O}_{2\text{peak}}\)) in POTS. Nineteen patients with POTS participated in a sequential study. \(V\dot{O}_{2\text{peak}}\) 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/cm\(^5\) vs. placebo 1,184.0 ± 50.8 dyn-s/cm\(^5\); \(P = 0.011\)), with no effect on HR or blood pressure. During exercise, saline did not produce differences in \(V\dot{O}_{2\text{peak}}\) (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 \(V\dot{O}_{2\text{peak}}\) 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 bicycling exercise to maximal effort. Maximal oxygen consumption (\(V\dot{O}_{2\text{max}}\)) is the gold standard measure of exercise capacity (21); however, in cases in which the \(V\dot{O}_{2}\) plateau is not evident, the highest achieved value is used (\(V\dot{O}_{2\text{peak}}\)) (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). Three patients declined to continue the study after the placebo study day (Fig. 1). Thus only 19 patients participated the day we infused 1 liter of iv saline (NaCl 0.9%) over 60 min, and measurements were taken within 2 h after the end of the infusion. The interventions were administered in an open label, nonrandomized fashion. Exercise testing was conducted in the Vanderbilt Human Autonomic Physiology Laboratory on a semirecumbent stationary bicycle (Ergometrics 800; Ergoline, Bitz, Germany) as previously described (1). Before the exercise test, patients completed stretching exercises followed by a 5-min warm-up session at 0 W resistance (baseline). Patients were then asked to maintain a speed of 60 revolutions per min (rpm) while the work load was increased by 25 W every 2 min until maximum effort was achieved, with verbal encouragement given by study investigators. Patients completed a brief cool-down period at 25 W resistance and were monitored for 10 min following cessation of exercise, with the entire testing period lasting ~30 min.

Oxygen consumption (VO\textsubscript{2}) was measured during exercise using a Food and Drug Administration–approved inert gas rebreathing test (Innocor; Innovision, Denmark) in which patients breathed normally through a mouthpiece with a one-way rebreathing valve connected to a bag containing room air and small amounts of the inactive gases N\textsubscript{2}O and SF\textsubscript{6}. VO\textsubscript{2} was assessed at rest and during graded exercise, with VO\textsubscript{2peak} determined during the final 1 min of exercise. Exercise testing was considered valid if two of the three following criteria were met: 1) predicted peak HR was obtained; 2) the respiratory exchange ratio (RER) reached >1.1 (satisfactory effort); or 3) VO\textsubscript{2} reached a plateau (25). Subjects were considered deconditioned if VO\textsubscript{2peak} was <80% VO\textsubscript{2max} predicted and severely deconditioned if VO\textsubscript{2peak} was <65%. Predicted VO\textsubscript{2max} was calculated from established thresholds for sedentary women. Predicted peak HR was determined from the following formula: predicted HR (bpm) = [210 – (age x 0.65)] (30). Predicted VO\textsubscript{2} and HR were expressed as the percent achieved of the predicted target during exercise testing. BP was measured at the end of each resistance cycle using an automated sphygmomanometer cuff (VitalGuard) and continuously with the finger volume clamp method (Nexfin; BMEYE, Amsterdam, Netherlands). HR was measured by continuous ECG (VitalGuard). Cardiac output (CO) and derived measures of SV and systemic vascular resistance (SVR) were measured at baseline (0 W) and at 75 W, a resistance near VO\textsubscript{2peak} that was reached by all patients with POTS using inert gas rebreathing (Innocor) (1).

**Statistical analysis.** Data are presented as means ± SE. Analyses were performed using SPSS software (version 21.0; IBM, Armonk, NY). A two-tailed P < 0.05 was defined as statistically significant. The primary objective of this study was to test the null hypothesis that VO\textsubscript{2peak} achieved following saline vs. placebo in patients with POTS. The primary outcome was selected a priori as the VO\textsubscript{2peak} achieved following saline vs. placebo. Secondary outcomes were selected as peak load and CO during exercise testing. Comparisons of clinical characteristics and outcomes between interventions within patients were analyzed using Wilcoxon signed-rank nonparametric paired analysis. The proportion of patients meeting criteria for deconditioning following placebo vs. saline were compared using a paired McNemar test.

**Sample size calculation.** In our previous study, there was an improvement in VO\textsubscript{2peak} of 3.1 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}, with a standard deviation of 3.9 ml·kg\textsuperscript{-1}·min\textsuperscript{-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
208 ± 22 pg/ml vs. standing 738 ± 119 pg/ml; \( P = 0.001 \).

Patients had a total blood volume deficit of 557 ± 57 ml, representing 13.4 ± 1.4% of their ideal blood volume, with 13 of these having deficits ≥10%.

**Effect of iv saline on exercise capacity.** Baseline \( \dot{V}O_2 \) (saline 5.84 ± 0.43 ml·min\(^{-1}\)·kg\(^{-1}\) vs. placebo 5.80 ± 0.45 ml·min\(^{-1}\)·kg\(^{-1}\); \( P = 0.896 \); Fig. 2A) and HR (saline 88 ± 3 bpm vs. placebo 92 ± 2 bpm; \( P = 0.285 \); Fig. 2B) were similar following saline vs. placebo administration. There was no effect of saline pretreatment on anaerobic threshold (AT) for \( \dot{V}O_2 \) (saline 15.62 ± 1.01 ml·min\(^{-1}\)·kg\(^{-1}\) vs. placebo 16.15 ± 1.01 ml·min\(^{-1}\)·kg\(^{-1}\); \( P = 0.546 \)), AT for HR (saline 132 ± 5 bpm vs. placebo 130 ± 3 bpm; \( P = 0.984 \)), \( \dot{V}O_2 \) at 75 W (saline 18.78 ± 1.06 ml·min\(^{-1}\)·kg\(^{-1}\) vs. placebo 19.21 ± 0.91 ml·min\(^{-1}\)·kg\(^{-1}\); \( P = 0.570 \); Fig. 2C), HR at 75 W (saline 151 ± 5 bpm vs. placebo 150 ± 4 bpm; \( P = 0.889 \); Fig. 2D), \( \dot{V}O_2 \) peak (saline 26.25 ± 1.23 ml·min\(^{-1}\)·kg\(^{-1}\) vs. placebo 27.74 ± 1.78 ml·min\(^{-1}\)·kg\(^{-1}\); \( P = 0.615 \); Fig. 2E), or peak HR (saline 174 ± 4 bpm vs. placebo 175 ± 3 bpm; \( P = 0.672 \); Fig. 2F). The percent predicted \( \dot{V}O_2 \) (saline 87 ± 5% vs. placebo 91 ± 6%; \( P = 0.904 \)), AT load (saline 57 ± 4 W vs. placebo 58 ± 4 W; \( P = 0.722 \)), peak load (saline 91 ± 7 W vs. placebo 100 ± 9 W; \( P = 0.430 \)), and peak RER (saline 1.19 ± 0.04 vs. placebo 1.19 ± 0.03; \( P = 0.643 \)) were also not significantly different between placebo and saline, suggesting that patients achieved a similar level of exertion on both study days. Eighty patients (42%) were deconditioned following placebo and 10 (53%) following saline (\( P = 0.625 \)). Severe deconditioning was observed in only one patient who achieved 59% (placebo) and 58% (saline) of predicted \( \dot{V}O_2 \).

**Effect of iv saline on hemodynamic function.** The effect of saline on hemodynamic function was examined in 12 out of 19 patients (Fig. 3). In these patients, at baseline or prior to exercise, saline significantly increased SV (saline 80 ± 8 ml vs. placebo 64 ± 4 ml; \( P = 0.010 \)), increased CO (saline 6.9 ± 0.5 liter/min vs. placebo 5.7 ± 0.2 liter/min; \( P = 0.021 \)), and reduced SVR (saline 992.6 ± 70 dyn·s·cm\(^{-5}\) vs. placebo 1,184 ± 50.8 dyn·s·cm\(^{-5}\); \( P = 0.011 \)) compared with placebo, with no effect on mean arterial pressure (MAP) (saline 85 ± 3 mmHg vs. placebo 85 ± 2 mmHg; \( P = 0.859 \)). Compared with baseline, exercise increased CO and MAP and reduced SVR at 75 W. There was no effect of saline pretreatment on hemodynamic parameters during exercise (Fig. 3): SV (saline 64 ± 4 ml vs. placebo 60 ± 4 ml; \( P = 0.347 \)), CO (saline 9 ± 0.4 liter/min vs. placebo 8.8 ± 0.4 liter/min; \( P = 0.583 \)), SVR (saline 832.2 ± 38.5 dyn·s·cm\(^{-5}\) vs. placebo 957.2 ± 50.3 dyn·s·cm\(^{-5}\); \( P = 0.158 \)), and MAP (saline 98 ± 3 mmHg vs. placebo 104 ± 3 mmHg; \( P = 0.182 \)).

Low-frequency variability of systolic blood pressure (LF\( \text{SYS} \)), an indirect measurement of sympathetic modulation was found to be decreased following acute saline infusion compared with placebo (saline 5.20 ± 0.85 mmHg\(^2\) vs. placebo 11.06 ± 1.97 mmHg\(^2\); \( P = 0.020 \)). There was no difference in high-frequency variability of HR (HF\( \text{RRI} \)), a measure of cardiac parasympathetic tone (saline 300.64 ± 75.96 ms\(^2\) vs. placebo 209.07 ± 55.88 ms\(^2\); \( P = 0.669 \)) or baroreflex sensitivity (saline 10.11 ± 1.28 ms/mmHg vs. placebo 8.37 ± 1.06 ms/mmHg; \( P = 0.367 \)) at baseline, between treatments.

**DISCUSSION**

The main finding of this study is that an iv saline infusion given prior to exercise does not increase semirecumbent 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 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 $V_{O2peak}$ following placebo vs. saline ($r^2 = 0.008, P = 0.733$). In support of this, rapid volume expansion also does not improve $V_{O2peak}$ 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 ($HF_{RRRI}$) 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).
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 patients with POTS following placebo or iv saline infusion at baseline (0 W) prior to exercise in the semirecumbent position. Baseline stroke volume (SV) (A) and cardiac output (CO) (C) were significantly higher following saline compared with placebo. There was no difference in mean arterial pressure (MAP) (E) between study days, but systemic vascular resistance (SVR) (G) was significantly lower following saline. Hemodynamic function was also assessed during semirecumbent exercise at 75 W (a submaximal resistance reached by all patients with POTS). There were no significant differences in SV (B), CO (D), MAP (F), or SVR (H) following saline vs. placebo administration.

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
REFERENCES


