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## The Benefits of Oral Rehydration on Orthostatic Intolerance in Children with POTS

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### Abstract

**Objective:** To evaluate whether equal volumes of oral rehydration solution (ORS) or intravenous saline provide similar improvements in cardiovascular status during controlled orthostatic challenge when administered to patients with postural tachycardia syndrome (POTS) with orthostatic intolerance.

**Study design:** We studied the neurovascular response to fluid loading during orthostatic stress using lower body negative pressure (LBNP) in 10 subjects with POTS with OI and 15 controls, and on subsequent days before, and 1 hour after intravenous saline or ingestion of ORS.

**Results:** Subjects with POTS exhibited reduced tolerance ( $P < .0001$ ) to LBNP compared with controls (Orthostatic Index of  $35,715 \pm 3,469$  vs.  $93,980 \pm 7,977$ , respectively). In POTS, following ORS but not saline, cerebral blood flow velocity ( $CBF_v$ ) was significantly higher than no treatment ( $p < 0.0005$ ) at  $-45$  mmHg. Although fluid loading did not confer any advantage in controls, subjects with POTS experienced a significant improvement in orthostatic tolerance following both saline ( $100 \pm 9.7$  vs.  $134.5 \pm 17.4$ ,  $p < 0.05$ ) and ORS ( $100 \pm 9.7$  vs.  $155.6 \pm 15.7$ ,  $p < 0.001$ ) when evaluated by normalized orthostatic index ( $p < 0.001$ , compared with untreated baseline).

**Conclusion:** Maintenance of  $CBF_v$  may have resulted in improved short-term orthostatic tolerance exhibited by POTS subjects following ORS administration. ORS is a convenient, safe and effective therapy for short-term relief of OI.

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## Keywords

Reduced Orthostatic Tolerance; Oral Rehydration Solution; Intravenous Saline; Postural Tachycardia Syndrome; Lower Body Negative Pressure

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The imposition of an orthostatic stress, such as standing up, causes a rapid gravitational displacement of approximately 500–700 ml of central blood volume into the splanchnic and lower extremity vascular beds.<sup>1</sup> If uncompensated, this can result in orthostatic intolerance. Normal circulatory compensation for orthostasis occurs rapidly via the sympathetic and parasympathetic arms of the autonomic nervous system for appropriate heart rate (HR) and blood pressure (BP) control<sup>2–6</sup>. The normal baroreflex response to decreased BP involves peripheral vasoconstriction and a reflex tachycardia<sup>7,8</sup>.

Orthostatic intolerance is accompanied by signs and symptoms that can include loss of consciousness, cognitive deficits, loss of vision or hearing, lightheadedness, headache, fatigue, nausea and abdominal pain, sweating and tremulousness<sup>9</sup>. Orthostatic intolerance is commonly seen in younger patients with postural tachycardia syndrome (POTS)<sup>10,11</sup>.

Patients with POTS experience chronic orthostatic intolerance plus excessive tachycardia when upright in the absence of hypotension. Symptoms occur daily, almost always interfere with work and/or school activities, and most patients are female<sup>12–14</sup>. Excessive tachycardia is defined by an increase of HR to >120 beats per minute during a 10-minute tilt or an increase of >30 beats per minute (bpm) in adults or an increase of >40 bpm in those under 19 years<sup>15</sup>.

Although the mechanisms of POTS are heterogenous, its effects resemble well-known forms of hypovolemia with reduced systemic venous return and reduced cardiac output<sup>16–19</sup>. A reduction in total blood volume has been reported in many cases<sup>20–22</sup>. Therefore, treatment has included attempts at repletion of blood volume using various substances including fludrocortisone, tested in adults, and erythropoietin. However, a study of orthostatic intolerance in patients with chronic fatigue syndrome (CFS) showed that low-dose mineralocorticoids did not mitigate symptoms compared with placebo<sup>23</sup>. In other cases, upright POTS patients demonstrated a reduction in central blood volume due to blood volume redistribution without a reduction in total blood volume; this results in reflex sympathetic excitation, vagal withdrawal and tachycardia<sup>22,24,25</sup>. Thus, reduced orthostatic central blood volume is common to both acute and chronic orthostatic intolerance.

More direct methods have been employed to mitigate the effects of orthostasis, including the administration of intravenous saline as this should improve all forms of orthostatic intolerance by increasing central blood volume and venous return. Thus, saline may prevent syncope<sup>26</sup> and improve orthostatic intolerance and heart rate changes in POTS patients<sup>27</sup>. Enthusiasm for the use of intravenous (IV) saline is diminished because of the expense, need for repeated infusions or unacceptable risks (bruising and infection) of chronic central venous catheterization<sup>28</sup>. Aside from IV saline, alternatives such as oral salt and water have been recommended to reduce orthostatic intolerance symptoms<sup>29,30</sup>.

We investigated whether equal volumes of oral rehydration solution (ORS) or intravenous saline provide similar improvements in cardiovascular status and in orthostatic tolerance when administered to patients with orthostatic intolerance. We evaluated orthostatic tolerance using lower body negative pressure (LBNP)<sup>31–33</sup> which is a controllable form of orthostatic challenge which has been used as a reversible simulation of central hypovolemia<sup>34,35</sup>.

## Methods

To test the hypothesis that increasing total blood volume with intravenous saline or ORS improves orthostatic intolerance and cardiorespiratory properties, we performed step-wise LBNP to measure changes in cardiorespiratory properties, BP and CO at different stages LBNP (–15, –30, and –45 mmHg, each for 5 min and at –60mmHg for up to 50 min until orthostatic intolerance is achieved) to determine the threshold for orthostatic tolerance for each subject. This was repeated on 3 separate days before which either no fluids were administered, subjects drank 1 liter of ORS (World Health Organization formulation containing Na<sup>+</sup> = 90 mEq/l and glucose = saline administered over 30 minutes. The order of testing was assigned randomly. All orthostatic testing was performed 1 hour after fluid administration.

## Subject Recruitment and Classification

Healthy control subjects and patients with orthostatic intolerance, aged 15 to 29 years old were recruited. We enrolled 15 healthy control subjects and 10 with a history of orthostatic intolerance and POTS. POTS cases had chronic, day-to-day symptoms of orthostatic intolerance for at least 3 months. POTS was confirmed by duplication of these symptoms associated with an excessive increase in HR for age during a clinical 70° upright tilt test<sup>30,36</sup>. Control subjects (N=15) were all free of orthostatic intolerance based on clinical history<sup>12</sup>. No subjects were taking neurally active, vasoactive or birth control drugs. Any prior medication was discontinued for at least 2 weeks prior to participation.

## Protocol:

all experiment days began between 9–10 am in a room at 25° C. Subjects refrained from eating for at least 4 hours and eliminated caffeinated beverages for at least 12 hours prior to testing. Upon arrival, all subjects were placed in the lower body negative pressure (LBNP) chamber and tested as described below. An intravenous catheter was placed in the left antecubital vein for administration of intravenous fluids. We used a finger photoplethysmograph to assess beat-to-beat BP, EKG for heart rate and rhythm (Finometer, FMS, The Netherlands)<sup>37,38</sup>. Mean arterial pressure (MAP) was calculated from systolic BP (SBP) and diastolic BP as  $(SBP + 2 * diastolic BP) / 3$ . Cardiac output (CO), expressed as L/min, was intermittently measured using the inert gas rebreathing (Innocor, Innovision, DE) and measured continuously using the FMS ModelFlow arterial pulse wave algorithm. Transcranial Doppler ultrasound was used to assess changes in middle cerebral artery blood flow velocity (CBF<sub>v</sub>) by insonation at a depth of 5–6 cm using a 2-MHz probe (Neurovision; Multigon, Yonkers, NY). Blood pressure, EKG, TCD, ModelFlow and cardiac output were acquired continuously to computer through an A/D conversion system using

custom computer software. Following instrumentation, all subjects rested for 30-minute while supine. After this rest period, we acquired 10 minutes of baseline cardiorespiratory properties.

### **LBNP:**

Subjects are placed supine with their lower body (legs and hips up to the iliac crest), within a sealed airtight chamber– the LBNP tank. A snug rubber diaphragm makes an air-tight seal without compressing the abdomen. Suction is provided by a vacuum pump which rapidly produces desired negative pressure and controlled with a variable autotransformer calibrated against an electronic manometer. Graded LBNP is applied sequentially at  $-15$ ,  $-30$ , and  $-45$  mmHg, for 5 min at each stage and at  $-60$ mmHg for up to 50 min until the threshold for orthostatic intolerance is achieved. BP by oscillometry and CO by ModelFlow was measured for 2 min at every stage of lower LBNP and for 2 min every 10 min during  $-60$ mmHg LBNP, along with continuous measurements of HR, BP, respirations, IPG regional blood flow and changes in regional blood volume.

*A priori* stopping criteria (end test) were signs and symptoms of presyncope defined as a decrease in systolic BP to 80 mmHg; a decrease in systolic BP to 90 mmHg associated with orthostatic intolerance symptoms of lightheadedness, pallor, hyperpnea, nausea, sweating, or diaphoresis; or progressive symptoms of orthostatic intolerance accompanied by a request to discontinue the test. This strategy has produced orthostatic intolerance in healthy volunteers and permits nearly instant recovery by release of negative pressure<sup>32</sup>.

### **Data Collection and Analyses:**

Multiple variables (eg, heart rate, blood pressure, cardiac output, cerebral blood flow velocity) were collected while supine and during LBNP. The total response to orthostatic stress for each subject, or orthostatic index (also referred to as the cumulative stress index), was calculated as the product of LBNP and time it took to reach the threshold of orthostatic intolerance<sup>17,32</sup>. Because all controls and POTS were able to tolerate some exposure to  $-45$  mmHg of LBNP, analysis of BP, CO and  $CBF_v$  was performed using data collected for a 2-minute period prior to stopping at the end of exposure to this pressure. Thus, data shown as  $-45$  mmHg is the response following 10 minutes of supine rest and the cumulative exposure to 5 minutes at  $-15$ ,  $-30$  and at least 2 minutes at  $-45$  mmHg pressure. These results are depicted graphically as “ $-45$  mmHg.”

To investigate the response of each dependent variable during LBNP, we used a linear mixed model regression approach to account for the within-subject correlation across interventions and pressure challenge. We used a hierarchical approach to determine which post-hoc analyses were conducted. For each model, a 3-way interaction term (group x treatment x pressure) was evaluated, along with all lower-level interaction terms. If the 3-way interaction term was significant, then all post-hoc comparisons of interest were examined. If the 3-way interaction was not significant, then it was removed and the 2-way interaction terms were evaluated. Significant 2-way interaction terms subsequently guided post-hoc testing. Within each model, post-hoc testing was adjusted for multiple comparisons using the Sidak approach.

The Institutional Review Board of New York Medical College reviewed and approved this protocol. Each subject received a detailed description of all protocols and was given an opportunity to have questions answered. Signed informed consent was obtained from all adult participants; those younger than 18 assented to participate and their parent or legal guardian signed an informed consent.

## RESULTS:

The demographics of the subjects are shown in the Table. The results are reported as Mean  $\pm$  SEM. There were no significant differences between controls and POTS in height, weight or body mass index, however POTS were younger than controls.

We compared the responses to the orthostatic challenge imposed by LBNP in the absence of supplemental fluid administration with that following oral rehydration solution ingestion and intravenous fluid infusion. Figure 1 shows these responses in a representative patient with orthostatic intolerance. The top panel shows the response on a day when no fluid was given (No Fluid) where fainting occurred while a  $-30$  mmHg negative pressure was generated by LBNP. Arrows are placed at times of transition in the top panel for convenience;  $-45$  or  $-60$  mmHg pressures were not achieved for this patient during the No Fluid day. Both saline administration (Saline) and oral rehydration solution (ORS) increased initial blood pressure and prolonged the time to faint. With saline, the patient fainted at the transition to  $-60$  mmHg. After ORS the patient shown fainted subsequent to the transition to  $-60$  mmHg as well.

Next we determined the orthostatic tolerance of controls and POTS subjects and expressed this as the Orthostatic Index (the sum of the product of LBNP negative pressure and time at each pressure required to reach the threshold of orthostatic intolerance). As expected, POTS participants with a history of OI, exhibited a significantly reduced tolerance ( $p < 0.001$ ) to LBNP compared with controls (Orthostatic Index of  $35,715 \pm 3,469$  vs  $93,980 \pm 7,977$ , respectively). POTS subjects were therefore significantly more susceptible to the influence an imposed orthostatic challenge than healthy controls.

We then evaluated the cardiovascular and circulatory changes that accompanied exposure to the orthostatic challenge imposed by LBNP while untreated, following infusion of 1 liter of saline, or following ingestion of 1 liter of ORS. Heart rate increased significantly upon exposure to  $-45$  mmHg which was similar for both Control and POTS, whether no treatment, saline or ORS were administered ( $p = 0.38$ ). On average, there was a similar significant ( $p < 0.001$ ) increase for control ( $59.3 \pm 1.9$  vs.  $73.6 \pm 3.4$  bpm,  $n=15$ ) and POTS ( $67.5 \pm 4.3$  vs.  $80.6 \pm 6.0$  bpm,  $n=10$ ) comparing no orthostatic challenge (normal atmospheric pressure - baseline) with  $-45$  mmHg pressure, regardless of group or treatment.

When evaluating the changes in MAP resulting from the imposed orthostatic challenge, a significant 3-way interaction emerged ( $p = 0.016$ ). Post-hoc testing indicated that in controls exposed to  $-45$  mmHg, MAP following IV saline, although higher than baseline, was not significantly increased ( $p = 0.055$ ). However, in controls, only ORS significantly increased MAP ( $p < 0.001$ ). Similar treatment and pressure effects were not evident in POTS subjects.

Measurements indicated that the CO of POTS subjects was significantly reduced compared with controls ( $4.4 \pm 0.3$  vs.  $5.6 \pm 0.3$  respectively,  $p < 0.001$ ). For CO, shown in Figure 2, the 3-way interaction was not significant ( $p = 0.85$ ), however, a significant 2-way interaction was calculated for group by treatment ( $p < 0.005$ ), which was independent of pressure. Post-hoc testing indicated that for POTS, CO was significantly higher following ORS, compared with no treatment (No Tx,  $p < 0.05$ ), both at baseline and  $-45$  mmHg and saline had no significant effect. Treatment effects for controls were not significantly different.

$CBF_v$  at baseline in controls and POTS was similar ( $76.6 \pm 2.5$  cm/sec vs.  $70.9 \pm 2.7$  cm/sec, respectively ( $p = 0.12$ )). To appreciate the effect of fluid administration comparing control with POTS,  $CBF_v$  was normalized to values measured while supine in the absence of LBNP. Figure 3 shows that in controls, normalized  $CBF_v$  was not significantly reduced at  $-45$  mmHg, nor did fluid administration result in any significant change. Interestingly however, a significant 2-way interaction was apparent for study group by treatments ( $p < 0.0005$ ) as POTS responded differently than controls regardless of pressure. Post-hoc evaluation indicated that in POTS,  $CBF_v$  following ORS was significantly higher than No TX ( $p < 0.0005$ ) as the normalized  $CBF_v$  for POTS was about 13 percent higher. This effect was independent of pressure.

To compare the influence of fluid administration (intravenous vs. oral) on the orthostatic challenge imposed by LBNP, we normalized the orthostatic intolerance for each group to that measured without treatment (Untreated) compared with I.V. saline or ORS. Figure 4 shows that although neither saline nor ORS increased orthostatic tolerance in untreated controls ( $p = 0.46$ ,  $N = 15$ ), both I.V. saline and ORS significantly improved orthostatic tolerance ( $p < 0.05$  and  $p < 0.001$ , respectively,  $N = 10$ ) in POTS subjects. Thus ORS, in contrast to saline, afforded a beneficial effect from the imposed orthostatic stress.

## DISCUSSION:

Previous studies have shown that infusion of IV saline improves orthostatic tolerance and autonomic symptoms in patients with orthostatic intolerance<sup>26,27,39,40</sup>. Although there have been reports describing improvement of qualitative outcomes associated with syncope with long-term ORS usage<sup>41,42</sup>, the quantitative effects of ORS on orthostatic tolerance have not been reported. In this study, orthostatic tolerance was evaluated using LBNP which we have used previously to induce orthostatic stress<sup>32,43</sup>. LBNP, standing and head-up tilt (HUT) cause many of the changes of neurovascular physiology which can result in signs and symptoms of orthostatic intolerance. For example, both HUT and LBNP produce central hypovolemia and comparable unloading of the cardiopulmonary and arterial baroreceptors<sup>32,33,44,45</sup>. It has also been shown that cerebral hemodynamic responses to LBNP to  $-45$  mmHg are similar to that which accompany blood loss up to 1,000 ml<sup>46</sup>.

The rapid beneficial effect of ORS may be caused by increasing blood volume given its efficacy in enhancing consistent and nearly complete fluid and salt absorption through the intestinal  $Na^+$ -glucose co-transport (GLUT2, symporter) carrier. This effective enteral salt and water transport system has been employed to combat the catastrophic fluid loss of infectious diarrhea<sup>47</sup>. ORS in POTS may temporarily correct the central hypovolemia that

has been reported in many subsets of patients with orthostatic intolerance and various types of syncope<sup>10,18,48</sup>. This may have resulted in part from the significantly higher CO that was measured following ORS, but not saline, in POTS patients.

In addition to facilitating the absorption of Na<sup>+</sup> and water, the ability of ORS to mitigate orthostatic intolerance in susceptible subjects may also be due in part to the gastropressor effect that occurs through sympathetic nervous system activation mediated through gut or portal osmoreceptors in the afferent signaling response to oral water<sup>49</sup>. The gastropressor response is a control mechanism that can lead to a marked increase in blood pressure after water, but not saline ingestion. An acute response peaks within 20 to 40 minutes and resolves within 60 to 90 minutes. In the current study, although there was a similar increase in HR with orthostatic challenge in both controls and POTS independent of fluid supplementation, ingestion of ORS only caused an increase in MAP in control subjects but not in POTS, suggesting that they are less capable of mounting a functional pressor response.

Several studies have demonstrated the acute benefits of supplemental intravenous hydration in improving orthostatic intolerance, showing that hemodynamic and symptomatic tolerance to repeated tilt-table testing can be restored following acute IV administration of saline<sup>26,50</sup>. Although there are reports of benefit to chronic or repeated saline administration, potential benefits must be considered within the context of the associated risks of infection, thrombi and the difficulty of administration<sup>28</sup>.

Orthostatic intolerance is often accompanied by loss of cognition referred to as brain fog. Standing results in gravitational blood transfer, reducing central and increasing splanchnic vasculature and lower extremity blood volumes<sup>1,14,38</sup>. There is often a period of initial orthostatic hypotension during which BP and CBF<sub>v</sub> transiently decrease, sometimes markedly, reaching their nadir 10 to 20 s after standing. A reflex tachycardia results, and BP and CBF<sub>v</sub> are restored within 30 to 60 s but CBF<sub>v</sub> recovers to somewhat less than supine<sup>30,51</sup>. When the effects of low CBF<sub>v</sub> on CNS function were examined using graded incremental head-up tilt, and executive working memory evaluation using N-Back testing as an objective measure of cognitive impairment, executive memory function was progressively impaired in POTS patients with increasing angle of tilt. Thus increasing orthostatic stress combined with a cognitive challenge impairs the neurocognitive abilities of working memory, accuracy and information processing in CFS/POTS<sup>52</sup>.

Although measurements of cognitive ability were not performed in this study, preservation of CBF<sub>v</sub> likely supported improved cognitive abilities in the POTS subjects. In this study using LBNP as a controlled orthostatic stressor, although POTS had about 30% of the orthostatic tolerance of controls, normalized CBF<sub>v</sub> was best preserved by ORS in the POTS subjects and may have contributed in part to the significant increase in orthostatic tolerance afforded by this treatment.

Giving ORS to POTS patients produced effective, short-term mitigation of their orthostatic intolerance, presumably by facilitating rapid repletion of salt and water. Within the short time course of this investigation, ORS was at least as effective in increasing orthostatic

tolerance than IV saline. This supports the use of ORS as an easy, safe, practical therapy to mitigate symptoms associated with orthostatic intolerance. Because ORS is inexpensive, safe and easily administered, it may be considered as an effective alternative to IV saline for rapid resolution of symptoms associated with orthostatic intolerance.

This study did not include evaluation of cognitive abilities during LBNP which would have provided additional information regarding orthostatic intolerance CBFv and executive function. In addition, we were not able to measure changes in blood volume during LBNP in the setting of fluid supplementation, either from saline or ORS. Obtaining subjective information about symptoms and other indices of wellness during imposition of LBNP, while desirable, would have been difficult to obtain. In addition, because LBNP imposes a negative pressure below the level of the iliac crest and is not gravitational, this orthostatic challenge does not replicate that of upright posture.

We only investigated the short-term use of fluids in subjects with orthostatic intolerance. Further investigations of long-term regular use of ORS are therefore warranted.

This study was also limited by the small number of participants. Although many physiological responses appear to have been influenced by the imposed maneuvers, not all reached statistical significance. It would have therefore been beneficial to compare the IV saline and the ORS arms in a larger cohort of age matched controls and patients.

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## ABBREVIATIONS

<b>BP</b>	blood pressure
<b>CBF<sub>v</sub></b>	cerebral blood flow velocity
<b>CFS</b>	chronic fatigue syndrome
<b>CO</b>	cardiac output
<b>HR</b>	heart rate
<b>HUT</b>	head up tilt
<b>IV</b>	intravenous
<b>LBNP</b>	lower body negative pressure
<b>MAP</b>	mean arterial pressure
<b>ORS</b>	oral rehydration solution
<b>POTS</b>	postural tachycardia syndrome

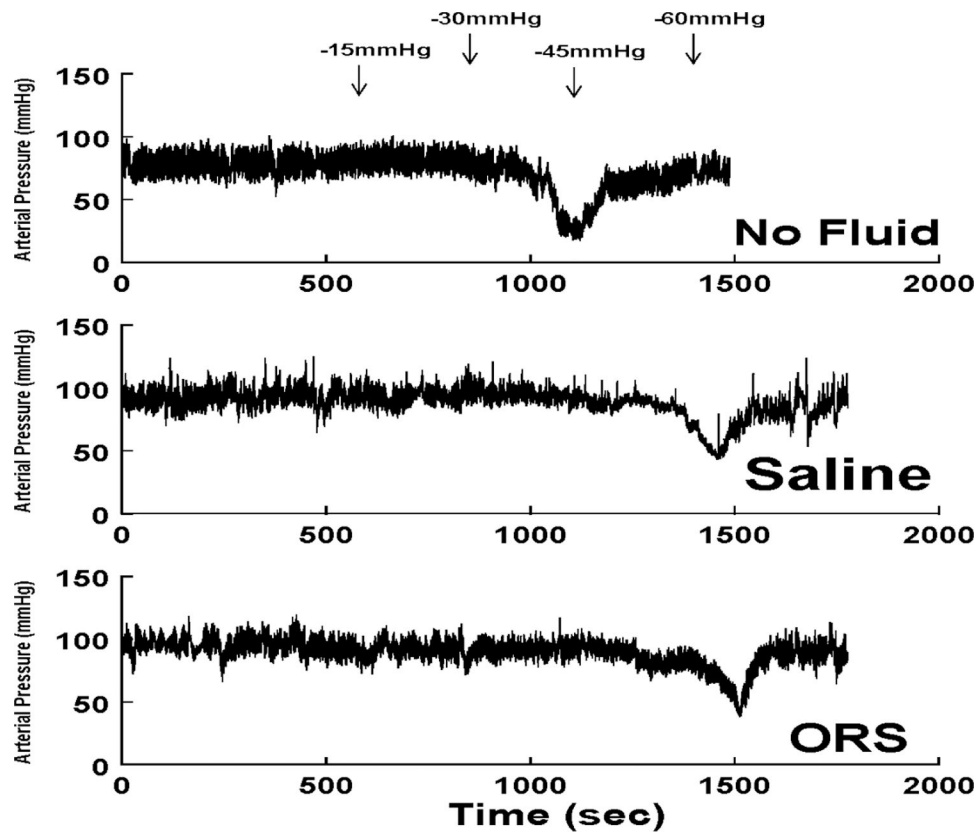


**SBP**                      systolic blood pressure**Reference List**

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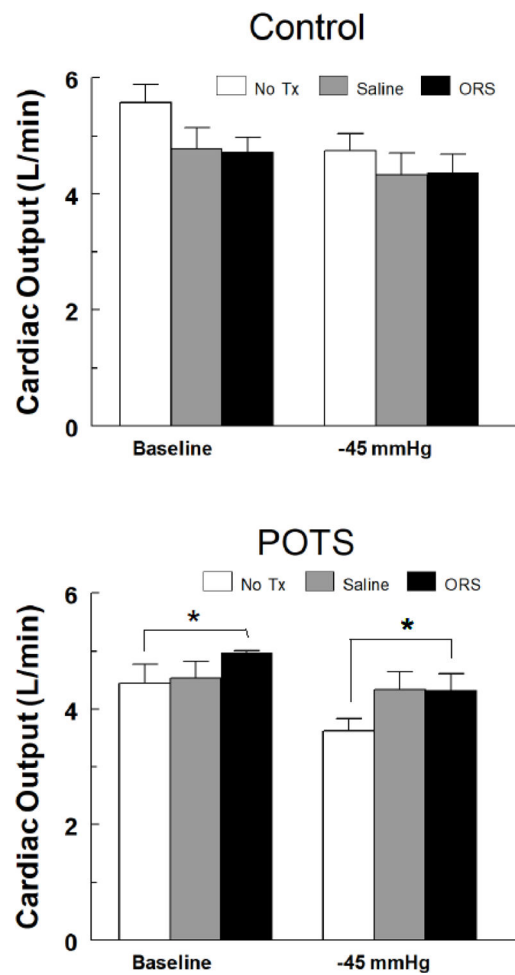
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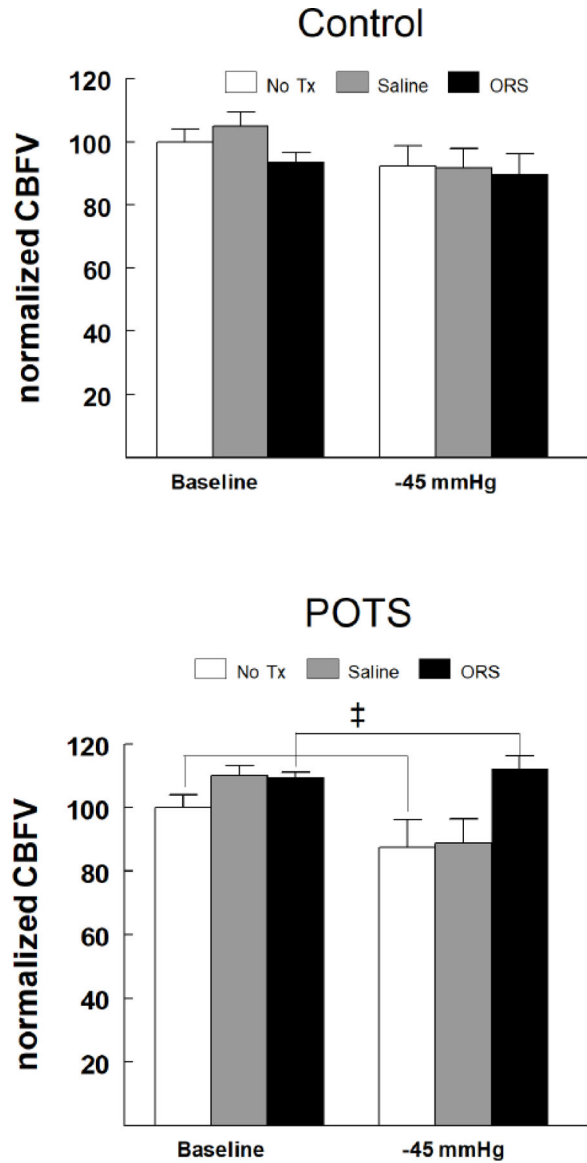


**Figure 1.**

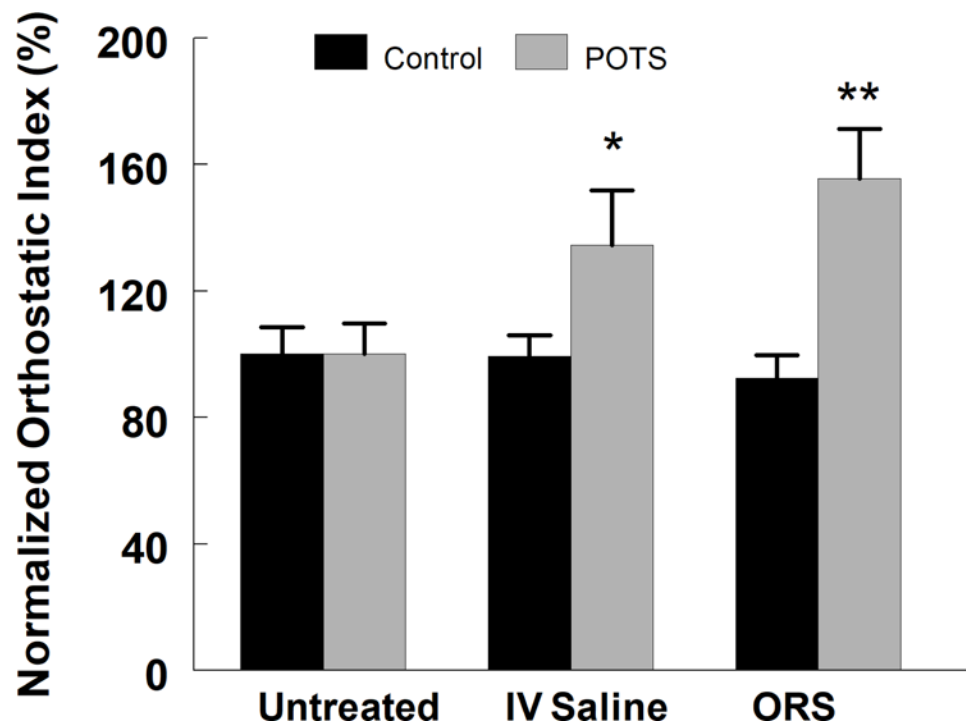
The response of a representative patient with OI to the imposition of a controlled orthostatic challenge using LBNP. The top panel shows that in the absence of supplemental fluid administration (No Fluid), presyncope occurred during exposure to  $-30$  mmHg negative pressure. Following IV saline (Saline, middle panel), and after ingestion of oral rehydration solution (ORS, lower panel), enhanced orthostatic tolerance was achieved as presyncope occurred during exposure to  $-60$  mmHg negative pressure.



**Figure 2.** Changes in cardiac output (CO in L/min) in control (top panel) and POTS patients with OI (bottom panel) during imposition of a controlled orthostatic challenge using LBNP following no treatment (No TX – white bars), IV saline (Saline – gray bars) and ingestion of oral rehydration solution (ORS – black bars). Treatment effects for controls were not significantly different. For POTS, CO was significantly higher following ORS, compared with no treatment (\* = No Tx,  $p < 0.05$ ), both at baseline and  $-45$  mmHg and saline had no significant effect.



**Figure 3.** Changes in normalized cerebral blood flow velocity (normalizedCBF<sub>v</sub>) in control (top panel) and POTS patients with OI (bottom panel) during imposition of a controlled orthostatic challenge using LBNP following no treatment (No TX – white bars), IV saline (Saline – gray bars) and ingestion of oral rehydration solution (ORS – black bars). Because there was no pressure effect, the comparisons reflect the combined effect (i.e., the weighted average) of the CBV<sub>v</sub> in the ORS group vs. No Tx. In controls, normalized CBF<sub>v</sub> was not significantly reduced at –45 mmHg, nor did fluid administration result in any significant change. In POTS, CBF<sub>v</sub> following ORS was significantly higher than No TX (‡ = p<0.0005), which was independent of pressure.



**Figure 4.** Changes in normalized orthostatic index (% of that measured without treatment in control (black bars) and POTS patients with OI (gray bars) measured following no treatment (Untreated), intravenous saline (IV Saline) and ingestion of oral rehydration solution (ORS). Neither saline nor ORS increased orthostatic tolerance in untreated controls ( $p=0.46$ ,  $N=15$ ); both I.V. saline and ORS significantly improved orthostatic tolerance ( $* = p<0.05$  and  $** = p<0.001$ , respectively,  $N=10$ ) in POTS subjects.

**Table 1.**

## Demographics of Study Subjects

	Age	Height	Weight	BMI (Kg/m <sup>2</sup> )	M/F
<b>Control (n=15)</b>	24.7±0.5	171.1±2.1	70.0±3.4	23.7±0.7	3/12
<b>POTS (n=10)</b>	19.5±1.4	168.6±3.0	62.6±4.2	22.0±1.2	1/9

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