



The Benefits of Oral Rehydration on Orthostatic Intolerance in Children with Postural Tachycardia Syndrome

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Objective To evaluate whether equal volumes of oral rehydration solution (ORS) or intravenous (IV) saline provide similar improvements in cardiovascular status during controlled orthostatic challenge when administered to subjects 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 orthostatic intolerance and 15 controls, and on subsequent days before and 1 hour after IV saline infusion or ingestion of ORS.

Results Subjects with POTS exhibited reduced tolerance to LBNP ($P < .0001$) compared with controls (Orthostatic Index of 35.715 ± 3469 vs 93.980 ± 7977 , respectively). In POTS, following ORS but not saline infusion, cerebral blood flow velocity (CBF_v) was significantly higher than that with no treatment, at -45 mm Hg ($P < .0005$). Although fluid loading did not confer any advantage in controls, subjects with POTS experienced a significant improvement in orthostatic tolerance following both saline infusion (100 ± 9.7 vs 134.5 ± 17.4 ; $P < .05$) and ORS (100 ± 9.7 vs 155.6 ± 15.7 ; $P < .001$) when evaluated by normalized orthostatic index ($P < .001$, compared with untreated baseline).

Conclusions Maintenance of CBF_v may have resulted in the improved short-term orthostatic tolerance exhibited by the subjects with POTS following ORS administration. ORS is a convenient, safe, and effective therapy for short-term relief of orthostatic intolerance. (*J Pediatr* 2019;214:96-102).

The imposition of an orthostatic stress, such as standing, causes a rapid gravitational displacement of approximately 500-700 mL of central blood volume into the splanchnic and lower extremity vascular beds.¹ 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.²⁻⁶ The normal baroreflex response to decreased BP involves peripheral vasoconstriction and reflex tachycardia.^{7,8}

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

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

Although the mechanisms of POTS are heterogeneous, its effects resemble well-known forms of hypovolemia, with reduced systemic venous return and reduced cardiac output (CO).¹⁶⁻¹⁹ A reduction in total blood volume has been reported in many cases.²⁰⁻²² 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 showed that low-dose mineralocorticoids did not mitigate symptoms compared with placebo.²³ In other cases, upright patients with POTS 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.^{22,24,25} Thus, reduced

BP	Blood pressure
CBF_v	Cerebral blood flow velocity
CO	Cardiac output
HR	Heart rate
HUT	Head-up tilt
IV	Intravenous
LBNP	Lower body negative pressure
MAP	Mean arterial pressure
ORS	Oral rehydration solution
POTS	Postural tachycardia syndrome
SBP	Systolic blood pressure

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Funded by the National Institute of Neurologic Disorders and Stroke (R21 NS 094644), the National Heart Lung and Blood Institute (R01 HL 112736 and R01 HL 134674), and the National Institutes of Health. The authors declare no conflicts of interest.

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<https://doi.org/10.1016/j.jpeds.2019.07.041>

orthostatic central blood volume is common in both acute and chronic orthostatic intolerance.

More direct methods have been used to mitigate the effects of orthostasis, including the administration of intravenous (IV) saline solution, which can improve all forms of orthostatic intolerance by increasing central blood volume and venous return. Thus, saline may prevent syncope²⁶ and improve orthostatic intolerance and HR changes in patients with POTS.²⁷ However, enthusiasm for the use of IV saline is diminished because of the expense, need for repeated infusions, and unacceptable risks (eg, bruising, infection) of chronic central venous catheterization.²⁸ Alternatives to IV saline, such as oral salt and water, have been recommended to reduce orthostatic intolerance symptoms.^{29,30}

We investigated whether equal volumes of oral rehydration solution (ORS) or IV 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)³¹⁻³³ which is a controllable form of orthostatic challenge which has been used as a reversible simulation of central hypovolemia.^{34,35}

Methods

To test the hypothesis that increasing total blood volume with IV saline or ORS improves orthostatic intolerance and cardiorespiratory properties, we performed stepwise LBNP to measure changes in cardiorespiratory properties, BP, and CO at different stages of LBNP (−15, −30, and −45 mm Hg, each for 5 minutes, and at −60 mm Hg for up to 50 minutes 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 L of ORS (World Health Organization formulation containing $\text{Na}^+ = 90$ mEq/L and glucose = 111 mmol/L with a total osmolality of 311) over 30 minutes or had 1 L of IV normal 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 subjects with orthostatic intolerance, aged 15-29 years were recruited. We enrolled 15 healthy control subjects and 10 with a history of orthostatic intolerance and POTS. POTS cases had chronic, daily 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.^{30,36} Control subjects ($n = 15$) were all free of orthostatic intolerance based on clinical history.¹² No subjects were taking neurally active, vasoactive, or birth control drugs. Any previous medication was discontinued for at least 2 weeks before participation.

Study Protocol

All experiments were initiated from 9 a.m. to 10 a.m. in a room at 25 °C. Subjects refrained from eating for at least 4 hours and eliminated caffeinated beverages for at least 12 hours before testing. On arrival, all subjects were placed in the LBNP chamber and tested as described below. An IV catheter was placed in the left antecubital vein for administration of IV fluids. Finger photoplethysmography (Finometer; Finapres Medical Systems, Enschede, The Netherlands) was used to assess beat-to-beat BP, ECG for HR, and rhythm.^{37,38}

Mean arterial pressure (MAP) was calculated from systolic BP (SBP) and diastolic BP as $(\text{SBP} + 2 \times \text{diastolic BP})/3$. CO, expressed as liters/minute, was measured intermittently using inert gas rebreathing (Innocor; Innovision, Glamsbjerg, Denmark) and measured continuously using the ModelFlow arterial pulse wave algorithm (Finapres Medical Systems). Transcranial Doppler ultrasound was used to assess changes in middle cerebral artery blood flow velocity (CBF_v) by insonation at a depth of 5-6 cm using a 2-MHz probe (Neurovision; Multigon, Yonkers, New York). BP, ECG, transcranial Doppler, ModelFlow, and CO data were acquired continuously through an A/D conversion system using custom computer software. Following instrumentation, all subjects rested for 30-minute while supine. After this rest period, 10 minutes of baseline cardiorespiratory parameters were acquired.

For LBNP, the subjects were placed supine with the lower body (legs and hips up to the iliac crest) within a sealed airtight chamber, the LBNP tank. A snug rubber diaphragm made an airtight seal without compressing the abdomen. Suction was provided by a vacuum pump, which rapidly produced the desired negative pressure, controlled with a variable autotransformer calibrated against an electronic manometer. Graded LBNP was applied sequentially at −15, −30, and −45 mm Hg for 5 minutes at each stage and at −60 mm Hg for up to 50 minutes until the threshold for orthostatic intolerance was achieved. BP by oscillometry and CO by ModelFlow were measured for 2 minutes at each stage of lower LBNP and for 2 minutes every 10 minutes during −60 mm Hg LBNP, along with continuous measurements of HR, BP, respirations, regional blood flow (by impedance plethysmography), and changes in regional blood volume.

A priori stopping criteria (end test) were signs and symptoms of presyncope, defined as a decrease in SBP to 80 mm Hg; a decrease in SBP to 90 mm Hg associated with symptoms of orthostatic intolerance, such as 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 through release of negative pressure.³²

Data Collection and Analyses

Multiple variables (eg, HR, BP, CO, CBF_v) were collected with the subject supine and during LBNP. The total response to orthostatic stress for each subject, or the orthostatic index (also referred to as the cumulative stress index), was

calculated as the product of LBNP and the time it took to reach the threshold of orthostatic intolerance.^{17,32} Because all controls and subjects with POTS were able to tolerate some exposure to -45 mm Hg of LBNP, BP, CO, and CBF_v were analyzed using data collected over a 2-minute period before stopping at the cessation of exposure to this pressure. Thus, data shown as -45 mmHg represent the response after 10 minutes of supine rest and the cumulative exposure to 5 minutes at -15 , -30 , and at least 2 minutes at -45 mm Hg pressure. These results are depicted graphically as -45 mm Hg.

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 challenges. We used a hierarchical approach to determine which post hoc analyses were conducted. For each model, a 3-way interaction term (group \times treatment \times 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 the study protocol. Each subject received a detailed description of the study protocol and was given an opportunity to have questions answered. Signed informed consent was obtained from all adult participants; those aged <18 years assented to participate, and a parent or legal guardian provided signed informed consent.

Results

Demographic data of the study subjects are shown in the **Table**. The results are reported as mean \pm SEM. There were no significant differences between controls and the subjects with POTS in height, weight, or body mass index; however, the subjects with POTS were younger than the controls.

We compared the responses to the orthostatic challenge imposed by LBNP in the absence of supplemental fluid administration with that after ORS ingestion and IV fluid infusion. **Figure 1** shows these responses in a representative subject with orthostatic intolerance. The top panel shows the response on a day when no fluid was given (ie, no fluid), with fainting occurring while a negative pressure of

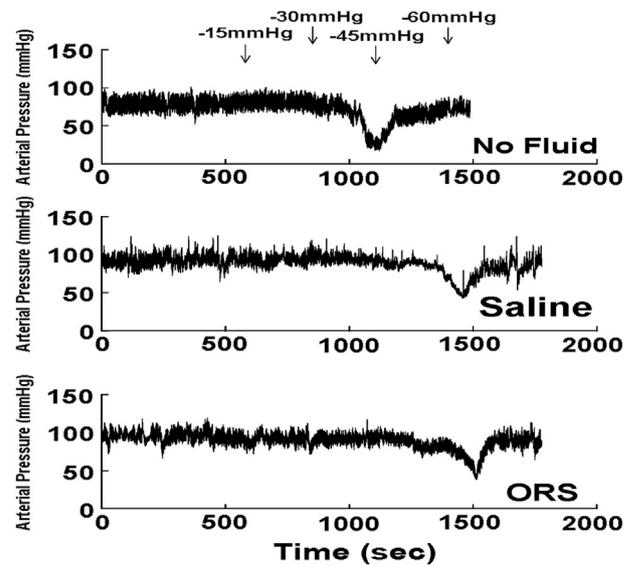


Figure 1. The response of a representative subject with orthostatic intolerance to the imposition of a controlled orthostatic challenge using LBNP. The *top panel* shows that in the absence of supplemental fluid administration (no fluid), presyncope occurred during exposure to -30 mm Hg negative pressure. Following IV saline (*middle panel*), and after ingestion of ORS (*lower panel*), enhanced orthostatic tolerance was achieved as presyncope occurred during exposure to -60 mm Hg negative pressure.

-30 mm Hg was generated by LBNP. Arrows are placed at times of transition in the top panel for convenience; -45 or -60 mm Hg pressures were not achieved for this subject during the no fluid day. Both saline infusion and ORS administration increased the initial BP and prolonged the time to fainting. With saline, the subjects fainted at the transition to -60 mm Hg. After ORS, the subjects also fainted after the transition to -60 mm Hg.

We next determined the orthostatic tolerance of controls and subjects with POTS and expressed this as the orthostatic index (ie, the sum of the product of LBNP negative pressure and time at each pressure required to reach the threshold of orthostatic intolerance). As expected, subjects with POTS with a history of orthostatic intolerance exhibited significantly reduced tolerance ($P < .001$) to LBNP compared with controls (orthostatic index of $35\,715 \pm 3469$ vs $93\,980 \pm 7977$, respectively). Thus, the subjects with POTS were significantly more susceptible to the influence of an imposed orthostatic challenge compared with healthy controls.

Table. Demographic data of the study subjects

Group	Age, y, mean \pm SD	Height, cm, mean \pm SD	Weight, kg, mean \pm SD	Body mass index, kg/m^2 , mean \pm SD	Males/females, n
Controls (n = 15)	24.7 \pm 0.5	171.1 \pm 2.1	70.0 \pm 3.4	23.7 \pm 0.7	3/12
POTS (n = 10)	19.5 \pm 1.4	168.6 \pm 3.0	62.6 \pm 4.2	22.0 \pm 1.2	1/9

We then evaluated the cardiovascular and circulatory changes that accompanied exposure to the orthostatic challenge imposed by LBNP while untreated, following infusion of 1 L of saline, or following ingestion of 1 L of ORS. HR increased significantly on exposure to -45 mm Hg to a similar degree in both controls and subjects with POTS, whether no treatment, saline, or ORS was administered ($P = .38$). On average, there was a similar significant ($P < .001$) increase in controls (59.3 ± 1.9 bpm vs 73.6 ± 3.4 bpm; $n = 15$) and subjects with POTS (67.5 ± 4.3 bpm vs 80.6 ± 6.0 bpm; $n = 10$) comparing no orthostatic challenge (normal atmospheric pressure - baseline) with -45 mm Hg pressure, irrespective of group or treatment.

Evaluation of the changes in MAP resulting from the imposed orthostatic challenge showed a significant 3-way interaction ($P = .016$). Post hoc testing indicated that in controls exposed to -45 mm Hg, MAP following IV saline infusion, although higher than baseline, was not significantly increased ($P = .055$). In controls, only ORS administration significantly increased MAP ($P < .001$). Similar treatment and pressure effects were not evident in the subjects with POTS.

Measurements demonstrated significantly lower CO in subjects with POTS compared with controls (4.4 ± 0.3 vs 5.6 ± 0.3 ; $P < .001$). For CO, the 3-way interaction was not significant ($P = .85$); however, a significant 2-way interaction was calculated for group by treatment ($P < .005$), which was independent of pressure (Figure 2). Post hoc testing indicated that in the subjects with POTS, CO was significantly higher following ORS administration compared with no treatment ($P < .05$), both at baseline and at -45 mm Hg, and saline infusion had no significant effect. Treatment effects in controls were not significantly different.

CBF_v at baseline was similar in the controls and subjects with POTS (76.6 ± 2.5 cm/seconds vs 70.9 ± 2.7 cm/seconds; $P = .12$). To appreciate the effect of fluid administration between controls and subjects with POTS, CBF_v was normalized to values measured with the subjects supine in the absence of LBNP. In controls, normalized CBF_v was not significantly reduced at -45 mm Hg, and fluid administration did not produce any significant change (Figure 3). Interestingly however, a significant 2-way interaction was apparent for study group by treatment ($P < .0005$), with subjects with POTS responding differently than controls regardless of pressure. Post hoc evaluation indicated that in subjects with POTS, normalized CBF_v was significantly higher after ORS administration compared with no treatment (approximately 13% higher; $P < .0005$). This effect was independent of pressure.

To compare the influence of fluid administration (IV vs oral) on the orthostatic challenge imposed by LBNP, we normalized the orthostatic index for each group to that measured without treatment compared with IV saline or ORS. Figure 4 shows that although neither saline nor ORS increased orthostatic tolerance in untreated controls ($P = .46$; $n = 15$), both IV saline and ORS significantly improved orthostatic tolerance ($P < .05$ and $< .001$,

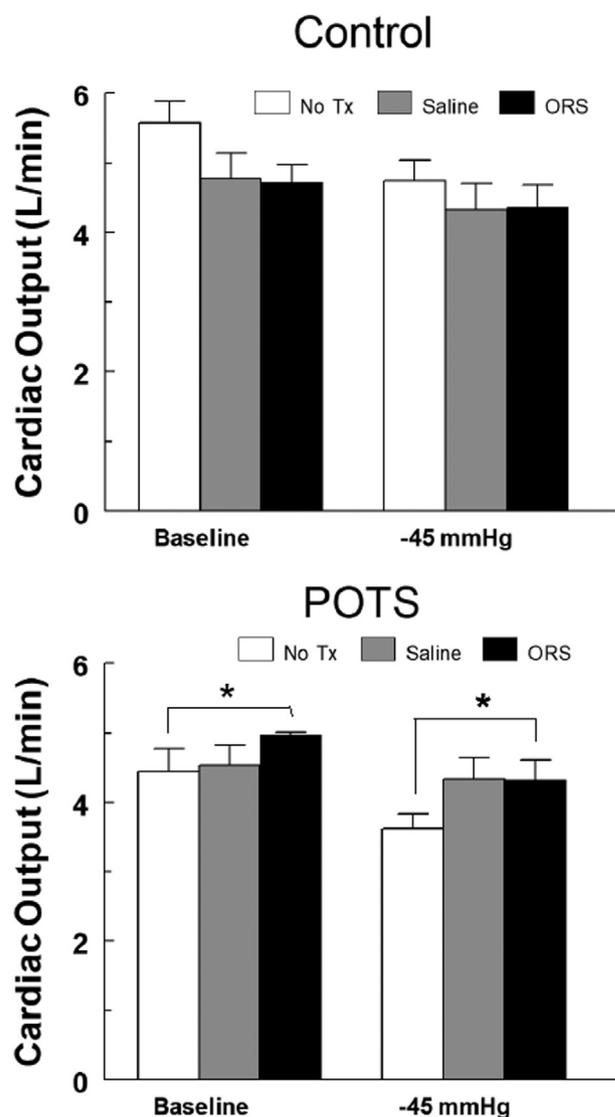


Figure 2. Changes in CO (in L/min) in controls (top panel) and subjects with POTS with orthostatic intolerance (bottom panel) during imposition of a controlled orthostatic challenge using LBNP following no treatment (No Tx; white bars), IV saline (gray bars) and ingestion of ORS (black bars). Treatment effects for controls were not significantly different. For the subjects with POTS, CO was significantly higher following ORS compared with no treatment (*No Tx; $P < .05$), both at baseline and at -45 mm Hg, and saline had no significant effect.

respectively; $n = 10$) in subjects with POTS. Thus, ORS, similar to IV 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 subjects with orthostatic intolerance.^{26,27,39,40} Although there

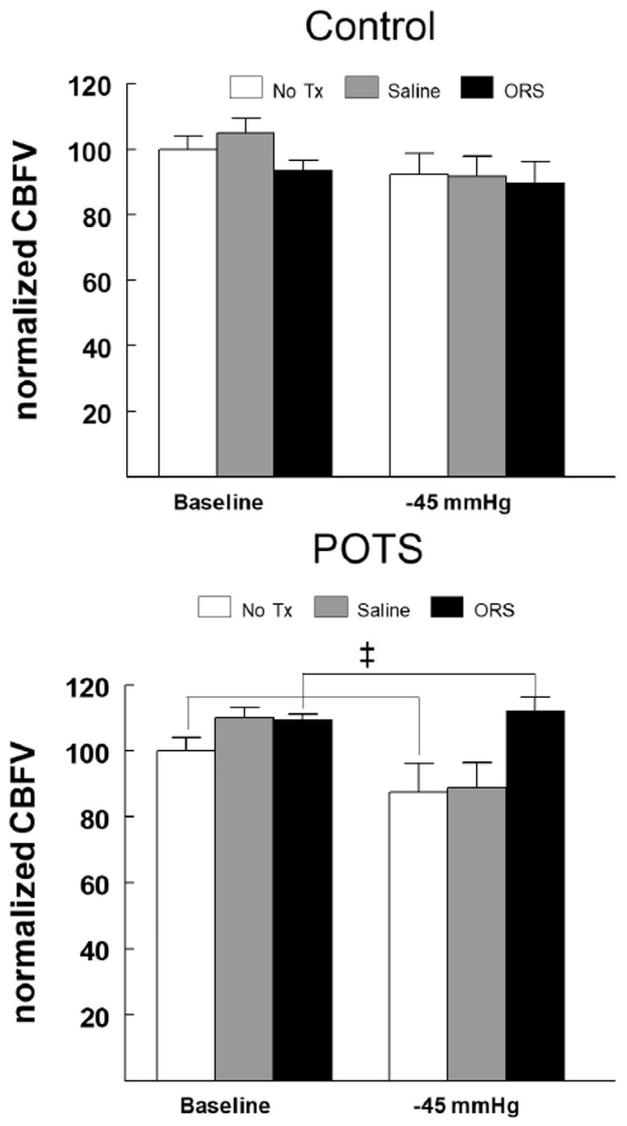


Figure 3. Changes in normalized CBF_v in controls (*top panel*) and subjects with POTS with orthostatic intolerance (*bottom panel*) during imposition of a controlled orthostatic challenge using LBNP following no treatment (No TX, *white bars*), infusion of IV saline (*gray bars*), and ingestion of ORS (*black bars*). Because there was no pressure effect, the comparisons reflect the combined effect (ie, weighted average) of the CBF_v in the ORS group vs the no treatment group. In controls, normalized CBF_v was not significantly reduced at -45 mm Hg, and fluid administration did not produce any significant change. In the subjects with POTS, CBF_v following ORS was significantly higher compared with no treatment ($^{\ddagger}P < .0005$), which was independent of pressure.

have been reports describing improvement of qualitative outcomes associated with syncope with long-term ORS use,^{41,42} 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.^{32,43} LBNP, standing, and head-up tilt (HUT) cause

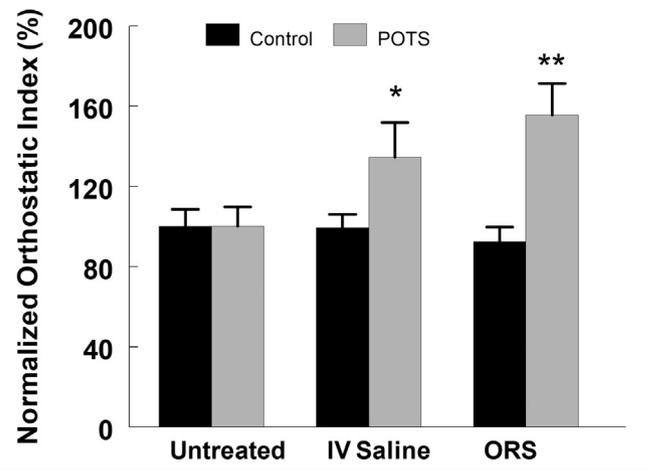


Figure 4. Changes in normalized orthostatic index (% of that measured without treatment in control (*black bars*) and subjects with POTS with orthostatic intolerance (*gray bars*) measured following no treatment (Untreated), after infusion of IV saline, and after ingestion of ORS. Neither saline nor ORS increased orthostatic tolerance in untreated controls ($P = .46$; $n = 15$), whereas both IV saline and ORS significantly improved orthostatic tolerance ($*P < .05$ and $**P < .001$, respectively; $n = 10$) in subjects with POTS.

many of the changes of neurovascular physiology that 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.^{32,33,44,45} It also has been shown that cerebral hemodynamic responses to LBNP to -45 mm Hg are similar to those that accompany blood loss up to 1000 mL.⁴⁶

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 used to combat the catastrophic fluid loss of infectious diarrhea.⁴⁷ ORS in subjects with POTS may temporarily correct the central hypovolemia that has been reported in many subsets of subjects with orthostatic intolerance and various types of syncope.^{10,18,48} This may have resulted in part from the significantly higher CO that was measured after ORS administration, but not IV saline infusion, in subjects with POTS.

Along with facilitating the absorption of Na^+ and water, the ability of ORS to mitigate orthostatic intolerance in susceptible individuals also may 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.⁴⁹ The gastropressor response is a control mechanism that can lead to a marked increase in BP after water ingestion, but not after saline ingestion. An acute response peaks within 20-40 minutes and resolves within 60-90 minutes. In the present study, although there was a similar increase in HR with orthostatic

challenge in both controls and POTS independent of fluid supplementation, ingestion of ORS caused an increase in MAP only in control subjects but not in subjects with POTS, suggesting that these subjects are less capable of mounting a functional pressor response.

Several studies have demonstrated the acute benefits of supplemental IV 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.^{26,50} Although there are reports of a benefit of chronic or repeated saline administration, potential benefits must be considered within the context of the associated risks of infection and thrombi and the difficulties in administration.²⁸

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.^{1,14,58} There is often a period of initial orthostatic hypotension during which BP and CBF_V transiently decrease, sometimes markedly, reaching their nadir at 10-20 seconds after standing. A reflex tachycardia results, and BP and CBF_V are restored within 30-60 seconds, but CBF_V recovers to somewhat less than supine values.^{30,51} In the subjects with POTS, evaluation of the effects of low CBF_V on CNS function using the graded incremental HUT test and executive working memory evaluation using N-Back testing as an objective measure of cognitive impairment revealed progressive impairment of executive memory function 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 chronic fatigue syndrome/POTS.⁵²

Although cognitive ability was not assessed in this study, preservation of CBF_V likely supported improved cognitive abilities in the subjects with POTS. In this study using LBNP as a controlled orthostatic stressor, although the subjects with POTS had approximately 30% of the orthostatic tolerance of controls, normalized CBF_V was best preserved by ORS in the subjects with POTS and may have contributed in part to the significant increase in orthostatic tolerance afforded by this treatment.

Administering ORS to the subjects with POTS produced effective short-term mitigation of 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 as IV saline in increasing orthostatic tolerance. This supports the use of ORS as an easy, safe, and practical therapy to mitigate symptoms associated with orthostatic intolerance. Because ORS is inexpensive, safe, and easily administered, it may be considered 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, CBF_V, and executive function. In addition, we were not able to measure

changes in blood volume during LBNP in the setting of fluid supplementation with either IV saline or ORS. Obtaining subjective information about symptoms and other indices of wellness during imposition of LBNP, although 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, and further investigations of long-term regular use of ORS are 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. Therefore, it would have been beneficial to compare the IV saline and the ORS arms in a larger cohort of age-matched controls and subjects. ■

Submitted for publication Apr 9, 2019; last revision received Jul 11, 2019; accepted Jul 15, 2019.

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Data statement

Data sharing statement available at www.jpeds.com.

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