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Effect of High Dietary Sodium Intake in Patients with Postural Tachycardia Syndrome

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Abstract

Background: High sodium intake is recommended for the treatment of postural tachycardia syndrome (POTS) to counteract the hypovolemia and elevated plasma norepinephrine that contribute to excessive orthostatic tachycardia, but evidence of its efficacy is not available.

Objectives: We tested whether a high sodium (HS) diet reduces orthostatic tachycardia (ΔHR) and upright heart rate (HR) compared with low sodium (LS) diet in POTS patients, and secondarily its effect on plasma volume (PV) and plasma norepinephrine.

Methods: We enrolled 14 POTS patients and 13 healthy controls (HC), 23–49 years old, in a crossover study with six days of LS (10 mEq sodium/day) or HS (300 mEq sodium/day) diet. We

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A high salt diet increases plasma volume, decreases plasma norepinephrine, and reduces orthostatic tachycardia in patients with Postural Tachycardia Syndrome.

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measured supine and standing HR, blood pressure, serum aldosterone, plasma renin activity, blood volume, and plasma norepinephrine and epinephrine.

Results: In POTS, HS diet reduced upright HR and ΔHR compared with LS diet. Total blood volume and PV increased, and standing norepinephrine decreased with HS compared with LS diet However, upright HR, ΔHR and upright norepinephrine remained higher in POTS than in HC on HS diet [117 (98–121) beats per minute (bpm), 46 (32–55) bpm, and 753 (498–919) pg/mL in POTS vs. 85 (77–95) bpm, 19 (11–32) bpm, and 387 (312–433) pg/mL in HC], despite no difference in the measured PV.

Conclusions: In POTS patients, high dietary sodium intake compared with low dietary sodium intake increases plasma volume, lowers standing plasma norepinephrine, and decreases ΔHR.

CONDENSED ABSTRACT—Postural Tachycardia Syndrome (POTS) is a chronic form of orthostatic intolerance. Augmented oral sodium intake is a frequently prescribed treatment and recommended in professional society scientific statements on POTS, but evidence supporting the effectiveness was lacking. We evaluated one week of a very high sodium diet compared to a very low sodium diet in POTS patients. The high sodium diet expanded the plasma volume and total blood volume, reduced standing plasma norepinephrine levels (a marker of sympathetic nervous system tone), and reduced the orthostatic tachycardia. These data provide supporting evidence for the use of high sodium diets in POTS patients.

ClinicalTrials.gov **Identifier:** NCT01547117

Keywords

Hypovolemia; orthostatic tachycardia; postural tachycardia syndrome; POTS; sodium

INTRODUCTION

Postural tachycardia syndrome (POTS) is a chronic disabling disorder characterized by excessive tachycardia and worsening of symptoms when upright, then improvement with recumbence (1–3). The 2015 Expert Consensus Statement of the Heart Rhythm Society (4) defines POTS by an orthostatic heart rate (HR) increase of at least 30 beats per minute (bpm) (or ≥ 40 bpm in individuals 12–19 years of age) in the absence of orthostatic hypotension [≥ 20 mmHg drop in systolic blood pressure (BP) with standing]. Estimates of the point prevalence of POTS range from 0.2–1.0% of the North American population (5).

Many POTS patients have a decreased plasma volume (6–8) and high standing plasma norepinephrine (9). Although a plasma volume deficit should stimulate the renin–angiotensin–aldosterone system to promote sodium retention, this regulatory link might be defective in POTS (6). Elevations in plasma norepinephrine suggest an increase in sympathoneural tone (10).

Symptoms improve in children with POTS following supplementation with sodium chloride capsules (11), and acute sodium and volume expansion with intravenous saline can reduce the orthostatic tachycardia (ΔHR) in adults (12). A high sodium diet (10–12 g NaCl/day equivalent to 170–205 mEq or mmoles sodium/day) and increased water intake (2–3L/day) are often prescribed to expand plasma volume in patients (3, 4, 10). In comparison, the

2020–2025 Dietary Guidelines for Americans recommend less than 100 mEq sodium/day with the average daily sodium intake in the USA being 137 mEq for females and and 186 mEq for males (13). There are no published data about the value of this simple dietary strategy. Specifically, it is unknown whether a high sodium diet increases plasma volume or improves ΔHR in POTS. Studies that reported a plasma volume deficit in POTS patients despite a normal- to high-sodium diet (≥150 mEq sodium/day) (6, 14, 15), suggest that patients may not effectively respond to dietary sodium with plasma volume expansion.

We therefore tested the hypothesis that a high sodium diet would decrease upright HR and ΔHR in comparison with a low sodium diet in POTS patients. We secondarily tested the hypothesis that a high sodium diet would increase plasma volume and reduce standing plasma norepinephrine levels in POTS patients compared to a low sodium diet.

METHODS

General Study Design

A randomized 2-arm crossover study compared the upright HR and ΔHR during a low sodium (10 mEq sodium/day, LS) or high sodium (300 mEq sodium/day, HS) diet in patients with POTS (Figure 1). We also assessed plasma norepinephrine and blood volumes for the two diets and compared the results in POTS with those in a healthy control group (HC). Participants ate a low-monoamine caffeine-free diet containing 150 mEq sodium on study Day 1 to mitigate effects of any dietary extremes prior to study. Thereafter, they consumed LS or HS diet for six days (Days 2–7) in a randomly determined order. Subjects were evaluated on Day 7 as described below. The two diet phases were scheduled at least one month apart and for the same phase of the menstrual cycle. Urinary sodium measurements confirmed diet compliance. Water intake was ad libitum. POTS patients were admitted to the Vanderbilt Clinical Research Center (CRC) prior to Day 1 for safety during medication withdrawal and for convenience for patients travelling to participate. Healthy control participants, who were local, were screened and consumed study diet as outpatients until admission on Day 5. The Vanderbilt Institutional Review Board approved this study, and it was registered on ClinicalTrials.gov (NCT01547117). All participants provided written informed consent prior to starting study-related activities.

Study Participants

We enrolled 14 female POTS patients (23–49 years; one Hispanic; all White; Table 1) from the Vanderbilt Autonomic Dysfunction Center. Patients were eligible if they had been diagnosed with POTS in accordance with the Consensus Statement of the American Autonomic Society (1) and they were ≥18 years of age. Thirteen female HC (23–43 years; one Hispanic; 11 White; one Asian; and one Black) were recruited from the Vanderbilt community. Potential study participants were screened with a physical examination, an electrocardiogram, and routine laboratory studies. Renal function, liver function, and hematologic screening were normal, and subjects with systemic illnesses that might affect autonomic function were excluded.

Study Protocol

Assessments on the morning of study Day 7 included: 1) supine and upright BP and HR measurements; 2) supine and upright blood draws for catecholamines, plasma renin activity (PRA) and aldosterone; 3) supine blood draw for hormones and electrolytes; 4) standing symptom burden; 5) plasma volume determination; and 6) 24h urine excretion of sodium, potassium and creatinine (collection started on Day 6).

Supine and Standing Posture Studies with Plasma Catecholamine Sample Collection

The standing test was performed to assess the hemodynamic and biochemical responses to increased central hypovolemia (accentuated by the gravitational stress). HR, BP, aldosterone, PRA, and plasma norepinephrine and epinephrine were assessed after overnight rest and fasting after midnight, as described previously (6). An intravenous catheter was inserted in the morning followed by at least 60 minutes of lying quietly. BP and HR were then measured, and a blood sample was collected in the supine position and again after subjects had been standing for up to 30 minutes (as tolerated). BP and HR, determined with an automated oscillometric recording device (DINAMAP, Critikon, GE Medical), are presented for 5 minutes standing (or maximal stand if <5 minutes) since several patients were unable to stand for 10 minutes. For catecholamine measurements, blood was collected in plastic syringes, transferred to chilled vacuum tubes with EDTA and immediately put on ice. The plasma was separated by centrifugation at −4°C and stored with added reduced glutathione (Amersham International PLC) at −70°C until the assay. Blood for aldosterone was collected in chilled vacuum tubes without preservative, and the serum was extracted and sent to the laboratory on ice.

Symptoms

Patients were asked to report their standing symptom burden at the end of the Stand portion of the posture study, using the Vanderbilt Orthostatic Symptoms Scale (VOSS) (16). They rated the severity of nine symptoms (palpitations, lightheadedness, mental confusion, blurred vision, shortness of breath, tremulousness, chest discomfort, headache, and nausea) on a 0 to 10 scale (with 0 reflecting an absence of symptoms). The sum of the scores was used to measure orthostatic symptom burden. This symptom score has been used in the past by our center (16–20), and the symptoms were chosen because they reflect common complaints of POTS.

Blood volume measurement

Plasma volume (PV) was determined by the indicator tracer-dilution technique, using the DAXOR BVA-100 Blood Volume Analyzer system (6) (DAXOR Corporation), on Day 7.

Total blood volume (TBV) was calculated from measured PV and microcapillary venous antecubital hematocrit. Red blood cell volume (RBV) was calculated as the difference between TBV and PV.

Expected PV and TBV were determined for each individual based on their height, weight, and gender (21). Results are presented as the percent deviation [(measured-expected)/ expected] x 100% of blood volumes.

Statistical Analysis—The primary outcomes for this study were ΔHR and upright HR in POTS patients while on HS diet compared to ΔHR and upright HR in these patients on LS diet. Secondary outcomes included upright plasma norepinephrine, % PV deviation, and symptoms score. Continuous data are presented as mean ± SD for demographics and median (interquartile range) for clinical and biochemical data. Demographics were compared with Student's t-test. Because most hormone and hemodynamic variables were not normally distributed, comparisons of LS with HS diets within HC and POTS patients were analyzed by the Wilcoxon Signed Ranks Test. Differences between POTS and HC within LS or HS diet treatments were analyzed by the Mann-Whitney U test. All P-values are two-sided and reported unadjusted. $P<0.05$ was considered statistically significant, except for the 2 primary outcomes where a $P<0.025$ threshold was used for statistical significance. SPSS 21.0 software (IBM Corporation, Armonk, NY, USA) was used for statistical analyses.

See Online Appendix for additional details of Methods, and Supplemental Table 1 for explanation of incomplete data sets.

RESULTS

Clinical characteristics

Baseline data are shown in Table 1. POTS patients and HC did not differ in age, height, weight or body mass index. Serum sodium was marginally higher in POTS than HC [139 (139–140) vs. 138 (136–139) mEq/L, P=0.035], but there were no other differences between the two groups.

Comparison between HS and LS diets response in POTS

Plasma and urinary electrolytes (Table 2)—Differences in plasma and urinary sodium in POTS patients were consistent with consumption of the LS and HS diets as scheduled. For sodium, potassium and chloride, 1 mEq = 1 mmol.

Supine and Standing Posture study (Table 3; Figures 2 and 3)—Compared with LS diet in POTS patients, HS diet was associated with a smaller ΔHR [46 (32–55) bpm on HS vs. 60 (55–64) bpm on LS, P=0.001; Figure 2]. These patients also had lower upright HRs on HS diets than on LS diets. Neither supine, upright, nor orthostatic change in systolic or diastolic BP differed between patients on HS vs. LS diets.

Supine plasma epinephrine was lower with HS diet than LS diet [11 (5.7–2.0) vs. 21 (12–31) pg/mL, P=0.009], but there were no differences in standing or Δ plasma epinephrine between diets. Although supine plasma norepinephrine in POTS patients did not differ between HS and LS diets, standing plasma norepinephrine was lower on HS than on LS diet [753 (498–919) vs. 959 (736–1161) pg/mL, P=0.017; Figure 3] and Δnorepinephrine during HS was less than during LS.

Supine PRA was lower with HS diet than LS diet in POTS patients [0.7 (0.2–1.6) vs. 4.1 (0.9–4.7) ng/mL/hr, P=0.039], as was standing PRA [2.9 (1.5–5.0) vs. 25 (11–28) ng/mL/hr, P=0.002] and the increase in PRA with standing. Serum aldosterone was also lower on the

HS diet than LS diet in POTS patients in both supine and standing postures and increased less with standing during the HS diet.

Symptom burden (Figure 4; Supplemental Figure 1)—There was a non-significant trend for a lower symptom burden score in POTS on HS diet than LS diet [16 (10–27) vs. 33 (24–41) au, P=0.109]. Although none of the nine individual symptom scores differed significantly between HS and LS diets, those for mental confusion [2 (0–3) vs. 5 (0–7) au, P=0.062], palpitations [2 (1–5) vs. 6 (3–8) au, P=0.125], lightheadedness [3 (0–5) vs. 6 (3–7) au, P=0.125] and headache [0 (0–2) vs. 4 (0–6) au, P=0.125] trended toward a lower score on HS diet (Supplemental Figure 1).

Blood volume (Table 4; Figure 5)—During the LS diet phase, TBV, PV and RBV in patients with POTS were all significantly less than the expected volumes estimated from the individual's sex, height and weight. The deficit in TBV was reduced with HS. This was based almost entirely on an increase in PV and a reduction in the PV deficit with the HS diet compared to LS diet [−.63 (−9.7–8.4) vs. – 11 (−17—2.6) %, P=0.001], as the RBV deviation remained similar during both diets.

Comparison between HS and LS diets response in healthy controls

Plasma and urinary electrolytes (Table 2)—Results of plasma and urinary sodium analyses in HC indicated compliance with the study diets.

Supine and Standing Posture study (Table 3; Figures 2 and 3)—There were no differences in supine HR [HS:62 (53–75) bpm; LS: 70 (57–73) bpm, P=0.133], upright HR [HS:85 (77–95) bpm; LS:96 (88–101) bpm, P=0.091] or ΔHR [HS: 19 (11–32) bpm; LS: 23 (19–36) bpm, P= 0.266)] with HS diet compared to LS diet in HC (Figure 2). Nor did supine, upright or Δsystolic and diastolic BPs differ between LS and HS diets for the control population.

There was a non-significant trend toward higher supine plasma epinephrine in HC on a HS diet than LS diet phase [20 (6.7–28) vs. 14 (6.6–19) pg/mL, P=0.060]. There was no difference in standing or Δplasma epinephrine between diets. Supine, standing, and Δplasma norepinephrine levels were lower for HC on the HS diet compared with the LS diet (Figure 3).

Supine PRA in HC was lower with a HS diet than a LS diet [0.3 (0.1–1.5) vs. 2.7 (1.5–5.0) ng/mL/hr, P=0.029], as was standing PRA [1.0 (0.8–1.9) vs. 7.3 (3.3–9.3) ng/mL/hr, P=0.008]. Serum aldosterone was also lower on the HS diet than LS diet in HC in both supine and standing postures. The orthostatic increase in aldosterone was significantly attenuated by HS vs. LS diet, but PRA's rise was not different between diets.

Symptom burden (Figure 4)—The orthostatic symptom burden was low for both the HS phase [0 (0–4.2) au] and the LS phase [1 (0–3.7) au] in HC.

Blood volume (Table 4; Figure 5)—During the LS diet phase, TBV, PV and RBV in HC were not significantly different from the expected volumes. There was a non-significant

trend for an increase in TBV deviation with HS diet compared with LS diet [8.3 (−1.3–29) vs. 3.7 (−6.6–11)%, P=0.064]. This was based almost entirely on an increase in PV deviation with the HS diet [15(1.8–38) vs. 5.6 (−2.0–14.9)% P=0.002], with no change in the RBV deviation between diets.

Comparison of Low Salt Diet Response between POTS and Healthy Controls

Supine and Standing Posture study (Table 3; Figures 2 and 3)—On a LS diet, POTS patients had a greater ΔHR and upright HR and lower upright and Δdiastolic BP than HC. Supine HR and other BP parameters were not different between groups.

Standing plasma epinephrine was higher in POTS patients than HC on a LS diet [59 (33–86) vs. 30 (24–46) pg/mL, P=0.030], but there were no differences in supine plasma epinephrine between groups. Both supine [248 (162–332) vs. 135 (104–225) pg/mL, P=0.030] and standing [959 (736–1161) vs. 520 (391–693) pg/mL, P<0.001] plasma norepinephrine, and orthostatic changes in plasma epinephrine and norepinephrine were greater in POTS than in HC on LS diet.

Symptom burden (Figure 4)—Patients with POTS were more symptomatic during the LS diet compared to HC.

Blood volume (Table 4; Figure 5)—Measured TBV and PV were significantly lower in POTS patients than HC during LS diet, while differences in measured RBV did not reach significance (P=0.060). Percent deviations in TBV, PV and RBV were greater in patients with POTS than HC.

Comparison of High Salt Diet Response between POTS and healthy controls

Supine and Standing Posture study (Table 3, Figures 2 and 3)—On a HS diet, POTS patients had a greater upright HR and ΔHR than HC, but other HR and BP parameters were not different between groups.

During the HS phase of the study, standing plasma norepinephrine and Δnorepinephrine were significantly higher for POTS patients than HC, but other cateholamine parameters were not different between POTS and HC.

Symptom burdern (Figure 4)—Patients with POTS were more symptomatic during the HS diet compared to HC.

Blood volume (Table 4; Figure 5)—Measured TBV and RBV, but not PV, were significantly lower in POTS patients than HC during HS diet. For TBV and PV, the small deficits compared to expected volumes in POTS contrasted with a surplus in HC.

DISCUSSION

Treatment of POTS patients remains an unmet medical need, with no medications yet approved by the FDA (10). Despite recommendations from the Heart Rhythm Society (4), the Canadian Cardiovascular Society (3) and personal physicians to consume a high sodium

diet, this is the first study to test whether increasing dietary sodium actually attenuates the orthostatic tachycardia of POTS (see Central Illustration). Zhang et al. (2012) (11) reported symptom improvement in children with POTS following supplements of sodium chloride capsules. Although they did not measure blood volume, they found an association between low baseline urinary sodium excretion, presumably concomitant with a lower PV, and response to salt supplementation. We have now demonstrated that HS diet, compared with LS diet, not only decreased ΔHR and upright HR in POTS, but it also corrected the PV deficit and reduced plasma norepinephrine. Similar changes in upright HR and orthostatic tachycardia were not noted in a normovolemic HC group. However, patients on HS for five full days still met the criteria for POTS of ΔHR≥ 30 bpm, and the upright symptom scores exceeded those for our HC, despite a deficit of <1% from the expected PV. Volume depletion, therefore, cannot totally explain POTS. Treatment with a HS diet, although helpful, is not sufficient to “normalize” patients with POTS (see Supplemental Table 2 and Supplemental Discussion).

Low Blood Volume in POTS

Our group and others have reported hypovolemia in a significant proportion of POTS patients (6, 14, 15, 22). In the current study, patients with POTS on a LS diet had a ~11% deficit in PV, and ~13% deficit in TBV relative to their expected volumes. POTS patients also had a reduction in RBV which was not affected by dietary salt. This RBV deficit has been observed previously in patients with orthostatic tachycardia (6, 23). Raj proposed that low RBV might be related to diminished erythropoietin production secondary to dysregulation of the renin-angiotensin system or in response to the PV deficit (6). Yet, we observed no difference between RBV on LS and HS diets in patients with POTS despite elimination of the PV deficit on HS.

The reduced PV could underlie the higher upright HR and ΔHR in patients with POTS. Standing upright is associated with central hypovolemia, which decreases venous return, causing reductions in stroke volume, cardiac output and BP. Changes are sensed by baroreceptors that stimulate the sympathetic nervous system and increase HR to maintain BP. The low PV in POTS might exaggerate the postural central hypovolemia, prevent adequate compensation for the drop in venous return and amplify ΔHR. Although we have previously found no difference in ΔDBP between patients with POTS and HC while consuming 150 mEq sodium/day (9), LS diet was associated with a lower upright and ΔDBP in patients than HC in the current study.

Sodium Loading in POTS

Reports of hypovolemia in patients with POTS have driven treatments that help patients retain fluid and thereby raise blood volume. Jacob et al. (12) found the acute intravenous infusion of 1L of normal saline to be more effective at improving ΔHR than midodrine or clonidine. They proposed that the HR response to saline was related to an increase in intravascular volume. Although an effective treatment, regular saline infusions are not recommended for POTS because of risks associated with long-term venous access (10).

Recently, a common approach in the management of POTS is consumption of >200 mEq dietary sodium/day and at least 2–3L of fluid/day (4). There has been a concern, however, that high salt diets alone may be inadequate in POTS due to compromised sodium retention associated with impaired renin-angiotensin-aldosterone system regulation (6, 8). In the current study, the ~11% PV deficit in patients with POTS on LS diet was reduced to <1% on HS diet. Under the conditions of this study, therefore, disturbed sodium retention ("salt wasting") did not prevent restoration of circulating blood volume, and HS diet led to improvement, although not normalization, of orthostatic tachycardia.

Supine and standing plasma norepinephrine were higher in POTS than HC during LS. After the elimination of the PV deficit by HS diet, supine plasma norepinephrine in POTS was no longer significantly different from HC, although upright plasma norepinephrine remained higher in POTS. Importantly, HS reduced upright plasma norepinephrine in POTS, even though the high plasma norepinephrine levels suggest that these patients with POTS were "hyperadrenergic".

Takeda et al. (24) reported that muscle sympathetic nerve activity in healthy premenopausal women is greater on LS than HS diet. Blood volume expansion by salt loading could load the baroreceptor and effect a decrease in nerve activity, with less subsequent release of synaptic norepinephrine, and the return of supine plasma norepinephrine to healthy control values, as demonstrated in our patients.

Symptom Burden with Salt Loading

Symptom scores improved from LS to HS diet in POTS, but this difference was not significant and the HS score remained higher than the score for HC. Our findings were limited because we lacked VOSS scores for some participants (see Supplemental Table 1) and there was significant inter-patient variability in responses due to the subjectivity of the VOSS tool. A tendency for some individual symptom scores to decrease with HS diet indicates that additional research is needed in this area. Some previous studies with VOSS showed an inverse relationship between standing HR and symptom burden (16–18, 20), while others have found no relationship (25, 26).

Study Limitations

The findings are limited by the relatively short-term design of our protocol. The ability of a HS diet to improve the HR, PV and norepinephrine abnormalities in POTS might not be maintained over the long term. The long-term effects of HS diet need to be assessed both for efficacy and safety. We did not obtain baseline measurements during "normal sodium diet" so we are unable to comment on changes from usual HR, plasma norepinephrine or blood volume as a result of sodium manipulation. Given that many POTS patients have adapted a HS diet (despite the prior paucity of evidence), a "normal sodium diet" would have been hard to define. Rather we used standardized amounts of sodium in the diet, with more extreme LS and HS diets designed to test proof of concept. We did not evaluate the "sodium sensitivity" of our participants, as this is not usually done in clinical practice either. Although participants were not told whether they were consuming LS or HS diet, we acknowledge that it was apparent. An alternative protocol could have provided a 10 mEq

sodium/day diet with placebo or salt pills in the HS phase, but increasing dietary sodium is more consistent with recommendations.

Conclusions

In the current study, patients with POTS experienced decreases in ΔHR, supine and upright HR, and standing plasma norepinephrine following a short-term period of dietary sodium intake of 300 mEq/day compared with a period of 10 mEq sodium/day. The deficit in PV evident in previous studies and in the LS phase of this study was eliminated by a HS diet, suggesting that the restoration of PV contributed to improvement, although not normalization, in POTS. This study provides solid data to support the recommendations for increased dietary sodium intake in POTS (3, 4).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

BP	blood pressure
HC	healthy control group
HR	heart rate
HS	high sodium
LS	low sodium
POTS	postural tachycardia syndrome
PV	plasma volume
RBV	red blood cell volume
TBV	total blood volume
VOSS	Vanderbilt Orthostatic Symptoms Scale

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Clinical Perspectives:

Competency in Patient Care: High dietary sodium intake can lower plasma norepinephrine levels and ameliorate standing and orthostatic tachycardia in patients with postural orthostatic tachycardia syndrome (POTS).

Translational Outlook:

Additional research is needed to evaluate the long-term effects of high sodium intake in patients with POTS.

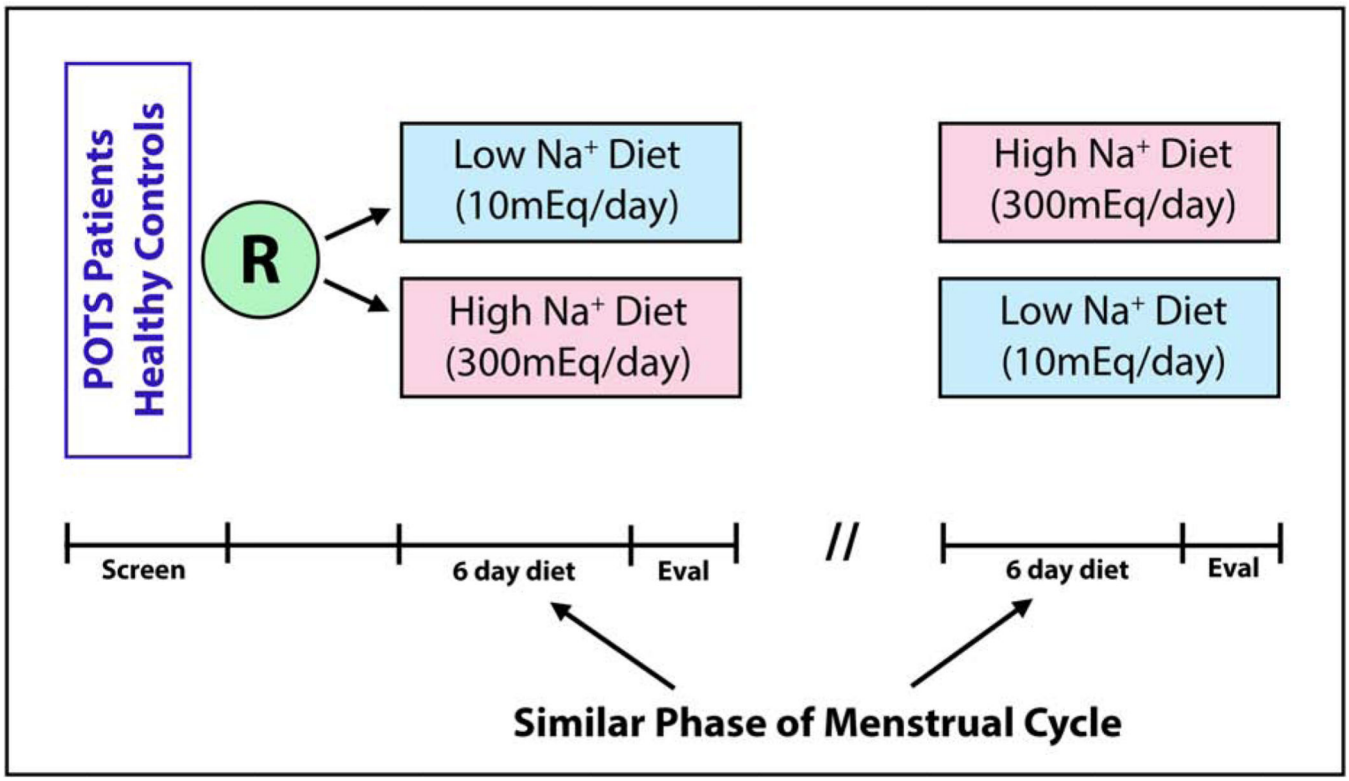


Figure 1: Crossover design of dietary sodium study in POTS.

Low sodium (10 mEq sodium/day) and high sodium (300 mEq sodium/day) diets were consumed for six-day-periods in random order and during the same phase of the menstrual cycle. At the end of each study diet, assessments included 1) supine and upright blood pressure and heart rate measurements; 2) supine and upright blood draws for catecholamines, plasma renin activity and aldosterone; 3) supine blood draw for hormones and electrolytes; 4) standing symptom burden; 5) plasma volume determination; and 6) 24h urine excretion of sodium, potassium and creatinine. Eval=evaluation; R=randomization.

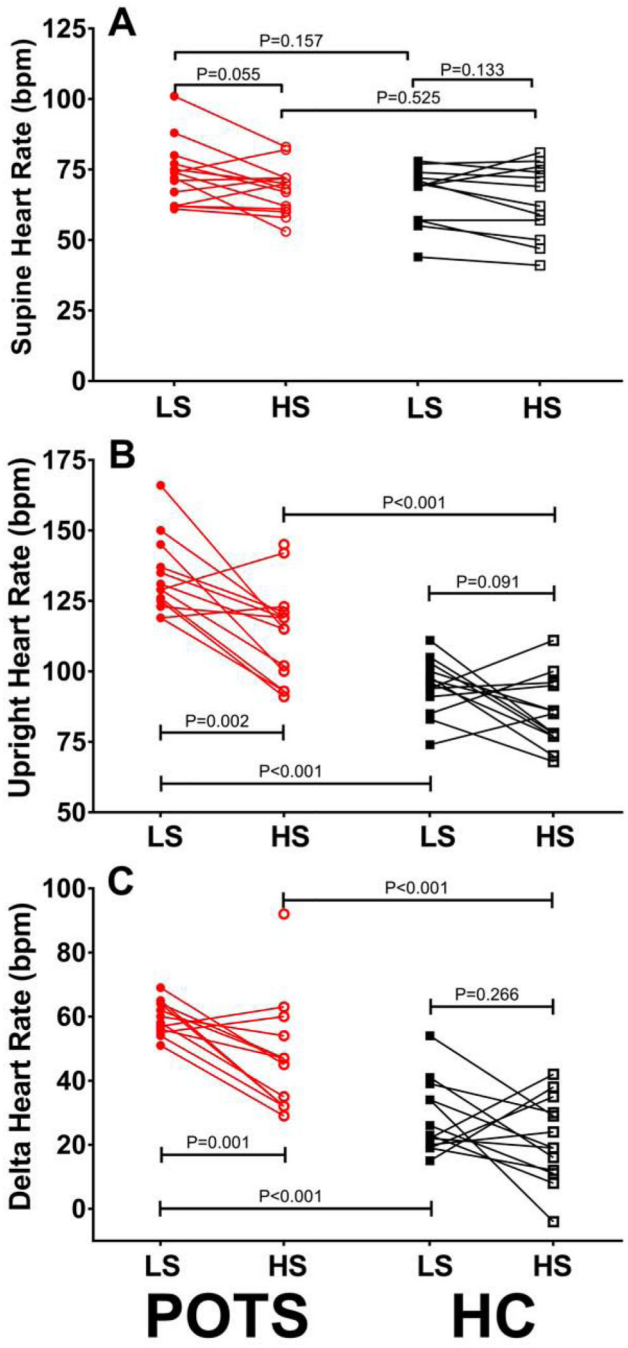


Figure 2: Heart rate responses to dietary sodium in POTS and Controls.

A standing test was performed to assess the hemodynamic and biochemical responses to increased central hypovolemia. HR measurements occurred after ≥ 60 minutes of lying quietly (Supine) and again after standing for 5 minutes or as long as tolerated up to 5 minutes (Upright). Individual HR data are shown for patients with POTS (●○) and HC (■□) on LS (filled) and HS (open) diets. Lines connect symbols for each participant. Upright (B) and ΔHR (C) were lower during HS in POTS, compared with LS. Nevertheless, these values remained higher than those for HC on HS diet. Δ=Delta=difference between

upright and supine; HC=healthy controls; HS=high sodium; HR=heart rate; LS=low sodium; POTS=postural tachycardia syndrome.

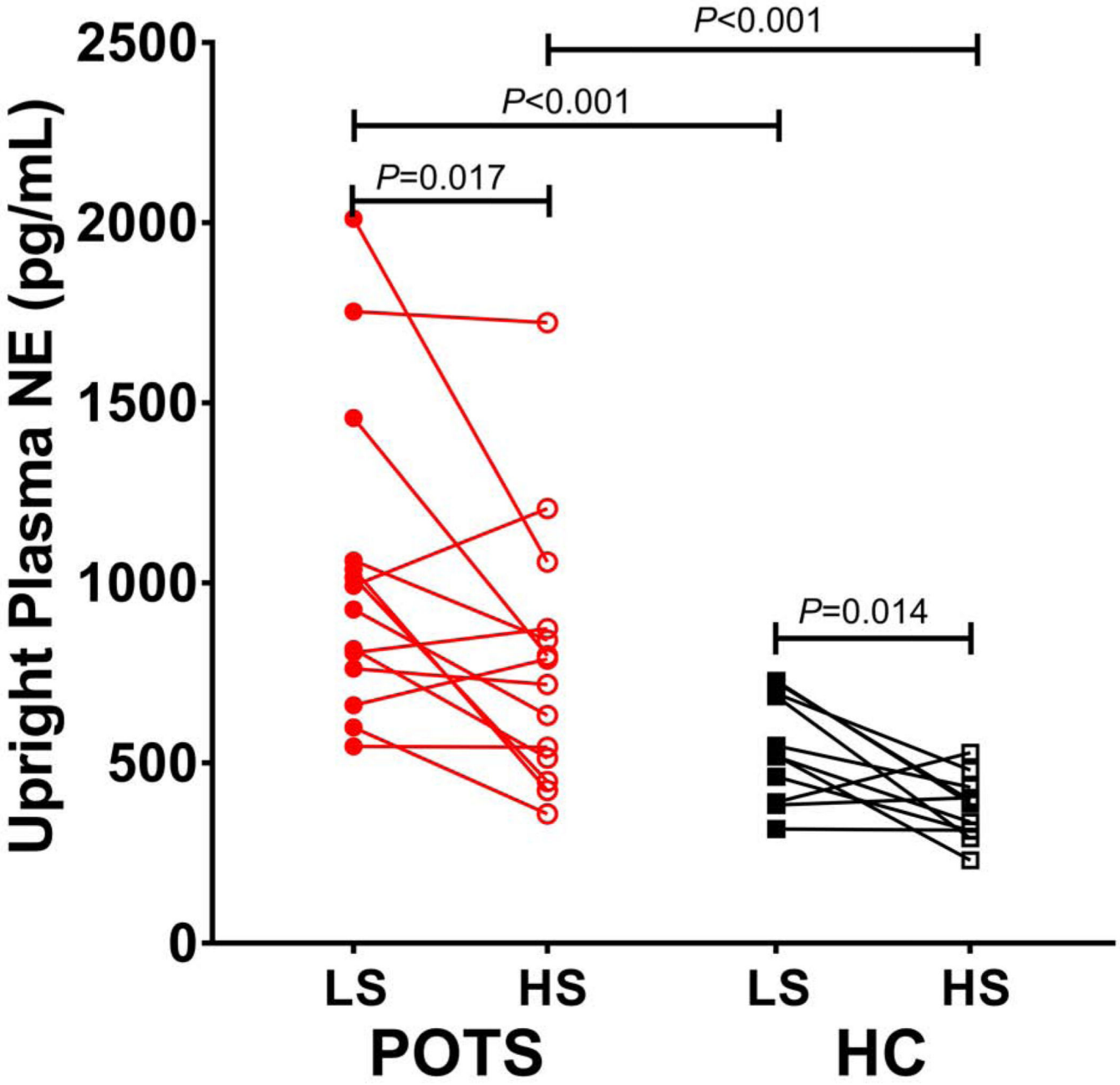


Figure 3: Upright norepinephrine response to dietary sodium in POTS and Controls.

Blood samples were collected after upright posture for up to 30 minutes. Individual data are shown for patients with POTS (●○) and HC (■□) on LS (filled) and HS (open) diets. Lines connect symbols for each participant. HS decreased upright NE below LS values in both patients with POTS and HC. Nevertheless, values in POTS remained higher than those of HC on both HS and LS diets. NE=norepinephrine. Other abbreviations as in Figure 2.

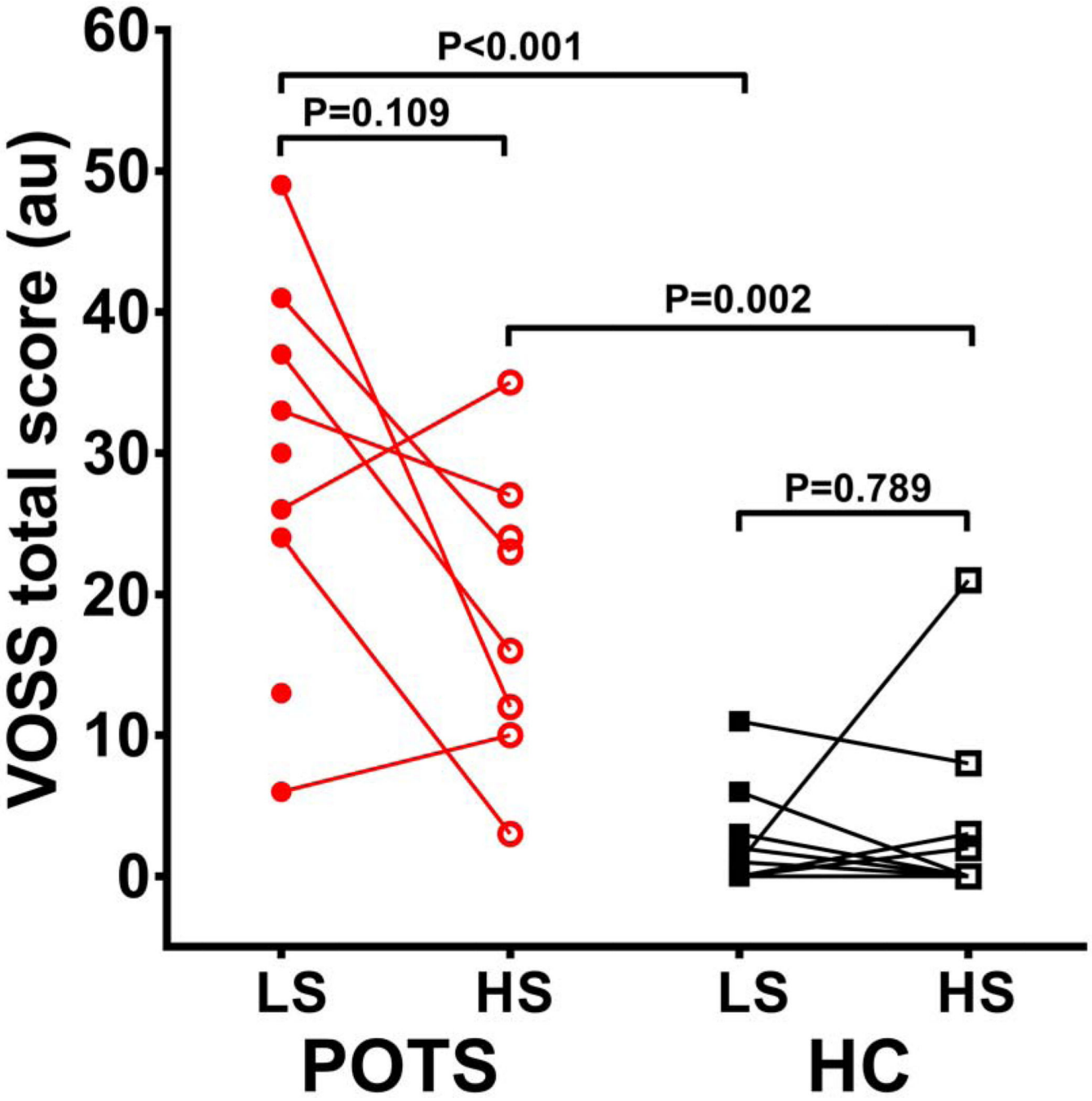


Figure 4: Orthostatic symptom burden on high and low sodium diets.

Symptoms were reported after upright posture for up to 30 minutes. Individual data are shown for total VOSS score for patients with POTS (●○) and HC (■□) on LS (filled) and HS (open) diets. Lines connect symbols for each participant. Scores during HS and LS diet phases did not differ in patients with POTS or HC. Patients with POTS had higher scores (worse upright symptoms) than HC during HS and LS diets. au=arbitrary units; VOSS=Vanderbilt Orthostatic Symptoms Scale. Other abbreviations as in Figure 2.

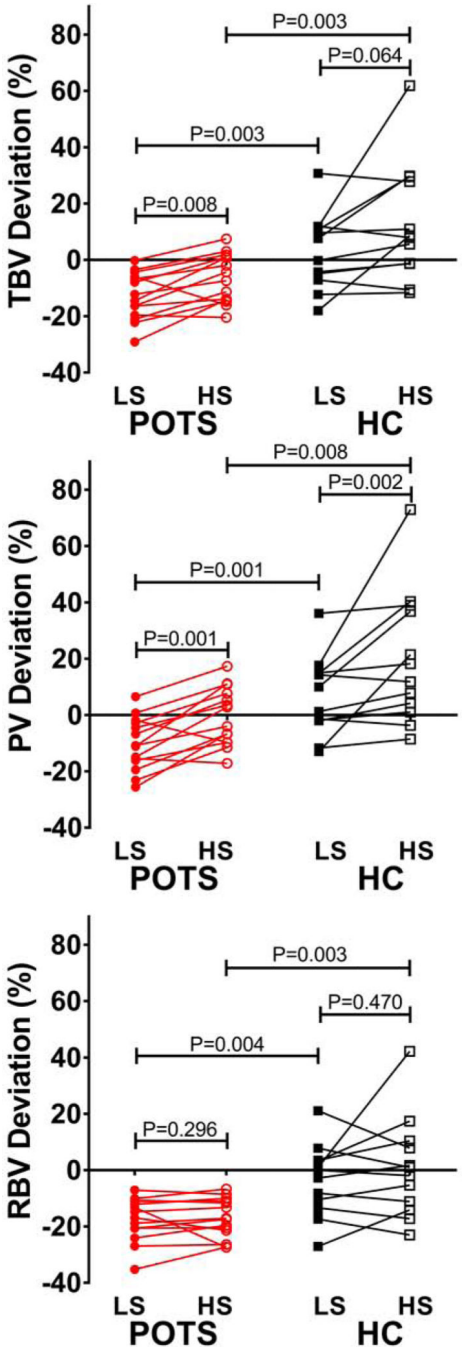
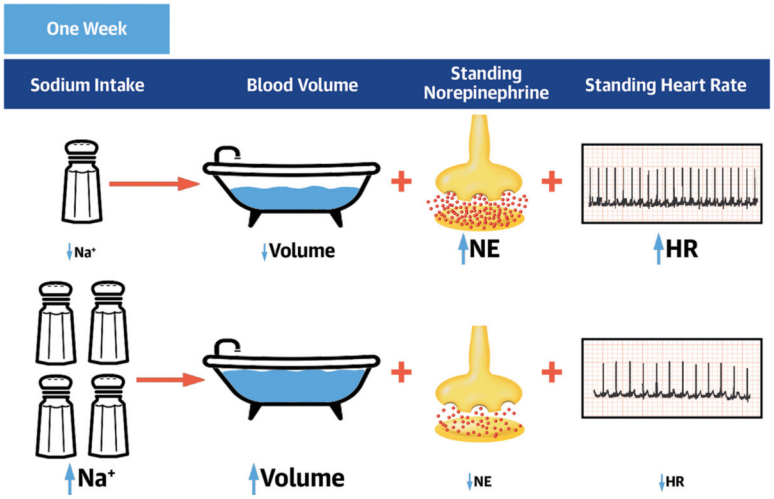


Figure 5: Blood Volume Deviations on high and low sodium diets.

Individual data are shown for TBV, PV and RBV, as percent deviation from expected volumes for patients with POTS (●○) and HC (■□) on LS (filled) and HS (open) diets. Lines connect symbols for each participant. Whereas HS diet decreased deviations in TBV and PV in patients with POTS, deviations in RBV remained similar during both diets. In HC, the TBV deviation tended to increase and the PV deviation increased with HS as volumes rose above expected values. The TBV, PV and RBV deviations in POTS differed

from HC. PV=plasma volume; RBV=red blood cell volume; TBV=total blood volume. Other abbreviations as in Figure 2.



Central Illustration: Effects of Low and High Sodium Diets in POTS.

In POTS patients, a low sodium (Na^+) diet for 1 week leads to lower blood volume, higher standing plasma norepinephrine (NE) levels (a marker of sympathetic nervous system tone) and higher standing heart rate (HR). When these patients go on a high sodium diet, the blood volume increases, whereas the standing plasma NE and HR both decrease.

Table 1:

Baseline characteristics of study participants

	POTS Patients	Controls	*P* value
Age (yr)	35 ± 8	31 ± 6	0.266
Height (cm)	166 ± 75	161 ± 85	0.159
Weight (kg)	64.0 ± 8.7	62.0 ± 7.7	0.530
Body mass index	23.3 ± 3.2	23.8 ± 2.8	0.675
Blood (mEq/L)			
Sodium	139 (139–140)	138 (136–139)	0.035
Potassium	3.9 (3.7–4.2)	4.0 (3.7–4.1)	0.727
Chloride	106 (105–108)	106 (104–106)	0.159
Hemoglobin (g/100mL)	13.1 (12.9–13.7)	13.2 (12.9–13.5)	0.746
Hematocrit (%)	39.0 (38.0–41.5)	40.0 (38.0–41.5)	0.819

Blood samples for routine chemistry and hematology screening were collected before any testing was carried out. For sodium, potassium and chloride, 1 mEq = 1 mmole. Values are mean ± SD for demographics and median (interquartile range) for clinical and biochemical data.

Table 2:

Blood and urinary responses to 6 days of study diets

	Low Sodium vs. High Sodium Diets						POTS vs. Controls	
	POTS			Controls			Diets	
	Low Sodium	High Sodium	*P* value	Low Sodium	High Sodium	*P* value	*P* value for Low Sodium	*P* value for High Sodium
Blood, mEq/L								
Sodium	137 (136–138)	139 (138–139)	**0.003**	136 (135–137)	138 (137–139)	**0.012**	0.232	0.094
Potassium	3.8 (3.8–3.9)	3.7 (3.7–3.8)	0.451	4.1 (3.8–4.1)	3.9 (3.7–4.0)	0.412	**0.013**	0.140
Chloride	104 (104–105)	108 (107–109)	**<0.001**	106 (104–107)	109 (107–110)	**<0.001**	0.062	0.600
24h Urine total								
Volume (mL)	2411 (1966-	2828 (2430-	0.583	1568 (1422-	2146 (1398-	**0.013**	**0.017**	0.094
Sodium (mEq)	18.2 (11.6–25.8)	242 (201–286)	**<0.001**	21.6 (14.6-	260 (187–292)	**<0.001**	0.458	0.756
Potassium	44.4 (36.2–51.6)	60.0 (52.6–65.2)	**<0.001**	48.1 (40.4-	64.1 (56.9-	**<0.001**	0.458	0.220
Creatinine (g)	1.15 (.91–1.30)	1.21 (1.08–1.33)	0.078	1.27 (1.10-	1.29 (1.13-	0.579	0.239	0.375

Values are median (interquartile range). For sodium, potassium and chloride, 1 mEq = 1 mmole. Significant differences at P<0.05 are in bold.

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Table 3.

Dietary sodium and responses to orthostatic stress

	Low Sodium vs. High Sodium Diets						POTS vs. Controls	
	POTS			Controls			Diet	
	Low Sodium	High Sodium	*P* value	Low Sodium	High Sodium	*P* value	*P* value for Low Sodium	*P* value for High Sodium
Supine								
Heart rate (bpm)	73 (62–78)	69 (61–72)	0.055	70 (57–73)	62 (53–75)	0.133	0.157	0.525
Systolic blood pressure (mmHg)	105 (103–108)	104 (99–115)	0.891	105 (100–112)	108 (98–118)	0.529	0.746	0.510
Diastolic blood pressure (mmHg)	65 (63–71)	64 (58–74)	0.775	65 (58–70)	67 (63–70)	0.332	0.952	0.746
Norepinephrine (pg/mL)	248 (162–332)	166 (90–332)	0.088	135 (104–225)	108 (84–162) *	**0.018**	**0.030**	0.193
Epinephrine (pg/mL)	21 (12–31)	11 (5.7–20)	**0.009**	14 (6.6–19)	20 (6.7–28) *	0.060	0.143	0.163
Plasma renin activity (ng/mL/hr)	4.1 (0.9–4.7) †	0.7 (0.2–1.6) ‡	**0.039**	2.7 (1.5–5.0) ‡	0.3 (0.1–1.5) §	**0.029**	0.606	0.734
Aldosterone (ng/dL)	206 (157–249)	46 (34–58)	**<0.001**	131 (103–204)	41 (30–53)	**<0.001**	0.094	0.430
Upright								
Heart rate (bpm)	129 (124–141) ‖	117 (98–121) #	**0.002**	96 (88–101)	85 (77–95)	0.091	**<0.001**	**<0.001**
Systolic blood pressure (mmHg)	112 (103–116) ‖	116 (111–122) #	0.424	112 (105–117)	111 (107–118)	0.720	0.910	0.422
Diastolic blood pressure (mmHg)	68 (62–73) ‖	71 (67–80) #	0.265	78 (69–80)	75 (74–80)	0.905	**0.026**	0.150
Norepinephrine (pg/mL)	959 (736–1161)	753 (498–919)	**0.017**	520 (391–693) **	387 (312–433) **	**0.014**	**<0.001**	**<0.001**
Epinephrine (pg/mL)	59 (33–86)	36 (12–68)	0.130	30 (24–46) **	24 (21–49) **	0.700	**0.030**	0.752
Plasma renin activity (ng/mL/hr)	24.6 (11.3–27.6) ††	2.9 (1.5–5.0) ‡‡	**0.002**	7.3 (3.3–9.3) ††	1.0 (0.8–1.9) §§	**0.008**	**0.011**	0.135
Aldosterone (ng/dL)	455 (359–650)	64 (52–91)	**<0.001**	444 (277–515)	74 (52–129)	**<0.001**	0.173	0.302
Change from Supine to Upright								
Heart rate (bpm)	60 (55–64)	46 (32–55)	**0.001**	23 (19–36)	19 (11–32)	0.266	**<0.001**	**<0.001**
Systolic blood pressure (mmHg)	4 (0–12)	8 (1–17)	0.576	5 (0–8)	4 (−1–11)	0.673	0.929	0.395
Diastolic blood pressure (mmHg)	2 (−1–9)	6 (0–9)	0.416	10 (4–16)	11 (7–13)	0.553	**0.019**	0.077
Norepinephrine (pg/mL)	692 (508–917)	535 (393–692)	**0.035**	295 (264–482)	304 (189–332)	**0.019**	**<0.001**	**<0.001**
Epinephrine (pg/mL)	34 (17–56)	23 (5.4–57)	0.290	21 (13–29)	15 (2.5–23)	0.773	**0.040**	0.363
Plasma renin activity (ng/mL/hr)	21.6 (10.9–25.3)	1.4 (0.5–4.6)	**0.008**	4.4 (0.6–6.9)	0.8 (0.6–1.4)	0.078	**0.023**	0.285

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	Low Sodium vs. High Sodium Diets						POTS vs. Controls	
	POTS			Controls			Diet	
	Low Sodium	High Sodium	*P* value	Low Sodium	High Sodium	*P* value	*P* value for Low Sodium	*P* value for High Sodium
Aldosterone (ng/dL)	261 (164–431)	23 (8.1–40)	**<0.001**	200 (147–351)	23 (12–79)	**0.002**	0.488	0.239

*1 sample hemolyzed;

†1 missing sample and 2 samples with insufficient volume;

‡1 missing sample and 1 sample with insufficient volume;

§2 missing samples and 1 sample with insufficient volume;

‖1 patient unable to stand for even 1 minute; data at 1 minute standing for 1 patient and at 3 minutes standing for 2 patients; data for all others at 5 minutes standing;

#data at 3 minutes standing for 1 patient;

**2 samples hemolyzed;

††1 missing sample;

‡‡2 missing samples;

§§3 missing samples and 2 samples with insufficient volume.

Values are median (interquartile range). Significant differences at P<0.05 are in bold.

Table 4:

Influence of dietary sodium on blood volume

	POTS Patients (n=14)			Controls (n=12)				
	Low Sodium Diets	**High Sodium Diets**	***P* value for POTS Diets**	**Low Sodium Diets**	**High Sodium Diets**	***P* value for Control Diets**	***P* value for Low Sodium Groups**	***P* value for High Sodium Groups**
Plasma volume								
Expected, ml	2746 (2592–2826)	2747 (2586–2852)	0.084	2514 (2421–2823)	2509 (2420–2842)	0.662	0.246	0.226
Measured, ml	2362 (2161–2715) *	2633 (2468–2961)	**0.001**	2816 (2428–2955)	3032 (2620–3482) *	**0.005**	**0.036**	0.106
Deviation, ml	−303 (−473−−77)	−19 (−280–244)	**0.002**	138 (−48–417)	388 (44–961)	**0.003**	**<0.001**	**0.009**
Deviation, %	−11 (−17−−2.6)	−.63 (−9.7–8.4)	**0.001**	5.6 (−2.0–14.9)	15 (1.8–38)	**0.002**	**0.001**	**0.008**
Red blood cell volume								
Expected, ml	1547 (1461–1592)	1548 (1456–1607)	0.080	1416 (1364–1591)	1413 (1363–1601)	0.814	0.246	0.226
Measured, ml	1262 (1175–1342) *	1249 (1208–1342) *	0.248	1422 (1242–1585)	1510 (1220–1611)	0.424	0.060	**0.037**
Deviation, ml	−253 (−326−−161)	−269 (−334−−154)	0.349	−23 (−216–48)	−9 (−167–137)	0.530	**0.003**	**0.002**
Deviation, %	−16 (−21−−11)	−17 (−23-−−11)	0.296	−1.4 (−13–3.5)	−.49 (−13–9.8)	0.470	**0.004**	**0.003**
Total blood volume								
Expected, ml	4293 (4052–4417)	4295 (4042–4459)	0.084	3929 (3785–4414)	3922 (3783–4443)	0.677	0.246	0.226
Measured, ml	3608 (3362–4042) *	3864 (3704–4260) *	**0.008**	4271 (3610–4532)	4609 (3778–5047)	0.077	**0.036**	**0.046**
Deviation, ml	−577 (−768−−242)	−263 (−624–47)	**0.008**	138 (−253–443)	308 (−51–1120)	0.077	**0.002**	**0.004**
Deviation, %	−13 (−20−−5.6)	−5.9 (−14–1.1)	**0.008**	3.7 (−6.6–11)	8.3 (−1.3–29)	0.064	**0.003**	**0.003**

* Significantly different from expected value, $P<0.05$ by Wilcoxon matched-pairs signed-ranks test

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