

Renin–Aldosterone Paradox and Perturbed Blood Volume Regulation Underlying Postural Tachycardia Syndrome

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Background—Patients with postural tachycardia syndrome (POTS) experience considerable disability, but in most, the pathophysiology remains obscure. Plasma volume disturbances have been implicated in some patients. We prospectively tested the hypothesis that patients with POTS are hypovolemic compared with healthy controls and explored the role of plasma renin activity and aldosterone in the regulation of plasma volume.

Methods and Results—Patients with POTS (n=15) and healthy controls (n=14) underwent investigation. Heart rate (HR), blood pressure (BP), plasma renin activity, and aldosterone were measured with patients both supine and upright. Blood volumes were measured with ¹³¹I-labeled albumin and hematocrit. Patients with POTS had a higher orthostatic increase in HR than controls (51±18 versus 16±10 bpm, *P*<0.001). Patients with POTS had a greater deficit in plasma volume (334±187 versus 10±250 mL, *P*<0.001), red blood cell volume (356±128 versus 218±140 mL, *P*=0.010), and total blood volume (689±270 versus 228±353 mL, *P*<0.001) than controls. Despite the lower plasma volume in patients with POTS, there was not a compensatory increase in plasma renin activity (0.79±0.58 versus 0.79±0.74 ng · mL⁻¹ · h⁻¹, *P*=0.996). There was a paradoxically low level of aldosterone in the patients with POTS (190±140 pmol/L versus 380±230 pmol/L; *P*=0.017).

Conclusions—Patients with POTS have paradoxically unchanged plasma renin activity and low aldosterone given their marked reduction in plasma volume. These patients also have a significant red blood cell volume deficit, which is regulated by the renal hormone erythropoietin. These abnormalities suggest that the kidney may play a key role in the pathophysiology of POTS. (*Circulation*. 2005;111:1574-1582.)

Key Words: tachycardia ■ renin ■ nervous system, autonomic ■ blood volume ■ aldosterone

Postural tachycardia syndrome (POTS) is the most common disorder among patients seen at several centers specializing in diseases of the autonomic nervous system. It affects an estimated 500 000 people in the United States alone.¹ POTS (excessive increase in heart rate [>30 bpm] on standing, associated with orthostatic symptoms in the absence of orthostatic hypotension) can produce substantial disability among otherwise healthy people.

The pathophysiology of POTS is poorly understood. Many of these patients have elevated levels of plasma norepinephrine, particularly when upright.² Subgroups of patients have a primary hyperadrenergic state,³ whereas others have partial dysautonomia that affects the lower limbs.⁴⁻⁷ The role of blood volume in the pathogenesis of POTS is unclear. Some investigators have found that patients with POTS have deficits in their plasma volumes^{8,9} and that some patients improve after acute¹⁰ or chronic⁹ plasma volume expansion.

Conversely, other investigative groups have reported normal plasma volumes in patients with POTS.^{11,12}

The renin–angiotensin–aldosterone system plays a key role in the neurohormonal regulation of plasma volume in humans.¹³ In response to hypovolemia, plasma renin activity and angiotensin II would be expected to increase to promote blood volume expansion. Angiotensin II promotes sodium and water retention, both directly by stimulating sodium reabsorption in the proximal tubules¹⁴ and indirectly by stimulating aldosterone secretion.¹⁵ The mineralocorticoid aldosterone governs sodium transport at several sites in the kidney. Jacob et al⁸ have reported that some patients with POTS have low plasma renin activity despite a low plasma volume, which suggests that a perturbation in the renin–angiotensin–aldosterone axis might have a role in the pathophysiology of POTS.

In this prospective, controlled study, we tested the hypothesis that patients with POTS have a deficit in plasma volume.

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We also explored the regulation of plasma volume by renin and aldosterone.

Methods

Subjects

Patients referred to the Vanderbilt University Autonomic Dysfunction Center with POTS between October 2002 and November 2003 were candidates for inclusion in this study. Patients met the current criteria for POTS.¹⁶ Briefly, patients developed symptoms of orthostatic intolerance accompanied by a heart rate rise ≥ 30 bpm (or a rate that exceeds 120 bpm) that occurred within the first 10 minutes of standing or head-up tilt, without any evidence of orthostatic hypotension (a fall in blood pressure of $>20/10$ mm Hg). Patients had at least a 6-month history of symptoms, in the absence of another chronic debilitating disorder or prolonged bed rest, and were at least 18 years of age. Healthy control subjects (who did not meet criteria for POTS, and were at least 18 years of age) underwent all of the same protocol elements. Patients and controls were free of medications that could impair autonomic tone¹⁷ and were not taking fludrocortisone for at least 5 days before testing. The Vanderbilt University Investigational Review Board approved this study, and written informed consent was obtained from each subject before the study began.

Protocol

Study investigations were performed at the Elliot V. Newman Clinical Research Center at Vanderbilt University. For 3 days before testing, subjects consumed a diet that contained 150 mEq of sodium per day and 70 mEq of potassium per day. The diet was free of caffeine-containing beverages.

Supine and Upright Posture Study

Heart rate, blood pressure, aldosterone, plasma renin activity, and plasma norepinephrine and epinephrine were assessed after overnight rest with subjects in the supine position and again after subjects had been standing for up to 30 minutes (as tolerated). The standing test was performed to assess the hemodynamic and biochemical responses to increased central hypovolemia (accentuated by the gravitational stress). For catecholamine measurements, blood was collected in plastic syringes and immediately transferred to chilled vacuum tubes with EGTA and reduced glutathione (Amersham International PLC) and immediately put on ice. The plasma was separated by refrigerated centrifugation at -4°C and stored at -70°C until the assay. Concentrations of norepinephrine and epinephrine were measured by batch alumina extraction, followed by high-performance liquid chromatography for separation with electrochemical detection and quantification.⁸ Plasma renin enzymatic activity was assayed by conversion of angiotensinogen to angiotensin I by a radioimmunoassay technique (antibodies from IgG Corporation)¹⁸ and reported in nanograms of angiotensin I per milliliter per hour. Blood for aldosterone was collected in chilled vacuum tubes without preservative, and the serum was extracted and sent to the laboratory on ice. Serum aldosterone was measured by radioimmunoassay (DPC Coat-a-Count, Diagnostic Products Corp). The aldosterone-to-plasma renin activity ratio was calculated with the conventional units for aldosterone (ng/dL; $1\text{ ng/dL}=27.7\text{ pmol/L}$) and plasma renin activity ($\text{ng} \cdot \text{mL}^{-1} \cdot \text{h}^{-1}$) and reported without units.

Blood Volume Assessment

Plasma volume was determined by the indicator dye-dilution technique. In the morning after an overnight fast, patients were placed in a supine position for a minimum of 60 minutes before collection of the baseline sample. A 20-gauge intravenous catheter was placed in an antecubital vein, and blood samples could be obtained without stasis. A baseline venous sample of 5 mL was collected before injection of the tracer. With a prefilled 1-mL syringe, up to 25 μCi of ^{131}I -labeled human serum albumin (Volumex, Iso-Tex Diagnostics Inc) was injected into the antecubital vein and flushed with 30 mL of

normal saline. Starting at 12 minutes after injection, 5 mL of venous blood was collected at 6-minute intervals until 30 minutes after injection (5 samples, including baseline sample). Hematocrit was measured in duplicate from each sample after 10-minute centrifugation at 11 500 rpm on an International Equipment Co microcapillary centrifuge and read on an International Equipment Co microcapillary tube reader. Plasma radioactivity was measured in duplicate and averaged (for each sample and a reference standard) with an automated counter (BVA-100 Blood Volume Analyzer, DAXOR Corporation). A least-squares regression of the volume of distribution at each time point was automatically performed to determine the volume of distribution at the time of injection. Plasma volume was determined as the volume of distribution of albumin.

Total blood volume was calculated from measured plasma volume and microcapillary venous antecubital hematocrit corrected for the plasma-packing ratio (0.99),¹⁹ the ratio of mean body hematocrit to peripheral (measured) hematocrit (0.91),²⁰ and the effects of heparin within the sampling syringe (0.97).²¹

Red blood cell volume was calculated as the difference between total blood volume and plasma volume. This DAXOR method of red blood cell volume assessment was recently found to correlate well with the traditional ^{51}Cr red blood cell-labeling method (Pearson correlation $R=0.96$), with a mean difference between the techniques of 0.9% (personal communication with Dr Howard Dworkin, William Beaumont Hospital, Royal Oak, Mich).

Ideal plasma and total blood volume was determined on the basis of the height, weight, and gender of the individual subject.²² Individual “deficits” in plasma volume, red blood cell volume, and total blood volume were calculated as the ideal minus measured volume (in milliliters), or this difference divided by the ideal volume (percentage).

Plasma Volume Shift With Upright Tilt

All studies occurred between 10 AM and noon in a quiet, dimly lit room at a comfortable ambient temperature (21°C to 24°C). An antecubital venous catheter was inserted (if not already in situ and functioning) for blood sampling at least 15 minutes before the beginning of the test, with the patient supine. Subjects were tilted head-up to 60° for 30 minutes or until the subject experienced presyncope that required test termination.

Blood was drawn at baseline and then at 5, 10, 15, 20, and 30 minutes of tilt for measurement of hematocrit in quadruplicate (see Blood Volume Assessment section for details of hematocrit assessment). Relative changes in hematocrit from baseline were used to calculate the change in plasma volume with upright tilt. The percentage change in plasma volume ($\Delta\text{PV}\%$) = $100 \times [(\text{Hct}_{\text{Baseline}} - \text{Hct}_{\text{Time}}) / \text{Hct}_{\text{Time}}] \times [1 / (1 - \text{Hct}_{\text{Baseline}})]$, with the absolute change in plasma volume (ΔPV) = $\Delta\text{PV}\% \times \text{measured plasma volume}$ (where $\text{Hct}_{\text{Baseline}}$ is hematocrit before tilt, and Hct_{Time} is hematocrit at a given time after tilt).²³ $\Delta\text{PV}_{\text{End}}$ and $\Delta\text{PV}\%_{\text{End}}$ were defined as the ΔPV at the time of the last measured hematocrit before tilt termination. $\Delta\text{PV}_{\text{End}}$ was used in place of the individual late time points to minimize the confounding effect of late data dropout due to premature tilt termination. A negative value reflects a shift in plasma volume out of the vascular space.

Gender Analysis

POTS is a disorder that affects women more often than men. In addition to an overall analysis that included all subjects, a separate analysis was performed that included only female subjects. This was to ensure that the results were not skewed by the small number of men.

Statistical Analysis and Sample Size Calculations

Our primary end point was the plasma volume deficit (measured plasma volume minus ideal plasma volume). The null hypothesis was that the plasma volume deficit would not be statistically different between patients with POTS and control subjects. We calculated the size of our required sample after determining that a 7.5% deficit in plasma volume in patients with POTS would be

TABLE 1. Baseline Information

	Overall Group			Female Subjects Only		
	POTS (n=15)	Control (n=14)	<i>P</i>	POTS (n=13)	Control (n=9)	<i>P</i>
Age, y	36±11	34±7	0.472	36±12	34±8	0.604
Height, cm	166±8	170±8	0.145	164±7	166±5	0.429
Mass, kg	66.3±19.3	74.5±13.0	0.195	66.2±20.8	67.3±7.7	0.886
Body mass index, kg/m ²	24.2±6.8	25.6±3.3	0.477	24.6±7.2	24.5±3.2	0.977
Na ⁺ , mEq/L	138±2	139±2	0.804	138±2	138±2	0.652
K ⁺ , mEq/L	4.1±0.3	4.2±0.3	0.461	4.1±0.3	4.2±0.3	0.542
Calculated osmolality, mEq/L	286±4	287±4	0.785	286±5	285±4	0.677
Hematocrit, %	37.8±2.4	38.0±3.0	0.812	38.9±2.5	38.1±3.3	0.559

All values are presented as mean±SD. *P* value for gender distribution from a Fisher exact test, other *P* values from Student *t* test.

clinically significant. We did not expect the control subjects to have a plasma volume deficit. Assuming a pooled SD of 5% (giving an effect size of 1.5), a sample size of 13 subjects in each group would give 95% power to detect a statistically significant difference with a Student *t* test with a 2-sided significance level of 0.05.²⁴ Differences between groups were analyzed with the Student *t* test. The Mann-Whitney *U* test was also used to confirm the results obtained from the Student *t* test, and the significance of the reported parameters was not different between the 2 tests. Categorical variables were analyzed with the Fisher exact test. Values are reported as means and SDs unless otherwise noted. Probability values of <0.05 were considered statistically significant, and all tests were 2 sided. Statistical analyses were performed with SPSS for Windows (version 12.0, SPSS). Sample size calculations were performed with nQuery Advisor (version 5.0). Prism for Windows 4 (version 4.02, GraphPad Software Inc.) was used for graphical presentation.

Results

Baseline Information

We enrolled 15 patients with POTS and 14 controls. The baseline characteristics are enumerated in Table 1. There was

no significant difference in baseline characteristics between patients with POTS and control subjects for the overall group or when just the female subjects were considered.

Supine and Upright Posture Study

As seen in Figure 1A, patients with POTS had a higher heart rate than control subjects both when supine (77±12 versus 64±12 bpm, *P*=0.008) and when standing upright for up to 30 minutes (128±18 versus 80±11 bpm, *P*<0.001). As would be expected on the basis of the diagnostic criteria for POTS, patients with POTS had a significantly greater increase in heart rate (51±18 bpm) on assuming the upright position than did the control subjects (16±10 bpm, *P*<0.001). The supine systolic blood pressure was similar between the 2 groups (POTS versus control, 111±14 versus 114±13 mm Hg; *P*=0.525; Figure 1B). Both groups experienced a small increase in systolic blood pressure that was not statistically significant on standing, with no difference between groups (POTS versus control, 123±20 versus

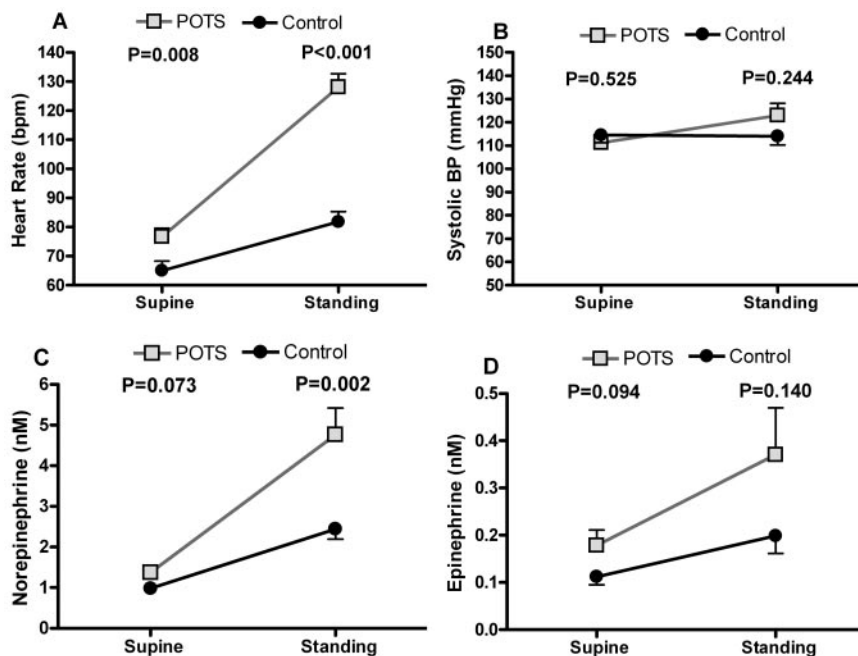


Figure 1. Hemodynamic parameters and catecholamines: supine and upright. Supine and upright values for heart rate (A), systolic blood pressure (BP; B), venous plasma norepinephrine (C), and venous plasma epinephrine (D) for patients with POTS and control subjects. Error bars represent SE. Probability values are from between-group comparison with Student *t* test.

115±14 mm Hg; $P=0.244$). Neither the diastolic blood pressures while supine (POTS 67±8 mm Hg; control 70±9 mm Hg; $P=0.321$) or standing (POTS 79±14 mm Hg; control 77±10 mm Hg; $P=0.636$) nor the mean blood pressures while supine (POTS 81±9 mm Hg; control 85±10 mm Hg; $P=0.367$) or standing (POTS 94±15 mm Hg; control 90±10 mm Hg; $P=0.417$) were different between the 2 groups.

Plasma catecholamines were drawn with subjects in both the supine and upright positions. The supine plasma norepinephrine (Figure 1C) values appeared to be slightly higher in patients with POTS (1.37±0.62 nmol/L) than in the control subjects (0.98±0.45 nmol/L), but this difference was not statistically significant ($P=0.073$). In response to standing, plasma norepinephrine increased significantly more in patients with POTS (>3-fold increase in norepinephrine) than in the control subjects (>2-fold increase in norepinephrine; $P=0.002$). Patients with POTS had a significantly higher upright plasma norepinephrine than did the control subjects (4.76±2.37 versus 2.44±0.89 nmol/L, $P=0.002$). In contrast to norepinephrine values, plasma epinephrine values were not different between the 2 groups in either the supine or the upright positions (Figure 1D), nor was the increase in epinephrine from supine to upright position significantly different between the groups ($P=0.350$).

Renin and Aldosterone

After 3 days of the study's fixed dietary salt intake, there was no difference in plasma renin activity (Figure 2A) between the patients with POTS and the control groups in the supine position (0.79±0.58 versus 0.79±0.74 ng · mL⁻¹ · h⁻¹, $P=0.996$). In contrast to the standing plasma norepinephrine values, there was no difference in standing plasma renin activity between patients with POTS and control subjects (2.03±1.26 versus 2.08±2.05 ng · mL⁻¹ · h⁻¹; $P=0.944$). The supine serum aldosterone (Figure 2B) was significantly lower in patients with POTS (190±140 pmol/L) than in control subjects (380±230 pmol/L; $P=0.017$). Serum aldosterone increased in both groups on standing. The upright serum aldosterone was significantly lower in patients with POTS (480±290 pmol/L) than in control subjects (810±370 pmol/L; $P=0.019$). The supine aldosterone–plasma renin activity ratio, a measure of the relationship between these 2 parameters, was significantly lower in patients with POTS (0.93±0.65) than in control subjects (3.19±3.29; $P=0.047$; Figure 2C).

Supine and Upright Posture Study in Females

The hemodynamic and biochemical responses of the female subjects to supine and standing posture are shown in the figure in the online-only Data Supplement. The results were qualitatively similar to those seen in the overall group analysis. In the standing position, female patients with POTS had a significantly higher heart rate ($P<0.001$), a significantly higher plasma norepinephrine level ($P=0.025$), and a significantly lower aldosterone level ($P=0.038$) than control subjects. There were no differences between the groups while standing for blood pressure, plasma epinephrine, or plasma renin activity. In the setting of the smaller sample size in this subgroup analysis, none of the supine hemodynamic and

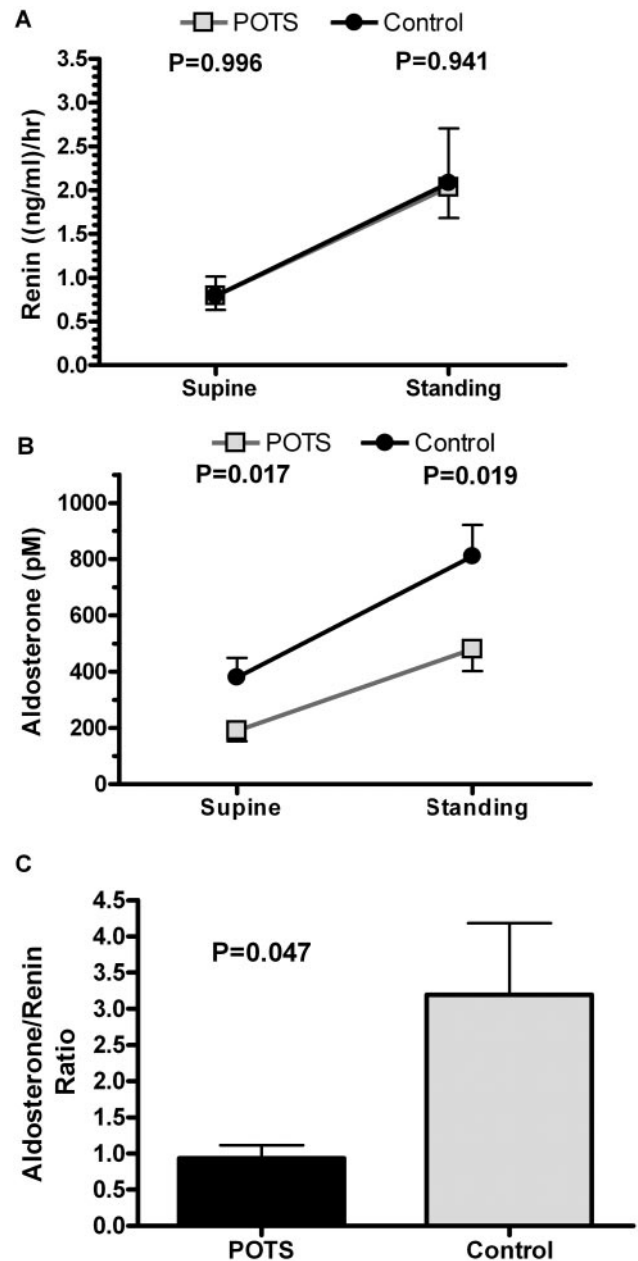


Figure 2. Renin and aldosterone. Supine and upright values for plasma renin activity (A) and serum aldosterone (B) for patients with POTS and control subjects. C, Aldosterone to renin ratio (in conventional units) in supine position, as measure of mismatch between renin activity and aldosterone response, for patients with POTS and control subjects. Ratio of aldosterone to plasma renin activity was calculated with conventional units for aldosterone (ng/dL; 1 ng/dL=27.7 pmol/L) and plasma renin activity (ng · mL⁻¹ · h⁻¹) and reported without units. Error bars represent SE. Probability values are from between-group comparison with Student *t* test.

biochemical parameters were significantly different between groups.

Blood Volumes

As shown in Table 2, plasma volume was significantly lower in patients with POTS (2348±438 mL) than in control subjects (2823±480 mL, $P=0.010$), whereas ideal plasma

TABLE 2. Blood Volumes

	Overall Group			Female Subjects Only		
	POTS (n=15)	Control (n=14)	<i>P</i>	POTS (n=13)	Control (n=9)	<i>P</i>
Plasma volume						
Measured, mL	2348±438	2823±480	0.010	2298±438	2579±286	0.107
Ideal, mL	2682±379	2833±287	0.239	2652±389	2674±158	0.878
Deficit, mL	334±187	10±250	<0.001	354±193	94±201	0.006
Deficit, %	12.8±7.6	0.8±8.8	<0.001	13.6±7.8	3.6±7.7	0.007
Red cell volume						
Measured, mL	1201±221	1510±405	0.016	1153±186	1272±163	0.137
Ideal, mL	1557±268	1729±330	0.134	1495±219	1507±89	0.879
Deficit, mL	356±128	218±140	0.010	342±132	235±83	0.044
Deficit, %	22.7±7.2	13.5±8.2	0.003	22.7±7.7	15.9±6.0	0.038
Total blood volume						
Measured, mL	3550±642	4334±868	0.010	3451±611	4334±868	0.106
Ideal, mL	4239±631	4562±608	0.173	4147±609	4180±247	0.878
Deficit, mL	689±270	228±353	<0.001	696±291	329±252	0.006
Deficit, %	16.5±6.8	5.6±7.8	<0.001	16.9±7.2	8.0±6.2	0.007

All values are presented as mean±SD. *P* values from Student *t* test. Blood volume deficits are calculated as the ideal volume minus the measured volume.

volumes were not significantly different. Calculating the plasma volume deficit controls for individual variations in ideal plasma volumes based on size and gender. Patients with POTS had a plasma volume deficit of 334±187 mL, which represented 12.8±7.6% of their ideal plasma volume, whereas control subjects had no deficit (10±250 mL [0.8±8.8%]). Figure 3A illustrates both this highly significant difference and the variability in plasma volume deficits within the 2 groups. The plasma volume of 1 patient with POTS actually exceeded expectations. Conversely, 3 patients with POTS had a plasma volume deficit of >20%, with a plasma volume deficit as high as 27% in 1 patient with POTS.

The measured red blood cell volume was also lower by a mean of >300 mL in patients with POTS than in control subjects (Table 2). Control subjects experienced a modest deficit in red blood cell volume. In contrast, patients with POTS had a mean deficit in red blood cell volume of >350 mL, which represented a 22.7% deficit from the expected red blood cell volume (Figure 3B). The difference between the 2 groups was highly significant (*P*=0.003). Supine hematocrit values were not different between patients with POTS and control subjects (37.8±2.4% versus 38.0±3.0%, *P*=0.812), which reflects the parallel decrease in both plasma volume and red blood cell volume in patients with POTS.

The total blood volume followed the same pattern as the plasma volume and red blood cell volume components. The measured total blood volume was significantly lower in patients with POTS than in control subjects (*P*=0.010; Table 2). Even after we corrected for individual differences in ideal total blood volume, patients with POTS still had a significantly larger relative deficit in total blood volume (16.5±6.8% versus 5.6±7.8%, *P*<0.001; Figure 3C). This works out to a mean absolute total blood volume deficit of 460 mL compared with the control subjects.

Blood volumes for the female subjects are shown in Figures 3D through 3F and in Table 2. Concordant with the overall group, each of the 3 measured blood volume deficits was greater for patients with POTS than for control groups.

Plasma Volume Shifts With Upright Tilt

Plasma volume shifts with upright tilt were calculated both early during the tilt (5 minutes [$\Delta PV\%_{5 \text{ minutes}}$]) and near the end of tilt ($\Delta PV\%_{\text{End}}$) as a percentage of the baseline plasma volume. Neither the mean $\Delta PV\%_{5 \text{ minutes}}$ ($-11.7\pm 3.2\%$ versus $-10.4\pm 3.5\%$, *P*=0.298) nor the mean $\Delta PV\%_{\text{End}}$ ($-16.6\pm 4.7\%$ versus $-15.3\pm 4.6\%$, *P*=0.463) was different in patients with POTS compared with control subjects. As can be seen in Figure 4, there was significant heterogeneity in the maximal plasma volume shift with upright tilt in both groups.

Discussion

This study sought to assess both blood volume and the role of the renin–angiotensin–aldosterone system in the regulation of blood volume in POTS. The main findings from this prospective study were that compared with control subjects, patients with POTS (1) have a significant deficit of plasma volume, (2) have a significantly lower level of serum aldosterone, (3) have an inappropriately low level of plasma renin activity given the degree of hypovolemia that they exhibit, and (4) have a significant deficit of red blood cell volume in the setting of an elevated standing heart rate and plasma norepinephrine.

Plasma Volume

Patients with POTS had a lower basal plasma volume (Table 2) than the control subjects. Accurate plasma volume assessments can be affected by several environmental, dietary, and patient-related factors.²⁵ These variables may in part explain

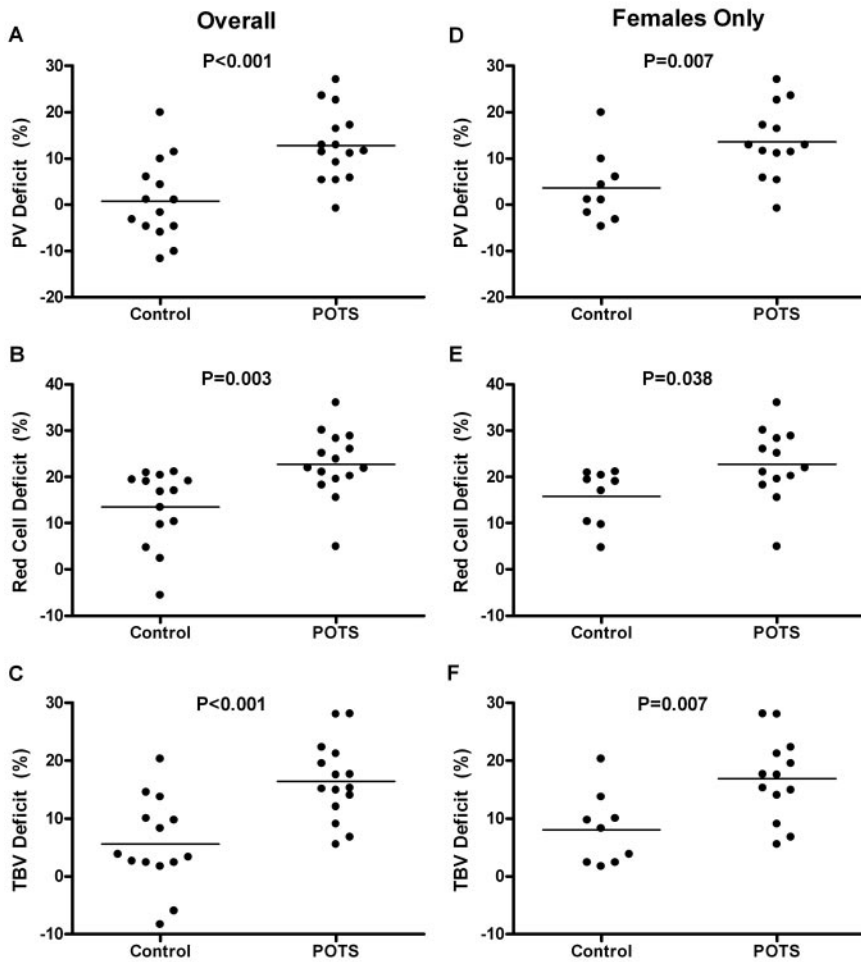


Figure 3. Blood volumes. Individual and mean values are presented for plasma volume (PV) deficit (A) as percentage (individual deficit=[ideal plasma volume–measured plasma volume]/ideal plasma volume) for control subjects and patients with POTS. Negative value for deficit implies excess in plasma volume. Probability values are from between-group comparison with Student *t* test. Similar figures are presented for red blood cell volume deficit (B) and total blood volume (TBV) deficit (C). D through F, Data when only female subjects were included.

the mixed results obtained by other investigators who have tried to assess plasma volume in patients with POTS.^{8,9,11,12} Several measures were undertaken in the present study to ensure that the plasma volume was measured accurately. Study subjects were withdrawn from all medications that might alter the plasma volume (such as fludrocortisone) for at

least 5 days before the study. They consumed a controlled sodium diet for at least 3 days before assessment, because sodium intake can alter activation of the renin–angiotensin–aldosterone axis and subsequently alter plasma volume. Finally, all plasma volume assessments were performed in the same temperature-controlled room on the research unit after the subjects had been supine for at least 1 hour. Other factors that can physiologically alter plasma volume include the subject’s size and gender.^{21,22} To correct for individual variations in subject size, we calculated the expected plasma volume for each subject based on his or her size and gender and subtracted the measured plasma volume to arrive at the individual’s actual plasma volume deficit, as shown in Figure 3A. Patients with POTS had a mean plasma volume deficit of almost 350 mL, whereas control subjects had no such deficit. The deficit of 13% in patients with POTS constitutes a moderate to severe hypovolemia. This reduction in effective circulating volume could trigger a cascade of perturbations associated with POTS. In the supine position, this hypovolemia may cause only modest or nonsignificant changes in heart rate and plasma norepinephrine. In the upright position, in the setting of gravitational blood pooling, the additional reduced volume could decrease the cardiac output and cause a reflex increase in sympathetic nerve activity. The result would be an increase in the upright plasma norepinephrine

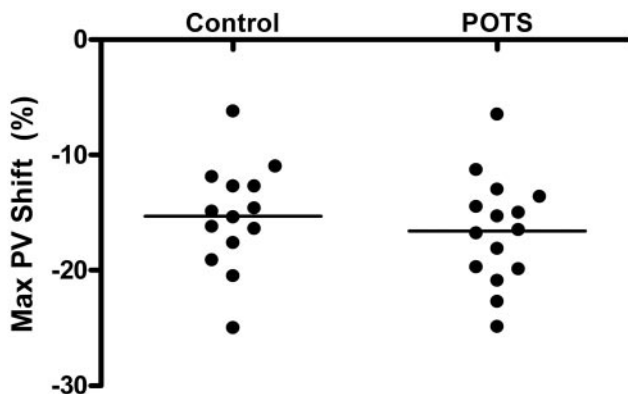


Figure 4. Plasma volume shift with upright tilt. Individual and mean shifts in plasma volume (PV Shift), as percentage of baseline plasma volume, in response to upright tilt are presented for control subjects and patients with POTS. Negative value represents shift of plasma volume from intravascular to extravascular space. Mean differences were not statistically significant between groups. Max indicates maximum.

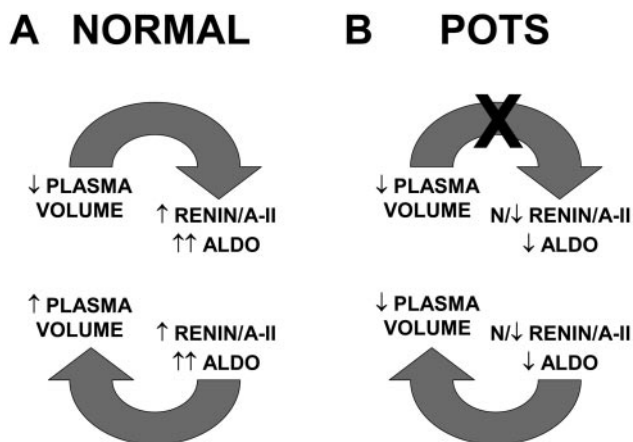


Figure 5. Aldosterone paradox in POTS. A, Under normal circumstances, low plasma volume is sensed in kidney (and in heart and aorta) and stimulates increase in plasma renin activity (renin), angiotensin II (A-II), and aldosterone (ALDO). Increase in plasma renin activity and aldosterone promotes salt and water retention, which leads to increase in extracellular fluid volume and plasma volume. B, In POTS, there is failure to sense and appropriately respond to low plasma volume. There is no appropriate increase in plasma renin activity, angiotensin-II, and aldosterone given the hypovolemia. Because plasma renin activity and aldosterone are not increased, salt and water retention is not increased, and plasma volume is not increased.

levels and an increase in standing heart rate, as seen in patients with POTS (Table 1).

Renin–Aldosterone Paradox

The renin–angiotensin–aldosterone system plays an important role in the regulation of plasma volume.¹³ Hypovolemia, acting via reduced renal blood flow and possible cardiorenal mechanisms,^{26,27} would be expected to increase plasma renin activity, which should augment levels of angiotensin II and subsequently lead to increased levels of aldosterone. Angiotensin II promotes renal sodium retention both directly, through receptors in the renal proximal tubule,¹⁴ and indirectly, by stimulating the secretion of the mineralocorticoid aldosterone.¹⁵ Through this augmented sodium retention, the renin–angiotensin–aldosterone axis should restore extracellular fluid volume (Figure 5A).

Plasma renin activity was similar in patients with POTS and control subjects, whereas supine and upright levels of aldosterone were significantly lower in patients with POTS (Figure 2). Given their degree of hypovolemia, however, one would expect both plasma renin activity and aldosterone levels to be significantly higher in the POTS group than in controls. Both the plasma renin activity and, to a greater extent, aldosterone levels were inappropriately low given the hypovolemic status of the patients with POTS. We have termed this dysregulation of plasma renin activity and aldosterone in POTS the “renin–aldosterone paradox” (Figure 5B).

Aldosterone secretion is controlled at many levels: it is stimulated by angiotensin II, potassium, and hyponatremia, and acutely by the adrenocorticotropic hormone; it is inhibited by dopamine and atrial natriuretic factor (ANF).²⁸ Electrolyte abnormalities are not likely to explain the low aldosterone as the sodium and potassium levels were similar in

the POTS group and controls (Table 1). Although we cannot exclude the possibility that there are abnormalities in ANF or increases in adrenal dopamine concentrations that could contribute to the low aldosterone state, the most likely explanation for the renin–aldosterone paradox is an inappropriately low level of angiotensin II.

The cause of the inappropriately low levels of plasma renin activity and aldosterone in POTS is not clear. Low-flow states across the juxtaglomerular apparatus (as is seen in renal artery stenosis) are known to increase plasma renin activity. It is possible that the opposite effect somehow occurs in POTS, presumably by impaired vascular function. Other possibilities include problems with the sensor mechanisms at the level of the macula densa, or in the transmission of this signal to the juxtaglomerular apparatus, or in the response of the juxtaglomerular apparatus.¹³ It is also possible that patients with POTS have a low blood vessel “capacitance” that in turn limits the blood volume. Such a phenomenon has been proposed to exist in patients with pheochromocytoma, who have low blood volume.^{29,30} Plasma volume and total blood volume increase in response to treatment with an α -adrenergic antagonist.³¹

Red Blood Cell Volume

In addition to deficits in plasma volume patients with POTS also had a significant reduction in red blood cell volume (Figure 3B and Table 2). This finding would not have been apparent on cursory assessment. Hematocrit levels were not different between the 2 groups (Table 1). Because there was a parallel reduction in the 2 largest components of blood volume (plasma volume and red blood cell volume), the percentage of the blood column that was due to the red blood cells appeared to be normal. Thus, we required a formal radioisotope dilution assessment of blood volumes to document the red blood cell volume deficit.

This red blood cell volume deficit has been observed previously in patients with POTS.^{11,12} The pathogenesis of this deficit, however, is not known. The renal hormone erythropoietin is the primary agonist for red blood cell production in the bone marrow.^{32–34} It is possible that a deficit in erythropoietin production might play a pathophysiological role in POTS, although this is not yet clear.

There are several pieces of evidence that point to an important role for angiotensin II and the renin–angiotensin–aldosterone axis in the regulation of erythropoietin production. First, in healthy subjects, infusions of angiotensin II caused serum erythropoietin levels to increase significantly, but this stimulation of erythropoietin was blocked when the subjects were premedicated with losartan, an angiotensin receptor blocker.^{35,36} Second, plasma renin activity is higher among hemodialysis patients who do not require exogenous erythropoietin to maintain a hematocrit of 30% (which suggests adequate endogenous erythropoietin) than in those patients who require exogenous erythropoietin.³⁷ Third, plasma ultrafiltration induced a doubling of plasma renin activity, which was accompanied by a 69% rise in serum erythropoietin over 4 hours.³⁷ This increase in erythropoietin was abolished with the use of an ACE inhibitor. Finally, some patients develop a persistently elevated hematocrit after renal

transplant.³⁸ Inactivation of the renin–angiotensin–aldosterone system by an ACE inhibitor or an angiotensin receptor blocker can correct this polycythemia,^{39,40} and conversely, withdrawal of the ACE inhibitor has been associated with “rebound” polycythemia.³⁸ Taken together, these pieces of evidence suggest that the paradoxically low renin activity seen in patients with POTS could be the cause of the low red blood cell volume through a direct hormonal effect.

Another possible explanation for the low red blood cell volume seen in POTS is that it is a direct result of the low plasma volume. The kidney may function as the key organ involved in the regulation of hematocrit, because it controls both plasma volume (through salt regulation) and red blood cell volume (through erythropoietin).⁴¹ To maintain an appropriate hematocrit (the hematocrit was similar between patients with POTS and controls), the red blood cell volume may be adjusted downward through a physiologically reduced level of erythropoietin to match the deficit in plasma volume.

Erythropoietin replacement, by itself, is not likely to restore normal physiological function in patients with POTS. Hoeldtke et al¹² studied 8 patients with POTS and found 6 of those patients to have a low red blood cell volume. Treatment with open-label erythropoietin improved the red blood cell volume but did not increase the plasma volume. The orthostatic tachycardia was corrected in only 1 of their patients, although 3 patients subjectively reported feeling better.

Study Limitations

We have found that plasma renin activity and aldosterone are not appropriately regulated in patients with POTS. The low aldosterone-renin ratio seen in POTS suggests a mismatch between these 2 hormones. One limitation of the present study was that levels of angiotensin II, a biochemical link between renin and aldosterone, were not measured directly. Other potential regulators of aldosterone secretion (dopamine and ANF) and salt and water regulation (such as antidiuretic hormone, serum osmolality, and B-type natriuretic peptide) may also provide useful insights into the renin–aldosterone paradox seen in POTS. Future studies will include an assessment of these markers.

Conclusions

In summary, we have found that patients with POTS have a reduction in plasma volume. They have inappropriately low levels of renin and low levels of aldosterone, 2 hormones that promote sodium retention and increase plasma volume and are regulated by the kidneys. These patients also have a significantly low volume of red blood cells. Red blood cell production is primarily stimulated by erythropoietin, a hormone that is released by the kidney. Taken together, these findings suggest that abnormalities in the kidney might be critical in the pathophysiology of POTS.

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