

Altered Systemic Hemodynamic and Baroreflex Response to Angiotensin II in Postural Tachycardia Syndrome

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Background—Postural tachycardia syndrome (POTS) is characterized by excessive orthostatic tachycardia and significant functional disability. We have previously found that patients with POTS have increases in plasma angiotensin II (Ang II) that are twice as high as healthy subjects despite normal blood pressures (BPs). In this study, we assess systemic and renal hemodynamic and functional responses to Ang II infusion in patients with POTS compared with healthy controls.

Methods and Results—Following a 3-day sodium-controlled diet, we infused Ang II (3 ng/kg per minute) for 1 hour in patients with POTS (n=15) and healthy controls (n=13) in the supine position. All study subjects were women with normal BP. Ages were similar for patients with POTS and controls (mean±SEM, 30±2 versus 26±1 years; $P=0.11$). We measured the changes from baseline mean arterial pressure, renal plasma flow, plasma renin activity, aldosterone, urine sodium, and baroreflex sensitivity in both groups. In response to Ang II infusion, patients with POTS had a blunted increase compared with controls in mean arterial pressure (10±1 versus 14±1 mm Hg, $P=0.01$) and diastolic BP (9±1 versus 13±1 mm Hg, $P=0.01$) but not systolic BP (13±2 versus 15±2 mm Hg, $P=0.40$). Renal plasma flow decreased similarly with Ang II infusion in patients with POTS versus controls (−166±20 versus −181±17 mL/min per 1.73 kg/m², $P=0.58$). Postinfusion, the decrease in plasma renin activity (−0.9±0.2 versus −0.6±0.2 ng/mL per hour, $P=0.43$) and the increase in aldosterone (17±1 versus 15±2 pg/mL, $P=0.34$) were similar in both groups. The decrease in urine sodium excretion was similar in patients with POTS and controls (−49±12 versus −60±16 mEq/g creatinine, $P=0.55$). The spontaneous baroreflex sensitivity at baseline was significantly lower in patients with POTS compared with controls (10.1±1.2 versus 16.8±1.5 ms/mm Hg, $P=0.003$), and it was further reduced with Ang II infusion.

Conclusions—Patients with POTS have blunted vasopressor response to Ang II and impaired baroreflex function. This impaired vasoconstrictive response might be exaggerated with upright posture and may contribute to the subsequent orthostatic tachycardia that is the hallmark of this disorder.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00962949.

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Key Words: tachycardia ■ autonomic nervous system ■ angiotensin II ■ aldosterone ■ renal plasma flow

Postural tachycardia syndrome (POTS) is a chronic disorder characterized by a marked increase in heart rate on upright posture in the absence of orthostatic hypotension. It is estimated that >500 000 patients are affected in the United States.¹ POTS predominantly affects young women of reproductive age.^{2,3} Patients often experience a myriad of orthostatic symptoms that include palpitations, lightheadedness, and mental clouding,⁴ and POTS is associated with significant functional disability and diminished quality of life.⁵

Clinical Perspective on p 180

Various mechanisms may contribute to the orthostatic tachycardia and orthostatic intolerance in POTS, but the exact pathophysiology of POTS is still uncertain. The proposed mechanisms include increased sympathetic activity,^{2,6} partial autonomic neuropathy,⁷ venous blood pooling, and low blood volume.⁸ Abnormal regulation of the renin-angiotensin-aldosterone system has been implicated in the pathogenesis of

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POTS. We previously reported that many patients with POTS have inappropriately low levels of plasma renin activity (PRA) and aldosterone in response to both standing and supine low blood volume.⁹ In addition to the blunted renin and aldosterone response, we and others demonstrated that there are 2-fold increases in the level of circulating angiotensin II (Ang II).^{10,11} The functional consequence of this high Ang II on POTS pathophysiology has not been fully elucidated. Furthermore, despite the high Ang II in POTS, the hemodynamic effects that would be expected with elevated Ang II (eg, high blood pressure [BP], fluid retention) were absent in POTS; instead, a major portion of patients with POTS have low blood volume in the supine position.⁸ These data suggest that Ang II type 1 (AT-1) receptors might be hyporesponsive to the effects of Ang II in POTS.

Given the abnormal blood volume regulation that has already been reported in POTS, the abnormal profile of the renin-angiotensin-aldosterone system in POTS, which includes high levels of Ang II and inappropriately low levels of PRA and aldosterone, we evaluated the responsiveness of different target tissues to Ang II infusion. We tested the hypothesis that patients with POTS have a state of decreased responsiveness to the action of Ang II, specifically involving the adrenal gland. The adrenal response was assessed by Ang II-induced aldosterone secretion. BP and renal plasma flow were both measured, which reflect the systemic and renal vascular response to Ang II.

Methods

Subjects

Premenopausal, normotensive women aged 18 to 50 years were studied. Fifteen patients with POTS were referred to the Vanderbilt University Autonomic Dysfunction Center between January 2009 and July 2010 and 13 healthy controls were included in this study. Because of the effect of sex hormones on the renin-angiotensin system,¹² all subjects were studied in the first 1 to 5 days of their menstrual cycle (early follicular phase); this information was obtained by a menstrual cycle history (counting days). Patients with POTS met the conventional criteria.^{9,13} Briefly, patients developed symptoms of orthostatic intolerance accompanied by a rise in heart rate (HR) of ≥ 30 beats/min that occurred within the first 10 minutes of standing up without any evidence of orthostatic hypotension (fall in BP of $\geq 20/10$ mm Hg). Patients had at least a 6-month history of symptoms in the absence of another chronic, debilitating disorder or prolonged bed rest. Healthy controls were similar in age to the patients with POTS (mean \pm SEM, 26 ± 1 versus 30 ± 2 years; $P=0.11$). All subjects underwent a detailed history and physical examination, including assessment of blood chemistry and complete blood count. BP, HR, and ECG were assessed in the supine and upright positions. None of the control subjects had an increase in HR ≥ 30 beats/min on standing or symptoms of orthostatic intolerance. Because of the strong female predominance in POTS, only female controls were recruited. Patients with POTS and controls were free of medications that could have an impact on autonomic tone for at least 5 half-lives and did not take fludrocortisone for at least 5 days before testing. The Ang II levels of the subjects were not known at the time of study enrollment. The Vanderbilt University Investigational Review Board approved this study, and written informed consent was obtained from each subject before the study began. The protocols reported here were part of the Renin-Aldosterone Axis in Postural Tachycardia Syndrome study.

Study Protocol

Study investigations were performed at the Elliot V. Newman Clinical Research Center of Vanderbilt University. For at least 3 days before testing, subjects consumed a standardized methylxanthine-free diet that provided 150 mEq/d of sodium and 100 mEq/d of potassium.

Twenty-four-hour (7:00 AM–7:00 AM) urine for assessment of urinary sodium and creatinine excretion was collected to determine compliance with the diet. Subjects reported to the unit the night before the study day. The study started at 8:00 AM after the subjects had been supine and fasting after midnight. An 18-gauge indwelling catheter was placed at least 2 hours before the start of the study in both arms; one was used for infusion of Ang II and *p*-aminohippurate (PAH), and the other was used for obtaining blood samples.

Each subject voided immediately before the start of the study. Before the Ang II infusion, baseline BP, HR, and renal plasma flow were obtained for 1 hour. Renal plasma flow was measured using PAH. An 8-mg/kg loading dose of PAH (Merck) was given intravenously followed by a continuous infusion of 12 mg/min to determine effective renal plasma flow, as we have previously described.^{13,14} Renal blood flow was calculated by dividing the effective renal plasma flow by 1–hematocrit. Renal vascular resistance was derived by dividing mean arterial pressure by the renal blood flow (expressed as mm Hg/L per minute). Automated oscillometric BP (Dinamap; Critikon) was measured every 10 minutes during the first hour (baseline). Blood was drawn for PRA, aldosterone, cortisol, sodium, potassium, creatinine, Ang II, and PAH (mean of 2 measurements). Subjects voided again at the end of the first hour, and urine was collected for electrolytes and creatinine.

Following 1 hour at baseline, as we have previously described,¹⁴ subjects received a continuous intravenous infusion of Ang II (Bachem) at an initial dose of 1 ng/kg per minute for 10 minutes followed by 3 ng/kg per minute for 60 minutes (second hour). BP was measured every 5 minutes during the second hour (Ang II infusion). At the end of the Ang II infusion, all preinfusion blood and urine samples were repeated.

Laboratory Assays

PRA was assayed by conversion of angiotensinogen to Ang I by a radioimmunoassay technique (antibodies from IgG Corporation) and reported in nanograms of Ang I per milliliter per hour. Blood for aldosterone assay 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).

Blood for determination of Ang peptides (10 mL) was poured into prechilled tubes that contained 0.5 mL of an inhibitor solution comprising 25 mmol/L $\text{NH}_4\text{-EDTA}$, 0.44 mmol/L *o*-phenanthroline (Sigma), 0.12 mmol/L pepstatin A (Sigma), and sodium *p*-hydroxymercuribenzoate (Sigma). This cocktail prevents the *in vitro* metabolism of Ang I and Ang II during manipulation of the sample. Blood samples were centrifuged at 3000 rpm for 20 minutes at 4°C, and aliquots of plasma were stored at -80°C until assayed. Angiotensin samples were analyzed at the Wake Forest Hypertension Core Laboratory. Plasma was extracted using Sep-Pak columns, as previously described.^{15,16} The sample was eluted, reconstituted, and split for the 3 radioimmunoassays. Recoveries of radiolabeled Ang added to the sample and followed through the extraction were 92% ($n=23$). Samples were corrected for recoveries. Ang II was measured using a kit produced by ALPCO Diagnostics as described previously.^{17,18} The minimum detectable level of the assay for Ang II was 0.8 pg/tube. Values at or below the minimum detectable level of the assay were arbitrarily assigned one half that value for statistical analysis. The interassay coefficient of variation for Ang II was 12%. The antibody used in the Ang II kit shows cross-reactivity with Ang III-(2–8) and Ang IV-(3–8) but no cross-reactivity with Ang I. Therefore, the values reported for Ang II do not distinguish among Ang II, Ang III, and Ang IV.

PAH concentrations (mean of 2 measurements) were determined by spectrophotometry.¹⁴ Serum cortisol level was measured by

radioimmunoassay. Serum and urine sodium, potassium, and creatinine analyses were performed in the clinical chemistry laboratory of Vanderbilt University Medical Center, and the reference ranges are those used by these laboratories.

Spectral Analysis and Baroreflex Sensitivity Analysis

The data were recorded using a WINDAQ (DI720; DATAQ) data acquisition system (14 bit, 500 Hz) and processed off line using custom-written software in PV-Wave language (Visual Numerics Inc). Beat-to-beat values of detected R-R intervals and BP values were interpolated, low-pass filtered (cutoff, 2 Hz), and resampled at 4 Hz. Data segments of 300 s recorded at baseline and at the end of the infusion step were used for spectral analysis. Linear trends were removed, and power spectral density was estimated with the fast Fourier transform-based Welch algorithm using 3 segments of 256 data points with 50% overlapping and Hanning window. The power in the frequency range of low frequencies was 0.04 to <0.15 Hz and of high frequencies, 0.15 to <0.40 Hz; these were calculated according to task force recommendations.¹⁹ Variability was also expressed as a percentage of total power or as normalized units to total power minus the power in the very-low-frequency range (<0.04 Hz).

Spontaneous baroreflex sensitivity (BRS) evaluation was based on analyzing simultaneous fluctuations in both BP and HR using cross-spectral analysis and the sequence method. Cross-spectra, coherence, and transfer function analysis were used to capture interrelationships between R-R interval and systolic BP (SBP). Baroreflex gain was defined as the mean magnitude value of the transfer function in the low-frequency band with negative phase and a squared coherence value >0.5.²⁰ The sequence method analyzes at least 3 heart beats in which both SBP and pulse intervals are steadily decreasing (BRS-sequence down). Spontaneous baroreflex slope was calculated as the slope of the linear regression line between SBP and the subsequent R-R intervals, using sequences with >0.01 mm Hg SBP per beat. Only those sequences for which changes in the 2 parameters had a correlation coefficient of 0.85 were analyzed.²⁰

Statistical Considerations

Data including baseline characteristics (demographics, clinical and biochemical data) are expressed as mean±SEM, unless otherwise noted. For continuous variables, data for the POTS and control groups were compared with the Student *t* test. The Mann–Whitney *U* test was used to confirm all the results obtained from the Student *t* test, and the significances of the reported parameters were not different between the 2 tests. Paired *t* test was used to compare the difference in means within the same group, and Wilcoxon signed rank test was used to confirm paired *t* test results. Relationships between 2 variables were assessed by bivariate correlations generating Pearson correlation coefficients. Statistical analyses were carried out with SPSS for Windows version 17.0 (SPSS Inc) statistical software. All tests were 2-sided, and *P*<0.05 was considered statistically significant.

Results

Baseline Characteristics

We studied 15 patients with POTS and 13 age-matched (all female) controls. Baseline characteristics were similar between the 2 groups and are summarized in the Table.

Baseline Renal and Systemic Hemodynamic Measurements

All baseline measurements were done in the supine position over 1 hour. Patients with POTS had a higher baseline HR than controls (72±2 versus 59±2 beats/min, *P*<0.001). The SBP, diastolic BP, and mean BP were all similar between the

Table. Baseline Data

	POTS (n=15)	Control (n=13)	<i>P</i>
Age, y	30±2	26±1	0.11
Body mass index, kg/m ²	24±1.2	25±1.0	0.42
Urine sodium, mg/g Cr	90±9	118±25	0.27
Cortisol	7.7±0.9	8.4±0.8	0.58
Serum potassium	4.1±1.2	4.1±1.2	0.57
Heart rate, beats/min	72±2	59±2	<0.001
Systolic blood pressure, mm Hg	97±2	99±1	0.52
Diastolic blood pressure, mm Hg	63±2	63±1	0.91
Mean arterial pressure, mm Hg	76±2	76±1	0.88
ERPF, mL/min per 1.73 m ²	641±30	639±39	0.97
RBF, mL/min per 1.73 m ²	1054±52	1026±68	0.74
RVR, mm Hg/L per min	0.07±0.004	0.08±0.006	0.54
PRA, ng/mL per h	1.6±0.3	1.0±0.2	0.16
Aldosterone, pg/mL	3.9±0.8	2.9±0.4	0.30
Ang II, pg/mL	59±6	32±5	0.004
Ang II(-1-7), pg/mL	8.6±2.0	9.0±1.0	0.84

Data are presented as mean±SEM.

POTS indicates postural tachycardia syndrome; Cr, creatinine; ERPF, effective renal plasma flow; RBF, renal blood flow; RVR, renal vascular resistance; PRA, plasma renin activity; Ang II, angiotensin II.

POTS and control groups (SBP, 97±2 versus 99±1 mm Hg [*P*=0.51]; diastolic BP, 63±2 versus 63±1 mm Hg [*P*=0.91]; mean BP, 76±2 versus 76±1 mm Hg [*P*=0.88]). Baseline effective renal plasma flow was not different between the 2 groups (641±30 versus 639±39 mL/min per 1.73 m², *P*=0.97). Renal blood flow and renal vascular resistance were also similar at baseline (Table).

Renal and Systemic Hemodynamic Responses to Ang II Infusion

Infusion of Ang II increased BP in both patients with POTS and controls. Patients with POTS had a diminished response to Ang II infusion (Figure 1) compared with controls, with a blunted increase in mean arterial pressure (10±1 versus 14±1 mm Hg, *P*=0.01) (Figure 1C) and in diastolic BP (9±1 versus 13±1 mm Hg, *P*=0.01) (Figure 1B) but not in SBP (13±2 versus 15±2 mm Hg, *P*=0.40) (Figure 1A). The HR change in response to Ang II infusion was minimal in both patients with POTS and controls (2±0.7 versus -1±0.9 beats/min, *P*=0.002). Post-Ang II infusion, renal plasma flow decreased to a similar extent in patients with POTS and controls (-166±20 versus -181±17 mL/min per 1.73 m², *P*=0.58) (Figure 2A). Renal blood flow and renal vascular resistance were not different between the 2 groups following Ang II infusion (data not shown).

Hormonal (PRA, Aldosterone, Angiotensin Species, Cortisol) Baseline and Response to Ang II Infusion

Baseline PRA was similar (Table) and suppressed to a similar extent in the 2 groups following infusion (-0.9±0.2 versus -0.6±0.2 ng/mL per hour, *P*=0.43) (Figure 3A). Baseline aldosterone level was similar in patients with POTS versus

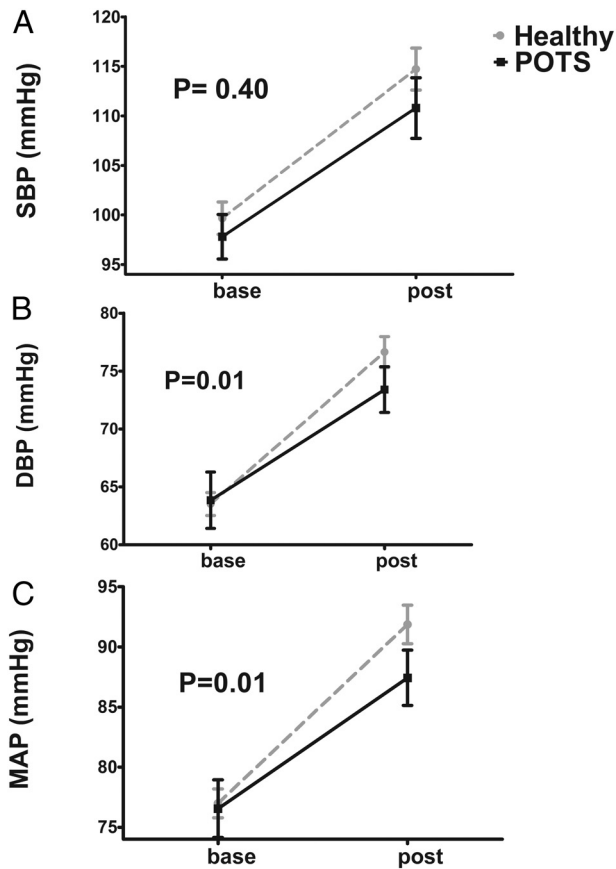


Figure 1. The net increase in SBP (A), DBP (B), and MAP (C) from baseline in response to angiotensin II infusion in patients with POTS and healthy controls. The pressor dose (3 ng/kg per minute) was started at time 0. The DBP and MAP responses were significantly different between the 2 groups. DBP indicates diastolic blood pressure; MAP, mean arterial pressure; POTS, postural tachycardia syndrome; SBP, systolic blood pressure.

controls (Table), and the increment in response to Ang II infusion was similar between the 2 groups (17 ± 1 versus 15 ± 2 pg/mL, $P=0.34$) (Figure 3B). Cortisol decreased similarly in both the POTS and the control group (-0.7 ± 0.6 versus -1.4 ± 0.6 ng/mL per hour, $P=0.43$).

Consistent with our previous findings, baseline plasma Ang II levels were 2-fold higher in the POTS group compared to the control group (Figure 4A). With Ang II infusion, the plasma Ang II level increased equally in both groups (Figure 4B).

Urine Sodium Response to Ang II Infusion

One hour of Ang II infusion decreased urine sodium from baseline to a similar extent in both patients with POTS and controls (Figure 2B). These experiments were carried out at the same time of the day to avoid diurnal variation in sodium excretion.

Baroreflex Function

The spontaneous BRS calculated by the sequence technique for down slopes of SBP (BRS-sequence down) at baseline was significantly lower in patients with POTS than in controls (13.7 ± 3.5 versus 26.0 ± 2.6 ms/mm Hg, $P=0.01$).

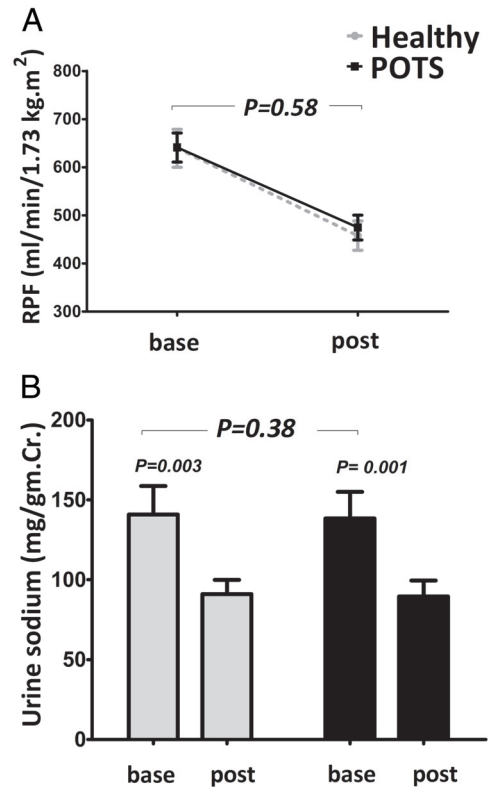


Figure 2. The change in RPF (A) and urine sodium excretion corrected for Cr (B) at baseline and in response to angiotensin II infusion. Angiotensin II decreased RPF and increased sodium reabsorption in both patients with POTS and healthy controls to a similar extent. Cr, indicates creatinine; POTS, postural tachycardia syndrome; RPF, renal plasma flow.

Ang II infusion decreased BRS in both groups (POTS, from 13.7 ± 3.5 to 10.4 ± 2.3 ms/mm Hg [$P=0.04$]; control, from 26.0 ± 2.6 to 18.9 ± 2.2 ms/mm Hg [$P=0.005$]) (Figure 5). BRS calculated as the mean value of the transfer function between SBP and pulse intervals in the low-frequency band demonstrated similar results. Baseline BRS-low frequency was lower in patients with POTS than in controls (10.1 ± 1.2 versus 16.8 ± 1.5 ms/mm Hg, $P=0.003$). Ang II infusion decreased BRS in both groups (POTS, from 10.1 ± 1.2 to 8.7 ± 1.3 ms/mm Hg [$P=0.07$]; control, from 16.8 ± 1.5 to 13.0 ± 1.3 ms/mm Hg [$P=0.01$]). The mean reduction in BRS between the 2 groups with both techniques was not statistically significant.

Correlation of BRS and Ang II Level

To examine the relationship between BRS and Ang II level, we performed correlation analysis between BRS values and Ang II levels using the Pearson test. There was significant negative correlation between baseline Ang II level and BRS in patients with POTS but not in controls based on the BRS-sequence down method ($r=-0.69$ [$P=0.009$] versus $r=0.40$ [$P=0.32$]). The decrease in BRS correlated with the increase in Ang II levels in patients with POTS. In contrast, there was no correlation in healthy controls.

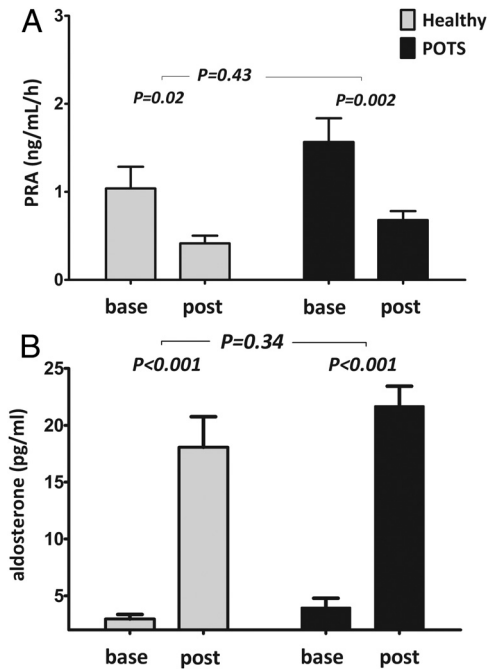


Figure 3. The response of PRA (A) and aldosterone (B) were similar between patients with POTS and healthy controls at baseline and postinfusion. POTS indicates postural tachycardia syndrome; PRA, plasma renin activity.

Discussion

The main new findings of this study are that in response to an Ang II infusion, patients with POTS have a blunted pressor response to Ang II, whereas there is normal renal plasma flow, aldosterone secretion, and sodium reabsorption by the

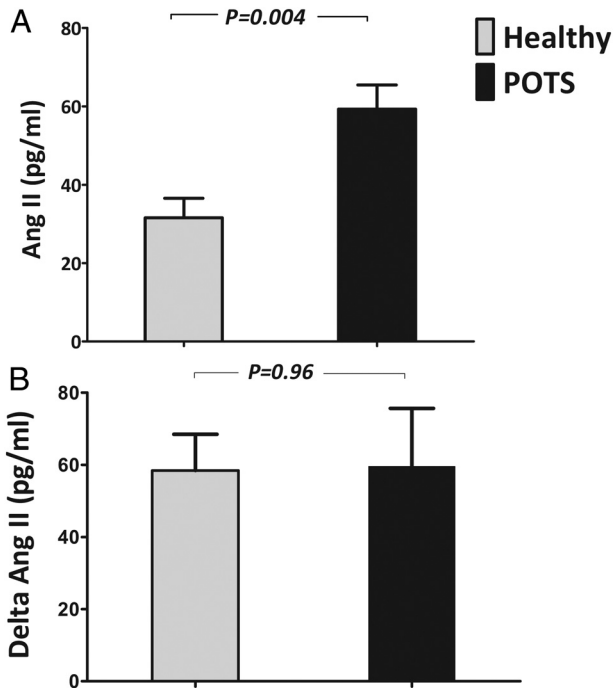


Figure 4. A, Plasma Ang II level at baseline was 2-fold higher in patients with POTS than in healthy controls. **B,** The increase in plasma Ang II levels following Ang II infusion was similar between the POTS and healthy control groups. Ang II indicates angiotensin II; POTS, postural tachycardia syndrome.

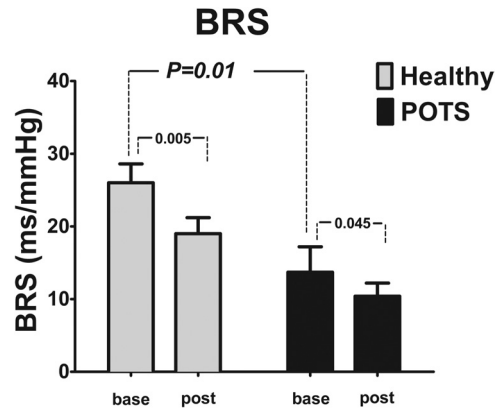


Figure 5. Baseline BRS calculated with the sequence technique (BRS-sequence down) was significantly lower at baseline in patients with POTS compared to healthy controls. In response to angiotensin II infusion, the BRS decreased significantly in both groups. The mean reduction in BRS was not different between the POTS and healthy control groups. BRS indicates baroreflex sensitivity; POTS, postural tachycardia syndrome.

kidneys. The rationale for this study was based on the finding that despite the fact that patients with POTS exhibit high levels of plasma Ang II, the hemodynamic effects expected for such an increase are absent, suggesting that AT-1 receptors are probably hyporesponsive to the effect of Ang II. We hypothesized that patients with POTS would display a blunted response to Ang II infusion, which might manifest as impaired renal and systemic vascular response, impaired aldosterone secretion, and impaired sodium reabsorption capacity by the kidneys.

BP and Renal Vascular Response to Ang II

The dose of Ang II used in this study produced a mild, but immediate response in the systemic vasculature, renal vasculature, and adrenal gland. The use of Ang II infusion at a physiological dose systemically provides a powerful and reproducible method of directly assessing the vascular response in vivo.²¹ In the present study, we demonstrated for the first time to our knowledge an attenuated systemic vascular response to Ang II infusion in POTS. This was evidenced by the significant smaller increment in mean arterial pressure in patients with POTS compared to healthy controls. The impaired vascular response in POTS may be related to the elevated level of circulating plasma Ang II that we and others have previously described in this population.^{10,11} The prolonged presence of high levels of Ang II have been shown to induce a state of relative vascular resistance to the pressor effect of Ang II²² in conditions such as Bartter syndrome, cirrhosis, and pregnancy.²³⁻²⁵ Furthermore, low sodium intake, a condition characterized by high Ang II, has been shown to reduce the pressor response to Ang II in healthy subjects.²¹

Vasoconstriction in response to Ang II involves binding of the hormone to AT-1 receptors located in the plasma membrane of smooth muscle cells. The mechanism of decreased AT-1 receptor responsiveness in the vasculature may be as simple as receptor downregulation in response to abundant substrate.²⁶ This might explain the inverse correlation be-

tween plasma Ang II levels and the pressor response to Ang II. Another possible explanation is that the blunted response to Ang II may reflect intravascular volume depletion in patients with POTS, although we did not measure the blood volume in this study. As an effector hormone, Ang II plays a fundamental role in the regulation of vascular tone under circumstances of sodium and volume depletion.²⁷ The dependence of the pressor effect of Ang II on the volume status is especially important in light of the clinical observation that patients with POTS feel better following acute volume expansion.²⁸ The pathophysiology of the blood volume depletion in POTS is not clear, but it is not due to the lack of Ang II-mediated sodium retention, as shown in the present study. Another possibility is that patients with POTS have a state of decreased ability to constrict vascular smooth muscle in response to pressor agonists. If present, however, such an abnormality should involve other pressor agonists, including norepinephrine, but the pressor response to norepinephrine has been shown to be preserved in patients with POTS.²⁹

We observed a normal renal vasoconstrictive response to Ang II, as measured by the renal plasma flow in this study. The discordant renal vascular and systemic vascular responses to Ang II are particularly intriguing. A similar discrepancy has previously been observed in other conditions.¹⁴ A major target vascular bed for the effect of Ang II is the splanchnic circulation,^{30,31} which is of great importance as a blood reservoir. Previous studies in POTS have shown significantly increased blood pooling in the splanchnic circulation with standing.^{32,33} It is possible that the blunted increase in vascular tone in response to Ang II may be primarily localized to the splanchnic circulation. This might contribute to the pathogenesis of blood pooling in POTS because of the impaired translocation of blood from the splanchnic circulation to the systemic arterial system on standing. However, we did not study the mesenteric blood flow in the present investigation. Furthermore, it is well established that patients with POTS have elevated sympathetic activity¹; this might be secondary to decreased sensitivity or responsiveness to other major nonadrenergic vasoconstrictor pathways, such as Ang II.

Normal Adrenal and Kidney Response to Ang II

Renal sodium reabsorption is mediated in part by Ang II both directly through stimulation of AT-1 receptors in the proximal tubules and indirectly by decreasing renal plasma flow in addition to promoting aldosterone secretion.³⁴ Renal sodium retention was appropriate in this study in response to Ang II infusion. This essentially rules out hyporesponsiveness to Ang II as an explanation for the low plasma volume and the tendency for salt wasting in patients with POTS.⁸ Ang II is a major stimulus of aldosterone secretion, which was similar in the POTS and control groups, and we controlled for other factors that might affect aldosterone secretion (including dietary sodium and potassium intake) and corticotropin-induced aldosterone secretion (cortisol level). The adrenal and renal responses were dissociated from the vascular response. This discrepancy might be partly due to different mechanisms of tissue interaction with Ang II. Downregula-

tion of AT-1 receptor with administration of Ang II has been reported in vascular smooth muscle cells,³⁵ whereas infusion of Ang II increases AT-1 receptor expression in the adrenal gland but not in the aorta or the kidney.^{36,37} Contrary to our previous findings of an inappropriately low aldosterone response to high Ang II and upright posture in POTS, the adrenal response to Ang II infusion is intact in POTS.^{9,11} The reason for this discrepancy is unclear. It is possible that the pressor dose used in our Ang II infusion might have excessively stimulated aldosterone production with increased AT-1 expression as previously reported,³⁶ or the immediate increase in aldosterone secretion in response to standing might be mediated by other factors, such as corticotropin.³⁸

Blunted BRS in POTS

BRS is generally defined as the amount of response in heart beat interval to a change in BP (as expressed in ms/mm Hg). A BP increment leads to an increment in interval within a few seconds. Both the POTS and the control groups had a comparable reduction in BRS during Ang II infusion. In POTS, the baseline spontaneous BRS was significantly diminished and strongly correlated with plasma Ang II level (negative correlation between Ang II level and BRS). In fact, the reduction in BRS seems to parallel the baseline level of circulating Ang II. The cardiac vagal activity can be inhibited by circulating Ang II in the absence of baroreflex loading, as suggested by Vaile et al.³⁹ Furthermore, chronically elevated Ang II can shift the cardiac baroreflex rest point to higher pressure by a BP-independent mechanism in animal models.⁴⁰ These findings of blunted BRS are similar to those observed in patients with POTS by Farquhar et al⁴¹ while using the modified Oxford technique. The relationship between the diminished spontaneous BRS and impaired orthostatic tolerance has been reported in both healthy men and healthy women following 7-day head-down bed rest.⁴² Taken together, these data indicate that patients with POTS might have impaired baroreflex control of the HR most likely because of high circulating levels of Ang II; this impaired baroreflex function results in an excessive increase in HR on standing and contributes to the elevated baseline HR and sympathetic activity in POTS.

Limitations

We studied the subjects while they were supine instead of upright (when the tachycardia would be greater). It would have been difficult to standardize standing time in each study subject given the various tolerances to standing. Blood pooling in the splanchnic circulation when upright is a characteristic of POTS and produces acute intravascular volume depletion. This volume depletion might be expected to make the Ang II-mediated vasoconstriction even more impaired, further exaggerating the differences between patients with POTS and controls. It is noted that the PRA and aldosterone levels were not lower in the patients with POTS in contrast to prior reports.^{9,11} Finally, the exogenous Ang II infusion that we used allows determination of AT-1 receptor sensitivity. It is not, however, intended specifically to determine the interaction of endogenous Ang II and AT-1 receptors.

Conclusions

This study revealed a blunted systemic vascular and baroreflex response to Ang II in patients with POTS. The adrenal aldosterone response and renal sodium reabsorption capacity in response to Ang II are intact in POTS. These results provide a putative mechanism for POTS: an inability to adequately elevate the systemic vascular resistance in response to Ang II, which is further aggravated by the presence of a blunted baroreflex response. Both processes are important circulatory adjustments to orthostatic stress. The mechanisms underlying the diminished vascular reactivity to Ang II remains to be elucidated.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Postural tachycardia syndrome is a heterogeneous disorder characterized by orthostatic tachycardia (rate increase of ≥ 30 beats/min with standing) in the absence of orthostatic hypotension. Symptoms include palpitations, exercise intolerance, lightheadedness, and fatigability, often with substantial functional disability. The pathophysiology of postural tachycardia syndrome is poorly understood, but many patients have abnormalities of the renin-angiotensin system, and elevated levels of circulating angiotensin II has been reported recently. The current study found that the high level of angiotensin II was also associated with a reduced pressor response to angiotensin II infusion and reduced baroreflex sensitivity. Both are importantly involved in adjusting to orthostatic stress. The pressor response to angiotensin II, which is known to correlate with intravascular volume, improves with volume repletion. The blunted baroreflex sensitivity improves with exercise. These findings are consistent with the benefit of volume expansion and exercise in postural tachycardia syndrome.

Altered Systemic Hemodynamic and Baroreflex Response to Angiotensin II in Postural Tachycardia Syndrome

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