Menstrual Cycle Affects Renal-Adrenal and Hemodynamic Responses During Prolonged Standing in the Postural Orthostatic Tachycardia Syndrome

Qi Fu, Tiffany B. VanGundy, Shigeki Shibata, Richard J. Auchus, Gordon H. Williams, Benjamin D. Levine

Abstract—Approximately 500,000 American premenopausal women have the postural orthostatic tachycardia syndrome (POTS). We tested the hypothesis that in POTS women during orthostasis, activation of the renin-angiotensin-aldosterone system is greater, leading to better compensated hemodynamics in the midluteal phase (MLP) than in the early follicular phase of the menstrual cycle. Ten POTS women and 11 healthy women (controls) consumed a constant diet 3 days before testing. Hemodynamics and renal-adrenal hormones were measured while supine and during 2-hour standing. We found that blood pressure was similar, heart rate and total peripheral resistance were greater, and cardiac output and stroke volume were lower in POTS subjects than in controls during 2-hour standing. In controls, hemodynamic parameters were indistinguishable between menstrual phases. In POTS subjects, cardiac output and stroke volume were lower and total peripheral resistance was greater in the early follicular phase than MLP after 30 minutes of standing; however, blood pressure and heart rate were similar between phases. Plasma renin activity (9±6 [SD] versus 13±9 ng/mL per hour; P=0.04) and aldosterone (43±22 versus 55±25 ng/dL; P=0.02) were lower in the early follicular phase than MLP in POTS subjects after 2 hours of standing. Catecholamine responses were similar between phases. The percentage rate of subjects having presyncope was greater in the early follicular phase than MLP for both groups (χ² P<0.01). These results suggest that the menstrual cycle modulates the renin-angiotensin-aldosterone system and affects hemodynamics during orthostasis in POTS. The high estrogen and progesterone in the MLP are associated with greater increases in renal-adrenal hormones and presumably more volume retention, which improve late-standing tolerance in these patients. (Hypertension. 2010;56:82-90.)

Key Words: orthostatic intolerance ■ renin-angiotensin-aldosterone system ■ hemodynamics ■ sex hormones

Patients with the postural orthostatic tachycardia syndrome (POTS; also called chronic orthostatic intolerance) are unable to stand or remain upright for prolonged periods of time because of intolerable palpitations, light-headedness, weakness, or near-syncope. This disorder affects ≈500,000 Americans, the majority of whom are young women. Severely affected patients are unable to work, attend school, or participate in recreational activities, resulting in substantial morbidity. However, the underlying pathophysiology remains unclear. It has been proposed that the mechanisms for POTS are heterogeneous.2 We found recently that, as a group, patients with POTS have a small heart coupled with reduced blood and plasma volume, which contributes to a small stroke volume, ultimately resulting in reflex tachycardia during orthostasis.3

The renin-angiotensin-aldosterone system (RAAS) plays an important role in the neurohumoral regulation of plasma volume and hemodynamic homeostasis in humans, especially during long-term orthostasis.4 Despite its importance in arterial pressure maintenance, results regarding the responses of the RAAS during upright posture in POTS patients are few and controversial; increased,5 decreased,6,7 or unchanged8 plasma levels of renin and/or aldosterone have been reported.

Although the majority of POTS patients are premenopausal women, there is no information available concerning the menstrual cycle effects on the RAAS in POTS. Hirshoren et al9 observed in young healthy women that fluid-regulatory hormones, plasma renin activity, and aldosterone increased, and plasma norepinephrine decreased along the luteal phase; however, blood pressure, heart rate, and their responses to orthostasis remained unchanged. Chidambaram et al10 demonstrated that the renal-adrenal response to orthostatic stress was significantly augmented in the luteal phase compared with the follicular phase. These observations were made in healthy euvoletic women; whether similar results are observed in POTS women, who have a small heart coupled with reduced plasma volume, is uncertain.

Received February 12, 2010; first decision March 10, 2010; revision accepted April 19, 2010.

From the Institute for Exercise and Environmental Medicine (Q.F., T.B.V., S.S., B.D.L.), Texas Health Presbyterian Hospital Dallas, Dallas, Tex; University of Texas Southwestern Medical Center at Dallas (Q.F., S.S., R.J.A., B.D.L.), Dallas, Tex; Brigham and Women’s Hospital (G.H.W.), Harvard Medical School, Boston, Mass. Correspondence to Qi Fu, Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, 7232 Greenville Ave, Suite 435, Dallas, TX 75231. E-mail QIFu@TexasHealth.org © 2010 American Heart Association, Inc. Hypertension is available at http://hyper.ahajournals.org DOI: 10.1161/HYPERTENSIONAHA.110.151787

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The primary objective of this study was to test the hypothesis that, in POTS women during orthostasis, activation of the RAAS is greater, leading to better compensated hemodynamics in the midluteal phase (MLP) than in the early follicular phase (EFP) of the menstrual cycle. To accomplish this objective, we evaluated comprehensively renal-adrenal and hemodynamic responses during prolonged standing in normally menstruating POTS women during the EFP (1 to 4 days after the onset of menstruation when both estrogen and progesterone are low) and during the MLP (19 to 22 days, when both hormones are high).

### Methods

#### Participants

The patient population consisted of 54 consecutive patients referred to our tertiary Autonomic Function Clinic between December 2004 and April 2008. Forty-six of these patients were screened, 28 ultimately were enrolled, and 10 normally menstruating POTS women agreed to participate in all phases of this study. All of the patients met the inclusion criteria for POTS and had a heart rate rise ≥30 bpm or a rate that exceeded 120 bpm that occurred after 10 minutes of standing without any evidence of orthostatic hypotension. Eleven age-matched healthy women (controls) were also enrolled. All had self-reported regular menstrual cycles of ≥28 days and had never taken or had not taken oral contraceptives for ≥6 months. All were nonsmokers. None was an endurance-trained athlete. All were screened with a careful medical history, physical examination, 12-lead ECG, and a 10-minute stand test. Patients had stopped taking medications that could affect the autonomic nervous system ≥2 weeks before screening and testing. All were informed of the purpose and procedures used in the study and gave their written informed consent to a protocol approved by the institutional review boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas. A summary of the descriptive data for POTS women and controls is presented in the Table.

#### Hemodynamic Measurements

**Heart Rate and Blood Pressure**

Heart rate was monitored from the ECG (Hewlett-Packard), and beat-to-beat arterial pressure was derived by finger photoplethysmography (Portapres). Arm-cuff blood pressure was measured by electrophysmomanometry (SunTech), with a microphone placed over the brachial artery to detect Korotkoff sounds. Respiratory excursions were detected by a nasal cannula.

**Cardiac Output**

Cardiac output was measured with the acetylene rebreathing technique, from the disappearance rate of acetylene in expired air, measured with a mass spectrometer (Marquette), after adequate mixing in the lung has been confirmed by a stable helium concentration. This method has been validated against standard invasive techniques, including thermodilution and direct Fick. Stroke volume was calculated from cardiac output and the heart rate measured during rebreathing. Total peripheral resistance was calculated as the quotient of mean arterial pressure and cardiac output, multiplied by 80 (expressed as dynes · second · centimeter⁻²). Mean arterial pressure was calculated as [(systolic pressure – diastolic pressure)/3] + diastolic pressure.

#### Experimental Protocol

All of the subjects were studied twice, once during the EFP and once during the MLP, with the order counterbalanced. Cycle phase was determined by the onset of menstruation and by the detection of the luteinizing hormone surge by an ovulation prediction kit (OvuQuick) and was verified by circulating estradiol and progesterone concentrations on each study day. Luteal phase progesterone ≥2 ng/mL was confirmed in all but 1 control and 3 POTS women. Subjects were on an isocaloric diet consisting of 200 mEq of sodium, 100 mEq of potassium, and 1000 mg of calcium. Fluid intake was ad libitum 3 days before screening and testing. All were informed of the purpose and procedures used in the study and gave their written informed consent to a protocol approved by the institutional review boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas. A summary of the descriptive data for POTS women and controls is presented in the Table.

### Table. Physical Characteristics in POTS Women and Controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>POTS Women (n=10)</th>
<th>Controls (n=11)</th>
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<tr>
<td>Height, cm</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>BMI, kg/m²</td>
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<td>23±2</td>
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<td>Menstrual cycle day, d</td>
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<td>3.9±.05</td>
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<td>32.4±8.9</td>
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<td>Progesterone, ng/mL</td>
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<td>0.9±0.5</td>
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<tr>
<td>Plasma volume, ml/kg</td>
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<tr>
<td>Blood volume, mL/kg</td>
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<td>4.2±0.1</td>
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<td>Ca²⁺, mmol/L</td>
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<td>1.11±0.02</td>
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<td>24-h urine output, ml</td>
<td>2390±900</td>
<td>2059±860</td>
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<td>Osmolality, mosmol/kg</td>
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<td>148.2±53.7</td>
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<tr>
<td>K⁺, mmol/24 h</td>
<td>65.6±32.2</td>
<td>52.4±20.6</td>
</tr>
</tbody>
</table>

Values are mean±SD. Mosmol indicates milliosmol; BMI, body mass index.

*P<0.05 vs EFP within the same group.
†P<0.05 vs controls during the same menstrual phase.
days before testing and assessed by 24-hour urine output the day before testing to verify dietary compliance. Subjects were required not to exercise ≥24 hours before testing. They took a pregnancy test and showed negative results on each study day.

The experiment was performed in the morning or afternoon 2 hours after a light breakfast or lunch and ≥72 hours after the last caffeinated or alcoholic beverage in a quiet, environmentally controlled laboratory with an ambient temperature of ~25°C. The subject was placed in the supine position, and an intravenous catheter was inserted into an antecubital vein for blood samples. Hemodynamic variables were measured after ≥30 minutes in the supine position and every 10 minutes after the subject began 2-hour standing. Blood samples were collected after ≥1 hour in the supine position and after 30 minutes and 1 and 2 hours of standing. Because Jacob et al. found previously that neurohumoral responses did not reach a plateau after 1 hour of standing, we implemented more prolonged (ie, 2-hour) standing in this study. Estradiol, progesterone, plasma renin activity, vasopressin, and aldosterone were measured by radioimmunoassay techniques, whereas plasma catecholamines were measured by high-performance liquid chromatography. Plasma volume was measured by a modified carbon monoxide rebreathing technique (please see the online Data Supplement at http://hyper.ahajournals.org for details).

Statistical Analysis
Data are expressed as mean ± SD unless otherwise noted. Physical characteristics between groups were compared using Mann-Whitney rank-sum tests and between menstrual phases within groups were compared using Wilcoxon signed-rank tests. Hemodynamic and renal-adrenal responses during 2-hour standing between phases and between groups were analyzed using 2-way repeated-measures ANOVA, and the Holm-Sidak method was used post hoc for multiple comparisons. The percentage rate of subjects having presyncope between menstrual phases and groups was compared using χ² tests. All of the statistical analyses were performed with a personal computer-based analysis program (SigmaStat, SPSS). A P value of <0.05 was considered statistically significant.

Results
POTS Versus Controls
POTS women and controls were not different in age, height, weight, or body mass index (Table). Blood electrolytes, 24-hour urine output, osmolality, and urine electrolytes did
not differ between groups (Table). Plasma volume was lower in POTS women than in controls (Table; \( P < 0.04 \)).

Systolic pressure remained stable, and diastolic pressure increased during 2-hour standing; these responses were not different between groups (Figure 1A and 1B). Heart rate increased during 2-hour standing and was much greater in POTS women compared with controls (Figure 1C). Both cardiac output and stroke volume decreased during 2-hour standing and were much lower in POTS women (Figure 2A and 2B). Total peripheral resistance increased during 2-hour standing and was much greater in POTS women than in controls (Figure 2C). Both heart rate and total peripheral resistance were negatively correlated with stroke volume, indicating that tachycardia and strong vasoconstriction were functions of a lower stroke volume in POTS women (Figure S1 in the online Data Supplement).

Plasma renin activity increased progressively during 2-hour standing and was greater in POTS women compared with controls (Figure 3A). This cannot be explained by different sodium intakes, because the urine sodium excretion was greater, although not significantly so, in POTS women than in controls (Table). Rather, a reduced plasma volume in POTS women may be responsible for the greater increases in plasma renin activity during standing. Aldosterone also increased gradually during 2-hour standing but did not differ between groups (Figure 3B). As a consequence, the aldosterone:renin ratio was lower in POTS women than in controls after 2 hours of standing (5.5±2.7 versus 14.0±7.2 during the MLP; \( P < 0.01 \)). Vasopressin increased after 1 and 2 hours of standing in POTS women during the EFP, which was associated with presyncope (Figure 3C). Hematocrit increased during 2-hour standing and tended to be greater in

![Figure 2](image-url). Cardiac output (CO; A), stroke volume (SV; B), and total peripheral resistance (TPR; C) during 2-hour standing in the EFP (open symbols) and MLP (closed symbols) of the menstrual cycle in POTS women and controls. S indicates supine. Values are expressed as mean±SE.
POTS women during the MLP (Figure 4A). Plasma norepinephrine increased progressively during 2-hour standing and tended to be greater in POTS women during the EFP compared with controls (Figure 4B). Plasma epinephrine increased during 2-hour standing and did not differ between groups (Figure 4C).

Both plasma renin activity and hematocrit were negatively correlated with stroke volume, suggesting that a greater reduction in central blood volume can cause a lower stroke volume and, thereafter, a greater activation of the renal system during prolonged standing in POTS women (Figure S2).

**EFP Versus MLP**

Circulating levels of estradiol and progesterone were greater in the MLP than in EFP for both groups (Table; both P<0.01). During the MLP, progesterone was lower in POTS women than in controls (P=0.04), although menstrual cycle days did not differ between groups. Plasma volume and blood volume were not affected significantly by the menstrual cycle in both groups (Table).

The menstrual cycle did not influence supine hemodynamics in POTS women and controls (Figure 1 and 2 and Table S1). Supine plasma renin activity was greater in the MLP than in the EFP for both groups, and supine aldosterone was greater in the MLP in POTS women only (Figure 3 and Table S1). The menstrual cycle did not affect blood pressure and heart rate responses during 2-hour standing in both groups (Figure 1). In controls, hemodynamic parameters were indistinguishable between phases. Interestingly, in POTS women during the initial 30 minutes of standing, cardiac output, stroke volume, and total peripheral resistance responses were not different between phases; however, cardiac output and stroke volume were lower, whereas total peripheral resistance was greater in the EFP than in the MLP after 30 minutes of standing (Figure 2; all P<0.05).

Plasma renin activity was lower in the EFP than in the MLP in both groups after 2 hours of standing (Figure 3A). Aldosterone was lower in the EFP than in the MLP in POTS women after 1 and 2 hours of standing, and it trended similarly in controls (Figure 3B). Plasma catecholamine concentrations were not affected by the menstrual cycle in both groups (Figure 4B and 4C).
Three POTS women and 2 controls developed presyncope during the EFP, whereas 1 POTS woman and no controls had presyncope during the MLP. The percentage rate of subjects experiencing presyncope was greater in the EFP than in the MLP for POTS women (30% versus 10%; \(P<0.01\)) and controls (9% versus 0%; \(P<0.01\)), suggesting a role for both estrogen and progesterone in promoting orthostatic tolerance in women. The rate was not different between groups (\(P=0.22\)).

**Discussion**

Our major findings are as follows: (1) plasma renin activity increases were greater in POTS women than in controls during 2-hour standing, presumably because of a reduced plasma volume in POTS; however, aldosterone responses did not differ between groups; (2) both plasma renin activity and aldosterone were lower in the EFP than in the MLP in POTS women during 2-hour standing; (3) in POTS women during the initial 30 minutes (ie, early) of standing, cardiac output, stroke volume, and total peripheral resistance responses were not different between phases; however, cardiac output and stroke volume were lower, whereas total peripheral resistance was greater in the EFP than in the MLP after 30 minutes (ie, late) of standing; and (4) the percentage rate of subjects having presyncope was greater in the EFP than in the MLP for both POTS and healthy women.

These results suggest that the menstrual cycle modulates the RAAS and affects hemodynamics during prolonged standing in POTS women. The high estrogen and progesterone in the MLP are associated with greater increases in renal-adrenal hormones and presumably more volume retention, which improve late-standing tolerance in these patients.

**RAAS Responses in POTS**

We found that standing plasma renin activity was markedly greater in POTS women than in controls, whereas standing...
aldosterone did not differ between groups. These observations are consistent in part with some8,6 but not all8 previous studies. The reasons for these conflicting results are unclear, although timing of hormonal measurements obviously contributes. In addition, differences in salt intake (ie, 150 mEq of sodium per day in previous studies versus 200 in our study) may be one potential explanation, because it has been demonstrated that dietary sodium can modulate the responses of the RAAS in humans.22,23 We used the relatively high-salt diet because many patients had already been requested by their physicians to increase dietary salt intake or to take salt tablets; moreover, the high-salt diet would allow us to detect a greater RAAS response during prolonged standing. The second possible explanation may be the influences of the menstrual cycle. It has been shown that the fluctuations of estrogen and progesterone during the menstrual cycle affect plasma renin activity and aldosterone in healthy women.9,10,23 All of the previous studies did not control for or standardize phase of the menstrual cycle in POTS women.5,6,8 In contrast, our study was well controlled not only for the diet but also for the menstrual cycle.

However, one observation is common in the current study and all previous studies, namely that POTS patients had a reduced aldosterone:renin ratio. Raj et al8 termed this dysregulation in POTS the “renin-aldosterone paradox.” It might be possible that the levels of aldosterone are so high in the upright posture that the aldosterone response has reached a physiological maximum in POTS women. Interestingly, a similar reduced aldosterone:renin ratio was also observed in healthy individuals after a period of bed rest (ie, simulated microgravity exposure), in which “deconditioning” (ie, cardiac atrophy and hypovolemia) occurs.24–26 Numerous studies have shown that real or simulated microgravity exposure can elicit a “POTS-like” syndrome even in healthy fit people. Conversely, a blunted adrenal response to angiotensin II or renin has been found in ~40% of patients with essential hypertension, and the concept of nonmodulating hypertension is based on this theory.27 It has also been found that nonmodulating hypertensive patients have a greater decrease in plasma volume when shifted from a high-salt diet to a low-salt diet28 and a greater increase in plasma norepinephrine concentration during standing compared with modulating hypertensive patients.29 Whether abnormalities in the RAAS contribute to POTS or whether the reduced aldosterone:renin ratio is a result of POTS (ie, deconditioning) needs to be determined.

**Menstrual Cycle Effects in POTS Women**

Consistent with previous findings in healthy women,10,30,31 we observed that plasma renin activity and aldosterone increases during 2-hour standing were greater in the MLP than in the EFP in POTS women. Studies using oral estrogen and progesterone in postmenopausal women have demonstrated that both hormones can activate the RAAS.32,33 However, other data suggest that only progesterone activates the RAAS, whereas estrogen might inhibit the activation of this system.34,35 Szmuilowicz et al23 showed that progesterone may directly contribute to increased luteal phase aldosterone production independent of the RAAS.

Activation of the RAAS can lead not only to salt and water retention but also to vasoconstriction. Given the higher plasma renin activity and aldosterone, we would predict greater cardiac output, stroke volume, and total peripheral resistance during 2-hour standing in the MLP compared with the EFP in POTS women. However, standing total peripheral resistance was actually lower in the MLP, although standing cardiac output and stroke volume were indeed greater. There are several possibilities for the lower standing total peripheral resistance during the MLP in POTS women. First, Chapman et al30 found that the hormonal changes in the luteal phase had a specific renal vasodilating effect, overriding secondary activation of other renal vasoconstricting systems, such as the RAAS. Second, animal and human studies showed that estrogen could upregulate NO and stimulate an increase in endothelial NO synthesis,36,37 producing a direct vasodilatory effect.38 In addition, NO can downregulate angiotensin II type 1 receptors in vascular tissue39 and adrenal glands40 and mitigate the actions of angiotensin II. Third, standing cardiac output and stroke volume were greater in the MLP in POTS women, which, in turn, could attenuate the increase in total

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**Figure 5.** Possible mechanisms for plasma renin activity (PRA), aldosterone (ALDO), and hemodynamic responses including cardiac output (CO), stroke volume (SV), total peripheral resistance (TPR), heart rate (HR), and blood pressure (BP) during prolonged standing in POTS women during the EFP and MLP of the menstrual cycle.
peripheral resistance during upright posture via the baroreflex mechanism.

In POTS women during early standing, cardiac output, stroke volume, and total peripheral resistance responses were not different between phases; however, cardiac output and stroke volume were lower, whereas total peripheral resistance was greater in the EFP compared with the MLP after 30 minutes of standing. These results suggest that a lower activation of the RAAS in the EFP, rather than any fundamental difference in the gravitationally mediated hemodynamics of the upright posture, or intrinsic impairment of baroreflex function may account for the different responses during different menstrual phases. The menstrual cycle modulated renal-adrenal increases during 2-hour standing in both POTS and healthy women, but it affected hemodynamics in POTS women only. It is possible that the vasodilatory effects of sex hormones may depend on the degree of vasoconstriction. POTS women had greater vasoconstriction in response to upright posture compared with controls, and, thus, the vasodilatory effects of estrogen and progesterone were greater in these patients. It is also possible that the sensitivity or density of estrogen and progesterone receptors on the blood vessels may be greater in POTS women than in controls. However, blood pressure and heart rate responses during prolonged standing in POTS women did not vary during the menstrual cycle, suggesting that POTS, per se, is not caused by the fluctuations of sex hormones but rather that these fluctuations influence the physiological compensation to orthostasis. Figure 5 depicts possible mechanisms for orthostatic tolerance in POTS women during different menstrual phases.

Limitations

First of all, although many patients had POTS symptoms during 2-hour standing, we did not document or quantify these symptoms during testing. However, patient overall well-being was assessed by the Short-Form 36 on each study day, and the results were not different between phases (Table S2). Second, we do not know whether some POTS women had the premenstrual syndrome. Rosenfeld et al11 found that women with premenstrual syndrome had increased fluid-regulatory hormones and disturbed fluid distribution only during the late-luteal phase, whereas our study was performed in the EFP and the MLP. Third, we did not measure luteinizing hormone and follicle-stimulating hormone, and, thus, we were unable to determine the contributions of these hormones to renal-adrenal and hemodynamic responsiveness in POTS women.

Perspectives

Results from our study suggest that POTS, per se, is not caused by the fluctuations of sex hormones during the menstrual cycle, and, therefore, we have ruled out a potential mechanism for this disorder. Conversely, these fluctuations can affect the physiological compensation to orthostasis in POTS women. Given the fact that POTS women are more susceptible to orthostatic intolerance when both estrogen and progesterone levels are low, one simple approach would be to use supplemental pharmacological therapy or perhaps behavioral modification during the EFP. Although POTS women demonstrated the anticipated changes in the RAAS during the menstrual cycle, namely, greater plasma renin activity and aldosterone increases during prolonged standing in the MLP compared with the EFP, the aldosterone:renin ratio was lower in these patients compared with healthy women. This observation could suggest a rationale for the common use of fludrocortisone in such patients, although the optimal timing and dose of this medication is unclear. Whether the blunted adrenal response is a consequence or signature of POTS or whether abnormalities in the RAAS contribute to this syndrome needs to be determined in future studies.

Acknowledgments

The time and effort put forth by the subjects is greatly appreciated. We thank Robin P. Shook, Kazunobu Okazaki, Jeffrey L. Hastings, M. Dean Palmer, Daniel L. Cresent, Colin L. Conner, Diane Bedenkop, and Peggy Fowler for their valuable laboratory assistance.

Sources of Funding

This study was supported by a National Institutes of Health K23 grant (HL075283), a National Space Biomedical Research Institute grant (CA00701), and a Clinical and Translational Research Center (formerly the General Clinical Research Center) grant (RR00633).

Disclosures

None.

References


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Hypertension. 2010;56:82-90; originally published online May 17, 2010;
doi: 10.1161/HYPERTENSIONAHA.110.151787
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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1,2Qi Fu, 1Tiffany B. VanGundy, 1,2Shigeki Shibata, 2Richard J. Auchus, 3Gordon H. Williams, 1,2Benjamin D. Levine

1Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas
2The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas
3Brigham & Women’s Hospital, Harvard Medical School, Boston, Massachusetts

Running title: Sex Hormones & RAAS in POTS

METHODS

Plasma Volume Measurement

Plasma volume was measured by a modified carbon monoxide (CO) rebreathing technique.1, 2 After an initial priming dose (15 mL) of 99.9% CO rebreathed for 10 min, blood was sampled into a capped 5-mL glass syringe pre-rinsed with heparin. A second dose (1.25 mL/kg) of 99.9% CO was then rebreathed for 10 min, after which a second blood sample was obtained while the subject remained on the rebreathing circuit. Medical-grade oxygen was bled in continuously at a rate of 200–350 mL/min. The change in percent carboxyhemoglobin was used to calculate total hemoglobin mass.1 Plasma volume was calculated from total hemoglobin mass, hemoglobin concentration, and hematocrit.2

REFERENCES

### Table S1. Supine hemodynamics and renal-adrenal hormones in POTS women and controls

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<th>Variables</th>
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<th>Controls ($n = 11$)</th>
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<td>EFP</td>
<td>MLP</td>
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<td>98 [90, 106]</td>
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<td>Diastolic Blood Pressure (mmHg)</td>
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<td>60 [55, 66]</td>
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<td>Heart Rate (bpm)</td>
<td>79 [74, 90]†</td>
<td>85 [79, 90]†</td>
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<td>Cardiac Output (L/min)</td>
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<td>Stroke Volume (mL)</td>
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<td>Total Peripheral Resistance (dyn⋅s⋅cm$^{-5}$)</td>
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<td>Plasma Renin Activity (ng/mL/h)</td>
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<td>2.1 [0.7, 3.0]**†</td>
</tr>
<tr>
<td>Aldosterone (ng/dL)</td>
<td>4.2 [2.9, 8.0]</td>
<td>7.8 [5.3, 10.9]*</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>37 [37, 39]</td>
<td>39 [37, 40]</td>
</tr>
<tr>
<td>Plasma Norepinephrine (pg/mL)</td>
<td>183 [105, 237]</td>
<td>180 [93, 314]</td>
</tr>
</tbody>
</table>

Values are expressed as median [25th, 75th percentile]. EFP, early-follicular phase; MLP, mid-luteal phase.

*P < 0.05 compared to MLP within the same group. †P < 0.05 compared to controls during the same menstrual phase.
**Table S2.** Patients’ overall well-being assessed by the SF-36 during the EFP and MLP

<table>
<thead>
<tr>
<th>SF-36 Scores</th>
<th>EFP</th>
<th>MLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Function</td>
<td>36.0 [26.0, 44.9]</td>
<td>23.4 [21.3, 40.2]</td>
</tr>
<tr>
<td>Role Physical</td>
<td>29.9 [22.0, 38.5]</td>
<td>27.5 [23.8, 43.4]</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>37.2 [37.1, 37.2]</td>
<td>37.2 [37.2, 38.2]</td>
</tr>
<tr>
<td>General Health</td>
<td>30.5 [25.8, 33.5]</td>
<td>30.5 [25.8, 36.6]</td>
</tr>
<tr>
<td>Vitality</td>
<td>30.2 [25.6, 36.5]</td>
<td>27.1 [23.2, 37.3]</td>
</tr>
<tr>
<td>Social Function</td>
<td>35.0 [32.3, 40.5]</td>
<td>35.0 [33.7, 40.5]</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>44.2 [24.8, 55.9]</td>
<td>36.4 [26.7, 50.0]</td>
</tr>
<tr>
<td>Mental Health</td>
<td>47.2 [32.4, 52.8]</td>
<td>35.9 [34.5, 47.9]</td>
</tr>
<tr>
<td>Transform Physical</td>
<td>32.3 [24.3, 38.9]</td>
<td>29.6 [23.2, 39.3]</td>
</tr>
<tr>
<td>Transform Mental</td>
<td>46.9 [29.0, 52.8]</td>
<td>36.3 [30.6, 47.7]</td>
</tr>
</tbody>
</table>

Values are expressed as median [25th, 75th percentile]. SF-36, the 36-item Short Form Healthy Survey; EFP, early-follicular phase; MLP, mid-luteal phase.
Figure S1. Heart rate (HR, A), total peripheral resistance (TPR, B), and systolic and diastolic blood pressure (SBP and DBP, C and D) in relation to stroke volume (SV) after 2 h of standing in POT women (filled circles) and healthy controls (open circles). Both HR and TPR were negatively correlated with SV, indicating that tachycardia and strong vasoconstriction were function of a lower SV in POTS. However, SBP and DBP did not have significant correlations with SV.
Figure S2. Plasma renin activity (PRA, A), aldosterone (B), hematocrit (C), and plasma norepinephrine (NE, D) in relation to stroke volume (SV) after 2 h of standing in POTS women (filled circles) and healthy controls (open circles). Both PRA and hematocrit were negatively correlated with SV, suggesting that a greater reduction in central blood volume can cause a lower SV, and then, a greater activation of the renal system during prolonged standing in POTS. However, aldosterone and plasma NE did not have significant correlations with SV.