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

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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 mid-luteal phase (MLP) than early-follicular phase (EFP) of the menstrual cycle. Ten POTS women and 11 healthy women (controls) consumed a constant diet 3 d prior to testing. Hemodynamics and renal-adrenal hormones were measured supine and during 2-h standing. We found that blood pressure was similar, heart rate and total peripheral resistance were greater, cardiac output and stroke volume were lower in POTS than controls during 2-h standing. In controls, hemodynamic parameters were indistinguishable between menstrual phases. In POTS, cardiac output and stroke volume were lower, total peripheral resistance was greater in the EFP than MLP after 30 min of standing; but blood pressure and heart rate were similar between phases. Plasma renin activity [9±6 (SD) *vs* 13±9 ng/ml/h, *P*=0.04] and aldosterone (43±22 *vs* 55±25 ng/dl, *P*=0.02) were lower in the EFP than MLP in POTS after 2 h of standing. Catecholamine responses were similar between phases. The percentage rate of subjects having presyncope was greater in the EFP than MLP for both groups (Chi-square, *P*<0.01). These results suggest that the menstrual cycle modulates the renin-angiotensin-aldosteron 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.

Keywords

orthostatic intolerance; renin-angiotensin-aldosterone system; hemodynamics; sex hormones

INTRODUCTION

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 due to intolerable palpitations, light-headedness, weakness, or near-syncope. This disorder

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affects approximately 500,000 Americans,[1] the vast 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 recently found 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 unchanged[8] plasma levels of renin and/or aldosterone have been reported.

Even though the vast majority of POTS patients are premenopausal women, there is no information available concerning the menstrual cycle effects on the RAAS in POTS. Hirshoren et al[9] 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 al[10] 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 euvolemic women; whether similar results are observed in POTS women, who have a small heart coupled with reduced plasma volume, is uncertain.

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 mid-luteal phase (MLP) than 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 patients met the inclusion criteria for POTS,[11] and had a heart rate rise ≥ 30 bpm or a rate that exceeded 120 bpm that occurred after 10 min of standing without any evidence of orthostatic hypotension.[8] 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 mo.[12] All were non-smokers. None was an endurance-trained athlete.[13] All were screened with a careful medical history, physical examination, 12-lead electrocardiogram, and a 10-min stand test. Patients had stopped taking medications that could affect the autonomic nervous system ≥ 2 wk 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 Table 1.

Hemodynamic Measurements

Heart Rate and Blood Pressure—Heart rate was monitored from the electrocardiogram (Hewlett-Packard), and beat-to-beat arterial pressure was derived by finger photoplethysmography (Portapres). Arm cuff blood pressure was measured by electrosphygmomanometry (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, [14] 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.[15, 16]

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 $dyn \cdot s \cdot cm^{-5}$). Mean arterial pressure was calculated as $[(\text{systolic pressure} - \text{diastolic pressure})/3] + \text{diastolic pressure}$.

Experimental Protocol

All 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 3 POTS and 1 control women. Subjects were on an isocaloric diet consisting of 200 mEq sodium, 100 mEq potassium, and 1000 mg calcium. Fluid intake was *ad libitum* 3 days prior to testing and assessed by 24-h urine output the day prior to testing to verify dietary compliance. Subjects were required not to exercise at least 24 h prior to testing. They took a pregnancy test and showed negative results on each study day.

The experiment was performed in the morning or afternoon ≥ 2 h after a light breakfast or lunch, and ≥ 72 h 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 min in the supine position and every 10 min after the subject began 2-h standing. Blood samples were collected after ≥ 1 h in the supine position, and after 30 min, 1 and 2 h of standing. Because Jacob et al[17] previously found that neurohumoral responses did not reach a plateau after 1 h of standing, we implemented more prolonged (i.e., 2 h) standing in this study. Estradiol, progesterone, plasma renin activity, vasopressin, and aldosterone were measured by radioimmunoassay techniques, [18] while plasma catecholamines were measured by high-performance liquid chromatography. [19] Plasma volume was measured by a modified carbon monoxide rebreathing technique (please see Online Supplement at http://hyper.ahajournals.org for details).[20, 21]

Statistical Analysis

Data are expressed as mean ± standard deviation 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-h standing between phases and between groups were analyzed using two way repeated-measures analysis of variance, 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 Chi-square tests.

All 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, and body mass index (Table 1). Blood electrolytes, 24-h urine output, osmolality, and urine electrolytes did not differ between groups (Table 1). Plasma volume was lower in POTS women than in controls (Table 1, *P* = 0.04).

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

Plasma renin activity increased progressively during 2-h standing, and was greater in POTS women compared to controls (Figure 3*A*). This can not be explained by different sodium intakes as the urine sodium excretion was greater, although not significantly so, in POTS women than in controls (Table 1). 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-h standing, but did not differ between groups (Figure 3*B*). As a consequence, the aldosterone-to-renin ratio was lower in POTS women than in controls after 2 h of standing (5.5 ± 2.7 *vs* 14.0 ± 7.2 during the MLP; *P* < 0.01). Vasopressin increased after 1 and 2 h of standing in POTS women during the EFP, which was associated with presyncope (Figure 3*C*). Hematocrit increased during 2-h standing, and tended to be greater in POTS women during the MLP (Figure 4*A*). Plasma norepinephrine increased progressively during 2-h standing, and tended to be greater in POTS women during the EFP compared to controls (Figure 4*B*). Plasma epinephrine increased during 2-h standing, and did not differ between groups (Figure 4*C*).

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 strove volume, and thereafter, a greater activation of the renal system during prolonged standing in POTS women (Figure 2S in the Online Supplement).

EFP versus MLP

Circulating levels of estradiol and progesterone were greater in the MLP than EFP for both groups (Table 1, both *P* < 0.01). During the MLP, progesterone was lower in POTS women than in controls (*P* = 0.04), even though 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 1).

The menstrual cycle did not influence supine hemodynamics in POTS women and controls (Figures 1 and 2, Table S1 in the Online Supplement). Supine plasma renin activity was greater in the MLP than EFP for both groups, and supine aldosterone was greater in the MLP in POTS women only (Figure 3, Table S1). The menstrual cycle did not affect blood pressure and heart rate responses during 2-h standing in both groups (Figure 1). In controls, hemodynamic parameters were indistinguishable between phases. Interestingly, in POTS women during the

initial 30 min of standing, cardiac output, stroke volume, and total peripheral resistance responses were not different between phases; however, cardiac output and stroke volume were lower, while total peripheral resistance was greater in the EFP than MLP after 30 min of standing (Figure 2, all $P < 0.05$).

Plasma renin activity was lower in the EFP than MLP in both groups after 2 h of standing (Figure 3*A*). Aldosterone was lower in the EFP than MLP in POTS women after 1 and 2 h of standing, and it trended similarly in controls (Figure 3*B*). Plasma catecholamine concentrations were not affected by the menstrual cycle in both groups (Figure 4*B* and 4*C*).

Three POTS women and 2 controls developed presyncope during the EFP, while 1 POTS woman and no controls had presyncope during the MLP. The percentage rate of subjects suffering from presyncope was greater in the EFP than MLP for POTS women (30% *vs* 10%, Chi-square, $P < 0.01$) and controls (9% *vs* 0%, Chi-square, $P < 0.01$), suggesting a role of both estrogen and progesterone in promoting orthostatic tolerance in women. The rate was not different between groups (Chi-square, $P = 0.22$).

DISCUSSION

Our major findings are that (1) plasma renin activity increases were greater in POTS women than in controls during 2-h standing, presumably due to 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 MLP in POTS women during 2-h standing; (3) in POTS women during the initial 30 min (i.e., 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, while total peripheral resistance was greater in the EFP than MLP after 30 min (i.e., late) of standing; and (4) the percentage rate of subjects having presyncope was greater in the EFP than 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, while standing aldosterone did not differ between groups. These observations are consistent in part with some[5, 6] but not all[8] previous studies. The reasons for these conflicting results are unclear, though timing of hormonal measurements obviously contributes. In addition, differences in salt intake (i.e., 150 mEq sodium per day in previous studies *versus* 200 in our study) may be one potential explanation, since 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 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 all previous and the current study; namely, that POTS patients had a reduced aldosterone-to-renin ratio. Raj et al[8] 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 physiologic maximum in POTS women. Interestingly, a similar reduced aldosterone-to-renin ratio was also observed in healthy individuals after a period bed rest (i.e., simulated microgravity exposure), in which "deconditioning" (i.e., cardiac atrophy, hypovolemia, etc.) 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 non-modulating hypertension is based on this theory.[27] It has also been found that non-modulating hypertensive patients have a greater decrease in plasma volume when shifted from a high salt diet to a low salt diet[28] and a greater increase in plasma norepinephrine concentration during standing compared to modulating hypertensive patients.[29] Whether abnormalities in the RAAS contribute to POTS or whether the reduced aldosterone-to-renin ratio is a result of POTS (i.e., "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-h standing were greater in the MLP than 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, while estrogen might inhibit the activation of this system.[34, 35] Szmuilowicz et al[23] 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-h standing in the MLP than EFP in POTS women. However, standing total peripheral resistance was actually lower in the MLP, even though 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 al[30] 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 nitric oxide and stimulate an increase in endothelial nitric oxide synthesis,[36, 37] producing a direct vasodilatory effect.[38] In addition, nitric oxide can downregulate angiotensin II type 1 receptors in vascular tissue[39] and adrenal glands,[40] 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 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, while total peripheral resistance was greater in the EFP than MLP after 30 min 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-h 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 to 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 physiologic compensation to orthostasis. Figure 5 depicts possible mechanisms for orthostatic tolerance in POTS women during different menstrual phases.

Limitations

First of all, even though many patients had POTS symptoms during 2-h standing, we did not document or quantify these symptoms during testing. However, patients' overall well-being was assessed by the Short-Form 36 on each study day, and the results were not different between phases (Table S2). Secondly, we do not know whether some POTS women had the premenstrual syndrome. Rosenfeld et al[41] found that women with premenstrual syndrome had increased fluid-regulatory hormones and disturbed fluid distribution only during the late-luteal phase, while our study was performed in the EFP and MLP. Thirdly, 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 physiologic 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 employ supplemental pharmacologic 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 than EFP, the aldosterone-to-renin ratio was lower in these patients compared to healthy women. This observation could suggest a rationale for the common use of fludrocortisone in such patients, though 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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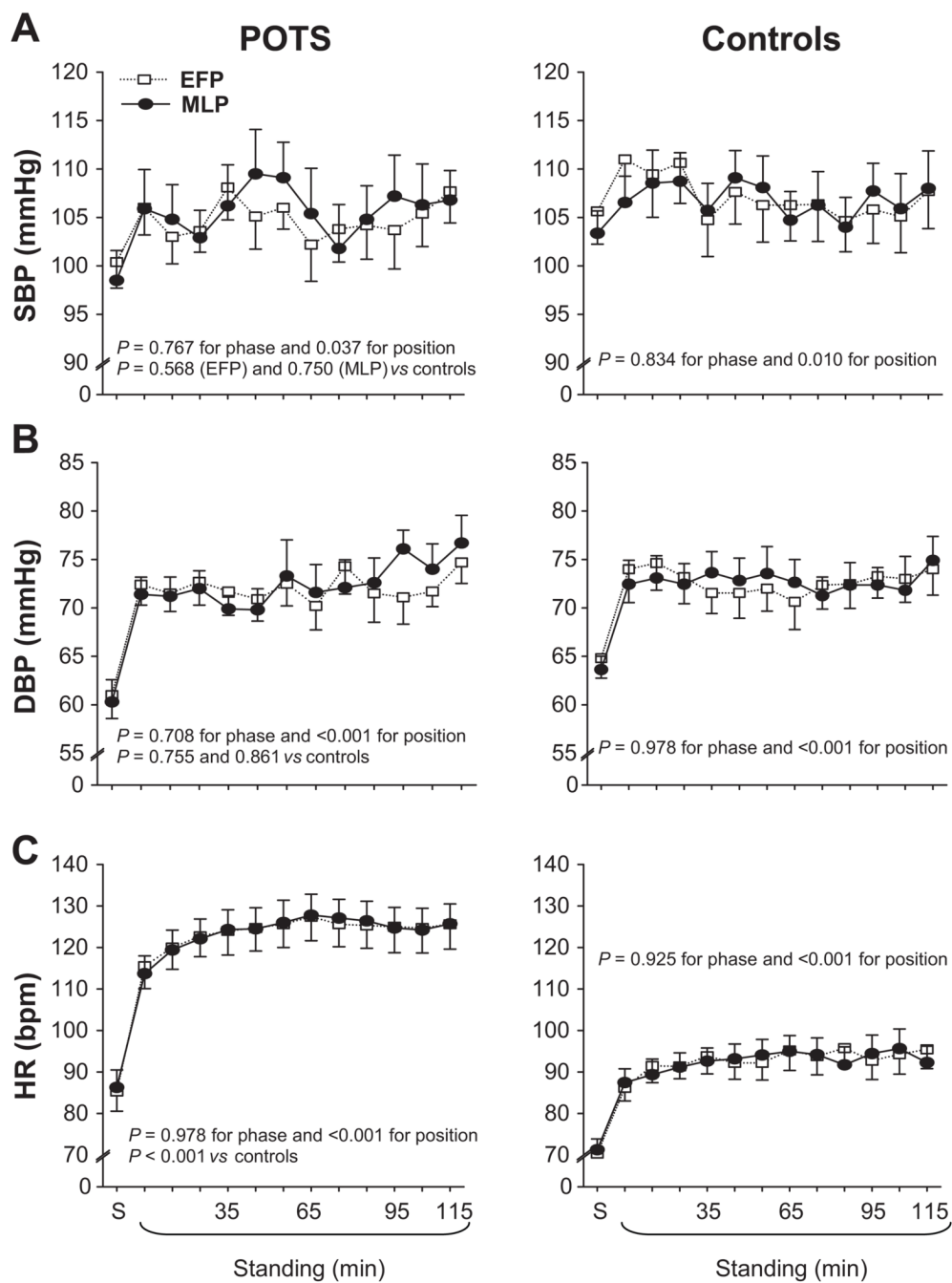
Figure 1.
Systolic blood pressure (SBP, *A*), diastolic blood pressure (DBP, *B*), and heart rate (HR, *C*) responses during 2-h standing in the EFP (open symbols) and MLP (closed symbols) of the menstrual cycle in POTS women and controls. S, supine. Values are expressed as mean ± standard error.

Figure 2.
Cardiac output (CO, **A**), stroke volume (SV, **B**), and total peripheral resistance (TPR, **B**) during 2-h standing in the EFP (open symbols) and MLP (closed symbols) of the menstrual cycle in POTS women and controls. S, supine. Values are expressed as mean ± standard error.
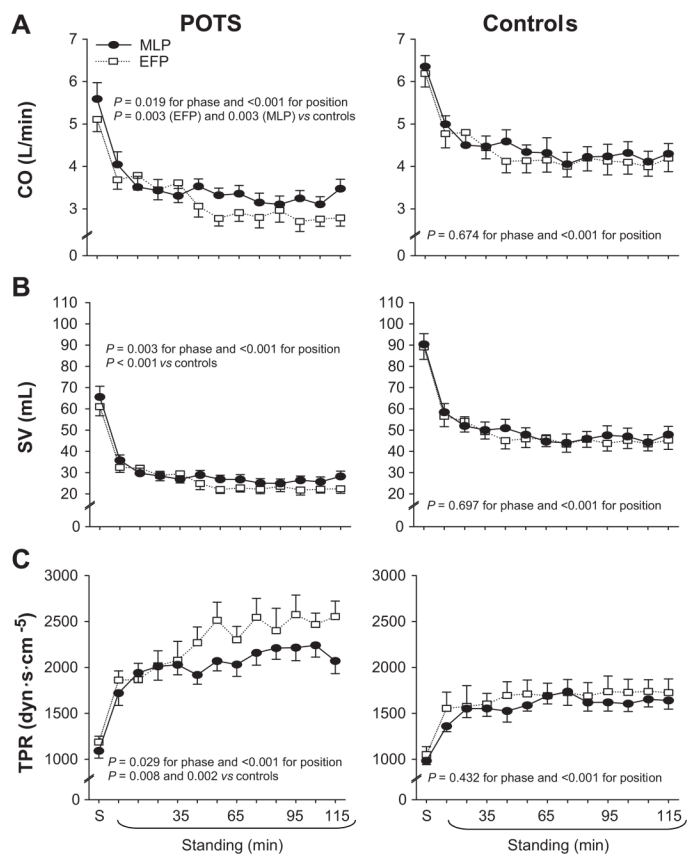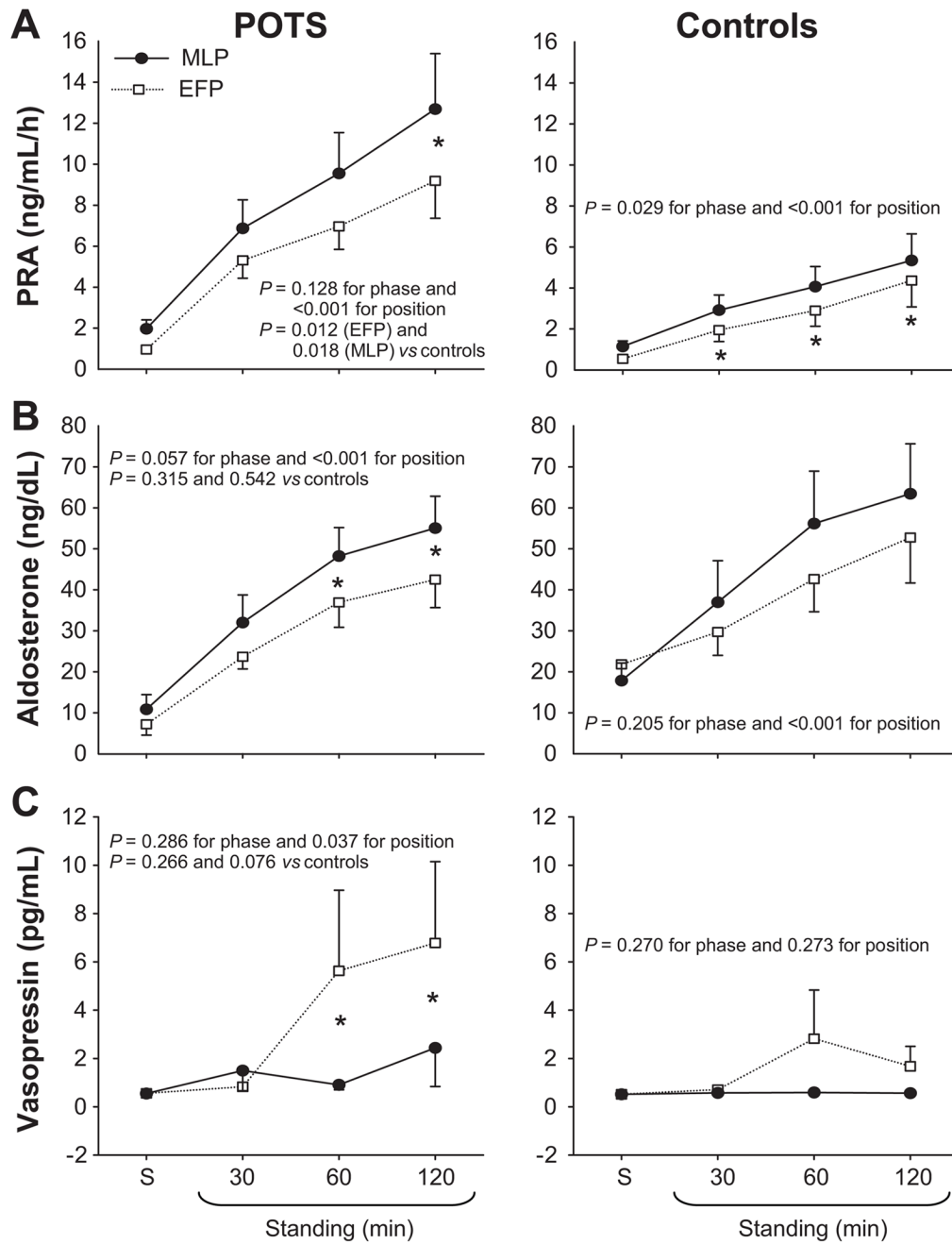
Figure 3.
Plasma renin activity (PRA, *A*), aldosterone (*B*), and vasopressin (*C*) responses during 2-h standing in the EFP (open symbols) and MLP (closed symbols) of the menstrual cycle in POTS women and controls. S, supine. Values are mean ± standard error. *$P < 0.05$ EFP *vs* MLP within the group.
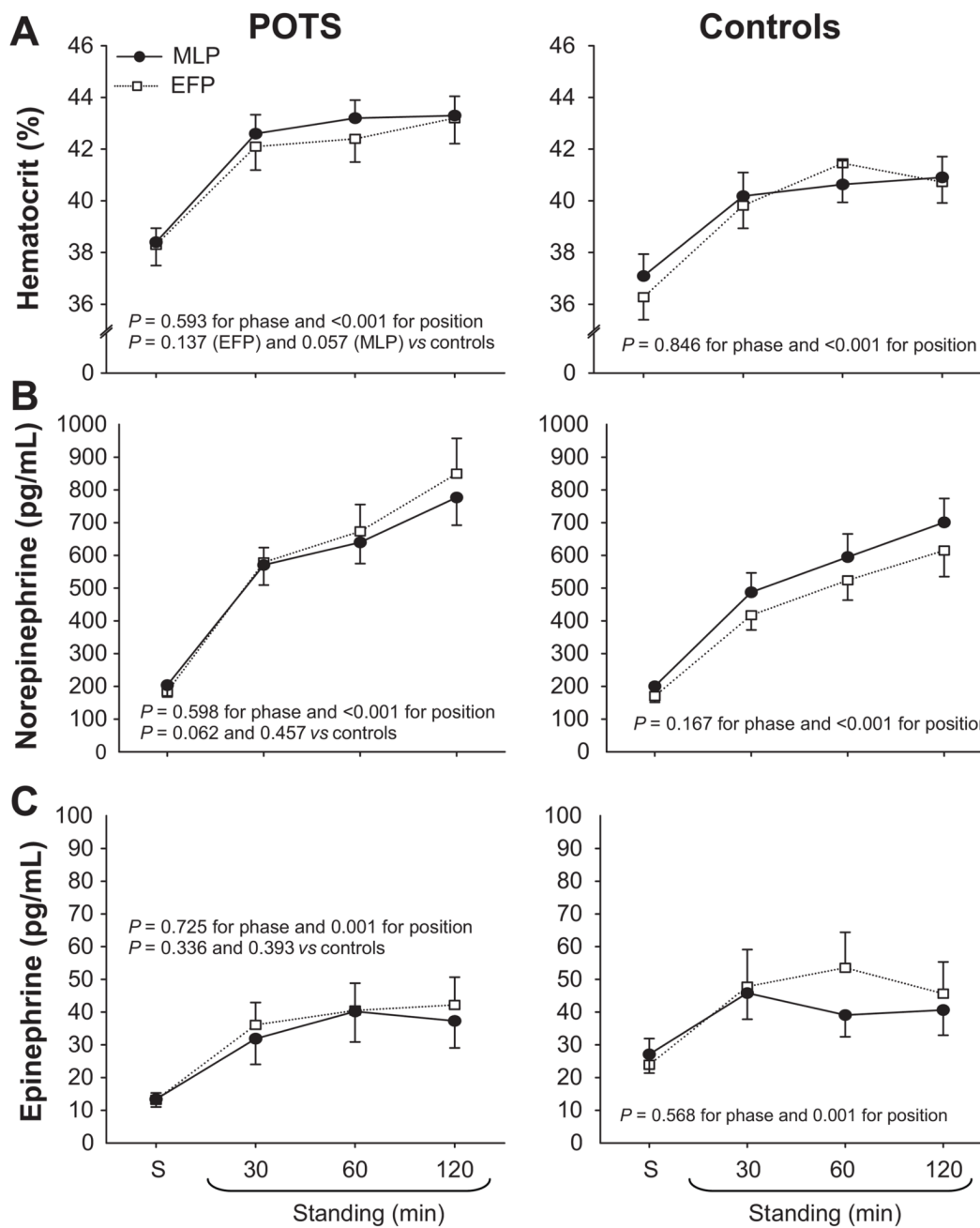
Figure 4.
Hematocrit (***A***), plasma norepinephrine concentration (***B***), and plasma epinephrine concentration (***C***) responses during 2-h standing in the EFP (open symbols) and MLP (closed symbols) of the menstrual cycle in POTS women and controls. S, supine. Values are mean ± standard error.
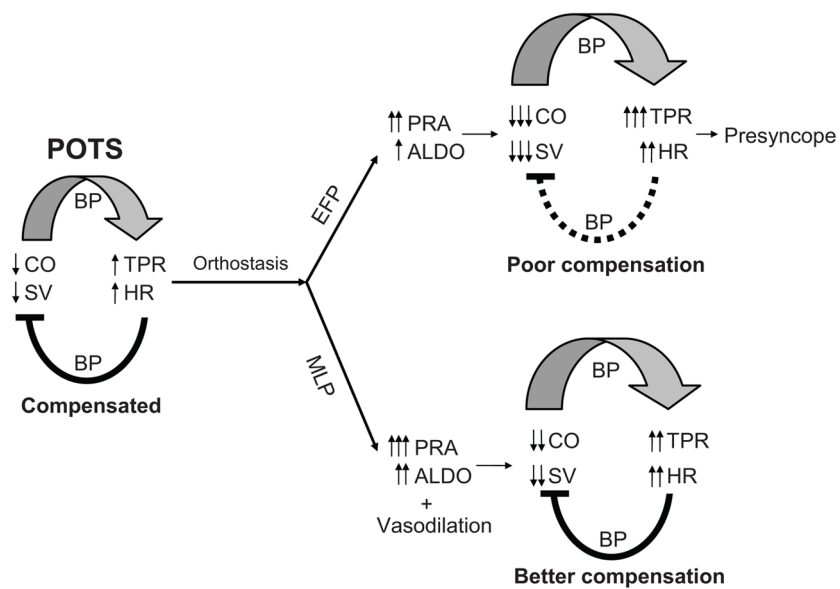
Figure 5.
Possible mechanisms for plasma renin activity (PRA), aldosterone (ALDO), and hemodynamics including cardiac output (CO), stroke volume (SV), total peripheral resistance (TPR), heart rate (HR), and blood pressure (BP), during prolonged standing in POTS women during the early follicular phase (EFP) and mid-luteal phase (ML) of the menstrual cycle.

Table 1

Physical characteristics in POTS women and controls

Variables	POTS Women ($n = 10$)		Controls ($n = 11$)	
	EFP	MLP	EFP	MLP
Age (yr)	27 ± 9		33 ± 10	
Height (cm)	167 ± 6		166 ± 6	
Weight (kg)	67 ± 12	66 ± 12	63 ± 7	64 ± 8
BMI (kg/m^2)	24 ± 4	24 ± 4	23 ± 2	23 ± 2
Menstrual Cycle Day (d)	4.0 ± 0.4	$20.9 \pm 0.9^*$	3.9 ± 0.5	$21.5 \pm 0.7^*$
Estradiol (pg/mL)	33.9 ± 8.3	$94.6 \pm 54.6^*$	32.4 ± 8.9	$91.8 \pm 46.7^*$
Progesterone (ng/mL)	0.8 ± 0.5	$7.2 \pm 6.1^{*\dagger}$	0.9 ± 0.5	$11.1 \pm 5.7^*$
Plasma Volume (mL/kg)	$41 \pm 5^\dagger$	$41 \pm 7^\dagger$	46 ± 5	46 ± 5
Blood Volume (mL/kg)	63 ± 8	62 ± 9	68 ± 7	68 ± 7
Blood pH	7.39 ± 0.01	7.38 ± 0.01	7.42 ± 0.02	7.41 ± 0.01
Na+ (mmol/L)	139 ± 1	138 ± 1	138 ± 1	138 ± 0.4
K+ (mmol/L)	4.2 ± 0.1	4.3 ± 0.1	4.2 ± 0.1	4.3 ± 0.1
Ca++ (mmol/L)	1.17 ± 0.02	1.15 ± 0.02	1.11 ± 0.02	1.15 ± 0.02
24-h Urine Output (mL)	2390 ± 900	2693 ± 1174	2059 ± 860	2338 ± 799
Osmolality (mOs/kg)	296 ± 121	344 ± 231	366 ± 93	360 ± 105
pH	6.7 ± 0.2	6.6 ± 0.2	6.5 ± 0.2	6.4 ± 0.2
Na+ (mmol/24 h)	185.9 ± 48.6	196.0 ± 72.2	148.2 ± 53.7	169.4 ± 48.8
K+ (mmol/24 h)	65.6 ± 32.2	64.2 ± 26.4	52.4 ± 20.6	56.7 ± 17.5
Ca++ (mmol/24 h)	2.0 ± 1.2	2.1 ± 1.5	1.3 ± 0.7	1.7 ± 0.9

Values are mean ± standard deviation. EFP, early-follicular phase; MLP, mid-luteal phase; BMI, body mass index.

[*] $P < 0.05$ compared to MLP within the same group.

[†] $P < 0.05$ compared to controls during the same menstrual phase.