Online Supplement

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

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

[1]Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas
[2]The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas
[3]Brigham & 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

1. Burge CM, Skinner SL. Determination of hemoglobin mass and blood volume with CO: evaluation and application of a method. *J Appl Physiol.* 1995;79:623-631.
2. Gore CJ, Rodriguez FA, Truijens MJ, Townsend NE, Stray-Gundersen J, Levine BD. Increased serum erythropoietin but not red cell production after 4 wk of intermittent hypobaric hypoxia (4,000-5,500 m). *J Appl Physiol.* 2006;101:1386-1393.

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

Variables	**POTS Women** (*n* = 10)		**Controls** (*n* = 11)	
	EFP	MLP	EFP	MLP
Age (yr)	27 [21, 33]		29 [27, 42]	
Body Mass Index (kg/m^2)	23.2 [21.2, 25.6]	22.8 [21.7, 25.7]	22.1 [21.2, 24.2]	23.1 [21.6, 24.2]
Systolic Blood Pressure (mmHg)	103 [93, 107]	98 [90, 106]	101 [98, 113]	104 [98, 108]
Diastolic Blood Pressure (mmHg)	58 [57, 63]	60 [55, 66]	64 [60, 65]	63 [61, 66]
Heart Rate (bpm)	79 [74, 90]†	85 [79, 90]†	69 [65, 76]	69 [64, 78]
Cardiac Output (L/min)	4.93 [4.30, 5.58]†	5.44 [4.68, 6.46]	6.20 [5.51, 7.19]	5.98 [5.79, 7.20]
Stroke Volume (mL)	59 [51, 64]†	57 [55, 83]†	93 [73, 99]	91 [77, 104]
Total Peripheral Resistance (dyn·s·cm^{-5})	1156 [1090, 1330]	1166 [850, 1264]	942 [899, 1053]	998 [844, 1044]
Plasma Renin Activity (ng/mL/h)	1.0 [0.6, 1.4]	2.1 [0.7, 3.0]*†	0.6 [0.3, 0.7]	1.0 [0.6, 1.6]*
Aldosterone (ng/dL)	4.2 [2.9, 8.0]	7.8 [5.3, 10.9]*	26.6 [4.5, 32.7]	9.2 [5.4, 33.3]
Hematocrit (%)	37 [37, 39]	39 [37, 40]	37 [33, 39]	37 [36, 40]
Plasma Norepinephrine (pg/mL)	183 [105, 237]	180 [93, 314]	151 [131, 184]	201 [172, 220]
Plasma Epinephrine (pg/mL)	12 [10, 13]	11 [10, 13]	13 [10, 32]	16 [14, 35]

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

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

Values are expressed as median [25^{th}, 75^{th} percentile]. SF-36, the 36-item Short Form Healthy Survey; EFP, early-follicular phase; MLP, mid-luteal phase.

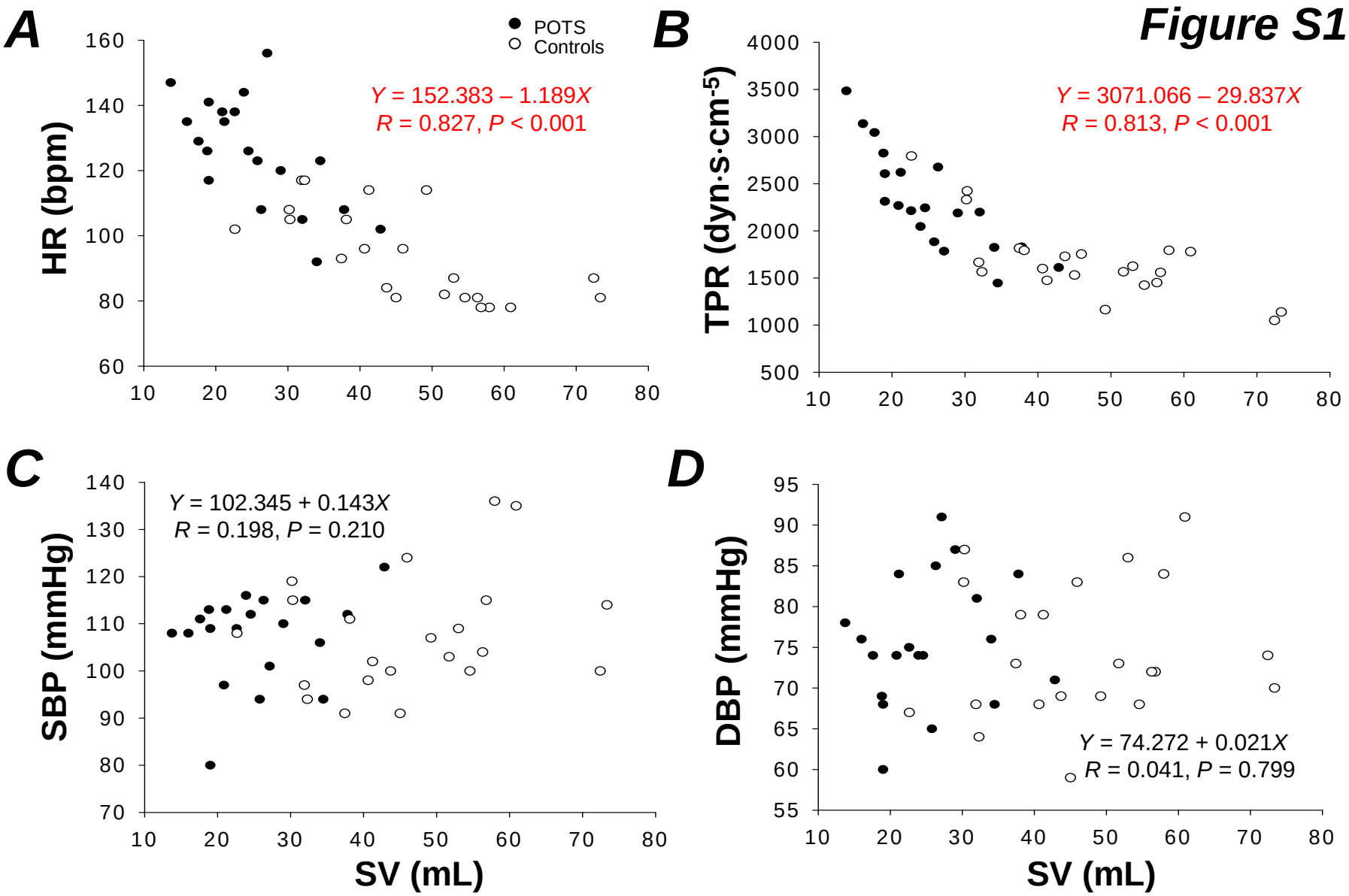

Figure S1. Heart rate (HR, ***A***), total peripheral resistance (TPR, ***B***), and systolic and diastolic blood pressure (SBP and DBP, ***C*** and ***D***) in relation to stroke volume (SV) after 2 h of standing in POT women (filled circles) and healthy controls (open circles). Both HR and TPR were 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.

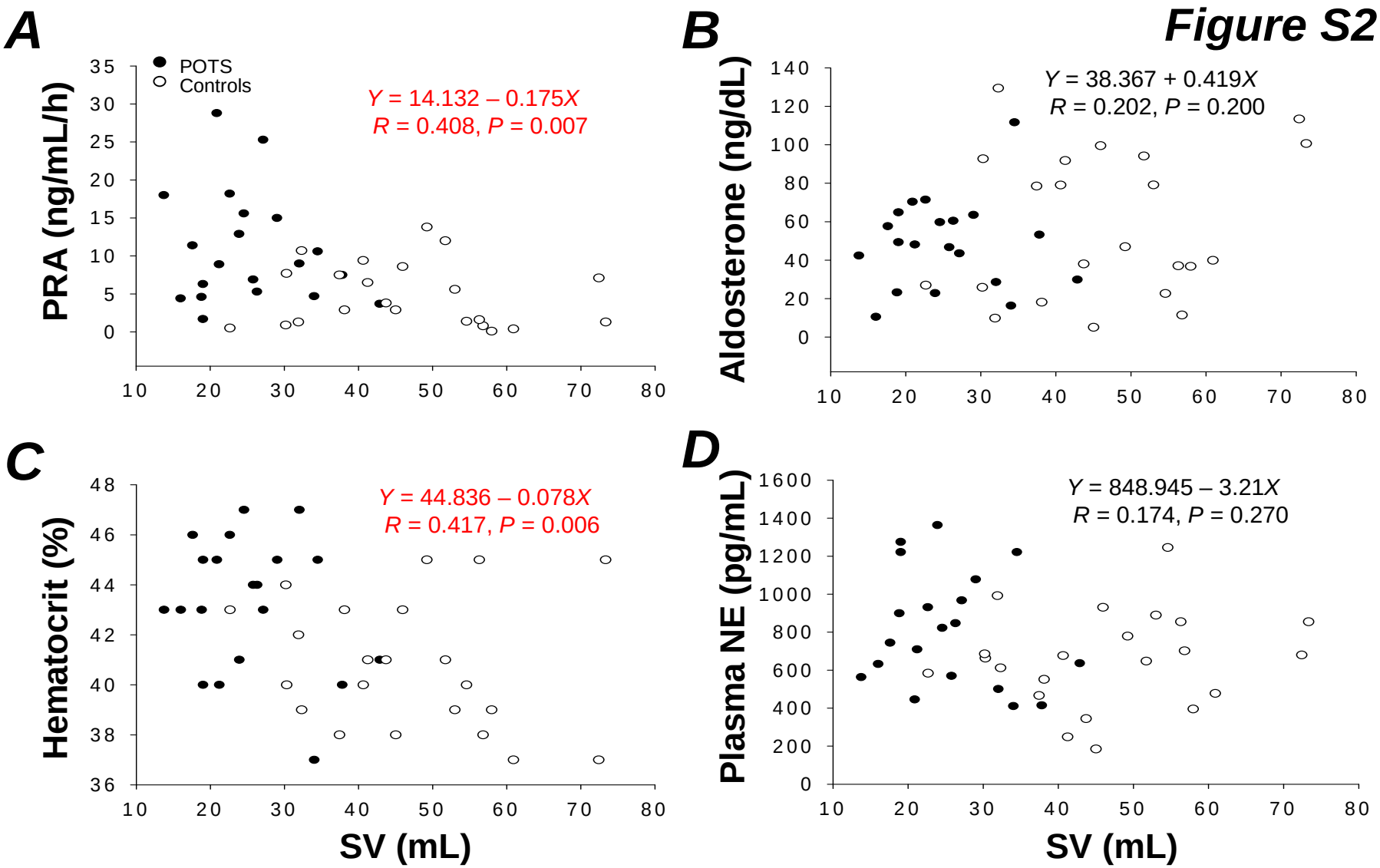

Figure S2. Plasma renin activity (PRA, ***A***), aldosterone (***B***), hematocrit (***C***), and plasma norepinephrine (NE, ***D***) in relation to stroke volume (SV) after 2 h of standing in POTS women (filled circles) and healthy controls (open circles). Both PRA and hematocrit were negatively correlated 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.