Role of the ovarian cycle on neural cardiovascular control in sleep-deprived women

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¹Department of Kinesiology and Integrative Physiology, Michigan Technological University, Houghton, Michigan; ²Department of Biological Sciences, Michigan Technological University, Houghton, Michigan; and ³Department of Neurology, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, Massachusetts

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Yang H. Durocher JJ, Larson RA, Carter JR. Role of the ovarian cycle on neural cardiovascular control in sleep-deprived women. J Appl Physiol 118: 419–426, 2015. First published December 24, 2014; doi:10.1152/japplphysiol.00626.2014.—The midluteal (ML) phase of the ovarian cycle is often sympathoexcitatory compared with the early follicular (EF) phase. We recently reported that 24-h total sleep deprivation (TSD) augmented cardiovascular reactivity in both men and women, but that sex differences existed in resting muscle sympathetic nerve activity (MSNA) responses to TSD. In the present study, we hypothesized increased resting MSNA and augmented cardiovascular reactivity to acute laboratory stressors during the ML phase in sleep-deprived women. Heart rate (HR), mean arterial pressure (MAP), forearm vascular conductance (FVC), and MSNA were measured in 14 eumenorrheic women (age, 20 ± 1 yr) during 10 min supine rest, 5 min mental stress (MS) trial, and 2 min cold pressor test (CPT) trial. Subjects were tested twice after TSD: once during EF phase and once during ML phase (randomized, crossover design). Estradiol (29 ± 2 vs. 63 ± 8 pg/ml, P = 0.001) and progesterone (1.6 ± 0.2 vs. 4.4 ± 0.7 ng/ml, P = 0.002) were elevated during the ML phase. Resting supine MAP (75 ± 2 vs. 72 ± 1 mmHg, P = 0.042) was lower during the ML phase. In contrast, resting supine HR, MSNA, and FVC were not significantly different between EF and ML phases. MAP, HR, and FVC reactivity to MS were not statistically different between the EF and ML phases. Similarly, MAP and HR reactivity to CPT were not different between the ovarian phases. Contrary to our original hypothesis, the ML phase was not associated with sympathoexcitation or exaggerated cardiovascular reactivity in sleep-deprived premenopausal women. However, our data reveal elevated resting blood pressure during the EF phase in sleep-deprived women.

arterial blood pressure; total sleep deprivation; microneurography; autonomic activity; cardiovascular reactivity

OVER THE PAST DECADE, several studies have investigated the role of the ovarian cycle on resting muscle sympathetic nerve activity (MSNA) and reported controversial results. While some studies report increased MSNA during the midluteal (ML) phase (32, 34, 36), others report similar MSNA between early follicular (EF) and ML phases (8, 9, 12, 15, 20, 28). However, a recent retrospective analysis that combined data from multiple laboratories revealed a dynamic interaction among estradiol, progesterone, and MSNA that might help explain some of the previously reported inconsistencies (7). Briefly, it was reported that changes in MSNA between the EF and ML phases of the ovarian cycle were significantly correlated to not only changes in estradiol, but also the ratio between changes in estradiol and progesterone (7), a finding that was consistent with the prevailing concept that estradiol is sympathoinhibitory and progesterone is sympathoexcitatory.

Evidence is accumulating to suggest that insufficient sleep may contribute importantly to the risk of developing cardiovascular disease. Specifically, recent epidemiological studies report consistent associations between short sleep and incidence of hypertension (5, 16, 17), as well as short sleep and cardiovascular-related morbidity and mortality (19). More recently, Cappuccio et al. (5) reported that the association between short sleep and hypertension existed in women, but not men. A recent study from our laboratory demonstrated total sleep deprivation (TSD) decreased resting MSNA only in men, but not in women (6), a finding that provided new mechanistic insight in understanding why women might be more prone to develop hypertension in response to sleep deprivation. It was also reported that TSD had a sex-specific impact on both progesterone and testosterone (6), but we could not probe into the influence of the ovarian cycle because all women were strictly tested during the EF phase.

Finally, exaggerated cardiovascular reactivity (i.e., blood pressure and heart rate responses) to acute laboratory stressors have been linked to increased risk of cardiovascular disease (31, 44, 47). The role of the ovarian cycle on cardiovascular reactivity remains conflicting; some have reported an augmented cardiovascular reactivity in the luteal phase compared with follicular phase (11, 37, 42), while others report similar cardiovascular reactivity between ovarian phases (10, 21, 40, 43). Recent data from our laboratory (48) and others (14) suggest that sleep deprivation magnifies cardiovascular reactivity, yet the role of the ovarian cycle on cardiovascular reactivity in sleep-deprived women remains unknown.

Accordingly, we investigated the role of the ovarian cycle on neural and cardiovascular control in sleep-deprived women. Due to the reported sympathoexcitatory effect during ML, we hypothesized that resting MSNA would be augmented in ML compared with EF phase in sleep-deprived women. Second, we hypothesized an augmented cardiovascular reactivity to acute stress during the ML phase in sleep-deprived women.

METHODS

Subjects

Fourteen healthy premenopausal women subjects participated in the study (see Table 1 for demographics). All subjects were nonsmokers and had no history of autonomic dysfunction, cardiovascular disease, asthma, or diabetes. All subjects were instructed to abstain from exercise, alcohol, and caffeine for 12 h prior to laboratory testing. Subjects could not participate if they were taking oral contraceptives or other hormonal supplemental. All subjects reported
Table 1. Subject characteristics, state anxiety, and sex steroids

<table>
<thead>
<tr>
<th>Variable</th>
<th>EF</th>
<th>ML</th>
<th>P Values</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>20 ± 1</td>
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<tr>
<td>BMI, kg/m²</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
<td>= 0.94</td>
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<tr>
<td>Raw STAI, a.u.</td>
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<td>= 0.96</td>
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<tr>
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<tr>
<td>Percentile STAI</td>
<td>60 ± 6</td>
<td>62 ± 5</td>
<td>= 0.45</td>
</tr>
<tr>
<td>Estradiol, pg/ml</td>
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<td>63 ± 8*</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Progesterone, ng/ml</td>
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<td>4.4 ± 0.7*</td>
<td>&lt; 0.01</td>
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<td>Testosterone, ng/dl</td>
<td>44 ± 5</td>
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<td>= 0.98</td>
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Values are means ± SE; EF, early follicular phase; ML, midluteal phase; BMI, body mass index; STAI, state-trait anxiety inventory; n = 14. *P < 0.05, EF vs. ML.

Table 2. Subject characteristics, state anxiety, and sex steroids

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regular menstrual cycles (range 26–30 days). Testing procedures were explained to all subjects before obtaining written informed consent approved by the Michigan Technological University Institutional Review Board.

Experimental Design

Subjects were tested after 24 h TSD in the laboratory twice: once during their EF phase (i.e., 2–5 days after start of menstruation) and once during their ML phase (i.e., 8–10 days after luteinizing hormone surge, which was determined using urine ovulation kits). Trial order (EF vs. ML) was randomized in all subjects, with a near equal distribution of subjects that began with each ovarian phase (i.e., 8 were initially tested during EF, 6 were initially tested during ML). Wrist actigraphy (ActivWatch-64, Respironics, Bend, OR) was used for a minimum of three consecutive nights immediately preceding each trial to estimate sleep time. All wrist actigraphy data were analyzed by a board-certified sleep physician (J. DellaValla) and revealed that subjects were getting adequate sleep for three consecutive nights immediately preceding each trial.

Microneurography. Multifiber recordings of MSNA were made by inserting a tungsten microelectrode (Haer, Bowdoinham, ME) into the peroneal nerve of the right leg. A reference electrode was inserted subcutaneously 2–3 cm from the microneurography electrode. Both electrodes were connected to a differential preamplifier, and then to an amplifier (total gain of 80,000) where the nerve signal was band-pass filtered (700–2,000 Hz), and integrated (time constant, 0.1 s) to obtain a mean voltage display of nerve activity. Quality recordings of MSNA were defined by spontaneous, pulse synchronous bursts that increased during end-expiratory apnea and remained unchanged during auditory stimulation or stroking of the skin.

Blood pressure and heart rate. Arterial blood pressures were obtained in both the seated position (described previously), and in the supine position immediately preceding each baseline. Both seated and supine resting arterial blood pressures were measured using an automated sphygmomanometer (Omrone HEM-907XL, Omron Health Care) three consecutive times (separated by ~1-min intervals) at the same time in the morning in both phases, and the mean values of these measurements are reported. Beat-to-beat arterial blood pressure was recorded continuously throughout the study using a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands). Arterial blood pressures are expressed as systolic (SAP), diastolic (DAP), and mean (MAP) arterial pressures. Heart rate was recorded continuously via a three-lead electrocardiogram, and respiratory rate was continuously measured using a pneumobelt.

Venous occlusion plethysmography. Forearm blood flow (FBF) was measured via venous occlusion plethysmography (EC6; Hokanson, Bellevue, WA). A brief, a mercury-in-Silastic strain gauge was placed around the subject’s forearm at the point of greatest circumference to measure changes in blood flow during the study. Cuffs were placed around the subjects left wrist and upper arm. The recording forearm was placed above the heart level during venous occlusion plethysmography. The occluding cuff placed on the wrist was inflated to 220 mmHg, while the upper arm cuff was inflated to 60 mmHg for 8 s and deflated for 7 s (i.e., 15 s blood flow intervals). Forearm vascular conductance (FVC) was calculated as FBF divided by MAP. All the delta values expressed in the figures were 5-min average changes during mental stress. During the stress challenge, BFB was not available to analyze in one subject; thus we present FBF and FVC for 13 subjects.

Blood analysis. Approximately 11 ml of venous blood was obtained to determine levels of estradiol, progesterone, and testosterone. Blood samples were clotted, centrifuged, and serum was separated and refrigerated until testing. Estradiol was measured utilizing a chemiluminescence immunoassay (CLIA) on an Ortho Vitros 5600 analyzer (Johnson and Johnson Healthcare Systems, Piscataway, NJ) at Portage Health Hospital. Progesterone and testosterone were measured utilizing a CLIA on an Ortho Vitros 3600 analyzer (Johnson and Johnson Healthcare Systems) at Marquette General Hospital.

Data Analysis

Muscle sympathetic nerve activity. Data were imported and analyzed in the WinCPRS software program (Absolute Alints; Turku, Finland). R-waves were detected and marked in the time series. Muscle sympathetic nerve bursts were automatically detected on the basis of amplitude using a signal-to-noise ratio of 3:1, within a 0.5-s window centered on a 1.3-s expected burst peak latency from the previous R-wave. Potential bursts were displayed and edited by one trained investigator. MSNA was expressed as burst frequency (bursts/min) and burst incidence (bursts/100 heart beats). Resting MSNA was successfully recorded during both EF and ML phases in eight subjects.

Statistical analysis. All data were analyzed statistically using commercial software (IBM SPSS Statistics 20.0, SPSS, New York). Paired t-tests were used to compare baseline values between EF and ML phases. We used repeated-measures ANOVA with phase (EF vs. ML) and time
(baseline vs. stress tests) as within-subject factors to compare the reactivity to mental stress and CPT. Paired t-tests were used for post hoc analysis when there was a significant time × phase interaction. Pearson correlation was used to compare ratio changes between estradiol and progesterone (ΔE/ΔP) and changes of MSNA (i.e., values in ML minus values in EF phases). Results are expressed as means ± SE. Means were considered significantly different at $P < 0.05$.

RESULTS

Resting Hemodynamic and Neural Comparisons Between EF and ML After TSD

Subject characteristics and sex steroids are summarized in Table 1. Anxiety levels were presented as raw, standard, and percentile STAI and showed no difference between EF and ML phases. Both estradiol and progesterone levels were significantly increased during ML phase compared with EF phase ($P < 0.01$); testosterone was similar between the two ovarian phases. The progesterone levels in 4 subjects did not reach the general accepted cutoff point (i.e., >3 ng/ml) which reflect an ovulatory cycle (46). In a subgroup ($n = 10$) subjects with progesterone levels over 3 ng/ml during ML (5.6 ± 0.7 ng/ml), the findings of anxiety level and hormones between EF and ML were similar as shown in the whole group.

Figure 1 demonstrates that supine SAP (101 ± 2 to 98 ± 2 mmHg, $P = 0.04$) and MAP (75 ± 2 to 72 ± 1 mmHg, $P = 0.04$) were significantly increased during EF phase compared with ML phase. It is important to note these are 2-tailed $P$ values because we did not have a directional hypothesis regarding resting blood pressure responses. Supine DAP (61 ± 2 to 60 ± 1 mmHg, $P = 0.37$) was similar between phases. Seated SAP (101 ± 2 to 100 ± 2 mmHg, $P = 0.46$), DAP (63 ± 2 to 61 ± 2 mmHg, $P = 0.08$), and MAP (76 ± 2 to 74 ± 1 mmHg, $P = 0.11$) were not different between the two ovarian phases. Resting HR was not different between EF and ML phases (60 ± 2 to 61 ± 2 beats/min, $P = 0.37$).

Figure 2 demonstrates similar resting MSNA when analyzed as either burst frequency (12 ± 2 to 12 ± 3 bursts/min, $P = 0.85$) or burst incidence (20 ± 4 to 20 ± 5 bursts/100 heart beats, $P = 0.92$) between EF and ML phases. No correlations were detected between changes of MSNA burst frequency and ΔE/ΔP ($r = 0.19$, $P = 0.64$) or MSNA burst incidence and ΔE/ΔP ($r = 0.21$, $P = 0.62$). Similarly, resting FBF (1.3 ± 0.2 vs. 1.4 ± 0.2 ml/100 ml of tissue$^{-1}$·min$^{-1}$, $P = 0.23$) and FVC (0.017 ± 0.002 vs. 0.020 ± 0.003 ml/100 ml of tissue$^{-1}$·min$^{-1}$·mmHg$^{-1}$, $P = 0.19$) were not different between EF and ML phases.

Cardiovascular Reactivity to Mental Stress and CPT

Subjects reported similar ratings of perceived stress (2.4 ± 0.2 and 2.5 ± 0.1 au, $P = 0.59$) after mental stress performed in the EF and ML phases, respectively. Figure 3 demonstrates MAP and HR were significantly increased in response to both mental stress and CPT (time, $P < 0.01$), but these increases were not different between ovarian phases. Percent changes of FBF and FVC to mental stress are depicted in Fig. 4. Mental stress increased FBF (Δ74 ± 19 and Δ54 ± 10%; time, $P < 0.01$) and FVC (Δ60 ± 17 and Δ39 ± 9%; time, $P < 0.01$) in both EF and ML phases, but these changes were not different between phases (phase × time, $P = 0.23$ and $P = 0.15$, respectively). Similar findings were observed for absolute changes in FBF and FVC (data not reported). In the subgroup dataset with women who met the progesterone criteria (10 subjects for hemodynamic data and 7 subjects for MSNA data), all the main findings were similar to when analyzed as a whole group.

DISCUSSION

The present study examined the role of the ovarian cycle on neural cardiovascular control in sleep-deprived women. We offer three novel findings. First, we reported an augmented supine blood pressure in EF compared with ML phase in
sleep-deprived women; combined with our recent finding examining TSD and sex differences (6), it is possible that TSD elicits an isolated pressor response during the low hormone phase. Second, contrary to our original hypothesis, resting MSNA was not different between EF and ML phases in sleep-deprived women. Third, cardiovascular and FBF reactivity to acute stressors were not different between ovarian phases in sleep-deprived women. Overall, this study is the first to examine the role of ovarian cycle on neural and cardiovascular control in sleep-deprived women and provides new insights regarding emerging relations between sleep deprivation, cardiovascular risk, and sex.

Resting Hemodynamics and Neural Control Between EF and ML Phases

Young premenopausal women appear to be more “protected” from developing hypertension and cardiovascular disease compared with age-matched men (38). Female sex hormones may play a role in resting blood pressure fluctuation throughout the ovarian cycle. More specifically, it has been reported that estrogen increases nitric oxide synthesis and release from the vascular endothelium (3, 33, 41), which in turn can cause vasodilation. In a recent study, Adkisson et al. (1) reported a pattern of reduced blood pressure and increased systemic vascular reactivity during late follicular phase in healthy premenopausal women, a time when estradiol and nitric oxide concentrations are highest. In contrast, several studies have reported similar blood pressures between EF and ML phases in women presumably obtaining normal sleep (7, 9, 15, 34).

We recently reported an acute pressor response to TSD in premenopausal women during EF phase (6). In the present study, blood pressure was augmented in EF compared with ML in sleep-deprived women. The vast majority of previous studies, including work from our laboratory, have not found differences in resting supine MAP between EF and ML phases in women that are presumably obtaining normal sleep. Given the present finding of a lower resting MAP in the ML relative to the EF phase in sleep-deprived women, and our previous findings of an acute pressor response to TSD during EF (6), we suggest that TSD might selectively augment blood pressure in the EF phase. However, further study is needed of baseline and TSD recordings in the same group of women at different menstrual phases. In the present study, we did not record the blood pressure on the present cohort of subjects after a normal sleep night, and this limitation is discussed later. Importantly, we acknowledge that the elevated supine pressor response during EF phase was not observed during the seated blood pressure readings. That said, there was a tendency for DAP and MAP to be elevated during the EF phase, and it is important to note that the blood pressure data were appropriately analyzed using 2-tailed hypothesis testing because we did not have a directional hypothesis. If we had originally hypothesized an augmentation of blood pressure during the low hormone phase, which in hindsight seems appropriate, we would have observed statistically significant, or nearly significant, changes in seated DAP (\( P = 0.04 \), 1-tailed) and seated MAP (\( P = 0.055 \), 1-tailed), which would have been more consistent with our supine blood pressure findings (Fig. 1).

Sympathetic overactivity plays an important role in the pathogenesis of hypertension and other cardiovascular disease. It has also been suggested that increased sympathetic activity is a potential contributor to the increased blood pressure observed after sleep deprivation (49), but direct evidence is lacking. More specifically, TSD has been reported to reduce resting MSNA in response to acute increases in blood pressure in humans (23, 35). More recently, we reported that this reduction of resting MSNA to acute pressor response after TSD is only observed in men; MSNA was unaltered by TSD in women during their EF phase (6).

While the data on resting MSNA in sleep-deprived women are very limited (6, 23, 35), no study has attempted to investigate the relations between sleep deprivation, the ovarian cycle, and MSNA. In the present study, we recorded MSNA during EF and ML phases in sleep-deprived women and reported similar resting MSNA between the two ovarian phases. We hypothesized that resting MSNA would be augmented during the ML phase based on a recent study supporting the concept that the ML phases is sympathoexcitatory if certain surges of estradiol and progesterone are observed (7). Contrary to our original hypothesis, we did not observe any changes in resting MSNA across the ovarian cycle in sleep-deprived women.

One potential explanation is the modest surges of estradiol, and more importantly progesterone. Previous studies report an average around 9–11 ng/ml of progesterone levels during ML when there is no sleep deprivation intervention (7–9). In the present study, we detected the progesterone levels in four
subjects did not reach the standard 3 ng/ml during ML (46), suggesting anovulation in these subjects or testing outside ML phase. Alternatively, progesterone may have been below the 3 ng/ml in the four participants due to TSD as discussed below. Nevertheless, even the subset of women who met the standard progesterone surge during ML (i.e., 3 ng/ml) showed a modest surge of progesterone (5.6 ± 0.7 ng/ml). In our previous study that reported MSNA responses to TSD in men and women, we observed significant reductions in progesterone in response to TSD in women (6). While this prior finding with progesterone went largely unnoticed and undiscussed (6) due to the excitement over observed significant reductions in progesterone in response to TSD in women (6). Therefore, the lack of change in resting MSNA may have not been strong enough to elicit changes in resting MSNA during the ML phase. Alternatively, progesterone may have been below the 3 ng/ml during ML (46), suggesting anovulation in these subjects or testing outside ML phase.

There are several lines of evidence suggesting that estradiol is sympathoinhibitory and that progesterone is sympathoexcitatory (12, 18, 34, 45), and a recent retrospective study including data from multiple laboratories suggests that increases of resting MSNA during the ML phase may depend importantly on the level of the estradiol and/or progesterone surge within an ovarian cycle (7). In the present study, we had very modest surges in estradiol and progesterone during the ML phase that may have not been strong enough to elicit changes in resting MSNA. Furthermore, no correlations were found between the changes of MSNA and ΔE/ΔP ratio as observed in presumably rested women (7). Therefore, the lack of change in resting MSNA reported in the present study may be the result of the blunted surge in progesterone, but more controlled studies are needed to truly address the potentially complex interactions between sleep deprivation, sex steroid surges during the ovarian cycle, and resting MSNA (see Limitations).

Finally, estrogen plays an important cardiovascular role by contributing to the vasodilation of blood vessels, mainly via increased nitric oxide synthesis and release from the vascular endothelium (3, 33, 41), and by increased β2-adrenergic-mediated vasodilation (13). Adkisson et al. (1) examined FBF in four phases of ovarian cycle and reported a peak of FBF during late follicular phase when the estrogen and nitric oxide concentrations were highest. However, when comparing FBF or FVC between EF and ML phases, other studies reported that FBF is not altered between these two phases (25, 27). In the present study, we observed no differences of FBF between EF and ML in sleep-deprived women, consistent with the findings in women presumably obtaining normal sleep.

**Cardiovascular Reactivity During EF and ML Phases in Sleep-Deprived Women**

Mental stress and CPT have been extensively studied as laboratory stressors because the extent of cardiovascular reactivity to mental stress and CPT has been shown to have some predictive value into the risk of hypertension (26, 30, 31, 44, 47). Studies of cardiovascular reactivity in premenopausal women throughout the ovarian cycle have been conflicting. Some report similar cardiovascular reactivity between phases (10, 21, 40, 43), while others demonstrate augmented cardiovascular reactivity in luteal phase compared with follicular phase (11, 29, 37, 42). Moreover, the hypothalamic-pituitary-adrenal (HPA) axis reactivity, assessed by cortisol responses to laboratory stressors, is greater during luteal compared with follicular phase in healthy women (22, 24, 29, 42). Therefore, the ovarian cycle might have potential effects on cardiovascular reactivity to stressors, with augmented cardiovascular reactivity in the luteal phase compared with the follicular phase.
neurography session was not an option for this project. Thus our primary study limitation, which was recognized prior to the study execution, is that we must incorporate our previous study in young women tested only during the EF phase for certain study interpretations (6, 48). As such, we have tried to be careful with our interpretations, but have strategically included the discussion of a potential isolated pressor response during the low hormone phase given the expanding literature on the importance of sex steroids in blood pressure regulation. The marked rise in hypertension after menopause remains unresolved. Given that menopause and aging are also associated with sleep disturbances, we believe further investigations examining neural cardiovascular control in postmenopausal women are warranted. Second, we have limited MSNA data at rest, and during several of the mental stress and/or CPT trials in our subjects the microneurography electrode was dislodged. Given the randomized, crossover approach (i.e., EF vs. ML), we were not comfortable repositioning the electrode and re-running baselines and interventions; we believed that providing a similar laboratory environment and experimental sequence was essential for the cardiovascular reactivity comparisons. While the MSNA data were critical for our resting baseline hypothesis, it was not viewed as essential for the mental stress and CPT trials because our primary hypotheses focused on the cardiovascular reactivity. Therefore, we acknowledge the lack of MSNA stress reactivity data as a limitation, but it did not limit our ability to address our primary hypotheses (i.e., resting MSNA and cardiovascular reactivity). Finally, our experimental approach used a 24-h TSD, which remains a primary and cost-effective experimental approach for examining physiological responses to sleep deprivation. However, chronic sleep restriction is more common in daily living. Future investigations might utilize novel sleep restriction models (i.e., short sleep over several days) to further examine the role of ovarian cycle and sleep deprivation in neural and cardiovascular control in women.

**Summary**

In conclusion, the present study examined neural and cardiovascular control between EF and ML in sleep-deprived women. We reported an augmented blood pressure during the EF compared with the ML phase in sleep-deprived women. In contrast, resting MSNA, as well as cardiovascular reactivity to mental stress and CPT, were similar between EF and ML phases. When combined with our recent study (6), these new findings suggest a potential isolated pressor response to TSD in the EF phase; future work might focus on neural cardiovascular responses to sleep deprivation in postmenopausal women when sex steroids are typically at nadir levels.

**ACKNOWLEDGMENTS**

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**GRANTS**

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).
AUTHOR CONTRIBUTIONS

Author contributions: H.Y., J.J.D., R.A.L., and J.R.C. performed experiments; H.Y., J.J.D., and J.R.C. analyzed data; H.Y., J.J.D., R.A.L., and J.R.C. interpreted results of experiments; H.Y. prepared figures; H.Y. drafted manuscript; H.Y., J.J.D., R.A.L., and J.R.C. edited and revised manuscript; H.Y., J.J.D., R.A.L., and J.R.C. approved final version of manuscript; J.R.C. conception and design of research.

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