Ovarian Cycle and Sympathoexcitation in Premenopausal Women

Jason R. Carter, Qi Fu, Christopher T. Minson, Michael J. Joyner

Abstract—The influence of the ovarian cycle on muscle sympathetic nerve activity (MSNA) remains controversial. Some studies report an increase of resting MSNA during the mid luteal (ML) phase of the ovarian cycle compared with the early follicular phase, whereas other studies do not. These inconsistent findings may be attributable, in part, to the variable surges in estradiol and progesterone. We tested the hypothesis that the degree of sympathoexcitation during the ML phase (ΔMSNA) is associated with changes in estradiol (ΔE2) and progesterone (ΔP). Multiple regression analysis of data from previous studies with complete recordings of mean arterial pressure, MSNA, E2, and P during both early follicular and ML phases were available from 30 eumenorrheic women (age, 28±1 years; body mass index, 23±0 kg/m²). ML phase increased E2 (37±2 to 117±9 pg/mL; P<0.001), P (1±0 to 11±1 ng/mL; P<0.001), and MSNA (12±1 to 15±1 bursts/min; P=0.02), but did not alter mean arterial pressure (83±2 to 83±2 mm Hg; P=0.91). ΔMSNA was correlated with ΔE2 (r=−0.50, P=0.003) and ΔE2/ΔP (r=−0.52, P=0.002) but not ΔP (r=0.21, P=0.13). There was no association between Δmean arterial pressure and ΔE2 (r=−0.13, P=0.49), ΔP (r=−0.04, P=0.83), or ΔE2/ΔP (r=0.01, P=0.98). In conclusion, sympathoexcitation during the ML phase of the ovarian cycle seems to be dependent, in part, on the degree of sex steroid surges. This dynamic interaction among E2, P, and MSNA likely explains previously reported inconsistencies in the field; it remains possible that other sex steroids, such as testosterone, might explain further variance. (Hypertension. 2013;61:395-399.)

Key Words: menstrual cycle ■ autonomic activity ■ microneurography ■ blood pressure

Sympathetic overactivity plays a critical role in the pathogenesis of hypertension, atherosclerosis, and congestive heart failure. Epidemiological studies consistently report that premenopausal women are at lower risk for cardiovascular disease compared with age-matched men, and it has been suggested that lower sympathetic tone may contribute importantly to this premenopausal cardioprotection.1 Conversely, cardiovascular risk accelerates more aggressively in postmenopausal women when compared with age-matched men, and eventually cardiovascular risk eclipses men in late life.2 The development of preventative and therapeutic strategies aimed at reducing the risk of cardiovascular disease in women, particularly after menopause, requires a comprehensive understanding of neural cardiovascular interactions across the entire lifespan of a woman (ie, pre- and postmenopause).

In recent years, several laboratories have used microneurographic techniques to directly assess postganglionic muscle sympathetic neural activity (MSNA) during the ovarian cycle in premenopausal, eumenorrheic women. Ettinger et al3 reported that MSNA did not differ between the early follicular (EF; low estradiol, low progesterone) and late follicular (high estradiol, low progesterone) phases of the ovarian cycle. However, when MSNA was compared between the EF and mid luteal (ML; high estradiol, high progesterone) phases, Minson et al4 reported higher resting MSNA during ML. Carter and Lawrence5 were unable to replicate this finding but did report augmented MSNA recovery to mental stress during the ML phase. Subsequent studies both support6-7 and refute8-12 the concept that resting MSNA is elevated during the ML phase. It has been suggested that estradiol and progesterone exert opposing actions on MSNA. More specifically, estradiol has been suggested to be sympathoinhibitory,13,14 whereas progesterone has been suggested to be sympathoexcitatory.15,16 Thus, it is possible that variable surges in these sex steroids during EF and ML might help explain inconsistencies in the field regarding resting MSNA and the ovarian cycle. Accordingly, we tested the hypothesis that the degree of sympathoexcitation during the ML phase (ΔMSNA) is associated with changes in estradiol and progesterone.

Methods

Subjects

Subjects were retrospectively analyzed from 5 previous studies.5,6,8-12 Original inclusion and exclusion criteria were consistent across laboratories (see original articles), and all studies were approved by the corresponding institutional review boards. For the present analysis, only subjects with concurrent measurements of resting MSNA, mean arterial pressure (MAP), estradiol, and progesterone during both the EF and ML...
or burst incidence ($P<0.013$). Resting heart rate and arterial blood pressures were not different between EF and ML phases.

The stepwise multiple regression excluded age and BMI in all analyses performed; thus age and BMI did not significantly influence reported relations. For the stepwise multiple regressions that included changes in $E_2$ and changes in $P$, model 1 included changes in $E_2$ as the independent variable and model 2 included changes in both $E_2$ and $P$ as independent variables. The Figure demonstrates that changes in MSNA were negatively correlated with changes in estradiol ($P<0.005$) and the $E_2/P$ ratio ($P=0.002$), and tended to be positively correlated with changes in progesterone ($P=0.13$). Changes in MAP were not significantly correlated with changes in estradiol ($r=-0.132, P=0.487$), progesterone ($r=-0.042, P=0.825$), or the $E_2/P$ ratio ($r=0.004, P=0.983$). Absolute (ie, raw) MSNA values expressed either as burst frequency or incidence were not correlated with absolute (ie, raw) estradiol or progesterone levels during either the EF or ML phase.

### Discussion

Consistent with our hypothesis, sympathoexcitatory responses to the ML phase of the ovarian cycle seem to be related, in part, to the degree of sex steroid surge. More specifically, increases in estradiol were significantly correlated with decreases in MSNA during the ML phase. Although changes in progesterone were not significantly correlated with MSNA, it is important to note there was a trend toward significance ($P=0.13$), and that the strongest association between the changes in sex steroids and MSNA was observed when changes in estradiol and progesterone were considered as a ratio (ie, $E_2/P$). Our findings are consistent with the prevailing concept that estradiol is sympathoinhibitory and progesterone is sympathoexcitatory. Collectively, our findings suggest that the variable surges in estradiol and progesterone likely explain previously reported inconsistencies in the field regarding the influence of the ovarian cycle on resting MSNA.

In addition to providing a unifying explanation for previously reported inconsistencies, our data suggest a need to more carefully consider interactions among various sex steroids. Our findings demonstrate that the strongest associations were between changes in MSNA and changes in the $E_2/P$ ratio. However, even the $E_2/P$ ratio explained only $\approx 27\%$ of the variance in $\Delta$MSNA. It remains plausible that

### Table. Neural and Hemodynamic Control at Rest in Eumenorrheic Women ($n=30$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Follicular</th>
<th>Mid Luteal</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol, pg/mL</td>
<td>37±2</td>
<td>117±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progesterone, ng/mL</td>
<td>$1.0±0.1$</td>
<td>$10.6±0.9$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>64±1</td>
<td>65±1</td>
<td>0.504</td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>112±2</td>
<td>112±2</td>
<td>0.854</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>67±1</td>
<td>67±1</td>
<td>0.550</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>83±2</td>
<td>83±2</td>
<td>0.913</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>12±1</td>
<td>15±1</td>
<td>0.017</td>
</tr>
<tr>
<td>MSNA, bursts/100 heartbeat</td>
<td>18±2</td>
<td>23±2</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Values are mean±SE. HR indicates heart rate; SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure; MAP, mean arterial blood pressure; MSNA, muscle sympathetic nerve activity.
other sex steroids may help explain additional variance. For example, Sverrisdottir et al\textsuperscript{17} reported that polycystic ovary syndrome was associated with elevated resting MSNA, and that the extent of sympathoexcitation was significantly related to testosterone. More recently, Carter et al\textsuperscript{18} suggested that relations between MSNA and testosterone may also exist in men. Although the cyclical fluctuations of estradiol and progesterone during the ovarian cycle are well recognized and studied, we need to acknowledge that testosterone (1) is produced in women and (2) fluctuates throughout the ovarian cycle. Much like progesterone, testosterone tends to be highest during the ML phase of the ovarian cycle, yet the relations between changes in testosterone and MSNA during the ovarian cycle have not been investigated. Moreover, the effects of other sex steroids (ie, follicle stimulating hormone, luteinizing hormone, etc) on MSNA also remain unclear. Given the dynamic interactions among estradiol, progesterone, and MSNA in the present study, it seems prudent to consider the potential action of other sex steroids that fluctuate throughout the ovarian cycle.

Recent evidence suggests that the complex relations among MSNA, vascular tone, and β-adrenergic sensitivity change with age. Specifically, in contrast to young women, postmenopausal women demonstrate a positive relationship between MSNA and total peripheral resistance in the absence of β-adrenergic blockade.\textsuperscript{19} These findings suggest that the ability to offset MSNA-mediated vasoconstriction with β-adrenergic vasodilation may be attenuated in older women. It remains unclear whether these altered neurovascular responses in postmenopausal women are related to the sudden drop in endogenous sex hormones or simply the aging process. And although it remains controversial, what is the role of estrogen replacement therapy? Weitz et al\textsuperscript{20} and Vongpatanasin et al\textsuperscript{14} have reported that transdermal estrogen replacement therapy decreases MSNA at rest in postmenopausal women, but neural–vascular interactions were not adequately examined. Thus, we maintain it is important to understand neural-vascular interactions across the entire female lifespan. The present data advance this important field by clarifying that sex steroid fluctuations in premenopausal women indeed influence resting MSNA, but that the level of sex steroid surge is important. Previous discrepancies in the field were likely attributable to the variability in surges of estradiol, progesterone, and, perhaps, other sex steroids during the ML phase among premenopausal women. In recent years, interindividual variability of MSNA has received much attention,\textsuperscript{21} and we posit that interindividual variability in sex steroid surges may also be fundamentally important when considering autonomic control in women. Moreover, as noted earlier, the interaction among the various sex hormones may be important, and this has received little attention to date.

In addition to sex steroids, changing levels of renal-adrenal hormones may also explain additional variance. It has been
found that the fluctuations of estrogen and progesterone during the menstrual cycle affect the renin-angiotensin-aldosterone system (RAAS) in young women.\textsuperscript{22-27} Specifically, the RAAS is activated during the ML phase. Studies using oral estrogen and progesterone in postmenopausal women have demonstrated that both hormones can activate the RAAS.\textsuperscript{28,29} However, other data suggest that only progesterone activates the RAAS, whereas estrogen might inhibit the activation of this system.\textsuperscript{30,31} Szmulowicz et al\textsuperscript{12} reported that progesterone may directly contribute to increased luteal phase aldosterone production independent of the RAAS. A recent study showed that there was a significant positive relationship between the change in resting MSNA and the change in direct renin and aldosterone during early human pregnancy.\textsuperscript{10} Thus, sympathoexcitatory responses to the ML phase may be attributable to the activation of the RAAS.

Although \(\beta\)-adrenergic sensitivity and RAAS mechanisms may help to explain a lack of sympathetic vascular transduction in the present study (ie, increase of MSNA during ML phase without parallel increase in MAP), they may not be the only explanation. Estradiol is known to elicit endothelial vasodilation via a variety of mechanisms that include NO and prostaglandins or by directly altering membrane ionic permeability of the vascular smooth muscle.\textsuperscript{32} It is possible that the increase of resting MSNA and subsequent \(\alpha\)-adrenergic vasoconstriction during the ML phase is offset by endothelial and non-endothelial vasodilation, resulting in no change in MAP. Additionally, renal vasoconstriction has been reported during the luteal phase of the ovarian cycle in young women;\textsuperscript{22} thus it is possible that vasodilation of the renal vascular bed may also offset MSNA-mediated vasoconstriction during the ML phase of the ovarian cycle.

Finally, it is worth noting that epidemiological studies suggest that women taking oral contraceptives are at heightened risk for hypertension,\textsuperscript{33} yet mechanisms remain unclear. Although this study focused on defining resting MSNA during EF and ML phases in eumenorrheic women, 3 studies from independent laboratories have each confirmed that women taking oral contraceptives do not demonstrate altered resting MSNA during the low and high exogenous hormone phase.\textsuperscript{6,15,34} However, the type, dosage, and methods of administration differed across and within these studies,\textsuperscript{6,15,34} and to date there has been no systematic study examining the influence of oral contraceptives on sympathetic neural control in women. Our results demonstrate that the ML phase of the ovarian cycle is characterized by sympathoexcitation, but that the degree of sympathoexcitation seems to be partially dependent upon the degree of sex steroid surges. Increases in estradiol were significantly correlated with decreases in MSNA during the ML phase, and this relation persisted when changes in estradiol and progesterone were considered as a ratio (ie, E/P). Our findings suggest a dynamic interaction among E\textsubscript{2}, P, and MSNA and likely explain previously reported inconsistencies in the field regarding the influence of the ovarian cycle on resting MSNA. Future studies might carefully consider investigating sympathetic neural interactions in women as they relate to changes in testosterone, estradiol, progesterone, and other sex steroids; such interactions may be critical in understanding mechanisms underlying the sudden surge in cardiovascular risk after menopause.

**Perspectives**

This study integrated data across multiple laboratories to better understand the role of the ovarian cycle in MSNA control in women. Our results demonstrate that the ML phase of the ovarian cycle is characterized by sympathoexcitation, but that the degree of sympathoexcitation seems to be partially dependent upon the degree of sex steroid surges. Increases in estradiol were significantly correlated with decreases in MSNA during the ML phase, and this relation persisted when changes in estradiol and progesterone were considered as a ratio (ie, E/P). Our findings suggest a dynamic interaction among E\textsubscript{2}, P, and MSNA and likely explain previously reported inconsistencies in the field regarding the influence of the ovarian cycle on resting MSNA. Future studies might carefully consider investigating sympathetic neural interactions in women as they relate to changes in testosterone, estradiol, progesterone, and other sex steroids; such interactions may be critical in understanding mechanisms underlying the sudden surge in cardiovascular risk after menopause.

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**Disclosures**

None.

**References**


Novelty and Significance

What Is New?

- The mid luteal phase of the ovarian cycle is associated with heightened sympathetic neural outflow, and this sympathoexcitation seems to be dependent, in part, on surges in sex steroids.
- These findings likely explain previously reported inconsistencies within the field regarding sympathetic neural control in premenopausal women.

What Is Relevant?

- Sympathetic overactivity plays a critical role in the pathogenesis of cardiovascular disease in both men and women.
- Defining sympathetic neural control throughout the female lifespan (ie, pre- and postmenopause) is critical to the development of preventative and therapeutic strategies aimed at reducing cardiovascular risk in women.

Summary

Sympathoexcitation during the mid luteal phase of the ovarian cycle seems to be dependent, in part, upon surges in estradiol and progesterone. It remains possible that other sex steroids, such as testosterone, might explain further variance.