Effect of sex and ovarian hormones on carotid baroreflex resetting and function during dynamic exercise in humans

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1Department of Medical Pharmacology and Physiology, 2Dalton Cardiovascular Research Center, University of Missouri, Columbia, Missouri; and 3School of Sport and Exercise Sciences, University of Birmingham, Edgbaston, Birmingham, United Kingdom

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Kim A, Deo SH, Fisher JP, Fadel PJ. Effect of sex and ovarian hormones on carotid baroreflex resetting and function during dynamic exercise in humans. J Appl Physiol 112: 1361–1371, 2012. First published January 19, 2012; doi:10.1152/japplphysiol.01308.2011.—To date, no studies have examined whether there are either sex- or ovarian hormone-related alterations in arterial baroreflex resetting and function during dynamic exercise. Thus, we studied 16 young men and 18 young women at rest and during leg cycling at 50% heart rate (HR) reserve. In addition, 10 women were studied at three different phases of the menstrual cycle: Five-second pulses of neck pressure (NP) and neck suction (NS) from +40 to −80 Torr were applied to determine full carotid baroreflex (CBR) stimulus response curves. An upward and rightward resetting of the CBR function curve was observed during exercise in all groups with a similar magnitude of CBR resetting for mean arterial pressure (MAP) and HR between sexes (P > 0.05) and at different phases of the menstrual cycle (P > 0.05). For CBR control of MAP, women exhibited augmented pressor responses to NP at rest and exercise during mid-luteal compared with early and late follicular phases. For CBR control of HR, there was a greater bradycardic response to NS in women across all menstrual cycle phases with the operating point (OP) located further away from centering point (CP) on the CBR-HR curve during rest (OP-CP; in mmHg: −13 ± 3 women vs. −3 ± 3 men; P < 0.05) and exercise (in mmHg: −31 ± 2 women vs. −15 ± 3 men; P < 0.05). Collectively, these findings suggest that sex and fluctuations in ovarian hormones do not influence exercise resetting of the baroreflex. However, women exhibited greater CBR control of HR during exercise, specifically against acute hypertension, an effect that was present throughout the menstrual cycle.

arterial baroreceptors; blood pressure; gender; estradiol; progesterone; menstrual cycle

The arterial baroreflex (ABR) plays an important role in beat-to-beat control of blood pressure (BP) via modulating autonomic neural activity to the heart and vasculature (46, 47). The ABR is reset during dynamic exercise partly due to the actions and interactions of two neural mechanisms, namely central command (feedback signals from higher brain centers) and the exercise pressor reflex (feedback signals from contracting skeletal muscles) (14, 19, 20, 32, 46, 47). Moreover, the ABR, together with central command and the exercise pressor reflex play an essential role in evoking appropriate neural cardiovascular responses to exercise. Indeed, sinoaortic denervation and reductions in ABR control have been shown to lead to exaggerated elevations in BP upon exercise (6, 56, 57). Thus appropriate ABR resetting and function are requisite for normal BP responses to dynamic exercise (14, 26, 46, 47).

Young men tend to exhibit greater pressor responses to exercise compared with age-matched women (7, 12, 29, 38); however, the reason for these differences remains unclear. Interestingly, studies have shown that the ovarian hormone estrogen appears to have a suppressive effect on exercise-induced elevations in BP both in animals and humans (10, 29, 42). Furthermore, estrogen may augment resting ABR sensitivity (11, 35, 40). More importantly, there is evidence indicating that estrogen attenuates both central command and exercise pressor reflex mechanisms, key contributors to ABR resetting with exercise (12, 13, 23, 49–51). However, to date, no studies have investigated whether sex and/or fluctuations in endogenous ovarian hormones during the menstrual cycle in young women have potential modulatory effects on ABR function and resetting during dynamic exercise in humans.

The potential for sex and hormonal differences in ABR function has been recently receiving attention under resting conditions; however, equivocal findings have been reported (1, 3, 5, 21, 22, 34). A potential reason for the inconsistent reports concerning sex differences in resting ABR control may be due to lack of control for alterations in ovarian hormones (i.e., estrogen and progesterone). In this regard, administration of exogenous estrogen enhances ABR control of heart rate (HR) in both female and male rats (11, 24, 35, 40, 48), whereas progesterone attenuates ABR control of sympathetic nerve activity in rats and enhances it in humans (25, 34). However, whether ABR control of BP is influenced by fluctuations in ovarian hormones in young women remains unclear. Recently, our laboratory has shown that during the early follicular phase of the menstrual cycle (low estrogen and progesterone), young women exhibit enhanced ABR control of BP to hypertensive stimuli at rest compared with men (28). Whether changes in endogenous ovarian hormone concentrations would affect these results is unknown. In addition, to our knowledge, no studies have investigated whether there are sex- and/or ovarian hormone-related alterations in ABR resetting and function during exercise.

In light of this background, the present study had two major objectives. First, to determine whether sex differences exist in ABR resetting and function during dynamic exercise, young women and men were studied at rest and during exercise. Second, to determine whether endogenous fluctuations in ovarian hormone concentrations modulate exercise ABR resetting and function, young women were studied at three different phases of the menstrual cycle. We hypothesized that ABR exercise resetting would be attenuated in women compared with men and that a reduced ABR resetting during dynamic exercise would coincide with elevations in endogenous estrogen.
METHODS

Subjects

For experimental protocol 1 (Sex and carotid baroreflex resetting and function during exercise), 18 young women (21 ± 0.4 yr) and 16 men (21 ± 0.4 yr) were recruited from the University of Missouri-Columbia. All subjects were healthy and recreationally active, engaging in low to moderate (e.g., running and cycling) intensity activities (2–3 days/wk). All experimental procedures and protocols conformed to the Declaration of Helsinki and were approved by the University of Missouri-Columbia Health Sciences Institutional Review Board. Each subject provided written informed consent and completed a medical health history. No subject had a history or symptoms of cardiovascular, neurologic, renal, hepatic, or respiratory diseases. All young women were studied during the early follicular (EF, days 1–5) phase of the menstrual cycle for protocol 1 where day 0 is the start of menstruation. Young women subjects, who had irregular menstrual cycles or were taking birth control medication, were excluded from the study. Women had a mean menstrual cycle length of 29 ± 2 days, which was identified prior to studies. For experimental protocol 2 (Menstrual cycle and CBR resetting and function during exercise), 10 of the women who participated in protocol 1 were also studied during two additional phases of their menstrual cycle, late follicular (LF, days 10–12) and midluteal (ML, days 22–26). These participants were asked to use a ClearBlueR Easy ovulation self test kit between days 9 and 15 of the menstrual cycle to detect the surge of luteinizing hormone in urine and more accurately identify the LF phase.

All subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for at least a day prior to any experimental sessions. On experimental days, the subjects arrived at the laboratory a minimum of 2 h following a light meal. For protocol 2, women were studied at the same time of the day for each of their three visits to the laboratory.

Familiarization Session

All subjects were familiarized with the equipment set-up and procedures prior to any experimental visits. During familiarization sessions subjects were screened to identify the location of the carotid sinus bifurcation using Doppler ultrasound to ensure that the neck collar fully enclosed the carotid sinuses. Indeed, although transmission to the carotid sinus has been shown to be near complete, there is variability in the location of the carotid sinuses that requires consideration (15, 45). Appropriate neck chamber placement was made by fitting the subjects based on location of the carotid sinus and neck size and then performing resting trials of neck pressure (NP) and neck suction (NS) to determine directionally appropriate and consistent cardiovascular responses. Two sessions were typically performed to assure subject familiarity and consistent responses to NP and NS.

Experimental Measurements

HR was continuously monitored using a standard lead II surface electrocardiogram (ECG, Quinton Q710 Foremost Equipment, Rochester, NY). A strain-gauge pneumobelt placed around the abdomen (Medical Instruments Raleigh, NC). Throughout the study, prior to obtaining Finometer recordings, the diastolic BP of the Finometer was matched with diastolic BP measurements obtained from the brachial artery of the right arm using the automated sphygmomonometer. The BP waveform and ECG signal were sampled at 1,000 Hz and beat-to-beat values of BP and HR were stored for offline analysis (Chart v5.2, Powerlab, AD Instruments, Bella Vista, NSW, Australia).

Carotid Baroreflex Function

Using the variable pressure neck chamber technique, 5-s pulses of NP at +40 and +20 Torr and NS at −20, −40, −60, and −80 Torr, were applied to selectively unload (simulated carotid hypotenension) and load (simulated carotid hypertension) the carotid baroreceptors, respectively. The application of NP and NS was performed using a malleable lead neck collar fitted around the anterior two-thirds of the neck. Each NP and NS stimulus was delivered 50 ms after the stimulus onset offset interval, which was identified prior to studies. No subject had a history or symptoms of cardiovascular, neurologic, renal, hepatic, or respiratory diseases. All young women were studied during the early follicular (EF, days 1–5) phase of the menstrual cycle for protocol 1 where day 0 is the start of menstruation. Young women subjects, who had irregular menstrual cycles or were taking birth control medication, were excluded from the study. Women had a mean menstrual cycle length of 29 ± 2 days, which was identified prior to studies. For experimental protocol 2 (Menstrual cycle and CBR resetting and function during exercise), 10 of the women who participated in protocol 1 were also studied during two additional phases of their menstrual cycle, late follicular (LF, days 10–12) and midluteal (ML, days 22–26). These participants were asked to use a ClearBlueR Easy ovulation self test kit between days 9 and 15 of the menstrual cycle to detect the surge of luteinizing hormone in urine and more accurately identify the LF phase.

All subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for at least a day prior to any experimental sessions. On experimental days, the subjects arrived at the laboratory a minimum of 2 h following a light meal. For protocol 2, women were studied at the same time of the day for each of their three visits to the laboratory.

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All subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for at least a day prior to any experimental sessions. On experimental days, the subjects arrived at the laboratory a minimum of 2 h following a light meal. For protocol 2, women were studied at the same time of the day for each of their three visits to the laboratory.

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rates the following equation:

\[ \text{logistic model described by Kent et al. (27).} \]

This function incorporates estimates of ECSP. The CBR stimulus-response data were fitted to the recorded via automated sphygmomanometry to provide accurate estimates. Beat-to-beat changes in MAP measured by photo-sinus pressure (ECSP), which was calculated as MAP minus neck HR evoked by NP and NS, respectively, against the estimated carotid chamber pressure. The CBR-mean arterial pressure (MAP) and cardiac (HR) responses were evaluated by plotting the peak and nadir changes in MAP and THR, point where no further increase in MAP (or HR) occurred at the operating point of the CBR function curve. The threshold (THR), point where no further decrease in ECSP, and the saturation (SAT), point where no further decrease in MAP (or HR) occurred despite increases in ECSP, were calculated by applying the following equations (31): \( \text{THR} = -2.944/A_2 + A_3 \) and \( \text{SAT} = 2.944/A_2 + A_3 \). These calculations of THR and SAT are the carotid sinus pressure at which MAP (or HR) is within 5% of the upper or lower plateau of the sigmoid function (31). Also, to compare the magnitude of exercise-induced baroreflex resetting in the young men and women we calculated the sum of the changes in \( A_3, A_4, \text{THR}, \) and SAT from rest to exercise for each subject as an estimate of the upward and rightward movement of the carotid-MAP and HR curve that occurs with exercise, as previously reported (17).

### Menstrual cycle and CBR resetting and function during exercise (protocol 2)

To determine whether fluctuations in ovarian hormones (i.e., estrogen and progesterone) influence CBR resetting and function, 10 young women who completed protocol 1 revisited the laboratory during two additional phases of their menstrual cycle (LF and ML). The menstrual cycle phase order in which these women visited the laboratory was randomly assigned. Blood samples for estrogen and progesterone concentrations were obtained before instrumentation, and the same experimental procedures described above in protocol 1 were performed.

### Data Analyses

**Derivation of CBR function curves.** Both at rest and during exercise, CBR-mean arterial pressure (MAP) and cardiac (HR) responses were evaluated by plotting the peak and nadir changes in MAP and HR evoked by NP and NS, respectively, against the estimated carotid sinus pressure (ECSP), which was calculated as MAP minus neck chamber pressure. Beat-to-beat changes in MAP measured by photoplethysmography were uniformly corrected to the absolute MAP recorded via automated sphygmomanometry to provide accurate estimates of ECSP. The CBR stimulus-response data were fitted to the logistic model described by Kent et al. (27). This function incorporates the following equation:

\[ \text{MAP (or HR)} = A_1 \times \left\{ 1 + \exp\left[ A_2 \times (ECSP - A_3) \right] \right\}^{-1} + A_4 \]

where MAP (or HR) is the dependent variable, \( A_1 \) is the range of response (maximum-minimum), \( A_2 \) is the gain coefficient, \( A_3 \) is the carotid sinus pressure required to elicit an equal pressor and depressor response (centering point), and \( A_4 \) is the minimum response. The data were fit to this model by nonlinear least-squares regression (using a Marquardt-Levenberg algorithm), which minimized the sum of squares error term to predict a curve of best fit for each set of raw data. The overall fit of the curves was similar between sexes with \( r^2 \) values of 0.984 ± 0.002 women vs. 0.987 ± 0.003 men for MAP and 0.989 ± 0.004 women vs. 0.986 ± 0.004 men for HR at rest and 0.983 ± 0.003 women vs. 0.988 ± 0.003 men for MAP and 0.985 ± 0.006 women vs. 0.979 ± 0.007 men for HR during exercise. The CBR-MAP and CBR-HR maximal gain and operating point gain were calculated using the following equations:

\[ G_{\text{MAX}} = -A_1A_2/4 \]

where \( G_{\text{MAX}} \) is the maximal gain of CBR function curve, \( G_{\text{OP}} \) is the gain of CBR function curve at the operating point, and \( A_1A_2 \) is the ECSP at the operating point (i.e., prestimulus MAP). The \( G_{\text{MAX}} \) was calculated as the gain at the centering point and used as an index of overall CBR function, whereas the \( G_{\text{OP}} \) was calculated as the gain at the operating point and used to provide a measure of responsiveness at the operating point of the CBR function curve. The threshold (THR), point where no further increase in MAP (or HR) occurred despite reductions in ECSP, and the saturation (SAT), point where no further decrease in MAP (or HR) occurred despite increases in ECSP, were calculated by applying the following equations (31): \( \text{THR} = -2.944/A_2 + A_3 \) and \( \text{SAT} = 2.944/A_2 + A_3 \). These calculations ofTHR and SAT are the carotid sinus pressure at which MAP (or HR) is within 5% of the upper or lower plateau of the sigmoid function (31). Also, to compare the magnitude of exercise-induced baroreflex resetting in the young men and women we calculated the sum of the changes in \( A_3, A_4, \text{THR}, \) and SAT from rest to exercise for each subject as an estimate of the upward and rightward movement of the carotid-MAP and HR curve that occurs with exercise, as previously reported (17).

### Statistical Analysis

Statistical analyses were conducted using SigmaStat (Jandel Scientific Software, SOSS, Chicago, IL). Group comparisons of cardiovascular and CBR variables were made using 2 × 2 (sex × condition; rest and exercise,) and 3 × 2 (menstrual phase × condition; rest and exercise) repeated-measures ANOVA tests. A Student-Newman-Keul’s test was employed post hoc to investigate significant main effects and interactions. When appropriate, an unpaired t-test was used to compare men and women, and one-way ANOVA was used to compare different phases of the menstrual cycle within young women. Statistical significance was set at \( P < 0.05 \). All data are presented as means ± SE.

### RESULTS

**Protocol 1: Sex and CBR Resetting and Function During Exercise**

**Subject characteristics.** Young women and men had a similar body mass index; however, young women had a lower body weight and body surface area (Table 1). Peak HR was similar between sexes, whereas peak oxygen uptake (V̇O₂peak) was significantly lower in young women (\( P < 0.05 \) vs. young men). However, according to ACSM reference values for age and sex, both men and women were in the same percentile for V̇O₂peak. Resting HR and diastolic BP were similar between young men (\( P < 0.05 \), Table 2). HR, MAP, systolic BP, and pulse pressure (PP) were significantly lower in young women compared with young men (\( P < 0.05 \), Table 2).

### Cardiovascular variables at rest and during steady-state exercise in young women and men

#### Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>65 ± 1</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>80 ± 2</td>
<td>85 ± 1*</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>108 ± 2</td>
<td>120 ± 2*</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>66 ± 2</td>
<td>68 ± 2</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>43 ± 2</td>
<td>51 ± 3*</td>
</tr>
</tbody>
</table>

Values are means ± SE. MAP, mean arterial pressure; BP, blood pressure; PP, pulse pressure. * \( P < 0.05 \) vs. women; † \( P < 0.05 \) vs. rest.
Fig. 1. Summary data showing the upward and rightward resetting of the modeled carotid baroreflex-MAP stimulus response curve from rest to moderate intensity cycling in young women and men. Lines and symbols denote actual group data for all subjects. Black symbols, young women; white symbols, young men. Squares indicate the centering points, triangles indicate the operating points, circles indicate the carotid sinus pressure thresholds, and inverted triangles represent the carotid sinus pressure saturations. Maximal gain (G_MAX; A), operating point gain (G_OP; B), and the difference between the operating point and centering point (OP-CP; C) in young men and women are also presented at rest and during exercise. Values are means ± SE.

Table 3. Logistic model parameters and derived variables describing carotid baroreflex control of mean arterial pressure in young women and men

<table>
<thead>
<tr>
<th></th>
<th>A1, mmHg</th>
<th>A2, au</th>
<th>A3, mmHg</th>
<th>A4, mmHg</th>
<th>Threshold, mmHg</th>
<th>Saturation, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Women</td>
<td>29 ± 2</td>
<td>0.08 ± 0.01</td>
<td>83 ± 3</td>
<td>65 ± 2</td>
<td>54 ± 4</td>
<td>112 ± 4</td>
</tr>
<tr>
<td>Men</td>
<td>20 ± 2</td>
<td>0.09 ± 0.01</td>
<td>87 ± 3</td>
<td>75 ± 1</td>
<td>61 ± 3</td>
<td>112 ± 4</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>24 ± 1</td>
<td>0.09 ± 0.01</td>
<td>99 ± 3</td>
<td>83 ± 2</td>
<td>73 ± 4</td>
<td>125 ± 4</td>
</tr>
<tr>
<td>Men</td>
<td>19 ± 1</td>
<td>0.09 ± 0.01</td>
<td>108 ± 3</td>
<td>91 ± 2</td>
<td>83 ± 4</td>
<td>134 ± 4</td>
</tr>
<tr>
<td>ANOVA</td>
<td></td>
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<td></td>
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<tr>
<td>Sex</td>
<td>0.002</td>
<td>0.310</td>
<td>0.059</td>
<td>0.002</td>
<td>0.041</td>
<td>0.324</td>
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<tr>
<td>Condition</td>
<td>0.029</td>
<td>0.534</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.158</td>
<td>0.461</td>
<td>0.335</td>
<td>0.570</td>
<td>0.788</td>
<td>0.211</td>
</tr>
</tbody>
</table>

Values are means ± SE. A1, response range; A2, gain coefficient; A3, centering point; A4, minimum response.
during exercise, whereas the minimum response ($A_2$) was significantly lower in young women ($P < 0.05$, Table 4). The maximal gain for the CBR-HR curve was different between young women and men (Fig. 2A), an effect that appeared to be driven by a reduction in $G_{\text{MAX}}$ from rest to exercise in men. The OP-CP increased from rest to exercise in both groups but remained greater in young women (Fig. 2C). Commensurate with the exercise-induced increase in OP-CP, $G_{\text{OP}}$ was significantly reduced from rest to exercise, although no differences were observed in $G_{\text{OP}}$ between groups (Fig. 2B). However, young women exhibited significantly greater reductions in HR with NS at rest (e.g., $-90$ beats/min) and during exercise (in beats/min: $-25.5 \pm 2.8$ women vs. $-12.3 \pm 2.2$ men; ANOVA, sex $P < 0.001$, condition $P = 0.223$, interaction $P = 0.079$). In contrast, increases in HR with NP were similar in young women and men at rest (e.g., $+40$ beats/min) and during exercise (in beats/min: $+3.1 \pm 0.4$ women vs. $+2.9 \pm 0.4$ men) with the magnitude of the change being reduced from rest to exercise in both groups (ANOVA, sex $P = 0.494$, condition $P < 0.001$, interaction $P = 0.656$).

### Protocol 2: Menstrual Cycle and CBR Resetting and Function During Exercise

#### Subject characteristics. Table 5 presents resting ovarian hormone concentrations across the menstrual cycle for the young women who participated in protocol 2. Plasma estradiol concentrations were significantly higher during LF and ML phases compared with EF phase ($P < 0.05$), whereas plasma progesterone level during ML phase was significantly higher than EF and LF phases ($P < 0.05$). In addition, the progesterone:estradiol ratio was significantly lower during LF phase compared with EF as well as ML phase where the ratio is the highest. HR, MAP, systolic BP, diastolic BP, and PP were similar both at rest and during exercise in all three menstrual cycle phases (EF, LF vs. ML phases; $P > 0.05$, Table 6). The increase in HR, MAP, systolic BP, and PP from rest to exercise was also similar in all three phases of the menstrual cycle ($P > 0.05$).

#### Menstrual cycle and CBR control of MAP at rest and during exercise. The CBR-MAP stimulus response curves and selected CBR parameters at rest and during dynamic exercise in three different phases of the menstrual cycle are shown in Fig. 2. Summary data showing the upward and rightward resetting of the modeled carotid-cardiac baroreflex stimulus response curve from rest to moderate intensity cycling in young women and men. Lines and symbols denote actual group data for all subjects. Black symbols, young women; white symbols, young men. Squares indicate the centering points, triangles indicate the operating points, circles indicate the carotid sinus pressure thresholds, and inverted triangles represent the carotid sinus pressure saturations. $G_{\text{MAX}}$ (A), $G_{\text{OP}}$ (B), and OP-CP (C) in young men and women are also presented at rest and during exercise. Values are means ± SE.

### Table 4. Logistic model parameters and derived variables describing carotid baroreflex control of heart rate in young women and men

<table>
<thead>
<tr>
<th>Subject</th>
<th>$A_1$, beats/min</th>
<th>$A_2$, au</th>
<th>$A_3$, mmHg</th>
<th>$A_4$, beats/min</th>
<th>Threshold, mmHg</th>
<th>Saturation, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>34 ± 3</td>
<td>0.06 ± 0.00</td>
<td>93 ± 3</td>
<td>44 ± 3</td>
<td>57 ± 2</td>
<td>129 ± 5</td>
</tr>
<tr>
<td>Men</td>
<td>26 ± 3*</td>
<td>0.08 ± 0.01</td>
<td>89 ± 3</td>
<td>48 ± 2*</td>
<td>56 ± 6</td>
<td>121 ± 6</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>32 ± 3</td>
<td>0.07 ± 0.01</td>
<td>127 ± 4</td>
<td>101 ± 3†</td>
<td>93 ± 4</td>
<td>161 ± 5</td>
</tr>
<tr>
<td>Men</td>
<td>14 ± 2*†</td>
<td>0.11 ± 0.01</td>
<td>118 ± 4</td>
<td>116 ± 2*†</td>
<td>95 ± 4</td>
<td>140 ± 6</td>
</tr>
</tbody>
</table>

ANOVA

| Sex     | 0.002 | 0.019 | 0.085 | 0.011 | 0.998 | 0.022 |
| Condition | <0.001 | 0.058 | <0.001 | <0.001 | <0.001 | <0.001 |
| Interaction | 0.006 | 0.438 | 0.409 | 0.017 | 0.703 | 0.187 |

Values are means ± SE. *$P < 0.05$ vs. women. †$P < 0.05$ vs. rest.

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3. Table 7 presents the logistic model parameters and derived variables describing CBR control of MAP at rest and during exercise across the three phases of the menstrual cycle. An upward and rightward resetting of the CBR-MAP stimulus response curve was observed in all phases as demonstrated by the significant increase in A3, A4, THR, and SAT from rest to exercise (Table 7). The magnitude of CBR resetting was not different across the phases (in a.u.: +74 ± 16 EF, +85 ± 15 LF vs. +84 ± 7 ML; P > 0.05). In addition, the response range (A1), GMAX, and GCP were similar among all phases of the menstrual cycle both at rest and during exercise. The OP-CP was slightly but significantly elevated in the young women during ML phase at rest but not during exercise (Fig. 3C). The increase in MAP with NP at rest (e.g., +40 Torr; in mmHg: +11.5 ± 1.3 EF, +12.4 ± 0.8 LF vs. +15.4 ± 1.3 ML) and during exercise (in mmHg: +10.2 ± 1.1 EF, +10.7 ± 1.1 LF vs. +12.7 ± 1.1 ML; ANOVA, phase P = 0.031, condition P = 0.097, interaction P = 0.681) was greater during the ML phase. In contrast, MAP responses to NS were similar between phases (ANOVA, phase P = 0.002, interaction P = 0.205). The HR responses to NS were similar at rest (e.g., −80 Torr; in beats/min: −17.5 ± 2.0 EF, −18.2 ± 1.2 LF vs. −19.7 ± 2.0 ML) and during exercise (in beats/min: −22.0 ± 3.6 EF, −25.5 ± 2.7 LF vs. −19.0 ± 2.3 ML) and between phases (ANOVA, phase P = 0.338, condition P = 0.085, interaction P = 0.143).

### DISCUSSION

The present study is the first to examine whether sex and/or fluctuations in endogenous ovarian hormones during the menstrual cycle in young women modulate CBR function and resetting during dynamic exercise. Contrary to our hypothesis, neither sex nor menstrual cycle phase were found to affect the magnitude of CBR resetting for both MAP and HR. However, for CBR control of MAP, women exhibited augmented pressor responses to NP at rest and exercise during the ML compared with EF and LF phases. Furthermore, there was a greater bradycardic response to carotid hypertension in young women at rest and during exercise that was present across all phases of the menstrual cycle. This was consistent with the operating point of the CBR-HR curve being located farther away from the centering point and closer to the threshold in women compared with men. Collectively, these findings suggest that sex and fluctuations in ovarian hormones do not influence exercise resetting of the baroreflex. However, augmented CBR-MAP responses to acute hypertension were observed in young women when progesterone and estrogen concentrations were both elevated. Furthermore, compared with men, women exhibited greater CBR control of HR at rest and during exercise, specifically against acute hypertension, an effect that was present throughout the menstrual cycle. Overall, these findings provide novel insight into understanding influences of sex and ovarian hormones on CBR control during exercise.

### CBR Resetting During Exercise

In the past decade, Raven and colleagues (19, 20, 36, 39, 44, 46, 47) have extensively investigated CBR function and its resetting during dynamic exercise in men. It is now well established that both CBR-MAP and CBR-HR function curves are reset to functionally operate at the prevailing BP elicited by exercise (41, 44, 47). However, there have been no reports regarding whether sex differences and/or ovarian hormones influence CBR resetting. The actions and interactions of central...
command and the exercise pressor reflex (i.e., mechano- and metabo-reflexes) have been shown to make an important contribution to the magnitude of CBR resetting during exercise (19, 20, 32, 46). Importantly, several studies have highlighted that sex and estrogen can modify both central command and the exercise pressor reflex (12, 13, 23, 49 –51). Furthermore, animal studies have shown that estrogen reduces the BP response to exercise by attenuating both central command and the exercise pressor reflex (23, 49 –51). In general agreement, young women exhibit attenuated muscle metaboreflex activation compared with men (12). Given these previously reported sex and ovarian hormone effects, we hypothesized that baroreflex resetting would be attenuated in women compared with men during dynamic exercise and that a reduced baroreflex resetting would coincide with the phases of the menstrual cycle associated with elevated endogenous estrogen. However, we found that the magnitude of the exercise-induced resetting of the CBR stimulus-response curve was not different between young women and men, nor was the CBR exercise resetting influenced by menstrual cycle phase in young women.

Our findings suggest that differences in endogenous ovarian hormone concentrations, both between sexes and in young women across the menstrual cycle, are of an insufficient magnitude to modulate CBR resetting during exercise. It is tempting to speculate that the similar CBR resetting during dynamic exercise in young women and men and in young

Table 7. Logistic model parameters and derived variables describing carotid baroreflex control of mean arterial pressure in three different phases of the menstrual cycle in young women

<table>
<thead>
<tr>
<th>Phase</th>
<th>A1, mmHg</th>
<th>A2, au</th>
<th>A3, mmHg</th>
<th>A4, mmHg</th>
<th>Threshold, mmHg</th>
<th>Saturation, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>31 ± 2</td>
<td>0.06 ± 0.01</td>
<td>81 ± 4</td>
<td>62 ± 2</td>
<td>45 ± 3</td>
<td>117 ± 6</td>
</tr>
<tr>
<td>LF</td>
<td>28 ± 1</td>
<td>0.07 ± 0.01</td>
<td>75 ± 2</td>
<td>66 ± 3</td>
<td>47 ± 2</td>
<td>103 ± 3</td>
</tr>
<tr>
<td>ML</td>
<td>32 ± 2</td>
<td>0.08 ± 0.01</td>
<td>72 ± 2</td>
<td>65 ± 2</td>
<td>43 ± 4</td>
<td>101 ± 5</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>23 ± 2</td>
<td>0.09 ± 0.01</td>
<td>96 ± 4</td>
<td>80 ± 2</td>
<td>75 ± 4</td>
<td>124 ± 6</td>
</tr>
<tr>
<td>LF</td>
<td>24 ± 2</td>
<td>0.09 ± 0.01</td>
<td>98 ± 5</td>
<td>82 ± 2</td>
<td>71 ± 4</td>
<td>126 ± 7</td>
</tr>
<tr>
<td>ML</td>
<td>23 ± 2</td>
<td>0.10 ± 0.01</td>
<td>94 ± 2</td>
<td>83 ± 2</td>
<td>72 ± 2</td>
<td>116 ± 4</td>
</tr>
<tr>
<td>ANOVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase</td>
<td>0.671</td>
<td>0.226</td>
<td>0.129</td>
<td>0.148</td>
<td>0.824</td>
<td>0.105</td>
</tr>
<tr>
<td>Condition</td>
<td>0.003</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.236</td>
<td>0.656</td>
<td>0.547</td>
<td>0.378</td>
<td>0.526</td>
<td>0.198</td>
</tr>
</tbody>
</table>

Values are means ± SE.
women across the menstrual cycle indicates that central command and the exercise pressor reflex effects on CBR are minimally influenced by either sex or ovarian hormones. However, on the basis of the present findings it would be imprudent to make statements regarding the direct influence of ovarian hormones on central command and the exercise pressor reflex in humans, as the present study was not specifically designed for such investigation and further studies are required. A important caveat in the animal studies demonstrating an influence of estrogen on BP responses as well as on central command and the exercise pressor reflex is that estrogen is directly infused into the central nervous system and/or a sustained administration of estrogen was used after ovariec-
omy (49 –51). Importantly, these procedures do not account for the normal fluctuation in ovarian hormones that occur in young women and may explain the lack of a difference in CBR exercise resetting across the menstrual cycle. In this regard, sustained hormone replacement therapy such as that used in postmeno-
pausal women may lead to an alternative outcome. Nevertheless, we show for the first time that in young women normal physiological fluctuations in ovarian hormones across the menstrual cycle do not influence CBR resetting with exercise.

**CBR Control of BP**

Our laboratory recently reported that compared with men, young women exhibit enhanced CBR control of BP to hypertensive stimuli at rest when studied during the EF phase of the menstrual cycle. Women have higher parasympathetic activity and lower sympathetic activity at rest, which would be expected to increase BP during stress (52) and lower BP during exercise (53) compared with men (54). Moreover, we recently demonstrated that compared with men, young women exhibit enhanced CBR control of BP to hypertensive stimuli at rest when studied during the EF phase of the menstrual cycle. The enhanced CBR control during the EF phase of the menstrual cycle is correlated with enhanced parasympathetic activity and decreased sympathetic activity at rest (53). Thus, the present study further extends our previous findings by demonstrating enhanced CBR control of BP to moderate intensity exercise during the EF phase of the menstrual cycle in young women. The present findings are consistent with a previous study demonstrating enhanced CBR control of BP to moderate intensity exercise during the EF phase of the menstrual cycle in young women (55).

**Table 8.** Logistic model parameters and derived variables describing carotid baroreflex control of heart rate in young women during different phases of the menstrual cycle

<table>
<thead>
<tr>
<th>Phase</th>
<th>A1, beats/min</th>
<th>A2, au</th>
<th>A3, mmHg</th>
<th>A4, beats/min</th>
<th>Threshold, mmHg</th>
<th>Saturation, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>EF</td>
<td>31 ± 2</td>
<td>0.07 ± 0.01</td>
<td>90 ± 5</td>
<td>43 ± 3</td>
<td>57 ± 2</td>
</tr>
<tr>
<td></td>
<td>LF</td>
<td>31 ± 2</td>
<td>0.06 ± 0.01</td>
<td>89 ± 4</td>
<td>44 ± 3</td>
<td>52 ± 3</td>
</tr>
<tr>
<td></td>
<td>ML</td>
<td>35 ± 3</td>
<td>0.05 ± 0.01</td>
<td>89 ± 4</td>
<td>44 ± 2</td>
<td>49 ± 3</td>
</tr>
<tr>
<td>Exercise</td>
<td>EF</td>
<td>30 ± 3</td>
<td>0.07 ± 0.01</td>
<td>125 ± 3§</td>
<td>101 ± 4</td>
<td>92 ± 4</td>
</tr>
<tr>
<td></td>
<td>LF</td>
<td>31 ± 3</td>
<td>0.07 ± 0.01</td>
<td>124 ± 4§</td>
<td>101 ± 4</td>
<td>91 ± 4</td>
</tr>
<tr>
<td></td>
<td>ML</td>
<td>28 ± 3</td>
<td>0.06 ± 0.01</td>
<td>110 ± 6++$</td>
<td>107 ± 2</td>
<td>75 ± 8</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Phase</td>
<td>0.839</td>
<td>0.509</td>
<td>0.105</td>
<td>0.085</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Condition</td>
<td>0.305</td>
<td>0.407</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Interaction</td>
<td>0.357</td>
<td>0.552</td>
<td>0.011</td>
<td>0.247</td>
<td>0.343</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. EF; †P < 0.05 vs. LF; §P < 0.05 vs. rest.
menstrual cycle (28). Such differences resulted from a differential balance in the relative contribution of the heart and peripheral vasculature to CBR control of BP in women and men with a greater contribution of cardiac output to BP changes in young women and greater contribution of peripheral vasculature in young men (28). In the present study, compared with men, young women also exhibited a significantly larger BP response to carotid hypertension at rest during the EF phase. Importantly, we now extend these findings to demonstrate that this greater CBR responsiveness to hypertension was unaffected by fluctuations in ovarian hormones. In addition, the modeling of full CBR stimulus-response curves in the present study revealed that the augmented depressor response to carotid hypertension in young women was not associated with an increase in maximal baroreflex gain (GMAX). However, the operating point gain (GOP) and response range (A1) was greater compared with men along with a lower minimum response (A0). Such observations may represent a beneficial protective mechanism in young women and indicate that women are well positioned to defend against increases in BP via the arterial baroreflex both at rest and during exercise. Interestingly, the CBR-MAP function curve in young women was located downward and leftward with respect to young men both at rest and during exercise. This appears to be due to a lower set point in both rest and exercise conditions; however, whether such sex differences result from differences in mechanical transduction, afferent signaling, central integration, autonomic efferent activity, or neural-vascular transduction remains unknown.

In general we observed minimal differences in CBR control of BP across the menstrual cycle in the young women. However, a significantly greater CBR-mediated pressor response to carotid hypotension at rest was observed during the ML phase when plasma progesterone concentrations were high compared with the EF and LF phases. Although a greater response to NP was also present during exercise in the ML phase, the magnitude of the difference compared with the EF and LF phases was minimized. These findings support the idea that progesterone may be a potent modulating factor for BP control via the baroreflex. In agreement, Minson et al. (34) demonstrated that during the ML phase young women showed greater baroreflex control of muscle sympathetic nerve activity compared with the EF phase. It is generally known that progesterone is not only an ovarian hormone but also an important endogenous neurosteroid produced from nerve cells that can regulate neuronal activities (33, 54, 58). Animal studies have shown that progesterone and its metabolites (e.g., pregnenolone, pregnenolone sulfate, allopregnenolone) modulate excitability of cells in the central nervous system that are involved in baroreflex control (30, 33). However, whether a central effect of progesterone underlies the CBR-MAP differences observed during the ML phase in young women in the present study is unclear.

CBR Control of HR

In a recent study we identified greater CBR-mediated bradycardic responses to hypertensive stimuli in young women at rest during the EF phase compared with men (28). The current findings are in agreement and extend these observations to include the LF and ML phases of the menstrual cycle. In addition, we now demonstrate that the response range (A1) of the modeled CBR-HR stimulus-response curve in young women is greater than in men at rest and during exercise. Notably, during exercise the response range was reduced in young men, in line with previous studies employing a similar intensity of dynamic exercise (39). However, to our surprise, the response range was well maintained in young women during dynamic exercise. The reason for this sex difference is unclear, but may be attributable to a greater vagal reactivity in young women compared with men. Animal studies have shown that female rats exhibit more marked parasympathetic control of HR by virtue of a greater acetylcholine release in response to vagal nerve stimulation and that this causes a greater reduction in HR (8). This may help explain the ability of young women to have such marked CBR-mediated reductions in HR at rest and during exercise.

The most striking difference in young women compared with men is that the operating point of the CBR-HR curve was located farther away from the centering point toward the threshold at rest and during exercise. This places the women in a more optimal position on the CBR-HR curve to defend against hypertensive stimuli. Interestingly, the movement of the operating point toward the threshold of the CBR-HR function curve during exercise was more marked in women compared with men (Fig. 2). Indeed, while the operating point moves away from the centering point to a locus of reduced responsiveness in men, as previous studies have shown (39, 44), this movement of the operating point with exercise was much greater in women with the exception of during the ML phase. Interestingly, the greater response range in women meant that the operating point appears to be functioning at a locus of similar gain in both sexes during exercise (i.e., GOP similar in women and men). In regards to maximal gain, no differences were observed at rest, whereas during exercise the men demonstrated a slight but significant reduction compared with women. This may be due to the higher absolute work load performed by the men. Overall, although matched for relative exercise intensity, consideration for the young men working at a greater absolute work load should be given when interpreting the results of the present study.

Perspective

A properly functioning ABR is required for the beat-to-beat regulation of BP both at rest and during exercise. Indeed, in humans who have surgically denervated carotid baroreceptors, resting BP variability is elevated and the BP response to physical stress is exaggerated (53, 55). These observations highlight the importance of understanding ABR function both at rest and during physical activity. However, to date, much of the information available regarding ABR control, particularly during exercise, has been obtained in young men. In the current study, we sought to examine how sex and ovarian hormones influence CBR control during exercise. To our surprise, neither sex nor menstrual cycle phase were found to affect the magnitude of CBR resetting with exercise. However, overall our findings suggest that in terms of CBR control women are better suited to defend against hypertension compared with men, an effect that is sustained throughout the menstrual cycle. Furthermore, young women do not appear to have impaired CBR responses to hypotension, suggesting that alterations in the ABR may not contribute to the greater orthostatic intolerance.
often reported in young women (52). In fact, responses to hypotension were augmented during the midluteal phase of the menstrual cycle. Collectively, from a baroreflex perspective, young women do not have marked differences in CBR control compared with men and, if anything, they appear to be better able to defend against acute changes in BP.

In summary, in contrast to our hypothesis, the results of the present study suggest that sex and fluctuations in ovarian hormones do not influence CBR resetting during dynamic exercise. However, augmented CBR-MAP responses to acute hypotension were observed in young women when progesterone and estrogen concentrations were both elevated. Furthermore, women exhibited greater CBR control of HR both at rest and during exercise, specifically against acute hypertension, an effect that was present throughout the menstrual cycle. Collectively, these findings provide novel insight into understanding influences of sex and ovarian hormones on CBR control during exercise.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES