Effect of menstrual cycle phase on the ventilatory response to rising body temperature during exercise

Keiji Hayashi,1 Takayo Kawashima,2 and Yuichi Suzuki2
1Junior College and 2School of Food and Nutritional Sciences, University of Shizuoka, Shizuoka, Japan
Submitted 26 September 2011; accepted in final form 14 May 2012

IT IS KNOWN that menstrual cycle phase influences control of breathing. During the luteal phase, for example, minute ventilation (VE) and tidal volume (VT) are augmented (8, 29–31), arterial PCO2 (Paco2) is reduced, and central and peripheral chemosensitivity to both hypercapnia and hypoxia are increased (10, 29, 40) relative to the follicular phase. Administration of medroxyprogesterone acetate also augments VE (30, 45) and central and peripheral chemosensitivity to hypercapnia and hypoxia (45), suggesting the augmented ventilatory response during the luteal phase is related to the higher progesterone level. Although the mechanism driving this hyperventilation is not fully understood, it is thought that ovarian hormones stimulate breathing driven by the chemoreflex and/or other reflexes (3, 8, 31).

It is also known that VE is stimulated by hyperthermia (5, 11–13, 16–18, 25), although the mechanism underlying hyperthermia-induced hyperventilation is not fully understood, and its physiological significance in humans is controversial. One hypothesis is that this hyperventilation functions to selectively cool the brain, but another is that hyperventilation causes a reduction in cerebral blood flow, reducing heat removal from the brain (26, 41, 43). Characterization of the response showed that in resting subjects there is a core temperature threshold (~38°C) for hyperpnea or hyperventilation (5, 12). During exercise, on the other hand, the existence of a core temperature threshold appears to depend on the exercise pattern and conditions. Whereas there appears to be a core temperature threshold for hyperventilation at an esophageal temperature (Tes) of 37.5–38.0°C during incremental exercise from rest to exhaustion (4, 42), ventilation increases in proportion to increasing core temperature without a threshold during constant-workload exercise at 50% of peak oxygen uptake (VO2peak) (11–13, 16–18). However, a core temperature threshold for hyperventilation was observed at ~37.0°C (Tes) during constant-workload exercise at 50% of VO2peak when Tes was reduced to ~36.0°C prior to starting the exercise (38). Moreover, during constant-workload exercise, there is a negative relationship between ventilatory sensitivity to hyperthermia (slope of the regression line relating VE and core temperature) and the sensitivity of cutaneous vasodilation (18). This suggests that the magnitude of the response to dissipate heat (e.g., sweating and cutaneous vasodilation) directly or indirectly influences ventilatory sensitivity to hyperthermia.

Menstrual cycle phase also reportedly influences sweating and cutaneous vasodilation (6, 19, 22, 23, 32, 34, 35). It is thus possible that the menstrual cycle influences the ventilatory response to rising body temperature. Furthermore, it was previously reported that the set-point Tes for behavioral thermoregulatory responses is 37.2–37.3°C during the follicular phase and 37.8–37.9°C during the luteal phase (7). It is therefore also possible that the ventilatory response to rising body temperature is influenced by this set-point temperature, although the effect of menstrual cycle phase on hyperthermia-induced hyperventilation is not known. Accordingly, the aim of the present study was to assess the effect of menstrual cycle on hyperthermia-induced hyperventilation. To address that issue, we compared the thermic ventilatory response and cutaneous vasodilatory response measured during the follicular and luteal phases of the menstrual cycle. It was our hypothesis that the ventilatory response to rising body temperature is stronger in the luteal phase than the follicular phase, i.e., the ventilatory sensitivity to hyperthermia is augmented or shifted upward in the luteal phase, compared with the follicular phase; and that the core temperature threshold for cutaneous vasodilation is higher in the luteal phase than the follicular phase.

METHODS

Subjects. Ten healthy female subjects [mean age = 22 ± 2 (SD) yr; height = 163.2 ± 6.4 cm; weight = 57.5 ± 5.0 kg; VO2peak = 41.4 ±
5.5 ml·kg\(^{-1}\)·min\(^{-1}\) participated in the study, which was approved by the Human Subjects Committee of the University of Shizuoka. None of the participants was taking oral contraceptives, which contain female hormones, and all had self-reported regular menstrual cycles of \(~32\) days. All participants provided written informed consent. Before any data were collected, the subjects were allowed to practice the cycle ergometer exercise they would be asked to perform during the experiments until they were accustomed to its style.

\(V_{O_2\text{peak}}\) test. Initially, \(V_{O_2\text{peak}}\) was determined during an incremental exercise test to volitional fatigue performed on a cycle ergometer (model 818, Monark). The exercise was started at 30 W, after which the load was increased at a rate of 15 W/min throughout the entire exercise period. Subjects pedaled at 60 rpm, and volitional fatigue was defined as an inability to pedal at more than 50 rpm. The subjects breathed into a mouthpiece containing a two-way valve. This enabled a mass-flow sensor (hot-wire type) and a gas-sampling tube to be connected to the mouthpiece, and the expired volume and gases could be analyzed using a metabolic cart (Vmax 29, Sensor Medics). The metabolic cart was calibrated with the aid of an appurtenant calibrating instrument that could blow a fixed volume (3 liters) of gases of known concentration. \(V_t\), oxygen uptake (\(V_{O_2}\)), and carbon dioxide output (\(V_{CO_2}\)) were calculated at 60-s intervals. \(V_{O_2\text{peak}}\) was taken as the highest value of \(V_{O_2}\) achieved by a given subject, as some subjects did not achieve a plateau (even though respiratory exchange ratio exceeded 1.1 when \(V_{O_2}\) reached peak value). The \(V_{O_2\text{peak}}\) test was carried out in an environmental chamber maintained at 25°C and 40–60% relative humidity.

**Experimental design.** Subjects were asked to abstain from strenuous exercise, alcohol, and caffeine for 24 h before performing the exercise protocols. They were asked to drink 10 ml water/kg body wt the night before the experiment and then again on the morning of the experiment. Each subject came to the laboratory after consuming only a light breakfast, and then rested for 30 min sitting in a chair. During this time, a thermocouple was inserted via the nasal passage to record \(T_{es}\). This thermocouple was inserted to a distance equivalent to one-fourth of the subject’s height. Thereafter, an intravenous blood sample (5 ml) was taken from the antecubital vein to assay serum estradiol and progesterone. The subject then voided urine, was weighed, and sat in a chair to rest for another 30 min. During this time, a heart rate (HR) monitor and thermocouples for recording skin temperature were attached, and the subjects put on a water-perfused jacket that covered their trunk and right arm. The left arm was left uncovered so that cutaneous blood flow could be measured. Then a mask for analyzing expired volume and gases and a laser-Doppler flowmetry (LDF) probe for measuring cutaneous blood flow were attached. A mass-flow sensor and a gas-sampling tube were connected to the mask just before measurements were begun, and the jacket was perfused with water at 35°C. The subjects performed the cycle exercise at 50% of \(V_{O_2\text{peak}}\). At the onset of the exercise, the temperature of the water perfusion was increased to 45°C, and the exercise was continued for 60 min or until volitional exhaustion. Exercise sessions were conducted during the follicular and luteal phases of the subjects’ menstrual cycle. Each subject completed the two sessions in random order. We asked them to consume similar diets for 24 h before both sessions. No fluid was provided during any session.

**Measurements.** We asked a clinical laboratory testing service (SRL) to assay serum estradiol and progesterone, which were determined using electrochemiluminescence immunoassays (ECLIA§). During the exercise sessions, \(T_{es}\) and skin temperature data were collected via copper constantan thermocouples, which were sampled every 1 s using a data logger system (WE7000, Yokogawa, Japan) and averaged over 30-s periods. Skin temperatures were collected at four sites (chest, upper arm, thigh, and calf) and used to calculate the mean skin temperature (\(T_{sk}\)) (28). The mean body temperature (\(T_b\)) was calculated as \(T_b = 0.9T_{es} + 0.1T_{sk} \) (14). HR was recorded every 5 s using an electrocardiogram (S810i, Polar, Finland), and averaged over 30-s periods. The expired gas was measured using the same analyzers used in the \(V_{O_2\text{peak}}\) test (see above). Cutaneous blood flow was monitored using LDF (AL21, Advance), recorded every 1 s using the data logger system (WE7000) and averaged over 30-s periods. The LDF probe was placed on the left forearm, taking care to avoid placing the end of the optical fiber directly over a superficial vein or hair follicle.

**Data analysis.** \(V_t\), \(V_e\), respiratory frequency (\(f_R\)), ventilatory equivalents for oxygen uptake (\(Ve/V_{O_2}\)) and carbon dioxide output (\(V_t/V_{CO_2}\)) measured during the exercise sessions were plotted as functions of \(T_{es}\), and we took the slopes of the linear regression lines calculated by the method of least squares as indexes of the ventilatory response to the increase in body temperature. To exclude the fast component of \(Ve\) kinetics, only data collected after the 5th minute of exercise were analyzed. Further, we confirmed that the effects of exercise time and skin temperature on the ventilatory responses to the increase in \(T_{es}\) were negligible (17).

All LDF values obtained during the two exercise sessions were converted to percentages of the baseline value [\(\%LDF = (LDF\text{- baseline LDF}) \times 100\)]. For each session, \(\%LDF\) was plotted as a function of \(T_{es}\), after which we determined the slopes of the linear components calculated using the method of least squares. The data collected after \(\%LDF\) reached a steady-level were not included in the linear regression equation. We then defined the greatest slope (second component slope) as the sensitivity of cutaneous vasodilation; and the temperature at which the first component slope intersected the second was taken as the \(T_b\) threshold for cutaneous vasodilation. The averaged \(\%LDF\) value at the plateau level was defined as the peak \(\%LDF\) value. We assumed these values to be indexes of the cutaneous vasodilatory response to the rise in \(T_b\). We could not obtain one subject’s data due to noise arising from movement of the arm. We therefore used the data from only the remaining nine subjects.

**Minimum sample size estimate.** The ventilatory sensitivity to hyperthermia [slope of the regression lines relating ventilatory parameters (\(Ve\), \(V_t\), \(f_R\)) and the body temperature threshold for cutaneous vasodilation were selected as important indexes, and for comparison of their means, minimum sample sizes were calculated on the basis of 80% power and a significance level of 0.05. Standard deviations for the ventilatory sensitivity to hyperthermia were available from our pilot experiments, and those for body temperature threshold for cutaneous vasodilation were available from Kuwahara et al. (23). Sample sizes enabling detection of menstrual cycle phase-related differences of 4.0 l·min\(^{-1}\)·°C\(^{-1}\) for the slope of the regression line relating \(V_t\) and \(T_{es}\), 50 ml·C\(^{-1}\) for the slope of regression line relating \(V_t\) and \(T_{es}\), and 3 breaths·min\(^{-1}\)·°C\(^{-1}\) for the slope of the regression line relating \(f_R\) and \(T_{es}\) were estimated to be 9, 8, and 9, respectively. The sample size enabling detection of a menstrual cycle phase-related difference of 0.3°C in body temperature threshold for cutaneous vasodilation was estimated to be 6. Therefore, our sample size of 10 subjects was larger than the estimated minimum sample size.

**Statistical analysis.** All values are reported as means ± SD. Two-way ANOVA with repeated measures was conducted using time (levels: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45 min) and menstrual cycle phase (levels: follicular phase and luteal phase) as factors. After the main effects had been identified, a post hoc test was conducted for each exercise time, irrespective of whether there was a significant interaction. Paired t-tests were used at minutes 0–30, but because the number of subjects differed at minutes 35–45, unpaired t-tests were used at those times. Paired t-tests were also used to compare the follicular and luteal phases with respect to the baseline values of the physiological parameters, the slopes and intercepts of their linear regression lines calculated after \(V_t\), \(V_e\), \(Ve/V_{O_2}\), and \(V_t/V_{CO_2}\) were plotted as functions of \(T_{es}\), and the sensitivity and the \(T_b\) threshold for the cutaneous vasodilatory response. Values of \(P < 0.05\) were considered significant.
RESULTS

Baseline comparisons. We found that plasma estradiol and progesterone levels were significantly higher during the luteal phase than the follicular phase (Table 1). In addition, baseline $T_{es}$, $T_{sk}$, $T_{b}$, $V_{E}$, $V_{t}$, and end-tidal $P_{O2}$ ($P_{ETO2}$) were all significantly higher during the luteal phase (Table 1). Baseline HR and end-tidal $P_{CO2}$ ($P_{ETCO2}$) did not significantly differ, although there was a tendency toward a difference ($P < 0.06$). On the other hand, baseline $f_R$, $V_{O2}$, $V_{C02}$, $V_{E}/V_{O2}$, and $V_{E}/V_{C02}$ did not significantly differ between the menstrual phases.

Comparisons during exercise. Figure 1 shows the changes in $T_{es}$, $T_{sk}$, and $T_{b}$ during exercise. $T_{es}$ rose during exercise, reaching $38.1 \pm 0.4°C$ at minute 45 in the follicular phase and $38.3 \pm 0.5°C$ in the luteal phase. There were significant main effects of menstrual cycle phase ($F = 43.52$, $P < 0.01$) and of exercise time ($F = 38.05$, $P < 0.01$) on $T_{es}$. $T_{es}$ values were significantly higher during the luteal phase than the follicular phase at minutes 0–30. Moreover, $T_{es}$ values were significantly higher at minutes 5–45 than at minute 0 in both the luteal and follicular phases. Both $T_{sk}$ and $T_{b}$ also increased during exercise. There were significant main effects of menstrual cycle phase on $T_{sk}$ ($F = 36.56$, $P < 0.01$) and $T_{b}$ ($F = 6.38$, $P = 0.01$) and of exercise time on $T_{sk}$ ($F = 39.00$, $P < 0.01$) and $T_{b}$ ($F = 5.60$, $P < 0.01$). $T_{sk}$ values were significantly higher during the luteal phase than the follicular phase at minutes 0–20, while $T_{b}$ values were significantly higher during the luteal phase at minutes 0–30. Both $T_{sk}$ and $T_{b}$ values were significantly higher at minutes 5–45 than at minute 0 in both the luteal and follicular phases. Both HR and %LDF increased during exercise. There were significant main effects of exercise time on HR ($F = 160.14$, $P < 0.01$) and %LDF ($F = 9.27$, $P < 0.01$). Although there were significant main effects of menstrual cycle phase on both HR ($F = 5.40$, $P = 0.02$) and %LDF ($F = 6.40$, $P = 0.01$), there were no significant differences related to menstrual phase were detected (Fig. 2). Both HR and %LDF were significantly higher at minutes 5–45 than at minute 0 in both the luteal and follicular phases.

Table 1. Baseline levels of physiological parameters

<table>
<thead>
<tr>
<th></th>
<th>Follicular Phase</th>
<th>Luteal Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol, pg/ml</td>
<td>$51 \pm 21$</td>
<td>$158 \pm 65^*$</td>
</tr>
<tr>
<td>Progesterone, ng/ml</td>
<td>$0.59 \pm 0.20$</td>
<td>$9.79 \pm 4.58^*$</td>
</tr>
<tr>
<td>$T_{es},{}°C$</td>
<td>$36.7 \pm 0.2$</td>
<td>$37.1 \pm 0.2^*$</td>
</tr>
<tr>
<td>$T_{sk},{}°C$</td>
<td>$34.4 \pm 0.5$</td>
<td>$35.1 \pm 0.5^*$</td>
</tr>
<tr>
<td>$T_{b},{}°C$</td>
<td>$36.5 \pm 0.2$</td>
<td>$36.9 \pm 0.2^*$</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>$80 \pm 6$</td>
<td>$87 \pm 11$ ($P &lt; 0.06$)</td>
</tr>
<tr>
<td>$V_{E}$, l/min</td>
<td>$11.1 \pm 2.0$</td>
<td>$12.6 \pm 1.7^*$</td>
</tr>
<tr>
<td>$V_{t}$, ml</td>
<td>$583 \pm 67$</td>
<td>$629 \pm 67^*$</td>
</tr>
<tr>
<td>$f_R$, breaths/min</td>
<td>$19 \pm 4$</td>
<td>$21 \pm 5$</td>
</tr>
<tr>
<td>$V_{O2}$, ml/min</td>
<td>$218 \pm 37$</td>
<td>$233 \pm 25$</td>
</tr>
<tr>
<td>$V_{C02}$, ml/min</td>
<td>$189 \pm 34$</td>
<td>$204 \pm 20$</td>
</tr>
<tr>
<td>$V_{E}/V_{O2}$</td>
<td>$51.8 \pm 7.4$</td>
<td>$55.3 \pm 10.3$</td>
</tr>
<tr>
<td>$Pr_{ETCO2}$, mmHg</td>
<td>$99.9 \pm 8.4$</td>
<td>$63.0 \pm 10.2$</td>
</tr>
<tr>
<td>$Pr_{ETCO2}$, mmHg</td>
<td>$109 \pm 5$</td>
<td>$112 \pm 3^*$</td>
</tr>
</tbody>
</table>

Values are means ± SD. $T_{es}$, esophageal temperature; $T_{sk}$, mean skin temperature; $T_{b}$, mean body temperature; $V_{E}$, minute ventilation; $V_{t}$, tidal volume; $f_R$, respiratory frequency; $V_{E}/V_{O2}$, ventilatory equivalents for oxygen uptake; $V_{E}/V_{C02}$, ventilatory equivalents for carbon dioxide output. *$P < 0.05$, follicular phase vs. luteal phase.

Figure 3 shows the changes in $V_{E}$, $V_{t}$, and $f_R$ during the exercise sessions. $V_{E}$ and $f_R$ increased sharply after the start of exercise, then increased more gradually during the remainder of the exercise sessions in both phases. There were significant main effects of menstrual cycle phase ($F = 4.43$, $P = 0.04$) and of exercise time ($F = 26.68$, $P < 0.01$) on $V_{E}$, and $V_{E}$ was significantly higher in the luteal than the follicular phase at minutes 0, 10, 20, and 30. In addition, $V_{E}$ was significantly higher at minutes 5–45 than at minute 0 in both the luteal and follicular phases. By contrast, although there was a significant main effect of exercise time on $f_R$ ($F = 7.87$, $P < 0.01$), there...
was no main effect of menstrual cycle phase on fR (F = 0.21, P = 0.65). fR was significantly higher at minutes 5–45 than at minute 0 in both the luteal and follicular phases. Vt also increased right after the start of exercise; however, Vt values then stabilized and were nearly constant for the remainder of the exercise in the follicular phase and decreased slightly in the luteal phase. Nonetheless, there was a significant main effect of menstrual cycle phase (F = 7.21, P < 0.01) and of exercise time (F = 30.29, P < 0.01) on Vt, and Vt was significantly greater in the luteal phase at minutes 0–10 and 20–30. Further, Vt was significantly higher at minutes 5–45 than at minute 0.

Figure 4 shows the changes in V˙E/V˙O2, V˙E/V˙CO2, and PETCO2 during the exercise sessions. Ve, fR, VE/VO2, and VE/VECO2 against Tes (Figs. 5 and 6). We found that Vt, for, Vt/Vo2, and Vt/VECO2 all increased with increases in Tes during exercise in both the follicular and luteal phases.

cise, then gradually declined during the remainder of the session in both phases. There were significant main effects of menstrual cycle phase (F = 12.03, P < 0.01) and of exercise time (F = 5.98, P < 0.01) on PETCO2, and PETCO2 was significantly lower in the luteal phase than the follicular phase at minutes 10–30. Further, PETCO2 was significantly higher at minutes 5–45 in the luteal phase and at minutes 5–35 in the follicular phase than at minute 0.

Tc-dependent changes in ventilatory responses. To assess the effect of menstruation phase on the relation between ventilatory responses and body temperature, we plotted Vt, for, Vt/Vo2, and Vt/VECO2 against Tes (Figs. 5 and 6). We found that Ve, fR, Ve/Vo2, and Ve/CO2 all increased with increases in Tc during exercise in both the follicular and luteal phases.
On the other hand, Vt remained nearly constant as $T_{es}$ rose in the follicular phase and declined slightly in the luteal phase. There were no significant menstrual phase-related differences in the slopes or intercepts for any of the ventilatory parameters (Table 2).

$T_{es}$-dependent changes in %LDF. Because $T_{es}$ changed significantly during the exercise sessions, and because changes in $T_{es}$ can influence forearm blood flow (39), we next plotted %LDF values against $T_{es}$. We found that %LDF increased with increasing $T_{es}$, and the threshold $T_{es}$ differed significantly between the follicular and luteal phases ($36.87 \pm 0.26$ vs. $37.20 \pm 0.30^\circ C, P < 0.05$) (Table 3). However, there were no significant phase-related differences in the slope (sensitivity of cutaneous vasodilation) or peak %LDF value (Table 3).

**DISCUSSION**

*Effect of menstrual cycle on ventilation.* It has been reported that in resting subjects, $V__E$ is greater during the luteal phase than the follicular phase (29, 31), and that administration of medroxyprogesterone acetate augments $V__E$ (30, 45), which suggests this hyperventilation is related to an increase in progesterone. Moreover, the progesterone-induced hyperventilation reportedly reflects an increase in Vt (8, 30). We also observed higher $V__E$ and Vt in the luteal phase than the follicular phase at baseline and during exercise. Although the mechanism for this hyperventilation was not addressed in the present study, we suggest that ovarian hormones stimulate the chemoreflex and/or other reflexes that drive ventilation (3, 8, 31). For example, Bayliss et al. (2) reported that an increase in phrenic nerve activity elicited by progesterone was dimin-

![Fig. 4](image-url) *Fig. 4. Time-dependent changes in the ventilatory equivalents for oxygen uptake ($V__E/V__O__2$; top), carbon dioxide output ($V__E/V__CO__2$; middle) and end-tidal $P__CO__2$ ($P_{ETCO__2}$; bottom) during exercise in the follicular (○) and luteal (●) phases. *$P < 0.05$, follicular phase vs. luteal phase. †$P < 0.05$ vs. minute 0 in the follicular phase. ‡$P < 0.05$ vs. minute 0 in the luteal phase.*

![Fig. 5](image-url) *Fig. 5. Esophageal temperature-dependent changes in minute ventilation (top), tidal volume (middle), and respiratory frequency (bottom) during exercise in the follicular and luteal phases.*
Temperature, $V\dot{E}$ and $V_t$ reportedly increase at 0.5 l/min and 61
hyperpnea or hyperventilation at subjects reportedly exhibit a core temperature threshold for
esophageal temperature after plotting the indicated ventilatory parameter against
$V\dot{E}$-$T_{es}$

Table 2. Slopes and intercepts of regression lines calculated
for oxygen uptake ($V\dot{E}/V\dot{O}_2$; top) and carbon dioxide output ($V\dot{E}/V\dot{CO}_2$; bottom)
during exercise in the follicular (○) and luteal (●) phases.

Table 3. Mean body temperature threshold for cutaneous vasodilation, slope of the regression lines for %LDF plotted against mean body temperature, and the peak value of %LDF

<table>
<thead>
<tr>
<th></th>
<th>Follicular Phase</th>
<th>Luteal Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{es}$ threshold, °C</td>
<td>36.87 ± 0.26</td>
<td>37.20 ± 0.30*</td>
</tr>
<tr>
<td>Slope, °C/C</td>
<td>1.870 ± 1.252</td>
<td>1.26 ± 0.776</td>
</tr>
<tr>
<td>Peak, %</td>
<td>991 ± 525</td>
<td>767 ± 361</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n = 9$ subjects. %LDF, percent laser-Doppler flow. *$P < 0.05$, follicular phase vs. luteal phase.

ml per 1°C increase in $T_{es}$, respectively (12). Based on these
parameters, the 0.4°C difference in baseline $T_{es}$ between the
luteal and follicular phases would increase $V\dot{E}$ by 0.2 l/min and
$V_t$ by 24.4 ml, suggesting the difference in the magnitude of the
increase in $T_{es}$ can explain 13% of the difference in $V\dot{E}$ and
53% of the difference in $V_t$ between the luteal and follicular phases. The remainder must be explained by other drives and/or reflexes.

Whether a core temperature threshold is detected during exercise depends on the exercise pattern. Whereas there does appear to be a core temperature threshold for hyperventilation during incremental exercise from rest to exhaustion (4, 42), ventilation increases with increasing core temperature without a threshold during constant-workload exercise at 50% of $V_{O2peak}$ unless body temperature is reduced prior to starting the exercise (11–13, 16–18, 38). In the present study, subjects exercised at a constant workload of 50% of $V_{O2peak}$ without a prior reduction in body temperature. $V\dot{E}$ increased proportionally with increases in $T_{es}$ in both menstrual phases, and there were no significant differences in the slopes or intercepts of the regression lines. $V_t$ was significantly higher in the luteal phase than the follicular phase at minutes 0–30 of exercise; however, due to the large individual differences in those measures there was no significant menstrual phase-related difference in the slope or intercept of the regression line. We therefore suggest that although a difference in $V_t$ between the luteal and follicular cycle phases during exercise was observed during mild hyperthermia ($T_{es} = 38°C$), that difference was likely diminished at moderate hyperthermia ($T_{es} > 38°C$). Accordingly, we further suggest that the difference in $V\dot{E}$ between the menstrual cycle phases during exercise reflects the increase in core temperature as well as the augmented $V_t$ seen during mild hyperthermia.

Ventilatory $O_2$ and $CO_2$ chemosensitivities are reportedly augmented in the luteal phase relative to the follicular phase (10, 29, 40). In women, the ventilatory recruitment threshold for $P_{ETCO_2}$ is 40–50 mmHg, irrespective of menstrual cycle phase (20, 31). In the present study, $P_{ETCO_2}$ during exercise was <45 mmHg in both menstrual phases, suggesting that the $P_{ETCO_2}$ values during exercise were around the threshold. When $P_{ETCO_2}$ is just above the ventilatory recruitment threshold, increases in $V\dot{E}$ are mainly caused by increases in $V_t$ (9). We therefore suggest that the augmented $V\dot{E}$ and $V_t$ we observed in the luteal phase are driven by augmented ventilatory $CO_2$ chemosensitivity. We further suggest that once $T_{es}$ reaches about 38°C, hyperventilation causes $P_{ETCO_2}$ to decline to the ventilatory recruitment threshold for $CO_2$. On the other hand, plots relating $V\dot{E}$ and alveolar partial pressure of $O_2$...
(\(P_{AO_2}\)) are hyperbolic \(\dot{V}_E = \dot{V}_0 + A/(P_{AO_2} - 32)\), where \(\dot{V}_0\) is the asymptote for \(\dot{V}_E\), and \(A\) is the ventilatory \(O_2\) chemosensitivity. Moreover, at normoxic \(P_{AO_2}\) levels the shape of the relation may be asymptotic, irrespective of the progesterone level (45). It is therefore suggested that even if ventilatory \(O_2\) chemosensitivity is augmented by progesterone, the effect on ventilation in the present study would be small or negligible, owing to the characteristics of the hyperbolic relation.

**Effect of menstrual cycle on thermoregulatory responses.** Our findings are consistent with earlier reports that the core temperature threshold for sweating (19, 22, 23, 35) and cutaneous vasodilation (19, 23, 35) are higher in the luteal phase than the follicular phase; progesterone reportedly increases the core temperature threshold for sweating and cutaneous vasodilation (6, 32), while estrogen reduces the core temperature threshold (33, 36). It was also previously reported that thermal sensation changes with the menstrual cycle phase, and that this change may reflect an increase in the set-point temperature during the luteal phase (7). Such an increase could influence behavioral thermoregulatory responses to keep the body temperature higher during the luteal phase than the follicular phase. It is therefore possible that the increase in the core temperature threshold for sweating and cutaneous vasodilation is related to a shift in the set-point temperature. On the other hand, most studies have found that menstrual phase has little effect on the sensitivity of the sweating and cutaneous vasodilatory responses were weaker in the luteal phase than the follicular phase. They suggested that the apparent discrepancy between their study and the others reflected differences in the workload and environmental conditions; i.e., the workload was 60–85% of maximal oxygen uptake in a hot environment (ambient temperature: 35–50°C) in the earlier studies, but was 50% of maximal oxygen uptake in a temperate environment (ambient temperature: 25°C) in Kuwahara’s study. In other words, the high level of heat stress present under hot conditions and higher exercise workload masks the effect of menstrual cycle phase on the sensitivity of cutaneous vasodilation. In the present study, menstrual phase had no significant effect on the sensitivity of the cutaneous vasodilatory response, even though we increased body temperature using a water-perfused suit for CO2 is unaffected by a 1.5°C increase in core temperature (24), which makes it difficult to conclude that the higher \(Vt\) seen in the luteal phase is to compensate for lowered cutaneous vasodilation.

**Limitations and the implications of the relationship between heat-dissipating responses and the hyperthermic ventilatory response.** It is possible that increased ventilatory chemosensitivity in the luteal phase is caused in part by a rise in body temperature. Earlier studies reported that the ventilatory \(O_2\) and \(CO_2\) chemosensitivities are augmented by hyperthermia (1, 24). To the best of our knowledge, a 0.7°C increase in core body temperature will increase ventilatory chemosensitivity (24). On the other hand, the ventilatory recruitment threshold for \(CO_2\) is unaffected by a 1.5°C increase in core temperature (1). Thus, examining the effect of body temperature (< 0.7°C increase in body core temperature) on the ventilatory chemosensitivity in a future study might give a clearer picture of the effect of progesterone on ventilatory chemosensitivity.

It has been reported that the ventilatory sensitivity to rising body temperature has a negative linear relationship with the sensitivity of cutaneous vasodilation in exercising heated humans (18). It has also been reported that subjects with congenital anhidrotic ectodermal dysplasia and those with spinal cord injuries leading to reduced sweating responses show greater increases in ventilation during hyperthermia at rest than healthy subjects (37, 44). These relationships suggest hyperthermia-induced hyperventilation may change in conjunction with sweating and cutaneous vasodilatory responses, although the physiological mechanism underlying the relationship between the hyperthermic ventilatory response and the thermoregulatory responses is unclear. Our results indicate that \(\dot{V}_E\) is augmented due to increased \(Vt\) and a delayed onset of cutaneous vasodilation, which suggests the increase in \(\dot{V}_E\) is to compensate for the reduced cutaneous vasodilation. However, our results also indicate the increase in \(Vt\) is caused by an increase in \(\dot{V}_E\), resulting in a decrease in \(PET_{CO_2}\). We have observed that \(\dot{V}_E\) is augmented due to increased \(Vt\) and a delayed onset of cutaneous vasodilation, which suggests the increase in \(\dot{V}_E\) is to compensate for the reduced cutaneous vasodilation. However, our results also indicate the increase in \(Vt\) is caused by an increase in \(\dot{V}_E\), resulting in a decrease in \(PET_{CO_2}\), which would be expected to induce a reduction of cerebral blood flow (16, 25, 27), although we did not measure cerebral blood flow in this study. Nybo et al. (27) reported that the reduction in cerebral blood flow caused by hyperthermia-induced hyperventilation decreased heat removal from the brain via cerebral blood flow, so that more heat was retained in the brain. Therefore, the reduction in \(PET_{CO_2}\) observed in the present study suggests heat removal from the brain via cerebral blood flow was reduced. Further, during thermal panting, \(Vt\) is increased under conditions of severe hyperthermia; this is the so-called “second-phase panting” (15, 21). The augmented \(Vt\) seen with mild hyperthermia would not effectively dissipate heat, which makes it difficult to conclude that the higher \(\dot{V}_E\) and \(Vt\) seen in the luteal phase is to compensate for lowered cutaneous vasodilation.

Alternatively, Cunningham and Cabanac (7) reported that the set-point temperature differed between the follicular phase and the luteal phase, and that the set-point during the luteal phase was 37.8–37.9°C (\(T_{es}\)), implying that thermal sensation functioned to raise body temperature to the set point when \(T_{es}\) was below it. In the present study, \(\dot{V}_E\) and \(Vt\) significantly differed between the follicular and luteal phases until \(T_{es}\) reached ~38°C. Increasing \(Vt\) without decreasing \(f_R\) led to reductions in both \(PET_{CO_2}\) and cerebral blood flow (16, 25, 27). It is therefore plausible that the increases in \(\dot{V}_E\) and \(Vt\) seen during mild hyperthermia (\(T_{es}\) ~ 38°C) were caused by a decrease in heat removal from the brain for the purpose of increasing brain temperature to the set point. As mentioned above, however, we suggest that differences in \(\dot{V}_E\) and \(Vt\) during mild hyperthermia reflect the ventilatory recruitment threshold for \(PET_{CO_2}\). Further studies are necessary to clarify whether it is the set-point temperature or the characteristics of the ventilatory chemoreceptor response that influences hyperthermia-induced hyperventilation and contributes to the higher \(\dot{V}_E\) and \(Vt\) during mild hyperthermia in the luteal phase.

**Conclusions.** In summary, we investigated the effect of menstrual cycle on the ventilatory sensitivity and cutaneous vascular responses to increasing body temperature during prolonged exercise at 50% of \(VO_2_{peak}\). We found that a change in menstrual phase can alter the mean body temperature threshold for the cutaneous vasodilatory response, and that \(Vt\) was
augmented in the luteal phase with mild hyperthermia during exercise. On the other hand, menstrual cycle phase did not affect ventilatory sensitivity to increasing body temperature. These observations suggest the effect of menstrual cycle on the ventilatory response to hyperthermia reflects an increase in Vt with mild hyperthermia (Tes ≈ 38°C) and is diminished with moderate hyperthermia (Tes > 38°C).

ACKNOWLEDGMENTS

We sincerely thank the volunteer subjects for participating in this study. We are also grateful to M. Miura, K. Imafuku, H. Takeda, and C. Fujimini (University of Shizuoka) for medical support, and to K. Tateyama (University of Shizuoka) for statistical support.

GRANTS

This study was supported by a grant-in-aid for Young Scientists from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (Grant 22700667) and a grant from the University of Shizuoka.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: K.H., T.K., and Y.S. conception and design of research; K.H. and T.K. performed experiments; K.H. and T.K. analyzed data; K.H., T.K., and Y.S. interpreted results of experiments; K.H. prepared figures; K.H. drafted manuscript; K.H. edited and revised manuscript; K.H., T.K., and Y.S. approved final version of manuscript.

REFERENCES

37. Tsuji B, Honda Y, Fujii N, Kondo N, Nishiyasu T. Effect of initial core temperature on hyperthermic hyperventilation during prolonged submaxi-


