Exercise $\dot{V}E$ and physical performance at altitude are not affected by menstrual cycle phase

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Exercise $\dot{V}E$ and physical performance at altitude are not affected by menstrual cycle phase. J. Appl. Physiol. 86(5): 1519–1526, 1999.—We hypothesized that progesterone-mediated ventilatory stimulation during the midluteal phase of the menstrual cycle would increase exercise minute ventilation ($\dot{V}E; \text{l/min}$) at sea level (SL) and with acute altitude (AA) exposure but would only increase arterial $O_2$ saturation ($SaO_2$, %) with AA exposure. We further hypothesized that an increased exercise $SaO_2$, with AA exposure would enhance $O_2$ transport and improve both peak $O_2$ uptake ($VO_2\text{peak}; \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and submaximal exercise time to exhaustion (Exh; min) in the midluteal phase. Eight female lowlanders [33 ± 3 (mean ± SD) yr, 58 ± 6 kg] completed a $VO_2\text{peak}$ and Exh test at 70% of their altitude-specific $VO_2\text{peak}$ at SL and with AA exposure to 4,300 m in a hypobaric chamber (446 mmHg) in their early follicular and midluteal phases. Progesterone levels increased ($P < 0.05$) ~20-fold from the early follicular to midluteal phase at SL and AA. Peak $\dot{V}E$ (101 ± 17) and submaximal $\dot{V}E$ (55 ± 9) were not affected by cycle phase or altitude. Submaximal $SaO_2$, did not differ between cycle phases at SL, but it was 3% higher during the midluteal phase with AA exposure, whether measured or calculated as Exh time was affected by cycle phase at SL or AA. We conclude that, despite significantly increased progesterone levels in the midluteal phase, exercise $\dot{V}E$ is not increased at SL or AA. Moreover, neither maximal nor submaximal exercise performance is affected by menstrual cycle phase at SL or AA.

LOW LEVELS OF ESTRADIOL and progesterone are found in the early follicular phase of the menstrual cycle, whereas high levels are found in the midluteal phase (26). The primary effects of estradiol and progesterone are related to reproductive behavior, but a number of reviews have addressed the role both progesterone and estradiol play in stimulating minute ventilation ($\dot{V}E$) (2, 28). There is ample evidence to suggest that progesterone is the major reason for the observed increase in resting $\dot{V}E$ in the midluteal phase. First, progesterone reaches peak values in the midluteal phase at the same time that end-tidal $PCO_2$ ($PET\text{CO}_2$) reaches a nadir (18). Second, there is a fivefold increase in progesterone in pregnant women, which is accompanied by a 35–50% increase in resting $\dot{V}E$ (32, 35). Third, when synthetic progesterone is administered to men, an increase in resting $\dot{V}E$ and chemosensitivity is observed (5, 42). However, estradiol may augment the stimulatory effects of progesterone on resting $\dot{V}E$ (8, 39) by increasing the number and affinity of progesterone receptors (8, 36).

Incremental increases in estradiol (10–55%) and progesterone (18–80%) also occur during both maximal and submaximal exercise at sea level (SL), with more pronounced increases occurring in the midluteal phase (6, 34). Given their stimulatory effects on resting $\dot{V}E$, midluteal-phase increases in estradiol and progesterone may increase exercise $\dot{V}E$. Several studies have reported an increased or similar exercise $\dot{V}E$ in the midluteal phase (15, 24, 41, 52), whereas others have reported no differences (3, 13, 22, 27). Thus the effect of cyclic variations in ovarian hormones on exercise $\dot{V}E$ at SL remains unclear.

Exercise $\dot{V}E$ plays a critical role in providing $O_2$ to exercising muscles. However, exercise $\dot{V}E$ is not considered to be a limiting factor during exercise at SL, given that normal healthy individuals rarely approach mechanical or diffusion limitations even at maximal exercise intensities (14). Regardless of whether SL studies have reported an increased or similar exercise $\dot{V}E$ in the midluteal phase, the literature is almost unanimous in reporting no differences in exercise performance between phases of the menstrual cycle (9, 10, 13, 15, 22, 27, 31, 41). In the two studies that reported an increase in submaximal exercise performance in the midluteal phase (24, 34), both attributed the increase to improvements in substrate utilization not submaximal exercise $\dot{V}E$. Thus cycle-phase differences in exercise $\dot{V}E$ do not appear to be a critical factor in limiting maximal or submaximal exercise performance at SL.

Although exercise performance may not be strongly influenced by ventilatory cycle-phase differences at SL, the same may not be true during an acute exposure to high altitude. Because arterial blood is ~96% saturated with $O_2$ at SL (20), a small increase (6–8%) (13) in exercise $\dot{V}E$ during the midluteal phase may not impart any exercise performance advantage at SL. At 4,300 m, however, arterial blood is ~84% saturated (20), and a small increase in exercise $\dot{V}E$ during the midluteal phase could raise the arterial $PO_2$ ($PaO_2$), increase arterial $O_2$ saturation ($SaO_2$), and thus increase arterial $O_2$ content. An increased arterial $O_2$ content would then create a larger peripheral diffusion gradient for $O_2$, enhance $O_2$ transport during exercise, and potentially...
improve both maximal and submaximal exercise performance during the midluteal phase at 4,300 m.

The purpose of this study was to determine the effect of ovarian hormone levels that are associated with the early follicular and midluteal phases of the menstrual cycle on maximal and submaximal exercise performance at SL and acute altitude (AA). We hypothesized that increased estradiol and progesterone levels in the midluteal phase would stimulate exercise $V_{\dot{E}}$ during SL and AA exposures, but such increased levels of exercise $V_{\dot{E}}$ would improve $S_aO_2$ only at AA, and thus would improve maximal and submaximal exercise performance only at AA.

**METHODS**

Volunteer test subjects. Ten nonsmoking women volunteers were originally enrolled in this study. Two of the 10 volunteers completed the study but were eliminated from further analysis because of inadequate menstrual cycle documentation. The remaining eight volunteers had an age, initial body weight, and height of $33 \pm 3$ (SD) yr, $58 \pm 6$ kg, and $163 \pm 8$ cm, respectively. Percent body fat, determined by hydrostatic underwater weighing, was $26 \pm 3\%$. All had menstrual cycles of consistent length (25–35 days) and had not taken oral contraceptives or hormone therapy for at least 6 mo before entering the study. None was pregnant, and none had been pregnant for at least 2 yr before starting the study. All had normal hemoglobin and serum iron stores.

All volunteers were lifelong residents at low altitude and had no exposure to altitudes $>1,000$ m for at least 6 mo before the study. All were healthy, physically active women who participated in aerobic exercise (2–3 h/wk) before and during the study. All provided written acknowledgment of their voluntary consent, and they were made aware of their right to withdraw without prejudice at any time. Investigators adhered to Army Regulation 70–25 and US Army Research and Materiel Command Regulation 70–25 on the use of volunteers in research.

Menstrual cycle documentation. Supportive evidence for normal ovulatory cycles was initially obtained by a menstrual cycle-history questionnaire. Evidence of ovulation was obtained by using the First Response Ovulation Predictor Test (Carter Wallace Products Division, New York, NY), which detected (within 24–36 h) the onset of the luteinizing hormone (LH) surge by using urine samples from the first morning void. Urine testing started 9–15 days after menses, depending on each woman's cycle length, and continued until the LH surge was detected. Volunteers kept a record of their first day of menses and ovulation test results for 1 mo before testing, during the 2–3 mo of testing, and for 1 mo after testing was completed.

Study protocol. The study used an unblinded, balanced experimental design in which each test volunteer's ovarian hormones, ventilatory parameters, and exercise performances were evaluated at SL and AA during both the early follicular (3–6 days after the beginning of menstruation) and midluteal (6–9 days after the LH surge) phases of her menstrual cycle. The four test conditions were defined as sea level, follicular (SL/F); sea level, luteal (SL/L); acute altitude, follicular (AA/F); and acute altitude, luteal (AA/L). During each test condition, 3 days were used to complete all exercise and ventilatory tests. On the first day, volunteers completed pulmonary function tests (PFT) and a treadmill peak $O_2$ uptake ($V_{\dot{O}_2peak}$) test. On the second day, during SL exposures only, volunteers completed hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR) tests. On the third day, they completed a treadmill sub maximal exercise to exhaustion (Exh) test conducted at 70% of altitude-specific $V_{\dot{O}_2peak}$. Each exercise and ventilatory test was performed at the same time of day for each volunteer in all four testing conditions. The order of menstrual cycle phase and altitude combination in which testing was performed was randomized.

Environmental conditions. All exercise testing was performed in a hypobaric chamber that was maintained at a temperature and relative humidity of $22 \pm 3^\circ C$ and $45 \pm 5\%$, respectively. After the volunteers entered the hypobaric chamber for the $V_{\dot{O}_2peak}$ and Exh tests during AA exposures, the chamber was decompressed to the barometric equivalent of 4,300 m (446 mmHg) over a period of $\sim 12$ min. All exercise tests in the hypobaric chamber were initiated within 30 min of arriving at 4,300-m equivalent altitude and were completed within 1–3 h, depending on how long the volunteers exercised to reach exhaustion.

Ovarian hormone analysis. Ovarian-hormone levels were measured to document menstrual cycle phase. A resting blood sample was obtained before both the $V_{\dot{O}_2peak}$ and Exh tests for analyses of estradiol and progesterone levels. The mean from these two testing occasions represents the resting estradiol and progesterone levels, respectively. A serum progesterone value $> 5$ ng/ml was accepted as confirmation of the midluteal phase (26). Additional blood samples for estradiol and progesterone were taken every 15 min and at exhaustion during the Exh test. The mean value from these time periods represents the exercise estradiol and progesterone levels, respectively. Serum concentrations of estradiol and progesterone were determined in duplicate by using a solid-phase radioimmunoassay (Diagnostic Products, Los Angeles, CA). The intra-assay variances for estradiol and progesterone were 4.7 and 7.4%, respectively. All samples for one volunteer were analyzed in the same assay to avoid interassay variations.

Ventilatory testing. Resting pulmonary function measurements of forced vital capacity (FVC), forced expired volume in 1 s (FEV1), and maximal voluntary ventilation (MVV) were obtained (BTPS) by standard protocols (21) with the use of a computerized dry-rolling seal spirometer (model PFT2450, SensorMedics, Yorba Linda, CA). Before the HVR test, the $P_{ETCO_2}$, a measure of resting $V_{\dot{E}}$, was measured by using a $CO_2$ analyzer (model LB-2, Beckman, Anaheim, CA) for $2–3$ min during resting breathing, and the mean value from the last minute was used. Resting control of breathing was assessed with the HVR and HCVR tests. The HVR was measured by inducing progressive isocapnic hypoxia, over an 8- to 10-min period (50), by using a rebreathing system containing an initial concentration of 21% $O_2$. Continuous measurements were made of $P_{ETCO_2}$, which was maintained within $\pm 2$ Torr of the resting level for that day by manual adjustment of the air flow through a $CO_2$-absorber circuit. The $V_{\dot{E}}$ was measured by using a dry-rolling seal spirometer (model 762609 spirometer, SensorMedics), and $S_aO_2$ was measured by finger pulse oximetry (Oxyshuttle, SensorMedics). The measurement error of this finger pulse oximeter is $\pm 2\%$ at $> 70\% S_aO_2$, and $\pm 3\%$ at $< 70\% S_aO_2$. The HVR slope (HVR-S), a measure of hypoxic chemosensitiveness, was reported as $\Delta V_{\dot{E}}/\Delta S_aO_2$, calculated by using least squares regression. The HCVR test was performed by inducing progressive hypercapnia and using a gas mixture with an initial composition of 7% $CO_2$-93% $O_2$, following the protocol described by Read (37). The $P_{ETCO_2}$ was allowed to rise $\sim 15$ Torr above resting levels for that day over a 5- to 7-min period. The HCVR slope (HCVR-S), a measure of hypercapnic...
were used to analyze the differences between menstrual cycle, exercise, and altitude. Two-way ANOVAs with repeated measures on each factor and a 15-min increase in Exh time at the altitude, luteal. Significant differences were observed between the early follicular and midluteal phases (P < 0.05). The Covariance analysis was performed by using the predicted mean size estimations were performed by using predicted mean size equations for the equation $V_{\text{E}} = S(P_{\text{ACO}} - B)$, where $P_{\text{ACO}}$ is alveolar (end-tidal) $P_{\text{CO}}$. The HCVR intercept, B, represents an imaginary threshold of the CO$_2$-sensing system and was reported as $P_{\text{ACO}}$.  

Exercise performance testing. Before all exercise tests, the volunteers were required to abstain from alcohol and caffeine for at least 24 h and to refrain from exercise on the testing day. The volunteers also maintained the same diet for 48 h before each of the four Exh tests. Twenty-four-hour dietary logs were analyzed for energy content and percent contribution of macronutrients by computer with the use of the Food Intake Analysis System (University of Texas Health Science Center, Houston, TX).  

Before each exercise test, the volunteer was weighed (wearing T-shirt, shorts, and socks) to the nearest 0.1 kg. During exercise, heart rate (HR) was determined from continuous electrocardiogram recordings (Cardiovit AT-6C; Schiller Canada, Nepean, ON, Canada). Respiratory gas measurements were made continuously during the VO$_{2\text{peak}}$ test and intermittently during the Exh test by using open-circuit calorimetry (model 2900 metabolic cart; SensorMedics) calibrated with certified gases and volume standard. The metabolic cart provided values for $V_{\text{E}}$, $O_2$ uptake ($V_{\text{O}}$), and carbon dioxide output ($V_{\text{CO}}$). The ventilatory equivalents for $O_2$ ($V_{\text{E}}/V_{\text{O}}$) and CO$_2$ ($V_{\text{E}}/V_{\text{CO}}$) were calculated from individual $V_{\text{E}}$, $V_{\text{O}}$, and $V_{\text{CO}}$ data to minimize intrasubject variability in $V_{\text{E}}$ due to different body sizes and metabolic rates. The $V_{\text{E}}$ and the rating of perceived exertion (RPE), using the whole-body Borg scale (7), were obtained at the end of peak exercise and every 15 min during submaximal exercise.  

Peak-exercise testing. The VO$_{2\text{peak}}$ was determined by a progressive-intensity, continuous, treadmill-running test to exhaustion modified from Costill and Fox (12). After a 3-min warm-up, the speed and grade were increased to 2.2–2.7 m/s and 2.0%, respectively, for the first 2 min. Thereafter, the speed was kept constant and the grade was increased by 2% every 2 min. The highest VO$_{2\text{peak}}$ achieved for 1 min before exhaustion was recorded as VO$_{2\text{peak}}$.  

Submaximal-exercise testing. After a 3-min warm-up, each volunteer exercised, until exhaustion, at 70% of her altitude-specific VO$_{2\text{peak}}$. Treadmill speed and/or grades were adjusted to reach the desired percentage of VO$_{2\text{peak}}$ for each volunteer. In all cases, the target VO$_{2}$ was obtained within 10 min of the beginning of exercise. Cardiorespiratory measurements were obtained during the last 5 min of every 15-min period of exercise, and the mean value was calculated from the last 3 min. A 28-item validated internal-state questionnaire (ISQ) (1) was given at minute 45 during the Exh test, and a respiratory distress symptom score (ISQ-R) and a fatigue symptom score (ISQ-F) were calculated from the answers to this questionnaire to determine the volunteer’s level of perceived breathlessness and fatigue during the Exh test. A typical question (i.e., “I cannot easily exhale the air from my lungs”) was rated by using a 6-point rating scale, with 0 standing for “not at all” and 5 standing for “extreme.” The volunteers were not aware of their ongoing exercise time during the Exh tests.  

Statistical analyses. Before the study was begun, sample size estimations were performed by using predicted mean phase differences and SD on VO$_{2\text{peak}}$ and Exh time from previous studies (9, 34). A sample size of 10 provided a 70% probability of detecting a 2 ml·kg$^{-1}$·min$^{-1}$ increase in VO$_{2\text{peak}}$ and a 15-min increase in Exh time at the P < 0.05 level (11). Two-way ANOVAs with repeated measures on each factor were used to analyze the differences between menstrual cycle phase (early follicular and midluteal) and altitude (SL and AA) for all physiological parameters measured during the VO$_{2\text{peak}}$ and Exh test. Three-way ANOVAs, with repeated measures on the additional factor of time, were used for estradiol and progesterone analyses. Significant main effects and interactions were analyzed by using Tukey’s least significant difference test. Dependent one-way t-tests were used to analyze resting $V_{\text{E}}$ and ventilatory control at SL. Pearson product-moment correlation coefficients were calculated for relationships between levels of ovarian hormones, measures of ventilation (both physiological and psychological), and measures of exercise performance. Statistical significance was set at P < 0.05. All data are presented as means ± SD.  

RESULTS  

Volunteer test subjects. Body weights, energy intakes, and percent contributions of macronutrients were not different between testing sessions. Mean length of menstrual cycle was 28 ± 2 days during the 4 mo of testing, and ovulation occurred 14 ± 6 days after the onset of menstruation. Among subjects in the early follicular phase, resting estradiol levels ranged from 22 to 73 pg/ml while progesterone levels ranged from 0.2 to 1.1 ng/ml. Among subjects in the midluteal phase, resting estradiol levels ranged from 62–200 pg/ml while progesterone levels ranged from 5 to 27 ng/ml. Mean resting and exercise estradiol and progesterone levels, presented in Table 1, are within previously reported normal ranges for eumenorrheic women (26).  

Pulmonary function and resting $V_{\text{E}}$ and control. PFT results, presented in Table 2, are within previously reported normal ranges (33). The FVC, FEV$_1$, and MVV were not affected by cycle phase. The MVV was increased at AA compared with SL. Resting PET$_{\text{CO}}$ was decreased (P < 0.03) during SL/F (36.3 ± 1.7 Torr) compared with during SL/F (38.9 ± 2.3 Torr). Individual resting ventilatory responsiveness to the change in progesterone from SL/F to SL/L is presented in Fig. 1. The HVR-S during SL/F (0.50 ± 0.25) and SL/L (0.64 ± 0.33) were not different. Similarly, the HCVR-S values during SL/F (1.93 ± 0.98) and SL/L (2.11 ± 1.35) were not different. The HCVR-B was decreased (P = 0.08) during SL/F (38.9 ± 2.8) compared with during SL/F (41.3 ± 5.6). There were no correlations between estradiol, progesterone, or progesterone/estradiol levels and respective PET$_{\text{CO}}$, HVR-S, HCVR-S, or HCVR-B during SL/F or SL/L. When results from SL/F and SL/L were combined, there was a negative correlation (r = −0.56; P < 0.02) between progesterone and PET$_{\text{CO}}$, but...
Peak-exercise testing. Cardiopulmonary measurements collected during the VO2peak test are presented in Table 3. There were no cycle-phase differences in VO2peak at SL or AA, but VO2peak was decreased ~28% at AA compared with SL. The peak VE was not affected by cycle phase or altitude, but VE/VO2peak was increased ~39% at AA compared with SL in both phases. Similarly, VE/peak VCO2 was increased ~40% at AA compared with SL in both phases. The peak SaO2 was not affected by cycle phase at SL or AA, but it was decreased ~28% at AA compared with SL. Although there were no cycle phase differences at SL or AA, peak HR was decreased ~5% at AA compared with SL.

Percent utilization of MVV during peak exercise was not affected by cycle phase, but it was decreased (P < 0.05) at both AA/F (65 ± 6%) and AA/L (68 ± 10%) compared with SL/F (82 ± 21) and SL/L (75 ± 11). Peak RPE (19 ± 1) was the same in all conditions. There were no correlations between progesterone levels and respective measurements of peak VE, VE/VO2peak, VE/peak VCO2, or peak SaO2 in any of the four test conditions. Furthermore, none of the ventilatory measurements during peak exercise was correlated with respective VO2peak measurements in any of the four testing conditions. However, VO2peak was positively correlated with Exh time at SL/F (r = 0.75; P < 0.03), not between any of the other previously mentioned parameters (Fig. 1). There were positive correlations between HCVR and mean submaximal VCO2 during both SL/F (r = 0.57; P = 0.08) and SL/L (r = 0.63; P = 0.09).

Submaximal-exercise testing. Submaximal cardiopulmonary responses collected during the Exh test are presented in Table 4. The Exh time was not affected by cycle phase or altitude. Submaximal VO2 (VO2sub) was not affected by cycle phase, but it was decreased ~28% at AA compared with SL, because volunteers were exercising at 70% of their altitude-specific VO2peak (i.e., a lower power output at AA). The submaximal VE (VEsub), was not affected by cycle phase or altitude, but VE/VO2sub was increased ~33% during AA compared with SL. The submaximal SaO2 (SaO2sub) did not differ between cycle phases, but it was increased ~40% during AA compared with SL. The submaximal SaO2 (SaO2sub) was decreased ~22% in both phases during AA compared with SL and showed a cycle-phase difference, being 2.4% higher during AA/L compared with AA/F. Although there were no cycle-phase differences at SL or AA, submaximal HR (HRsub) was decreased ~7% during AA compared with SL.

Percent utilization of MVV during submaximal exercise was not affected by cycle phase but was decreased (P < 0.05) during AA/F (35 ± 6) and AA/L (37 ± 5) compared with SL/F (45 ± 11) and SL/L (46 ± 11).

Table 2. Pulmonary function test results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SL/F</th>
<th>SL/L</th>
<th>AA/F</th>
<th>AA/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, liters</td>
<td>4.20 ± 0.62</td>
<td>4.12 ± 0.51</td>
<td>4.13 ± 0.54</td>
<td>4.09 ± 0.65</td>
</tr>
<tr>
<td>FEV1, liters</td>
<td>3.23 ± 0.39</td>
<td>3.19 ± 0.31</td>
<td>3.30 ± 0.33</td>
<td>3.31 ± 0.39</td>
</tr>
<tr>
<td>MVV, l/min</td>
<td>131 ± 17</td>
<td>128 ± 17</td>
<td>154 ± 23</td>
<td>152 ± 20</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, 8 women. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; MVV, maximal voluntary Ve.

Table 3. Peak oxygen uptake and peak cardiopulmonary responses measured during an incremental peak exercise test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SL/F</th>
<th>SL/L</th>
<th>AA/F</th>
<th>AA/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2peak, ml·kg⁻¹·min⁻¹</td>
<td>46.8 ± 4.0</td>
<td>46.3 ± 5.6</td>
<td>33.3 ± 3.7</td>
<td>33.3 ± 3.7</td>
</tr>
<tr>
<td>VEpeak, l/min</td>
<td>107 ± 28</td>
<td>95 ± 11</td>
<td>100 ± 14</td>
<td>103 ± 14</td>
</tr>
<tr>
<td>VE/VO2peak</td>
<td>39 ± 9</td>
<td>36 ± 3</td>
<td>52 ± 4</td>
<td>53 ± 3</td>
</tr>
<tr>
<td>VE/peak VCO2</td>
<td>37 ± 7</td>
<td>33 ± 3</td>
<td>49 ± 4</td>
<td>50 ± 4</td>
</tr>
<tr>
<td>SaO2peak, %</td>
<td>94 ± 3</td>
<td>94 ± 3</td>
<td>68 ± 6</td>
<td>69 ± 3</td>
</tr>
<tr>
<td>HRpeak, beats/min</td>
<td>183 ± 8</td>
<td>183 ± 8</td>
<td>172 ± 8</td>
<td>176 ± 8</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, 8 women. VO2peak, peak oxygen uptake; VEpeak, peak minute Ve; VE/VO2peak, peak ventilatory equivalent for oxygen; VE/peak VCO2, peak ventilatory equivalent for carbon dioxide; SaO2peak, peak arterial oxygen saturation; HRpeak, peak heart rate. *Significant difference from SL/F and SL/L, †from AA/F.

Fig. 1. Individual resting ventilatory responsiveness at sea level to change in progesterone levels from follicular (i.e., low progesterone, left) to luteal (i.e., high progesterone, right) conditions. PETCO2, end-tidal PCO2. Each symbol represents 1 subject in both the follicular and luteal phase of her menstrual cycle.
There were no correlations between progesterone levels and respective measurements of $V_e_{\text{sub}}$, $V_e/V_O_2_{\text{sub}}$, $V_e \cdot V_{CO_2}_{\text{sub}}$, or $S_a_{O_2}_{\text{sub}}$ in any of the four test conditions. Furthermore, none of the ventilatory measurements during submaximal exercise was correlated with respective Exh times in any of the four testing conditions. Perceptions of exertion and internal state during the Exh test are presented in Table 5. The RPE during submaximal exercise was similar in all four testing conditions. Although there were no cycle phase differences, ISQ-R was increased during AA compared with SL. The ISQ-F showed no cycle-phase or altitude differences. There were no correlations between RPEs during submaximal exercise and respective Exh times in any of the four conditions. Both ISQ-R and ISQ-F were negatively correlated (range: −0.66 to −0.95; P < 0.05) with their respective Exh times in each of the four testing conditions.

**DISCUSSION**

The principal findings of this study are that, despite significantly increased progesterone levels in the midluteal phase, exercise $V_e$ was not increased at SL or AA. Furthermore, neither maximal nor submaximal exercise performance was affected by menstrual cycle phase at SL or during an AA exposure. This study also found that resting $V_e$ was increased in the midluteal phase, but resting chemosensitivity was not affected by cycle phase at SL.

A critical aspect of this study was confirmation of appropriate differences in ovarian hormone levels when the early follicular and midluteal phases of the menstrual cycle are compared. Urinary LH-surge-predictor kits and past, as well as current, data on menstrual history were used to predict the different phases of the menstrual cycle. Data were accepted only if the subjects had normal length (i.e., 25- to 35-day) consistent menstrual cycles, exhibited an LH surge every menstrual cycle, and had resting estradiol and progesterone levels within previously accepted normal ranges (26). These criteria resulted in appropriate differences in ovarian-hormone levels between cycle phases.

Resting SL measures of $V_e$ were used in this study to establish the sensitivity of our instrumentation and to provide evidence that our subjects were normal, healthy women. The increase in resting $V_e$ (i.e., 2.7-Torr lower $P_{ETCO_2}$) in the midluteal phase was expected and consistent with the mean phase difference (i.e., 2.6-Torr lower $P_{ETCO_2}$) calculated from seven previous studies (18, 38, 41, 44–46, 51). Thus, our instrumentation was sensitive enough to detect small differences in resting $V_e$, and the results confirm the magnitude of cycle-phase differences in resting $V_e$ reported in other studies.

In this study, resting measurements of ventilatory control were made to provide potential explanations for any observed cycle phase differences in exercise $V_e$. Although progesterone levels were significantly increased in the midluteal phase, resting chemosensitivity was not altered by cycle phase at SL. Others have also reported that HVR and HCVR are not increased in the midluteal phase, despite increased resting $V_e$ (38, 45, 46). However, several studies have reported an increased HVR and HCVR in the midluteal phase (16, 17, 24, 41, 44, 52). In addition, one study reported an increased HVR but similar HCVR (51), whereas another study found the opposite results (15). In evaluation of these studies, serum measurements of estradiol and progesterone must be considered, because anovulatory cycles can occur even with consistent, normal-length menstrual cycles (48). However, even when only studies providing hormonal documentation are considered (15, 17, 24, 38, 41, 51, 52), the results remain equivocal.

Controversy regarding the effect of ovarian hormones on ventilatory chemosensitivity is probably due to 1) a wide range of estradiol and progesterone among subjects in the same study, as well as between studies, 2) individual responsiveness to a given ovarian hormone level, and 3) the relatively large within-subject, between-day variability inherent in measures of ventilatory chemosensitivity (40). There is a huge range, among subjects, in midluteal values (i.e., 6–9 days after LH surge) for estradiol (60–320 pg/ml) and progesterone (5–28 ng/ml) in a normal menstrual cycle (26). Thus it is difficult to compare the results from studies in which subjects had low mean values of estradiol and progesterone with results from studies in which subjects had high mean values of these ovarian hormones.

As shown in Fig. 1, there is also a large variation among women in ventilatory responsiveness to any given level of progesterone. Data from men and pregnant women also suggest a lack of correlation between progesterone levels and resting ventilatory responsiveness (5, 32, 35). Furthermore, medroxyprogesterone acetate, a synthetic progesterone with 15 times the progestational activity of progesterone, stimulates $V_e$ to the same degree as does progesterone on a gram-for-gram basis (47). All of this evidence suggests that perhaps target receptors for progesterone, rather than circulating progesterone levels, are critical for mediation of the resting ventilatory response. Because estradiol levels may be critical for inducing progesterone receptors (8, 36), we considered whether the level of estradiol or the progesterone-to-estradiol ratio was related to chemosensitivity, and we found no correlations. Thus differing results for HVR and HCVR between studies may have to do with whether the women...
studied were responders or nonresponders to circulating levels of estradiol and progesterone.

The large variability associated with measurements of HVR and HCVR (40) also makes comparisons between studies difficult. In our laboratory, the coefficients of variation for HCVR (42.7%) and HVR (62.9%) are large. Thus, if cycle-phase differences exist, large subject numbers are required to show significance. In the present study, there was no trend for either the HVR or HCVR slope to exhibit phase differences, but the lower HCVR intercept (P = 0.08) in the midluteal phase might have been significant if the numbers of subjects were increased. A definitive study employing a large number of subjects, accompanied by measurements made daily or every other day of both ovarian hormones and ventilatory control, is certainly warranted, given the current equivocal findings in the literature.

Although resting $V_{\varepsilon}$ was increased in the midluteal phase at SL, neither maximal nor submaximal exercise $V_{\varepsilon}$ was increased at either SL or AA. This finding agrees with the results of some studies (3, 13, 22, 27) but disagrees with others (15, 41, 52). In one study, an increase in maximal but not submaximal exercise $V_{\varepsilon}$ was reported in the midluteal phase (24). In a recent study that found an increased exercise $V_{\varepsilon}$ at both 55 and 85% $V_{O2max}$ in the midluteal phase, there was also a reported increase in $V_{O2}$ (52). Thus the increase in submaximal $V_{\varepsilon}$ in their study may have been secondary to the increased $V_{O2}$ and not to progesterone-mediated stimulation of $V_{\varepsilon}$. Alternatively, the discrepancy between the study of Williams and Krahrenbul (52) and the present study could be due to the fact that our mean progesterone values were comparable to their progesterone levels in the early luteal and late luteal phases, in which they found no increases in submaximal exercise $V_{\varepsilon}$. The overall lack of a correlation between progesterone levels and submaximal ventilatory measurements in any of our four test conditions suggests that additional factors, such as changes in central motor command and reflexes from the exercising limbs, may have a greater influence on exercise $V_{\varepsilon}$ than do endogenous levels of progesterone (49).

In other studies on women that report an increased exercise $V_{\varepsilon}$ in the midluteal phase an increased resting HCVR has typically been reported (15, 24, 41, 52). Previous studies in men have also shown that exercise $V_{\varepsilon}$ is positively correlated with resting HCVR (29, 30). We also found a positive correlation between HCVR-S and exercise $V_{\varepsilon}$ in both cycle phases. However, because there was no cycle-phase difference in HCVR-S in the present study, it was not surprising that exercise $V_{\varepsilon}$ was also not affected by cycle phase at SL or AA.

The lack of a cycle-phase effect on exercise $V_{\varepsilon}$ does not appear to be related to a mechanical limitation to $V_{\varepsilon}$ at SL or AA in the midluteal phase. In the present study, consistent with a previous report (10), there were no cycle-phase differences in the mechanics of breathing at SL or AA. Furthermore, even though MVV was increased at AA because of the reduced density of the air, the percent utilization of MVV during both peak and submaximal exercise at SL and AA was similar between phases of the menstrual cycle. Thus, in our study, there did not seem to be a mechanical limitation to $V_{\varepsilon}$ that would impair ovarian hormone-mediated increases in exercise $V_{\varepsilon}$.

Because there was no improvement in exercise $V_{\varepsilon}$ during submaximal exercise in the midluteal phase at AA, the 3% increase in $SaO2$ in the midluteal phase during the Exh test at AA was surprising. The $SaO2$ may not always track changes in $V_{\varepsilon}$ during exercise at altitude, as reported by Bender et al. (4). In the present study, there was also no correlation between exercise $V_{\varepsilon}$ and $SaO2$; this suggests that the elevated exercise $SaO2$ may reflect an improvement in pulmonary gas exchange. Alternatively, the 3% increase in $SaO2$ in the midluteal phase could reflect the 2% measurement error inherent in the pulse oximeter. However, any measurement error of the pulse oximeter should be randomly distributed, making it unlikely that it was the main reason for the observed difference in $SaO2$ between phases of the menstrual cycle.

Although submaximal exercise $SaO2$ was increased in the midluteal phase at AA, Exh time was not affected by cycle phase during an AA exposure. We had hypothesized that the improvement in $SaO2$ during AA in the midluteal phase would result in an increased arterial $O2$ content, $O2$ transport, and exercise performance at AA. However, the small increase in exercise $SaO2$ that was observed in the midluteal phase obviously was not large enough to affect submaximal exercise performance.

This study also confirms the findings of some that neither maximal (13, 15, 22, 31, 41) nor submaximal (9, 10, 13, 27, 31) exercise performance is affected by the phase of the menstrual cycle at SL, but the study also refutes the findings of others that have reported cycle-phase differences in submaximal exercise performance (24, 34). Reasons for discrepant findings between studies concerning submaximal exercise performance may have to do with 1) the fitness level of subjects (41), 2) the large variability associated with the measurement of endurance-exercise performance (23), and 3) varying submaximal intensities used to measure endurance-exercise performance (24, 34). In one study reporting an increased submaximal exercise performance in the midluteal phase (34), the significance was borderline (P = 0.06) with small subject numbers. In the other study (24), a 90% $V_{O2max}$ exercise-until-exhaustion test was used, which may not be an appropriate measurement of submaximal endurance capacity. In the present study, the variability for Exh time was larger than was anticipated on the basis of previous studies (9, 27, 34). Thus we cannot discount the probability of a type II error in our significance testing. However, there was absolutely no trend for Exh time to be increased in the midluteal phase at SL, and even if we had higher numbers of subjects, the results likely would have been the same. Thus our analysis suggests that menstrual cycle effects, if present, are small and do not significantly affect submaximal exercise performance at SL.

We also examined whether there was a relationship between the other variables measured and submaximal
exercise performance. The three variables most correlated with Exh time in all four testing conditions were ISQ-R, ISQ-F, and $V_{O2peak}$. (Table 5). The high negative correlation between ISQ-R and ISQ-F and Exh time suggests that perceptions of respiratory distress and fatigue have a strong relationship with Exh time. Schoene et al. (41) also suggested that a high degree of adverse respiratory sensations, which were experienced in the luteal phase, limited exercise performance in their low-altitude study. However, in our study, perceptions of respiratory distress (i.e., ISQ-R) and fatigue (i.e., ISQ-F) were not affected by cycle phase. Thus it was not surprising that Exh time was also not affected by cycle phase.

Surprisingly, RPE was not correlated to Exh time in any of the four testing conditions. This may be due to the fact that ISQ-F assesses perception of future events (i.e., “I think I can continue this exercise for 30 more min”), whereas the RPE assesses perception of fatigue at that moment in time. Furthermore, the ISQ-R isolates respiratory sensations, whereas the RPE evaluates whole-body fatigue. The high correlation between $V_{O2peak}$ and Exh time corresponds with the research of others that have shown that $V_{O2max}$ is highly positively correlated to ISQ-R, ISQ-F, and Exh time in all four testing conditions were ISQ-R, ISQ-F, and $V_{O2peak}$ (Table 5). The high negative correlation between ISQ-R and ISQ-F and Exh time suggests that perceptions of respiratory distress and fatigue have a strong relationship with Exh time. Schoene et al. (41) also suggested that a high degree of adverse respiratory sensations, which were experienced in the luteal phase, limited exercise performance in their low-altitude study. However, in our study, perceptions of respiratory distress (i.e., ISQ-R) and fatigue (i.e., ISQ-F) were not affected by cycle phase. Thus it was not surprising that Exh time was also not affected by cycle phase.

In summary, the present study found that, despite significantly increased progesterone levels in the mid-luteal phase, exercise $V_e$ was not increased at SL or AA. Moreover, neither maximal nor submaximal exercise performance was affected by cycle phase at SL or AA. This may have important implications for individuals whose work, athletic competition, or recreation schedules involve short-term exposures to altitude.

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