Women at altitude: ventilatory acclimatization at 4,300 m

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Women at altitude: ventilatory acclimatization at 4,300 m. J Appl Physiol 91: 1791–1799, 2001.—Women living at low altitudes or acclimatized to high altitudes have greater effective ventilation in the luteal (L) compared with follicular (F) menstrual cycle phase and compared with men. We hypothesized that ventilatory acclimatization to high altitude would occur more quickly and to a greater degree in L women in their L compared with women in their F menstrual cycle phase, and 2) in women compared with men. Studies were conducted on 22 eumenorrheic, unacclimatized, sea-level (SL) residents. Indexes of ventilatory acclimatization [resting ventilatory parameters, hypoxic ventilatory response, hypercapnic ventilatory response (HCVR)] were measured in 14 women in the F phase and in 8 other women in the L phase of their menstrual cycle, both at SL and again during a 12-day residence at 4,300 m. At SL only, ventilatory studies were also completed in both menstrual cycle phases in 12 subjects (i.e., within-subject comparison). In these subjects, SL alveolar ventilation (expressed as end-tidal PCO2) was greater in the L vs. F phase. Yet the comparison between L- and F-phase groups found similar levels of resting end-tidal PCO2, hypoxic ventilatory response parameter A, HCVR slope, and HCVR parameter B, both at SL and 4,300 m. Moreover, these indexes of ventilatory acclimatization were not significantly different from those previously measured in men. Thus female lowlanders rapidly ascending to 4,300 m in either the L or F menstrual cycle phase have similar levels of alveolar ventilation and a time course for ventilatory acclimatization that is nearly identical to that reported in male lowlanders.

Relative to the number of studies on men, few studies have specifically examined ventilatory adaptations to high altitude in women. Women living at low altitude or acclimatized to high altitudes have greater ventilation relative to carbon dioxide production [lower end-tidal PCO2 (PETCO2)] compared with men (1, 8, 13, 17, 42). This greater effective ventilation in women compared with men is even present in the follicular phase of the menstrual cycle when ovarian hormone levels are low (1). Furthermore, in normally menstruating women at low altitudes, resting ventilation is elevated in the midluteal phase compared with the follicular phase (3, 9–12, 19, 20, 23, 31, 34–37, 42, 44). Progesterone is primarily responsible for increasing ventilation in the luteal phase, although estradiol potentiates the ventilatory effects of progesterone (7, 31, 32, 38). The ovarian hormones increase ventilation by acting on receptor-mediated mechanisms at both central and peripheral sites (2, 7, 15, 32, 39). Progesterone increases carotid body sensitivity, and estradiol raises central nervous system translation of the carotid body signal into increased ventilation (15, 16). Furthermore, estradiol is also needed to induce progesterone receptors (7).

In women, however, menstrual cycle phase effects on hypoxic and hypercapnic ventilatory chemosensitivity are difficult to demonstrate. In eumenorrheic women, the hypoxic ventilatory response (HVR) was increased during the luteal compared with the follicular phase in three studies (34, 35, 42) but was unchanged in three other studies (3, 9, 31). Similarly, in 11 studies that made repeated measures of the hypercapnic ventilatory response (HCVR) throughout the menstrual cycle, six studies (9–11, 20, 34, 44) reported an increase in the slope of the HCVR in the luteal compared with the follicular phase, whereas five studies (3, 31, 36, 37, 42) found no change. The inconsistency of findings does not

VENTILATORY RESPONSES TO ENVIRONMENTAL hypoxia have been the subject of a great amount of scientific inquiry over the last 100 yr. Humans compensate for the decreased inspired PO2 of high altitude by a progressive, time-dependent increase in ventilation, termed ventilatory acclimatization (5). After rapid ascent to 4,300 m elevation, ventilation increases progressively during the first 6–8 days (30). An increase in carotid body sensitivity to hypoxia occurs with acclimatization and likely plays a key role in the acclimatization process (18, 40).

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appear to be related to the methods used to assess the HVR or HCVR or to the frequency at which these measures were made throughout the menstrual cycle. The absence of a clear increase in HVR and HCVR in the luteal phase of the menstrual cycle may be affected by the wide range of endogenous ovarian hormone levels common in the luteal phase (21) and the considerable inherent variability in these measures of ventilatory drive (33). In contrast, in women, the effect of ovarian hormones on the HVR is obvious when endogenous levels are high, as in pregnancy (24, 25), or absent after ovariectomy (32).

Gender may also influence the rate and magnitude of ventilatory acclimatization (1, 8, 13, 17, 42). Hannon (17) studied unacclimatized women lowlanders during their first 2 wk at 4,300 m and concluded that they achieved ventilatory acclimatization more rapidly than men did. This finding suggests that women may be predisposed to a more rapid ventilatory acclimatization response by virtue of their higher effective ventilation.

To our knowledge, no previous studies of female lowlanders have examined the influence of ovarian hormones on ventilatory acclimatization at high altitude. The presence of a ventilatory effect at sea level and the finding of increased ventilation compared with men suggest that there is the potential for the female ovarian hormones to modulate ventilatory acclimatization to high altitude. Therefore, we hypothesized that ventilatory acclimatization to high altitude would occur more quickly and to a greater degree in female lowlanders in their early-to-midluteal phase compared with female lowlanders in their follicular menstrual cycle phase, because of the ventilatory and stimulatory effects of the ovarian hormones in the luteal phase. Second, we hypothesized that, compared with male lowlanders at the same altitude, women would have higher resting effective ventilation and accelerated ventilatory acclimatization. To test these hypotheses, indexes of ventilatory acclimatization (resting ventilatory parameters and ventilatory chemosensitivity) were measured at sea level and throughout a 12-day residence at 4,300-m altitude in women either in their follicular or luteal phase of the menstrual cycle. To test possible gender effects, data on men were obtained from previously published studies at the same altitude (14, 27, 30).

METHODS

Subjects. Twenty-seven women volunteers participated in this study. Twenty-two subjects completed the ventilatory protocols at sea level and high altitude and had correspond- ing ovarian steroid hormone profiles and menstrual cycle histories that substantiated their normal menstrual cycle status. The subjects were nonsmoking, eumenorrheic, sea-level residents of average fitness. No volunteer had altitude exposure >1,500 m within the 6 mo before the study. The 22 women completing the study had a mean age of 22.5 ± 0.8 (SE) yr, weight of 65.6 ± 2.4 kg, height of 166.1 ± 1.2 cm, and a peak O$_2$ uptake ($\dot{V}$O$_2$) (cycle ergometry) of 39.5 ± 1.7 ml·kg$^{-1}$·min$^{-1}$. All subjects read and signed an informed consent approved by the Human Subjects Committees from the University of Colorado Health Sciences Center, Stanford University, and the US Army Surgeon General’s Human Use Review Committee.

Study design. This study used a between-group (follicular vs. luteal) with repeated-measures, within-group (sea level and 4,300 m) design in which the resting ventilation and ventilatory chemosensitivity of unacclimatized women were measured during either the follicular or luteal phase of their menstrual cycle at sea level and again at 4,300-m altitude. Because of logistical constraints, the study was conducted during the spring and summer of 1996 and 1998. In 1996, attempts were made to study 19 subjects at sea level in both their follicular and luteal phases. The sea-level experiments were conducted during two identical 12-day test periods separated by 1–8 wk, depending on personal schedule requirements. Volunteers were then divided into two groups, with one-half assigned to arrive at high altitude at the beginning of their follicular phase and the other group to arrive at the beginning of their luteal phase (see Menstrual cycle documentation). In 1998, eight subjects were studied during a single 12-day test period at sea level. In addition, because of difficulties in scheduling tests to coincide with the onset of the follicular and luteal phases, these subjects entered testing without specific regard to the status of their menstrual cycle phase. After sea-level testing was completed, analyses of serum progesterone and estradiol concentrations were used to confirm the menstrual cycle phase in which testing was performed. Attempts were then made to schedule subjects to commence their high-altitude tests in the same menstrual cycle phase in which they completed their sea-level testing. The same protocols, study personnel, and equipment were used during the 12-day test periods in 1996 and 1998.

All sea-level studies were conducted at facilities of the Palo Alto Veterans Affairs Health Care System, Palo Alto, CA (elevation 15 m, barometric pressure 748–762 Torr). Approximately 1–3 mo after completing the sea-level studies, volunteers were transported by airline to Colorado Springs, CO (elevation 1,850 m) and within a few hours by car to the 4,300-m summit of Pikes Peak (barometric pressure 458–464 Torr), where 12 days of studies were conducted in the US Army Pikes Peak Laboratory Facility. The subject’s day of arrival on the summit was designated as day 1 of the high-altitude study period. During the sea-level and altitude test phases, volunteers were maintained on a caffeine-free, controlled diet designed to maintain body weight and minimize the influence of changes in endogenous energy substrate availability during exercise testing. Subjects kept an activity log and strived to maintain a regular daily program of light-to-moderate-intensity exercise during both sea-level and altitude test phases.

Menstrual cycle documentation. A minimum of a 3-mo menstrual cycle history was documented by diary or by information provided by the subject before the start of testing. Each subject kept a menstrual cycle diary noting the dates of her menses, the duration of her menstrual cycle, and the day of detection of luteinizing hormone in her urine (OvuQuick ovulation prediction kit, Becton-Dickson, Rutherford, NJ). The follicular phase was defined as beginning with the first day of menses and lasting until detection of ovulation, at which time the luteal phase began. At sea level and high altitude, day 1 of a study period was the day after menses began or detection of ovulation. Blood samples for analysis of ovarian steroid hormones were obtained by venipuncture at sea level and high altitude on days 1, 3, 6, 9, 10, and 12. After all testing was completed, progesterone and estradiol serum concentrations were determined by RIA (Diagnostic Products Coat-A-Count kit) and/or chemilumines-
cent enzyme immunoassay (Diagnostic Products Immulite kits) and used in conjunction with each subject’s menstrual cycle diary to finalize menstrual cycle phase assignments. Women whose cycles were abnormal (hormone levels below detectable limits or consistently low) were classified as being in the follicular phase for the purpose of analyses, because low estradiol and progesterone concentrations are characteristics of the early follicular phase. Poststudy analysis of plasma progesterone and estradiol, along with menstrual cycle histories, revealed that 8 women were in their luteal phase and 14 were in their follicular phase on arrival and during the first 3–7 days at 4,300 m. Each of these subjects had sea-level studies in the corresponding cycle phase.

In the luteal-phase women compared with the follicular-phase women, the resting serum progesterone and estradiol concentrations (Table 1) were higher at sea level (+7.0 ng/ml, P = 0.001, 95% CI = 4.0–10.1 ng/ml progesterone; and +36.5 pg/ml, P = 0.014, 95% CI = 8.2–64.9 pg/ml estradiol) and on day 3 at high altitude (+5.3 ng/ml, P = 0.003, 95% CI = 2.0–8.6 ng/ml progesterone; and +48.5 pg/ml, P = 0.002, 95% CI = 19.9–76.6 pg/ml estradiol). By day 7 at high altitude, progesterone was still higher in the luteal group (+6.3 ng/ml, P = 0.004, 95% CI = 2.4–10.3 ng/ml), although estradiol was not (+12.0 pg/ml, P = 0.63, 95% CI = −40.8–64.8 pg/ml). The increased estradiol concentration in the follicular group of women by day 7 at high altitude is consistent with the subjects entering the late follicular phase. Between days 4 and 9 at 4,300 m, three follicular group subjects and five luteal group subjects transitioned to the other phase of their menstrual cycle. Within each group, residence at 4,300 m did not alter ovarian hormone levels compared with that in sea level.

Ventilatory studies. At both sea level and high altitude, ventilatory studies were normally performed before breakfast and always more than 2 h after a meal. At sea level, resting ventilation and ventilatory chemosensitivity studies (isocapnic HVR and HCVR) were measured on days 1 or 2 and 7 or 8 of each sea-level 12-day test period. Sea-level ventilatory studies were usually performed in the morning. At high altitude, resting ventilation studies were performed the afternoon of day 1 (2–3 h after arrival) and on the mornings of days 2, 3, 5, 7, and 12. The ventilatory chemosensitivity studies were conducted on the mornings of days 2, 7, and 12.

All ventilatory tests were performed with the volunteers resting in a seated position. The volunteer breathed through a low-resistance respiratory valve and breathing circuit connected to a computer-controlled, breath-by-breath metabolic measurement system (Vmax229, SensorMedics, Yorba Linda, CA). Resting ventilation tests measured breath-by-breath minute ventilation (Ve), VO2, carbon dioxide elimination, end-tidal PO2 (PETO2), and PETCO2. Simultaneously, arterial oxygen saturation (SaO2) and pulse rate were measured by finger pulse oximetry (Nellcor N-200). Resting ventilation tests were ~20 min in duration. Resting ventilatory parameters were obtained and mean values were calculated from the last 8–10 min of the session.

The HVR was measured by using a progressive isocapnic hypoxia protocol of 7–10 min in duration. Subjects accommodated to the breathing circuit on room air for 5 min before beginning the HVR test. At sea level, the test began with the subject breathing room air, whereas at high altitude the test was initiated with 1–2 min of breathing a fraction of inspired O2 of 0.36 to restore alveolar PO2 (PAO2) to sea-level values. In 1996, the inspired PO2 was slowly reduced by the addition of nitrogen to the circuit, and isocapnia was maintained by adding CO2 to the inspired gas. The target PETCO2 for isocap-
nia used values obtained during the baseline period on room air for the sea-level tests and the $P_{ETCO_2}$ during the last minute of the hyperoxia baseline period for the high-altitude tests. The HVR test was terminated when the $S_{ao_2}$ decreased to 75–80% (mean 78 ± 0.5%). In 1998, the progressive hypoxia was achieved by rebreathing from a spirometer with an initial volume of rebreathing gas equal to the subject’s forced vital capacity + 1 liter. With this rebreathing method, iso-capnia was maintained by selectively scrubbing CO$_2$ with barium hydroxide from the rebreathing circuit. These changes simplified the HVR protocol, did not alter the circuit’s airflow resistance or dead space volume, and produced identical results during head-to-head comparisons. Otherwise, the 1998 HVR protocol was identical to that of 1996.

Two HVR tests, separated by at least 10 min, were performed. If the two HVR measurements disagreed by >30%, a third HVR test was performed. All ventilatory parameters were averaged over 10 s. The HVR shape parameter $A$ was calculated (Sigma Plot 4.0, SPSS) by fitting the $V_e$ and $P_{ETCO_2}$ data to the following equation: $V_e = V_a + A/P_{ETCO_2} - 32$, where $V_a$ is the asymptote for $V_e$ obtained by extrapolation, and 32 is the $P_{ETCO_2}$ asymptote (41). The HVR is also reported as the slope ($HVR_S$; $\Delta V_e/\Delta S_{ao_2}$, in 1 min$^{-1} \cdot \%^{-1}$, where $\Delta$ is change) calculated using least squares regression. For each subject, the reported HVR is the average of the two HVR tests in closest agreement.

The HCVR was performed using the same equipment described above, configured as a rebreathing system, following the protocol described by Read (29). The volunteer breathed room air during the baseline period. After a stable $P_{ETCO_2}$ was attained, she rebreathed a gas mixture with an initial composition of 7% CO$_2$-balance O$_2$ for 4–5 min. One HCVR was performed during each test session. All ventilatory parameters were averaged over 10 breaths. The linear part of the curve relating $V_e$ to $P_{ETCO_2}$ was analyzed by using least squares regression to obtain the slope ($HCVR_S$; $\Delta V_e/\Delta P_{CO_2}$, in 1 min$^{-1} \cdot $Torr$^{-1}$) and x-axis intercept ($HCVR_B$: $P_{CO_2}$ in Torr).

Arterial blood gases. In the first year of this study, on day 10 at sea level and high altitude, resting arterial samples were drawn anaerobically from an indwelling radial artery catheter ~90 min after catheter insertion. Subjects were seated in a semirecumbent posture for ~60 min before the samples were collected. The samples were immediately placed on ice and analyzed within 30 min for arterial $P_O_2$, $P_{CO_2}$, $P_{ACO_2}$, and pH (pH$_{E}$) (ABL 300, Radiometer, Copenhagen, Denmark).

Statistical analysis. Differences between menstrual cycle phases were compared by a two-factor ANOVA (menstrual cycle phase and time at altitude) with repeated measures in both their follicular and luteal phases. Within-subject repeated measures (paired $t$-test) found lower $P_{ETCO_2}$, (37.1 ± 0.7 vs. 39.3 ± 0.7 Torr, $P = 0.005$, 95% CI = −3.8 to −0.7 Torr) in the luteal phase compared with their follicular-phase measurements, respectively. $P_{ACO_2}$, measured in nine of these subjects 1–2 days after the ventilatory measures, was also lower (39.2 ± 0.6 vs. 40.9 ± 0.7 Torr, $P = 0.027$, single-tailed $t$-test, 95% CI = −3.6–0.1 Torr) in the luteal phase compared with the follicular phase, respectively. Although HVR $A$ parameter and HCVR $S$ were not different between the follicular and luteal phases in these 12 women, the HCVR $B$ was lower (38.6 ± 1.3 vs. 40.6 ± 0.9 Torr, $P = 0.038$, 95% CI = −3.7 to −0.1 Torr) in the luteal compared with follicular phase, respectively.

Effect of altitude exposure on ventilation. Because there were no statistically significant differences between follicular and luteal groups at high altitude, the data were pooled. Resting $P_{ETCO_2}$ and $S_{ao_2}$ were significantly lower and $V_e$ was greater than at sea level in which they had arrived. Between days 4 and 7, two subjects in the follicular phase and one subject in the luteal phase transitioned to the other phase of their menstrual cycle (see Menstrual cycle documentation). Therefore, because of the decreasing number of subjects remaining within their respective menstrual cycle phase with time at 4,300 m, analysis of the possible effects of menstrual cycle phase on ventilatory acclimatization to altitude was limited to the first 7 days at high altitude and the corresponding menstrual cycle phase tests at sea level. As shown in Table 1, resting $V_{o_2}$, $S_{ao_2}$, and $V_e$ or $P_{ETCO_2}$, as an index of effective alveolar ventilation, were similar in the follicular- and luteal-phase groups at sea level and during the first 7 days at high altitude. The time course for the development of ventilatory acclimatization, expressed as the rate of decline in $P_{ETCO_2}$ per day ($P_{ETCO_2}$/day) relative to mean sea-level values, was not significantly different between menstrual cycle phases during the first 2 days (follicular: 3.6 ± 0.4 Torr $P_{ETCO_2}$/day; luteal: 3.2 ± 0.5 Torr $P_{ETCO_2}$/day) or 6 days (follicular: 1.5 ± 0.1 Torr $P_{ETCO_2}$/day; luteal: 1.4 ± 0.1 Torr $P_{ETCO_2}$/day) at high altitude. Similarly, the HVR $A$ parameter, HCVR $S$, and HCVR $B$ were not significantly different between the follicular and luteal groups at sea level or high altitude (Table 1). However, the power of the performed ANOVAs of these variables was <0.80. The only arterial blood-gas parameter that was significantly different between the two groups was the resting $P_{ACO_2}$ on day 10 at sea level. In five luteal-phase subjects with $P_{ACO_2}$ measurements, the $P_{ACO_2}$ was lower (~2.4 Torr, $P = 0.032$, 95% CI = −5.0–0.2 Torr) compared with nine follicular-phase subjects at sea level (38.8 ± 1.1 vs. 41.2 ± 0.70 Torr, luteal vs. follicular). Arterial blood gases were not measured in the first 7 days at high altitude. Overall, there were no statistically significant menstrual cycle phase effects on ventilatory acclimatization during the first 7 days of residence at 4,300 m.

Twelve subjects had sea-level studies performed in both their follicular and luteal phases. Within-subject repeated measures (paired $t$-test) found lower $P_{ETCO_2}$, (37.1 ± 0.7 vs. 39.3 ± 0.7 Torr, $P = 0.005$, 95% CI = −3.8 to −0.7 Torr) in the luteal phase compared with their follicular-phase measurements, respectively. $P_{ACO_2}$, measured in nine of these subjects 1–2 days after the ventilatory measures, was also lower (39.2 ± 0.6 vs. 40.9 ± 0.7 Torr, $P = 0.027$, single-tailed $t$-test, 95% CI = −3.6–0.1 Torr) in the luteal phase compared with the follicular phase, respectively. Although HVR $A$ parameter and HCVR $S$ were not different between the follicular and luteal phases in these 12 women, the HCVR $B$ was lower (38.6 ± 1.3 vs. 40.6 ± 0.9 Torr, $P = 0.038$, 95% CI = −3.7 to −0.1 Torr) in the luteal compared with follicular phase, respectively.

Comparison between menstrual cycle phases. During the first 7 days of altitude exposure, 19 subjects remained within the same phase of their menstrual cycle
within a few hours of arrival at 4,300 m (Table 2). As indicated by the decreasing PETCO2, ventilation continued to increase (P < 0.001) throughout the 12 days of high-altitude residence, although the change between days 7 and 12 was not statistically significant. SaO2 increased (P < 0.05) rapidly during the first 5 days, with no significant change thereafter. On day 10, resting PaCO2, pHa, and SaO2 (28.9 ± 0.6 Torr, 7.446 ± 0.005, and 51.0 ± 1.2 Torr, respectively) were significantly different (P < 0.001) compared with sea-level day 9 (40.4 ± 0.6 Torr, 7.415 ± 0.005, and 107.4 ± 2.8 Torr, respectively). The HVR A parameter and HCVR S were not increased on day 2 but were higher (P < 0.05) by day 7, with no further increase noted on day 12 (Table 2). However, the HCVR B decreased (P < 0.05) from sea-level values on day 2 and continued to fall to day 12. There were no statistically significant changes in resting VO2 between sea level (0.231 ± 0.011 l/min) and any day at high altitude. There were no statistically significant correlations observed between the subjects’ ovarian hormone concentrations or estrogen-to-progesterone ratio and resting PETCO2, HVR A parameter, HCVR S, and HCVR B at sea level or any day at altitude.

At both sea level and high altitude, there was a wide distribution in PETCO2, ranging from 34.3 to 42.2 Torr at sea level. There was a similar spread of ~10 Torr between the minimum and maximum PETCO2 at all days at high altitude. The PETCO2 measured on all days at high altitude was positively correlated with the preascent normoxic PETCO2 at sea level (Table 3) when measured within the same menstrual cycle phase. In the women with sea-level resting PETCO2 measures in both menstrual cycle phases, the correlation with high-altitude PETCO2 was greater when comparisons were confined to a given cycle phase than when comparisons were conducted between cycle phases (Table 4). Additionally, we found significant correlations (range: r = −0.49 to −0.65) between sea-level PETCO2 and resting SaO2 throughout the period of high-altitude exposure. No correlations were found between the sea-level HVR A parameter and any ventilatory measurement at high altitude.

Gender comparisons. Plotted in Fig. 1 are the resting PETCO2 for 37 men at sea level and 4,300 m from Ref. 30 and for the 22 women in the present study. At sea level, resting PETCO2 was lower (P < 0.001, 95% CI = −4.9 to −1.9 Torr) in the women compared with the men. However, at 4,300 m the women’s resting PETCO2 values were not statistically different. Similarly, there were no significant differences in resting SaO2 between the genders throughout the altitude exposure (30). Furthermore, the women’s resting PaO2 and pHa measured on day 10 (see above) did not differ from those reported in five men (14) after 10 or 11 days’ residence at 4,300 m (48.2 ± 1.2 Torr and 7.449 ± 0.006, respectively). However, in the men, resting PaO2 (25.2 ± 0.85 Torr) was lower (P = 0.003, 95% CI = 1.44–6.01 Torr) compared with that in the

Table 3. Relationship (y = ax + b) of preascent normoxic PETCO2 with high-altitude (4,300 m) PETCO2 values

<table>
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<tr>
<th>Day</th>
<th>a</th>
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<th>r</th>
<th>n</th>
<th>P</th>
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<tr>
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<tr>
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<td>6.6</td>
<td>0.65</td>
<td>22</td>
<td>0.003</td>
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</tbody>
</table>

Sea-level resting PETCO2 was measured in same menstrual cycle phase as subject’s ascent phase. n, no. of subjects.

Table 4. Effect of sea level menstrual cycle phase on relationship (y = ax + b) of preascent normoxic PETCO2 with high-altitude (4,300 m) PETCO2 values

<table>
<thead>
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<th>Days at 4,300 m</th>
<th>Within-Cycle Phase</th>
<th>Opposite-Cycle Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
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</tr>
<tr>
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<td>0.012</td>
</tr>
<tr>
<td>3</td>
<td>0.69</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Subject’s preascent sea-level normoxic PETCO2 was measured once within same menstrual cycle phase of subsequent altitude exposure and once in opposite cycle phase. n, no. of subjects.
There are several possible explanations for our findings. First, we have to consider the limitations of our experimental design. The best experimental design to address our hypothesis would have been a crossover design in which each subject would have gone to altitude twice, once in each phase of their menstrual cycle. However, this design would have required a period of 3–6 mo for deacclimatization between altitude sojourns. Given the limited seasonal access to the Pikes Peak laboratory, a crossover design would have necessitated that each subject maintain adherence to the protocol for ~18 mo. Because of this and other resource limitations, we had to use a between-groups (cross-sectional) design. Thus, we may not have observed significant menstrual cycle effects on ventilation because of an inadequate sample size. Based on the previously cited literature, the within-subject, between-phase mean resting PETCO2 difference is ~2.6 Torr. Prestudy, we expected a similar mean resting PETCO2 difference between our luteal and follicular groups. Thus, with the use of a standard deviation of 2.4 Torr (31), the calculated sample size to obtain a power >0.80 was 14 subjects for each group. As noted in METHODS, we started with 27 volunteers. However, because of subject withdrawal and several abnormal ovarian hormone profiles, the luteal group lost several subjects, and poststudy the power of the performed ANOVA of resting PETCO2 between the luteal and follicular groups was only 0.11. Except for the between-groups difference in PaCO2 at sea level, our data are absent of even a trend of a difference between the luteal and follicular groups that would be consistent with our hypothesis. Because the interindivudal range of resting PETCO2 was ~10 Torr within either phase of the menstrual cycle, we attempted to minimize between-subject variability by normalizing individual PETCO2 data (not presented) to sea-level resting PETCO2. However, even the normalized data did not reveal any significant differences in the ventilatory acclimatization response between the follicular and luteal groups. Recently, Loeppky et al. (22) reported that women had greater ventilation (i.e., lower PaCO2) in the luteal compared with follicular menstrual cycle phase at their baseline altitude (~1,646 m) and during 12-h exposure to 4,880 m in a hypobaric chamber. However, the ventilatory difference between the luteal and follicular phases decreased and was not statistically different by the 12th h of altitude exposure (22). This latter finding, as well as ours, suggests that the sustained exposure to hypoxia induces time-dependent changes in ventilatory control that attenuate ovarian hormonal stimulatory effects on ventilation.

Contributing to the absence of a significant menstrual cycle phase effect on ventilatory acclimatization may have been a lack of consistency in when the luteal-phase subjects were studied within their cycle, particularly at high altitude. After ovulation, the time course and magnitude of the normal rise and decline in serum progesterone are quite variable (21). Furthermore, not only are circulating ovarian hormone concentrations important but also progesterone receptor
number and their distribution are likely important (7, 16). We do not know what the receptor populations were in our subjects. However, given that all subjects experienced normal cycles, the receptor populations were likely to have been in the normal range. Although attempts were made to test the subjects in their early- to midluteal phase when progesterone concentrations were likely to be greatest, poststudy analyses of plasma progesterone and estradiol samples suggest that sea-level and high-altitude test days did not always coincide with the subjects’ early- to midluteal phase. In fact, five of eight luteal-phase subjects entered their follicular phase after 5–9 days at high altitude, suggesting that they arrived at 4,300 m in their midluteal rather than early luteal phase. Although serum ovarian hormone concentrations were within accepted clinical limits for normally menstruating women in their luteal phase, the large interindividual variation and lack of concurrence between our subjects’ peak ovarian hormone levels and our ventilatory measures may have obscured the ventilatory stimulus effects. However, similar to prior studies (3, 6, 25, 28), we did not find a correlation between progesterone levels and any measure of resting ventilation or chemoresponsiveness at sea level or 4,300 m. On the other hand, at sea level, we measured a within-subject mean resting PETCO2 difference of 2.2 Torr between the luteal and follicular phases. That observation verifies that the timing and sensitivity of our ventilatory tests were appropriate for measuring menstrual cycle phase differences on resting ventilation and that our subjects exhibited menstrual cycle phase effects on ventilation that were consistent with previous reports (3, 9–12, 20, 23, 31, 34–37, 42).

Inhibitory influences of hypocapnia on the HVR may have suppressed ovarian hormone augmentation of ventilatory acclimatization in the luteal-phase women. On arrival at high altitude, hypocapnia and sustained hypoxia blunt the ventilatory response to the hypobaric hypoxic environment (18). By decreasing central chemoreceptor drive, the hypocapnia may also blunt the stimulant effects of the ovarian hormones on the HVR. At low altitudes, hypocapnia may have contributed to the absence of a clear increase in HVR in the luteal phase of the menstrual cycle (3, 9, 31, 34, 35, 42). Similarly, in studies in which synthetic progestins (medroxyprogesterone acetate) were administered, an increase in HVR was reported in only three of five studies (6, 26, 31, 32, 45) and then only when measured at the higher PETCO2 present before medroxyprogesterone acetate administration (26, 32, 45). These observations underscore the influence of central chemoreceptor ventilatory drive on the HVR. We did not standardize our measurement of HVR at the same level of central drive for either menstrual cycle phase or elevation (sea level and 4,300 m). Therefore, it is likely that our measurements of HVR are not accurate representations of ovarian hormonal and chronic hypoxic exposure influences on peripheral chemoreceptor sensitivity. Thus the lack of a menstrual cycle phase effect on the HVR at sea level or 4,300 m does not negate the possibility that carotid body activity was increased in the luteal phase in our subjects. Rather, our measurements of HVR reflect the integrated responses of the respiratory controller to the prevailing ovarian hormonal and acid-base milieu. Because women ascending to high altitudes do so under poikilocapnic conditions, our results suggest that menstrual cycle phase influences on ventilation may not be of practical consequence in acclimatizing female lowlanders.

Interindividual differences in ventilation at sea level were more important than menstrual cycle phase in determining subsequent ventilation at high altitude. Sea-level normoxic resting PETCO2 was related significantly to that at altitude on all days measured. These results in women agree with those previously reported (30) for men at the same altitude and location. The correlations were highest using sea-level resting PETCO2 values obtained in the same menstrual cycle phase that the subject was in at altitude. This observation suggests that menstrual cycle phase effects on ventilation contribute to the interindividual differences in resting PETCO2 at sea level and high altitude.

Previous studies of women and men residing at high altitude report greater overall ventilation in women than men (8, 13, 17, 22). In one earlier study on Pikes Peak, female lowlanders had a higher level of effective ventilation (i.e., lower resting Paco2 and higher PaO2) during the first 14 days of residence at 4,300 m than did male lowlanders (17). Because we had previously studied the ventilatory acclimatization response in male lowlanders residing in our Pikes Peak laboratory (27, 30, 43), we designed our studies in women to be similar to the studies of these men. As expected (42), at sea level, resting PETCO2 was lower in the women compared with the men. However, during the nearly 2 wk of high-altitude residence, the women’s and men’s resting PETCO2 values were remarkably similar (Fig. 1).

Furthermore, other indexes of ventilatory acclimatization (SaO2, HVR, HCVR) were not significantly different from those previously measured in men (27, 30, 43). Although the women’s resting PaO2 and pH measured on day 10 did not differ from those reported in men (14) after 10–11 days of residence at 4,300 m, the men’s Paco2 values were significantly lower than our women’s values, suggesting greater alveolar ventilation in the men. Thus our findings do not agree with the lowlander gender comparisons reported by Hannon (17) at the same high-altitude location. The reason for this difference is unclear. We relied mainly on comparisons of PETCO2 values to arrive at our conclusion that ventilatory acclimatization follows a similar magnitude and time course in women and men at 4,300 m. On the other hand, Hannon reported differences in arterial blood gases. Interestingly, his reported Paco2 values are higher than the corresponding PaO2 values at high altitude in his subjects. This inconsistency between his arterial and alveolar gas composition data suggests a possible methodological error that may explain the lack of agreement with our results.

The lack of a gender difference in the magnitude and rate of ventilatory acclimatization may be due to lower
ventilatory chemosensitivity in women relative to men. White et al. (42) reported that normally menstruating women had a lower HVR than men. Similarly, our women's sea-level isocapnic HVR is lower than reported for men residing at sea level (30). The close correlation between sea-level isocapnic HVR and subsequent ventilation at high altitude (18, 30), a lower HVR in women may predispose them to a smaller increase in effective alveolar ventilation during the initial weeks of hypobaric hypoxic exposure. Although our results suggest that women do not acclimatize at a rate or magnitude greater than men do, the previous studies (8, 13, 22) of altitude-acclimatized women showing higher effective alveolar ventilation than men imply that eventually women reestablish their higher levels of alveolar ventilation. Bender et al. (4) found that ventilatory acclimatization in men was complete by day 8 at 4,300 m. Our results in women are essentially similar, in so far as resting PeTCO₂ did not change significantly after day 7, although there was a 1.7-Torr decline from days 7 to 12 (Table 2). Over 78 days at 4,300 m, resting PΑO₂ rose ~4 Torr from days 14 to 78 (17), suggesting that ventilatory acclimatization may continue in women for a longer period of time than in men. This would reconcile our conclusion that there is no gender effect during the initial weeks of ventilatory acclimatization to high altitude with previous reports (8, 13) of greater effective ventilation in women compared with men after longer term residence at high altitude.

In summary, the data from this cross-sectional study do not support the view that ventilatory acclimatization to high altitude will occur more quickly and to a greater degree in women in their early-to-midluteal phase compared with women in their follicular phase. Independent of menstrual cycle phase, women demonstrated a wide range of interindividual differences in ventilation at sea level and high altitude, and the differences at altitude were related to those present before ascent. Finally, we conclude that female lowlanders rapidly ascending to 4,300 m have similar levels of alveolar ventilation and follow a time course for ventilatory acclimatization that is nearly identical to that reported in male lowlanders under similar ascent conditions.

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REFERENCES


8. Cudkowicz L, Spielvogel H, and Zubigeta G. Respiratory studies in women at high altitude (3,600 m or 12,200 ft and 5,200 m or 17,200 ft). Respiration 29: 393–426, 1972.


