Relationship of ovarian hormones to hypoxemia in women residents of 4,300 m

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Léon-Velarde, F. M. Rivera-Chira, R. Tapia, L. Huicho, and C. Monge-C. Relationship of ovarian hormones to hypoxemia in women residents of 4,300 m. Am J Physiol Regulatory Integrative Comp Physiol 280: R488–R493, 2001.—Prevalence of excessive erythrocytosis, the main sign of chronic mountain sickness (CMS), is greater in postmenopausal Andean women than in premenopausal women. It is uncertain whether this greater prevalence is related to the decline in female hormones and ventilatory function after the occurrence of the menopause. To study this, we compared the physiological variables involved in the physiopathology of CMS [end-tidal CO2 (PETCO2, Torr) and end-tidal O2 (PETO2, Torr), arterial oxygen saturation (SaO2, %), and Hb concentration (g/dl)] and progesterone and estradiol levels between postmenopausal and premenopausal women, both in the luteal and follicular phases. Women residing in Cerro de Pasco (n = 33; 4,300 m) aged 26–62 yr were studied. Postmenopausal women compared with premenopausal women in the luteal phase had lower PETCO2 (48 ± 4 vs. 53 ± 2 Torr, P < 0.005) and SaO2 levels (82 ± 12 vs. 88 ± 12%, P < 0.005) and higher PETO2 (34 ± 2 vs. 29 ± 3 Torr, P < 0.005) and Hb concentration (19 ± 1 vs. 14 ± 2 g/dl, P < 0.005). In addition, plasma progesterone was negatively correlated with PETCO2, and positively correlated with PETO2 and SaO2. No clear relationship was found among the cycle phases between estradiol and the variables studied. In conclusion, our results reveal that, before menopause, there is better oxygenation and lower Hb levels in women long residing at altitude, and this is associated with higher levels of progesterone in the luteal phase of the cycle.

menopause; chronic mountain sickness; end-tidal oxygen pressure; end-tidal carbon dioxide pressure; polycythemia; oxygen saturation

Hypoventilation is commonly regarded as the primary cause of chronic mountain sickness (CMS, Monge’s disease), which occurs as a consequence of the loss of acclimatization or due to the incapability of subjects to completely acclimate to residence at high altitude (5, 8, 11, 34, 37). After the hypoventilation has been established, the logical physiopathological sequence that follows is: hypoxemia [low oxygen saturation (SaO2)], excessive erythrocytosis, and, as a consequence, the signs and symptoms of the disease (12, 19). Excessive erythrocytosis, defined as a disproportionately high (more than 2 SD) Hb concentration and hematocrit for the particular altitude of residence, is the outstanding diagnostic feature of CMS (14). Our studies have shown that the prevalence of CMS increases with advancing age, both in men and women (13, 16), and that this increase is associated with age-related declines in ventilation, peak expiratory flow, and SaO2 (13, 19, 29, 36). Blood oxygen desaturation produced during sleep at high altitude, particularly during sleep-disordered breathing, has been considered an additional factor that contributes to excessive erythrocytosis (10, 23). However, although these changes occur uniformly with age in men, women demonstrate a pronounced change at the time of menopause (16). This finding suggests the important role of menopause, and particularly of progesterone, in the susceptibility to develop CMS. Progesterone has been shown to raise ventilation and chemosensory responsiveness in humans and in experimental animals (26, 32, 33). The administration of exogenous progesterone increases ventilation in both women and men (25, 30). In addition, progesterone administration has been shown to reduce the duration and severity of sleep-disordered breathing in some cases of hypoventilation syndromes (17, 31). All of this information suggests that the ventilatory stimulus effects of the ovarian hormones may be increasing resting ventilation in Andean women. However, no studies have examined if there is a relation between the decline in the ovarian hormones after menopause and the degree of hypoxemia in women residing at high altitude. We hypothesized that the predisposition of postmenopausal high-altitude women to develop excessive erythrocytosis (16) could be due to an increased hypoxemia, related to a decreased concentration of female hormones.

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MATERIAL AND METHODS

Subjects. Amerindian women residing in Cerro de Pasco (Perú; 4,300 m, 460 Torr) participated in this study. Informed consent was obtained from the subjects, and the study was approved by the Ethics Committee of the Scientific Research Office of Cayetano Heredia University. This city has a population of ~75,000 inhabitants, 87% of whom were born at 4,300 m (12). All subjects were residing at Cerro de Pasco for more than 10 years. The women who were selected for study were either premenopausal (regular menstrual cycles from 26 to 30 days length; n = 17) or postmenopausal (menstrual cycle has stopped at least 1 yr before the beginning of the study; n = 17). Premenopausal women were divided into subjects in the follicular phase and in the luteal phase after the hormone measurements had been completed. Women whose progesterone levels were lowest were considered to be in the follicular phase, and women whose progesterone levels were highest were considered to be in the luteal phase. The first day of the menstrual cycle was used as a supplementary indicator. Additional inclusion criteria were that women were between the ages of 26 and 62, were not taking contraceptives, did not smoke, and had not visited sea level on more than two occasions during the previous year or within 3 mo of the study. Women were examined by a local physician, and those with a history of cardiovascular, respiratory, or renal disease were excluded from the study.

Measurements. After the woman had rested for 15 min, end-tidal \( \text{O}_2 \) (\( \text{P}_{\text{ETO}_2} \)) and \( \text{CO}_2 \) (\( \text{P}_{\text{ETCO}_2} \)) pressures (Torr) were determined with the subject in a sitting position. Respiratory gases were sampled using a fine catheter taped just inside one nostril. The respiratory gases were analyzed continuously through a gas analyzer (Normocap 200 Oxy, no. CD2–02–21–00; Datex) from which the end-tidal values were detected using the algorithm incorporated in the instrument. Each measurement lasted ~30 min, and a minimum of 15 end-tidal values was recorded after the subject was calm and quiet. The respiratory coefficient (RQ) associated with the obtained end-tidal values was calculated as recommended by West (35) using the percentage values of \( \text{CO}_2 \) and \( \text{O}_2 \) (Normocap) to determine the respective alveolar fractions. The values with an RQ >0.9 or <0.75 were discarded, since these were likely to indicate the presence of hyperventilation or hypoventilation. After the measurements of the respiratory gases, subjects were allowed to rest in a quiet and temperate room (18°C) for 30 min. Blood \( \text{SaO}_2 \) (%) and pulse frequency were measured three times for each woman in the sitting position using a Nellcor pulse-oxymeter attached to the forefinger. Blood was drawn from an antecubital vein for Hb and hormone estimation. Blood was allowed to clot, and serum was separated by centrifugation. Serum samples were kept refrigerated at 4°C and were transported to Lima (sea level) where progesterone (ng/ml) and estradiol (µg/ml) blood concentrations were determined in duplicate by RIA techniques (diagnostic biochemical sensitivity: progesterone, 0.1 ng/ml; estradiol, 5 pg/ml). \( \text{Hb} \) concentration (g/dl) was measured by spectrophotometry using a B-Hb photometer (Hemocue no. US 8847–0029). Mean blood pressure was also determined [diastolic + (systolic – diastolic)/3] using a sphygmomanometer. All of the evaluations on a given woman were completed on a single day.

Data analysis. The premenopausal vs. postmenopausal women and the follicular vs. luteal phases within the premenopausal group were compared using one-way ANOVA with Tukey’s test for post hoc comparisons. All of the variables demonstrated homogeneous variance at 95% confidence limits by the Levene’s test. In addition to these analyses, progesterone concentrations were log transformed before assessing their relationship with other variables by means of regression analysis. We used log progesterone figures because progesterone concentrations in the follicular phase and postmenopausal women were distributed in a very condensed range of values (0.15–0.75 ng/ml) when compared with progesterone concentrations in the total sample (0.15–17 ng/ml). Comparisons were considered statistically significant when \( P \) was <0.05.

RESULTS

A total of 33 female volunteers was identified as suitable for inclusion in the study. Sixteen were premenopausal women: 8 were in the follicular phase, and 8 were in the luteal phase. Seventeen women were postmenopausal. Results are summarized in Table 1. Premenopausal women in the luteal phase showed higher \( \text{P}_{\text{ETO}_2} \) (\( P < 0.005 \)), lower \( \text{P}_{\text{ETCO}_2} \) (\( P < 0.005 \)), higher \( \text{SaO}_2 \) values (\( P < 0.005 \)), and lower \( \text{Hb} \) concentration (\( P < 0.005 \)) than postmenopausal women. Premenopausal women in the luteal phase also showed higher \( \text{P}_{\text{ETO}_2} \) (\( P < 0.05 \)), lower \( \text{P}_{\text{ETCO}_2} \) (\( P < 0.05 \)), higher \( \text{SaO}_2 \) values (\( P < 0.05 \)), and lower \( \text{Hb} \) concentration (\( P < 0.005 \)) compared with postmenopausal women in the follicular phase. Postmenopausal women showed closer values to those found in premenopausal women in the follicular phase. However, they still presented lower values of \( \text{P}_{\text{ETO}_2} \) (\( P < 0.05 \)) and \( \text{SaO}_2 \) (\( P < 0.05 \)) and higher \( \text{Hb} \) concentration (\( P < 0.005 \)), but with similar values of \( \text{P}_{\text{ETCO}_2} \).

Figure 1 shows that log plasma progesterone and \( \text{P}_{\text{ETCO}_2} \) of pre- and postmenopausal women showed a negative relationship (\( \text{P}_{\text{ETCO}_2} = -2.7 \) log progesterone + 32.3, \( r = 0.6; P < 0.0001 \)). It also shows the inverse situation (\( \text{P}_{\text{ETO}_2} = 2.7 \) log progesterone + 50.7, \( r = 0.53; P < 0.001 \)). \( \text{SaO}_2 \) shows a positive rela-

Table 1. Physiological parameters measured in pre- and postmenopausal women

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age, yr</th>
<th>Wt, kg</th>
<th>PR, beats/min</th>
<th>MBP, mmHg</th>
<th>( \text{P}_{\text{ETO}_2} ), Torr</th>
<th>( \text{P}_{\text{ETCO}_2} ), Torr</th>
<th>( \text{SaO}_2 ), %</th>
<th>Hb, g/dl</th>
<th>Progesterone, ng/ml</th>
<th>Estradiol, µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopause</td>
<td>16</td>
<td>35 ± 7.11</td>
<td>57 ± 8.68</td>
<td>73 ± 7.60</td>
<td>67 ± 11.15</td>
<td>52 ± 2.29</td>
<td>31 ± 2.12</td>
<td>87 ± 2.39</td>
<td>16 ± 2.16</td>
<td>3.2 ± 4.59</td>
<td>78 ± 38.9</td>
</tr>
<tr>
<td>Follicular phase</td>
<td>8</td>
<td>37 ± 8.45</td>
<td>62 ± 9.85</td>
<td>77 ± 5.93</td>
<td>55 ± 11.95</td>
<td>51 ± 2.30</td>
<td>33 ± 2.18</td>
<td>55 ± 3.04</td>
<td>17 ± 1.38</td>
<td>0.6 ± 0.31</td>
<td>75 ± 43.6</td>
</tr>
<tr>
<td>Luteal phase</td>
<td>8</td>
<td>33 ± 5.18</td>
<td>52 ± 7.21</td>
<td>73 ± 9.24</td>
<td>51 ± 7.07</td>
<td>53 ± 2.31</td>
<td>29 ± 2.94</td>
<td>88 ± 1.52</td>
<td>14 ± 2.56</td>
<td>5.69</td>
<td>4.74</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>17</td>
<td>44 ± 4.00</td>
<td>57 ± 6.64</td>
<td>77 ± 9.97</td>
<td>60 ± 10.35</td>
<td>48 ± 3.37</td>
<td>34 ± 2.25</td>
<td>82 ± 2.48</td>
<td>19 ± 1.37</td>
<td>0.2 ± 0.04</td>
<td>7.5 ± 5.76</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of women in each group. PR, pulse rate; MBP, mean blood pressure; \( \text{P}_{\text{ETO}_2} \), end-tidal \( \text{O}_2 \) pressure; \( \text{P}_{\text{ETCO}_2} \), end-tidal \( \text{CO}_2 \) pressure; \( \text{SaO}_2 \), blood oxygen saturation. †\( P < 0.05 \) and ‡\( P < 0.005 \) for comparison with the postmenopause group. ††\( P < 0.05 \) and †‡\( P < 0.005 \) for comparison of premenopause follicular vs. premenopause luteal women.
tionship with log progesterone concentration, likely as a consequence of the decreased ventilation (as suggested by the low \( \text{PETCO}_2 \)) with decreasing values of progesterone concentration \( (\text{SaO}_2 = 2.8 \log \text{progesterone} + 85.3, r = 0.5; P < 0.005) \). Coincidently, postmenopausal women show higher Hb concentrations than premenopausal women, particularly when compared with premenopausal women in the luteal phase. Figure 2 shows the individual values of Hb for these groups (follicular phase, \( P < 0.05 \); luteal phase, \( P < 0.005 \)). No clear relationship has been found in estradiol concentration among the cycle phases and the variables studied (Fig. 3).

**DISCUSSION**

Hormonal influences at high altitude, not only because of the gender differences but also because of the rise in Hb after menopause, have been suspected by our group (16) and by other researchers (33). The respiratory, hematomal function, and hormone levels in women native to high altitude have been studied also (6, 21, 27, 28). It has been shown that, on average, estradiol level is higher at high altitude than at sea level, but it changes throughout the cycle phases, and progesterone concentration at days 5 and 8–12 is lower at high altitude than at sea level (6). Yet, this is the first study to show the relationship of the hormones to breathing and to Hb level on the phases of the cycle and to associate these findings with CMS. Our results show that high-altitude postmenopausal women compared with premenopausal women in the luteal phase had lower \( \text{PETO}_2 \) and \( \text{SaO}_2 \) levels and higher \( \text{PETCO}_2 \) and Hb concentration. In addition, plasma progesterone is negatively correlated with \( \text{PETCO}_2 \) and positively correlated with \( \text{PETO}_2 \) and \( \text{SaO}_2 \). This is an indication that, after menopause, oxygenation is impaired in women long residing at altitude, and this seems to be associated with lower levels of progesterone. This study also suggests that, during their reproductive life, postmenopausal women may be protected from hypoxia, particularly during the luteal phase. This is evidenced by the lower \( \text{PETO}_2 \) and \( \text{SaO}_2 \) values associated with the follicular phase and higher \( \text{PETO}_2 \) and \( \text{SaO}_2 \) values associated with the luteal phase. The cyclic hormonal and respiratory pattern that is repeatedly present during the whole premenopausal period of life may explain, at least in part, why excessive erythrocytosis in women is less frequently described than in men. Higher progesterone levels during the luteal phase in premenopausal women would act to increase ventilation and arterial PO\(_2\), which, in turn, will act to decrease the hematopoietic stimulus. In our study, the progesterone level of women in the luteal phase seems to be related to an
have not found a clear relationship between estradiol among the cycle phases and $\text{PET}_{\text{CO}_2}$, and $\text{PETO}_2$, the higher estradiol concentration in the follicular phase women when compared with postmenopausal women may have played a role in improving blood oxygenation (26, 33). A second possible reason for this observation may be that hypoxia produces larger changes in $\text{PET}_{\text{CO}_2}$ than in $\text{PETO}_2$ (37) and thus differences in $\text{PETO}_2$ are more evidenced than variations in $\text{PET}_{\text{CO}_2}$. A third conceivable reason may be that the increase in Hb attained in the luteal phase is not completely lost in the follicular phase.

Normally, menstruating women at low altitudes show an elevated resting ventilation and low $\text{PET}_{\text{CO}_2}$ in the luteal phase that is associated with an increase in progesterone levels (3, 4, 7, 32). However, the menstrual cycle phase seems not to influence the initial phase of the ventilatory acclimatization to high altitudes in the study of Muza et al. (22). The hormonal changes between the follicular and luteal phases could not be a possible reason for this phenomenon, because plasma progesterone concentrations showed an average of ~6 ng/ml between days 2 and 10 of the luteal phase in the latter study and in ours. The possible explanation for the observation of Muza et al. (22) is that any potential effect of progesterone in the luteal phase has been overwhelmed by the important and variable effect on ventilation caused by the hypoxic exposure. Furthermore, the early effects of hypopacnia in women on arrival at altitude could have masked the effect on ventilation caused by the cycle phase. Compared with the ventilatory changes between the follicular and luteal phases reported at low altitudes, the hypoxia of 4,300 m produces much larger changes in ventilation and $\text{PET}_{\text{CO}_2}$ (3, 22, 32) despite the lower levels of progesterone concentration (6). Thus differences in hypoxic stress between long-term and acute hypoxia could also explain the independence of ventilation and $\text{PET}_{\text{CO}_2}$ from the cycle phases in the initial phase of exposure to hypoxia.

It is often said that menstruation is an “autophlebotomy” phenomenon that would protect high-altitude women from CMS. It is also a common belief that menstruation would produce a mild decrease in the iron stores of the body and thus a slight degree of anemia. Even though we cannot rule out that other physiological factors may be involved in erythrocyte production, the present data suggest that the cyclic increase in ventilation could protect high-altitude women from developing the physiopathology of CMS, thus favoring a “progesterone-induced” ventilatory control and not a self-bleeding-induced hematological control. Besides, other factors are worth mentioning that could contribute to protect women from CMS. For example, we should not rule out the beneficial effect of progesterone in sleep-disordered breathing patterns at high altitude, because it has been shown that progesterone improves the alveolar ventilation and nocturnal oxygen desaturation (8). Indeed, the disorder of the regulation of breathing during sleep has also been considered a risk factor for developing CMS (10, 17, 23, 24).
31). Additionally, it has been shown that estrogens reduce erythropoietin (18) and that estradiol potentiates the ventilation effects of progesterone (1). In rats exposed to chronic hypoxia, the absence of ovarian sexual hormones increases erythremic and cardiopulmonary responses, characteristics that are usually present in CMS, i.e., excessive erythropoiesis and right cardiac hypertrophy (24). Furthermore, when progesterone and estradiol are elevated, cardiac output, stroke volume, and renal plasma flow tend to be greater than in the follicular phase. These changes produce a better oxygen supply at the renal level, which should result in a lower erythropoietin synthesis stimulus in the luteal phase compared with the follicular phase. Conversely, substantially lower progesterone levels that appear with cessation of menstrual cycles will act to decrease ventilation and will lead to hypoxemia and to an increased hematopoietic stimulus, resulting presumably in excessive erythropoiesis, a prominent feature of CMS. The same sequence of physiopathological events (decreased respiratory function, hypoxemia, and excessive erythrocytosis) has been found to be associated in subjects with lower chronic respiratory disorders and CMS, which happens to be a risk factor for developing CMS (14).

Because the occurrence of CMS increases with age (13, 20, 29, 36), it may be argued that the physiopathological parameters of CMS are more evident in postmenopausal than premenopausal women because of their older age. However, we have demonstrated that hematocrit increases with advancing age in women at high altitude only after the menopause (15, 16). It is worth mentioning that at the same altitude of the study, there are no differences in the hematological parameters (Hb, hematocrit, and erythrocytes) between girls and boys before puberty (15), but the differences indeed appear later during adolescence.

In conclusion, the association of a decreased resting ventilation (higher P ETCO2) with lower Sa O2 and increased Hb concentration found in postmenopausal women adds weight to the presumption that menopause is involved as a contributing factor in the appearance of CMS in high-altitude women.

Perspectives

Future studies may incorporate additional and very accurate measurements of oxygen transport and delivery, relating them to the phases of the menstrual cycle. Also of great interest will be the effects of hormone replacement, not only in the study of the control mechanisms of CMS but essentially in its therapeutic functions. Medroxyprogesterone (20–60 mg/day for 10 wk) has been used in men suffering from CMS living at 3,100 m. This drug has proven to increase ventilatory rate and normalize alveolar and arterial O2 pressures with a parallel drop in excessive hematocrit. Additionally, hormone therapy has produced in men a subsequent reduction of symptoms of CMS for up to 5 yr. The study of hormone replacement therapy in CMS may be essential for the physician’s information about the management of menopausal women living at high altitudes.

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