Resting Pulmonary Ventilation and Dead Space Ventilation during the Menstrual Cycle

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Summary By reanalyzing our previous study (TAKANO *et al.*, 1981) of resting ventilation and $P_{A_{CO_2}}$ during the menstrual cycle of eight healthy women, we found that relative to the follicular phase, a 9.4% increase in $\dot{V}_A$ ($p < 0.05$) and a 2.5 mmHg decrease in $P_{A_{CO_2}}$ ($p < 0.001$) occurring during the luteal phase, both of which have been reported previously, were attributable mostly to a decrease in $\dot{V}_D$ (-7.2% , $0.05 < p < 0.1$) but not to an increase in $\dot{V}_E$ ($+1.9\%$, N.S.), the latter two changes producing an 8.7% decrease in $\dot{V}_D/\dot{V}_T$ ($p < 0.01$).

Key Words: menstrual cycle, pulmonary ventilation, physiological dead space.

It is known that progesterone and some progestational agents cause hyperventilation and a fall in $P_{A_{CO_2}}$ (SKATRUD *et al.*, 1978). Due to this effect, physiologically, normal adult women exhibit a 2–8 mmHg drop in $P_{A_{CO_2}}$ during the luteal phase of the menstrual cycle (ENGLAND and FARHI, 1976) and further drops during pregnancy (LUCIUS *et al.*, 1970; PERNOLL *et al.*, 1975). Since progesterone has little effect on CO_2 production (TYLER, 1960; SKATRUD *et al.*, 1980; TAKANO *et al.*, 1981), the decrease in $P_{A_{CO_2}}$ during progesterone stimulation was ascribed to an increase in $\dot{V}_A$ (TAKANO *et al.*, 1981). During pregnancy (PERNOLL *et al.*, 1975) and administration of progesterone (CULLEN *et al.*, 1959; TYLER, 1960; SKATRUD *et al.*, 1978, 1980), the increase in $\dot{V}_A$ has been attributed to a greater increase in $\dot{V}_E$ relative to the concomitant increase in physiological dead space ventilation ($\dot{V}_D$). To our knowledge, however, little has been reported on $\dot{V}_E$ during the menstrual cycle, although the $P_{A_{CO_2}}$ has been much studied. HEERHABER (1948) observed in one normal woman that $P_{A_{CO_2}}$ continuously decreased during the luteal phase while $\dot{V}_E$ did not increase steadily. Very recently, SCHOENE *et al.* (1981) reported that twelve menstruating women showed a 24% increase in $\dot{V}_E$ and a 2.3 mmHg decrease in $P_{A_{CO_2}}$ during the luteal phase, compared with those occurring during the follicular phase. In our previous study (TAKANO

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et al., 1981), we paid much attention to the version of $\dot{V}_A$ of our experimental results, in order to assess the functional characteristics of the feedback loop of $P_{A_{CO_2}}$ control operating during the menstrual cycle. We observed that a 9.4% increase in $\dot{V}_A$ and a 2.5 mmHg decrease in $P_{A_{CO_2}}$ occurred during the luteal phase of eight menstruating women.

Now, on reviewing the results for $\dot{V}_E$ obtained in the course of our previous study (TAKANO *et al.*, 1981), we became aware that the increase in $\dot{V}_E$ observed during the luteal phase of our subjects was too small to explain the 9.4% increase in $\dot{V}_A$, unless $\dot{V}_D$ decreased during the luteal phase. We now report the results for $\dot{V}_E$ and $\dot{V}_D$ during the menstrual cycle, using the data we obtained in our previous study.

Experimental procedures are given in detail in our previous study (TAKANO *et al.*, 1981). Eight subjects, ages 22–42, were studied. The study was repeated on 4–10 different days of two menstrual cycles in each subject, once a day at the same time of day. The time scale of the menstrual cycle was normalized to 28 days based on the record of the basal oral temperature measurement.

During the study, the subject lay in a half-reclining position. After 30 min rest, oral temperature (T_{oral}) was measured and a respiratory mask (mask dead space: 60 ml) was then applied. In the steady state, 5-min measurement of minute ventilation ($\dot{V}_E$), tidal volume (V_T), and respiratory frequency (f) was made by means of a Tissot spirometer, and 5-min measurement of end-tidal P_{CO_2} ($P_{A_{CO_2}}$), by means of an infrared CO_2 analyzer (Beckman LB-1) calibrated with two standard gas mixtures previously analyzed using a Scholander gas analyzer. The data were taken every minute and then averaged. Then, mixed expired gas was collected for 10 min, the CO_2 content ($F_{E_{CO_2}}$) being measured by a Scholander gas analyzer. Physiological dead space (V_D) was calculated from V_T , $P_{A_{CO_2}}$, and $F_{E_{CO_2}}$ using the Bohr equation. Ventilatory volumes were expressed in BTPS.

Only the data obtained between day 3 and day 12 of each follicular and luteal phase were used for statistical analysis. Because of unequal quantities of data obtained between the two phases in each subject, we considered that the mean value for each phase in each subject and hence the difference between the two phases for each subject could not be estimated properly. We estimated the mean value of the whole experimental group for each follicular and luteal phase, and subsequently, the difference between the two phases was tested by the Student's *t*-test for unpaired comparisons, as described in our previous study (TAKANO *et al.*, 1981). The mean value of a given variable (X) of the experimental group was calculated for each phase through the following steps: (1) a ratio between the measured value on day n of each phase and the grand mean ($X_n/\bar{X}$) for each subject, (2) the averaged value of the ratios obtained in all subjects for each follicular (F) and luteal (L) phase ($(\bar{X}_n/\bar{X})_F$ and $(\bar{X}_n/\bar{X})_L$, respectively), (3) the grand mean for the experimental group ($\sum \bar{X}/N$, in which N =number of subjects), and (4) the mean value of the experimental group for each follicular and luteal phase as $(\sum \bar{X}/N) \times (\bar{X}_n/\bar{X})_F$

Table 1. Ventilatory measurement during each follicular and luteal phase.

	Follicular	Luteal	Dif.	% Change	<i>p</i>
Measurements	15	24	—	—	—
Toral* (°C)	36.6±0.05	36.9±0.03	0.3	—	<i>p</i> <0.001
<i>P</i> _{ACO₂} * (mmHg)	36.8±0.52	34.3±0.36	-2.5	—	<i>p</i> <0.001
$\dot{V}_E$ (liters·min ⁻¹ ·m ⁻²)	4.28±0.085	4.36±0.087	0.08	1.9	N.S.
$\dot{V}_D^{**}$ (liters·min ⁻¹ ·m ⁻²)	1.95±0.055	1.81±0.055	-0.14	-7.2	N.S.
$\dot{V}_A^*$ (liters·min ⁻¹ ·m ⁻²)	2.33±0.055	2.55±0.069	0.22	9.4	<i>p</i> <0.05
<i>f</i> (breaths·min ⁻¹)	16.2±0.25	16.3±0.26	0.1	—	N.S.
<i>V</i> _D ^{**} / <i>V</i> _T	0.46±0.009	0.42±0.009	-0.04	-8.7	<i>p</i> <0.01

All values are mean±S.E. Body surface area (mean±S.D.) of the subjects was 1.48±0.061 m².

* Presented in our previous study (TAKANO *et al.*, 1981) and shown here for reference.

** Includes dead space in respiratory mask.

and $(\sum \bar{X}/N) \times (\bar{X}_n/\bar{X})L$, respectively.

The experimental results are summarized in Table 1. The subjects exhibited normal biphasic fluctuations in *Toral* and *P*_{ACO₂} during the menstrual cycle, indicating that they had been subjected to normal periodic progesterone stimulation. It was noted that $\dot{V}_E$ did not significantly increase during the luteal phase, while *P*_{ACO₂} decreased by 2.5 mmHg. $\dot{V}_D$ showed a decrease of 7.2% during the luteal phase but the magnitude thereof was not statistically significant (0.05<*p*<0.1). The slight increase in $\dot{V}_E$ (+1.9%) and the small decrease in $\dot{V}_D$ (-7.2%) resulted in a significant decrease in *V*_D/*V*_T of 8.7%.

The dead-space volume of the respiratory mask used in the present study turned out to be 35% of the *V*_D value, which resulted in the greater *V*_D/*V*_T ratio than that in women studied using mouthpieces (PERNOLL *et al.*, 1975). If it is assumed that the anatomical and alveolar dead spaces were not affected by addition of the extra-corporeal dead space, we can estimate "real *V*_D" and "real *V*_T" by subtracting the mask dead space from the actually measured *V*_D and *V*_T, respectively. The "real $\dot{V}_D$ " (liters·min⁻¹·m⁻²) was 1.29 for the follicular phase and 1.15 for the luteal phase, the % change being -10.9% but not significant (0.05<*p*<0.1). On the other hand, the "real *V*_D/*V*_T" ratio was 0.36 for the follicular phase and 0.31 for the luteal phase, the difference being significant (*p*<0.01).

It has been reported that in normal males and patients with hypercapnia, progesterone administration results in 10-20% increases in $\dot{V}_E$ associated either with 10-30% increases in $\dot{V}_D$ (CULLEN *et al.*, 1959; TYLER, 1960; SKATRUD *et al.*, 1978, 1980) or with no change in $\dot{V}_D$ (KRYGER *et al.*, 1978). As a result of this, the *V*_D/*V*_T either decreased by 3-15% (CULLEN *et al.*, 1959; TYLER, 1960; KRYGER *et al.*, 1978) or remained unchanged (SKATRUD *et al.*, 1978, 1980). PERNOLL *et al.* (1975) have shown that during pregnancy in which progesterone stimulation and an increase in $\dot{V}_{CO_2}$ exist concomitantly, both $\dot{V}_E$ and $\dot{V}_D$ increase and *V*_D/*V*_T de-

crease. Thus, in the cases of pregnancy and administration of progesterone, the relatively large increases in $\dot{V}_A$ (+10–20%) seem to be due to sufficiently large increases in $\dot{V}_E$ in spite of concomitantly increasing $\dot{V}_D$. On the other hand, in the case of the luteal phase in our subjects, the relatively small increase in $\dot{V}_A$ (+9.4%) appears to be attributable mostly to the decrease in $\dot{V}_D$ with little change of $\dot{V}_E$, resulting in a significant decrease in V_D/V_T . A significant change in respiratory frequency was not seen after the ovulation in our subjects (Table 1), this result being in agreement with those obtained after the administration of progesterone (KRYGER *et al.*, 1978; SKATRUD *et al.*, 1978, 1980).

We cannot yet explain the discrepancies between our findings and those of others. Possible reasons are as follows. (1) The higher the level of blood progesterone, the greater the increase in $\dot{V}_E$ and V_T . The levels of blood progesterone during progesterone administration were double during the luteal phase (SKATRUD *et al.*, 1978, 1980) and those during pregnancy quadrupled during the luteal phase (GOLDMAN and ZARROW, 1973; TAGATZ and GURPIDE, 1973). However, SCHOENE *et al.* (1981) have cast doubts on this possibility. (2) A greater increase in V_T tends to be accompanied by a greater increase in V_D (BOUHUYS, 1964). (3) Progesterone possibly decreases the lung compliance (ITO and AVIADO, 1968; FARIDY, 1981). This effect might result in decreases in FRC (FARIDY, 1981) and the $\dot{V}_A/\dot{Q}$ ratio, the former leading to a decrease in anatomical dead space and the latter, to a decrease in alveolar dead space (BOUHUYS, 1964). However, there has been no study made as to whether FRC and/or the $\dot{V}_A/\dot{Q}$ ratio decrease during the luteal phase. (4) The above two opposing effects of (2) and (3) on V_D may offset each other. That is, when the magnitude of increase in V_T in response to increased progesterone is smaller, the net increase in V_D will be smaller, and in some cases, it will become negative. In the case of our subjects with no significant increases in V_T during the luteal phase, their V_D values are likely to decrease due to this sequence. In our recent study on a further five menstruating subjects (TAKANO, 1981), we again observed that there was no significant increase in $\dot{V}_E$ (+0.4%) but a significant decrease in $P_{A_{CO_2}}$ (–3.2 mmHg) during the luteal phase. We cannot explain the disagreement between Schoene's subjects (SCHOENE *et al.*, 1981) and ours in regard to the $\dot{V}_E$ response during the luteal phase. Data on the $\dot{V}_D$ of Schoene's subjects have not yet become available. It is not known whether racial differences play a role in the sensitivity and availability of progesterone receptor sites.

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