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Analysis of Alveolar P_{CO_2} Control during the Menstrual Cycle

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Abstract. We attempted to analyze how $P_{A_{CO_2}}$ is regulated during progesterone-induced hyperventilation in the luteal phase. A model for the CO_2 control loop was constructed, in which the function of the CO_2 exchange system was described as $P_{A_{CO_2}} = 0.863 \times \dot{V}_{CO_2}/\dot{V}_A$ (gain $H = dP_{A_{CO_2}}/d\dot{V}_A$) and that of the CO_2 sensing system as $\dot{V}_A = S(P_{A_{CO_2}} - B)$. Using this model, we estimated (1) the primary increase in $\dot{V}_A$ ($\Delta\dot{V}_A$ (op)) produced by progesterone stimulation and (2) the effectiveness (E) of the loop to regulate $P_{A_{CO_2}}$, defined as $\Delta P_{A_{CO_2}}$ (op)/$\Delta P_{A_{CO_2}}$ (cl) in which op signifies open-loop and cl, closed-loop. These respiratory variables were investigated throughout the menstrual cycle in 8 healthy women. During the luteal phase, on average, $\dot{V}_A$ increased by 9.4% and $P_{A_{CO_2}}$, B and H decreased by 0.33 kPa (2.5 mm Hg), 0.47 kPa (3.5 mm Hg) and 13.6%, respectively, while S and $\dot{V}_{CO_2}$ did not change significantly. $\Delta\dot{V}_A$ (op) increased progressively on successive days of the luteal phase while E remained unchanged at a value of 7.9, thus there was a progressive decrease in $P_{A_{CO_2}}$. The decrease in H was considered to lessen $\Delta P_{A_{CO_2}}$ (op) and so reduce the final deviation of $P_{A_{CO_2}}$ ($\Delta P_{A_{CO_2}}$ (cl)) during the luteal phase. The decrease in B was found to be dependent on $\Delta\dot{V}_A$ (op).

Key words: Menstrual cycle – Progesterone – Alveolar ventilation – Alveolar P_{CO_2} control – Ventilatory CO_2 response

Introduction

Since the work of Hasselbalch and Gammeltoft [11], many investigations have confirmed that women exhibit increases in ventilation accompanied by reductions of $P_{A_{CO_2}}$ during the luteal phase of the menstrual cycle and during pregnancy [cf. 17, 22]. Maximum fluctuations of $P_{A_{CO_2}}$ during the cycle are 0.40 to 1.07 kPa (3 to 8 mm Hg) [cf. 8]. These changes have been attributed to an excitatory effect of progesterone on respiration [17, 22]. The mechanism of respiratory stimulation by progesterone, however, has remained unsettled. Most recently, Skatrud et al. [29] investigated the problem in man and concluded that the effect may be produced via some central mechanism other than the central and peripheral chemoreceptors. However, Tok and Loeschcke [30] did find that progesterone added to mock CSF covering the ventral surface of the medulla oblongata of the cat was able to increase ventilation.

Levels of $P_{A_{CO_2}}$ and $\dot{V}_A$ in euoxic conditions are regulated by a closed feedback loop comprising the two CO_2 control systems, the CO_2 exchange system in the lung and the tissues being the "controlled system" and the CO_2 sensing system which is mainly in the brain being the "controlling system" [4]. The CO_2 exchange system can be described by the equation $P_{A_{CO_2}} = 0.863 \times \dot{V}_{CO_2}/\dot{V}_A$. The relationship between $P_{A_{CO_2}}$ and $\dot{V}_A$ at a given $\dot{V}_{CO_2}$ can be represented on a $\dot{V}_A$-$P_{A_{CO_2}}$ diagram (abscissa: $\dot{V}_A$) by the metabolic hyperbola [4]. On the other hand, the characteristics of the CO_2 sensing system can be determined by a CO_2 ventilatory response test and is conventionally described by the equation $\dot{V}_A = S(P_{A_{CO_2}} - B)$. This can be represented by a near straight line on a $P_{A_{CO_2}} - \dot{V}_A$ diagram (abscissa: $P_{A_{CO_2}}$), and is usually referred to as a CO_2 response line. The parameter S in this equation is the ventilatory responsiveness of the system to a unit change in $P_{A_{CO_2}}$, while the parameter B is an imaginary threshold of the system expressed in terms of $P_{A_{CO_2}}$. Thus, at a steady state for CO_2, the values of $P_{A_{CO_2}}$ and $\dot{V}_A$ at a given $\dot{V}_{CO_2}$ are such that the operations of the CO_2 exchange system and the CO_2 sensing system are mutually geared. On a $P_{A_{CO_2}} - \dot{V}_A$ diagram, these values are represented by the intersection point of a metabolic hyperbola and a CO_2 response line under a given condition [4].

In the present study, we constructed a simple loop model of the CO_2 control system, as shown in Fig. 1, from which we attempted to analyze how $P_{A_{CO_2}}$ is regulated during the progesterone stimulation which occurs in the luteal phase. Progesterone acting on unknown sites (r) of the loop may primarily cause an increase in ventilation ($\Delta\dot{V}_A$ (op)), which may in turn cause a decrease in $P_{A_{CO_2}}$ ($\Delta P_{A_{CO_2}}$ (op)). However, the final deviations of $\dot{V}_A$ and $P_{A_{CO_2}}$ ($\Delta\dot{V}_A$ (cl) and $\Delta P_{A_{CO_2}}$ (cl), respectively) from the normal values will be regulated so as to be minimized by the negative feedback loop of the CO_2 control system. The effectiveness (E) of the loop to regulate $P_{A_{CO_2}}$ can be defined by a ratio $\Delta P_{A_{CO_2}}$ (op)/$\Delta P_{A_{CO_2}}$ (cl), from the definition proposed by Loeschcke [19].

The purpose of this study was to measure all the variables and parameters involved in the CO_2 control system throughout the menstrual cycle and, by using our model, to evaluate the magnitudes of $\Delta\dot{V}_A$ (op) and E during the luteal phase.

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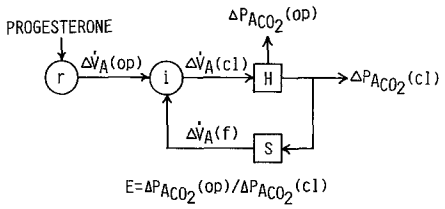

Fig. 1. A model of the CO_2 control loop. The loop includes the receptor site (r) receiving the progesterone stimulus and producing a primary increase in $\dot{V}_A$ ($\Delta\dot{V}_A$ (op)), the input site (i) receiving and integrating information (in terms of $\Delta\dot{V}_A$) from all receptors involved in the loop, the CO_2 exchange system (H) with the open-loop gain H, and the CO_2 sensing system (S) with the open-loop gain S. The progesterone stimulus will produce a much greater increase in $\dot{V}_A$ ($\Delta\dot{V}_A$ (op)) and a much greater accompanying decrease in $P_{A_{CO_2}}$ ($\Delta P_{A_{CO_2}}$ (op)) when the loop is open than when it is closed, the changes here being $\Delta\dot{V}_A$ (cl) and $\Delta P_{A_{CO_2}}$ (cl). $\Delta\dot{V}_A$ (f) is the quantity of $\dot{V}_A$ fed back by the CO_2 sensing system. The effectiveness (E) of the CO_2 control loop can be calculated as shown in the figure

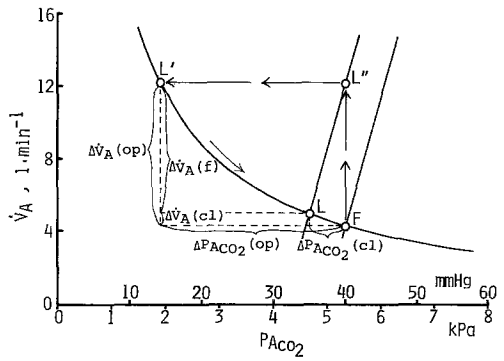

Fig. 2. A $P_{A_{CO_2}} - \dot{V}_A$ diagram with two CO_2 response lines and a metabolic hyperbola. Arrows show the sequence of changes in $\dot{V}_A$ and $P_{A_{CO_2}}$ during progesterone stimulation. For symbols see text

Methods

A Model of the CO_2 Control Loop – Mathematical Analysis in Steady State (see Fig. 1). The characteristics of the CO_2 exchange system can be defined as:

$$P_{A_{CO_2}} = 0.863 \times \dot{V}_{CO_2}/\dot{V}_A \quad (\text{if } P_{I_{CO_2}} = 0) \tag{1}$$

where $\dot{V}_{CO_2}$ is expressed in ml · min^{-1} (STPD) and $\dot{V}_A$ in l · min^{-1} (BTPS). Eq. (1) can be plotted as a metabolic hyperbola on a $P_{A_{CO_2}} - \dot{V}_A$ diagram, as shown in Fig. 2. The gain of this system is:

$$H = dP_{A_{CO_2}}/d\dot{V}_A = -(P_{A_{CO_2}})^2/(0.863 \times \dot{V}_{CO_2}). \tag{2}$$

The relationship between the input ($\Delta\dot{V}_A$ (cl)) and the output ($\Delta P_{A_{CO_2}}$ (cl)) of this system can be described as:

$$\Delta P_{A_{CO_2}}\,(\text{cl}) = H \cdot \Delta\dot{V}_A\,(\text{cl}). \tag{3}$$

The characteristics of the CO_2 sensing system can be defined as:

$$\dot{V}_A = S\,(P_{A_{CO_2}} - B) \tag{4}$$

and can be plotted as a CO_2 response line on the $P_{A_{CO_2}} - \dot{V}_A$ diagram, as in Fig. 2. The gain of this system is indicated by S in Eq. (4). The relationship between the input ($\Delta P_{A_{CO_2}}$ (cl)) and the output ($\Delta\dot{V}_A$ (f)) of this system can be described as:

$$\Delta\dot{V}_A\,(\text{f}) = S \cdot \Delta P_{A_{CO_2}}\,(\text{cl}). \tag{5}$$

The input entering the CO_2 exchange system ($\Delta\dot{V}_A$ (cl)) is determined by the sum of the two inputs entering the input site, i.e.:

$$\Delta\dot{V}_A\,(\text{cl}) = \Delta\dot{V}_A\,(\text{op}) + \Delta\dot{V}_A\,(\text{f}) \tag{6}$$

where if the feedback control by the CO_2 sensing system operates negatively, $\Delta\dot{V}_A$ (f) has a negative sign. Combining Eqs. (3), (5) and (6) gives:

$$\Delta P_{A_{CO_2}}\,(\text{cl}) = \Delta\dot{V}_A\,(\text{op}) \cdot H/(1 - S \cdot H). \tag{7}$$

Eq. (7) shows the relationship between the input ($\Delta\dot{V}_A$ (op)) and the output ($\Delta P_{A_{CO_2}}$ (cl)) of the whole closed CO_2 control loop, and the coefficient $H/(1 - S \cdot H)$ expresses the closed-loop gain.

An example of the sequence of changes in $\dot{V}_A$ and $P_{A_{CO_2}}$ which might be produced by progesterone stimulation in the luteal phase is shown in Fig. 2. The $P_{A_{CO_2}} - \dot{V}_A$ point may be displaced from F (a control point or a point during the follicular phase) to L'' (a primary increase in $\dot{V}_A$ due to the progesterone stimulation while the CO_2 exchange system remains unchanged), then to L' (a secondary decrease in $P_{A_{CO_2}}$ due to the change in the operation of the CO_2 exchange system while the CO_2 sensing system remains unchanged), and finally to L (a steady state point during the progesterone stimulation or the luteal phase with operation of the closed CO_2 control loop). If $\dot{V}_{CO_2}$ (therefore H) and/or S are changed with the progesterone stimulation, points L' and L would be at different positions.

$P_{A_{CO_2}}$ and $\dot{V}_A$ values at L' can be obtained from:

$$\dot{V}_{A_{L'}} = \dot{V}_{A_F} + \Delta\dot{V}_A\,(\text{op}) \tag{8}$$

$$\text{and } P_{A_{CO_2L'}} = 0.863 \times \dot{V}_{CO_2L}/\dot{V}_{A_{L'}}, \tag{9}$$

where subscripts L', L and F signify the conditions at points L', L and F in Fig. 2, respectively. The $\Delta\dot{V}_A$ (op) in Eq. (8) can be obtained from Eq. (7), and in Eq. (9) it was assumed that $\dot{V}_{CO_2L'} = \dot{V}_{CO_2L}$.

The effectiveness of the CO_2 control loop can then be calculated as:

$$E = \Delta P_{A_{CO_2}}\,(\text{op})/\Delta P_{A_{CO_2}}\,(\text{cl}) = (P_{A_{CO_2L'}} - P_{A_{CO_2F}})/(P_{A_{CO_2L}} - P_{A_{CO_2F}}). \tag{10}$$

Similar mathematical derivations have been made by Loeschcke [18], although he preferred to consider the pH of the extracellular fluid of the brain as the controlled element.

Subjects. The subjects were 8 healthy adult women who showed normal biphasic changes in the basal oral temperature during the menstrual cycle. All subjects gave their informed consent to undergo this study. The study on each subject was performed once a day at the same time of day and more than 3 h after a meal. The study was repeated on 4 – 10 different days of two menstrual cycles, half of these days being during the follicular phase and half during the luteal phase.

Experimental Procedures and Measurements. The subject lay in a comfortable half-reclining position throughout the study. After 30 min rest, oral temperature (T_{oral}) was measured. Then a respiratory mask (overall dead space: 60 ml) was applied and the expired gas was collected for 10 min. The volume of the expired gas was analysed with a wet gasometer and the O_2 and CO_2 contents with a Scholander gas analyzer. O_2 consumption ($\dot{V}_{O_2}$) and CO_2 production ($\dot{V}_{CO_2}$) were then calculated. Values of $F_{E_{CO_2}}$ obtained at this time were used to calculate dead space (V_D). After this metabolic measurement, the subject underwent a steady state CO_2 ventilatory response test. She breathed air for 10 min, and then a sequence of gas mixtures of 3, 5 and 7% CO_2 in 30% O_2, each for 15 min, with intervals of 3-min air breathing interposed. Minute ventilation ($\dot{V}_E$), mean tidal volume (V_T) and respiratory frequency (f) were measured continuously by a Tissot-type spirometer and end-tidal P_{CO_2} (hereafter referred to as $P_{A_{CO_2}}$) was monitored by an infrared CO_2 analyzer (Beckman LB-1). During the last 5 min of each air and CO_2 breathing period, values for $\dot{V}_E$ and $P_{A_{CO_2}}$ were obtained every min and then averaged to obtain the steady state values. V_D was calculated from the Bohr equation using the values for V_T, $P_{A_{CO_2}}$ and $F_{E_{CO_2}}$ obtained during air breathing. The V_D thus obtained was assumed to remain unchanged during CO_2 breathing, and alveolar ventilation ($\dot{V}_A$) was calculated for each of the air and CO_2 breathing periods.

Analysis of the Data. The following analyses were made on each experimental day for each subject. The relationship between $\dot{V}_A$ and $P_{A_{CO_2}}$ obtained from the steady state CO_2 ventilatory response test was analyzed by least-square regression, and parameters S and B were obtained from Eq. (4). Based on the data of $P_{A_{CO_2}}$ and $\dot{V}_{CO_2}$ during air

Table 1. Metabolic variables in each subject (mean ± SD)

Subject	Age yrs	Height cm	Weight kg	N	T_{oral} °C	$\dot{V}_{O_2}$ (STPD) ml · min^{-1} · m^{-2}	$\dot{V}_{CO_2}$ (STPD) ml · min^{-1} · m^{-2}
EM	22	158	50	4	36.8±0.15	123.3± 3.0	97.6± 2.6
SK	23	162	43	7	36.7±0.35	144.4±18.8	118.4±13.0
HR	23	160	54	7	36.8±0.28	111.5±10.1	82.2± 6.6
NM	22	160	51	4	37.0±0.39	135.1±13.5	110.4±15.2
TK	31	156	52	5	36.7±0.15	132.3± 8.8	112.3± 8.7
IY	37	148	45	8	36.7±0.16	110.5±12.3	87.3± 9.1
TN	42	158	49	10	36.8±0.22	110.7±22.0	88.6±19.0
YR	22	159	52	8	36.5±0.24	116.4± 5.4	91.3± 9.1
Mean ± SE					36.7±0.10	123.0±4.5	98.5±4.1

Table 2. Respiratory variables and parameters in each subject (mean ± SD)

Subject	N	$\dot{V}_A$ (BTPS) l · min^{-1} · m^{-2}	$P_{A_{CO_2}}$ kPa (mm Hg)	S l · min^{-1} · m^{-2} · kPa^{-1} (l · min^{-1} · m^{-2} · mm Hg^{-1})	B kPa (mm Hg)	H kPa · l^{-1} · min · m^2 (mm Hg · l^{-1} · min · m^2)
EM	4	2.43±0.28	4.81±0.43	10.65±1.58	4.61±0.46	−2.08±0.43
SK	7	3.00±0.47	4.69±0.22	4.28±0.83	4.05±0.45	−1.64±0.29
HR	7	2.17±0.28	4.56±0.48	4.88±1.20	4.44±0.65	−2.23±0.45
NM	4	2.98±0.34	4.44±0.17	7.20±0.38	4.07±0.20	−1.57±0.19
TK	5	2.78±0.29	4.83±0.38	4.80±1.28	4.24±0.43	−1.81±0.27
IY	8	2.21±0.25	4.72±0.32	8.93±1.50	4.56±0.35	−2.25±0.37
TN	10	2.12±0.38	4.93±0.24	6.30±1.58	4.64±0.25	−2.47±0.45
YR	8	2.14±0.21	5.07±0.19	9.83±1.65	5.03±0.26	−2.45±0.27
Mean ± SE		2.48±0.14	4.76±0.12 (35.7 ±0.93)	7.13±0.53 (0.95±0.07)	4.45±0.15 (33.4±1.16)	−2.07±0.13 (−15.5±1.0)

breathing (resting $P_{A_{CO_2}}$ and $\dot{V}_{CO_2}$), the parameter H at resting $P_{A_{CO_2}}$ was calculated from Eq. (2).

As the lengths of the menstrual cycle varied between 27 and 43 days within a subject as well as among subjects, the time scale of the cycle of each subject was normalized to 28 days, of which 14 days before the ovulation were considered to be the follicular phase and the remaining 14 days including the day of the ovulation to be the luteal phase. The day of the ovulation was considered to be the day on which the oral basal temperature was lowest in the middle of the cycle.

Results

A total of 53 measurements were carried out, of which 23 were made during the follicular phase and 30 during the luteal phase. Tables 1 and 2 show the mean values of the variables and parameters studied in each subject. For women with a normal menstrual cycle, the mean coefficients of variation (SD/mean) from day to day were about 10% for resting $\dot{V}_{CO_2}$, $\dot{V}_{O_2}$ and $\dot{V}_A$ and about 20% for S and H. Standard deviations for $P_{A_{CO_2}}$ and B were 0.27 − 0.67 kPa (2 − 5 mm Hg) from day to day. The variations of S and B in our subjects as obtained from the steady state CO_2 ventilatory response test were greater than those in the subjects (23 males and 3 females) of Hey et al. [13]. As will be shown later, part of the great variation observed in our subjects can be ascribed to cyclic changes during the menstrual cycle.

Changes during the Menstrual Cycle. As there were considerable differences between subjects in the absolute values of each variable (Tables 1 and 2), the fluctuation of each variable

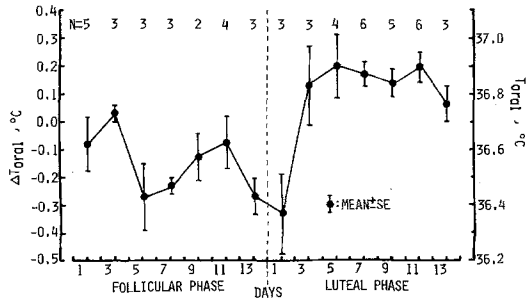

Fig. 3. Fluctuation of T_{oral} during the menstrual cycle. Numbers at the top of the figure indicate the number of data (N) pooled every two consecutive days during the cycle

during the menstrual cycle was analysed by calculating the deviation of the value obtained on each experimental day from the mean value for each subject. In Figs. 3, 4 and 6, for any given variable X, the deviation ΔX refers to the difference between the value on day n (X_n) and the mean value for each subject ($\bar{X}$, as shown in Tables 1 and 2), and the deviation $X/\bar{X}$ refers to the ratio of X_n to $\bar{X}$. For each variable, all the results obtained from 8 subjects were pooled every two consecutive days of the menstrual cycle and the pooled values were averaged. Between two and six values were pooled for each pair of consecutive days, as shown in Fig. 3.

Figure 3 shows the average fluctuation of T_{oral} during the cycle. After days 3 − 4 of the luteal phase T_{oral} was consistently

Table 3. Variables in each of the follicular and the luteal phases (mean ± SE)

Variable	Follicular ($N = 15$)	Luteal ($N = 24$)	Dif.	% Change	P^a
T_{oral}, °C	36.6±0.05	36.9±0.03	0.3	–	$P<0.001$
$\dot{V}_A$, l · min^{-1} · m^{-2}	2.33±0.055	2.55±0.069	0.22	9.4	$P<0.05$
$\dot{V}_{CO_2}$, ml · min^{-1} · m^{-2}	95.4±2.36	96.8±2.46	1.4	1.5	NS
$P_{A_{CO_2}}$, kPa	4.91±0.07	4.57±0.05	−0.34	–	$P<0.001$
(mm Hg)	(36.8±0.52)	(34.3±0.36)	(−2.5)		
S, l · min^{-1} · m^{-2} · kPa^{-1}	7.35±0.28	6.83±0.29	−0.52	−7.1	NS
(l · min^{-1} · m^{-2} · mm Hg^{-1})	(0.98±0.037)	(0.91±0.039)	(−0.07)		
B, kPa	4.67±0.07	4.20±0.07	−0.47	–	$P<0.001$
(mm Hg)	(35.0±0.55)	(31.5±0.50)	(−3.5)		
H, kPa · l^{-1} · min · m^2	−2.25±0.07	−1.95±0.07	−0.30[b]	−13.3[b]	$P<0.01$
(mm Hg · l^{-1} · min · m^2)	(−16.9±0.50)	(−14.6±0.55)	(−2.3[b])		

[a] Tested by the Student t-test in unpaired samples
[b] Compared in the absolute value

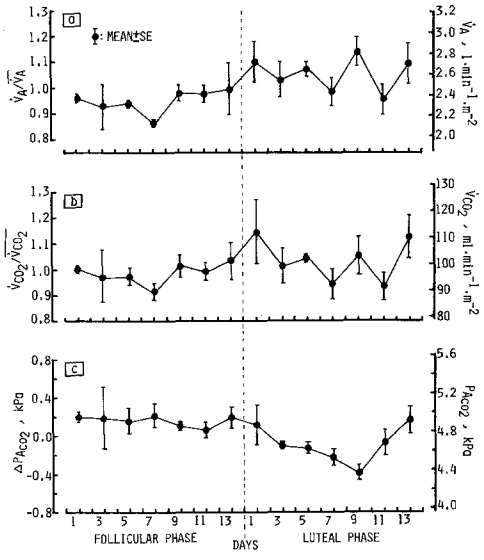

Fig. 4. Fluctuations of $\dot{V}_A$ (*a*), $\dot{V}_{CO_2}$ (*b*) and $P_{A_{CO_2}}$ (*c*) during the menstrual cycle

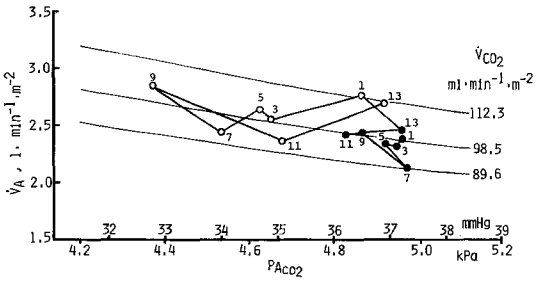

Fig. 5. Time courses of changes in $\dot{V}_A$, $P_{A_{CO_2}}$ and $\dot{V}_{CO_2}$ during the cycle as plotted in a $P_{A_{CO_2}} - \dot{V}_A$ diagram. Metabolic hyperbolas are drawn at three different levels of $\dot{V}_{CO_2}$. ●: points during the follicular phase, and ○: points during the luteal phase. Numbers near the points show the days during each phase

and significantly higher than during the follicular phase, the mean difference between the two phases being 0.3°C (Table 3).

Figure 4 shows the average changes in the three variables concerned with the CO_2 exchange system. Resting $\dot{V}_A$ (Fig. 4, a) fluctuated in an almost biphasic pattern, the lowest value appearing in the middle of the follicular phase and the peak occurring on days 9–10 of the luteal phase. The mean increase in $\dot{V}_A$ during the luteal phase was 0.221 · min^{-1} · m^{-2}, corresponding to 9.4% of that of the follicular phase (Table 3). The pattern of fluctuation of resting $\dot{V}_{CO_2}$ (Fig. 4, b) during the menstrual cycle seems to be similar to that of $\dot{V}_A$, although the day-to-day fluctuation is not significant (Table 3). Resting $P_{A_{CO_2}}$ (Fig. 4, c) fluctuated in a definitely biphasic pattern during the cycle; it remained fairly constant during the follicular phase but after ovulation it gradually decreased and reached the lowest level on days 9–10 of the luteal phase. The maximum drop was 0.53 kPa (4 mm Hg) and the mean decrease during the luteal phase was 0.34 kPa (2.5 mm Hg) (Table 3).

The sequence of changes in $\dot{V}_A$, $\dot{V}_{CO_2}$ and $P_{A_{CO_2}}$ during the cycle, based on the data presented in Fig. 4, are shown on a $P_{A_{CO_2}} - \dot{V}_A$ diagram (Fig. 5). The $P_{A_{CO_2}} - \dot{V}_A$ point remained at a virtually constant level during the follicular phase, but after ovulation it changed reaching a point with a 0.53 kPa (4 mm Hg) decrease in $P_{A_{CO_2}}$ and a 20% increase in $\dot{V}_A$ on days 9–10 of the luteal phase, after which it returned to the initial level. This excursion proceeded along a virtually constant $\dot{V}_{CO_2}$ line. Consequently, the decreases in $P_{A_{CO_2}}$ during the luteal phase must be ascribed almost exclusively to increases in $\dot{V}_A$.

Figure 6 shows average changes in parameters S, B and H of the CO_2 sensing and the CO_2 exchange systems. S (Fig. 6, a) varied irregularly throughout the menstrual cycle and there seemed to be no significant difference between the values of S in the follicular and the luteal phases (Table 3). B (Fig. 6, b) varied in a biphasic pattern, remaining virtually constant during the follicular phase and then decreasing toward the lowest value on days 9–10 of the luteal phase. The decrease was 0.47 kPa (3.5 mm Hg) on average (Table 3) and 0.76 kPa (5.7 mm Hg) at maximum. H (Fig. 6, c) also varied in a biphasic pattern similar to that of B. The mean value of H during the luteal phase was 13.6% less than that during the follicular phase (Table 3).

Thus, as seen in Figs. 3–6, T_{oral}, resting $\dot{V}_A$ and $P_{A_{CO_2}}$, and parameters B and H fluctuated in roughly biphasic patterns. The transitions seemed to occur approximately at the time of

ovulation and at the time of menstruation. Thus, we have taken mean values for each of the parameters during the follicular and the luteal phases, and compared them (Table 3); the means were calculated from data obtained between days 3–12 of each phase.

The values of $\Delta\dot{V}_A$ (op), $\Delta\dot{V}_A$ (f) and E during the luteal phase were calculated from Eqs. (7), (6) and (10), respectively, using values of $\dot{V}_A$, $\dot{V}_{CO_2}$, P_{ACO_2}, S and H for the follicular phase from Table 3, and for the luteal phase from Figs. 4 and 6. As shown in Table 4, the results were such that $\Delta\dot{V}_A$(op) increased up to days 9–10 of the luteal phase and $\Delta\dot{V}_A$(f) changed in parallel with $\Delta\dot{V}_A$ (op), $\Delta\dot{V}_A$(cl) consequently remained almost constant and small. The magnitude of ΔP_{ACO_2} (op) increased up to days 9–10 due to the progressive increase in $\Delta\dot{V}_A$(op) while the values of E remained almost constant at 7.9 throughout days 3–12.

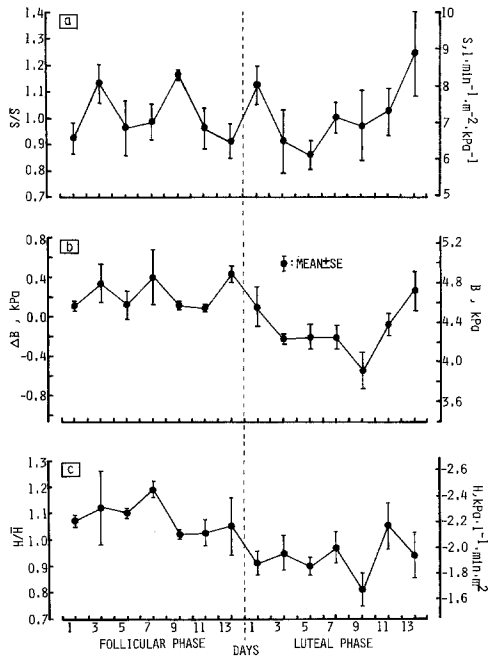

Fig. 6. Fluctuations of parameters S (*a*), B (*b*) and H (*c*) during the menstrual cycle

Discussion

Metabolic Rate

The mechanism responsible for the rise in body temperature during the luteal phase has not been fully elucidated, although a hypothesis of a higher setting of the hypothalamic thermostat has been proposed [16]. Regardless of the mechanism, it might be expected that the temperature rise either results in or from an increase in the metabolic rate at rest. Griffith et al. [10] and Conklin and McClendon [2] have observed that $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ gradually increased after the ovulation and reached the highest values in the last half period of the luteal phase, the increases being at most 3% of the values in the middle of the follicular phase. In the present study, the difference between the means of $\dot{V}_{CO_2}$ in the follicular and the luteal phases (1.5%) was not significant (Table 3), the pattern of change during the cycle being similar to that reported by previous investigators. Thus, it may be concluded that at the very most there might be a 3% increase in $\dot{V}_{CO_2}$ occurring in the last half of the luteal phase.

Slope of the CO_2 Response Line

The effect of progesterone on S seems rather controversial: no changes in normal men [6, 29], or increases in normal men [20], in obese patients [21] and in dogs [23] after administration of progesterone. During pregnancy, progressive increases in S have been observed by Döring and Loeschcke [5]. During the menstrual cycle in one woman, Heerhaber [12] observed a progressive increase in S in the days after the ovulation. In our subjects, however, there was no consistent trend in the changes of S during the cycle. Controversies

Table 4. Fluctuations of variables concerned with the CO_2 control model during the luteal phase

Days	$\Delta\dot{V}_A$ (op) $l \cdot min^{-1} \cdot m^{-2}$	$\Delta\dot{V}_A$ (f) $l \cdot min^{-1} \cdot m^{-2}$	$\Delta\dot{V}_A$ (cl) $l \cdot min^{-1} \cdot m^{-2}$	ΔP_{ACO_2} (op) kPa (mm Hg)	ΔP_{ACO_2} (cl) kPa (mm Hg)	E	ΔB, kPa (mm Hg)	
							observ.	hypothet.
1–2	0.34	0.06	0.40	−0.07 (−0.5)	−0.04 (−0.3)	1.7	−0.12 (−0.9)	−0.01 (−0.1)
3–4	1.76	−1.54	0.22	−2.11 (−15.8)	−0.25 (−1.9)	8.3	−0.44 (−3.3)	−0.37 (−2.8)
5–6	1.87	−1.55	0.32	−2.11 (−15.8)	−0.28 (−2.1)	7.5	−0.41 (−3.1)	−0.37 (−2.8)
7–8	2.85	−2.75	0.10	−2.85 (−21.4)	−0.37 (−2.8)	7.6	−0.43 (−3.2)	−0.51 (−3.8)
9–10	4.00	−3.50	0.50	−3.03 (−22.7)	−0.53 (−4.0)	5.7	−0.76 (−5.7)	−0.55 (−4.1)
11–12	1.75	−1.72	0.03	−2.32 (−17.4)	−0.23 (−1.7)	10.2	−0.29 (−2.2)	−0.41 (−3.1)
13–14	−0.12	0.49	0.37	0.84 (6.3)	0.01 (0.1)	63.0	0.04 (0.3)	0.15 (1.1)

about the effect of progesterone on S are probably due to (1) considerable variability of S itself from day to day even in normal men [26], (2) different progesterone levels in the blood of the subjects of different investigators, and (3) sex difference in the effect of progesterone on the CO_2 sensing system. No studies on the latter two possibilities have been reported.

Primary Increase in Ventilation due to Progesterone

It may be assumed that $\Delta \dot{V}_A$ (op) obtained in the present study represents a ventilatory response to the progesterone stimulus acting at a receptor site within the respiratory control system. As shown in Table 4, $\Delta \dot{V}_A$ (op) gradually increased during the first 9 – 10 days of the luteal phase. On the other hand, it has been well documented that the concentration of plasma progesterone is maintained at a level of 10 – 30 ng/ml plasma during days 5 – 10 of the luteal phase [27, 28]. This difference between the behaviors of $\Delta \dot{V}_A$ (op) and the progesterone concentration suggests an altered stimulus-response relationship at the receptor site. The progressive increase in $\Delta \dot{V}_A$ (op) is likely to be due to a synergistic effect of estrogen which increases temporarily during days 7 – 11 of the luteal phase [28]. Or else, if the central chemosensitive areas in the medulla oblongata are also the receptor site for progesterone as reported most recently by Tok and Loeschcke [30], any changes in blood and CSF [HCO_3^-] during the luteal phase, probably occurring as a result of compensatory mechanisms for the respiratory alkalosis due to the progesterone-induced hyperventilation, might be responsible for the altered progesterone effect during the luteal phase. At present, the localization of the progesterone receptor affecting respiration seems to be controversial. Huang and Lyons [14] and Skatrud et al. [29] have suggested some central areas other than the medullary chemoreceptors while Mei et al. [23] have shown that progesterone does not act on the carotid chemoreceptors.

Effectiveness of the CO_2 Control System during the Luteal Phase

Loeschcke [19] proposed an "effectiveness" parameter as an index of the effectiveness of the feedback controller on the controlled element (X). This parameter was calculated as $\Delta X_{op}/\Delta X_{cl}$, where ΔX_{op} is the primary shift of X, that is the shift which would occur if no feedback control were acting, and ΔX_{cl} is the final deviation of X from its original value. Loeschcke [18] argued that so far as the respiratory controller is concerned, the pH of the extracellular fluid in the brain is a more rigidly controlled element than the $P_{A_{CO_2}}$ or the P_{CO_2} of the brain tissue. However, he also showed that there was quite good agreement as far as ventilatory function is concerned between the model of the respiratory controller with pH of the extracellular fluid as the controlled element and the model with $P_{A_{CO_2}}$ as the controlled element. In the present study, in order to deduce how well $P_{A_{CO_2}}$ is regulated during the progesterone-induced hyperventilation in the luteal phase, Loeschcke's "effectiveness" parameter was calculated. As shown in Table 4, E remained almost constant at a value of 7.9 throughout almost all periods of the luteal phase. This figure is comparable to that obtained during 5% CO_2 inhalation [19]. The constancy of E resulted in a slight progressive decrease in $P_{A_{CO_2}}$ during the luteal phase with a progressive increase in $\Delta \dot{V}_A$ (op) (Table 4).

The $\Delta P_{A_{CO_2}}$ (op) is dependent on the characteristics of the CO_2 exchange system. When the metabolic hyperbola is shifted to the right by an increased $\dot{V}_{CO_2}$, the $\Delta P_{A_{CO_2}}$ (op) is decreased under a constant $\Delta \dot{V}_A$ (op) (cf. Fig. 2). In the present study, the function of the CO_2 exchange system was expressed in terms of the parameter H which was found to decrease by 13.6% during the luteal phase (Table 3). This decrease in H was brought about by a slight (but not significant) increase in $\dot{V}_{CO_2}$ and a decrease in $P_{A_{CO_2}}$ during the luteal phase (Table 3). Consequently, the decrease in H during the luteal phase might serve to diminish $\Delta P_{A_{CO_2}}$ (op) and so lessen the final deviation of $P_{A_{CO_2}}$ ($\Delta P_{A_{CO_2}}$ (cl)), if other factors, e.g., blood flows in the brain, in the lung and in the other tissues, remain constant.

Leftward Shifts of the CO_2 Response Line during the Luteal Phase

We observed that parameter B of the CO_2 response line remained virtually constant during the follicular phase and gradually decreased during the luteal phase. The maximum decrease was 0.76 kPa (5.7 mm Hg) on days 9 – 10. Heerhaber [12] has reported a similar deviation of the CO_2 response line during the cycle.

Leftward shifts of the CO_2 response line are seen not only as a consequence of administration of progesterone but also during acclimatization to hypoxia and metabolic acidosis [25]. A common phenomenon occurring in altitude acclimatization [15] and chronic metabolic acidosis [9] is a decrease in CSF [HCO_3^-]. Although no information of CSF [HCO_3^-] during the menstrual cycle is available, a decrease is likely to occur during the luteal phase, much as it does during pregnancy [24] and during treatment with progesterone [29]. A decrease in CSF [HCO_3^-] appears to be a factor which lowers parameter B. However, Tok and Loeschcke [30] found that a mock CSF-progesterone solution covering the ventral surface of the medulla oblongata caused a leftward shift of the CO_2 response line in the cat at normal pH and P_{CO_2}. This result appears to suggest that progesterone acts directly on the central chemoreceptors, resulting in a decrease in the CO_2 threshold even at normal CSF [HCO_3^-], and consequently bringing about a primary increase in $\dot{V}_A$ (i.e., $\Delta \dot{V}_A$ (op)).

On the other hand, voluntary hyperoxic hyperventilation lasting for 8 – 24 h [1, 7] also causes a leftward shift of the CO_2 response line. Eger et al. [7] found that the magnitude of this shift, expressed in terms of $P_{A_{CO_2}}$, is related to the $P_{A_{CO_2}}$ drop occurring during an 8-h hyperventilation, i.e.: a 0.18 mm Hg shift per mm Hg drop in $P_{A_{CO_2}}$ during hyperventilation. The $\Delta P_{A_{CO_2}}$ (op) defined in our study could be considered to be equivalent to the $P_{A_{CO_2}}$ drop in the voluntary hyperventilation experiment of Eger et al. [7]. Applying our data of $\Delta P_{A_{CO_2}}$ (op) to their results, we estimated a hypothetical B decrement. As shown in the last two columns of Table 4, the hypothetical ΔB is compatible with the actually observed value, suggesting that the decrease in B during the luteal phase is dependent on $\Delta P_{A_{CO_2}}$ (op) and hence on $\Delta \dot{V}_A$ (op). However, this result does not answer the question as to which is the cause and which the effect of a decrease in B and an increase in $\dot{V}_A$ (i.e., $\Delta \dot{V}_A$ (op)) as occurs after a rise in progesterone levels.

The functional characteristics of the CO_2 sensing system might be expressed more rationally in terms of the CSF pH-$\dot{V}_A$ relationship than in terms of the $P_{A_{CO_2}} - \dot{V}_A$ relationship (the CO_2 response line) [18]. Fencl et al. [9] obtained a CSF pH-$\dot{V}_A$ line for normal men using a steady state CO_2 ventilatory response test. The question is: Do subjects with progesterone stimulation as in the luteal phase have a CSF

pH-$\dot{V}_A$ relationship identical with that of Fencl et al. [9]? Since with progesterone stimulation, the CO_2 response line in the cat is displaced to the left even with normal CSF pH [30] and the CSF pH in man rises by 0.01 to 0.03 pH [24, 29], it might be suspected that the CSF pH-$\dot{V}_A$ line for the subjects with progesterone stimulation might be displaced to the more alkaline side of CSF pH than for normal men, this aspect resembling that in altitude hypoxia [3]. Further investigations on CSF pH and [HCO_3^-] during progesterone stimulation plus CO_2 inhalation will be required.

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