EFFECTS OF THE MENSTRUAL CYCLE ON TIMING AND DEPTH OF BREATHING AT REST

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Abstract : Volume and timing components of resting ventilation were measured serially in 40 women aged 18 to 36 yr, during menstrual, follicular and luteal phases of menstrual cycle. Resting minute ventilation (V_E) was significantly higher (P<0.001) in luteal phase than in menstrual and follicular phases; in the two latter phases V_E was almost equal. This increment in V_E during the luteal phase was due to a significant rise (P<0.001) in tidal volume (V_T). Respiratory frequency (f) was unchanged throughout the cycle. Although there was a mean increases in inspiratory time (T_I) during the luteal phase compared to the other two phases, the difference did not reach statistical significance. Duty cycle, T_I / T_{tot}, was also unchanged throughout menstrual cycle. However, mean inspiratory flow, V_T / T_I, was significantly higher (P<0.05 and P<0.01) during luteal phase as compared to that during menstrual or follicular phases respectively. Pulmonary mechanics, as measured by forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced mid expiratory flow rate ($FEF_{25\%-75\%}$), were within normal limits and remained unaltered during the menstrual cycle. Therefore, in the absence of alteration of pulmonary mechanics, the luteal increase in ventilation and inspiratory flow suggests a possible role for progesterone in stimulating the respiratory drive, either centrally or through the peripheral chemoreceptors or by both.

Key words :   menstrual cycle   pulmonary ventilation
                   pulmonary mechanics   progesterone

INTRODUCTION

It has been reported that hyperventilation and increase in oxygen consumption occur during the luteal phase of menstrual cycle and that if pregnancy occurs, the respiratory stimulation continues throughout gestation (1, 2). Probably progesterone plays a key role in

the phenomenon. It is also reported that the tendency for central apnea and hypopnea is reduced during pregnancy and that could be due to increased progesterone levels (3). However, the mechanism through which endogenous progesterone acts as ventilatory stimulus is not confirmed (4). Therefore, the present study of timing and depth of breathing, which influence

ventilation, was undertaken to observe whether these indicators alter with the phases of menstrual cycle, particularly during luteal phase when the progesterone level is normally high.

METHODS

Forty healthy female volunteers, 18–36 years of age, were studied throughout their menstrual cycle. They were not taking any contraceptive medication either before or during the study. Their age, height and weight (mean ± SD) were 22.6 ± 4.21 yr, 159.5 ± 4.22 cm and 50.8 ± 4.71 kg respectively. The selection of the subjects was based on fairly normal and regular menstrual history (28 ± 2 days cycle). Determination criteria of different phases of menstrual cycle have been described earlier (1). In brief, the period of ovulation was judged from daily basal oral temperature. Menstrual phase was based on the subject's statement. Ventilation recorded after 3–4 days of cessation of the bleeding, on 8th–12th day of the cycle, has been taken as representative for the follicular phase and that recorded on 20th–24th day of the cycle was taken to be the data for luteal phase.

A closed circuit apparatus, Expirograph (Godart, Holland), containing CO_2 absorber was used for measuring ventilation. Emotional and physiological distress were avoided by allowing a few trials of mouth breathing through the apparatus with the nose clipped before the day of actual test. The experiment was carried out under almost similar environmental conditions at the basal state in morning hours. After 15 minutes rest on the actual test day, each

subject was studied in sitting position. After the steady state of ventilation measured at slow paper speed (60 mm/min), for the duration of 10 minutes, the timing and volume for both inspiration and expiration were measured at high paper speed (1200 mm/min) at least for 10 respiratory cycles. The procedure was repeated on the next consecutive day. To minimize the effect of training, if at all, the subjects were randomly allocated to be studied first in any of the three phases. At the end of 10 min period of quiet breathing after the first experiment, the forced vital capacity (FVC), forced expiratory volume in first second (FEV_1) and forced midexpiratory flow rate ($FEF_{25\%-75\%}$) were recorded in standing position in each phase using the same instrument after some modifications.

We have measured minute ventilation (V_E) not only in terms of its classical components, tidal volume (V_T) and breathing frequency (f) from the slow expirogram, but also in relation to the duration of inspiration (T_I) and the mean inspiratory flow (V_T/T_I) as measured from the record taken at high paper (20 mm/sec) :

$$V_E = V_T \times f = V_T/T_I \times T_I/T_{tot} \times 60 \ 1/min \ (5, 6).$$

where T_{tot} is the average duration of each breath (60/f, s) and T_I/T_{tot}, i.e. the proportion of each breath spent on inspiration, is termed as the inspiratory duty ratio (5, 6). All the volumes were expressed in terms of body temperature, pressure and saturated with water vapour (BTPS).

The values of respiratory timings and flows were averaged from minimum of 10 respiratory cycles for each phase. Outcome was expressed as mean ± SD. The subjects acted as their own controls; the differences

in paired values were used for determining the statistical significance by Fisher test. The alpha error for a significant test was set at 5% level.

RESULTS

The minute ventilation with its different components, timing and depth, and pulmonary mechanics during different phases of menstrual cycle are presented in Table I. V_E increased significantly (P<0.01) in luteal phase compared to both menstrual and follicular phases. The increase was

Pulmonary mechanics as measured by FVC, FEV_1 and $FEF_{25\%-75\%}$ (Table I) were within normal limits and remained unaltered during different phases of menstrual cycle.

The basal oral temperature (°F) recorded during luteal phase (98.46 ± 0.26) was significantly higher (P<0.001) than that during either menstrual (97.71 ± 0.53) or follicular (97.76 ± 0.41) phase. The increase in basal body temperature during luteal phase in each subject indicates that the cycles were ovulatory.

TABLE I :   Pulmonary ventilation and mechanics during menstrual cycle (n = 40).

	Menstrual phase	Follicualr phase	Luteal phase
Ventialtion			
f, /min	17.70±6.07	18.00±6.60	17.10±6.22
V_T mL	581±196	591±213	697±220**
V_E, L/min	9.76±3.76	9.79±2.64	10.88±2.85*
T_I, S	1.67±0.86	1.70±0.85	1.83±1.10
T_I/T_{tot},	0.43±0.05	0.44±0.06	0.43±0.04
V_T/T_I, L/s	0.37±0.14	0.36±0.10	0.41±0.10·
Mechanics			
FVC, L	2.72±0.40	2.68±0.32	2.70±0.34
FEV_1, L	2.40±0.31	2.38±0.31	2.41±0.28
$FEV_{25\%-75\%}$, L/s	3.01±0.70	3.04±0.64	3.08±0.70

Data are presented as mean ± SD. +P<0.05, *P<0.01, **P<0.001 compared with the values of menstrual and follicular phases.

almost 12 percent. This increment in V_E was basically due to significant (P<0.001) rise in V_T. The f remained unchanged, as derived from T_{tot}. Although there was an increase in T_I noted during the luteal phase, the difference did not reach statistical significance. Duty cycle, T_I/T_{tot}, was also unchanged. Mean inspiratory flow, V_T/T_I, was significantly increased in luteal phase as compared to that in menstrual and follicular phases (P<0.05 and P<0.01 respectively).

DISCUSSION

Normal ventilation is a complex process involving several interactions. Behavioural, chemical and central neuromuscular drives influence breathing profoundly. The altered state of breathing during menstrual cycle probably involves all or any such mechanisms. Earlier studies indicate, that hyperventilation during luteal phase of menstrual cycle and during pregnancy are associated with increased progesterone

concentration (1, 2). Further, administration of progesterone to normal men and post menopausal women produces hyperventilation (7, 8). Progesterone has also been used for treating hypoventilating patients (9, 10). In this study, significant increase (P<0.01) in minute ventilation was noted during luteal phase compared to both menstrual and follicular phases. Ventilation during the two latter phases was almost equal. Hyperventilation during the luteal phase was significantly rise in V_T only, without any appreciable change in respiratory rate. Inspiratory time did not change significantly, although a gradual increase from menstrual to luteal phase was noted. Therefore, the larger V_T was due to an increase in inspiratory flow, V_T/T_I. The variables, V_T/T_I and T_I/T_{tot} have been interpreted as drive and timing components of ventilation which may be independently controlled (11). The central inspiratory neural drive can be assessed by measurement of V_T/T_I or by mouth occlusion pressure ($P_{0.1}$), which is the inspiratory pressure generated at the end of 0.1 sec after the beginning of inspiratory efforts. The V_T/T_I are dependent on, and affected by, changes in pulmonary mechanics, whereas $P_{0.1}$ is independent of the mechanical properties of respiratory system (12). Although we have not measured $P_{0.1}$, our observation of FVC, FEV$_1$, and FEF$_{25\%}$-$_{75\%}$ in the same subjects during each phase reflect the unchanged mechanical properties of lungs during the menstrual cycle. FEV$_1$ in fact is the measure of flow rate during the first second of forced expiratory spirography. It includes sufficient flows at lower lung volumes to reflect the small airway patency in addition to large airway changes. Thus increase in inspiratory flow (V_T/T_I) during luteal phase, without any

alteration is pulmonary mechanics, mainly indicates an augmented central ventilatory drive, although the role of peripheral chemoreceptor can not be entirely ruled out. However, evidences suggest that both lutel phase of menstrual cycled and pregnancy are associated with central ventilatory drive as indicated by increase in mouth occlusion pressure (4,13). In this study effective time ratio or duty cycle, T_I/T_{tot}, was essentially unchanged. This indicates that inspiratory muscle activity probably did not alter during the menstrual cycle. Present observation supports earlier findings of unchanged effective time ratio and respiratory muscle strength during menstrual cycle (14).

Increase in brain adrenergic receptors during pregnancy is associated with behavioural changes which can modify ventilation (15). Recently it has been reported that luteal phase of menstrual cycle is also associated with increased adrenoreceptor density (16). However, to assess respiratory control at its most physiological and with least interference from behavioural influences, the emphasis has shifted away from stimulation by hypercapnia and hypoxaemia to more detailed analysis of resting breathing (17). The usual causes of hyperventilation associated with disease are absent as our all subjects were healthy. Probably there was not even an enlargement of dead space, which can influence ventilation, as the ventilation was augmented mainly by tidal volume rather than respiratory rate. This hyperventilation could be attributed to progesterone, as it was observed only during the luteal phase of menstrual cycle. Further, several evidences suggest that administration of progesterone to

volunteers, both male and female, and to patients with alveolar hypoventilation syndrome, increases ventilation (10,18). The sits of action of progesterone is thought to be either the respiratory center or peripheral chemoreceptors, or a combination of both. There may be a threshold to pCO2 and hence an increase in peripheral chemoreceptor sensitivity (4,19). The central chemoreceptor stimulation has an important influence on cholinergic outflow of the airways (20). It may cause reflex increase in ventilation and hypocarbia in spontaneously breathing subjects with hypoxic bronchoconstriction (21).

In conclusion, our finding in healthy subjects demonstrate that hyperventilation during luteal phase is associated with an increase in inspiratory flow without any alteration in pulmonary mechanics. This study also suggests the possible mechanism of decrease in carbon dioxide tension in blood after hyperventilation induced by synthetic progesterone in patients with obstructive pulmonary disease (22).

REFERENCES

1. Das TK, Jana H. Basal oxygen consumption during different phases of menstrual cycle. *Indian J Med Res* 1991; 94 : 16–19.

2. Milne JA. The respiratory response to pregnancy. *Postgrad Med J* 1979; 55: 318–324.

3. Brownell LG, West P, Kryger MH. Breathing during sleep in normal pregnant women. *Am Rev Respir Dis* 1986; 133: 38–41.

4. Contreras G, Gutierrez M, Beroiza T, Fantin A, Oddo H, Villarroel L, Cruz E, Lisoba C. Ventilatory drive and respiratory muscle function in pregnancy. *Am Rev Respir Dis* 1991; 144: 837–841.

5. Clark FJ, VonEuler C. On the regulation of depth and rate of breathing. *J Physiol* 1972; 222: 267–295.

6. Milic Emili J, Grunstein MM. Drive and timing components of ventilation. *Chest* 1976;70 Suppl. 1: 131–133.

7. Mikami M, Tatsumi K, Kimura Honda Y, Kuriyama T. Respiration effect of synthetic progestin in small does in normal men. *Chest* 1989; 96: 1073–1075.

8. Smith CA. Progesterone and control of breathing. Dissertation Abstracts International. D. *The Sciences and Engineering* 1978; 39: 3178–3179.

9. Lyons HA, Huang CT. Therapeutic effect of progesterone in alveolar hypoventilation associated with obesity. *Am J Med* 1968; 44: 881–888.

10. Sutton FD, Zwillich CW, Creagh CE, Pierson DJ. Wiel, JV. Progesterone for outpatient treatment of pickwickian syndrome. *Annals Intern Med* 1975; 83: 476–479.

11. Gibson GJ. Tests of ventilatory control. In : Clinical tests of respiratory function. Raven Press, New York, 1984 : 107.

12. Burki NK. Measurements of ventilatory regulation. *Clinics in Chest Medicine* 1989; 10: 215–226.

13. Schoene RB, Robertson HT, Pierson DJ, Peterson AP. Respiratory drives and exercise in menstrual cycles of athletic and non athletic women. *J Appl Physiol* 1981; 50: 1300–1305.

14. Chen H, Tang Y. Effects of menstrual cycle on respiratory muscle function. *Am Rev Respir Dis* 1989; 140: 1359–1362.

15. Smiley RM, Finster M. Do receptors get pregnant too? Adrenergic receptors alterations in human pregnancy. *J Maternal Fetal Med* 1996; 5: 106–114.

16. Tan KS, Mcfarlane LC, Lipworth BJ. Beta adrenoreceptor regulation and AMP reactivity during the menstrual cycle in female asthmatics. *Thorax* 1995; 50 Suppl 2: 60.

17. Milic Emili J. Recent advances in clinical assessment of control of breathing. *Lung* 1982; 160: 1–17.

18. Goodland RL, Reynolds JG, McCord AB, Pommerenke WT. Respiratory and electrolyte effects induced by estrogen and progesterone. *Fert Steril* 1953; 4: 300–317.

19. Hannhart B, Pickett CK, Moore LG. Effects of estrogen and progesterone on carotid body neural output responsiveness to hypoxia. *J Appl Physiol* 1990; 68: 1909–1916.

20. Mitchell RA, Herbert DA, Baker DG. Inspiratory rhythm in airway smooth muscle tone. *J Appl Physiol* 1985; 58: 911–920.

21. Perez Fontan JJ. Mechanical function of the lungs and airways during hypoxia. In : Tissue oxygen deprivation. From molecular to integrated function. Eds by Haddad GG, Lister G. Marcel Dekker Inc., New York 1996: 340.

22. Skatrud JB, Dempsey JA. Relative effectiveness of acetazolamide versus medroxyprogesterone acetate in correction of chronic carbondioxide retention. *Am Rev Respir Dis* 1983; 127: 405–412.