RESTING VENTILATION (23) and ventilatory responses to hypercapnia (13) vary throughout the normal menstrual cycle in response to varying levels of serum progesterone, with an increase in both during the luteal phase. In addition, resting oxygen consumption has been shown to be significantly greater during the luteal phase of the menstrual cycle (1).

Blood pressure is known to be more reactive to physical pressor-inducing stimuli such as the hand-grip test and the cold-pressor test during the luteal phase of the menstrual cycle (19). The pressor response to cocaine is enhanced in ewes after administration of concentrations of progesterone similar to those found during pregnancy (9). The reasons for the increased pressor response are unclear; however, there are a number of studies that link high serum progesterone concentrations and increased sympathetically mediated responses (8, 9, 20).

In men, acute hypercapnia leads to a pressor response in the systemic circulation (14, 15, 17), which is at least partially mediated via an increased sympathetic tone (17), but this response has not been reported in female subjects. The purpose of this study was to investigate the pressor effect of acute hyperoxic hypercapnia during the normal menstrual cycle.

METHODS

Subjects. Eleven healthy Caucasian women, aged 25 ± 1 (SE) yr (range 22–36 yr), all with normal menstrual cycles, were included in the study. None of the subjects had clinical evidence of a sleep disorder. All subjects had normal spirometry; none was taking any regular medication, and none was overweight (body mass index < 26 kg/m²).

Protocol. The subjects were studied on at least two occasions, once during the follicular phase (days 2–14) and at least once during the luteal phase of the cycle (days 15–27). The average day (absolute) on which the women were studied during the follicular phase was day 8 of the menstrual cycle, and the average day on which the study was performed during the luteal phase was day 23. The average cycle length for the group was 30 days. The phase of the cycle in which the first study was performed was chosen arbitrarily; in seven subjects, the first study was in the follicular phase and in four the luteal phase (P = not significant). All tests were performed at the same time of day. Venous blood was drawn on each occasion before ventilatory-response testing for analysis of serum estradiol and progesterone (CLIA-chemiluminescent immunoassay on immulite). The intra- and interassay coefficients of variation for estradiol were 15 and 16%, respectively, and for progesterone 13 and 13%, respectively. Two subjects had anovulatory cycles (indicated by an absence of an increase in progesterone), and their tests were repeated during the luteal phase of their next menstrual cycle.

The effect of acute hyperoxic hypercapnia on arterial blood pressure and ventilation was measured with a modification of the Read (11) rebreathing method while the subjects were sitting awake and relaxed with background music playing. Caffeine was withheld for at least 4 h, and consumption of food was restricted for 2 h before each test.

The apparatus used for the studies consisted of a completely closed 6-liter biased-flow circuit comprising a 4-liter flow-through bag, variable-bypass soda lime absorber, and fixed-speed blower. The subjects were connected to the circuit, which was filled with 100% O₂ via a mouthpiece with the nose occluded. Hypercapnia was induced by the addition of a bolus of CO₂, and the subjects were asked to take three deep breaths to equilibrate the contents of the bag with the lungs. If a plateau in inspired and expired CO₂ was reached within six breaths (indicating that the mixed venous, and thus brain, PCO₂ was near the expired PCO₂ (12)), the soda lime absorber was disconnected and the subject was allowed to rebreathe their own expired CO₂. In the first test on each subject, rebreathing was sustained for 4 min or until the subject could no longer tolerate further increases in end-tidal PCO₂ (PETCO₂). On subsequent tests, subjects rebreathed until their maximum PETCO₂ matched that obtained on the first test. Airflow was measured with a pneumotachograph and differential pressure transducer (DP45-14, Validyne, Northbridge, CA). Tidal volume was calculated by digitally integrating the airflow signal, and minute ventilation (Vi) was calcu-
HYPERCAPNIC PRESSOR RESPONSES DURING THE MENSTRUAL CYCLE

Systolic and cardiovascular recordings.

PETCO₂, was measured at the mouth with a capnometer (HP-47210A, Hewlett-Packard, Waltham, MA). Arterial oxygen-hemoglobin saturation (SaO₂) and heart rate were measured transcutaneously from the ear lobe with a pulse oximeter (Biox 3700E, Ohmeda, Englewood, CO). Arterial blood pressure was measured noninvasively with a self-calibrating finger photoplethysmograph (Finapres, Ohmeda, Englewood, CO). PETCO₂, SaO₂, blood pressure (systolic, diastolic, and mean arterial), heart rate, and Vi were analyzed by breath with customized software (Laboratory Software, Leona, Australia). The ventilatory and blood pressure responses to hypercapnia were calculated from the slope of the regression line plotted against PETCO₂ and expressed as the change in Vi (in l/min) and blood pressure (systolic, diastolic, and mean arterial; in mmHg/Torr (1 Torr = 1 mmHg rise in PETCO₂)).

A 5-min control period was recorded during quiet breathing to provide a baseline measurement of systemic blood pressure, heart rate, PETCO₂, and Vi. During the control period, all expired CO₂ was absorbed by the soda lime and SaO₂ was maintained by computer-controlled addition of O₂ to the rebreathing circuit. Values obtained during the control period for all subjects are expressed as means of the 5-min recordings.

Of 11 subjects, 9 had 1 pair of studies with 1 data set obtained in the follicular phase and another in the luteal phase. The remaining two subjects had anovulatory cycles (their serum progesterone concentration in the luteal phase being <2 nmol/l), and these subjects were restudied in the luteal phase of their next menstrual cycle. All values are expressed as means ± SE for the group. Within-group comparisons between the follicular and luteal phases were made with a paired Student’s t-test. A two-tailed P value < 0.05 was considered significant. P values > 0.1 are reported as not significant.

RESULTS

Serum hormone concentrations. Serum estradiol concentration (Table 1) was not significantly different during the luteal and follicular phases. Estradiol concentration ranged from 45 to 1,089 pmol/l in the follicular phase and from 78 to 885 pmol/l in the luteal phase. Serum progesterone concentration (Table 1) was found to be greater during the luteal phase of the cycle, with the range in the follicular phase being 0.7–2.7 nmol/l and during the luteal phase 8.6–108 nmol/l.

Baseline recordings. During baseline recordings (Table 1), there was no significant difference in ventilatory and cardiovascular variables between the follicular and luteal phases. However, there was a trend toward PETCO₂ being lower during the luteal phase of the menstrual cycle, but this did not reach the stipulated level of significance. Similarly, diastolic and mean arterial blood pressures tended toward being lower during the follicular phase of the menstrual cycle; however, these also did not reach significance.

Ventilatory responses. As previously reported, the ventilatory responses during the luteal phase of the menstrual cycle were significantly higher than during the follicular phase (Fig. 1). The mean ventilatory responses for the group during the follicular and luteal phases of the menstrual cycle were 2.43 ± 0.28 l·min⁻¹·Torr⁻¹ (range 0.6–4.6 l·min⁻¹·Torr⁻¹) and 3.81 ± 0.49 l·min⁻¹·Torr⁻¹ (range 1.3–6.2 l·min⁻¹·Torr⁻¹), respectively (Table 2).

Blood pressure responses. There was a high variation in the systolic blood pressure response among the subjects; however, the slope for each subject was always higher during the luteal phase of their ovulatory cycles than during the follicular phase. The range of systolic blood pressure responses during the follicular phase was 0.2–4.2 mmHg/Torr and during the luteal phase was 1.2–7.6 mmHg/Torr (Fig. 2). The range of diastolic blood pressure responses during the follicular phase was 0.1–2.9 mmHg/Torr and during the luteal phase was 0.7–3.1 mmHg/Torr (Fig. 2). The average mean arterial blood pressure responses during the follicular and luteal phases of the menstrual cycle were 1.35 and 2.71 mmHg/Torr, respectively (P < 0.005).

The systolic blood pressures during the follicular and luteal phases of the menstrual cycle at the onset of hypercapnia were 132 and 126 mmHg, respectively (P = 0.39) and at the conclusion of hypercapnia were 140 and 162 mmHg, respectively (P < 0.02). The diastolic blood pressures for the follicular and luteal phases at the onset of hypercapnia were 74 and 74 mmHg, respectively (P = 0.95). At the conclusion of hypercapnia, the diastolic blood pressures for the follicular and luteal phases of the menstrual cycle were 76 and 96 mmHg, respectively (P < 0.01).

In the two subjects who had anovulatory cycles, there was little difference in the blood pressure responses during the two different phases of the menstrual cycle. The systolic blood pressure responses for these two subjects were 2.17 and 2.07 mmHg/Torr during the follicular phase and 2.18 and 1.25 mmHg/Torr during the luteal phase.

Heart rate responses. The mean heart rate responses were similar during the follicular (1.4 ± 0.6 beats · min⁻¹ · Torr⁻¹) and luteal phases (1.7 ± 0.3 beats · min⁻¹ · Torr⁻¹; P = 0.57) of the menstrual cycle. The range of heart rate responses in the follicular and luteal phases were 0.0–3.3 and 0.2–4.6 beats · min⁻¹ · Torr⁻¹, respectively.

Table 1. Mean baseline ventilatory and cardiovascular recordings

<table>
<thead>
<tr>
<th></th>
<th>Follicular Phase (Days 2–14)</th>
<th>Luteal Phase (Days 15–28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone, nmol/l</td>
<td>2.1 ± 0.7</td>
<td>50.4 ± 9.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estradiol, pmol/l</td>
<td>324 ± 101</td>
<td>416 ± 71</td>
<td>NS</td>
</tr>
<tr>
<td>Vi, l/min</td>
<td>6.8 ± 0.3</td>
<td>7.2 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>PETCO₂, Torr</td>
<td>40.7 ± 2.9</td>
<td>36.6 ± 0.9</td>
<td>0.09</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>125 ± 1.6</td>
<td>123 ± 3.3</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>73 ± 4.0</td>
<td>66 ± 3.6</td>
<td>0.09</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>92 ± 3.3</td>
<td>85 ± 2.9</td>
<td>0.07</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>73 ± 3.1</td>
<td>75 ± 3.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE from baseline recordings; n = 11 subjects. Vi, minute ventilation; PETCO₂, end-tidal PCO₂; SBP, DBP, and MAP, systolic, diastolic, and mean arterial blood pressure, respectively; HR, heart rate. Venous blood for mean progesterone and estradiol concentration was drawn before onset of baseline recording. P values were calculated with paired 2-tailed t-tests. NS, not significant. P values are >0.1.
DISCUSSION

This study has demonstrated that the systemic arterial blood pressure response to acute hyperoxic hypercapnia is greater during the luteal phase of the menstrual cycle. Furthermore, we have shown that the heart rate response to hypercapnia is unchanged between the two phases of the menstrual cycle.

The phase of the menstrual cycle during which the first study was conducted was chosen arbitrarily and was equally liable to have been performed in either of the phases of the cycle, making it unlikely that an order effect influenced our findings.

Previous studies have shown that anovulatory menstrual cycles are common in normal premenopausal women who report regular menstrual cycles (22). For this reason, it was important, even in subjects reporting regular menstrual cycles, to confirm ovulation by the measurement of serum concentrations of progesterone and estradiol. The importance of this was demonstrated during the protocol when two of the women studied had anovulatory cycles. Notably, these two

| Table 2. Ventilatory, MAP, and HR response slopes during follicular and luteal phases |
|-----------------------------------|---------------|--------|--------|----------------|--------|
| Ventilatory response, l·min⁻¹·Torr⁻¹ | Follicular Phase (Days 2–14) | Luteal Phase (Days 15–28) | P Value |
| Ventilatory response, l·min⁻¹·Torr⁻¹ | 2.4 ± 0.3 | 3.8 ± 0.5 | <0.02 |
| MAP response, mmHg/Torr | 1.4 ± 0.2 | 2.7 ± 0.3 | <0.005 |
| HR response, beats·min⁻¹·Torr⁻¹ | 1.4 ± 0.3 | 1.7 ± 0.3 | NS |

Values are means ± SE for each mmHg change in PETCO₂ (Torr); n = 11 subjects. P values were calculated with paired 2-tailed t-tests.
subjects had no change in their pressor response between the two phases.

The Finapres device that was used for recording arterial blood pressure during these studies is a commonly used noninvasive method of accurately recording arterial blood pressure. The device has been correlated with the intra-arterial ipsilateral blood pressure recordings in both the steady-state and dynamic blood pressure systems. Even for rapidly dynamic blood pressure recordings (in a range of 86–266 mmHg), the measurements obtained by the device correlate closely with intra-arterial recordings. The correlation coefficients for systolic, diastolic, and mean arterial blood pressures in this study were 0.97, 0.93, and 0.97, respectively (4).

Progesterone is a respiratory stimulant (26) and increases the ventilatory drive to hypercapnia (23), and thus basal Vi is significantly higher (18) and PETCO2 significantly lower (13) in the luteal phase of the menstrual cycle. In the present study, basal Vi did not change significantly over the course of the menstrual cycle; however, we did demonstrate a trend toward a lower PETCO2. The principal goal of this study was to examine ventilatory and systemic arterial blood pressure responses to hypercapnia and not specifically to reexamine changes in baseline Vt. Interestingly, there was also a trend toward lower basal systolic and diastolic blood pressure measurements during the luteal phase of the menstrual cycle. Although the aim of this study was to measure pressor responses to hypercapnia and not basal changes in blood pressure, we demonstrated a trend toward lower basal diastolic (P = 0.09) and mean arterial blood pressures (P = 0.07) during the luteal phase of the menstrual cycle, findings in agreement with Dunne et al. (2).

We propose that a major factor influencing the increased pressor response to hypercapnia during the luteal phase of the menstrual cycle is the upregulation of catecholamine receptors within the cardiovascular system. There are a number of studies that suggest that catecholamine receptors are upregulated in the presence of higher levels of progesterone. The toxic response to cocaine (a sympathomimetic) is much greater after administration of progesterone than those occurring during pregnancy. Re et al. (10) have suggested that parental administration of progesterone results in increased sympathetic tone in the heart muscle. Both Mehta and Chakrabarty (8) and Tollan et al. (20) showed evidence of increased sympathetic activity (increased blood pressure and increased sweating) during the luteal phase of the menstrual cycle. However, Tollan et al. (20) also showed that even though blood pressure is increased in the luteal phase of the cycle, net serum catecholamine concentrations are reduced. Trzebski and Kubin (21) have suggested that the pressor response to hypercapnia in male subjects is mediated via central control mechanisms increasing peripheral sympathetic tone. Thus it is probable that although acute hyperoxic hypercapnia leads to a similar increase in sympathetic output during the two different phases of the cycle, the postulated upregulation of sympathetic receptors by progesterone during the luteal phase results in a greater response.

Other potential mechanisms of the increased pressor response to hypercapnia must be considered. Progesterone increases intravascular volume, and this could lead to an increased mean circulatory filling pressure and hence an increased cardiac output (mediated via a greater stroke volume). Mean circulatory filling pressure increases reflexly under hypercapnic conditions due to stimulation of aortic arch chemoreceptors (14). Under these circumstances, the pressor effect of hypercapnia would be increased in the presence of a greater intravascular volume. It is unlikely that alterations in parasympathetic tone contributed to the increased pressor response to hypercapnia, because parasympathetic function is believed to be unaltered by the phase of the menstrual cycle (8).

It is clear from the results of this study that the menstrual cycle is an important factor in determining the blood pressure response to hypercapnia. There are a number of implications of these findings when considered in conjunction with other studies reporting greater systemic blood pressure responses to a variety of pressor-inducing stimuli during the luteal phase of the menstrual cycle. Importantly, these results suggest an increased risk of cardiovascular accidents during pressor-inducing activities in the luteal phase of the menstrual cycle. However, obstructive sleep apnea (OSA) in premenopausal women may be another very important public health issue when considered in the context of the results reported in the present study. Blood pressure increases acutely in response to apnea in men with OSA (16). One mechanism that may be involved in the acute pressor response after apnea is the transient increase in PETCO2. Although OSA is classically reported to occur predominantly in men and postmenopausal women (24), there is increasing evidence that OSA also occurs commonly in premenopausal women, with one
epidemiological study suggesting that 4.9% of women aged 30–49 yr have significant OSA (25). According to the data presented here, premenopausal women may have an enhanced pressor response to apnea during the luteal phase of each menstrual cycle. Male sleep apneics often present with daytime hypertension (3), and OSA is suggested to be a major risk factor for the development of hypertension (3, 6, 7, 17). The risk of stroke and acute myocardial infarct are also increased in men with OSA (5). No similar data on cardiovascular morbidity and mortality in OSA exist for premenopausal women. However, if the pressor response to obstructive sleep apnea is enhanced in premenopausal women during the luteal phase of the menstrual cycle, then the occurrence of OSA may pose an even greater risk for the development of hypertension and vascular disease in these women.

In conclusion, this study has demonstrated an increased pressor response to acute hyperoxic hypercapnia during the luteal phase of the menstrual cycle. This effect is associated with higher serum progesterone concentrations, which may either modify the sympathetic response to hypercapnia by upregulation of sympathetic adrenoceptors at the level of the heart and blood vessels or increase intravascular volume. The results suggest a profound influence of the menstrual cycle on cardiovascular control in premenopausal women with OSA.

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