Ventilatory decline after hypoxia and hypercapnia is not different between healthy young men and women

A. S. Jordan, P. G. Catcheside, R. S. Orr, F. J. O'Donoghue, N. A. Saunders, and R. D. McEvoy. Ventilatory decline after hypoxia and hypercapnia is not different between healthy young men and women. J. Appl. Physiol. 88: 3–9, 2000.—The gradual decay in ventilation after removal of a respiratory stimulus has been proposed to protect against cyclic breathing disorders such as obstructive sleep apnea (OSA). The male predominance of OSA, and the increased incidence of OSA in women after menopause, indicates that the respiratory-stimulating effect of progesterone may provide protection against OSA by altering the rate of poststimulus ventilatory decline (PSVD). It was therefore hypothesized that PSVD is longer in premenopausal women than in men and is longer in the luteal menstrual phase compared with the follicular phase. PSVD was measured in 12 men and in 11 women at both their luteal and follicular phases, after cessation of isocapnic hypoxia and normoxic hypercapnia. PSVD was compared between genders and between women in the luteal and follicular phases by repeated-measures ANOVA. There were no significant differences in PSVD between any of the groups after either respiratory stimulus. This suggests that the higher occurrence of OSA in men does not reflect an underlying gender difference in PSVD and implies the increased prevalence of OSA in women after menopause is not representative of an effect of progesterone on PSVD. 

Female sex hormones could potentially protect women from sleep-disordered breathing by slowing the rate of ventilatory decline after a brief stimulus. This could occur through either a general upregulation of the respiratory controller or a direct increase in neuronal short-term potentiation. Neural activity has been shown to be altered by sex hormones at both pre- and postsynaptic levels (1), and progesterone influences synapse density in the adult rat brain (20). Thus there is the potential for female sex hormones to modulate the phenomenon of neural short-term potentiation. This idea is supported by the finding that the decline in
ventilation after voluntary hyperventilation is longer in the luteal phase of the menstrual cycle than in the follicular phase in normal young women (24). The half time of decay in minute ventilation after the voluntary task ceased was 23.7 s in the luteal phase and 17.7 s in the follicular phase, both values being considerably longer than that reported in men after hypoxia (9.7 s) (12). Although the difference in the half times between men and women in these two studies could be due to several methodological factors, such as the different respiratory stimuli used and level of hyperventilation reached, it could represent a gender difference in ventilatory afterdischarge or respiratory short-term potentiation.

In the present experiments we have compared, in healthy young men and women, the rate of ventilatory decline after two respiratory stimuli: isocapnic hypoxia and normoxic hypercapnia. We have chosen the more general term poststimulus ventilatory decline (PSVD) to describe the ventilatory decay after these stimuli. The hypoxic stimulus can be terminated rapidly with a single breath of 100% O₂, and therefore the decay in ventilation after this protocol most closely resembles respiratory short-term potentiation and is often referred to as ventilatory afterdischarge. The decline in ventilation after hypercapnia, however, would likely be influenced by the slower withdrawal of the respiratory stimulus and so is more accurately described as PSVD. We argued that the off-transient after both stimuli could provide potentially important information in terms of inherent respiratory stability-instability between the genders. We hypothesized that the PSVD is longer in women than in men and is longer in the luteal phase of the menstrual cycle than the follicular phase.

METHODS

Subject selection. The selection criteria for this study were as follows. All subjects were required to be healthy nonsmokers with normal lung function determined by spirometry and body plethysmography. Women needed to have regular menstrual cycles and not be pregnant or taking the oral contraceptive pill. All subjects were also required to have regular breathing patterns at rest (a coefficient of variation of minute ventilation of <20% during 5 min of quiet breathing). Twelve men and 14 women met the criteria and gave informed written consent to participate in the study. Three women were subsequently found to be anovulatory (plasma progesterone \(2.33 \pm 1.29\) (SE) nmol/l during the luteal phase) and were excluded from further analysis, leaving 12 men and 11 women (mean age 25.7 ± 1.24 yr) who completed the study. The study was approved by the Research and Ethics Committee of the Daw Park Repatriation General Hospital.

General procedures. All experiments were conducted in the morning, after subjects had eaten a light breakfast and had abstained from caffeine, alcohol, and other stimulants. Subjects were seated comfortably on a bed with back support, in a temperature-controlled environment (23°C) for all periods of data collection. They were encouraged to read and listen to nonrhythmic, spoken tapes to distract them from their breathing and experimental interventions. Data were collected in two or three sessions lasting 1–1.5 h. In each session, multiple periods of hypoxia and hypercapnia were used to stimulate respiration.

Women were tested during the luteal (days 20–23) and follicular (days 6–11) phases of their menstrual cycle, whereas men were tested only once. Menstrual phase was confirmed by plasma progesterone levels, which were measured by chemiluminescence (ACS:180 Progesterone assay, Chiron Diagnostics, Chiron Healthcare, Victoria, Australia). A subject was considered to be anovulatory if plasma progesterone was below 7 nmol/l in the luteal phase.

Equipment and measurements. The gas-delivery system (Fig. 1) consisted of a five-way Gatlin-Shape valve system (series 2440C, Hans Rudolph, Kansas City, MO), the output of which was attached to a pneumotachograph (PT36, Erich Jaeger) in series with the inspiratory port of a Hans Rudolph breathing valve and mask. Foil bags (20–300 liters, Scholle Industries) containing various gases were connected to the four inlet ports on the Gatlin-Shape valve (Fig. 1, A–C) by using several Hans Rudolph two-way taps (Fig. 1, 1–3). Each inlet port could be individually opened and closed by rapidly inflating or deflating a small balloon within the Gatlin-Shape valve. Only one port was open at any time, and all transitions between ports were conducted during expiration. Ports A and B were used for isocapnic hypoxia trials, and port C was used for room-air breathing and hypercapnia trials.

Inspiratory flow was measured (pneumotachograph) breath by breath and integrated electronically to give tidal volume (VT). Inspiratory time (TI), expiratory time (TE), total breath time (TT), peak inspiratory flow (PIF), mean inspiratory flow (V˙I), and inspired minute ventilation (VI) were determined for room-air breathing and experimental interventions. Data were collected in

![Fig. 1. Breathing circuit and gas-delivery system consisted of the subject’s mask and Hans Rudolph breathing valve, with a pneumotachograph and Gatlin-Shape valve system (4 inputs and 1 output) in series with inspiratory side of the breathing valve. Three of four ports of the Gatlin-Shape valve were connected to a low-O₂/100% N₂ flow-O₂ + CO₂ supply (A), 100% O₂ (B), and a high-CO₂ supply/open to room air (C). Only 1 input port was open at a time. Arrows, direction of airflow; 1–3, Hans Rudolph 2-way taps.](http://jap.physiology.org/Downloaded_from%20http://jap.physiology.org/Downloaded_from%20http://jap.physiology.org/)
target a 150% increase in \( \dot{V}I \) by the end of intervention. (PETCO2

firmed to be awake by electroencephalogram (C3-A2 placement), left and right electroocculogram, and masseter electromyogram (Compumedics S series preamplifier, Abbotsford, Victoria, Australia). All data were acquired on an IBM laptop computer by using an analog-to-digital converter (DATAQ Instruments) and a sampling rate of 150 Hz per channel.

Isocapnic hypoxia. The inspirate was switched from room air to 100% N\(_2\) for 1–7 breaths to cause a rapid drop in end-tidal partial pressure of O\(_2\) (PET\(_{O2}\)). The inspirate was then changed to 9% O\(_2\) in N\(_2\) for the remainder of the 45-s period. The number of N\(_2\) breaths was altered between trials to target a ventilation increase at the end of the hypoxic period of 150% of the resting level, without Sa\(_O2\) falling below 75%. Hypoxia was terminated with one breath of 100% O\(_2\), producing a rapid rise in PET\(_{O2}\) to above baseline levels within one to two breaths. Isocapnia was maintained by adding CO\(_2\) into the inspirate, starting during 100% N\(_2\) breathing and continuing after the hyperoxic breath as necessary.

Normoxic hypercapnia. For the 45-s intervention period, 3.5-7% (mean 4.7%) CO\(_2\) was introduced into the inspirate, after which the inspirate was returned to room air. No attempt was made to control end-tidal partial pressure of CO\(_2\) (PET\(_{CO2}\)) in the postintervention period. The amount of CO\(_2\) added to the inspirate was added from one trial to the next to target a 150% increase in \( \dot{V}I \) by the end of intervention.

Individual trial inclusion criteria. Trials were only accepted for further analysis if all of the following criteria were met. 1) Isocapnic conditions were maintained in hypoxic trials. There was no significant difference between mean preintervention PET\(_{CO2}\) and both mean PET\(_{CO2}\) in the last 15 s of intervention and mean PET\(_{CO2}\) in the 45-s postintervention period. 2) Resting ventilatory patterns were stable. The coefficient of variation of breath-by-breath \( \dot{V}I \) in the 30 s before the intervention was <20%. 3) Adequate hyperventilation was achieved. An increase of >120% of the resting \( \dot{V}I \) was reached. 4) There were no sighs in the last 15 s of intervention or in the 45-s postintervention period. Sighs were characterized by a change in VT of >75% between two adjacent breaths and a change in TE of >40% between the same two breaths.

Data analysis. The first step in the data analysis involved determining the time at which the stimulus had been removed (stimulus-off time). For hypoxia trials the stimulus had not ceased until hypoxemia at the peripheral chemoreceptors was reversed. The stimulus-off time after hypoxia was therefore estimated by combining the delay time from inspiratory circuit to lung with that for the lung to peripheral chemoreceptor (circulatory delay). The delay time for inspiratory circuit to lung was estimated from the time that the manual switching of gas in the inspiratory circuit occurred, until the onset of the first breath after the complete displacement of the circuit dead space (500–515 ml depending on facial structure). The circulatory delay has been calculated by previous investigators to be 6–8 s (16, 19). To establish whether a similar circulatory delay was present in our study population, we estimated the circulatory delay in a group of 20 subjects (10 women). Sixteen were included in the present study, and four were enrolled in the study but were subsequently excluded because they were anovulatory (2) or failed to complete the protocols (2). Group mean age and body mass index in these 20 subjects did not differ from those in the 23 subjects included in the main study. Circulatory delay was measured during repeated hypoxia trials (mean of 6 trials/subject) by calculating the delay between the beginning of the 100% \( \dot{V}I \) breath used to terminate hypoxia and the time at which ear Sa\(_O2\) began to rise. Preliminary experiments showed the sudden rise in ear Sa\(_O2\), could only be detected accurately if Sa\(_O2\) had fallen below 90%, thus precluding measurements in some of the study subjects. There were no gender or menstrual phase differences in circulatory delay (men 8.2 ± 0.5 s, women in the luteal phase 7.3 ± 0.5 s, and women in follicular phase 7.8 ± 0.3 s, \( P > 0.05\); thus the mean delay of 7.8 s was used for all subjects participating in the study. Determining the stimulus-off time for hypercapnia trials is problematic because it involves not only release of the peripheral chemoreceptor stimulus but also washout of CO\(_2\) from the cerebrospinal fluid and medullary surrounding central chemoreceptors. Because there is no practical way of determining the contribution of the latter, we chose to use the circulatory delay alone in estimating the stimulus-off time, recognizing that this would, of necessity, involve some inaccuracy.

Because the breathing frequency varied among subjects and because we wished to examine group mean data, the method of linear interpolation was employed to transform all breath-by-breath \( \dot{V}I \) measurements into a 4-s interval time base. The duration of 4 s was chosen because it was approximately equivalent to the mean VT for all subjects across all trials in the 45-s postintervention period.

The postintervention \( \dot{V}I \) vs. time data were fit to a monoexponential decay function \( \dot{V}I = A exp(\beta t) + C \). The decay half time \( t_{1/2} = ln(2)/B \) and time for ventilation to reach the preintervention level were calculated for the mean interpolated data in each subject for both respiratory stimuli. Trials in which \( \dot{V}I \) did not fit the exponential function (\( P > 0.05\)) were excluded from the half-time analysis.

Statistical procedures. The circulatory delay was compared between men and women by an unpaired Student’s \( t \)-test and between women in the two menstrual phases by a paired Student’s \( t \)-test. Student’s \( t \)-tests were also used to examine \( PET_{CO2} \) control during each trial. One unpaired Student’s \( t \)-test was used to compare \( PET_{CO2} \) in the preintervention and last 15 s of intervention periods. Another was used to compare \( PET_{CO2} \) between preintervention and 45 s postintervention. Maintenance of isocapnia was considered appropriate if both t-tests were nonsignificant (\( P > 0.05\)). Plasma progesterone was compared between the luteal and follicular phases by a paired Student’s \( t \)-test.

For women, a two-way analysis of variance (ANOVA) for repeated measures was used to examine menstrual phase and time effects for each variable measured (\( \dot{V}I \), VT, breathing frequency, Ti, Te, TT, PIF, \( V_i/VTi \), PET\(_{CO2}\)). Changes in these variables after the stimulus-off time were analyzed for 44 s after hypoxia and for 84 s after the hypercapnia trials. Two-way ANOVAs were used to compare the same variables between men and women in both luteal and follicular phases. \( \dot{V}I \) was compared during the 44-s poststimulus period between the two respiratory stimuli by using two-way ANOVA. Tukey’s post hoc tests were used wherever significant ANOVA effects were found. The \( \tau \) of the exponential decay profiles after each respiratory stimulus were compared by using unpaired Student’s \( t \)-tests. The Student’s \( t \)-test was also used to examine for differences between genders and between follicular and luteal phases. Data are expressed as means ± SE. \( P < 0.05 \) was considered statistically significant.

RESULTS

Resting characteristics. There were no significant differences in age, body mass index, or lung function...
between the men and women in this study (Table 1); however, resting ventilatory parameters were different between the groups (Table 2). Among women, resting \( V_{I} \) was higher in the luteal phase than in the follicular phase due to a significant shortening of \( T_{E} \), and \( \text{PET}_{\text{CO}_2} \) was correspondingly lower in the luteal phase. Men had a higher resting \( V_{I} \) and, consequently, \( V_{I} \) compared with women in the follicular phase. However, \( V_{I} \) was not different between men and women in the luteal phase despite differences in \( V_{T} \), respiratory timing, and \( \text{PET}_{\text{CO}_2} \). Plasma progesterone was significantly higher in the luteal phase (29.6 \( \pm \) 4.2 nmol/l) than the follicular phase (16.0 \( \pm \) 2.0 nmol/l).

Trial exclusion. A total of 532 trials was completed, of which 281 did not meet one or more of the inclusion criteria (see Methods): 77 trials were excluded due to sighs, 1 because the subject was asleep, 23 due to insufficient stimulation of breathing, 17 due to a high coefficient of variation in \( V_{I} \) during the prerandomization period, and 163 because of inadequate CO\(_2\) control. This resulted in a mean of five (range 1–8) trials being available for analysis in each subject for each respiratory stimulus.

Maintenance of isocapnia. Excluding hypercapnia, there were no differences between pre- and posttrial \( \text{PET}_{\text{CO}_2} \) at any time in any group. In addition there were no gender-by-time or phase-by-time interactions in \( \text{PET}_{\text{CO}_2} \) after hypoxia, indicating strict CO\(_2\) control (Fig. 2). There were significant menstrual-phase differences in \( \text{PET}_{\text{CO}_2} \) (luteal \( \text{PET}_{\text{CO}_2} \) levels lower than follicular levels) after both respiratory stimuli.

Breathing patterns after hyperventilation. There were no gender-by-time or phase-by-time interactions in \( V_{I} \) (Fig. 3) or any other respiratory measurement (\( V_{T} \), breathing frequency, TI, TE, TR, PIF, VT/TI) for either respiratory stimulus. \( V_{I} \) remained above resting levels significantly longer after hypercapnia compared with hypoxia. The ventilatory decay curves for each subject were fit by an exponential function, with mean values ranging from 0.89 to 0.92. Curve \( \tau \) for hypoxia PSVD was not different between men (4.5 s) and women in either the follicular phase (5.1 s) or the luteal phase (4.7 s) or between the two phases of the female menstrual cycle. Posthypercapnia \( \tau \) (20.2 s) differed significantly from posthypoxia \( \tau \), but the \( \tau \) after this stimulus was also not different between the genders nor between the phases of the menstrual cycle.

**DISCUSSION**

The main finding of this study was that in healthy young adults, the rate of PSVD was not different between the genders and was not different between the

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**Table 1. Subject characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>( V_{I} ), l/min</th>
<th>( \text{PET}_{\text{CO}_2} ), Torr</th>
<th>( V_{T} ), liters</th>
<th>( F_{B} ), breaths/min</th>
<th>( T_{I} ), s</th>
<th>( T_{E} ), s</th>
</tr>
</thead>
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<tr>
<td>Men</td>
<td>9.05 ( \pm ) 0.34( ^{*} )</td>
<td>40.1 ( \pm ) 0.93( ^{t} )</td>
<td>0.58 ( \pm ) 0.02( ^{t} )</td>
<td>15.52 ( \pm ) 0.59( ^{t} )</td>
<td>1.6 ( \pm ) 0.07( ^{t} )</td>
<td>2.38 ( \pm ) 0.1( ^{t} )</td>
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<td>Follicular</td>
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<td>17.7 ( \pm ) 0.78*</td>
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**Table 2. Resting breathing characteristics**

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<tr>
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Values are means \( \pm \) SE. n, No. of subjects; Resting minute ventilation (\( V_{I} \)), end-tidal CO\(_2\) (\( \text{PET}_{\text{CO}_2} \)), tidal volume (\( V_{T} \)), breathing frequency (\( F_{B} \)), inspiratory time (\( T_{I} \)) and expiratory time (\( T_{E} \)) in men (n = 12) and in women (n = 11) in the follicular and luteal phases of the menstrual cycle. *Significant difference compared with women in the follicular phase. †Difference compared with women in the luteal phase. All P < 0.05.
Male OSA patients was time for ventilatory decline (12). However, Georgopoulos et al. reported that the half-life of PSVD on respiratory control during sleep (16). It is unclear whether it differs between wakefulness and sleep are significantly to the rate of ventilatory decline across the menstrual cycle. Takano (24) also reported more delayed ventilatory decline in normal women after voluntary hyperventilation than in the present study. In Takano's study ventilation during the voluntary hyperventilation task was ~350% of resting ventilation and was therefore greater than in the present study (~150%), and the subjects in his study hyperventilated for 15 s longer.

In contrast to the present study in which no difference was observed in PSVD between the follicular and luteal phases of the menstrual cycle, Takano (24) found the ventilatory decline \( \tau \) after voluntary hyperventilation to be 6 s longer in the luteal compared with the follicular phase. Takano proposed that this was a result of a 3.1-Torr reduction in resting \( \text{PETCO}_2 \) from the follicular to the luteal phase, because he and Durlinger (11) found an inverse relationship between \( \text{PETCO}_2 \) and the duration of PSVD. However, a direct relationship between \( \text{PETCO}_2 \) and the rate of ventilatory decline has also been found in animal studies (9, 10) and one study in sleeping humans after hypoxia (2). It does appear from these studies that \( \text{PETCO}_2 \) exerts an influence on PSVD, but the direction of its effect and whether it differs between wakefulness and sleep are uncertain. If there is an inverse relationship between \( \text{PETCO}_2 \) and the duration of PSVD in awake female subjects as suggested by Takano (24), the 1.9-Torr fall in \( \text{PETCO}_2 \) observed between the follicular and luteal phases in the present study would have resulted in a smaller and possibly insignificant change in PSVD. Another possible contributing factor to the different results in Takano's study and ours relates to the precision of \( \text{PETCO}_2 \) control. Takano maintained \( \text{PETCO}_2 \) within 2 Torr of the subjects' resting levels. We rejected trials in which \( \text{PETCO}_2 \) was statistically different from preintervention levels. Mean \( \text{PETCO}_2 \) in our study was thus maintained within 0.5 Torr of preintervention levels. Less precise control of \( \text{PETCO}_2 \), combined with the previously reported difference in ventilatory responsiveness to arterial partial pressure of \( \text{CO}_2 \) between the menstrual phases (8), could lead to systematic errors in measurement of the rate of ventilatory decline across the menstrual cycle.

Fig. 3. Decay in minute ventilation (Vi) expressed as a percentage of preintervention levels after 45 s of hypoxia (A) and hypercapnia (B) in men (n = 12) and women (n = 11) in both menstrual phases. There was no significant gender- or phase-by-time interactions after either respiratory stimulus. Values are means ± SE.
There were significant differences in PSVD duration after hypoxia and hypercapnia. The longer PSVD after hypercapnia probably reflects the delay in washout of CO₂ from the CSF and medulla surrounding central chemoreceptors. OSA patients develop acute hypercapnia during apneas, and this contributes to the post-apnea-/hypopnea hyperventilation. The ventilatory decline after a hypercapnic stimulus could therefore be relevant to the perpetuation of unstable patterns of breathing during sleep. Our findings suggest that differences in PSVD after brief hypercapnia are unlikely to contribute to the gender difference in OSA prevalence.

A secondary finding was that the circulatory delay between lung and peripheral chemoreceptors after brief hypoxia was not different between men and women. The circulation time between lung and peripheral chemoreceptors is considered to be an important factor in the maintenance of respiratory stability, and a markedly prolonged circulation time has been shown in theoretical models (17) and experimental animal preparations (14) to destabilize breathing. The identical circulatory delay shown between men and women in this study makes it unlikely that differences in the peripheral chemoreceptor feedback loop would contribute to gender differences in sleep-disordered breathing.

It is important to note that the findings of this study do not exclude PSVD as a factor contributing to the higher occurrence of OSA in men and postmenopausal women. This study has indicated that no gender or menstrual phase differences in PSVD exist in healthy young volunteers; however, the incidence of sleep-disordered breathing is low in this group (27). A gender difference in PSVD may only become apparent in more elderly individuals in whom OSA is more common. The present study also measured PSVD in subjects while awake, but some aspects of breathing control have been shown to change during sleep. For example, the hypoxic ventilatory response is reduced during sleep in men (7) but not altered from wakefulness to sleep in women (28). The ventilatory pattern after removal of a brief hypoxic stimulus appears to be reduced from wakefulness to sleep in men (13) and to our knowledge has not been reported in sleeping women. It is possible that there are state-related gender differences in PSVD, which could contribute to the higher occurrence of OSA in men.

In conclusion, this study has measured PSVD in awake healthy young adults and found no evidence of a gender or menstrual-phase difference. These findings do not support the hypothesis that the higher occurrence of OSA in men and postmenopausal women is due to altered PSVD. However, should PSVD change differently in men and women with increasing age or during sleep, then it may still contribute to the gender difference in OSA.

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